Forty Years after the "*Heterodiene syntheses with α,β-unsaturated carbonyl compounds*": Enantioselective Syntheses of 3,4-Dihydropyran Derivatives

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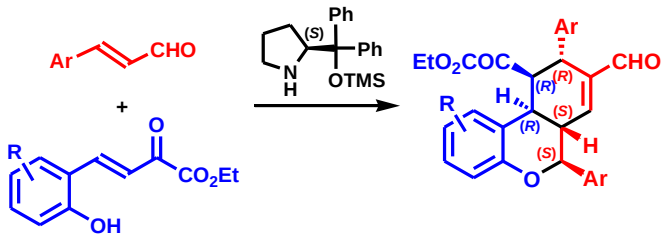
ABSTRACT: The manuscript is focused on the enantioselective synthesis of 3,4 dihydropyran derivatives, whose importance as chiral building blocks in the synthesis of bioactive molecules and natural products is well acquired. The review analyses the different synthetic strategies by grouping them as a function of the atom numbers of the reagents involved in. Starting from the classical [4+2] and [2+4] approaches, the [3+3], [5+1], and [6] strategies have been sequentially analyzed, and, for each of them, the asymmetry induced by both chiral metal complexes and different kinds of organocatalysts has been examined. More than 400 papers have been reviewed, whose results have been described in the highest synthetic manner, in the attempt to emphasize the mechanism of the chirality transfer from the chiral messengers to the reaction products. This analysis allows to evidence the great flexibility of the diverse catalytic systems, the complementary of the results obtained from the different reaction pathways, and the very high level of control of the achievable molecular complexity.

A clean one pot creation of five chiral centers in >99% ee is not a miracle



It is the green power of asymmetric catalysis!

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1. Introduction

Forty years ago, one of us was the co-author of a review on "*Heterodiene Syntheses with α,β-Unsaturated Carbonyl Compounds*"[1] in which the cycloaddition reactions of these reagents with a double bond were discussed in terms of perturbation molecular orbital (PMO) theory. A figure was reported (Figure 1) with the estimated π-frontier orbital energies for acrolein, as the model compound of the heterodiene, and different olefins (R = alkyls; C = conjugated; Z = CO, CN; X = NR_2, OR). The solid arrow indicated the dominant interaction determining the reactivity between the LUMO of the heterodiene (the electrophilic reagent) and the HOMO of the dienophile (the nucleophilic reagent).

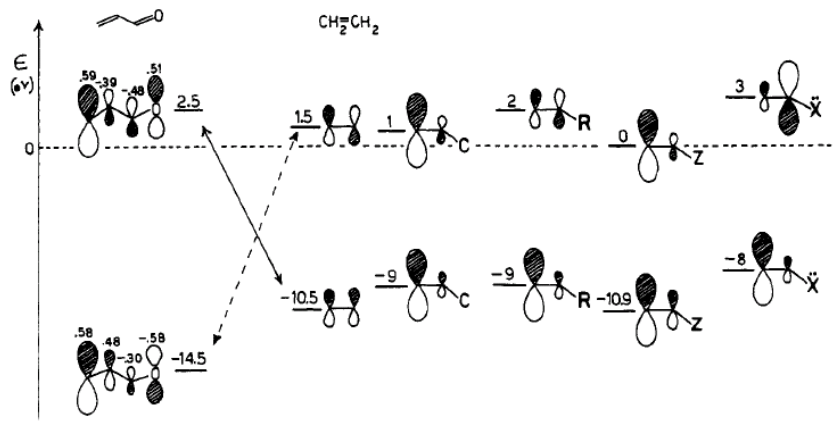


Figure 1. Original picture used in 1975 to describe the Frontier Molecular Orbital interaction in hetero Diels-Alder reactions.

In the last section of the review, the acid catalysis in the hetero-Diels-Alder (HDA) cycloaddition was briefly discussed, since, at that time, a single example was reported in the literature. The rate variations were found to be really small and depending on the specific dienophile involved in the reaction and they were rationalised on the basis of FMO interactions. Obviously, the use of chiral Lewis acids in asymmetric synthesis was not considered simply because, at that time, no examples of the enantioselective catalysis of the Diels-Alder (DA) cycloaddition were known in the literature.

The early papers reporting the first examples of enantioselective syntheses by asymmetric catalysis began to appear in the early ’80 and with the new millennium an impressive increase of the number of publications in the field was observed (Figure 2).

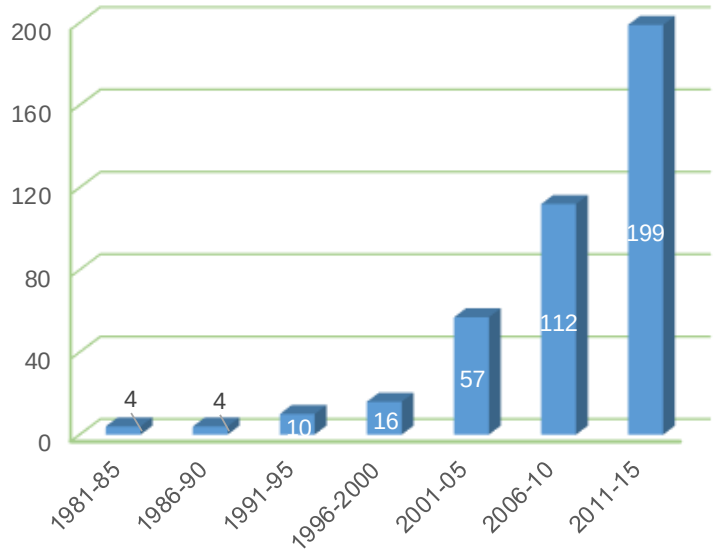
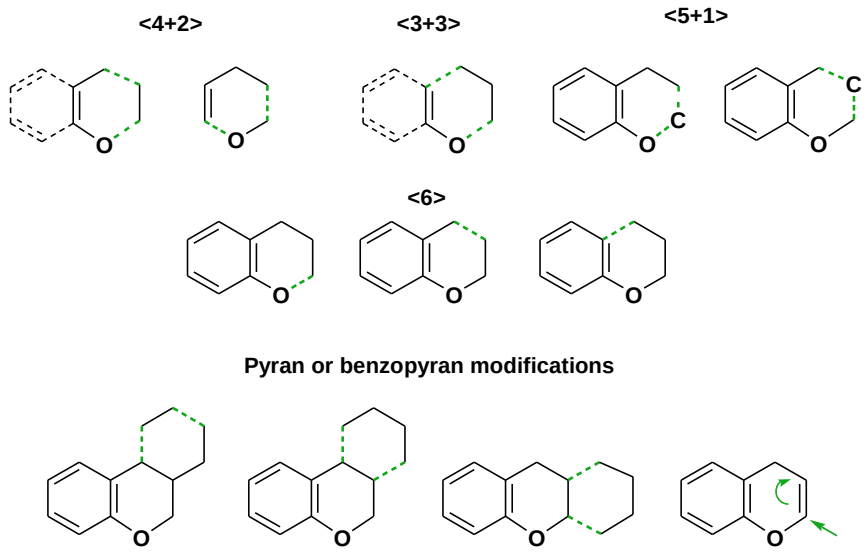


Figure 2. Number of papers dealing with the asymmetric catalyzed synthesis of 3,4-dihydro-2*H*-pyrans and 3,4-dihydro-2*H*-chromene derivatives.

Starting from these considerations, the present review will be focused on the enantioselective syntheses of 3,4-dihydropyran derivatives by catalyzed reactions. The topic will be presented starting from the typical [4+2] approach in which the HDA cycloadditions with either direct or inverse electro-demand are frequently the synthetic pathway followed. Then the [3+3] approach will be discussed, in which the O(1)-C(2) and C(4)-C(5) bonds of the the pyran ring are formed. This strategy is often used in the synthesis of benzopyran derivatives. The last intermolecular approach, the [5+1] strategy, is quite rare and the few examples reported considered the formation of either the O(1)-C(2) and C(2)-C(3) or the C(2)-C(3) and C(3)-C(4) bonds in the benzopyran structure. The intramolecular strategies have found useful application in the benzopyran synthesis only, and involved the formation three different bonds of the target structure: (i) the O(1)-C(2) bond; (ii) the C(3)-C(4) bond; (iii) the C(4)-C(4a) bond. Finally, the asymmetric modifications

of both pyran (less frequent) or benzopyran nuclei (more frequent), by either addition or cycloaddition reactions, will be described (Scheme 1).

Scheme 1. Synthetic Approaches to 3,4-Dihydro-pyran Derivatives.



2. The Enantioselective Acceptor/Donor [4+2] Cyclization to 3,4-Dihydropyran Derivatives

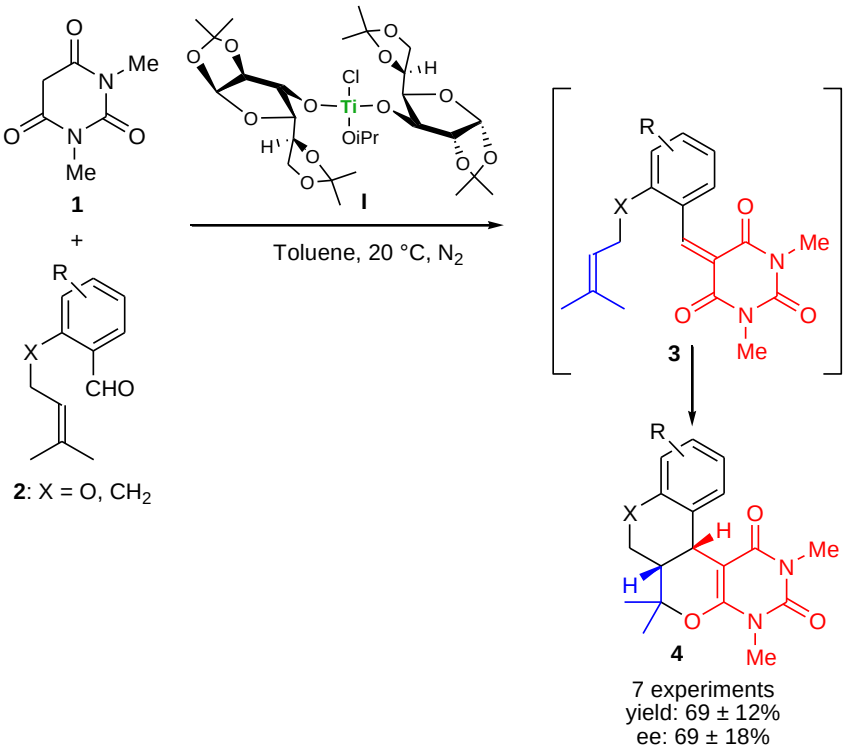
The [4+2] approach to the 3,4-dihydropyran nuclei is the most frequently used synthetic route. About the 60% of the papers discussed in the present review involves this kind of enantioselective cyclization, which is mainly based on the DA reaction with both inverse (reaction between an heterodiene with an electron rich dienophile) and normal electron demand (cycloaddition between an electron-rich diene with an heterodienophile).[2,3] Beside these traditional approaches, in the last 10 years the cyclization of *ortho*-substituted phenols has attracted the interest of many researches.

2.1. Heterodiene Syntheses with α,β-Unsaturated Carbonyl Compounds

The first examples of enantioselective syntheses of 3,4-dihydro-pyran derivatives were reported in the early ’90 by using Ti(IV) based chiral catalysts in both intramolecular[4,5] and intermolecular[6] HDA cycloadditions. The intramolecular HDA reactions of 1-oxa-1,3-butadienes **3**, obtained *in situ* by Knoevenagel condensation of aromatic aldehydes **2** and *N*,*N*′-dimethylbarbituric

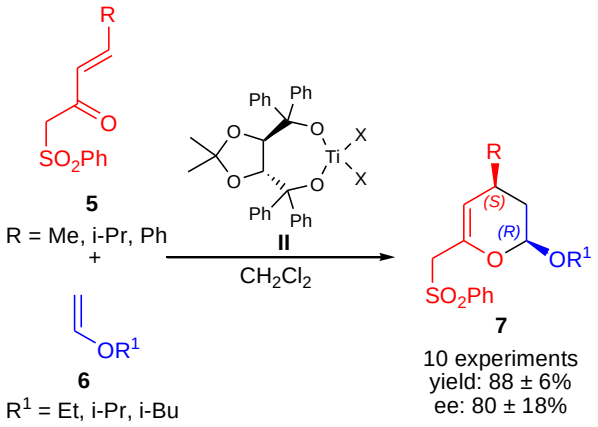
acid **1**, were enantioselectively catalysed using an excess of the chiral complex **I**, formed *in situ* by reaction of Ti(IV) with 1,2:5,6-di-*O*-isopropyledene-α-D-glucofuranose as the chiral ligand (Scheme 2). The tandem Knoevenagel-HDA proceeded with good overall yields (from 55 to 86%) and appreciable enantioselectivities (from 30 to 88% enantiomeric excess (ee), even if an excess of chiral complex was required to obtain good results.[4,5] The enantioselectivities were found to depend on both temperature and solvent polarity. The highest ee were obtained at room temperature, and the use of higher or lower temperature significantly decreased the enantiomer ratio. Considering the solvent effect, polar solvents ($CHCl_3$, THF, and DCM) lowered the enantioselectivity, while apolar aromatic solvents (the best one was found to be isodurene) gave the highest ee.[5]

Scheme 2. Tandem Knoevenagel-Hetero Diels-Alder Cycloaddition Catalyzed by a Ti(IV)-Based Chiral Catalyst.[4,5]



The HDA reaction between (*E*)-2-oxo-1-phenylsulfonyl-3-alkenes **5** and vinyl ethers **6** was enantioselectively catalysed by 5-10 mol % of the Ti(IV)-TADDOLate complex **II**, Scheme 3.[6] The cycloaddition gave adducts **7** with very good yields and high control of stereo- and enantioselectivity (only endo-adducts with up to 97% ee).

Scheme 3. Asymmetric HDA Reaction Between Oxo-sulfonyl Alkenes and Vinyl Ethers Catalyzed by Ti(IV)-TADDOLate.[6]



After these first examples, the enantioselective synthesis of 3,4-dihydropyran derivatives by HDA cycloadditions became more familiar, in particular by using chiral Lewis-acid complexes that represented the main strategy until 2005 when the use of organocatalysts rapidly attracted new attention of chemical researches. The first organocatalytic approach involved the use of chiral amines (aminocatalysis), and more recently (in 2015) the use of chiral Brønsted-acids added further applications in this field (Figure 3).

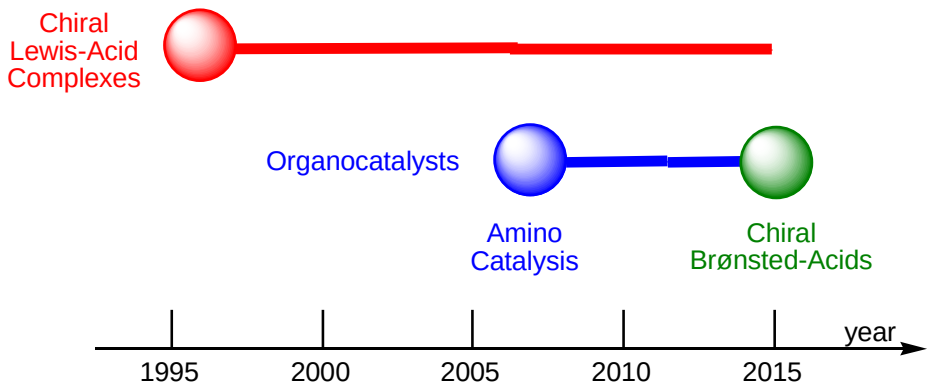


Figure 3. Chronological order of the differing enantioselective strategies to run asymmetric HDA reactions.

The analysis of the enantioselective approach to dihydropyrans by HDA cycloadditions will follow this chronological order, starting from the use of chiral Lewis-acid complexes and closing with the very recent achievements obtained with chiral Brønsted acids.

2.1.1. Hetero Diels-Alder (HDA) Reactions and Other [4+2] Cyclization Processes Catalyzed with Chiral Lewis-acid Complexes

A chiral Lewis-acid catalyst consists of a cation coordinated to an optically active ligand. The chiral complex must have at least one vacant Lewis acid site suitable to coordinate and to activate the reagent. To obtain good level of enantioselection, an appropriate reagent orientation favoring the approach to one specific face of the reagent will be required. In order to reduce the number of possible reacting complexes, the use of C_2-symmetric chiral ligands is very frequent in asymmetric catalysis. To have a homogeneous comparison between the stereochemical results of the reactions, and to avoid different descriptors due to the different substituent priorities, the substituent R will be conventionally considered to be a phenyl group (Figure 4), and the preferred approached face will be referred to the β-carbon, with the α,β-unsaturated moiety in a *s*-cis conformation.

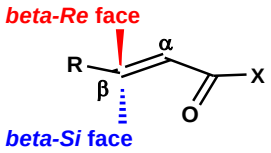


Figure 4. Addition to the enantiotopic faces at the double bond of the α,β-unsaturated carbonyl derivative.

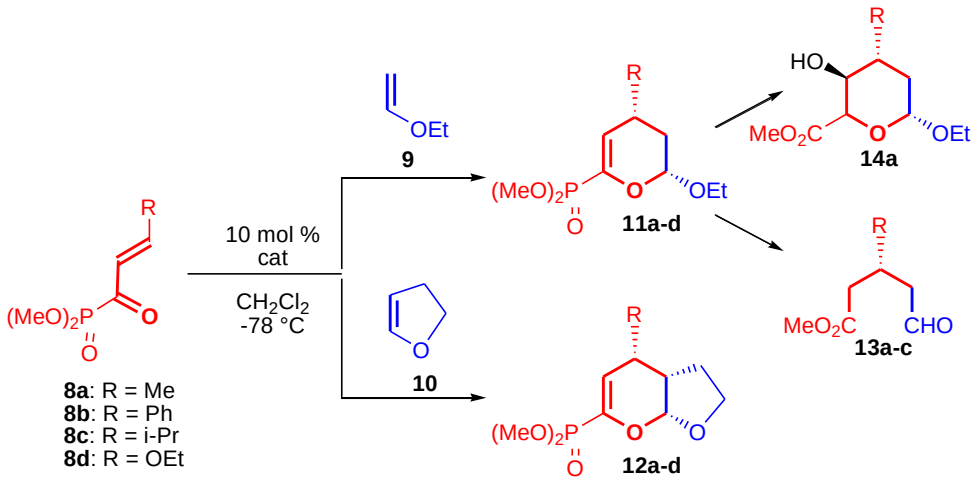
2.1.1.1. Box-based Complexes as Catalysts

The first examples concerning the use of C_2-symmetric chiral bis(oxalines) (box) as ligands in asymmetric catalysts appeared in the early '90 when two back-to-back communications were published in the *Journal of the American Chemical Society*, the first by Evans,[7] the second one by

Corey.[8] After these two short communications, the boxes quickly became one of the most frequently used bidentate ligands used in a large variety of highly enantioselective reactions.[9-12]

The first example of useful application of box-based catalysts in enantioselective HDA cycloaddition was reported by Evans in 1998.[13] The Cu(II)-Box complexes catalyzed the reaction of enol ethers with α,β-unsaturated acyl phosphonates derivatives, Scheme 4.

Scheme 4. Asymmetric HDA Reaction Between Acyl Phosphonate Derivatives and Vinyl Ethers Catalyzed by Cu(II)-Box Complexes.[13,16]



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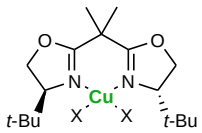
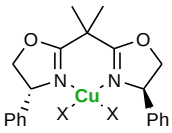


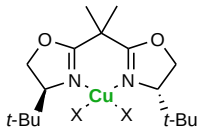
(*S*)-**IIIa**: X = $OTf^{\ominus}$

11a: 89% yield; endo:exo 99:1; 99% ee
12a: 91% yield; endo:exo >99:1; 95% ee



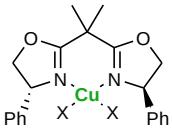
(*R*)-**IVa**: X = $OTf^{\ominus}$

11a: 85% yield; endo:exo >99:1; 94% ee
12b: 100% yield; endo:exo 171:1; 93% ee



(*S*)-**IIIb**: X = $SbF_6^{\ominus}$

11a: 84% yield; endo:exo 69:1; 93% ee
12c: 79% yield; endo:exo 98:2; 90% ee
12d: 99% yield; endo:exo >99:1; 97% ee



(*R*)-**IVb**: X = $SbF_6^{\ominus}$

11a: 100% yield; endo:exo >99:1; 93% ee
11b: 98% yield; endo:exo 167:1; 98% ee
11c: 99% yield; endo:exo 146:1; 96% ee

The 3,4-dihydro-pyran derivatives **11** and **12** were obtained with excellent yields, endo selectivities, and enantioselectivities. Catalysts (*S*)-**III** and (*R*)-**IV** were found efficient also at higher temperature, since stereo- and enantioselectivities were only slightly decreased by running the reactions at ambient temperature. The enantiopure cycloadducts **11** and **12** were transformed in

useful chiral synthon. For instance, **11a-c** were converted within good yields into aldehydic esters **13a-c**, which are formally the conjugate adducts of aldehyde enolates with β-substituted acrylates, while the functionalization of the double bond of **11a** afforded lactone **14a** as a single diastereomer.

The sense of the asymmetric induction for all the (*S*)-**III** complexes is consistent with a dienophile approach to the less hindered face of the heterodiene coordinated to Cu(II)-Box complex with a square planar geometry (complex **15**, Figure 5). This is the classical geometry of *t*-Bu-Box-Cu(II) complexes that rationalizes the stereochemical outcome of a large variety of enantioselective reactions catalyzed by these complexes.[11,12]

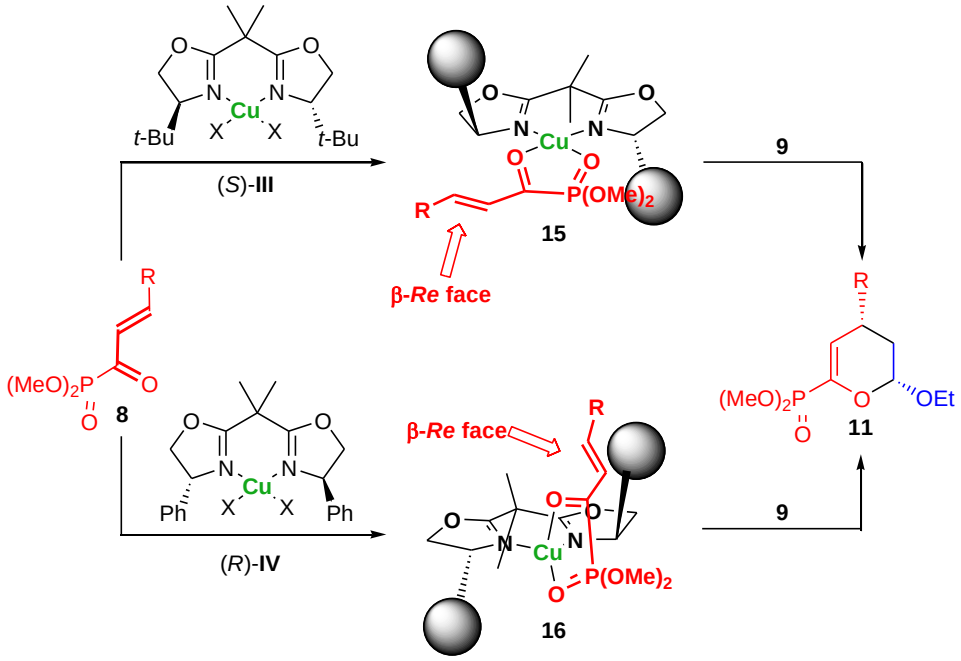


Figure 5. Reactive intermediate complexes **15** and **16** proposed to rationalize the same stereochemical result obtained by using Cu(II)-Box complexes with opposite stereochemistry of the chiral ligand.

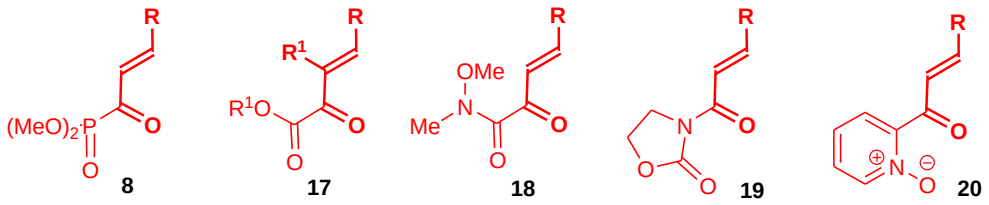
Interestingly, the use of the (*R*)-**IV** complexes, which have the opposite stereochemistry of (*S*)-**III**, afforded the adducts **11** and **12** with the same stereochemistry. These results are quite frequent in the field, since many examples are reported in which the opposite enantiomers are selectively obtained by using the complexes of Cu(II) with either *t*-Bu-Box or Ph-Box having the

same stereochemistry. Two different models have been proposed to rationalize these findings. The first one was proposed by Jørgensen to explain the inversion in the stereochemical outcome of the adducts obtained by using **IV** instead **III** observed in the asymmetric HDA reactions involving glyoxylates as heterodienophiles.[15] The model proposed a change in the geometry of the intermediate reacting complex from the typical square-planar geometry to a tetrahedral one. In the present case, the use of Box ligands with opposite stereochemistry give rise to two different intermediates with either a square-planar or tetrahedral geometry [complexes **15** for (*S*)-*t*-Bu-box and **16** for (*R*)-Ph-Box, Figure 5] that exposed the same β-*Re* face to the favored approach of ethyl vinyl ether **9**.

The second model was proposed by Evans on the basis of some experimental evidences that indicated a reduced propensity of the Cu(II)-Ph-Box complexes **IV** to distort from square planarity relative to their *t*-Bu-Box counterparts.[16] Hence, if a square-planar geometry is operative also in the reactions catalyzed by (*R*)-**IV**, the dienophile approach must occur syn to the oxazoline substituent. To rationalize such an occurrence, the proposal considered that the π surface of the phenyl substituent on the oxazoline ring is able to stabilize the partial positive charges developed on the vinyl ether fragment during the asynchronous transition state.

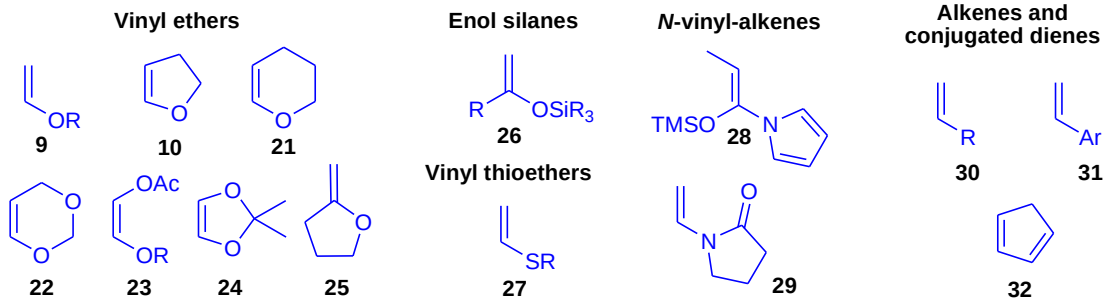
A common feature of the heterodienes used as substrates in enantioselective catalyzed HDA reactions is their ability to behave either as 1,2- or 1,3-bicoordinating reagents. The heterodienes employed in catalyzed cycloadditions with electron-rich alkenes are summarized in Chart 1: α,β-unsaturated acyl phosphonates **8**,[13,14,16] α,β-unsaturated keto esters 17,[14,16-28] α,β-unsaturated keto amides **18**[4,16] are typical 1,2-bicoordinating reagents, while acyloxazolidinones **19**[16,29] and alkenoyl pyridine-*N*-oxides **20**[30-32] are 1,3-chelating substrates (Chart 1).

Chart 1. Heterodienes Used in Asymmetric HDA Reactions Catalyzed by Box-based Chiral Catalysts



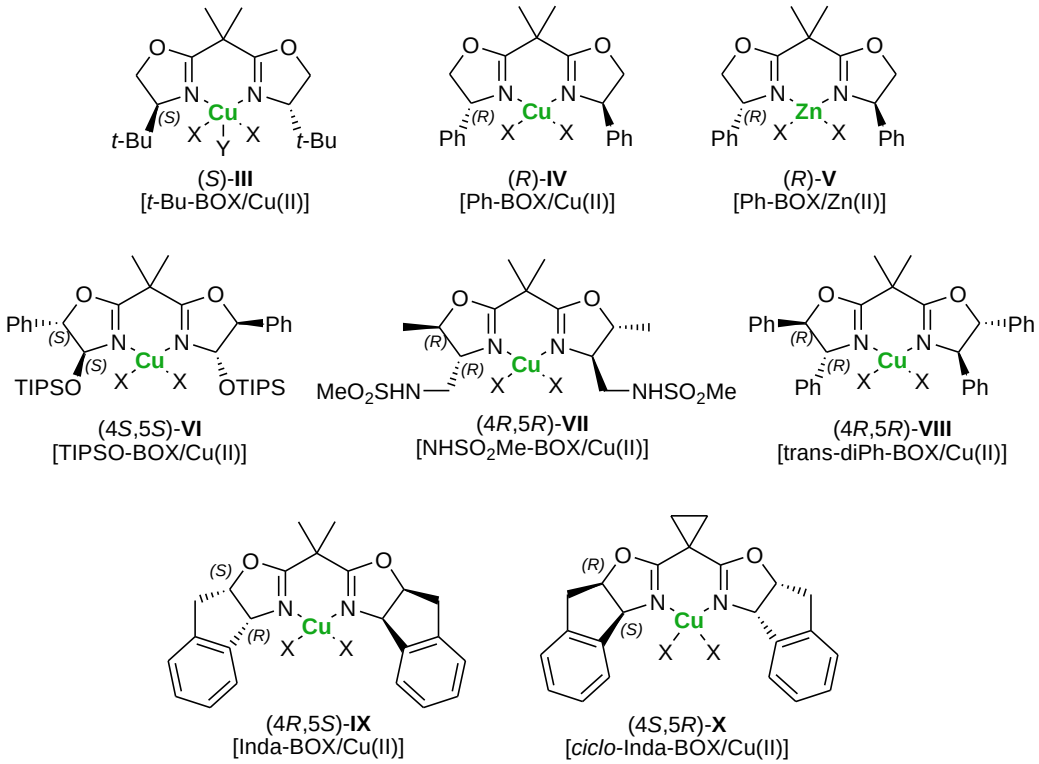
The heterodienes in Chart 1 have been reported to give enantioselective cycloadditions with several electron rich alkenes, such as vinyl ethers **9**,[13,14,16-19,24,26,27,30] **10**,[13,14,16-19,30] **21-25**,[13,16,18,19,23,25,28,30,31] enolsilanes **26**,[16,29,32] vinyl thioethers **27**,[16,30] *N*-vinyl derivatives **28**[29] and **29**,[30] alkyl or aryl-substituted alkenes **30**[21] and **31**,[30] and conjugated dienes **32**[13,16] (Chart 2).

Chart 2. Heterodienophiles Used in Asymmetric HDA Reactions Catalyzed by Box-based Chiral Catalysts



The most frequently used Box-based catalysts are those derived from *t*-Bu- and Ph-Box chiral ligands with the Cu(II) cation as the Lewis acid center, even if interesting examples of 4,5-disubstituted Box have been reported, and only one catalyst involving a different Lewis acid – the Zn(II) cation – has been described. Chart 3 collects the different Box-based catalysts that found useful applications in asymmetric HDA reactions.

Chart 3. Box-based Chiral Catalysts Used in Asymmetric HDA Reactions.



The results of the enantioselective catalyzed HDA cycloadditions obtained by using Box-based complexes are collected in Table 1. For each kind of heterodienophile and with the same Box-based catalyst the Table reports the number of experiments with the average values (and the relative standard deviations, s.d.) for the reaction yields, the stereo- (diastereomeric excess, de; diastereoisomer ratio, dr) and the enantioselectivities observed. This choice is made for sake of simplicity and to illustrate in a better way the efficiency and flexibility of each enantioselective catalyst.

Heterodienophiles **8** bearing a large variety of substituents in the β-position react with several vinyl ethers and thiovinyl ethers to give, in the presence of Cu(II)-Box catalysts, very good yields of cycloadducts with almost complete endo-selectivity and excellent enantioselectivities. The entry 1 of Table 1 collects the results of 15 different reactions run in the presence of (*S*)-**III** (with either TfO^- or $SbCl_5^-$ as counterion, or of the corresponding triflate-aqua complex): the reactions are highly endo-selective and proceed with good yields and ee frequently higher than 95%.

Table 1. Average Values and Standard Deviations (s.d.) of Reaction Yields, Diastereo-, and Enantioselectivities for the HDA Reactions Between the α,β-Unsaturated Carbonyl Derivatives in Chart 1 and the Alkenes in Chart 2 Catalyzed by the [Box/Cu(II)] Complexes in Chart 3.

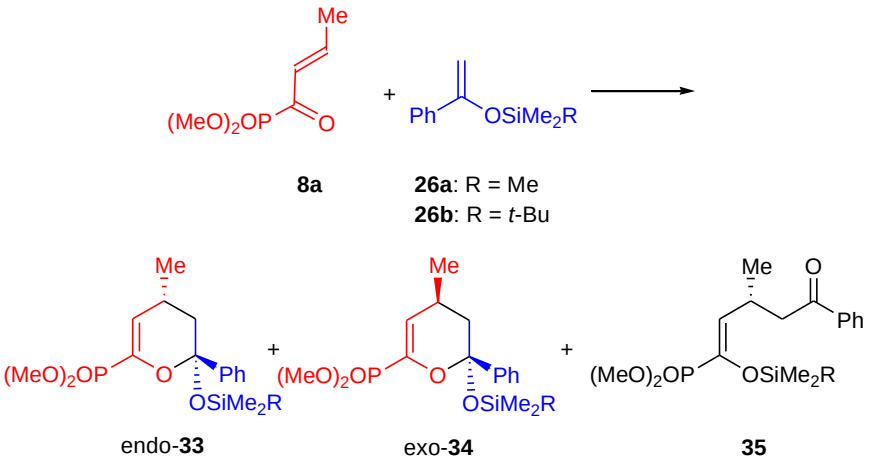
Entry	Heterodiene	Dienophile	Box	n. Exp.	aver. Yield % (s.d.)	aver. de (s.d.)	aver. ee % (s.d.)	Attached face	Ref.
1	**8**	**9, 10, 21, 27**	(*S*)-**III**	15	77 (26)	84 (32)	88 (11)	β-*Re*	13,16
2	**8**	**9, 10, 27**	(*S*)-**IV**	12	92 (14)	97 (5)	82 (26)	β-*Si*	13,16
3	**17, 18**	**9, 10, 22-25, 27**	(*S*)-**III**	36	83 (15)	85 (14)	95 (8)	β-*Re*	14,16-19
4	**17**	**9**	(*S*)-**IV**	2	99	84 (18)	38 (37)	β-*Si*	17,18
5	**17**	**9, 10, 24, 25**	(*R*)-**V**	5	88 (21)	76 (21)	80 (11)	β-*Re*	19
6	**17**	**9**[a]	(*S*)-**III**	17	n.r.[b]	86 (7)	93 (4)	β-*Re*	23
7	**17**	**9**[c]	(4*R*,5*S*)-**IX**	10	n.r.	85 (2)	92 (5)	β-*Si*	25
8	**17**	**30** (allylsilane)	(4*R*,5*R*)-**VII**	16	87 (14)	65 (25)	97 (5)	β-*Si*	21
9	**20**	**9, 10, 27, 29, 31**	(*S*)-**IVa**	12	95 (6)	92 (19)	95 (6)	β-*Si*	30

[a] Vinyl ethers **9** supported on 500 – 600 μm PS macrobeads. [b] All products were obtained with a purity ≥ 95%. [c] Vinyl ethers **9** are polymer supported.

The use of (*S*)-**IV** (Table 1, entry 2, 12 examples) give usually better yields and higher endo selectivities than those obtained by using (*S*)-**III**, while the average ee is a little bit lower (82 vs 88%). The more relevant feature is that, as said before, the use of Box with the same (4*S*)-configuration leads to the opposite enantiomers: (*S*)-**III** affords (2*R*,4*R*)-**11** as the result of the heterodienophile approach to the β-*Re* face of the coordinated heterodiene, while (*S*)-**IV** leads to (4*S*,6*S*)-**11** as the result of a β-*Si* face vinyl ether approach. The only exception to this systematic behavior is given by the catalyzed cycloaddition between **8a** and silyl enol ethers **26**, which are 1,1-disubstitued enol ethers, a reaction allowing to obtain quaternary stereocenters (Table 2).[16] When the cycloadditions involving the TMS enol ether **26a** were catalyzed by either (*S*)-**IIIb** or (*S*)-**IVb**, besides the expected HDA adducts **33** and **34**, the Michael adduct **35** was obtained either as side-product [reaction catalyzed by (*S*)-**IIIb**] or as dominant product [reaction catalyzed by (*S*)-**IVb**], entries 1 and 2 in Table 2. The increasing of the steric hindrance in **26b** (R = *t*-Bu) determined the formation of only the HDA cycloadducts with excellent [(*S*)-**IIIb** as the catalyst] or negligible endo-selectivity [(*S*)-**IVb** as the catalyst], entries 3 and 4 in Table 2. In any case, very high enantioselectivities of (2*R*,4*R*)-**33** were always observed (96-99% ee) independently from the use of *t*-Bu- or Ph-Box based chiral catalyst. The absolute configuration of the adduct is in accordance with a β-*Re* face approach of the silyl enol ether **26** to the reactive complex **15** having a square-planar geometry. This experimental evidence is a support to the Evans's model previously discussed.

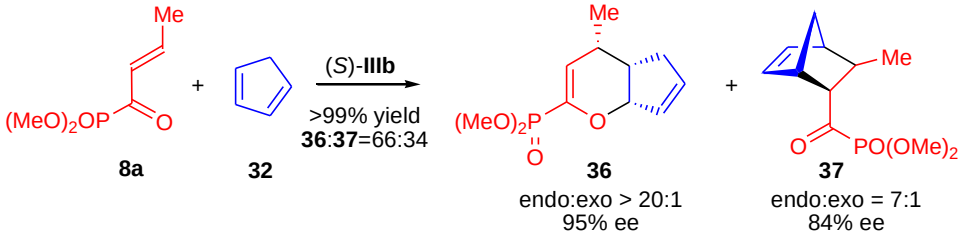
When cyclopentadiene **32** was used as cycloaddend in the reaction with **8**, a competition between HDA and DA pathways was observed, Scheme 5. The reaction catalyzed by (*S*)-**IIIb** gave a quantitative yield of HDA and DA adducts **36** and **37** in a ratio of about 2:1. These products may be related by a [3,3] sigmatropic rearrangement, and the HDA adduct **36** was obtained with excellent endo-selectivity and with 95% ee.

Table 2. Catalyzed HDA Reactions Between Crotonyl Phosphonate **8a** and Silyl Enol Ethers of Acetophenone.[16]



Entry	R	Catalyst	Product ratio endo-**33** : exo-**34** : **35**	% ee endo-**33**
1	Me	(*S*)-**IIIb**	57 : 5 : 38	99
2	Me	(*S*)-**IVb**	18 : 2 : 80	97
3	*t*-Bu	(*S*)-**IIIb**	93 : 7 : 0	99
4	*t*-Bu	(*S*)-**IVb**	60 : 40 : 0	96

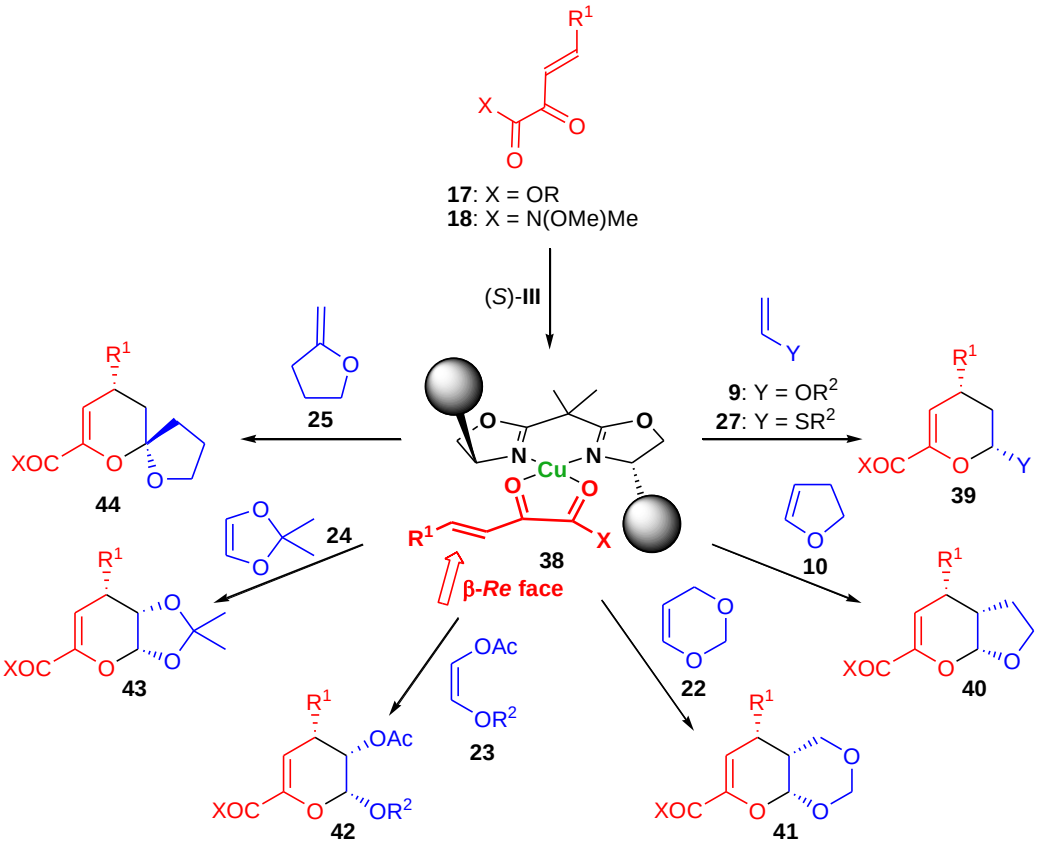
Scheme 5. Competition between HDA and DA Cycloaddition in the Reaction Between Acyl Phosphonate 8a and Cyclopentadiene 32 Catalyzed by (*S*)-IIIb.[13,16]



α-Keto esters **17** and amides **18** are useful 1,2-bicoordinating heterodienes in asymmetric HDA cycloadditions. Entry 3 in Table 1 reports the average results of 36 examples of cycloadditions between **17** (or **18**) with mono-substituted, 1,2- and 1,1-disubstituted vinyl ethers, and simple vinyl thioether catalyzed by (*S*)-**IIIa-d** catalysts (Scheme 6): The yields and the endo-

selectivities are very good, while the enantioselectivities are frequently higher than 95% ee. In all cases the absolute stereochemistry of the reaction products is consistent with an heterodienophile approach to the β-*Re* face of the coordinated heterodiene in the square planar complex **38** (Scheme 6). Cycloadducts **41-43** were usefully transformed into optically active carbohydrate[18] and amino sugar derivatives (**17**, R^1 = NHBoc or NPht).[19]

Scheme 6. HDA Cycloadditions of 17 and 18 with Different Enol Ethers and Thioenol Ethers Catalyzed by (*S*)-III.[14,16-19]



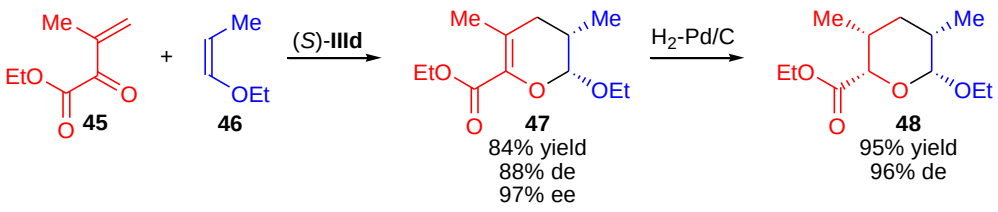
The Ph-Box-based catalyst (*S*)-**IV** was used in only two examples (Table 1, entry 4). Reaction yields and endo-selectivities were comparable to those obtained by using (*S*)-**III**, but the enantioselectivities were unsatisfactory.[17,18] In any case the usual inversion in the absolute stereochemistry in going from *t*-Bu-Box to Ph-Box was observed (Table 1, entry 3 vs 4). The use of the (*R*)-Ph-Box/Zn(II) catalyst (*R*)-**V** gives results that are comparable to those obtained by using the Cu(II)-*t*.Bu-Box complex (*S*)-**III** (Table 1, entry 5):[19] again, the Zn(II) complex of Ph-Box has

an opposite stereochemical induction to that obtained by using *t*-Bu-Box/Cu(II) complexes as the catalysts.

The catalysis of the cycloaddition of **17** with vinyl ethers, supported either on PS macrobeads[23] or on polymer,[25] was usefully performed by using (*S*)-**III** or (4*R*,5*S*)-**IX** as asymmetric catalysts (Table 1, entries 6 and 7). The reactions proceed well to give the dihydropyran cycloadducts with appreciable stereo- and enantioselectivities. On the contrary, the use of Box/Cu(II) either on exchanged microporous and mesoporous catalysts,[24] or supported on silica,[26] or immobilized in ionic liquids[27] to catalyze the HDA reaction between **17** and **9** was unsatisfactory.

(*S*)-**IIId** in Et_2O was the catalyst of choice for the synthesis of **48**, the precursor of the E-ring fragment of (+)-Azaspiracid-1 (Scheme 7).[22,28] The desired synthon **48** was obtained with excellent selectivity by reduction of the tetrasubstituted dihydropyran **47**, which was the product achieved from the enantioselective catalyzed cycloaddition between **45** and **46**, and it was obtained under optimized condition with up to 97% ee.

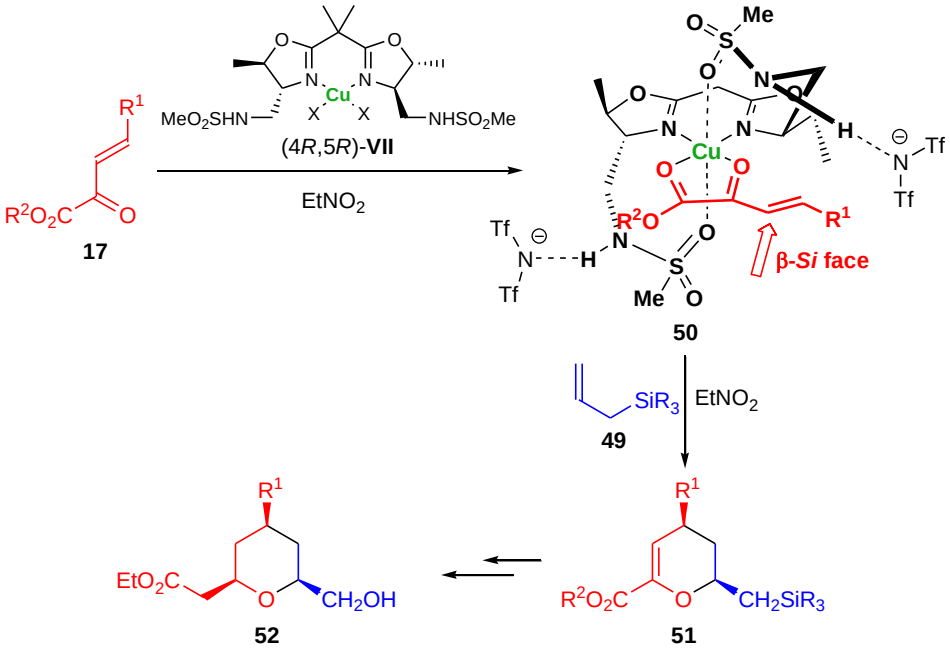
Scheme 7. Synthesis of the Tetrahydropyran 48 by Enantioselective Catalyzed HDA Cycloaddition.[22,28]



The cycloaddition of **17** with allylsilanes **49** was catalyzed by (4*R*,5*R*)-**VII** in $EtNO_2$ (Scheme 8).[21] Entry 8 in Table 1 summarized the results obtained in 16 different experiments with different substituents either on the ester group, or on the β-position of the heterodiene, or on the silyl derivative: The reaction yields were good, the de moderate, while the ee were excellent. The stereochemical result of the reaction is consistent with the alkene approach to the less hindered β-*Si*-face of the coordinated heterodiene in the octahedral reactive complex **50** in which the Box side-

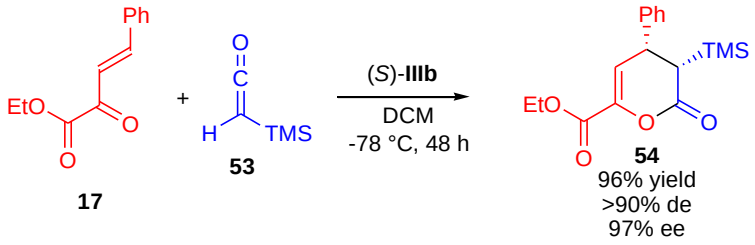
arms coordinates the Cu(II) cation on the apical positions. Cycloadducts **51** have been converted through a sequence of reduction, Dess-Martin oxidation, Wittig alkylation, and final oxidative conversion of the trialkyl silyl group into OH to furnish chiral oxanes **52** without any loss of enantiomeric excess (99% ee).

Scheme 8. Enantioselective HDA Reactions of 17 with Allylsilanes 49 Catalyzed by (4*R*,5*R*)-VII.[21]



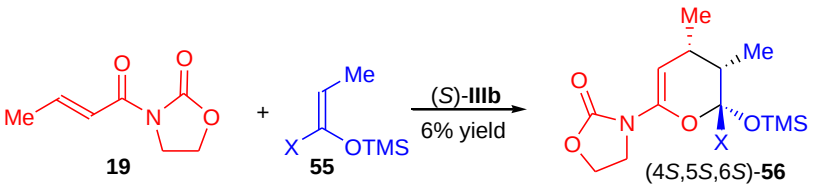
The heterodiene **17** reacts with trimethylsilylketene **53** in the presence of (*S*)-**IIIb** as asymmetric catalyst to give the δ-lactone **54** in high yield, appreciable diastereoselectivity and excellent ee (Scheme 9).[20] The stereochemical outcome of the cycloaddition is again consistent with a ketene approach to the less hindered β-*Re* face of **17** coordinated to Cu(II) and Box in square planar complex.

Scheme 9. Enantioselective HDA Reaction of 17 with Ketene 53 Catalyzed by (*S*)-IIIb.[20]



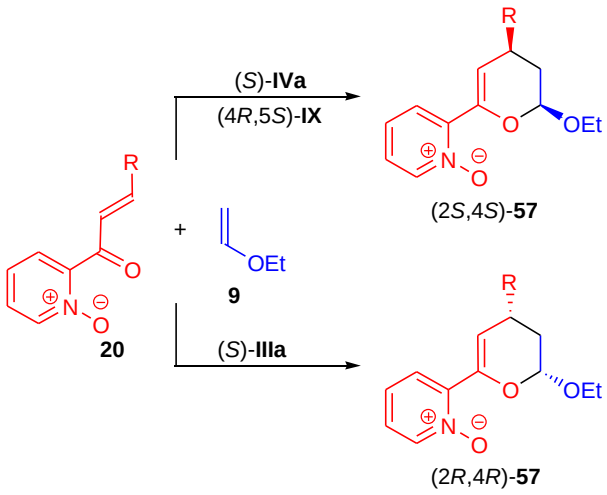
Alkenoyl oxazolidinones **19** are typical dienophile in DA cycloadditions, while their behavior as heterodienes in HDA reactions is unusual. Evans proposed the dihydropyran **56**, deriving from an HDA cycloaddition, as the intermediate in the Michael addition of enaolsilanes **55** to **19.** This hypothesis was supported by several experimental data, and was further confirmed by the isolation of 6% yield of product **56** deriving from the cycloaddition of the *N*-pyrrolyl enolsilane **55** (X = *N*-pyrrole) to **19** catalyzed by (*S*)-**IIIb**, Scheme 10.[29]

Scheme 10. HDA Reaction of 19 with Silylenol Ether 55 Catalyzed by (*S*)-IIIb.[29]



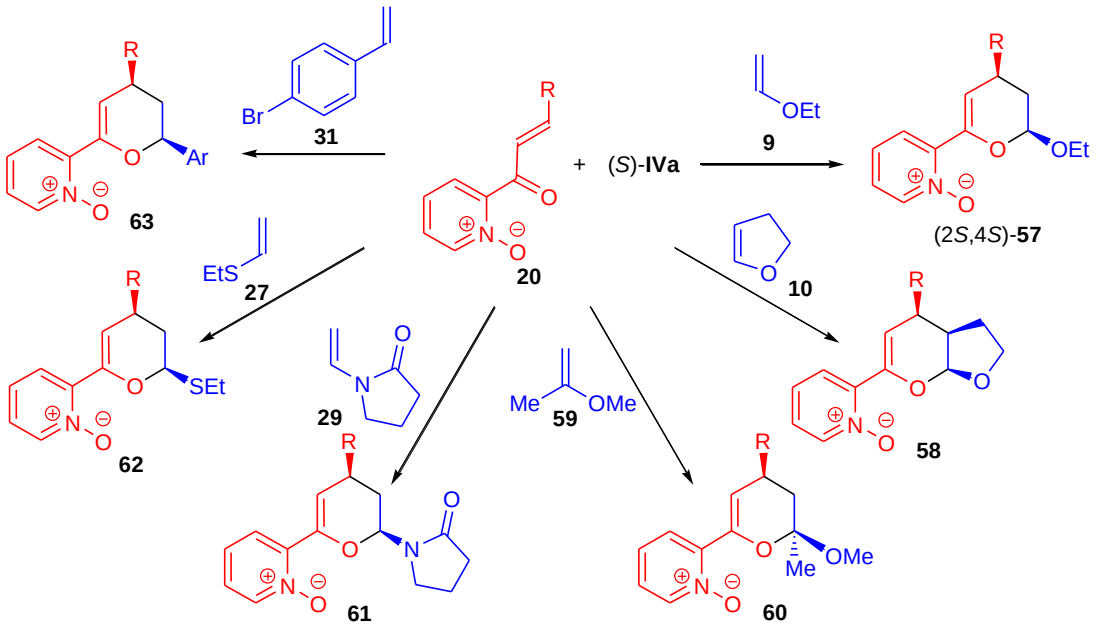
2-Alkenoylpyridine *N*-oxides have been found useful substrates in the enantioselective catalysis of several reactions such as DA, HDA, and 1,3-dipolar cycloadditions, Michael additions, and Friedel-Crafts alkylations.[33] Pyridine-*N*-oxides **20** easily react with electron-rich alkenes such as ethyl vinyl ether **9** in the presence of Cu(II)/Box complexes to give dihydropyrans **57** in high yields, and excellent diastereo- and enantioselectivities (Scheme 11).[30]

Scheme 11. Enantioselective HDA Reaction of 20 with Ethyl Vinyl Ether 9 Catalyzed by Box/Cu(II) Complexes.[30]



As previously observed, also in this case (*S*)-**III** and (*S*)-**IV** induced opposite enantioselectivities, and, after optimization of the reaction conditions (ligand, cation, solvent, and temperature), the use of (*S*)-**IVa** in DCM at -40 °C was extended to a variety of heterodienes (different R in **20**) and dienophiles as reported in Scheme 12. Entry 9 of Table 1 summarized the results of the 12 experiments run under (*S*)-**IIIa** catalysis: The reaction yields are about quantitative, the cycloaddition is highly endo-selective, and the enantioselectivities are excellent (average ee = 95 ± 6%). In all cases the stereochemistry of cycloadducts is in accordance with an heterodienophile approach to the β-*Si* face of the coordinated heterodienes **20**.

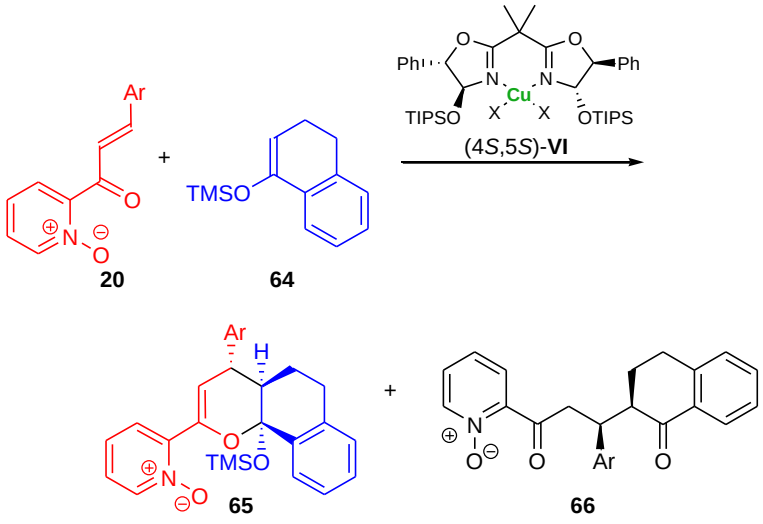
Scheme 12. Enantioselective HDA Reaction of 20 with Several Dienophiles Catalyzed by (*S*)-IVa.[30]



The reaction between **20** enolsilane **64** is catalyzed by Cu(II)/Box complexes to give mixture of HDA cycloadducts **65** and Michael products **66**. **65** have been demonstrated to be the primary reaction product, obtained as the favored one at -70 °C or within shorter reaction times. The use of either higher temperature (-40 °C) or prolonged reaction times shifted the reaction selectivity towards the formation of the open chain product **66**. This rationale was confirmed by stirring **65** (99.9% ee) at ambient temperature for 8 h in DCM with a catalytic amount of $Cu(OTf)_2$. The

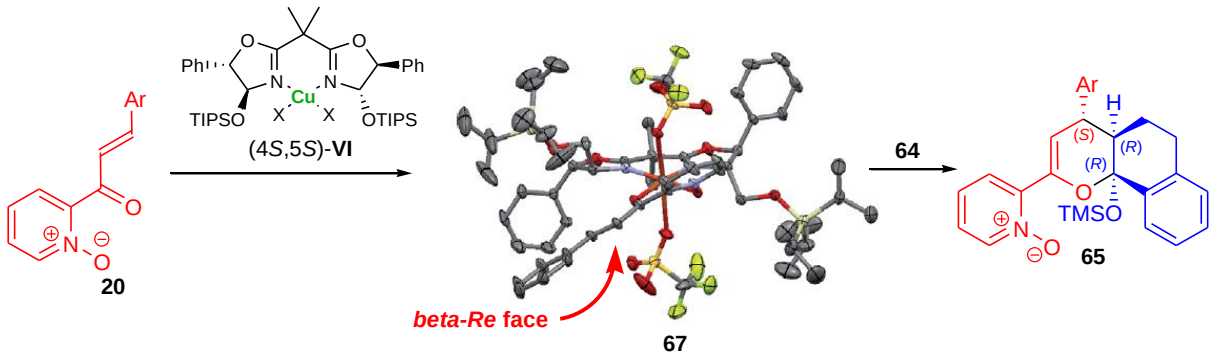
starting product was quantitatively converted into **66** without any loss of the enantiomeric purity, Scheme 13).[32]

Scheme 13. Competition between HDA and Michael Reaction in the Reaction of 20 with Enol Silyl Ether 64 in the Presence of (4*S*,5S)-VI.[32]



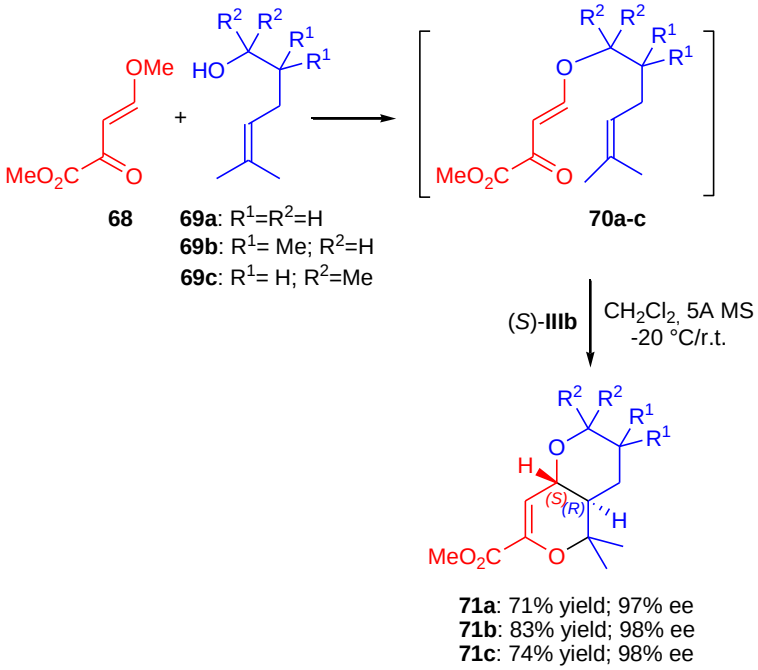
Among the different Box-based catalyst, the most efficient one was found to be (4*S*,5*S*)-**VI** that at -70 °C gave 85% yield of (4*S*,4a*R*,10b*R*)-**65** with 99.9% ee. The stereochemical outcome is in accordance with the approach of **64** to the less hindered β-*Re* face of heterodiene **20** coordinated to (4*S*,5*S*)-**VI** in the reacting intermediate **67** in Scheme 14, whose X-ray structure was previously determined.[31]

Scheme 14. Reacting Intermediate 67 in the HDA Reaction of 20 with 64 to Give (4*S*,4a*R*,10b*R*)-65.[31,32]



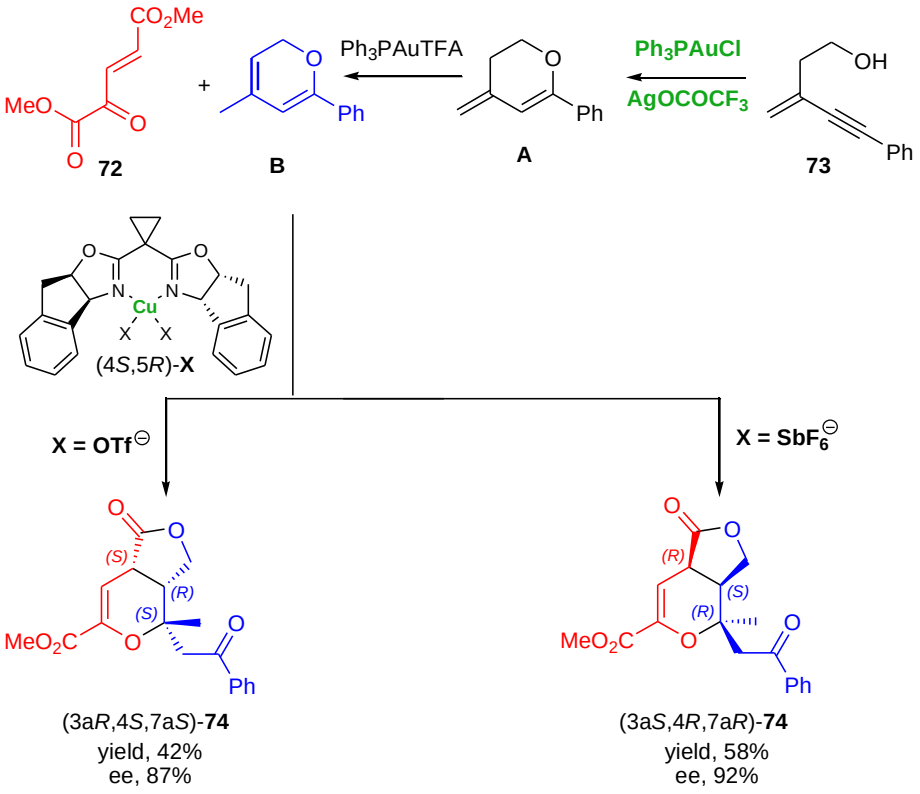
Few examples of enantioselectively catalyzed intramolecular HDA reactions by using Box-based chiral catalysts have been reported in the literature.[34-36] Starting from (*E*)-4-methoxy-2-oxo-buteneoate **68**, the *in situ* transetherification with δ,ε-unsaturated alcohols **69a-c** produces the intermediates **70a-c** that, in the presence of (*S*)-**IIIb**, cyclized to pyrano[4,3-*b*]pyran systems with good yields (71-83%) and excellent enantioselectivities (97-98% ee), Scheme 15.[34,35] The stereochemical outcome is again consistent with an approach of the 2π system to the less hindered face of the heterodiene moiety of **70** coordinated to Cu(II)/Box catalyst in a square planar complex. As previously observed, the use of (*S*)-**IVb** inverts the enantioselectivity, but in this case a dramatic drop in ee was observed (13-14% ee of the opposite enantiomer). An efficient catalytic double asymmetric induction of this process was also developed.[35]

Scheme 15. Enantioselective Tandem Transetherification-Intramolecular HDA Reaction of Methyl (*E*)-4-Methoxy-2-oxo-buteneoate with δ,ε-Unsaturated Alcohols Catalyzed by (*S*)-IIIb.[34,35]



Enyne alcohols like **73** can react as precursor of dienophile in asymmetric intramolecular HDA reactions. Thus, the cascade reaction between **72** and **73**, run in the presence of $Ph_3AuCl/AgOCOCF_3$ with (4*S*,5*R*)-**X**/Cu(II) as co-catalyst, gives the furo[3,4-*c*]pyran cycloadduct within moderate yields (≈50%) and appreciable enantioselectivities (≈90%ee), Scheme 16.[36]

Scheme 16. Asymmetric Gold/Cu(II)/Box Catalyzed Cascade Reaction of 72 with Enyne Alcohol 73.[36]



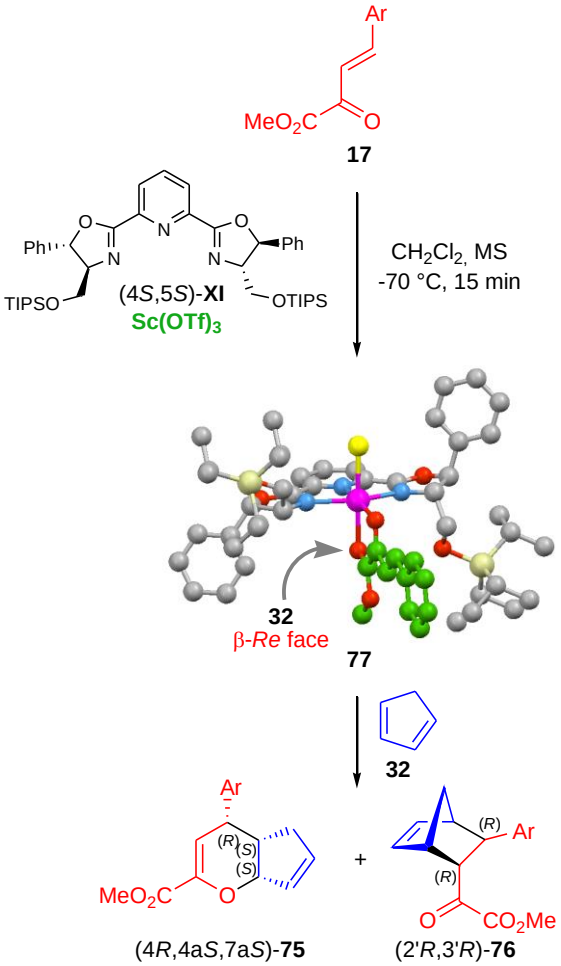
Even if the mechanism of the asymmetric catalysis is not defined, mechanistic investigations pointed out the crucial role of the co-catalyst that isomerized the former intermediate (**A**) into the reactive dienophile having the 2*H*-pyran structure **B** (Scheme 16). The remarkable feature of this process is represented by the inversion of enantioselection observed by changing the Cu(II) counter-ion from triflate to hexafluoroantimonate. This variation is quite unusual since the change of the counterion in Cu(II)/*t*-bu-Box complexes have been reported to influence mainly the reactivity, while the effects on enantioselectivity are of scarce entity.[16]

2.1.1.2. Other Oxazoline-based Complexes as Catalysts

The change of the isopropylidene spacer in the Box ligands with a pyridine ring gives rise to a new class of tridentate bis(oxazolines) chiral ligands (pyridine-2,6-bis oxazolines – Pybox) that found a lot of application in asymmetric synthesis.[37] Pybox (4*S*,5*S*)-**XI** was found a useful ligand in lanthanide based chiral catalysts. Among a variety of different triflates, the Sc(III)-based complex

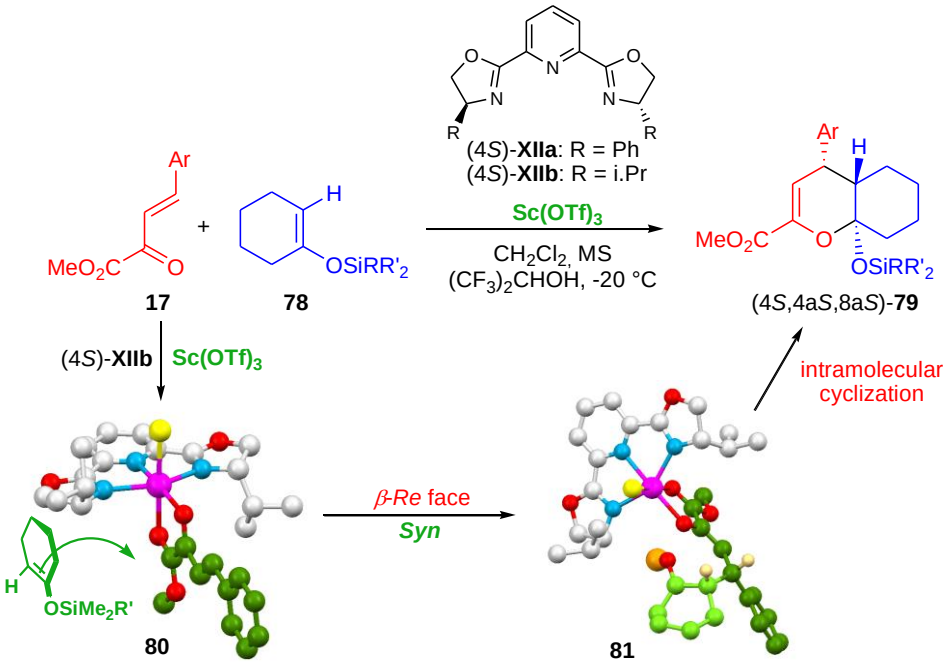
was found to catalyse the asymmetric cycloaddition, between **17** and cyclopentadiene **32**, Scheme 17. The cycloaddition is completed after 15 min at -70 °C and gives a mixture of HDA and DA adducts (**75** and **76** respectively) in a ratio of about 2:1. The enantioselectivity observed in both adduct formation is very high (ee ≥ 99%) and the stereochemical outcome is in accordance with a cyclopentadiene approach to the less hindered face of coordinated **17** in the complex 77 whose X-ray structure was previously determined. The increasing of the temperature and/or prolonged reaction times evidences a change in the periselectivity since a stereospecific [3,3]-Claisen rearrangement is observed.[38,39] A screening of different Ln(III) cations was performed, and a linear enantioselectivity decrease with the increase of the lanthanide ionic radius was observed.

Scheme 17. Asymmetric DA vs HDA Cycloaddition of 17 with 32 Catalyzed by Sc(III)/(4*S*,5*S*)-XI Complex.[38,39]



The reaction between **17** and 1-trialkylsiloxy-1-cyclohexene (**78**) was catalyzed by [Pybox/Sc(OTf)$_3$] complexes to give cycloadducts **79** (Scheme 18).[40] The catalyst of choice was the Ph-Pybox (4*S*)-**XIIa**, which furnishes **79** in appreciable yields (73%) and excellent enantioselectivities (99% ee). Products **79** could be regarded as the result of a HDA reaction in which **1** behaves as a heterodiene and **78** is the dienophile. However, the *trans* ring fusion observed in **79** contradicts the Diels-Alder basic principle of the retention of configuration of the reagents in the product. After a careful investigation of the desilylation process, this formal HDA cycloaddition was interpreted as being the result as a stepwise sequence of two reactions: (i) a Mukaiyama-Michael addition (formation of the C4-C4a bond and of the first stereocenter); (ii) an intramolecular ring closure (formation of the C1-C8a bond and of the second stereocenter).

Scheme 18. Asymmetric Formal HDA Cycloaddition of 17 with 78 Catalyzed by Sc(III)/(4*S*)-XII Complex.[40]

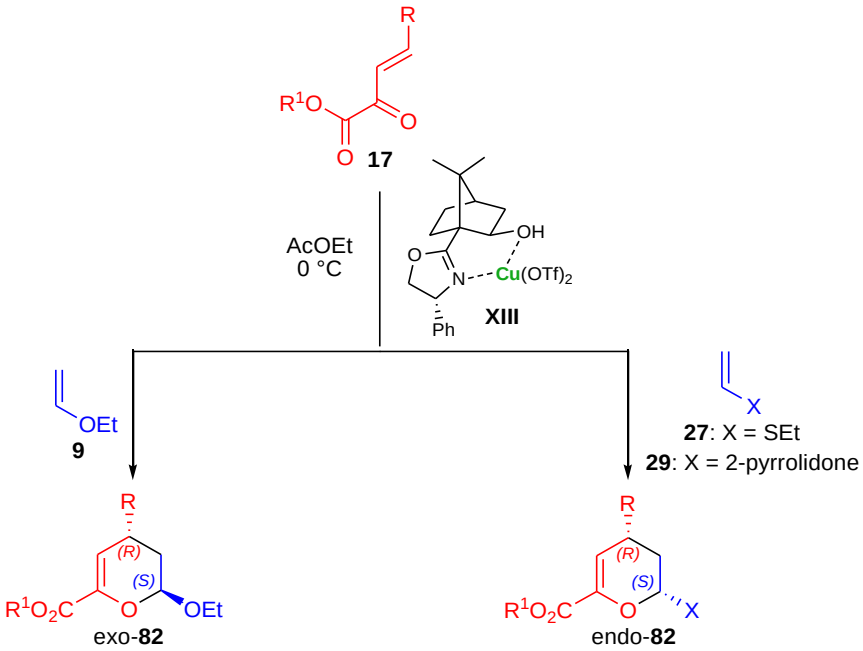


In the first step (the Mukaiyama-Michael addition), **78** attacks the less shielded β-*Re* face of **17**, coordinated in the octahedral complex **80**, with the more favourable "*syn*" approach determining the observed (4*S*,4a*S*) stereochemistry. The final step is the intramolecular cyclization of the oxygen

atom to the oxonium carbon atom in **81** leading to the thermodynamically favored *trans* ring junction with formation of the third stereocenter with the (8a*S*) configuration.

One of the few examples of exo-selective HDA cycloadditions was obtained by using the Cu(II) complexes of hydroxy oxazolines derived from (*S*)-ketopinic acid.[41] After optimization of the chiral ligand and reaction conditions (solvent and temperature), catalyst **XIII** in AcOEt at 0 °C was found the best one to give exo-**82** with good selectivities an appreciable ee (Scheme 19). Ten examples of cycloaddition involving vinyl ether **9** reacting with **17** having different R and R^1 substituents give exo-**82** adducts with an average yield of 88 ± 5%, an [exo:endo] ratio ranging from 2 to 6, and an enantioselectivities of 77 ± 14% ee. The use of either thiovinyl ether **27** or *N*-vinyl-2-pyrrolidone **29** as dienophiles turned the stereoselectivity in favor of endo-**82**, which were obtained with low enantioselectivities (32-37 % ee).

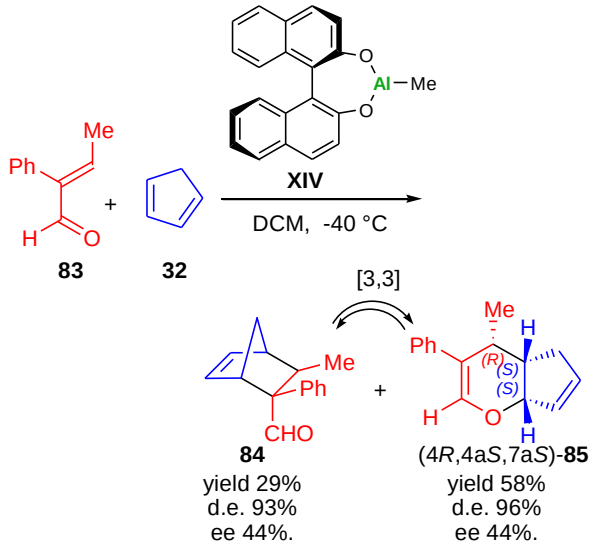
Scheme 19. Asymmetric HDA Cycloaddition of 17 with Electron-rich Alkenes Catalyzed by Complex XIII.[41]



2.1.1.3. BINOL-based Complexes as Catalysts

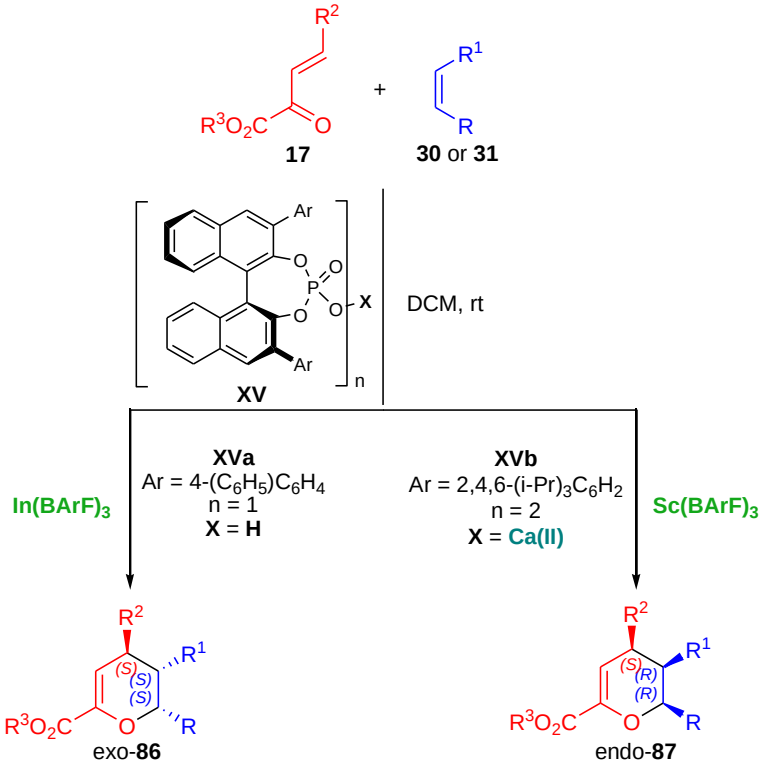
The previously discussed asymmetric HDA reactions involved activated enone derivatives bearing electron-withdrawing substituents such as phosphonate or ester groups. One example of HDA cycloadditions involving inactivated heterodiene is given by the reaction 2-phenyl-2-butenal **83** with cyclopentadiene **32** catalyzed by the Al(III)/BINOL complex **XIV** (Scheme 20).[42] The inverse electron demand cycloaddition proceeds giving rise to a mixture of DA and HDA adducts (**84** and **85**, respectively) in a ratio of about 1:2 with high diastereo selectivity (93-96% de), but only moderate enantioselectivity (44% ee). A nice and detailed mechanistic investigation pointed out that the major pathway for the dihydropyran formation was a Lewis acid-catalyzed tandem Diels-Alder/retro-Claisen rearrangement.

Scheme 20. Asymmetric HDA Cycloaddition of 83 with Cyclopentadiene Catalyzed by the Al(III)/BINOL Complex XIV.[42]



Turning back to activated enones **17**, the asymmetric cycloaddition involving simple alkyl or aryl substituted alkenes (**30** and **31** respectively) was usefully catalyzed by Sc(III) or In(III)-based catalysts having the phosphoric acid derivatives **XV** as the chiral ligands (Scheme 21).[43-45] The most interesting feature of this process was the possibility to drive the stereoselectivity toward the selective formation of the exo-**86** or endo-**87** adducts by using a different metal center.

Scheme 21. Asymmetric HDA Cycloaddition of 17 with Alkenes 30,31 Catalyzed by BINOL XV-based Chiral Catalysts.[43]



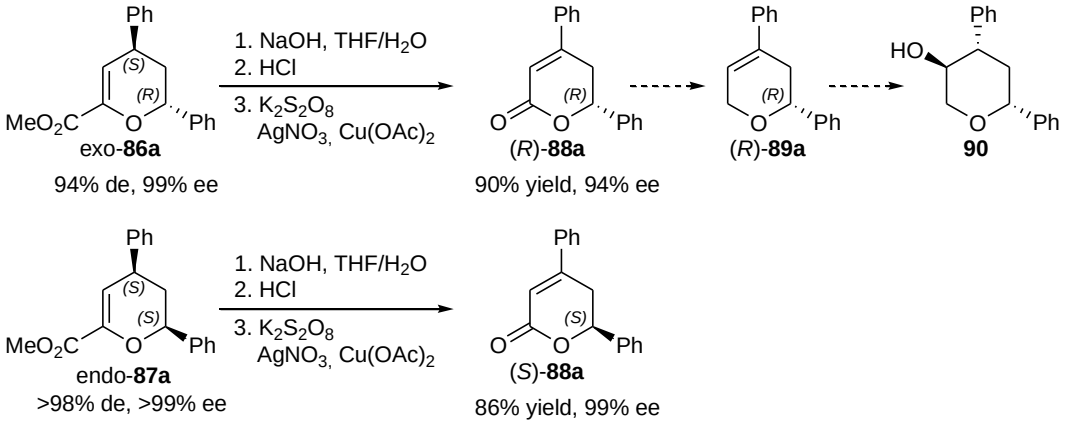
The cycloadditions run in the presence of the chiral phosphoric acid **XVa** and $In(BArF)_3$ in the ratio 2:1 proceeded smoothly to afford HDA cycloadducts in high yields, excellent exo- and enantioselectivities (average de = 91 ± 7%, average ee = 91 ± 11%), entry 1 in Table 3. These results were found independent from the nature of the alkene substituents, but required an aromatic group as substituent on the β-position of **17** (R^2). The cycloaddition run on an aliphatic α-keto ester (R^2 = Me) afforded the corresponding cycloadduct with good enantioselectivity, but with negligible diastereoselectivity (de ≈ 0).

The use of the Ca(II) salt of the phosphoric acid **XVb** with $Sc(BArF)_3$ shifted the stereoselectivity in favor of endo-**87**, which were obtained with even better diastereo- and enantioselectivities (average de, 96 ± 4%; average ee, 96 ± 4%), entry 2 in Table 3. In this case, also the β-alkyl substituted α-keto ester (R^2 = Me) afforded the corresponding cycloadduct with excellent enantioselectivity and appreciable diastereoselectivity (de = 88%).

The endo selectivity observed in the Sc(III)-catalyzed HDA reactions is not surprising, but the exo selectivity observed by changing Sc(III) with In(III) in the chiral binary acid complex is quite unusual. The exo selectivity was tentatively explained by invoking a stepwise pathway that find an experimental evidence by the isolation of a trace of an open-chain by-product deriving from the nucleophilic addition of the olefin to the β-position of **17**.[43]

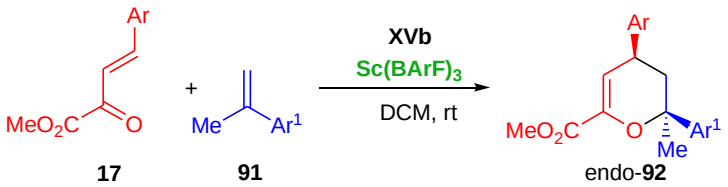
Independently from the nature of the mechanism involved in their formation, exo-**86** and endo-**87** adducts found a useful application in the conversion in the opposite enantiomer of δ-lactones **88a** (Scheme 22). Saponification and decarboxylation of exo-**86a** afford (*R*)-**88a** in good yields under oxidative conditions. This latter could be chemoselective reduced to 3,6-dihydro-2*H*-pyran (*R*)-**89a**, which can be further elaborated to **90**. This transformation sequence can be readily applied to the asymmetric synthesis of sugirenisol and doremox, starting from the appropriate HDA cycloadducts.[43]

Scheme 22. Transformation of exo-86a and endo-87a into δ-Lactones (*R*)- and (*S*)-88.[43]



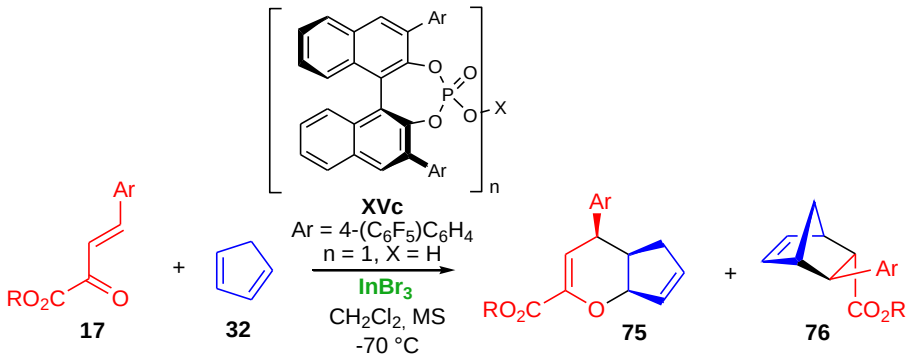
The endo-selective Sc(III)-based chiral catalyst was also found efficient in the HDA cycloadditions between **17** and 1-aryl-1-methyl-ethenes **91** (Scheme 23). The cycloadducts endo-**92**, which bear a quaternary stereogenic center, were obtained in good yields, high diatereoselectivity, and excellent enantioselectivity: in 9 different experiments, endo-**92** was obtained with an average yield of 83 ± 6%, an average de of 90 ± 5%, and an average ee of 92 ± 8% (Table 3, entry 3).

Scheme 23. Asymmetric HDA Cycloaddition of 17 with Alkenes 91 Catalyzed by Sc(III)/XVb Chiral Catalyst.[43]



The asymmetric binary-acid catalysis with In(III) was also tested on the DA vs HDA competition observed in the reaction between **17** and cyclopentadiene **32** and previously illustrated in Scheme 17. After optimization of the chiral ligand, the pentafluoro derivative of the phosphoric acid **XVc** was found the optimal ligand in the In(III)-based catalyst able to induce good periselectivity and excellent diastereo- and enantioselectivities.[44] Thus, the reactions of **17** with cyclopentadiene **32**, under **XVc**/$InBr_3$ catalysis (in the ratio 2:1), proceeded to give a mixture of about 4:1 of the HDA and DA cycloadducts (**75** and **76**, respectively) with excellent enantioselectivities (Scheme 24). The asymmetric catalysis was efficient with several esters of β-aryl-substituted heterodienes. The average values for the cycloadditions of 8 different substrates are: yield, 98 ± 4%; periselectivity, [**75**]:[**76**] = 4.4 ± 0.9; ee, 99 ± 1% (Table 3, entry 4).

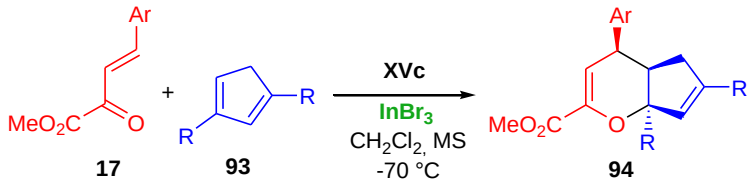
Scheme 24. Asymmetric HDA Cycloaddition of 17 with Cyclopentadiene 32 Catalyzed by [In(III)/XVc] Chiral Catalyst.[44]



When mono-substituted cyclopentadienes are used, then the DA pathway is usually preferred, while the reactions involving 1,3-disubstituted cylopentadienes **93** were completely regio- and

periselective in favor of adducts **94** (Scheme 25), which were isolated as single isomer in very good reaction yields (in 10 experiments the average yield is 90 ± 4%) and excellent enantioselectivities (average ee of 97 ± 2%, entry 5 in Table 3).[44]

Scheme 25. Asymmetric HDA Cycloaddition of 17 with 1,3-Disubstituted Cyclopentadienes 93 Catalyzed by [In(III)/XVc] Chiral Catalyst.[44]



A further useful application of **XVb** without any other added Lewis acid (the Ca(II) cation acts directly ac activator) was found in HDA reaction between 2-oxoindolin-3-ylidene derivatives **95** (acting as heterodienes) with either vinyl ethers **9** or vinyl thioethers **27** to give tetrahydropyrano[2,3-*b*]indole adducts **96** (Scheme 26).[45] The cycloadducts endo-**96** (18 experiments) were obtained with appreciable yields (average yields = 84 ± 15%), and very good diastereo- and enantioselectivities (average de = 95 ± 10%; average ee = 93 ± 11%), see entry 6 in Table 3. The (2*S*,4*S*)-absolute configuration of **96** was determined by X-ray structure analysis of the 6-bromo-derivative.

Scheme 26. Asymmetric HDA Cycloaddition of 95 with Vinyl Ethers 9 and Vinyl Thioethers 27 Catalyzed by XVb Chiral Catalyst.[45]

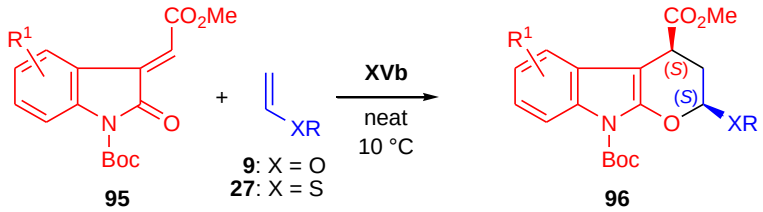


Table 3. Average Values and Standard Deviations (s.d.) of the Reaction Yields, Diastereo-, and Enantioselectivities for the HDA Reactions Catalyzed by **XVa-c**-Based Chiral Complexes.

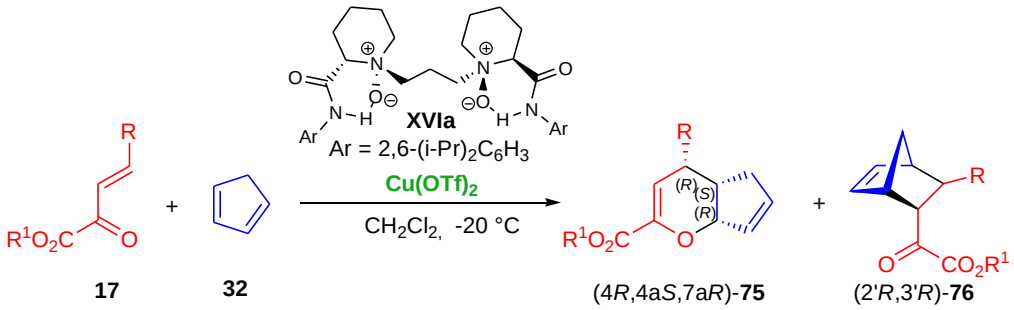
Entry	Heterodiene	Dienophile	Catalyst[a]	n. Exp.	aver. Yield % (s.d.)	aver. de (s.d.)	Reaction Product	aver. ee % (s.d.)	Ref.
1	**17**	**30,31**	$In(BArF)_3/(\mathbf{XVa})_2$	13	80 (13)	91 (7)	exo-**86**	91 (11)	43
2	**17**	**30,31**	$Sc(BArF)_3$/**XVb**	11	88 (9)	96 (4)	endo-**87**	96 (4)	43
3	**17**	**91**	$Sc(BArF)_3$/**XVb**	9	83 (6)	90 (5)	endo-**92**	92 (8)	43
4	**17**	**32**	$InBr_3/(\mathbf{XVc})_2$	8	98 (4)	4.4 (0.9)[b]	endo-**75**	99 (1)	44
5	**17**	**93**	$InBr_3/(\mathbf{XVc})_2$	10	90 (4)	*c*	endo-**94**	97 (2)	44
6	**95**	**9,27**	**XVb**	18	84 (15)	95 (10)	endo-**96**	93 (11)	45

[a] BArF = $[3,5\text{-}(CF_3)_2C_6H_4]_4B$. [b] The value refers to the de of HDA adducts respects to DA products (**75** and **76**, respectively).. [c] No exo-adducts were observed in any experiment.

2.1.1.4. Other Chiral Complexes as Catalysts

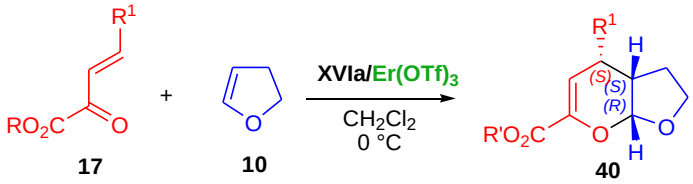
The HDA cycloaddition between **17** and cyclopentadiene **32** was catalyzed by $Cu(OTf)_2$ complex of chiral *N,N′*-dioxide **XVIa** (Scheme 27).[46] The reactions were quantitative and highly enantioselective, but the control of periselectivity was only in part satisfactory since, under optimized conditions, the ratio between HDA and DA cycloadducts **75** and **76**, respectively, was about 1:1. Entry 1 in Table 4 reports the average results of 18 experiments with different R and R^1 substituents on **17**. In all case the reaction yields were >99% and the ee > 99%, while the average ratio between HDA and DA products was from 0.9 to 1.5. The strong positive nonlinear effects for both HDA and DA cycloadducts suggests that the reactions involved a polymeric **XVIa**/$Cu(OTf)_2$ complex species as the catalysts. Moreover, the positive nonlinear effect makes it possible that the high enantioselectivity of the reaction could be also achieved by using ligand **XVI** with moderate enantiopurity.[46]

Scheme 27. Asymmetric HDA Cycloaddition of 17 with Cyclopentadiene 32 Catalyzed by the Cu(II) Complex of the Chiral *N,N′*-Dioxide XVIa.[46]



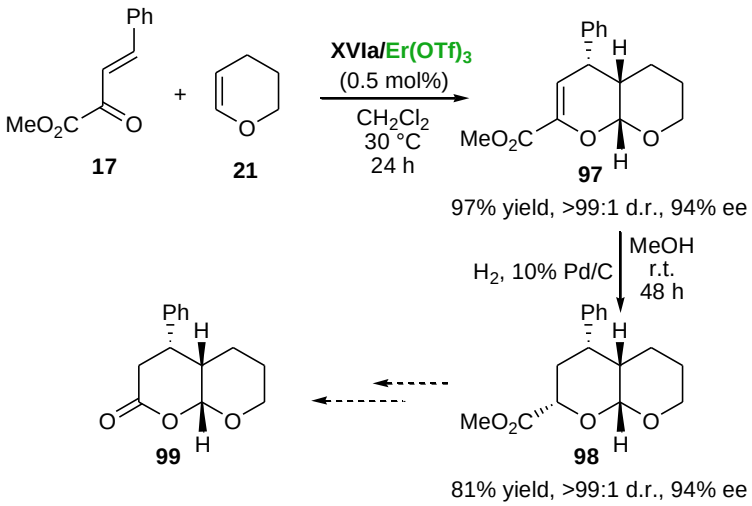
N,N′-dioxide **XVIa** was found to be an efficient chiral ligand in the complex with $Er(OTf)_3$, acting as a Lewis acid, in the asymmetric catalysis of the HDA reaction between **17** and 2,3-dihydrofuran **10**, Scheme 28.[47] The catalyst can be used with a low loading (0.5 mol%) and furnishes quantitative yields of the HDA adducts **40** with almost complete control of the endo selectivity. Also the enantioselectivities were excellent, since the reaction of 16 different substrates gives an average ee of 96 ± 2% (Table 4, entry 2).

Scheme 28. Asymmetric HDA Cycloaddition of 17 with 3,4-Dihydro-Furan 10 Catalyzed by the Er(III) Complex of the Chiral *N*,*N*′-Dioxide XVIa.[47]



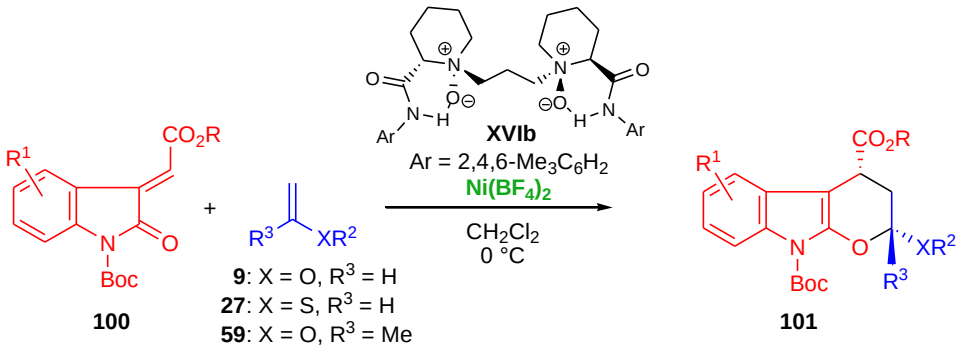
The enantioselective catalysis of the HDA reaction involving **17** with a phenyl group in the β-position was then extended to other electron-rich alkenes such as 3,4-dihydro-2*H*-pyran **21**, several vinyl ethers **9** and thiovinyl ethers **27**, and 2-methoxy-propene **59**. In any case, a very low loading of the catalyst (0.5 mol%) was required to obtain quantitative yields of the products with an excellent control of the stereo- and enantioselectivities (average de = 98%; average ee = 97 ± 2%), entry 3 in Table 4. As an example of potential transformations of the ring-fused bicyclic HDA adducts, the adduct **97** deriving from the cycloaddition with pyran **21** was stereoselectively hydrogenated to give the single isomer **98**, which was obtained in 81% yield and without loss of enantioselectivity. **98** can be further converted into the bicyclic lactone **99**, a useful intermediate in the synthesis of blepharocalyxin D (Scheme 29).[47]

Scheme 29. Examples of a Synthetic Application of HDA Cycloadducts.[47]



The *N,N′*-dioxide **XVIb** was found to be an efficient ligand in Ni(II)-based chiral catalysts, which found useful applications in the enantioselective catalysis of the HDA reaction between methyleneindolinones **100**, acting as heterodienes, with several electron-rich olefins such as vinyl ethers **9**, vinyl thioethers **27**, dihydropyran **21**, and 1,1-disubstitued alkenes **59** (Scheme 30).[48] In the 25 reported different examples, the reactions yields were acceptable (average yield, 82 ± 10%), the endo-selectivities were very good (average de, 91 ± 6%), and the enantioselectivities were excellent (average ee, 98 ± 2%), see entry 4 in Table 4. The synthetic utility of the catalyst was tested by running the reaction on a gram-scale in the presence of 2 mol% of the catalysts: the cycloadduct was obtained within 92% yield (>90% de, 99% ee).

Scheme 30. Asymmetric HDA Cycloaddition of 100 with Electron-rich Alkenes Catalyzed by the Ni(II) Complex of the Chiral *N,N′*-Dioxide XVIb.[48]



The structure of the reacting complex was investigated by ESI-MS. The study confirmed a ratio between Ni(II), chiral ligand **XVI**, and reacting substrate **100** of 1:1:1. This result, together with the absolute configuration of the cycloadducts, allowed to propose a model for the transition state of the reaction rationalizing the stereochemical outcome of the reaction. The proposed structure of the reacting complex has an octahedral geometry with the Ni(II) coordinating both the chiral ligand **XVIb** and the reacting substrate **100**: The two apical positions are occupied by the oxygen atoms of the carbonyl groups of **XVIb**, while the two oxygen atoms of the *N*-oxides are in two equatorial positions; the remaining equatorial positions are occupied by **100**, which is bi-coordinated through its oxygen atoms of the amidic groups.

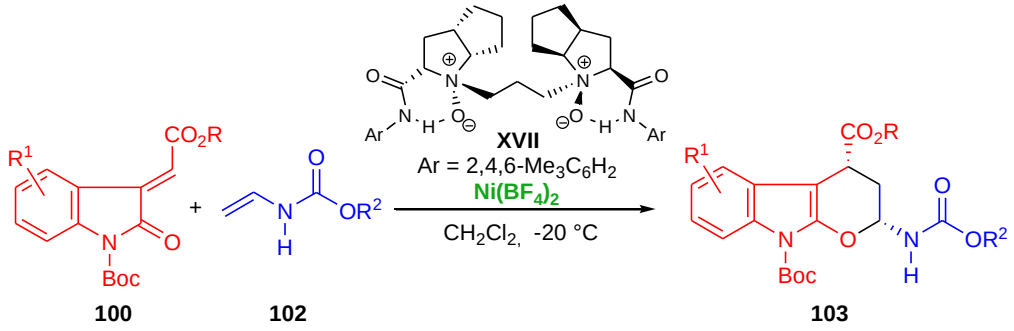
Table 4. Average Values and Standard Deviations (s.d.) of the Reaction Yields, Diastereo-, and Enantioselectivities for the HDA Reactions Catalyzed by *N*,*N*′-Dioxide Complexes Between **XVI-XVII** and Cu(II), Er(III), and Ni(II), by Catalyst **XVIII**, and by **XIX**/$Y(OTf)_3$ Bifunctional Chiral Catalyst.

Entry	Heterodiene	Dienophile	Catalyst[a]	n. Exp.	aver. Yield % (s.d.)	aver. de (s.d.)	Reaction Product	aver. ee % (s.d.)	Ref.
1	**17**	**32**	$Cu(OTf)_2$/**XVIa**	18	99 (--)	1.2 (0.3)[a]	**75**	99.5 (--)	46
2	**17**	**10**	$Er(OTf)_3$/**XVIa**	16	92 (12)	99 (--)	**40**	96 (2)	47
3	**17**	**9, 21, 27, 59**	$Er(OTf)_3$/**XVIa**	9	97 (3)	98 (--)	**40**	97 (2)	47
4	**100**	**9, 21, 27, 59**	$Ni(BF_4)_2$/**XVIb**	25	82 (10)	91 (6)	**101**	98 (2)	48
5	**100**	**102**	$Ni(BF_4)_2$/**XVII**	7	62 (6)	39 (12)	**103**	94 (1)	48
6	**104**	**9**	**XVIII**	15	77 (13)	92 (--)	**105**	95 (3)	49
7	**17**	**120**	**XIX**/$Y(OTf)_3$	20	74 (12)	68 (10)	**121**	95 (3)	53

[a] The value refers to the ratio between HDA and DA adducts (**75** and **76**, respectively).

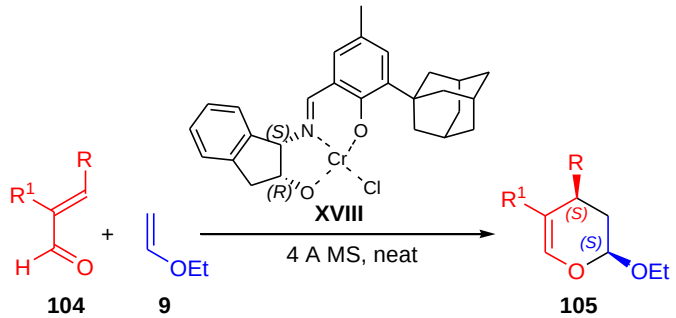
The asymmetric HDA reaction of the indole derivatives **100** was then extended to enecarbamates **102** to obtain dihydropyranamine-fused indoles **103** (Scheme 31).[48] The use of the Ni(II)/**XVIb** was in this case less efficient than in the previous examples. On the contrary, the optimized chiral ligand **XVII** gave appreciable yields of the cycloadducts with a lower diastereoselectivity, but with very good enantioselectivities (Table 4, entry 5).

Scheme 31. Asymmetric HDA Cycloaddition of 100 with 102 Catalyzed by the Ni(II) Complex of the Chiral *N,N′*-Dioxide XVII.[48]



The development of asymmetric HDA cycloadditions involving simple α,β-unsaturated aldehydes would improve the utility of this methodology. This task presents a clear challenge, since an effective activation and enantiofacial discrimination of the carbonyl solely through one-point to catalyst are required. The tridentate (Schiff base)/Cr(III) complex **XVIII** was found to catalyze with high level of diastereo- and enantioselectivity the HDA reaction between aldehydes **104** and ethyl vinyl ether **9** (Scheme 32).[49]

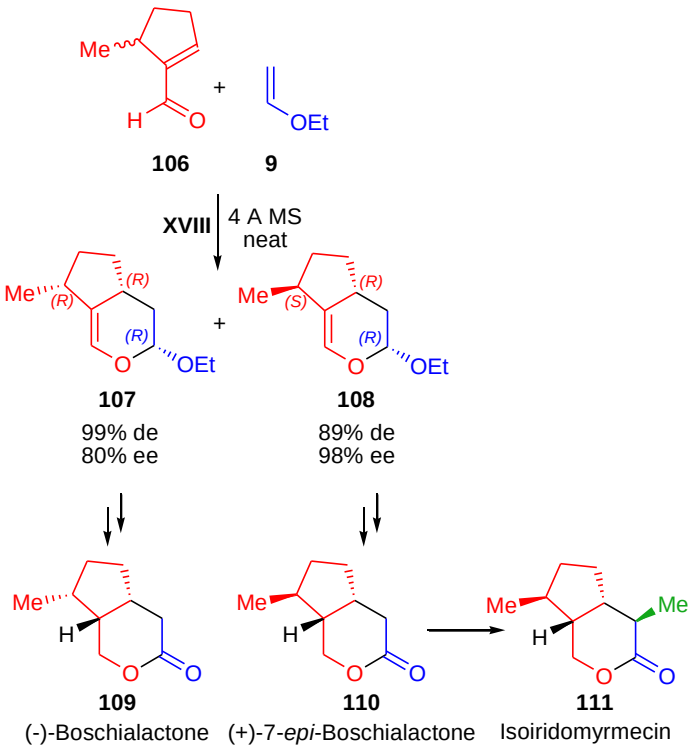
Scheme 32. Asymmetric HDA Cycloaddition Between α,β-Unsaturated Aldehydes 104 with Ethyl Vinyl Ether Catalyzed by XVIII.[49]



The catalyzed cycloaddition was performed on 15 different substrates with both electron-donating and electron-withdrawing groups on the β-position of **104**. The optimized conditions were obtained by running the reactions under solvent-free conditions with an excess of ethyl vinyl ether **9** at ambient temperature. The average reaction yield was 77 ± 13%, the endo selectivity was 96% in all the examined reactions, and endo-**105** was obtained with an average ee of 95 ± 3% (entry 6 in Table 4). The obtained cycloadducts were useful building blocks in further stereoselective reactions, and the enantioselectively catalyzed HDA reaction by using the Schiff base-Cr(III) catalyst was the key step in the synthesis of several natural products.

Racemic 5-methyl-1-cyclopentene-1-carboxaldehyde **106** was allowed to react with ethyl vinyl ether **9** in the presence of **XVIII** to give cycloadducts **107** and **108** in a ratio of 1.2:1 with very good level of diastereo- and enantioselectivity. This cycloaddition is an interesting example of a selective parallel kinetic resolution process (Scheme 33).[50]

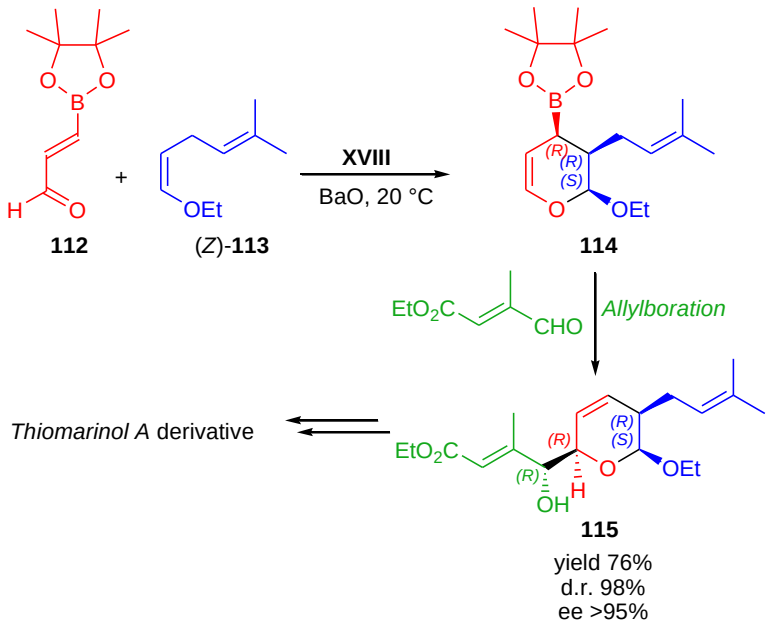
Scheme 33. Parallel Kinetic Resolution of 106 by Asymmetric HDA Cycloaddition Catalyzed by XVIII.[50]



The inseparable mixture of diastereoisomers was directly submitted to hydrogenation (H_2/PtO_2) to give the corresponding reduced products in a stereoselective manner. These latter were separated, hydrolyzed, and oxidized to furnish (-)-boschnialactone **109** and (+)-7-*epi*-boschnialactone **110** that can be converted into isoiridomyrmecin **111**.

The total synthesis of a member of the thiomarinol class of marine antibiotics was achieved through the key-intermediate **115**, obtained by a sequence involving an enantioselective catalyzed HDA cycloaddition and an allylboration reaction.[51] The α,β-unsaturated aldehyde **112** reacts with enol ether (*Z*)-**113** in the presence of **XVIII** as enantioselective catalyst. After separation of the catalyst, the HDA cycloadduct **114** was directly submitted to the allylboration reaction with the commercial available crotonoate derivative to give **115** in a 76% overall yield, with almost complete diastereoselectivity and with excellent enantioselectivity (ee > 95%), Scheme 34.

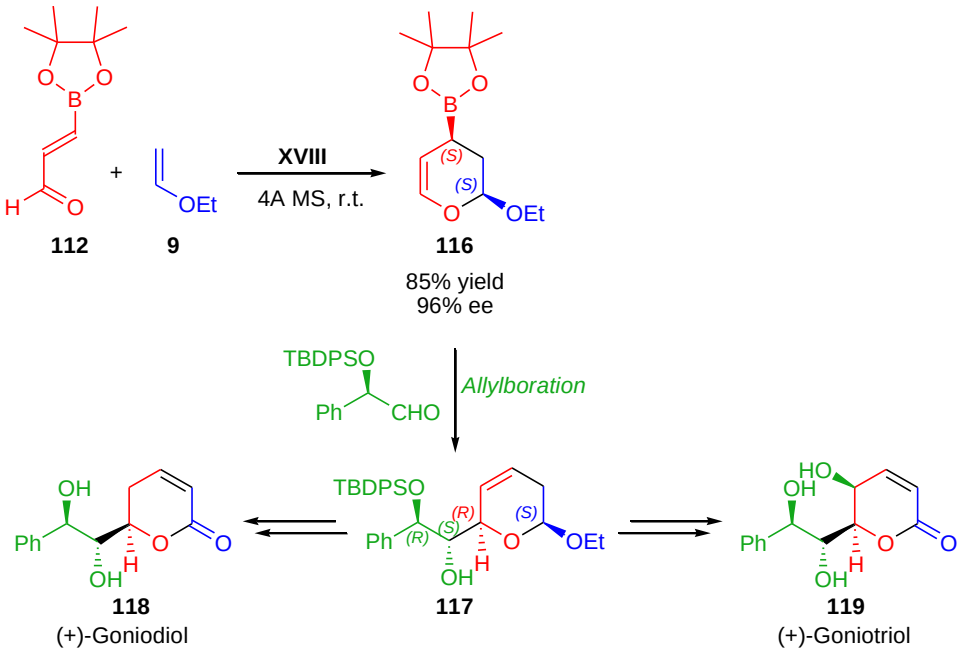
Scheme 34. Asymmetric HDA Cycloaddition Between 3-Boronoacrolein Pinacolate 112 with (*Z*)-1-Ethoxy-5-methylhexa-1,4-diene Catalyzed by XVIII.[51]



The HDA/allylboration sequence was also applied in the synthesis of several bioactive styryl lactones. Hence, the cycloaddition between **112** and ethyl vinyl ether **9** was efficiently catalyzed by **XVIII** to give **116** in good yield as a single diastereoisomer with excellent enantioselectivity (96%

ee). The cycloadduct was then submitted to allylboration with the protected aldehyde derived from (*R*)-mandelic acid to furnish **117** as a unique stereoisomer in 65% yield (Scheme 35).[52] Dihydropyran **117** was the key-intermediate for the synthesis of several derivatives such as (+)-goniodiol **118** and (+)-goniotriol **119**.

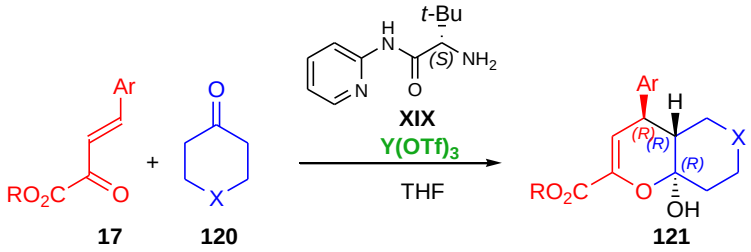
Scheme 35. Asymmetric HDA Cycloaddition Between 3-Boronoacrolein Pinacolate 112 with Ethyl Vinyl Ether Catalyzed by XVIII.[52]



The last example of this section concerns the use of an enamine/metal Lewis acid bifunctional catalyst and represents the ideal bridge with the topic of the next section regarding the use of organocatalysts.

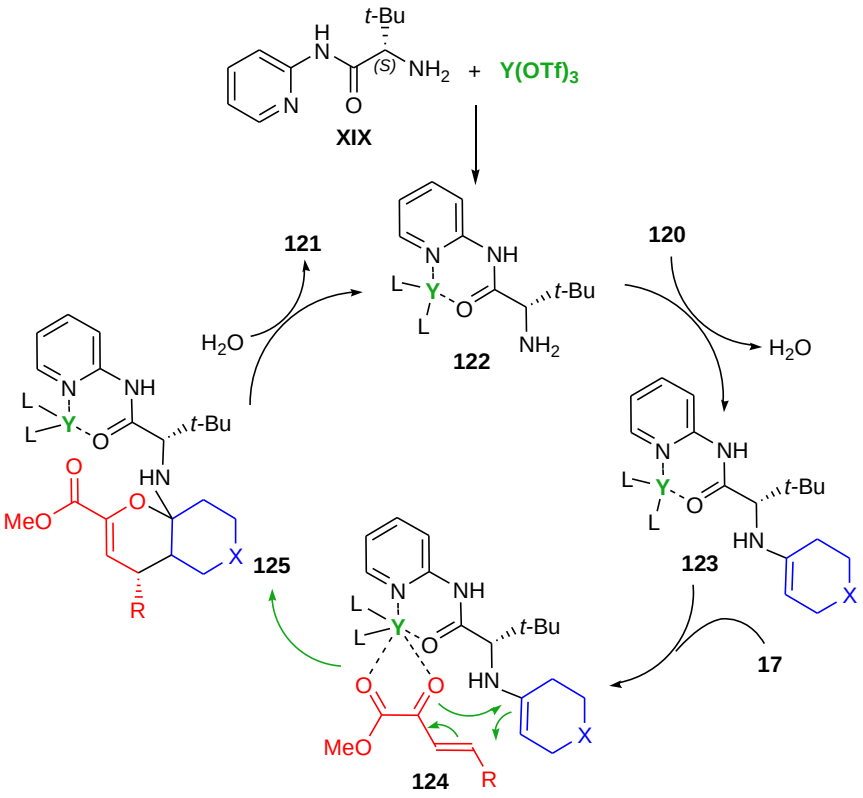
The reaction between **17** and **120** was run in the presence of ligand **XIX** (derived through the coupling of the corresponding amine and the *N*-protected L-aminoacid) and $Y(OTf)_3$ to give the trans-fused bicyclic adducts with good yields and stereoselectivities, and with excellent enantioselectivities (Scheme 36).[53,54] In the 20 reported different experiments involving different β,γ-unsaturated-α-ketoesters **17** and several six-membered cyclic ketones **120** (X = CH_2, O, S) the average yield was 74 ± 12%, the average de was 68 ± 10%, and the average ee was 95 ± 3% (Table 4, entry 7).

Scheme 36. Asymmetric HDA Cycloaddition Between 17 with Ketones 120 Catalyzed by XIX and $Y(OTf)_3$.[53,54]



The bifunctional nature of the catalyst is clearly revealed by the fact that neither the ligand **XIX** nor the $Y(OTf)_3$ alone could catalyzed the reaction. The proposed mechanism, depicted in Scheme 37, involves the in-situ formation of the enamine **123** starting from the complex **122** (nucleophile activation), followed by coordination of **17** to give **124** (electrophile activation). Cyclization furnishes the cyclic aminal **125**, that generates the HDA product **121** through hydrolysis and releasing the catalyst **122** to complete the catalytic cycle.

Scheme 37. Proposed Catalytic Cycle of the Asymmetric HDA Cycloaddition Between 17 and 120 Catalyzed by Primary Amine XIX/$Y(OTf)_3$ Bifunctional Catalyst.[53,54]



2.1.2. HAD Reactions and Other [4+2] Cycloaddition Processes Catalyzed with Organocatalysts

In the last fifteen years, organocatalysis has gained a pivotal role in asymmetric synthesis. Several reviews on this topic appeared in the literature in order to summarize the incredible number of contributions, and, among them, the Jørgensen's paper "Organocatalysis – after the gold rush" represents one of the best *tutorial* review on aminocatalysis.[55] More recently, other reviews concerning asymmetric organocatalytic cycloadditions appeared in the literature.[56,57]

The first example of organocatalytic enantioselective HDA reaction was described by Jørgensen in 2003.[58] The reaction between heterodienes **17** with aldehydes **126** in the presence of chiral pyrrolidines **XX** (10 mol%), followed by oxidation with PCC, furnishes with good yields and high selectivities the δ-lactones **127** (Scheme 38). The procedure works well with different substrates and the average overall yield in 10 different experiments was 74 ± 9%, the endo-selectivity was almost complete (average de was 99 ± 1%), and the enantioselectivity was appreciable (average ee of 86 ± 6%), entry 1 in Table 5.

Scheme 38. Asymmetric HDA Cycloaddition Between 17 with Aldehydes 126 Catalyzed by XX.[58]

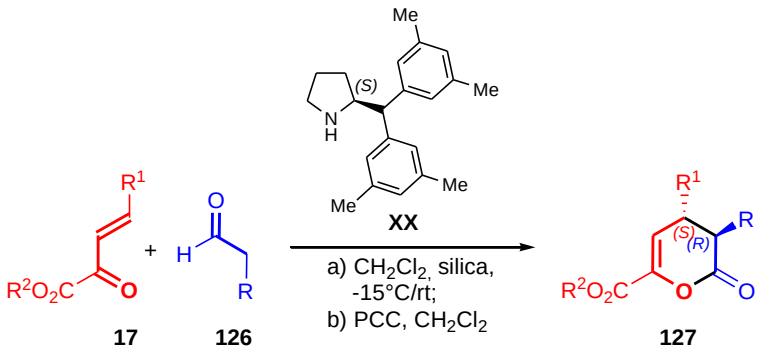


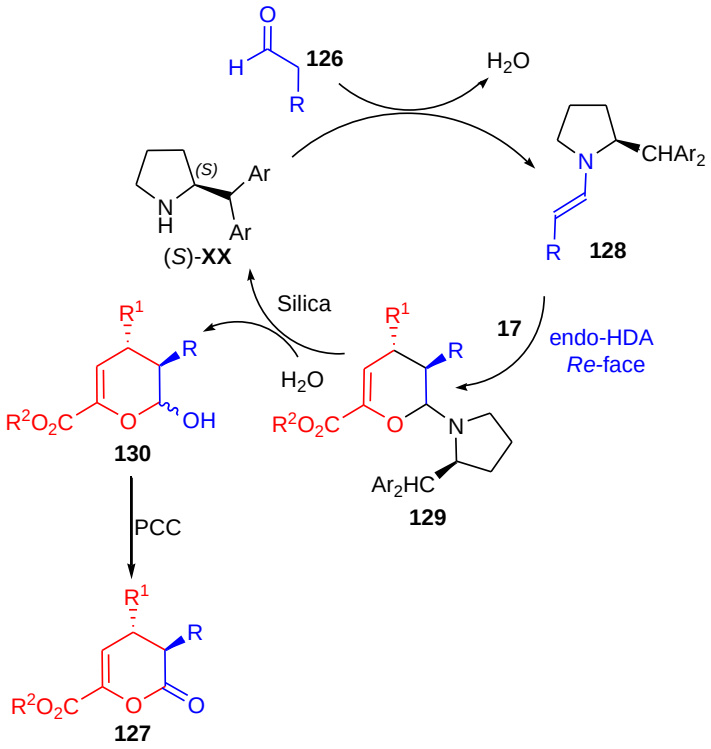
Table 5. Average Values and Standard Deviations (s.d.) of the Reaction Yields, Diastereo-, and Enantioselectivities for the HDA Reactions Catalyzed by Different Organocatalysts.

Entry	Heterodiene	Dienophile	Catalyst	n. Exp.	aver. Yield % (s.d.)	aver. de (s.d.)	Reaction Product	aver. ee % (s.d.)	Ref.
1	**17**	**126**	(*S*)-**XX**	10	74 (9)	99 (1)	**127**	86 (6)	58
2	**8**	**126**	(*S*)-**XXI**	10	80 (9)	99 (-)	**132**	85 (7)	59
3	**133**	**126**	(*S*)-**XXIIa**	10	61 (8)	91 (2)	**136**	88 (15)	60
4	**137**	**138**	(*S,S*)-**XXIII**	17	65 (10)	75 (8)	**140** or **141**	92 (2)	61
5	**147**	**138**	(2*S*,4*R*)-**XXIV**	17	78 (2)	77 (6)	**148**	90 (4)	62
6	**150**	**126**	(*S*)-**XXIIa**	19	59 (8)	87 (7)	**152**	99 (1)	63
7	**156**	**126**	(*S*)-**XXIIa**	10	---	---	**158** or **159**	97.5 (1.5)	64
8	**160**	**126**	(*S*)-**XXIIa**	5	81 (5)	---	**161**	88 (4)[a]	65
9	**17**	**162**	(2*R*,4*aR*,7*aS*)-**XXV**	16	91 (3)	99 (-)	**163**	89 (4)	66
10	**17**	**164**	(2*R*,4*aR*,7*aS*)-**XXV**	28	87(12)	99 (-)	**165**	93 (3)	67

[a] The value refers to the average ee of the major anomer (the corresponding value for the minor anomer is 77 ± 17% ee).

The proposed mechanism of the organocatalytic reaction (Scheme 39) starts with the generation of the chiral enamines **128** from the organocatalyst **XX** and aldehydes **126** that react with heterodienes **17** in a stereoselective HDA cycloaddition to give aminals **129**. Hydrolysis of these latter produces hemiacetals **130** and releases organocatalysts **XX** to complete the catalytic cycle. In situ PCC oxidation of **130** produces the final cycloadducts **127** (Scheme 39).

Scheme 39. Proposed Catalytic Cycle for the Asymmetric Organocatalytic HDA Cycloaddition Between 17 and Aldehydes 126 Catalyzed by (*S*)-XX.[58]

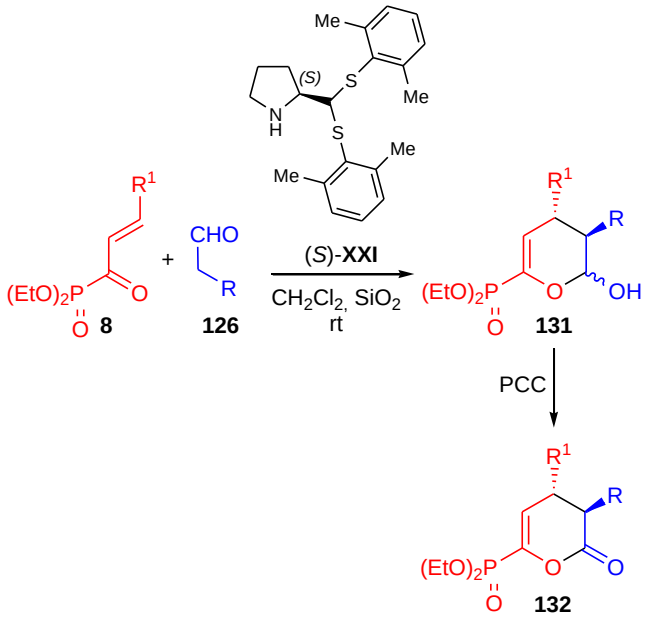


The absolute stereochemistry of **127** (R = i-Pr, R^1 = 4-Cl-C_6H_4; R^2 = Me) was found to be (4*S*,5*R*) by X-ray crystal analysis, and it was consistent with the proposed mechanism. The regioselectivity was governed by the electronic properties of the enamine, while the 2,2-diaryl-methyl substituent on the pyrrolidine ring shields the *Si*-face of **128**, which is approached by **17** to its less hindered *Re*-face in an endo-selective fahion.[58]

2.1.2.1 Proline Derivatives and Analogues as Organocatalysts

After the Jørgensen's first example of organocatalytic enantioselective HDA reaction, several other enantioselective organocatalysts were applied in cycloadditions involving more or less activated heterodienes. The HDA reaction between β,γ-unsaturated α-ketophosphonates **8** was catalyzed by several chiral prolinal derivatives, and the catalyst of choice was found to be the prolinal dithioacetal (*S*)-**XXI** (Scheme 40),[59] which activated aldehydes **126** through the same mechanism described in Scheme 39.

Scheme 40. Asymmetric HDA Cycloaddition Between 8 with 126 Catalyzed by (*S*)-XXI.[59]

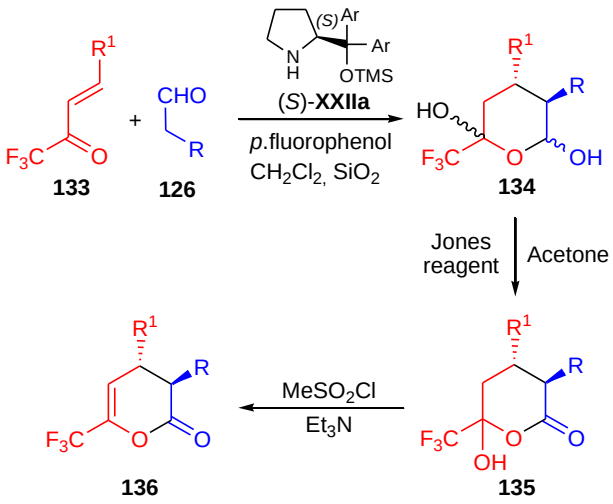


The primary products obtained from the HDA reaction (**131**) may be regarded as glycal phosphonate derivatives, compounds that can exhibit multiple biological activities. Three new stereogenic centers are generated in the reaction, but only two diastereoisomers were obtained in a ratio ranging from 60:40 to 80:20. In any case, only trans-cycloadducts (referred to R and R^1) were isolated and PCC-oxidation of the anomeric mixtures gives δ-lactones **132** with up to 94% ee. When R^1 is an alkyl group the enantioselectivity is excellent. In 10 different experiments the average yield was 80 ± 9%, and only endo-adducts **132** were obtained with an average ee of 85 ± 7% (Table 5, entry 2). When the β,γ-unsaturated α-ketophosphonates **8** has an aromatic substituent

on the β-position, then the enantioselectivity drops to 19% ee only. The absolute configuration of **132** was not determined, but is quite interesting to note that the use of (*R*)-**XX** as the organocatalysts furnishes the same enantiomer respect to that obtained by using (*S*)-**XXI**.[59]

The HDA cycloaddition between α,β-unsaturated trifluoromethyl ketones **133** and aldehydes **126** was usefully catalyzed by the chiral proline derivative (*S*)-**XXIIa** (Scheme 41).[60] The primary adducts obtained from the hydrolysis of the cycloaddition products were the tetrahydro-pyran hemiketals **134**, which were oxidized to **135**, and then submitted to dehydration with $MeSO_2Cl/Et_3N$ to furnish the final dihydropyranone derivatives **136**.

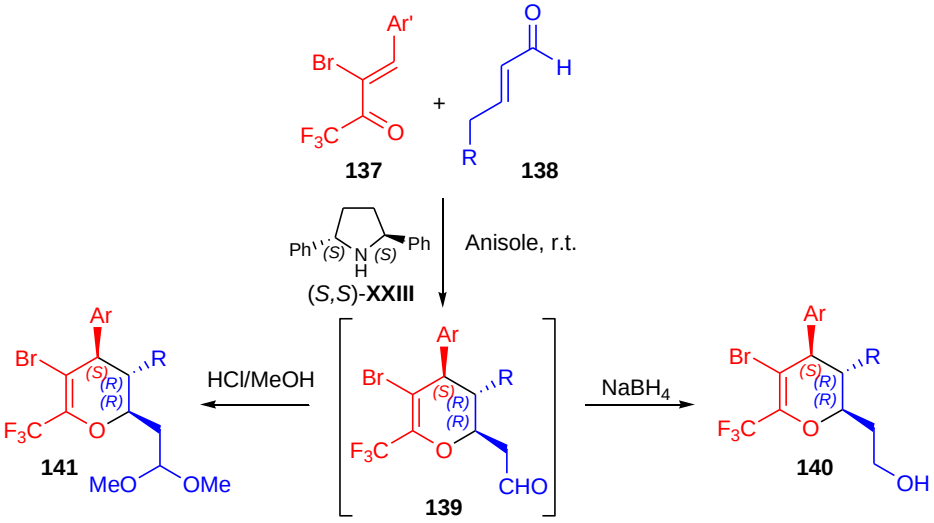
Scheme 41. Asymmetric HDA Cycloaddition Between 133 with 126 Catalyzed by (*S*)-XXIIa.[60]



Under the optimized conditions, the cycloaddition tolerated both electron-rich and electron-poor phenyl-substituted unsaturated ketones: The average reaction yield in 10 different experiments was 61 ± 8% (overall yield of the three synthetic steps), while the diastereo- and the enantioselectivities were more appreciable: the average de was 91 ± 2% and the average ee was 88 ± 15% (Table 5, entry 3).

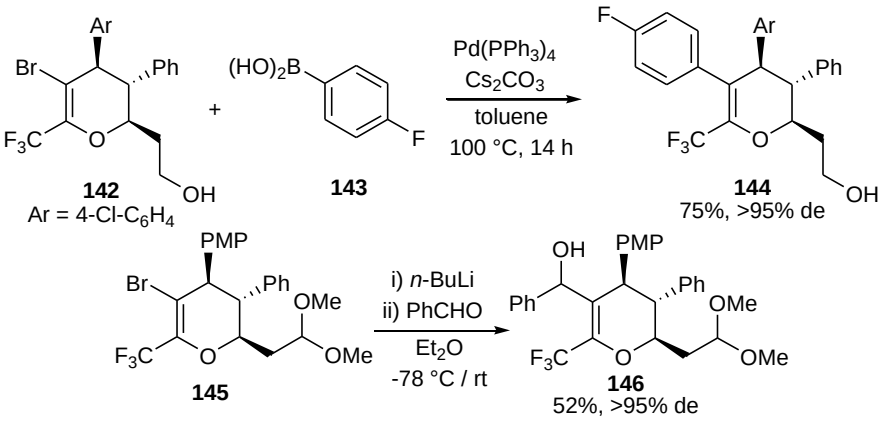
C$_2$-symmetric 2,5-diphenylpyrrolidine (*S*,*S*)-**XXIII** was an efficient organocatalysts in the HDA reaction between α-bromo-trifluoromethyl-enones **137** and α,β-unsaturated aldehydes **138** (Scheme 42).[61]

Scheme 42. Asymmetric HDA Cycloaddition Between 137 with 138 Catalyzed by (*S*,*S*)-XXIII.[61]

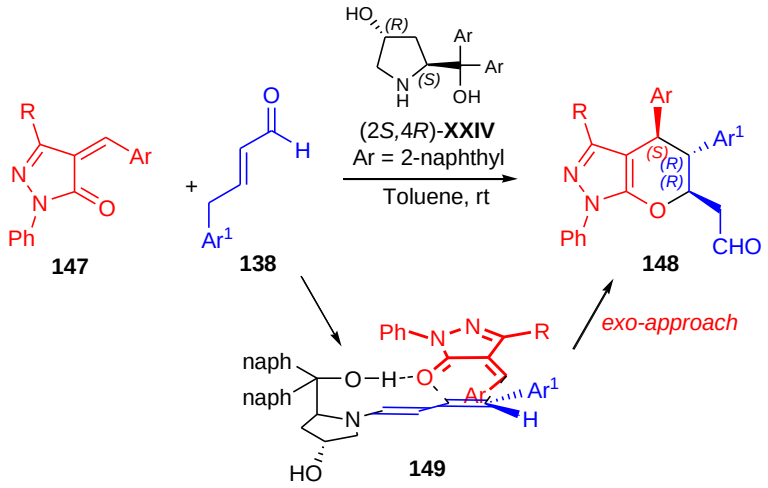


The primary adducts **139** were directly converted to more stable products by either $NaBH_4$ reduction to primary alcohols **140** or by reaction with MeOH/HCl to give acetals **141**. Cycloadducts **139** and **140** were obtained within moderate yields, good diastereoselectivities and excellent enantioselectivities: over 17 different experiments, the average yield was 65 ± 10%, the de was 75 ± 8%, and the ee 92 ± 2% (Table 5, entry 4). The presence of bromine on an sp^2-hybridized carbon atom was usefully exploited in further functionalizations by either coupling reactions or lithiation protocols (Scheme 43). Compound **142** reacted selectively with the arylboronic acid **143** in a Suzuki coupling to give **144** in 75% yield, while acetal **145** was submitted to lithiation by *n*-BuLi, followed by addition of an appropriate electrophile (PhCHO) to furnish the addition product **146** with 52% yield. The selectivity in the formation of the fourth new stereocenter was only moderate (d.r. of 4.8:1).

Scheme 43. Functionalizations at Position 5 of the 3,4-2*H*-dihydropyran Skeleton.[61]



Scheme 44. Asymmetric HDA Cycloaddition Between 147 with 138 Catalyzed by (2*S*,4*R*)-XXIV.[62]



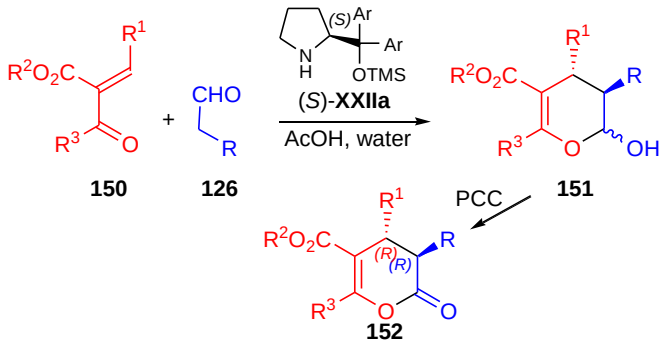
Alkylidene pyrazolones **147** and α,β-unsaturated aldehydes **138** reacted in the presence of the chiral proline derivative (2*S*,4*R*)-**XXIV** to give the tetrahydro-pyrano[2,3-*c*]pyrazole derivatives **148** (Scheme 44).[62] The reaction proceeds smoothly with excellent regioselectivity and high stereoselectivity; the average reaction yield in 17 different experiments is 78 ± 8%, the average de is 77 ± 6%, and the average ee is 90 ± 4% (Table 5, entry 5). The absolute configuration of **148** was determined by X-ray analysis and was consistent with TS **149** in which the more stable dienamine conformer approaches the (*Z*)-heterodienes **147** in an exo fashion. The preference for such attack is justified by of two factors: (i) the H-bonding between the hydroxyl group of the diarylprolinol ant the carbonyl of the pyrazolone and (ii) the repulsion between the pyrazolonic aromatic group and the dienamine.

The last examples above discussed of organocatalyzed reactions are typical HDA reactions proceeding through concerted transition state. In other cases, the formation of [4+2] cycloadducts derives from a stepwise mechanism, a tandem process in which the first step is a Michael addition to give an intermediate that cyclize to the cyclic pyran derivative.

α-Keto-α′,β′-unsaturated esters **150** were allowed to react with aldehydes **126** in the presence of diarylprolinol (*S*)-**XXIIa** in AcOH/water to give cyclic hemiacetals **151** through a cascade

Michael addition and cyclization process, these latter being directly oxidized (with either PCC or Dess-Martin reagent) to furnish the highly functionalized 3,4,5,6-tetrasubstituted dihydropyrones **152** (Scheme 45).[63] The optimized conditions were applied to variously substituted ketoesters and aldehydes, and the average overall reaction yield over 19 different reagent combinations was 59 ± 8%, the average de in favor of the cis-adducts was 87 ± 7%, while the enantioselectivity was always excellent (average ee of 99 ± 1%), Table 5, entry 6.

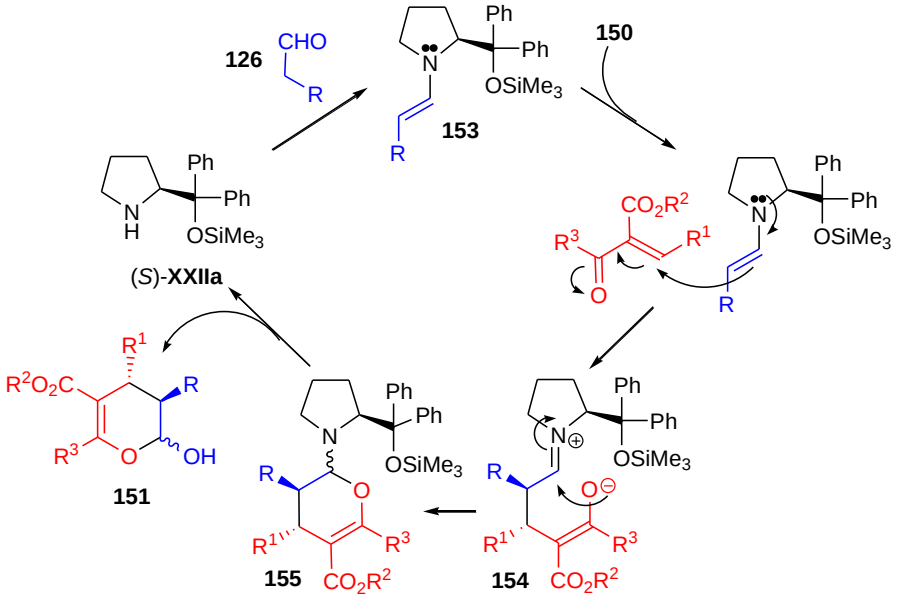
Scheme 45. Asymmetric Cycloaddition Reaction Between 150 with 126 Catalyzed by (*S*)-XXIIa.[63]



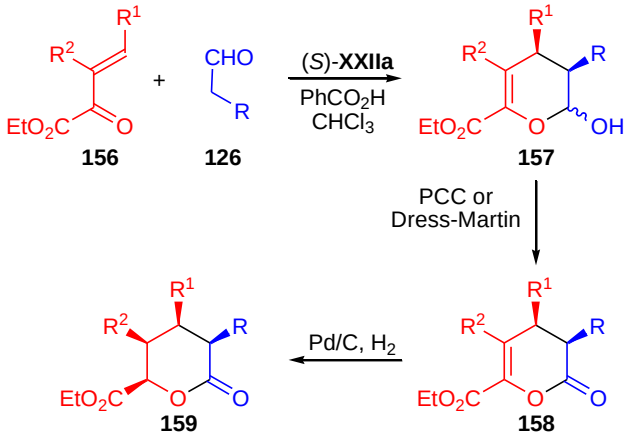
The proposed mechanism starts with the formation of the enamine **153** by reaction of aldehydes **126** with proline (*S*)-**XXIIa**. The activated nucleophile gives a Michael addition to electrophile **150** with an approach to the less hindered face of **153** to give the intermediate zwitterion **154** that undergoes an intramolecular attack of enol anion to iminium ion to provide the cyclized product **155**. Hydrolysis of **155** produces the cyclic hemiacetal **151** releasing prolinol (*S*)-**XXIIa** that completes the catalytic cycle (Scheme 46).

Diarylprolinol silyl ether (*S*)-**XXIIa** catalyzes the Michael addition/cyclization cascade reaction between oxo-butenoate **156** with aldehydes **126** to give cycloadducts **157**. As in the previous examples, these intermediates were oxidized to dihydro-pyranones **158**, which were then hydrogenated to δ-lactones **159** with good diastereoselectivity, Scheme 47.[64] The overall reaction yields over the three steps ranged from 20 to 50%, while in all the 10 reported examples the enantioselectivity was excellent (average ee of 97.5 ± 1.5%, entry 7 in Table 5).

Scheme 46. Proposed Mechanism for the Tandem Michael/Cyclization Reaction Between 150 with 126 Catalyzed by (*S*)-XXIIa.[63]

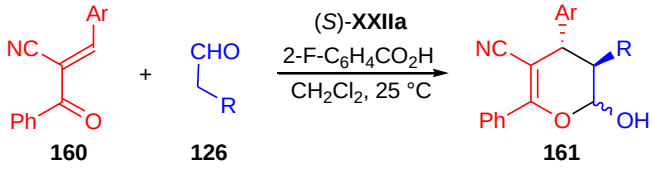


Scheme 47. Asymmetric Cycloaddition Reaction Between 156 with 126 Catalyzed by (*S*)-XXIIa.[64]



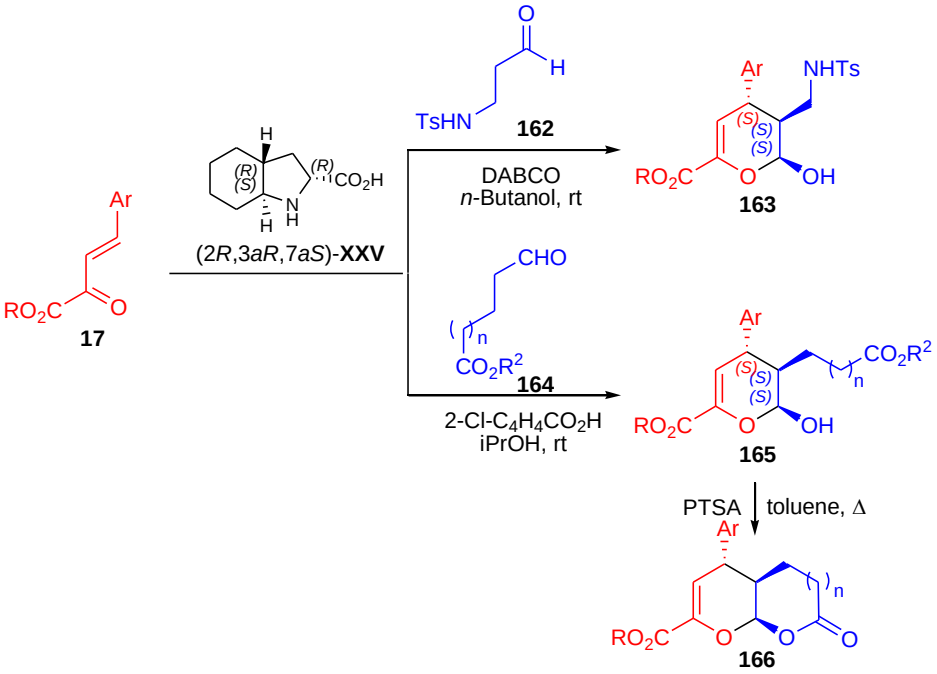
α-Cyano-α,β-unsaturated aromatic ketones **160** underwent tandem Michael addition/cyclization processes by reacting with aldehydes **126** in the presence of (*S*)-**XXIIa** to give anomeric mixtures of adducts **161** (Scheme 48).[65] The anomeric mixtures were obtained in good yields with an anomeric ratio ranging from 1:1.3 to 3:1; the average ee of the major anomer in 5 different experiments was 88 ± 4%, entry 8 in Table 5.

Scheme 48. Asymmetric Cycloaddition Reaction Between 160 with 126 Catalyzed by (*S*)-XXIIa.[65]



Trans-perhydroindolic acid (2*R*,4a*R*,7a*S*)-**XXV** was an efficient organocatalyst in tandem Michael addition/cyclization reactions between α-keto-β,γ-unsaturated esters **17** with aldehydes substituted with either an amino[66] or an ester group,[67] **162** and **164** respectively (Scheme 49). The reactions proceed smoothly to give pyrans **163** and **165** with excellent yields, diastereo- and enantioselectivities (Table 5, entries 9 and 10). Hemiacetal **165** were easily transformed in pyrano[2,3-*b*]pyran derivatives **166**, a subunit exhibiting interesting biological properties present in several natural products.

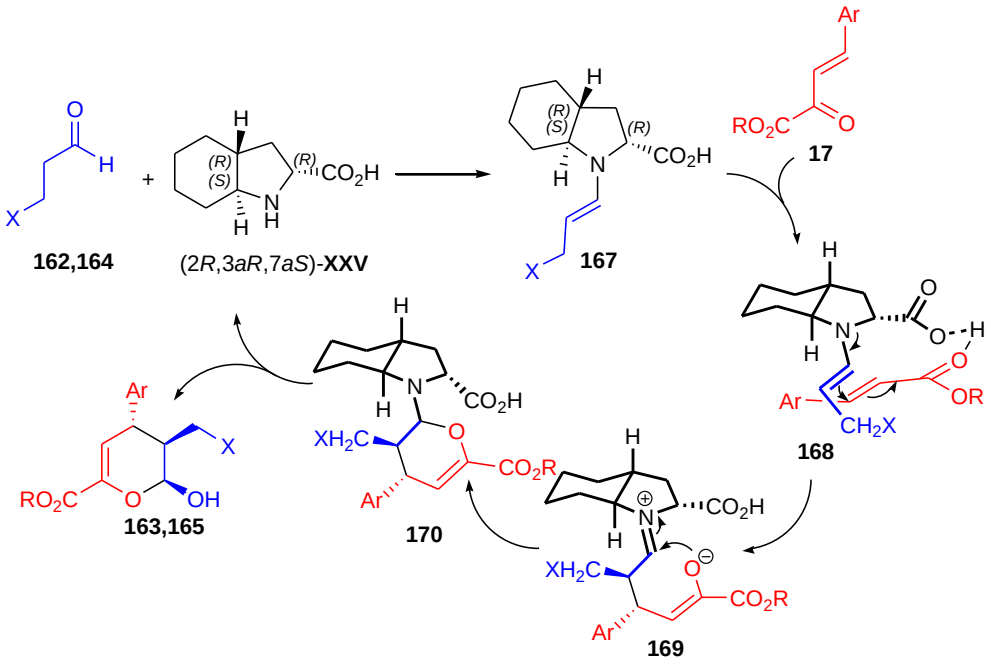
Scheme 49. Asymmetric Cycloaddition Reaction Between 17 with 162 and 164 Catalyzed by (2*R*,4*aR*,7*aS*)-XXV.[66,67]



The reaction mechanism was proposed on the basis of the stereochemical outcome of the tandem reaction (Scheme 50). As in previous cases, aldehydes reacted with the amino-

organocatalyst to give enamine **167**, the activated nucleophile. The electrophile **17**, in the s-trans conformation, is activated by the hydrogen bonding in TS **168** and driven in the addition to the nucleophilic double bond to give the enolimine intermediate **169.** The cyclization to **170** is followed by the front-side attack of H_2O to furnish cycloadducts **163** and **165** together with the catalyst (2*R*,4*aR*,7*aS*)-**XXV** that complete the catalytic cycle.

Scheme 50. Proposed Reaction Mechanism for the Tandem Michael Addition/Cyclization Reaction Between 17 with Aldehydes 162 and 164 Catalyzed by (2*R*,4*aR*,7*aS*)-XXV.[66,67]



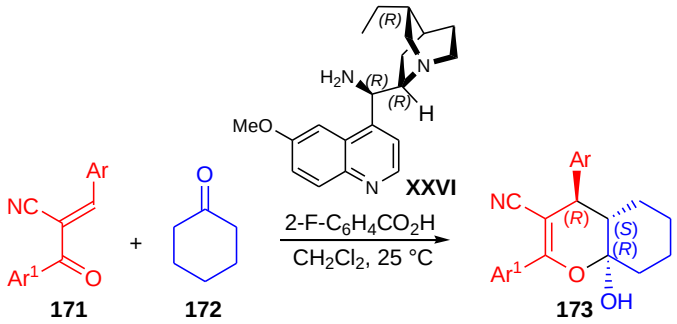
2.1.2.2. Alkaloid Derivatives as Polar Organocatalyst

An important class of organocatalysts is that of alkaloid derivatives, which can act through nucleophile activation either by deprotonation with the tertiary amine or by enamine formation when a NH_2 group is present.

The *Cinchona*-based primary amine 9-amino-dihydroepiquinine (3*R*,8*R*,9*R*)-**XXVI** was a useful organocatalyst in the tandem Michael addition/cyclization reaction between diaryl-α-cyano-α,β-unsaturated ketones **171** with cyclohexanone **172** to give adducts **173** (Scheme 51).[65] Under the optimized reaction conditions, the adducts, characterized by three contiguous stereocenters, one of which is a quaternary one, were obtained within good yields (in only one of the 14 described

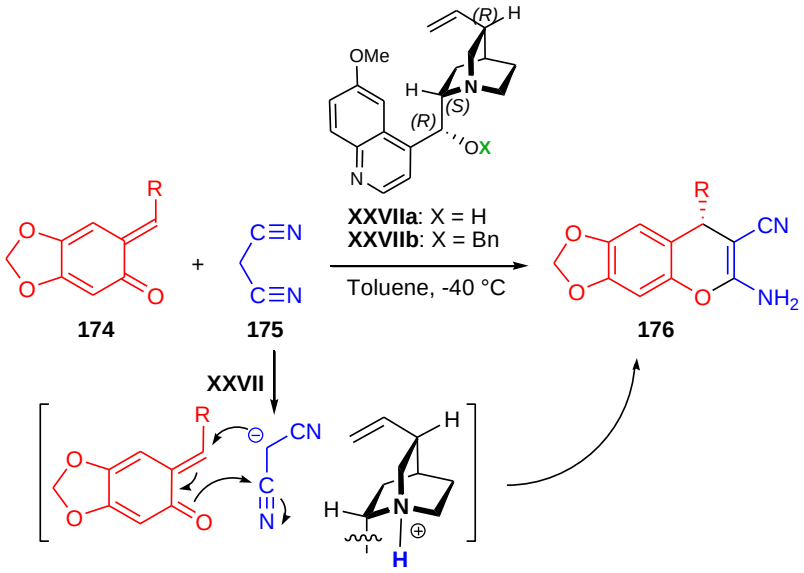
examples the yield was lower than 75%) and appreciable diastereoselectivities (the anomeric ratio ranged from 3.2 to 9.0:1). The enantioselectivity ranged from good (3 cases) to excellent (in the other 11 examples), and the average ee over 14 different derivatives of **171** was 88 ± 12 (Table 6, entry 1).

Scheme 51. Asymmetric Cycloaddition Reaction Between 171 with 172 Catalyzed by (3*R*,8*R*,9*R*)-XXVI.[65]



The quinine derivative **XXVIIa** (X=H) is an interesting example of bifunctional organocatalyst with the tertiary amine acting as a Lewis base (nucleophile activation by deprotonation) and with the OH group acting as H-bond donor (electrophile activation). The formal [4+2] cycloaddition between *ortho*-quinone methides **174** and malonitrile **175** was usefully catalyzed by **XXVIIa** to give 4-substituted-2-amino-3-cyano-4*H*-chromenes **176** (Scheme 52).[68]

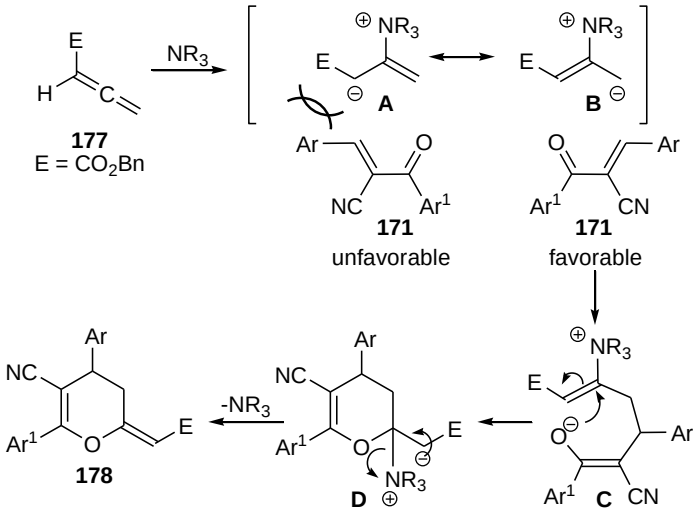
Scheme 52. Asymmetric Cycloaddition Reaction Between 174 with 175 Catalyzed by XXVII.[68]



Even if the example does not fit fully the topic of the review, it is important for the relevance of the bifunctional activity of the organocatalyst. The adducts were obtained with excellent yields and very good enantioselectivities (over 10 different experiments, the average reaction yield was 97 ± 1%, while the average ee was 91 ± 1%, see entry 2 in Table 6).

The proposed mechanism is depicted in Scheme 52 in which the organocatalyst **XXVIIa** deprotonates malonitrile through its tertiary amine and activates **174** through H-bond. The importance of the latter interaction in determining the enantioselectivity is clearly evidenced by the result obtained by using **XXVIIb** as the organocatalyst. When the OH group is protected as benzyl ether, then the enantioselectivity drops to 34% ee only. The enantioenriched 2-amino-3-cyano-4*H*-chromenes **176** showed potential activity as antitumor agents. Hence, the scale up of the reaction to a gram scale was performed without any loss in reaction yields and enantioselectivities.

Scheme 53. Proposed Mechanism for the [4+2] Annulations of Oxo-dienes with Allenoates Catalyzed by Tertiary Amines.[69]



Lewis base catalyzed reactions of allenoates with oxo-dienes represent an interesting method to synthetize dihydropyrans with a high level of complexity and diversity. The proposed mechanism for such annulations is depicted in Scheme 53 and starts with the addition of the catalyst (a tertiary amine) to the allenoate **177** to form the zwitterionic intermediated described by the resonance structures **A** and **B**. Subsequently, electrophile **171** interacts preferentially with **B** over **A** owing to the less steric hindrance between the ester group and the aryl substituent forming the enolate

intermediate **C**. Then, the intramolecular Michael addition of the nucleophilic oxygen to the β-position of **C** leads to intermediates **D** that, after elimination of the tertiary amine, furnishes dihydropyrans **178** and regenerates the catalyst to accomplish the [4+2] annulation reaction.[69]

The use of a suitable chiral amine catalyst may induce an asymmetric Michael addition in the approach of **B** to **171** to give intermediate **C**, thus leading to the construction of a stereogenic center at the C-4 position of **178**. The cinchona alkaloids are suitable candidates to behave as chiral bases and after a screening of several derivatives, the quinine derivative **XXVIIc** was found to be the chiral base of choice to run the asymmetric [4+2] annulation. The reaction procedes at -30 °C in toluene as the solvent to give good yields of (*E*,*S*)-**178** with a complete control of the *E* selectivity of the exocyclic double bond and with high control of the enantioselectivity (Scheme 54). In order to obtain good results, the presence of the cyano group on the oxodiene **171** is required, but the method was found very efficient in several diarylsubstituted oxodienes **171**, and over 13 different substrates the average reaction yield was 82 ± 13% and the average ee was 87 ± 4% (Table 6, entry 3). The (*S*) absolute configuration of the C-4 was determined by X-ray crystal analysis and it is in accordance with the nucleophile approach to the β-*Re* face of **171** (see the convention arbitrarily assumed and described in Figure 4). Respect to the example described in Scheme 52 where the -OH free quinine **XXVIIa** worked better than the benzyl-protected quinine **XXVIIb**, in this case the role of the H-bond ability of the organocatalyst is negative since the use of **XXVIIa** produces (*E*,*S*)-**178** with a lower enantioselectivity (78% ee only).

Scheme 54. Asymmetric [4+2] Annulations of 171 with Allenoate 177 Catalyzed by XXVIIc.[69]

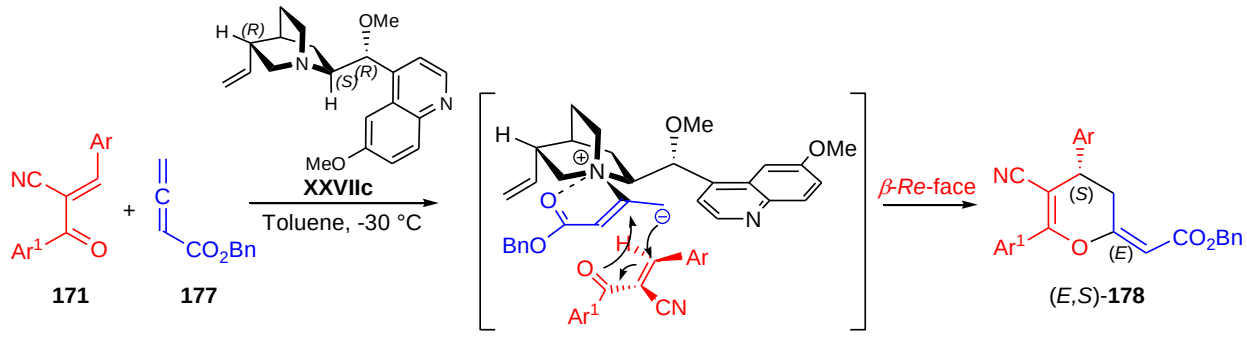


Table 6. Average Values and Standard Deviations (s.d.) of the Reaction Yields, Diastereo-, and Enantioselectivities in the Synthesis of Dihydropyrans by [4+2] Cyclization Processes Catalyzed by Alkaloid Derivatives as Organocatalysts.

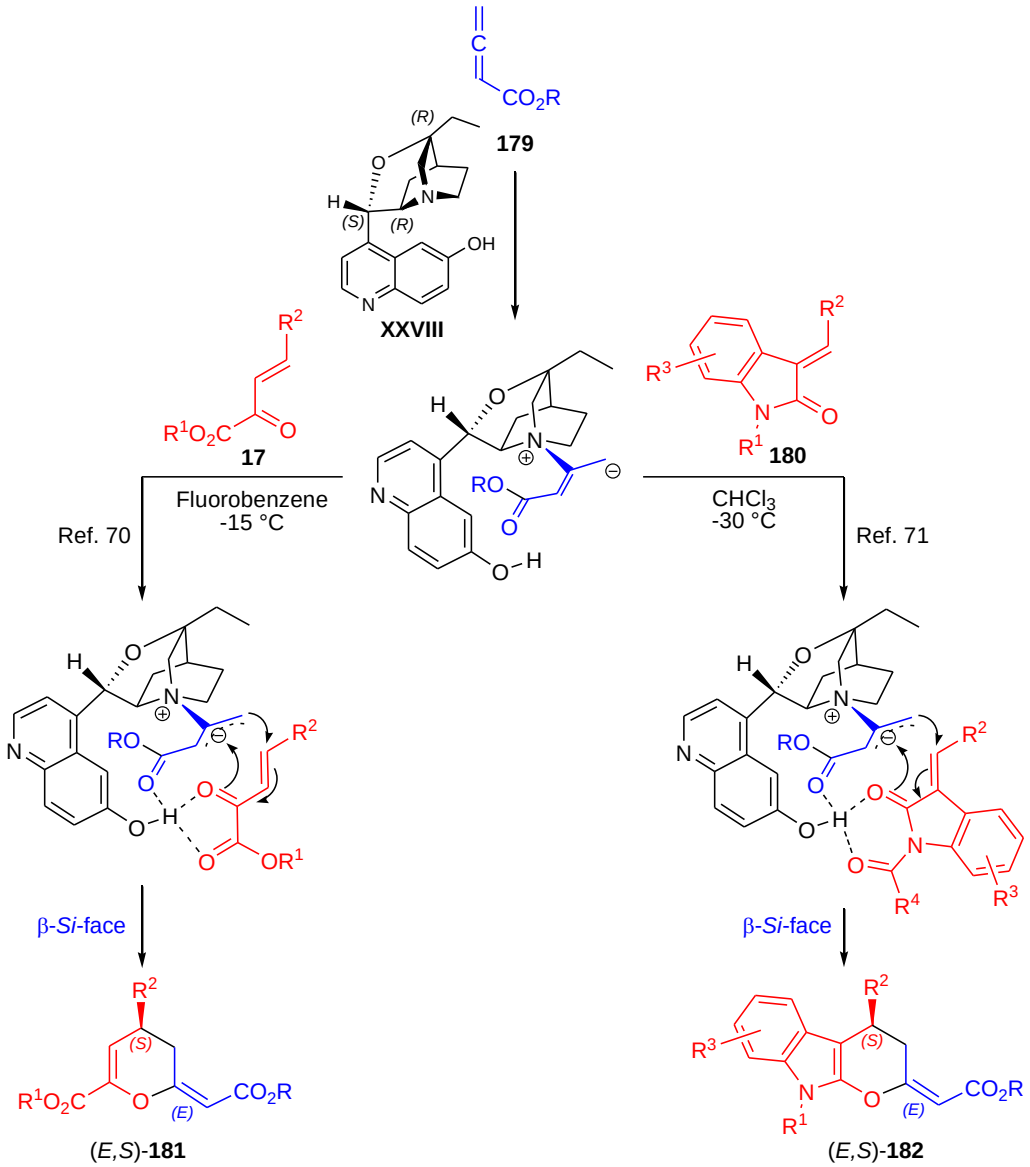
Entry	Heterodiene	Nucleophile	Catalyst	n. Exp.	aver. Yield % (s.d.)	aver. de (s.d.)	Reaction Product	aver. ee % (s.d.)	Ref.
1	**171**	**172**	**XXVI**	14	79 (14)	66 (8)[a]	**173**	88 (12)	65
2	**174**	**175**	**XXVIIa**	10	97 (1)	---	**176**	91 (1)	68
3	**171**	**177**	**XXVIIc**	13	82 (13)	---	**178**	87 (4)	69
4	**17**	**179**	**XXVIII**	18	85 (6.5)	---	**181**	87 (4)	70
5	**180**	**179**	**XXVIII**	25	69 (30)	---	**182**	76 (23)	71
6	**183**	**179**	**XXIX**	17	78 (13)	b	**184** [**185**][c]	98 (3) [95 (3)]	72
7	**17**	**186**	**XXX**	15	85 (12)	---	(5*R*,6*S*)-**188**	89 (7)	73
8	**189**	**190a**	**XXXI**	9	96 (4)	---	**192a**	90 (5)	74
9	**189**	**190b**	**XXXI**	14	95 (3)	97 (4)	**192b**	85 (19)	74
10	**174a**	**193**	**XXXII**	7	87 (2)	84 (4)	**194**	81(5.5)	75

[a] Average de refers to the anomeric ratio. [b] Regioisomeric ratio **184**:**185** ranges from 80:20 to 23:77. [c] Co-products of the reaction between **183** and **179** catalyzed by **XXIX**.

In a similar manner, the asymmetric [4+2] annulation of allenic esters **179** with either α-keto-β,γ-unsaturated esters **17**[70] or 3-aryliden-2-oxindole **180**[71] was catalyzed by Lewis bases. In these enantioselective cycloadditions the chiral base of choice was β-isocupreidine **XXVIII** (Scheme 55).

The [4+2] annulation reactions of **179** with **17** catalyzed catalyzed by **XXVIII** was run in fluorobenzene at -15 °C (optimized conditions) to give high reaction yields of pyrans (*E*,*S*)-**181** with appreciable enantioselectivities. Over 18 different experiments the average yield was 85 ± 6.5% and the average ee was 87 ± 4% (Table 6, entry 4).

Scheme 55. Asymmetric Cycloaddition Reactions Between 179 with Oxodienes 17 and 180 Catalyzed by β-Isocupreidine XXVIII.[70,71]

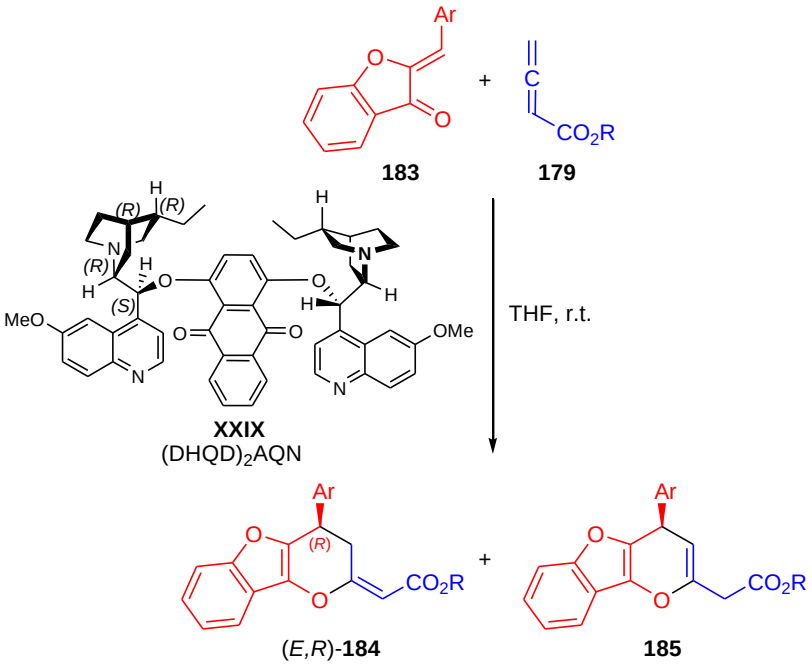


The same organocatalyst **XXVIII** was found to catalyze the [4+2] annulation between **179** and **180**. The reaction proceeded at -30 °C in $CHCl_3$ to furnish the pyrano[2,3-*b*]indole derivatives (*E*,*S*)-**182** with yields ranging from 10 to 96% (the average yield is 69 ± 30%) and moderate-excellent enantioselectivities (the average ee is 76 ± 23%), Table 6, entry 5.

Despite to the high variability of reactivity and selectivity as a function of specific substituents, both reactions in Scheme 55 proceed with the same mechanism, which is very similar to that described in Scheme 54. β-Isocupreidine **XXVIII** plays a dual role: the nitrogen atom of the tertiary amine reacts with **179** activating the nucleophile, while the –OH group on the C-6 of the quinoline ring acts as H-bond donor activating the electrophile (**17** or **180**) and driving the nucleophile approach to the β-*Si*-face of the oxodienes. Hence the use of **XXVIII** determines a stereochemical outcome opposite to that obtained by using **XXVIIc** as the organocatalyst (see Scheme 54).

Allenoates **179** react with the benzofuranone derivatives **183** under Lewis base catalysis to give mixtures of regioisomeric tricyclic adducts **184** and **185** (Scheme 56).[72]

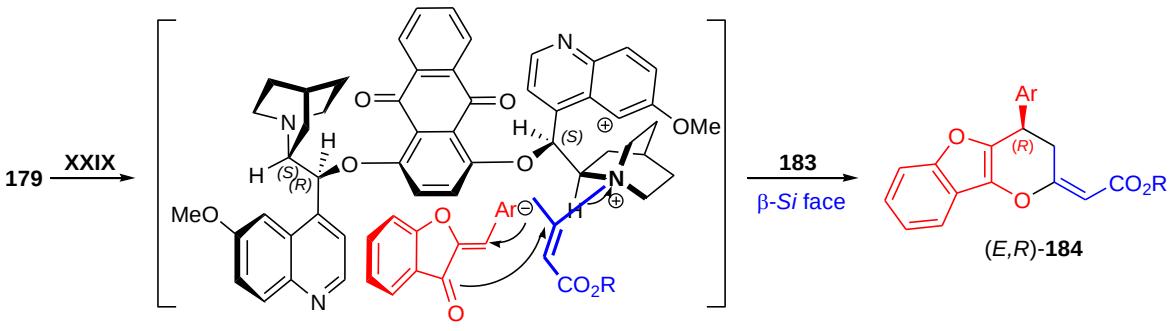
Scheme 56. Asymmetric Cycloaddition Reactions Between 179 with Oxodienes 183 Catalyzed by (DHQD)$_2$AQN XXIX.[72]



The reaction catalyzed by β-isocupreidine **XXVIII** proceeds at ambient temperature to give good yields of adducts **184** and **185** in a ratio of 2:1 but with unsatisfactory enantioselectivity (the ee for both products were around 60%). Better results were obtained by using $(DHQD)_2AQN$ **XXIX** as chiral base since, under optimized conditions, the average reaction yields in 17 different experiments was 78 ± 13% (Table 6, entry 6). Even if the regioselectivity was poor (products **184** and **185** were obtained in a ratio ranging from 80:20 to 23:77 depending on the substituents), the enantioselectivity was always excellent in both cycloadducts: the average ee values were 98 ± 3% for (*E*,*R*)-**184** and 95 ± 3% for **185** (Table 6, entry 6).

On the basis of the absolute configuration of **184**, determined by X-ray analysis, a plausibile transition state was proposed (Scheme 57). With the catalyst in the open conformation, the 2-olefinic benzofuran-3-one, which is stabilized by the π-π stacking with the quinoline moiety, was approached by the nucleophile (the usual zwitterionic intermediate resulting from the combination of allenoate and the nitrogen atom of the chiral base) from its β-*Si* face (under the usual convention defined in Figure 4) to obtain the cycloadducts in a highly enantioselective manner.[72]

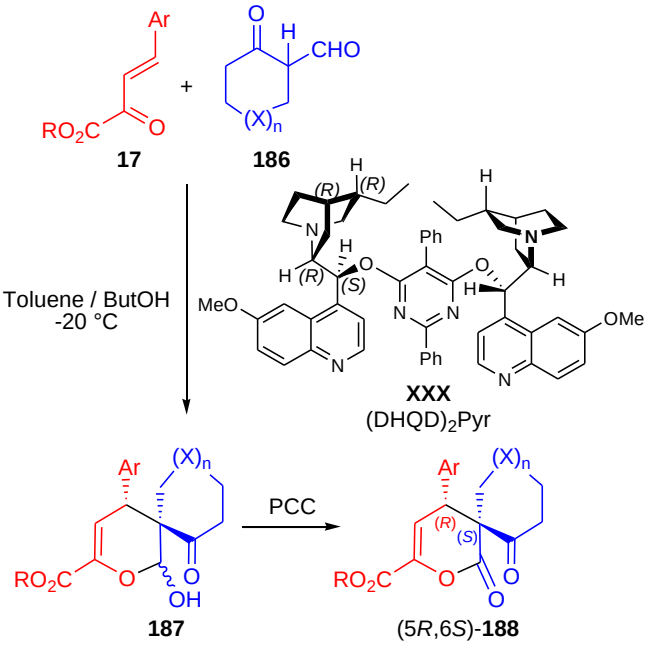
Scheme 57. Proposed Transition State Rationalizing the Stereochemical Outcome in the Reactions Between 179 with 183 Catalyzed by $(DHQD)_2AQN$ XXIX.[72]



The domino Michael addition/cyclization reaction between aromatic β,γ-unsaturated α-keto esters **17** with cyclic β-oxo-aldehydes **186** to give spiro-dihydropyran architectures **187** was usefully catalyzed by $(DHQD)_2Pyr$ **XXX** (Scheme 58).[73] The primary adducts **187** were obtained within good reaction yields as a mixture of the two anomers (the average reaction yield over 15

different experiments was 85 ± 12%, entry 7 in Table 6). These latter were oxidized with PCC to the corresponding δ-lactones **188**, which were obtained as a single diastereoisomer with excellent enantioselectivities (the average ee was 89 ± 7%, entry 7 in Table 6). This example of asymmetric amino-catalysis represents a new and promising method for the enantioselective synthesis of complicated spiro-3,4-dihydropyran structures with potential synthetic and biological uses.

Scheme 58. Asymmetric Cycloaddition Reactions Between 17 with β-Keto-Aldehydes 186 Catalyzed by (DHQD)$_2$Pyr XXX.[73]

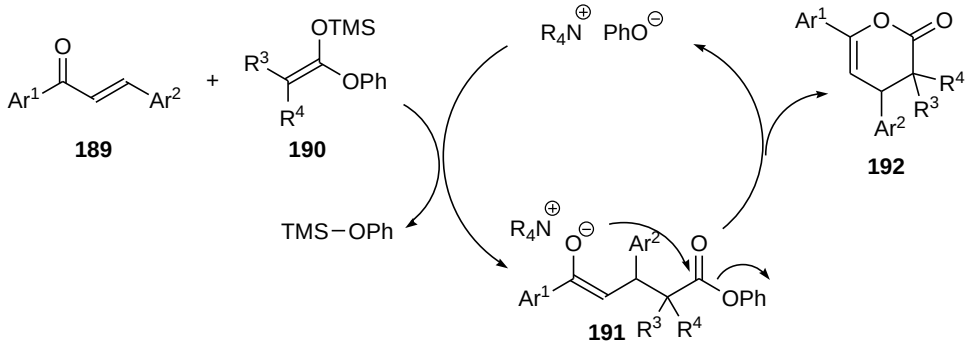


The Mukaiyama-Michael addition of ketene silyl acetals (derived from phenyl carboxylates) with aromatic α,β-unsaturated ketones in the presence of a catalytic amount of quaternary ammonium phenoxide produces, after lactonization, 3,4-dihydropyran-2-one derivatives. The proposed catalytic cycle for such phenoxide-ion-catalyzed domino conjugated addition and lactonization is illustrated in Scheme 59.[74]

In the presence of tetraalkylammonium phenoxide, ketene silyl acetals **190** were activated by nucleophilic attack of the phenoxide ion on the silicon center, to react with electrophiles **189** affording Michael-adduct intermediates **191** and TMSOPh. The intramolecular nucleophilic attack produced the 3,4-dihydro pyranones **192** along with the elimination of the phenoxide anion that

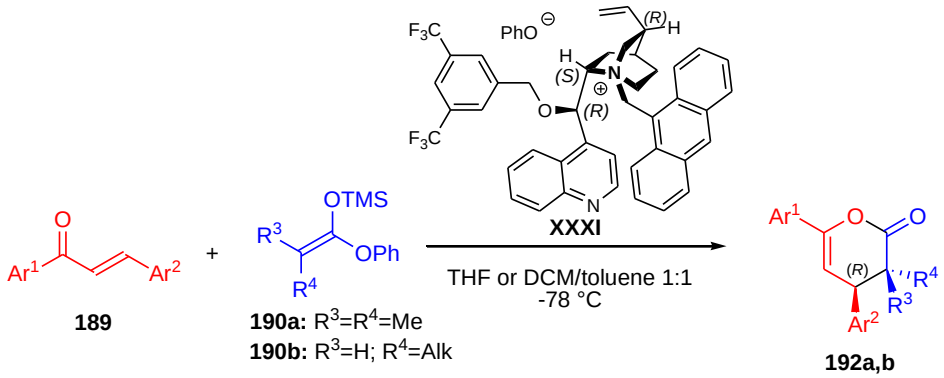
completed the catalytic cycle. Hence, the use of a chiral quaternary ammonium phenoxide should be expected to induce enantioselectivity in an asymmetric synthesis of 3,4-dihydropyran-2-one derivatives.

Scheme 59. Proposed Mechanism for the Phenoxide-ion-catalyzed Domino Michael Addition Lactonization Between α,β-Unsaturated Ketones 189 and Ketene Silyl Acetals 190.[74]



As seen before, cinchona alkaloids have been often employed in asymmetric synthesis of pyran derivatives, and after a deep screening of several cinchona-alkaloid-derived chiral quaternary ammonium phenoxides, the *N,O*-diarylmethylated cinchonidium phenoxide **XXXI** was found to be the most efficient derivative to catalyze the domino Michael addition/lactonization reaction in an enantioselective manner (Scheme 60).[74] The reactions of chalcones **189** with the ketene silyl acetal **190a** derived from phenyl isobutyrate, carried out in THF at -78 °C in the presence of cinchonidium phenoxide **XXXI**, and afforded chiral dihydro-pyrans **192a** with excellent reaction yields and enantioselectivities: in a cluster of reations involving 9 different chalcones the average reaction yield was 96 ± 4%, while the average ee was 90 ± 5% (Table 6, entry 8). When the tandem reaction was run on unsymmetrically substituted ketene silyl acetals **190b** ($R^3 \neq R^4$) a further level of selectivity must be controlled. The reaction of **190b** with **189** prodeeded with high control of the trans-selectivity and with appreciable enantioselectivities. The average reaction yield in 14 different experiment was 95 ± 3%, the de was 97 ± 4%, while the average ee evidenced a good value (85%), but whith a high s.d. (19%), entry 9 in Table 6.

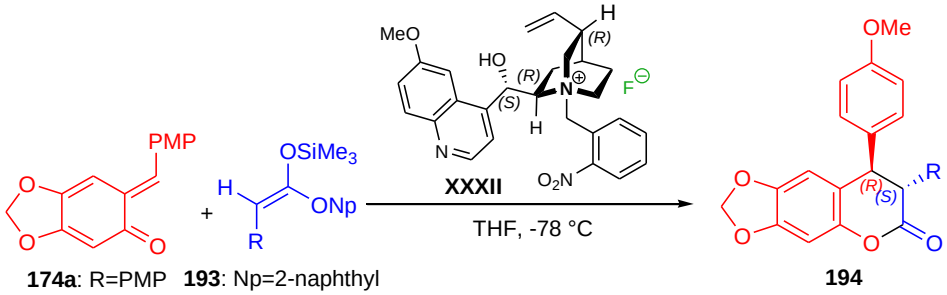
Scheme 60. Asymmetric Cycloaddition Reactions Between 189 with Ketene Silyl Acetals 190a,b Catalyzed by Cinchonidine Derived Catalyst XXXI.[74]



The large s.d. value is due to the low ee's value observed when R^4 has a low steric demand. In these cases, better enantioselectivities were obtained by changing the phenyl group in **190b** with more sterically demanding substituents such as the 2-i.Pr-substituted phenyl ring.

In an analogous manner, the *ortho*-quinone methide **174a** reacted with several silyl ketene acetals **193** in the presence of the quinidinium-derived ammonium fluoride catalyst **XXXII** to produce 3,4-dihydrocoumarin products **194** in excellent yields and good selectivities (Scheme 61).[75] Over 7 different experiments, the average yield was 87 ± 2%, the average de was 84 ± 4%, and the average ee of (3*S*,4*R*)-**194** was 81 ± 5.5%, Table 6, entry 9.

Scheme 61. Asymmetric Cycloaddition Reactions Between 174a with Ketene Silyl Acetals 193 Catalyzed by Quinidium Derived Catalyst XXXII.[75]

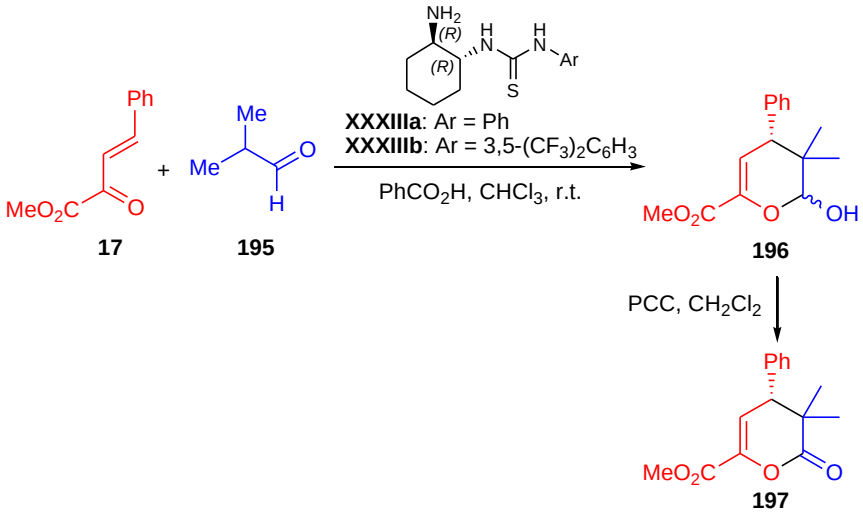


2.1.2.3. Thiourea-derivatives as H-Bonding Organocatalysts

A further category of organocatalysts collects compounds that can activate electrophile by H-bond donor group. Among the most popular compounds thiourea, and squaramide derivatives will be discussed in the present and in the next section.

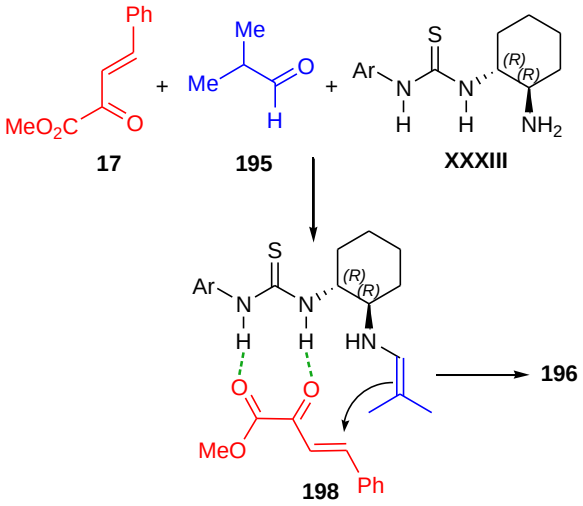
The reaction of isobutyraldehyde **195** with 2-oxo-butenoate **17** was catalyzed by the thiourea-derived organocatalysts **XXXIIIa,b** to give the hemiacetal **196**, which was oxidized by PCC to furnish the enantio-enriched δ-lactone **197** (Scheme 62).[76] Both organocatalysts gave good reaction yields of **197** (71-82%), but **XXXIIIb** induced a better enantioselectivity than **XXXIIIa** (58 and 71% ee, respectively).

Scheme 62. Asymmetric Cycloaddition Reaction Between 17 with Aldehyde 195 Catalyzed by XXXIII.[76]



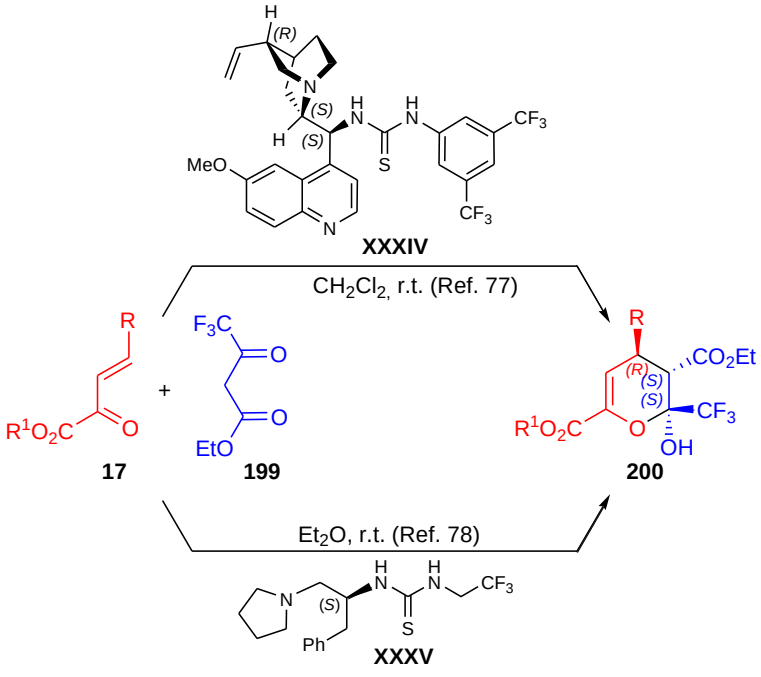
Organocatalysts **XXXIIIa,b** act as bifunctional catalysts: the $–NH_2$ group activates the nucleophile through the classical amino-catalysis above discussed, while the thiourea moiety can interact through a double H-bond with the electrophile **17** (Scheme 63). The H-bond interactions affect the reaction in two co-operative ways: (a) the electrophilicity of the 2-oxo-butenoate **17** is increased, and (b) the pre-organization of the reacting substrates **17** and **195** in intermediate **198** controls the stereochemical outcome of the reaction.

Scheme 63. Proposed Reacting Complex in the Asymmetric Cycloaddition Reactions Between 17 with Aldehyde 195 Catalyzed by XXXIII.[76]



The cascade Michael addition/hemiketalization reactions between α-keto butenoate **17** with trifluoromethyl β-keto esters **199** were developed in an asymmetric fashion by using several organocatalysts. Among them, the quinine-derived thiourea **XXXIV** was found the catalyst of choice to optimize the enantioselective reaction in order to obtain 2,3-dihydro pyrans **200** in excellent yields, diastereo-, and enantioselectivities (Scheme 64).[77]

Scheme 64. Asymmetric Cycloaddition Reactions Between 17 with β-Keto Ester 199 Catalyzed by the Thio-urea Derivatives XXXIV[77] and XXXV[78] as Organocatalysts.

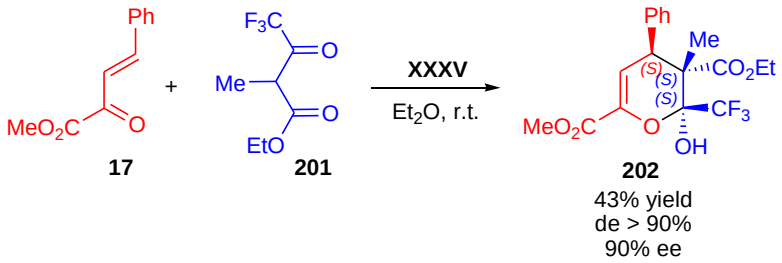


In 13 different experiments the average yield was 87 ± 6%, the average de (referred to the anomeric position) was 94 ± 2%, and the average ee was 94 ± 3% (Table 7, entry 1). The (2*S*,3*S*,4*R*) absolute configuration was tentatively assigned to **200** on the basis of a conformational analysis of the corresponding Mosher esters.[77]

Very similar results were obtained by using **XXXV** as the organocatalyst (Scheme 64), since (2*S*,3*S*,4*R*)-**200** was again obtained in good yields and with excellent enantioselectivities (Table 7, entry 2).[78]

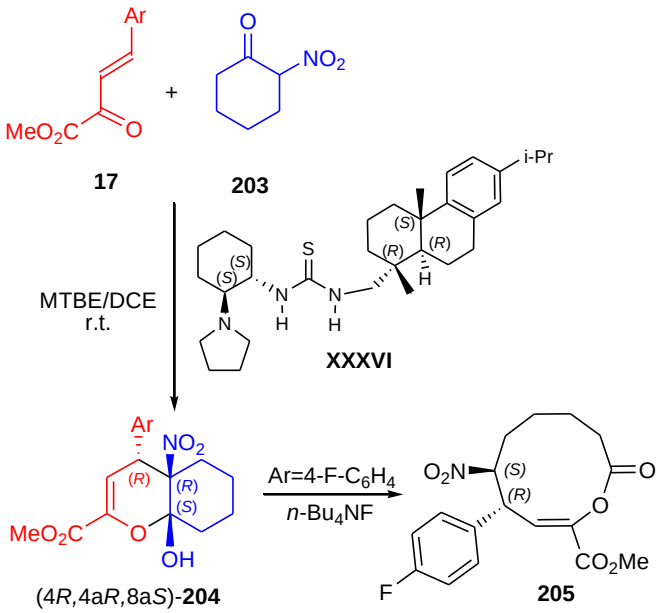
Organocatalyst **XXXV** was also applied in the reaction involving α-methyl-β-keto ester **201** and the adduct **202**, having two contiguous quaternary stereocenters, was obtained in moderate yield, but with an excellent control of the diastereo- and the enantioselectivity (Scheme 65).[78]

Scheme 65. Asymmetric Cycloaddition Reactions Between 17 with α-Methyl-β-keto Ester 201 Catalyzed by Organocatalyst XXXV.[78]



A nice example of asymmetric HDA reaction involves α-nitro-cyclohexanone **203**, as precursor of the 2π component in cycloadditions, with α-oxo-β,γ-unsaturated butenoates **17** to give hexahydro-4*H*-chromene derivatives **204** (Scheme 66).[79] A screening series of rosin-derived tertiary-amine-thiourea derivatives identified **XXXVI** as the bifunctional organocatalyst of choice, which was applied in several reactions under optimized reaction conditions to furnish **204** in good yields, moderate diastereoselectivities, and high enantioselectivities: in 15 different experiments, the average reaction yield was 77 ± 4%, the average de 69 ± 7.5%, and the average ee 91 ± 5%, entry 3 in Table 7. The absolute configuration of **204** was found to be (4*R*,4a*R*,8a*S*) by X-ray crystal analysis.

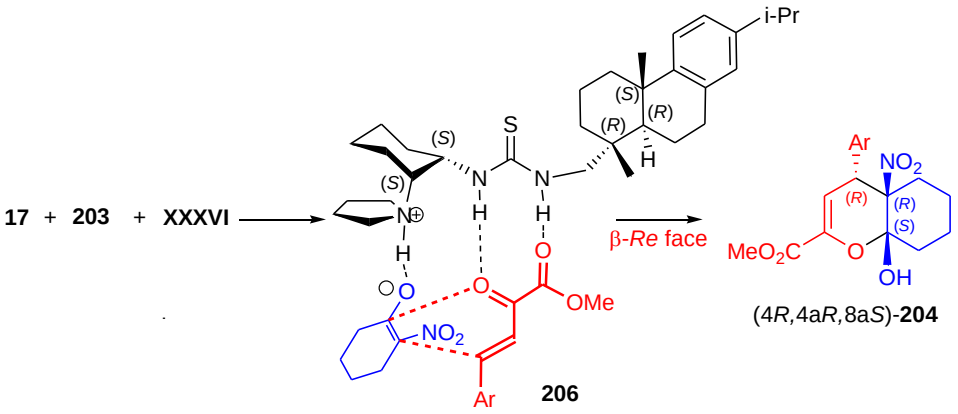
Scheme 66. Asymmetric Cycloaddition Reactions Between 17 with α-Nitro Cyclohexanone 203 Catalyzed by Organocatalyst XXXVI.[79]



The successful construction of the chiral bicyclic skeletons **204** was usefully exploited by their conversion into valuable macrolide derivatives **205** by a retro-Henry-type cleavage with catalytic amounts of TBAF in a single step, and the enantioenriched ten-membered lactones **205** were obtained in appreciable reaction yields.

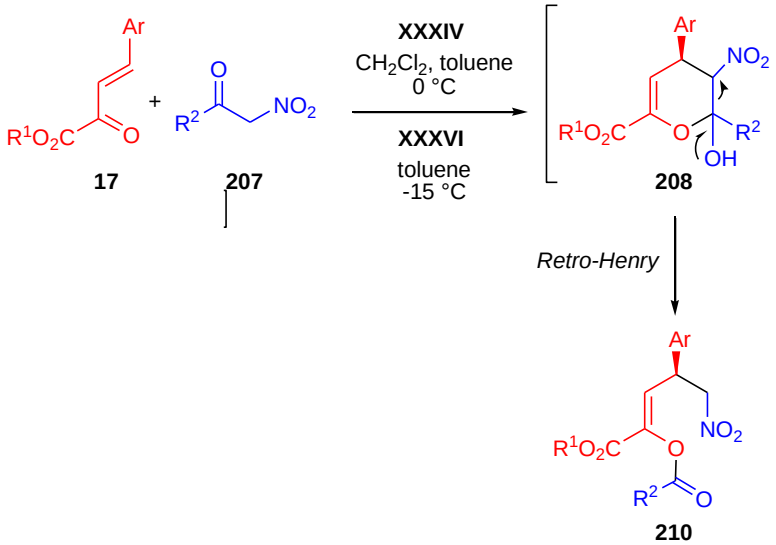
On the basis of the experimental results, a possible bifunctional catalytic mode to account the stereochemical outcome was proposed (Scheme 67). The reacting intermediate complex involves: (i) a LUMO activation of **17** by the H-bond interactions between the thiourea NH groups and the two oxygen atom of the ketonic and the ester groups in **17**; (ii) a HOMO activation of **203** by deprotonation at its α-carbon atom (enolization) by the tertiary amine; (iii) the pre-organization of both the 2π and 4π-component in the reacting intermediate **206** drives the approach of the nucleophile to the β-*Re* face of the coordinated electrophile to furnish cycloadducts **204** with the observed absolute configuration. MS-ESI experiments confirmed the existence of several intermediates involving **XXXVI** and either **17** or **203**, but more important was the evidence for the presence of a ternary intermediate with **XXXVI**, **17**, and **203** in a ratio 1:1:1.[79]

Scheme 67. Proposed Reacting Intermediate Complex in the Asymmetric Cycloaddition Between 17 with α-Nitro Cyclohexanone 203 Catalyzed by Organocatalyst XXXVI.[79]



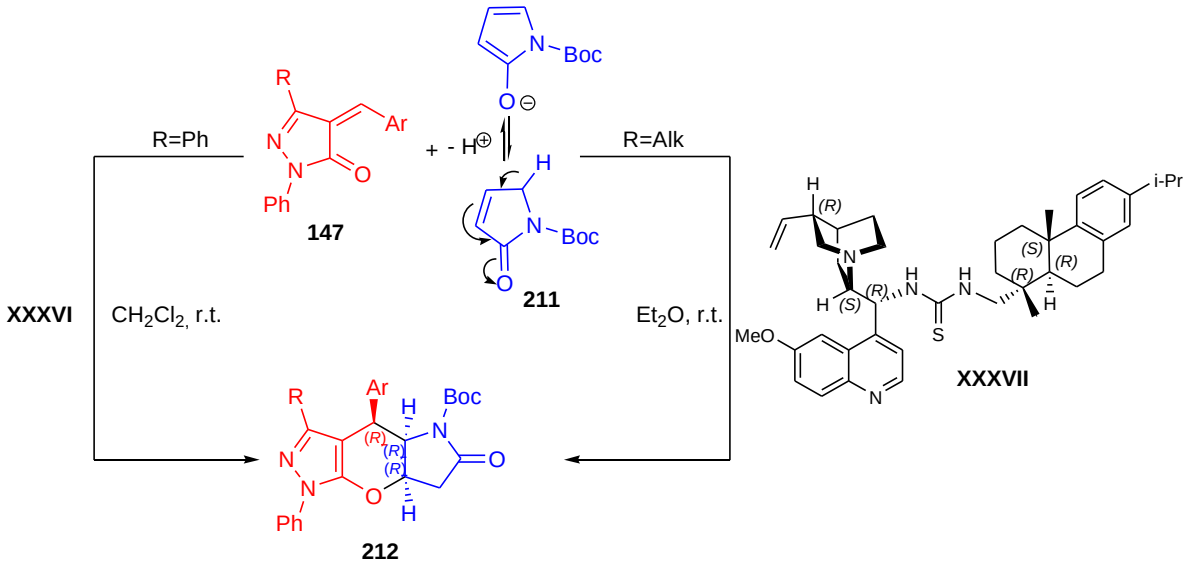
When the α-nitro ketone is an acyclic derivative (**207**), then the dyhydropyran **208** become unstable and is directly opened to enantioenriched 5-nitro-pentenoate through a retro-Henry reaction (Scheme 68).[80-83] The best organocatalysts were **XXXIV** and **XXXVI** which allowed to obtain the final valuable synthons **210** with up to 99% yields with excellent enantioselectivities (in many examples ee > 99%).

Scheme 68. Asymmetric Cycloaddition Reactions Between 17 with α-Nitro Ketones 207 Catalyzed by Organocatalysts XXXIV and XXXVI.[80-83]



The same organocatalyst **XXXVI** was found to catalyze the HDA reaction between pyrazolone derivatives **147** (R = Ph) with butyrolactams **211** to give tricyclic adducts **212** (Scheme 69). The reaction proceeds with good yields and high diastereo- and enantioselectivities (Table 7, entry 4), and the organocatalyst act through the same mechanism above described: LUMO activation of **147** by H-bond; HOMO activation of **211** by deprotonation.

Scheme 69. Asymmetric Cycloaddition Reactions Between 147 with 211 Catalyzed by Organocatalysts XXXVI and XXXVII.[84]

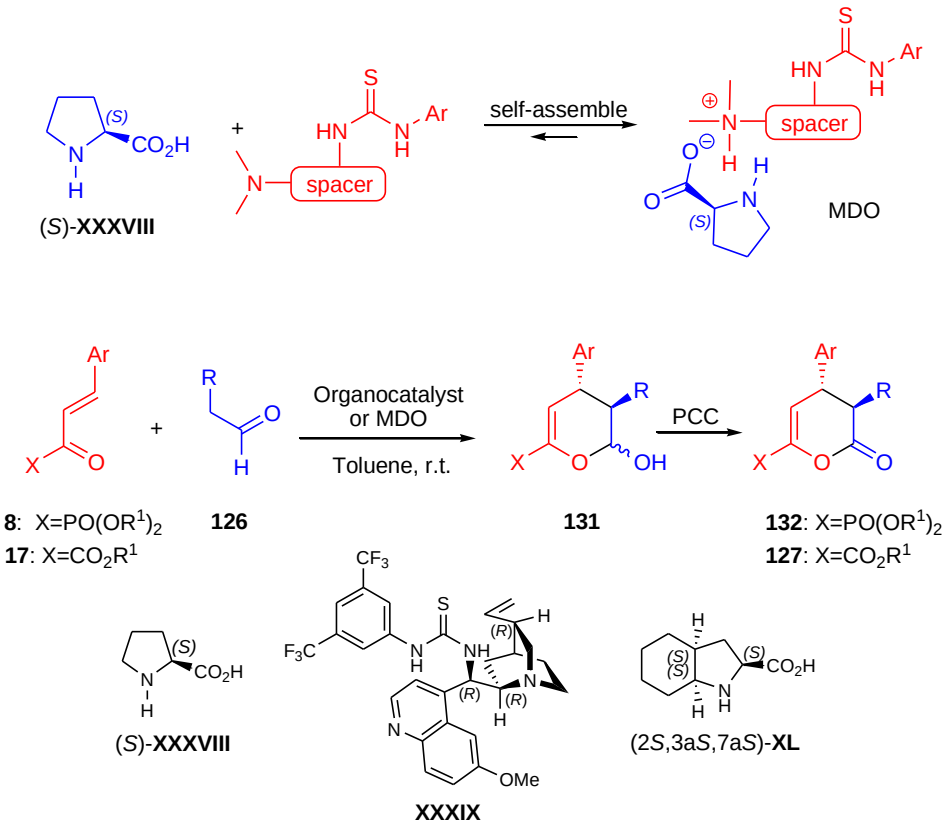


If the pyrazolone derivatives has an alkyl group as the substituent in the 3-position (**147**, R=Alk), then the more efficient organocatalyst was the quinine-thiourea derivative **XXXVII** that gave the corresponding adducts **212** within moderate yields, but with excellent diastereo- and enantioselectivities (Table 3, entry 5).[84]

In the last examples, the organocatalyst acted as a bi-functional catalyst able to activate both the nucleophilic and the electrophilic component involved in the cycloaddition. An original approach to optimize the enantioselectivity obtainable by the use of organocatalysts was the so-called modularly designed organocatalysts (MDOs) through the self-assembly of amino-acids (fragment activating the nucleophile) and thiourea derivatives of cinchona alkaloids (fragment activating the electrophile) by ionic interactions. Compared to conventional organocatalysts, the

structure of self-assembled organocatalysts is easy to modify and allows a simple and convenient access to large catalyst library of self-assembled organocatalysts for high-throughput screenings. Scheme 70 exemplifies the MDOs approach.[85] The formation of MDO from the precatalyst molecules has been confirmed by ^{1}H NMR and NOESY experiments and by HRMS studies.

Scheme 70. Formation of MDOs Through Self-assembly and Asymmetric Cycloaddition Reactions Between 17 or 8 with Aldehydes 126 Catalyzed by MDO from XXXIX and XL.[85]



The HDA reaction between aldehydes **126** with either oxo-butenoates **17** or keto-phosphonates **8** was catalyzed by the proline derivatives (*S*)-**XX** and (*S*)-**XXI** in the presence of MS (or of an acidic additive). When **17** was allowed to react with aldehydes **126** in the presence of either (*S*)-proline **XXXVIII** or the quinidine thiourea derivative **XXXIX** in toluene without MS the reaction do not proceed and negligible amounts of **131** were evidenced (Scheme 70).[85]

On the contrary, when the reaction between **8** and **126** was run in the presence of both (*S*)-**XXXVIII** and **XXXIX** (10 mol % loading each) for prolonged reaction time, the cycloadduct **131** (X=CO_2Me, Ar=Ph, R=Me) was isolated in 92% yield as a 4:1 mixture of the two anomers. The mixture was directly oxidized to give the dihydropyranone **127** as a single trans diastereomer in 90% ee. This result is an unequivocal demonstration that the MDO of **XXXVIII** and **XXXIX** is much superior to the individual precatalyst modules. MDOs derived from other thiourea-quinidine derivatives or other amino acids combination were screened evidencing that **XXXIX** was the best quinidinic component and (2*S*,3a*S*,7a*S*)-octahydro-1*H*-indole-2-carboxylic acid **XL** the best amino acidic additive. This MDO was then applied under optimized reaction conditions to several cycloadditions involving either **8** or **17** as heterodienes and aldehydes **126** as the nucleophilic counterpart (the mechanism of the catalytic cycle has been already discussed in Scheme 39). Both reactions proceeded with very good yields and excellent enantioselectivities over a large number of experiments (Table 7, entry 6 for **17** and entry 7 for **8**). The diastereomeric excess of the anomeric mixture was good for the reaction of **17**, low for that involving **8**; in any case, the oxidation step to give the corresponding lactones overwhelmed the low diastereoselectivity.

2.1.2.4. Squaric Acid Derivatives as H-Bonding Organocatalysts

As seen for the thiourea-based organocatalysts, also the squaric acid derivatives are bifunctional organocatalysts able to activate the electrophilic component by H-bond, and the nucleophilic counterpart by either amino-catalysis or by deprotonation with the suitably placed tertiary amine.

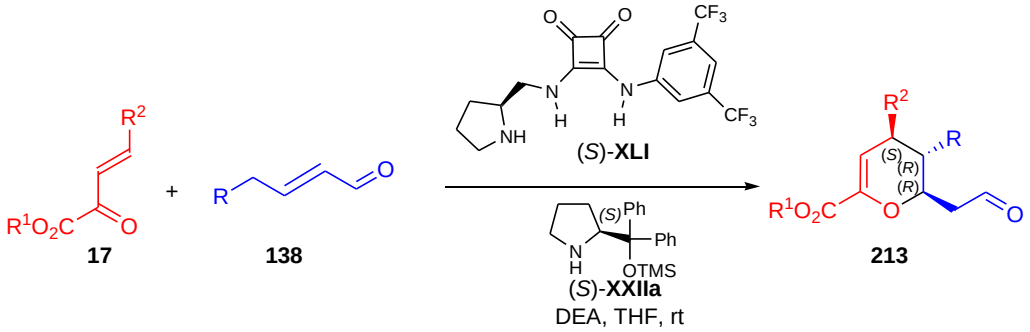
The sinergestic effect deriving from the contextual activation of both the reactants is clearly evidenced by the example in Scheme 71, in which the reaction of β,γ-unsaturated α-keto esters **17** with α,β-unsaturated aldehydes **138** was run in the presence of either the proline derivative (*S*)-**XXIIa** or the proline-derived squaric acid (*S*)-**XLI**.[86]

Table 7. Average Values and Standard Deviations (s.d.) of the Reaction Yields, Diastereo-, and Enantioselectivities in the Synthesis of Dihydropyrans by [4+2] Cyclization Processes Catalyzed by Thiourea- and Squaric Acid Derivatives as H-bonding Organocatalysts.

Entry	Heterodiene	Dienophile	Catalyst	n. Exp.	aver. Yield % (s.d.)	aver. de (s.d.)	Reaction Product	aver. ee % (s.d.)	Ref.
1	**17**	**199**	**XXXIV**	13	87 (6)	94 (2)[a]	(2*S*,3*S*,4*R*)-**200**	94 (3)	77
2	**17**	**199**	**XXXV**	12	78 (8)	>90[a]	(2*S*,3*S*,4*R*)-**200**	95 (3)	78
3	**17**	**203**	**XXXVI**	15	77 (4)	69 (7.5)[a]	(4*R*,4a*R*,8a*S*)-**204**	91 (5)	79
4	**147**	**211**	**XXXVI**	10	81 (7)	>91 (---)	**212**	89 (12)	84
5	**147**	**211**	**XXXVII**	10	63 (4)	>91 (---)	**212**	92 (4)	84
6	**17**	**126**	**XXXIX+XL**	13	90 (6)	71 (10)[a]	(3*R*,4*S*)-**127**	94 (2)	85
7	**8**	**126**	**XXXIX+XL**	6	93 (6)	29 (10)[a]	(3*R*,4*S*)-**132**	91 (4)	85
8	**17**	**138**	(*S*)-**XLI**	18	66 (11)	79 (10)	(2*R*,3*R*,4*S*)-**213**	87 (5)	86
9	**8**	**138**	(*S*)-**XLI**	19	73 (9)	79 (7)	(2*R*,3*R*,4*S*)-**219**	88 (4)	87
10	**17**	**186**	**XLII**	14	78 (10)	93 (9)	(1*R*,5*S*,6*S*)-**220**	92 (13)	88
11	**221**	**222**	**XLIII**	11	78 (4)	---	**223**	92 (4)	89

[a] The average de refers to the anomeric ratio.

Scheme 71. Asymmetric Cycloaddition Reactions Between 17 with α,β-Unsaturated Aldehydes 138 Catalyzed by Organocatalysts (*S*)-XLI or (*S*)-XXIIa.[86]

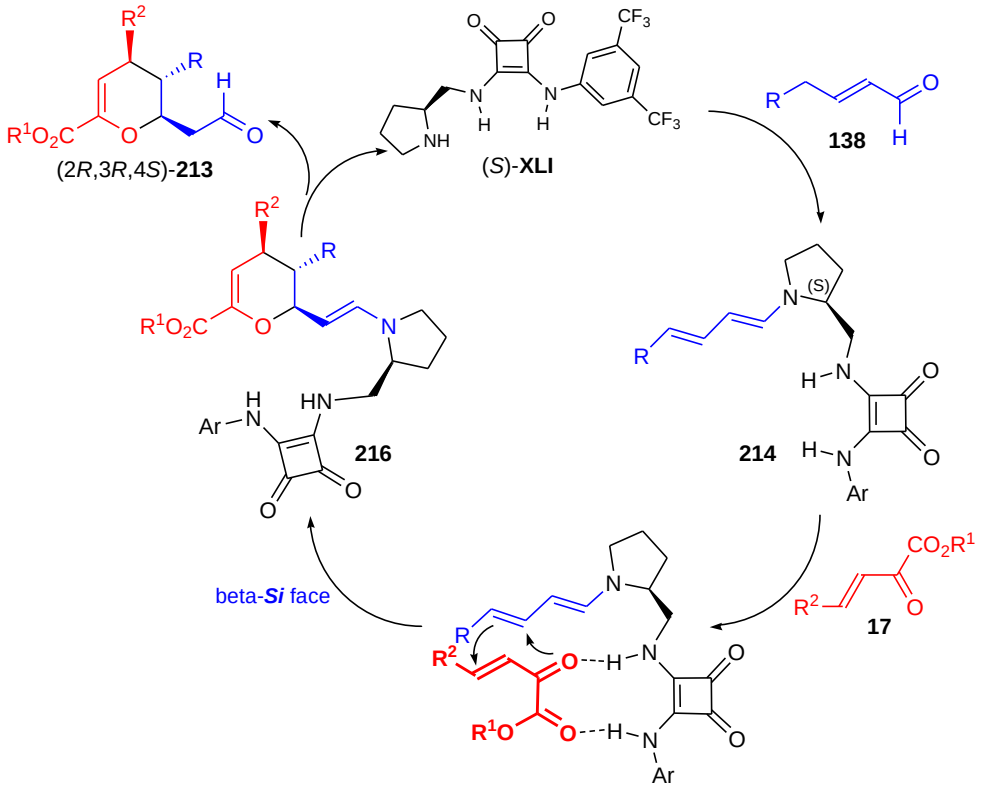


Both organocatalysts promoted the HDA cycloaddition between **17** and **138**, since the reaction yields were very high (>90%), while the diastereoselectivity was appreciable. When the enantioselectivity was considered, the steric shielding catalyst (*S*)-**XXIIa** gave unsatisfactory results (25% ee), while the H-bond directing catalysts (*S*)-**XLI** gave more promising results (78% ee). Hence, after optimization of the reaction conditions, this latter catalyst was used in several different experiments giving rise to the formation of **213** within moderate to good yields (the average value in 18 different experiments is 66 ± 11%), discrete diastereoselectivity (average de = 79 ± 10%), and very good enantioselectivity (average ee = 87 ± 5%), see entry 8 in Table 7.

The absolute configuration of the products was unambiguously assigned by single-crystal X-ray analysis. To rationalize the stereochemical outcome, a transition state model was proposed, and the reaction mechanism involved the initial condensation of the aminocatalyst **XLI** with the α,β-unsaturated aldehyde, followed by deprotonation/isomerization, to give the corresponding dienamine intermediate **214** (Scheme 72). Subsequently, the heterodiene **17**, reacting in its s-trans conformation, is recognized by the squaramide moiety of the catalyst through H-bonding interactions. In such a manner, the two reagents become independently activated (the α,β-unsaturated aldehyde through HOMO activation and the β,γ-unsaturated α-ketoester through LUMO lowering), and positioned in close spatial proximity, with the enone system overlapping the remote enamine double bond, which attacks the β-*Si* face of the coordinated **17** to give intermediate **216** that, after

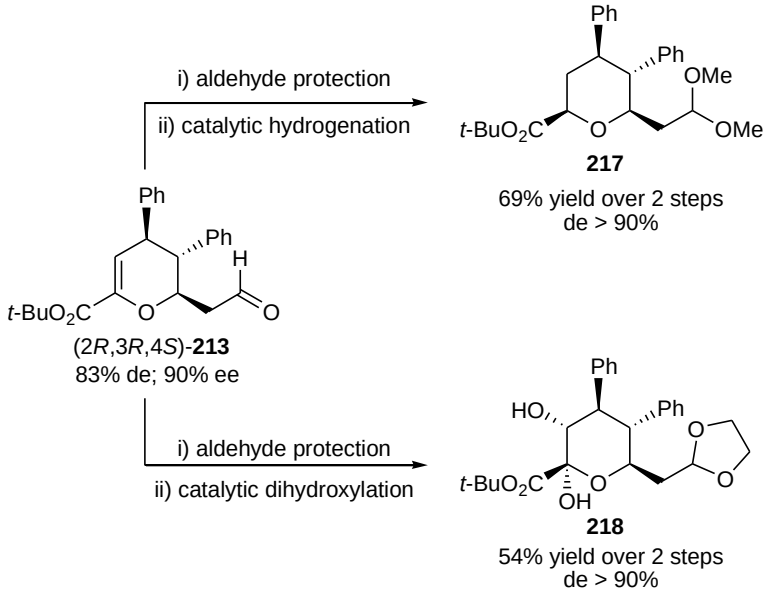
hydrolysis give rise to the organocatalyst and the reaction product (2*R*,3*R*,4*S*)-**213**. Taking into account the observed diastereoselectivity, a step-wise mechanism of the [4+2] cycloaddition can be assumed.

Scheme 72. Proposed Mechanism for the Asymmetric Cycloaddition Reactions Between 17 with α,β-Unsaturated Aldehydes 138 Catalyzed by (*S*)-XLI.[86]



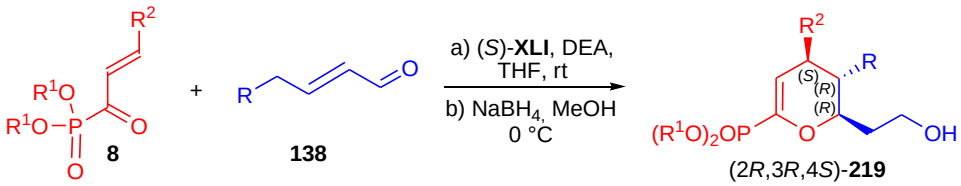
The chiral dihydropyran framework was the starting product for the construction of more elaborated derivatives having with up to five contiguous stereocenters (Scheme 73). The stereoselective functionalization of the olefinic moiety in adduct **213** required the preventive protection of the aldehyde group as cyclic or acyclic acetal. Then the catalytic hydrogenation by using H_2/Pd furnishes the tetrahydro pyran derivative **217** as a single isomer. The diastereoselective dihydroxylation by using catalytic amounts of $K_2OsO_2(OH)_4$ was also performed, and the tetrahydropyran **218**, containing five contiguous stereocenters, was obtained as a single diastereoisomer. Remarkably, a hemiacetal quaternary stereocenter was also introduced (Scheme 73).[86]

Scheme 73. Diastereoselective Transformations of HDA Adducts 213 to Optically Active Tetrahydropyrans 217 and 218.[86]



Analogous results were obtained by using as heterodienes the corresponding keto-phosphonates derivatives **8**.[87] Following the same catalytic cycle depicted in Scheme 72, the organocatalyst (*S*)-**XLI** activated the [4+2] cyclization between **8** and **138** to give the corresponding cycloadducts that were directly submitted to $NaBH_4$ reduction to furnish the corresponding carbinols **219** (Scheme 74).[87] The final products were obtained in good yields, good diastereoselectivities, and high enantioselectivities (Table 7, entry 9). As in the previous example, also in this case the synthetic utility of the reaction was demonstrated by further stereoselective elaborations of the cycloadducts into valuable and complex synthons.

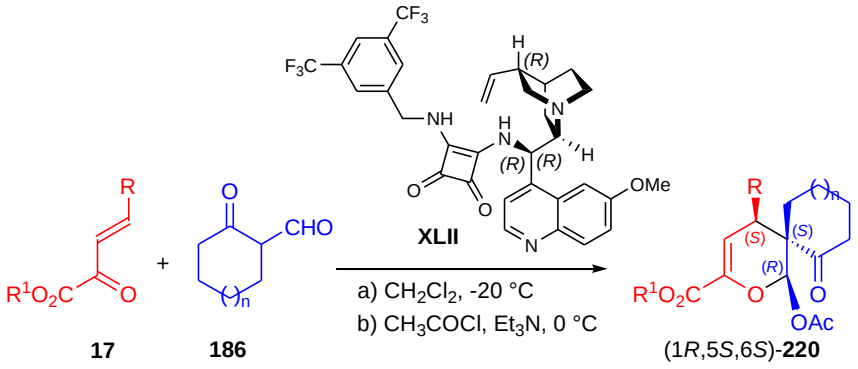
Scheme 74. Asymmetric Cycloaddition Reactions Between 8 with α,β-Unsaturated Aldehydes 138 Catalyzed by (*S*)-XLI.[87]



The bifunctional organocatalysts containing the squaramide moiety (electrophile activation) and the quinine component (nucleophile activation) were proposed as useful organocatalysts in [4+2] cyclization processes involving 1,3-dicarbonyl derivatives as nucleophiles.[88,89]

The spiroannulation of cyclic β-oxo-aldehydes **186** has been described in Scheme 58, and involved aromatic substituted β,γ-unsaturated α-keto esters [$(DHQD)_2Pyr$ **XXX** was the organocatalyst of choice]. The reaction involving aliphatic unsaturated α-keto esters as the electrophilic reagent was efficiently catalyzed by chiral amino-squaramides to give, after acetylation of the primary adducts, spiro-3,4-dihydropyran derivatives **220** bearing three contiguous stereocenters (Scheme 75).[88] The use of the thiourea-quinine derivative **XXXIX** as the organocatalyst was unsatisfactory because the selectivities were excellent (**220** was obtained with 98% de and 97% ee), but the reaction yield was too low to be acceptable (17% yield). The change of the thiourea fragment with the squaramide unit increased the reactivity and maintained the high selectivities. Hence **XLII** was the organocatalyst of choice for the spiroannulation reaction, and over 14 different experiments, the average yield was good, while diastereo- and enantioselectivities were excellent (Table 7, entry 10).

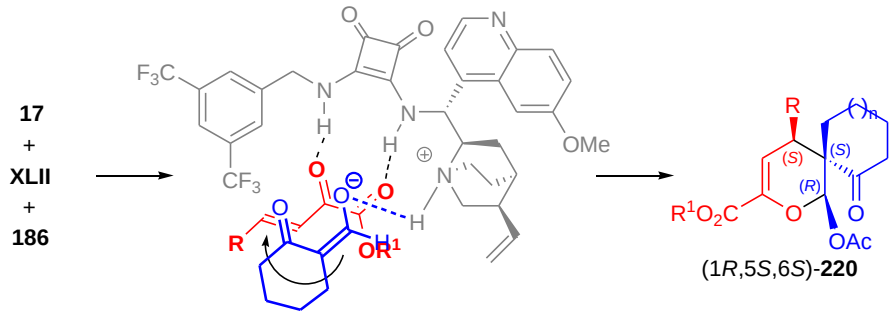
Scheme 75. Asymmetric Cycloaddition Reactions Between 17 with β-Oxo-aldehydes 186 Catalyzed by XLII.[88]



The absolute configuration of the spiroannulated products **220** as depicted in Scheme 75 was determined by X-ray crystallographic analysis. A possible reacting intermediate was then proposed (Scheme 76), in which the simultaneously activation of both the electrophile **17** and the nucleophile

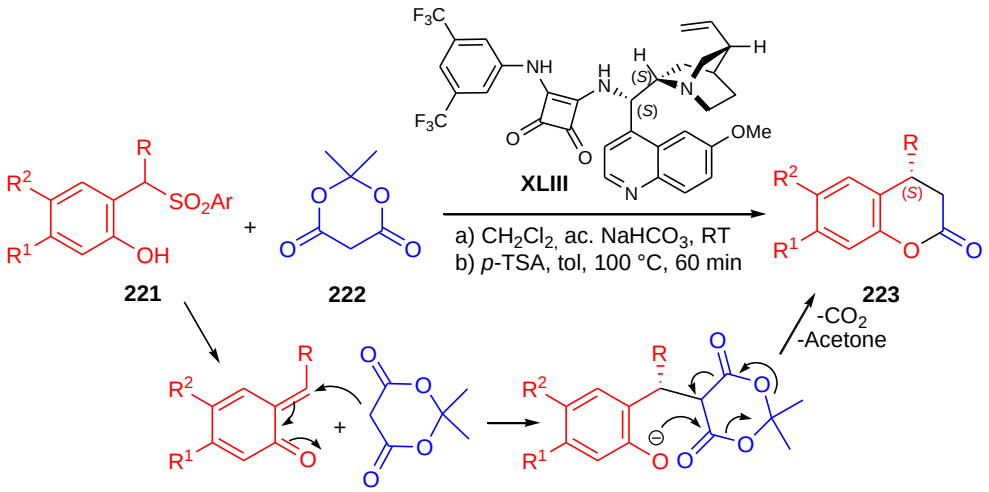
186 takes place. The approach of the nucleophile to the electrophile **17** *Si*-face furnishes the spiroannulated product with the observed absolute stereochemistry.

Scheme 76. Proposed Model of Interaction in the Asymmetric Cycloaddition Reaction Between 17 with β-Oxo-aldehydes 186 Catalyzed by (3*R*,8*R*,9*R*)-XLII.[88]



The last example of this section concerns the in-situ formation of *ortho*-quinone methides from 2-sulfonylalkyl phenols **221** through base-promoted elimination of sulfinic acid. The higly reactive intermediate is captured by Meldrum's acid **222** to give an intermediate that give rise to an intramolecular nucleophilic substitution followed by elimination of CO_2 and acetone to furnish the benzopyran derivatives **223** (Scheme 77).[89] The method was applied in the reaction of several sulfonylalkyl phenols **221**, and in 11 different experiments the average yield was very good (78 ± 4%) and the average ee excellent (92 ± 4%), entry 11 in Table 7.

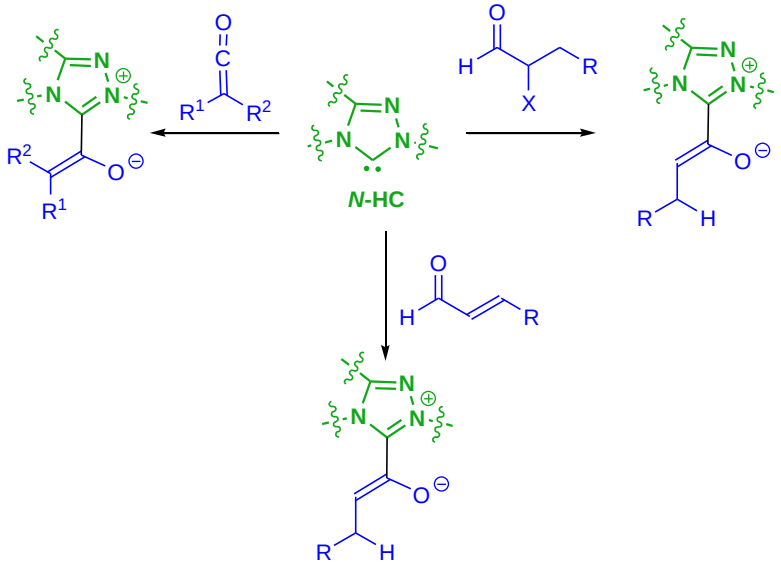
Scheme 77. Asymmetric Cycloaddition Reactions Between 221 with Meldrum's Acid 222 Catalyzed by XLIII.[89]



2.1.2.5. N-Heterocyclic Carbenes (N-HC) as Organocatalysts

The great development in enantioselective catalysis within fifteen years changed *N*-heterocyclic carbenes (*N*HC) from a curiosity to a simple, flexible, and precious catalyst for many synthetic preparations of chiral products. The field has periodically been reviewed, and the most recent reports appeared in 2007[90] and in 2015.[91] This latter, for its comprehensiveness, gives a complete and exhaustive panorama of the field. For this reason, a deep discussion of the theme will be avoided, being focused on the topic of the present review. Hence, the following discussion will concern the use of *N*-HC organocatalysts in the [4+2] cycloadditions involving either ketenes, α-substituted aldehydes, or α,β-unsaturated aldehydes as the 2π components in the synthesis of chiral δ-lactones (Scheme 78), which will be presented in this order.

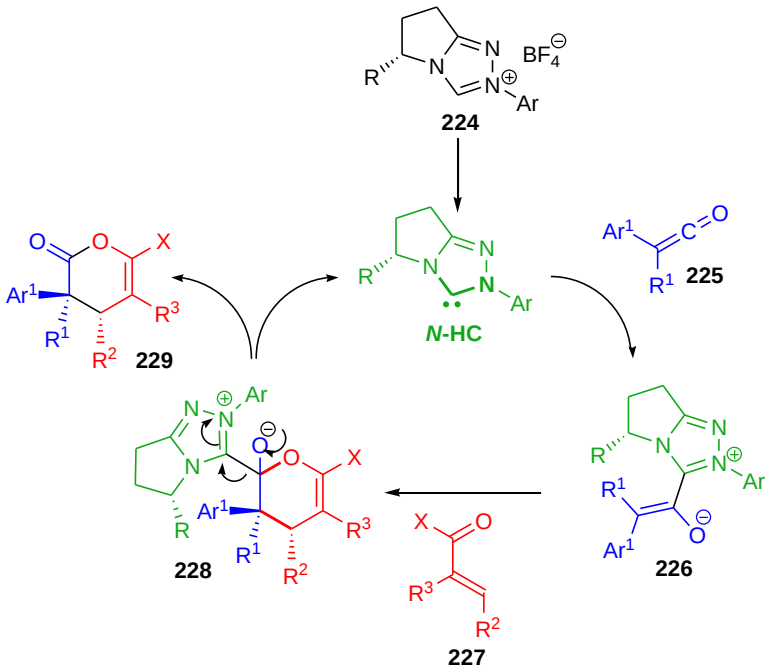
Scheme 78. Schematic Representation of the *N*-HC Organocatalyst Interaction with Either Ketenes or Aldehyde Derivatives as 2π Components in [4+2] Cycloaddition.



2.1.2.5.a. N-HC as Organocatalyst of Cycloadditions Between Enones and Ketenes

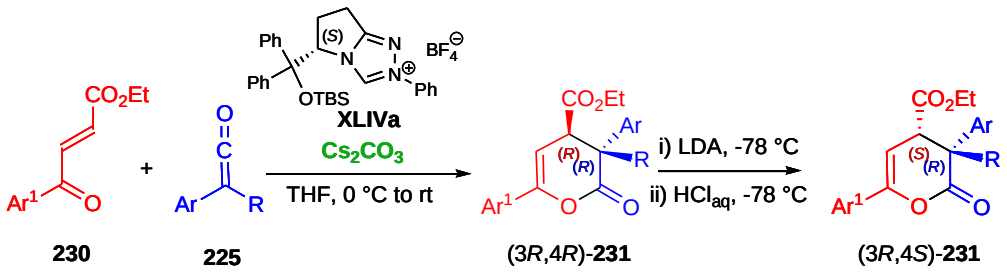
The *N*-HC catalysed reactions generate the active carbene in situ by deprotonation of the corresponding azolium salt **224**. The nucleophilic addition of *N*-HC to alkyl-aryl-substituted ketenes **225** furnishes the azolium enolates **226** that react as dienophiles in [4+2] cycloaddition reactions with electron-poor heterodiene **227** to produce 2,3-dihydropyranones **229** (Scheme 79).

Scheme 79. Catalytic Cycle of the *N*-HC Catalyzed Cycloaddition Involving Ketenes 225.



Chiral *N*-HC precursor **XLIVa**, easily prepared from L-pyroglutamic acid, was employed under optimized reaction conditions in the cycloaddition between aryl(alkyl) ketenes **225** with enones **230** to give δ-lactones **231** with α-quaternary-β-tertiary stereocenters (Scheme 80).[92] An excess of Cs_2CO_3 respect **XLIVa** is required to avoid drops in stereoselectivities due to cycloadduct epimerization, with a temperature in going from 0 °C (during the slow ketene addition) to ambient temperature. Under these optimized conditions a series of ketones was allowed to react and in 11 different experiments the average yield was good with a high level of control of both the diastereo- and the enantioselectivity (Table 8, entry 1).

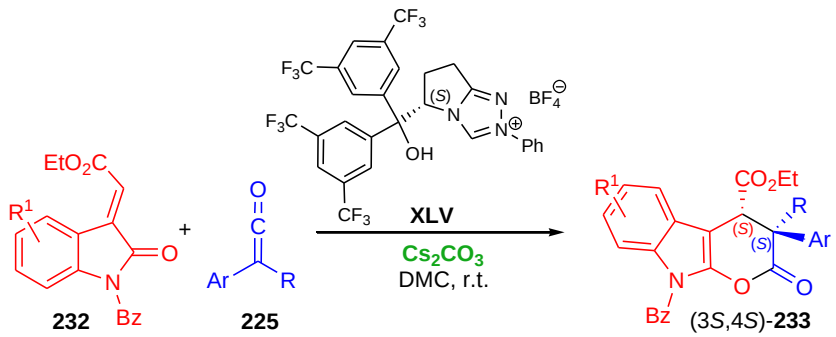
Scheme 80. Asymmetric Cycloaddition Reactions Between 230 with Ketenes 225 Catalyzed by (*S*)-XLIVa.[92]



The reaction follows the mechanism described in Scheme 79 and can be successfully run by generating in situ the ketenes by elimination from the corresponding acyl chlorides. Furthermore, the epimer (3*R*,4*S*)-**231** has been obtained by deprotonation of (3*R*,4*R*)-**231**, followed by kinetically controlled protonation of the resulting carbanion.

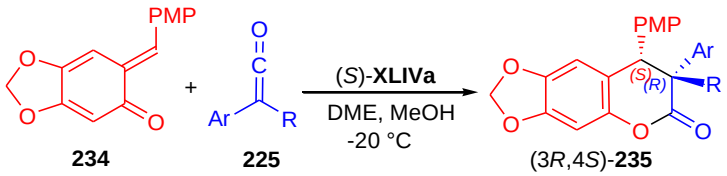
The chiral *N*-HC organocatalyst (*S*)-**XLV** was the catalyst of choice in the formal [4+2] cycloaddition between 3-alkenoyl-oxindoles **232** with alkyl(aryl)ketenes **225** to give 3,4-dihydropyrano[2,3-*b*]indol-2-ones **233** in excellent yields, and with good diastereo- and enantioselectivities (Scheme 81):[93] Over 10 different experiments, the average yield was 94 ± 4%, the average de 73 ± 9%, and the average ee 83 ± 7% (Table 8, entry 2). Respect to the previous example in Scheme 80, it is remarkable to observe that the use of the free OH organocatalyst **XLV**, instead of the TMS-protected one, leads to obtain the cycloadducts with the opposite absolute configuration, pointing out the possible role of steric vs H-bonding interactions giving rise to opposite stereochemical outcomes.

Scheme 81. Asymmetric Cycloaddition Reactions Between 232 with Ketenes 225 Catalyzed by (*S*)-XLV.[93]



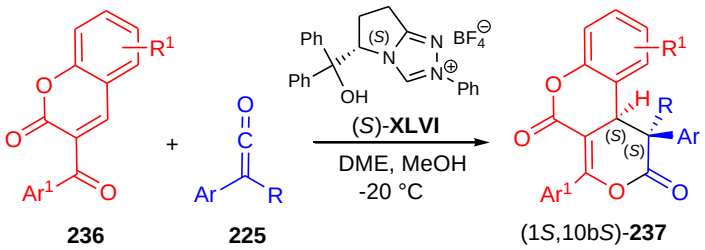
N-HC (*S*)-**XLIVa** was the organocatalyst of choice in the formal [4+2] cycloaddition reaction between ketenes **225** and *o*-quinone methide **234** also (Scheme 82).[94] The adducts **235** were obtained with good yields; the diastereoselectivity was only moderate, while the enantioselectivity was more appreciable (Table 8, entry 3). Both selectivity and reactivity dropped when the aromatic substituent on ketene **225** was substituted in its *ortho* position.

Scheme 82. Asymmetric Cycloaddition Reactions Between 234 with Ketenes 225 Catalyzed by (*S*)-XLIVa.[94]



The non-protected *N*-HC organocatalyst (*S*)-**XLVI** was an efficient catalyst in the [4+2] cyclization between alkyl(aryl) ketenes **225** with 3-aroyl-coumarins **236** to furnish the dihydropyrano[3,4-*c*]chromene derivatives **237** (Scheme 83).[95] Over 16 different experiments, the reaction yields were very good, as well as the diastereo- and the enantioselectivity (Table 8, entry 4). Also in this case, ketenes with an *o*-substituted aromatic group gave negligible yields of cycloadducts.

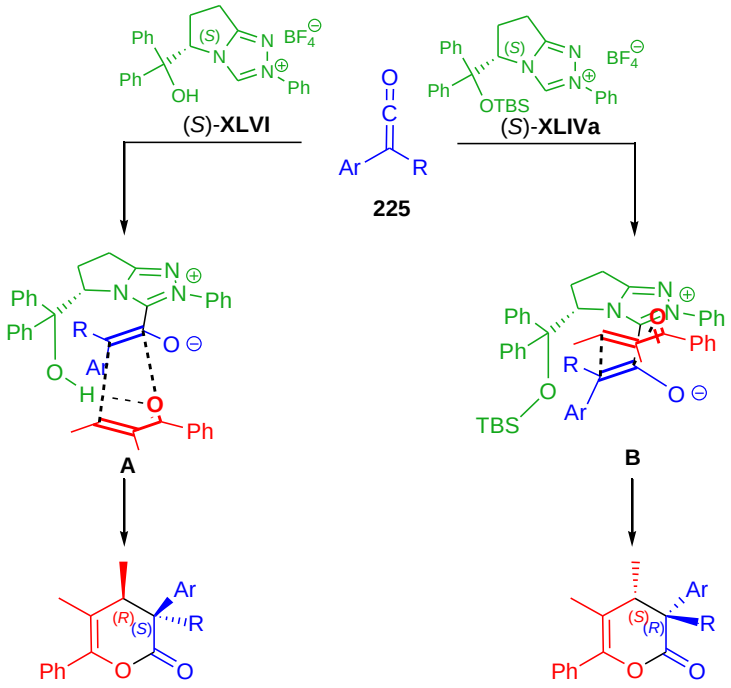
Scheme 83. Asymmetric Cycloaddition Reactions Between 236 with Ketenes 225 Catalyzed by (*S*)-XLVI.[95]



The absolute configurations of adducts **235** and **237** were determined by X-ray analysis. The use of a chiral *N*-HC catalyst bearing the OH group protected as silyl ether determined a change of the favoured approached face of the reacting nucleophile respect to the case involving the catalyst with a free –OH group. As represented in Scheme 84, the proposed stereochemical model in the reaction catalysed by (*S*)-**XLIV** and (*S*)-**XLVI** involved that the enolated generated by addition of the *N*-HC to ketene favors its *Z*-isomer, which minimizes the steric repulsion. Then, in the case of **XLVI**, the possibility to bind by H-bond the carbonyl oxygen atom determines the observed facial

selectivity through an approach like **A**. When the H-bond is not possible, as in the case of **XLIV**, the approach of the heterodiene is on the less hindered face of the nucleophile (model **B**).

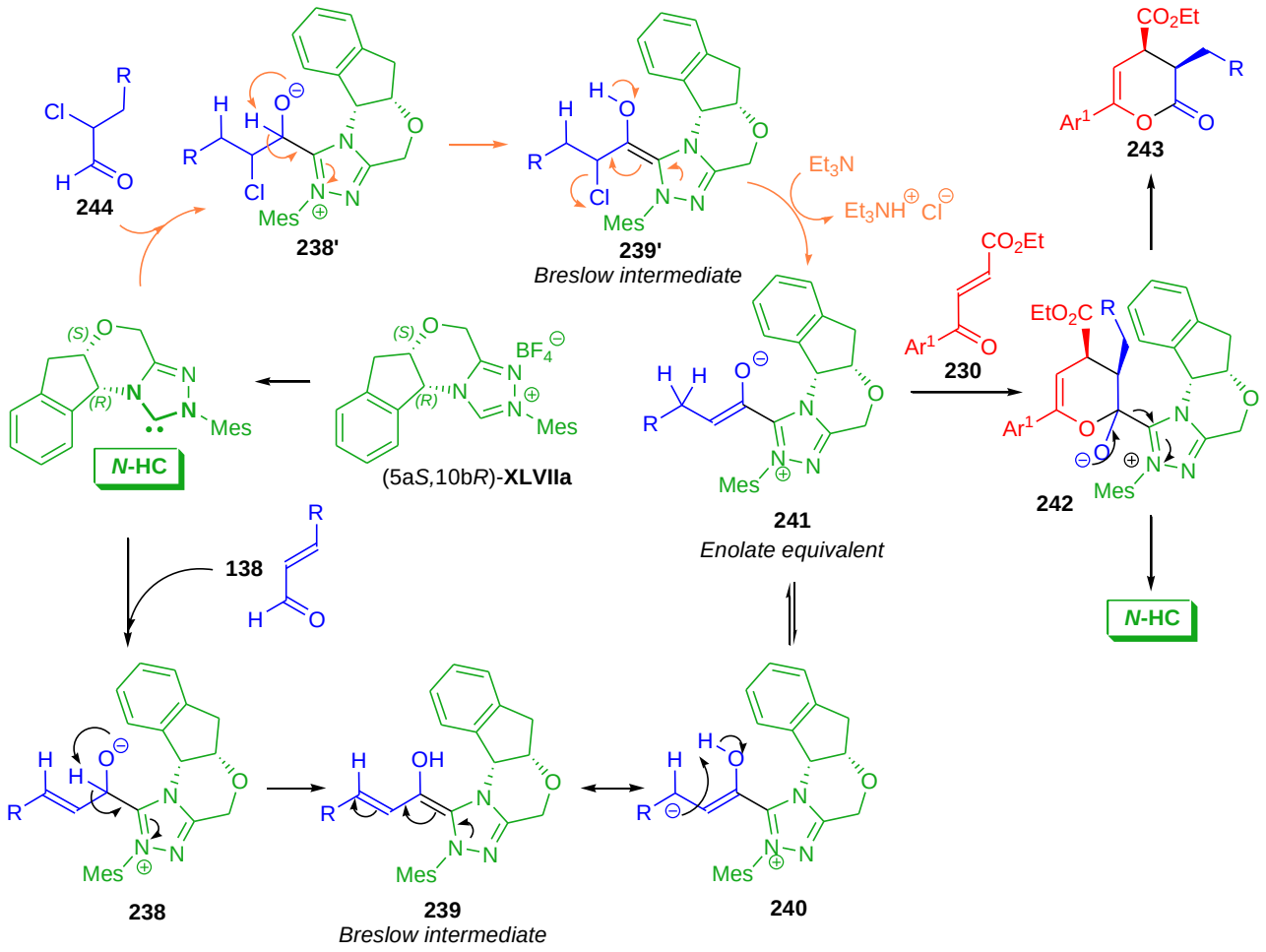
Scheme 84. Proposed Stereochemical Models to Rationalize the Stereochemical Outcome in the Asymmetric Cycloaddition Reactions Involving (*S*)-XLIV and (*S*)-XLVI as the Organocatalysts.[94,95]



2.1.2.5.b. N-HC as Organocatalysts of Cycloadditions Between Enones and Enals (or α-Substituted Aldehydes)

α,β-Unsaturated aldehydes have a peculiar reactivity compared to aromatic or aliphatic analogues since the typically electrophilic C=C double bond can acquire a nucleophilic character so becoming a useful 2π component in [4+2] cycloaddition reactions with electron-poor heterodienes. The general mechanism for this transformation is depicted in Scheme 85. The free carbene *N*-HC derived from **XLVIIa** adds in a 1,2-fashion to unsaturated aldehydes **138** to produce the tetrahedral intermediate **238**, which undergoes a proton transfer to form the Breslow intermediate **239**, the so-called *homoenolate* equivalent. This latter is in resonance with the carbanion **240**, which give rise to a proton transfer to form the *enolate equivalent* **241**.

Scheme 85. Catalytic Cycle of the *N*-HC Catalyzed Cycloaddition Involving Either α,β-Unsaturated Aldehydes 138 or α-Chloro Aldehydes 244.[90]



Then, the intermediate **241** is attached by the heterodienes **230** to its less hindered face to give the adducts **242** that eliminated the *N*-HC organocatalyst to produce the pyranone derivatives **243**.

In an analogous manner, the free carbene performs a nucleophilic attack on α-chloro substituted aldehydes (or aldehyhes bearing in the α-position a good leaving group) **244**, leading to the formation of the chlorinated Breslow intermediate **239′** through proton transfer on the addition product **238′**. Subsequent HCl elimination produces the enolate equivalent **241** that completes the catalytic cycle as previously described (Scheme 85).

Table 8. Average Values and Standard Deviations (s.d.) of the Reaction Yields, Diastereo-, and Enantioselectivities in the Synthesis of Dihydropyrans by Intermolecular [4+2] Cyclization Processes Catalyzed by *N*-HC Organocatalysts.

Entry	Heterodiene	Dienophile	Catalyst	n. Exp.	aver. Yield % (s.d.)	aver. de (s.d.)	Reaction Product	aver. ee % (s.d.)	Ref.
1	**230**	**225**	(*S*)-**XLIVa**	11	74 (10)	92 (3)	(3*R*,4*R*)-**231**	90 (2)	92
2	**232**	**225**	(*S*)-**XLV**	10	94 (4)	73 (9)	(3*S*,4*S*)-**233**	83 (7)	93
3	**234**	**225**	(*S*)-**XLIVa**	8	88 (10)	66 (15)	(3*R*,4*S*)-**235**	92 (17)	94
4	**236**	**225**	(*S*)-**XLVI**	16	84 (4)	80 (13)	(1*S*,10b*S*)-**237**	79 (16)	95
5	**17**	**244**	(5a*R*,10b*S*)-**XLVIIa**	5	79 (7)	>98 (---)	(3*S*,4*S*)-**127**	97 (2)	97
6	**230**	**244**	(5a*R*,10b*S*)-**XLVIIa**	8	84 (8)	81 (15)	(3*S*,4*S*)-**243**	97 (4)	97
7	**17**	**244**	(5*R*,6*R*)-**XLVIII**	4	64 (9)	83 (9)	(3*R*,4*R*)-**127**	93 (5)	98
8	**230**	**244**	(5*R*,6*R*)-**XLVIII**	7	68 (16)	80 (12)	(3*R*,4*R*)-**243**	63 (20)	98
9	**17** or **230**	**245**	(5a*R*,10b*S*)-**XLVIIa**	15	74 (13)	>98 (---)	(3*S*,4*S*)-**127** or **243**	96 (7)	99
10	**246**	**244**	(5a*R*,10b*S*)-**XLVIIa**	6	64 (13)	72 (9)	(3*S*,4*R*)-**247**	98 (1)	100
11	**180**	**244**	(5a*R*,10b*S*)-**XLVIIa**	16	82 (10)	>98 (---)	(3*S*,4*S*)-**248**	97 (4)	101
12	**147**	**244**	(5a*R*,10b*S*)-**XLVIIa**	14	89 (5)	82 (1)	(4*S*,5*S*)-**249**	98 (2)	102
13	**251**	**250**	(5a*R*,10b*S*)-**XLVIIa**	22	69 (12)	>90 (---)	(3*S*,4*S*)-**252**	99 (0.5)	103

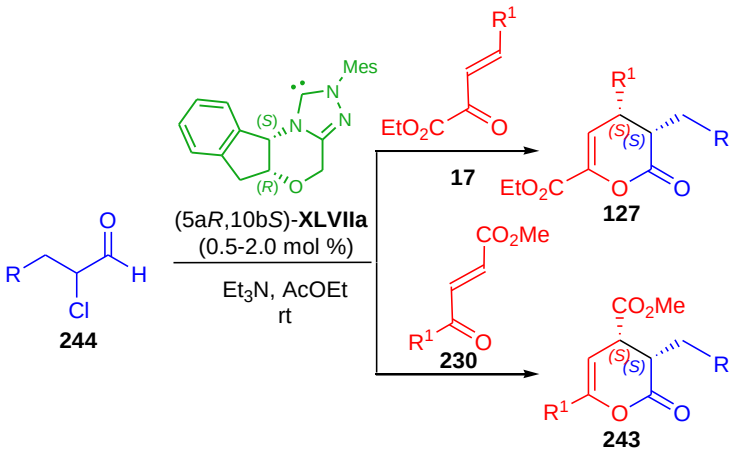
14	(*E*)-**253**	**250**	(5a*R*,10b*S*)-**XLVIIa**	12	66 (8)	87 (5)	syn-**254**	>99 (---)	104
15	(*Z*)-**253**	**250**	(5a*R*,10b*S*)-**XLVIIa**	5	70 (6)	85 (5)	anti-**254**	97 (2)	104
16	**255**	**250**	(5a*R*,10b*S*)-**XLVIIa**	6	77 (12)	89 (4)	(3*S*,4*S*)-**256**	99 (0.5)	105
17	**189**	**265**	(5a*R*,10b*S*)-**XLVIIa**	30	75 (20)	88 (4)	(3*S*,4*S*)-**266**	≥99 (---)	106
18	**189**	**138**	(5a*R*,10b*S*)-**XLVIIa**	21	74 (10)[a]	88 (4)	(3*S*,4*S*)-**268**	>98 (---)	107
19	**270**	**271**	(5a*R*,10b*S*)-**XLVIIa**	23	72 (10)[a]	87 (3)	**272**	98 (2)	108
20	**273**	**138, 271**	(5a*R*,10b*S*)-**XLVIIIf**	24	65 (13)	65 (23)	(6*S*,7*S*)-**274**	96 (4)	109
21	**17, 230, 276, 278**	**138**	(5a*S*,10b*R*)-**XLVIIa**	26	80 (17)	>90 (---)	**127, 243, 277, 279**	99 (1)	110
22	**189a**	**271**	(5a*S*,10b*R*)-**XLVIIa**	21	75 (10)	90 (2)	(3*R*,4*R*)-**280**	99 (---)	111
23	**281**	**282**	(5a*S*,10b*R*)-**XLVIIa**	16	92 (13)	>92 (---)	(4a*R*,5*R*,10b*S*)-**283**	95 (4)	112
24	**17**	**288**	(2*S*,3*R*)-**L**	21	72 (7)	83 (10)	(3*R*,4*R*)-**289**	95 (5)	113

[a] The average value of the **268:269** ratios is 11 ± 6.

The mechanisms described in Scheme 85 have been investigated by theoretical calculations at HF/6-31G (d) level.[96] Even if the computational studies rendered ambiguous the origins of the selectivity, it was shown that a concerted, but highly asynchronous, Diels-Alder reaction occurs rather than the stepwise Michael-type or Claisen-type pathways. Furthermore, the developed computational model successfully estimates the enantioselectivities obtained in the HDA reaction by using several *N*-HC organocatalysts.

The first example of asymmetric cycloaddition involving racemic α-chloro-aldehydes as precursor of the nucleophilic 2π component was reported in 2006 by Bode and co-workers.[97] The reactions of either α-oxo-γ,δ-unsaturated esters **17** or γ-oxo-α,β-unsaturated esters **230** (acting as heterodienes) with α-chloro-aldehydes **244** were run in the presence of 0.5-2.0 mol % of *N*-HC organocatalyst (5a*R*,10b*S*)-**XLVIIa** to give substituted pyran-2-one derivatives **127** and **243**, respectively (Scheme 86). When the heterodienes are the α-oxo-esters **17**, the reactions produced the adducts **127** within good yields and with an almost complete control of the diastereoselectivity since in all the reported examples (five cases) only a single diastereoisomer was detected in the unpurified reaction mixtures. The enantioselectivities were always excellent in favour of (3*S*,4*S*)-**127** (Table 8, entry 5).

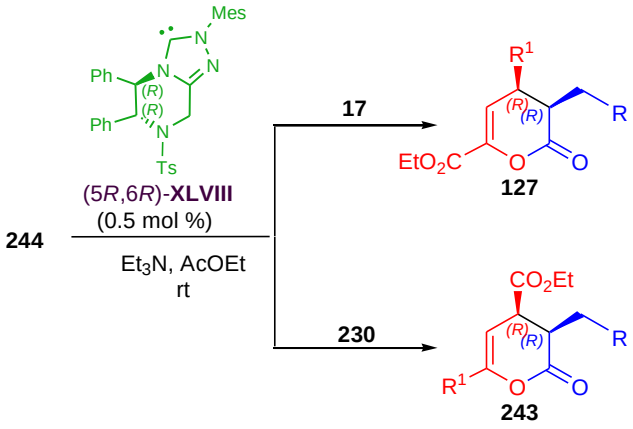
Scheme 86. Asymmetric Cycloaddition Reactions Between 17 or 230 with α-Chloro-Aldehydes 244 Catalyzed by (5a*R*,10b*S*)-XLVIIa.[97]



When the heterodienes are the γ-oxo-esters **230**, the reactions proceed with good yields, but with a lower control of the diastereoselectivity (average de = 81 ± 15%). The enantioselectivities was always excellent in favour of the (3*S*,4*S*)-**243**: the average ee over 8 different experiments was 97 ± 4% (Table 8, entry 6).

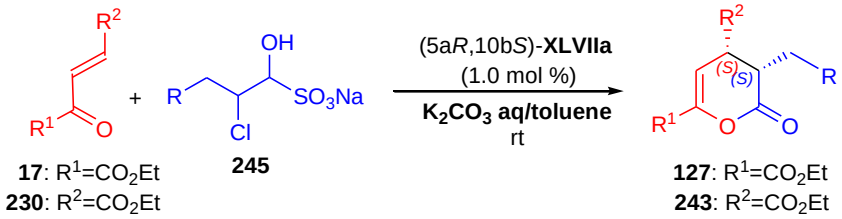
The same cycloaddition reactions in Scheme 86 were catalysed by the *N*-HC organocatalyst (5*R*,6*R*)-**XLVIII** derived from (1*R*,2*R*)-diphenyl ethylenediamine (Scheme 87).[98] This catalyst works worse than the previous one, particularly in the reaction involving **230** as heterodienes (Table 8, entries 7 and 8 vs entries 5 and 6). The most interesting feature is the opposite stereochemical outcomes obtained by using the two *N*-HC organocatalysts, pointing out the crucial role of the stereochemistry of the carbon closest to the reacting carbene centre. The (5*R*) configuration in **XLVIII** forces the enantioselectivity toward the formation of (3*R*,4*R*)-**127** or **243**, while the (10b*S*) configuration in **XLVII** leads to the preferential formation of the opposite (3*S*,4*S*) enantiomer.

Scheme 87. Asymmetric Cycloaddition Reactions Between 17 or 230 with α-Chloro-Aldehydes 244 Catalyzed by (5*R*,6*R*)-XLVIII.[98]



An interesting variant of the protocols above described concerned the use of α-chloroaldehyde bisulphite salts **245**, a commercially available and bench-stable starting materials, which allow the possibility to run the enantioselective cycloaddition in a successful manner under biphasic conditions (toluene/K_2CO_3 aq), Scheme 88.[99]

Scheme 88. Asymmetric Cycloaddition Reactions Between 17 or 230 with α-Chloroaldehydes Bisulfite Salts 245 Catalyzed by (5a*R*,10b*S*)-XLVIIa Under Biphasic Conditions.[99]



17: R^1=CO_2Et
230: R^2=CO_2Et

245

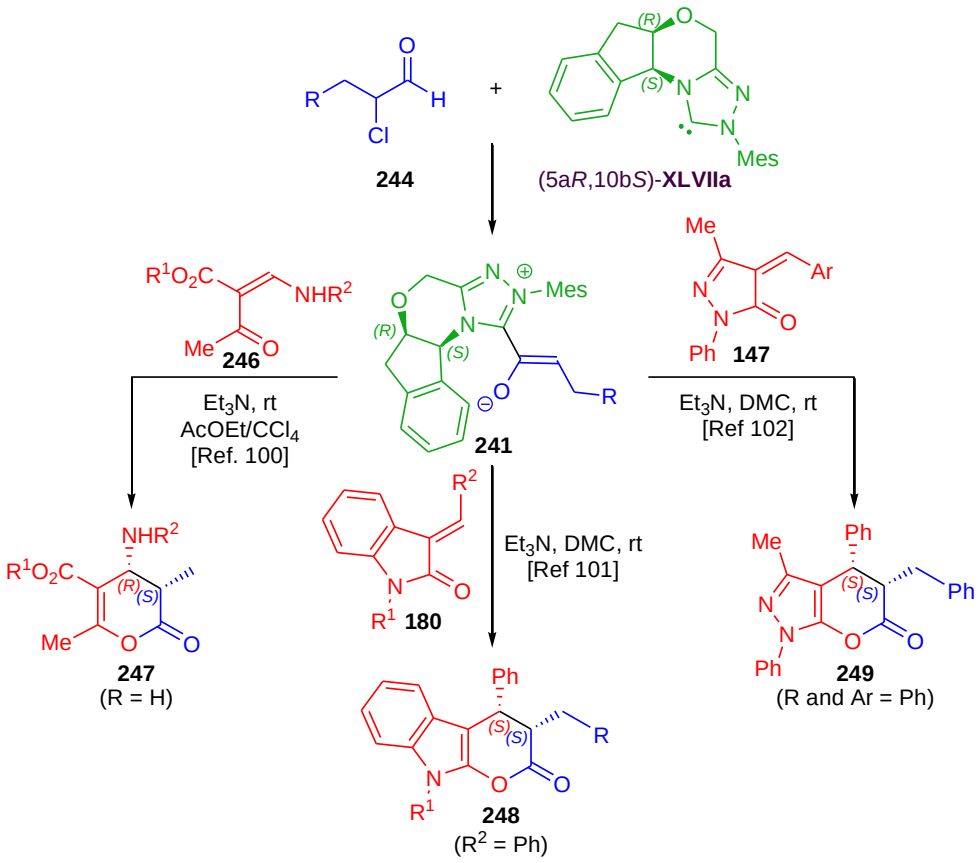
127: R^1=CO_2Et
243: R^2=CO_2Et

The reaction proceeds with good yields and excellent selectivities on both heterodienes: products **127** and **243** were obtained as a single diastereoisomer within discrete yields and excellent enantioselectivities: over 15 different experiments the average reaction yield was 74 ± 13%, and the average ee was 96 ± 7% (Table 8, entry 9). Hence, this specific protocol represented the first enantioselective *N*-HC catalysed reaction that was water tolerant.

Organocatalyst **XLVIIa** in both its enantiomeric forms has been employed to efficiently catalyse the cycloadditions involving several other heterodienes acting as electrophiles (Scheme 89). For sake of simplicity, the results in Scheme 89 and Table 8 (entries 10-12) are homogeneously referred to the same enantiomer of organocatalyst **XLVIIa**.

The reactions involving β-amino substituted α,β-unsaturated ketones **246**, having an (*E*)-configuration of the C=C double bond, with 2-chloropropanal **244** (R = H), which requires an elaborate preparation due to its high volatility and lability, were successfully catalysed by **XLVIIa** to produce in moderate yields and diastereoselectivities the 3,4-cis-dihydropyranones **247** with a (3*S*,4*R*)-absolute configuration.[100] The enantiomeric excess of **247** were greater than 97% ee, reaching >99% ee after a single recrystallization (Table 8, entry 10). The preferential formation of the 3,4-cis adducts was quite surprisingly because an endo-approach of *E*-**246** to the activated intermediate **241** should be expected to furnish the adduct with a 3,4-trans relationship. Since the *E*/*Z* isomerization of the starting material was experimentally excluded, the Authors concluded that a two-step process consisting of Michael addition followed by ring closure might be involved in the present cycloaddition.

Scheme 89. Asymmetric Cycloaddition Reactions Between Heterodienes 147, 180 or 246 with α-Chloroaldehydes 245 Catalyzed by (5a*R*,10b*S*)-XLVIIa.[100-102]



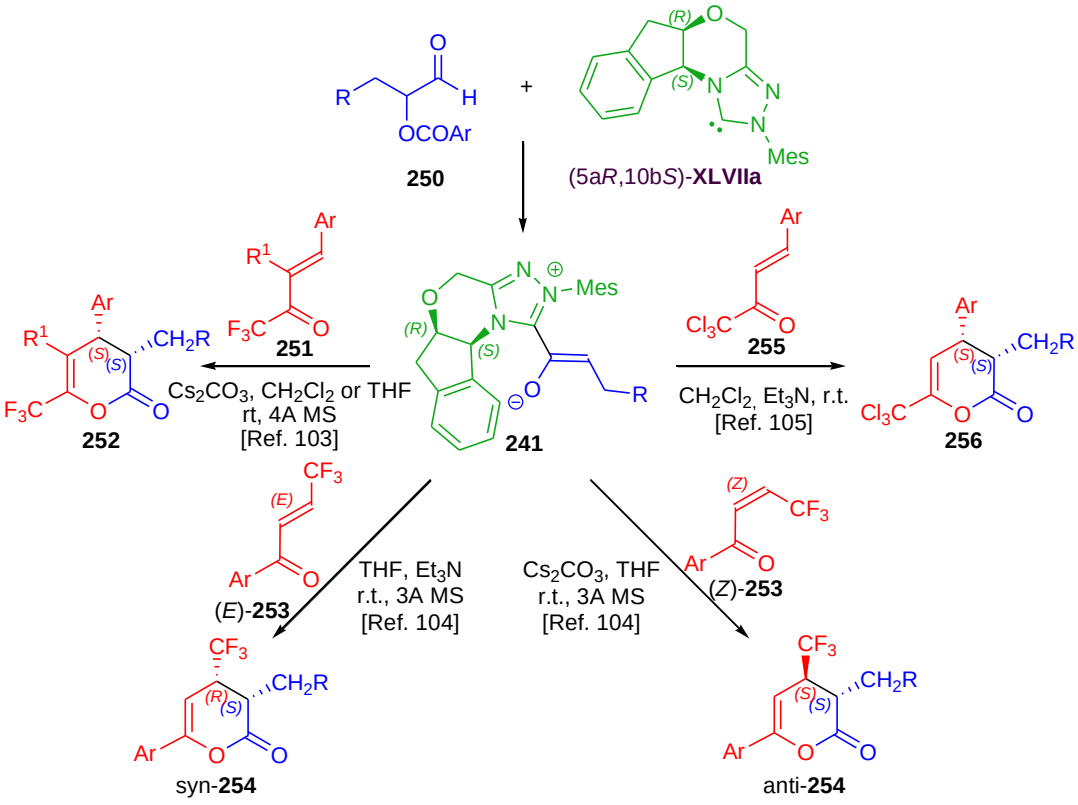
The cycloaddition involving 2-oxoindolin-3-ylidenes **180** and α-chloro aldehydes **244** leads to the formation of fused pyrano[2,3-*b*]indoles **248** (Scheme 89).[101] The use of **XLVIIa** as the organocatalyst allows to obtain in high yields, complete diastereo- and excellent enatioselectivities the chiral pyranone derivatives with the expected 3,4-cis relationship: In 16 different experiments the average yield was 82 ± 10%, the de was >98% (only one isomer was detected), and the average ee was 97 ± 4% (Table 8, entry 11).

The pyrazolone derivatives (*Z*)-**147** were also used as heterodienes in analogous cycloadditions to give pyrano[2,3-*c*]pyrazoles cycloadducts **249**. The reaction yields were very good (average yield, 89 ± 5%), the diasteroselectivities were appreciable (average de, 82 ± 1%), while the enantioselectivities were excellent (average ee, 98 ± 2%), see entry 12 in Table 8. The absolute configuration of **249**, determined by X-ray analysis, was found to be (4*S*,5*S*).

In all the three examples in Scheme 89, as well as in those reported in Schemes 86 and 88, the stereochemical outcomes of the cycloadditions catalysed by (5a*R*,10b*S*)-**XLVIIa** and involving structurally different heterodienes is always the same (what can be change is the priority order of the substituents to the stereocenter), pointing out that the same chiral intermediate **241** is involved in the catalytic cycle, intermediate that is always approached by the heterodiene to its less hindered face (Scheme 89). Obviously, the use of the enantiomeric catalyst (5a*S*,10b*R*)-**XLVIIa** (as happens in some of the above examples) will produce adducts with the opposite absolute stereochemistry.

The change of the good leaving group from chlorine to aroyloxy substituents does not modify the efficiency and the stereochemical outcome of the [4+2] cycloadditions involving (5a*R*,10b*S*)-**XLVIIa** as the organocatalyst (Scheme 90).[103-105] α-Aroyloxyaldehydes **250** are bench-stable derivatives that react with *N*-HC organocatalyst to produce the usual enolate equivalent **241**, which has been demonstrated to react with several α,β-unsaturated ketones.

Scheme 90. Asymmetric Cycloaddition Reactions Between Heterodienes 251, (*E*)- and (*Z*)-253, and 255 with α-Aroyloxyaldehydes 250 Catalyzed by (5a*R*,10b*S*)-XLVIIa.[103-105]



The reactions of several α,β-unsaturated trifluoromethylketones **251** acting as heterodienes in formal [4+2] cycloadditions with aldehydes **250** in the presence of (5a*R*,10b*S*)-**XLVIIa** proceed with appreciable reaction yields and with an almost complete control of diastereo- and enantioselectivity to give (3*S*,4*S*)-**252**: Over 22 different experiments, the average reaction yield was 69 ± 12%, while the de was >90% and the ee >99% (Table 8, entry 13).[103]

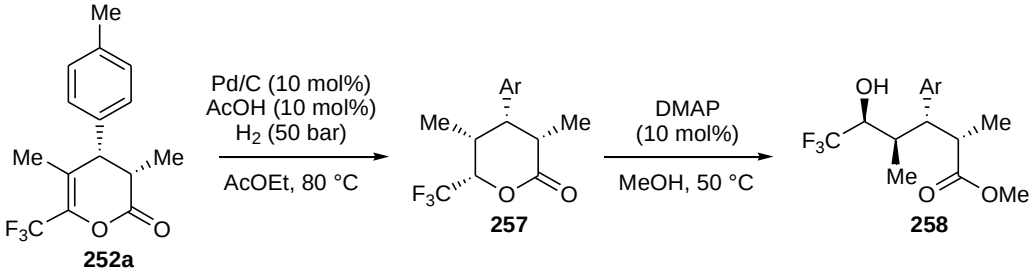
Also β-trifluoromethyl-α,β-unsaturated aromatic ketones **253** react as heterodienes with aldehydes **250** in the presence of **XLVIIa** to give with satisfactory yields and excellent diastereo- and enantioselectivities dihydropyranones **254** (Table 8, entries 14 and 15).[104] Respect to the cycloadditions involving **147** and **246** as heterodienes that, despite their (Z) configurations, always produced the syn adducts **249** and **247**, the use of (*E*)- or (*Z*)-**253** gives rise to the selective formation of syn- and anti-**254** respectively, through a concerted endo-transition state.

α,β-Unsaturated trichloromethyl ketones **255**, which can be considered as ester or amide equivalents, behave in an analogous manner: They react with aldehydes **250** in the presence of (5a*R*,10b*S*)-**XLVIIa** to give in good yields dihydropyranones (3*S*,4*S*)-**256** with an excellent control of the diastereo- and the enantioselectivity (Table 8, entry 16).[105] In all the four examples depicted in Scheme 90, the stereochemical outcome is again that expected from an heterodiene approach to the less hindered face of the chiral enolate **241**.

Enantiopure 3,4-dihydropyranones **252**, **254**, and **256** were further functionalised to give, after ring-opening, valuable chiral synthons.

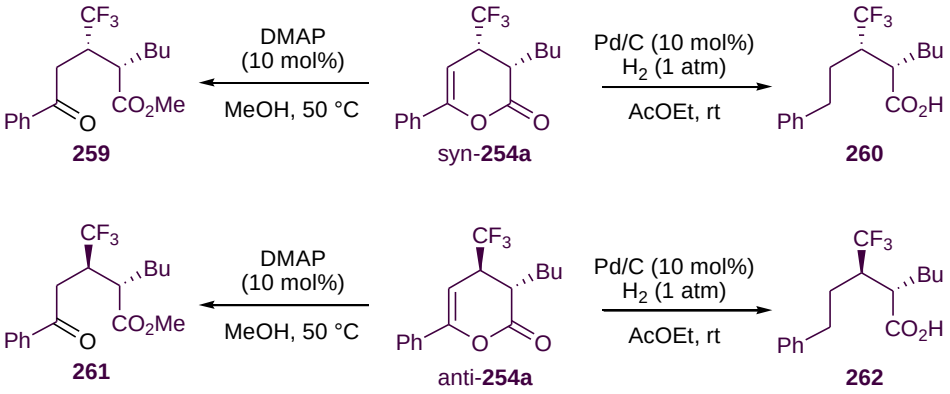
The dihydropyranone **252a** was hydrogenated to furnish the δ-lactone **257** containing four contiguous stereocenters in good yield (76%) and as a single diastereoisomer. Ring opening of **257** by treatment with catalytic amounts of DMAP in methanol provided δ-hydroxy ester **258** within 86% yield and excellent diastereo- (de >90%) and enantioselectivity (ee >99%), Scheme 91.[103]

Scheme 91. Hydrogenation of Dihydropyranone 252a and Ring Opening to Hydroxyester 258.[103]



The syn- and anti-adducts **254a**, which were prepared on a gram scale also, were derivatized to produce useful building blocks containing again a trifluoromethyl group on a stereogenic center (Scheme 92).[104] Treatment of syn-**254a** with methanol and catalytic DMAP produces the ring opened δ-oxo-ester **259** in good yield (73%) and excellent selectivity (de >95%; 97% ee), while its hydrogenolysis resulted in reduction of the C=C double bond with concomitant C–O cleavage to give acid **260** in 82% yield as single diastereoisomer. The same functionalizations can be usefully performed on anti-**254a** also to give the diastereoisomeric ester **261** and acid **262** within good yields and excellent selectivities.

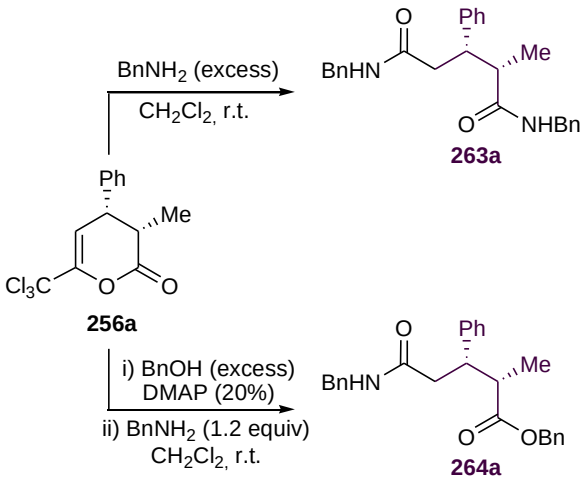
Scheme 92. Derivatization Reactions of Dihydropyranone syn-254a and anti-254a.[104]



The synthetic utility of the trichloromethyl substituent as an ester/amide equivalent was exploited on dihydropyranones **256** (Scheme 93).[106] The treatment of the crude adduct **256a**, obtained with de >90% and ee >99%, with an excess of $BnNH_2$ determined the ring opening by the reaction of the first equiv of nucleophile to give the in-situ formation of the open-chain trichloromethyl ketone.

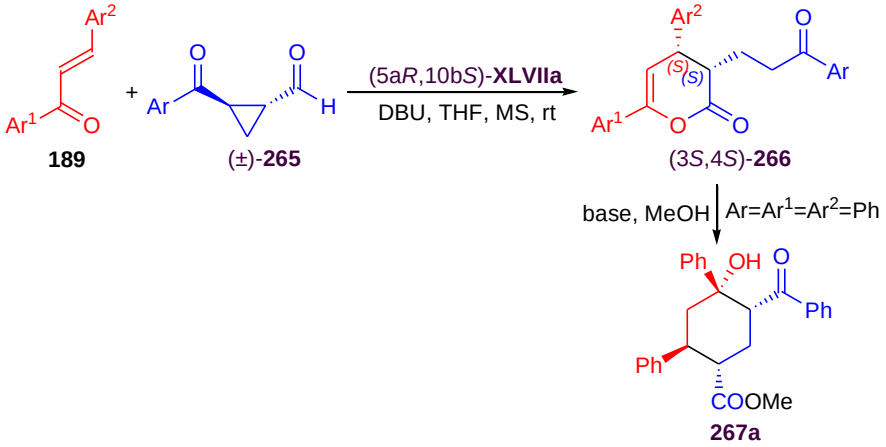
This latter is then attacked by the second equiv of nucleophile to furnish the chiral diamide **263a**, which was obtained as single diastereoisomer in excellent yield (85%). Two different nucleophiles could be involved in the two-step conversion; in this case, the less reactive one has to be employed first. Hence, the reaction of **256a** with an excess of BnOH followed by addition of a 1.2 equiv of $BnNH_2$ produced in low yield (32%) the chiral carboxylate amide **264a** as a single diastereoisomer.

Scheme 93. Derivatization Reactions of Dihydropyranone 256a.[105]



Chalcones **189** are rarely employed as heterodienes in catalysed HDA reactions. An example of the use of these substrates as 4π components in cycloadditions was proposed in *N*-HC catalysed processes involving racemic formylcyclopropanes (±)-**265** as the enolate precursors (Scheme 94).[106] (5a*R*,10b*S*)-**XLVIIa** was the organocatalyst of choice and allowed to obtained the functionalised δ-lactone (3*S*,4*S*)-**266** with an high level of diastereoselectivity and an almost complete control of the enantioselectivity: over 30 different experiments, the average yield was 75 ± 20%, the average de was 88 ± 4%, and the average ee was ≥99% (Table 8, entry 17). The adducts **266** are amenable for further transformations under simple conditions. The cycloadduct **266a** (Ar = Ar^1 = Ar^2 = Ph) was submitted to a transesterification followed by regio- and stereoselective aldol reaction to give the highly functionalized cyclohexane **267a** as a single stereoisomer in good yields (73%): the two new stereocenters were formed with nearly complete stereocontrol.

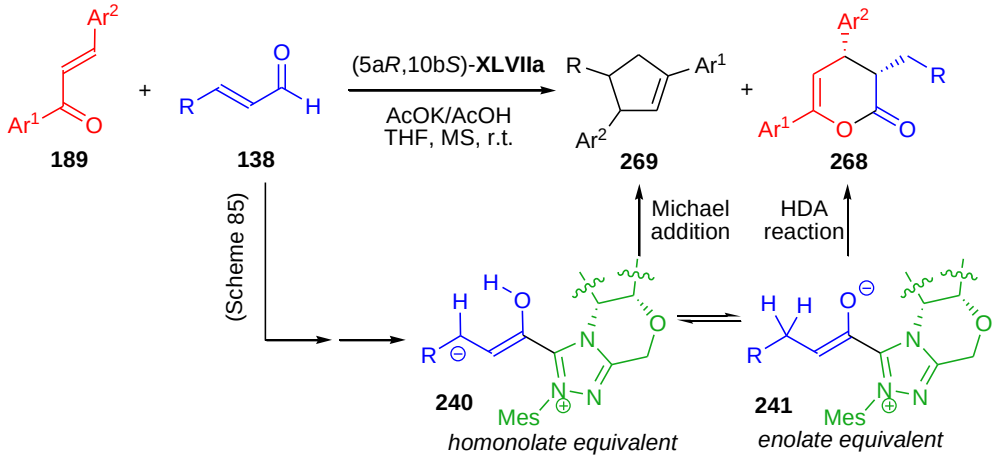
Scheme 94. Asymmetric Cycloaddition Reactions Between Chalcones 189 with Formyl-cyclopropanes (±)-265 Catalyzed by (5a*R*,10b*S*)-XLVIIa.[106]



The complete reaction sequence **189** + **265** to give **267** can be run in single-pot operation with appreciable reaction yields and excellent selectivities. In this way, a formal [3+3] synthetic strategy of highly functionalized cyclohexane derivatives was obtained.

Chalcones **189** react with α,β-unsaturated aldehydes **138** to give under *N*-HC catalysis a mixture of dihydropyranones **268** and the cyclopentene derivatives **269**, Scheme 95. The first product derived from the formal HDA reaction of the enolate equivalent **241** (see Scheme 85), which acts as dienophile in the cycloaddition with the heterodiene **189**, while cyclopentenes **269** derives from the Michael addition of the homoenolate **240** to **189**.[107]

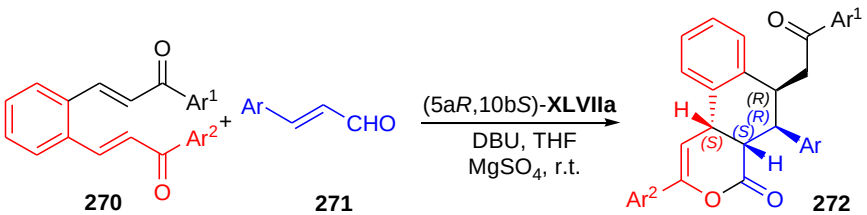
Scheme 95. Asymmetric Cycloaddition Reactions Between Chalcones 189 with α,β-Unsaturated Aldehydes 138 Catalyzed by (5a*R*,10b*S*)-XLVIIa.[107]



In order to control the two competing processes in Scheme 95 towards the selective formation of the HDA adducts **268**, a different approach from that requiring structural changes in the reacting substrates was undertaken. The promotion of the enal β-protonation by increasing the effective proton concentration was obtained by adjusting the acid loading and under the optimized conditions the HDA cycloadducts were selectively obtained: Over 21 different experiments, the ratio [**268**:**269**] ranges from [4:1] to [26:1], with an average value of the ratio of 10.7 ± 5.7. The organocatalyst (5a*R*,10b*S*)-**XLVIIa** was again efficient since the reaction yield were appreciable (average yield, 74 ± 10%), the diastereoselectivity was very good (average de, 88 ± 4%), and the enantioselectivity was excellent (ee >98%), Table 8, entry 18.[107]

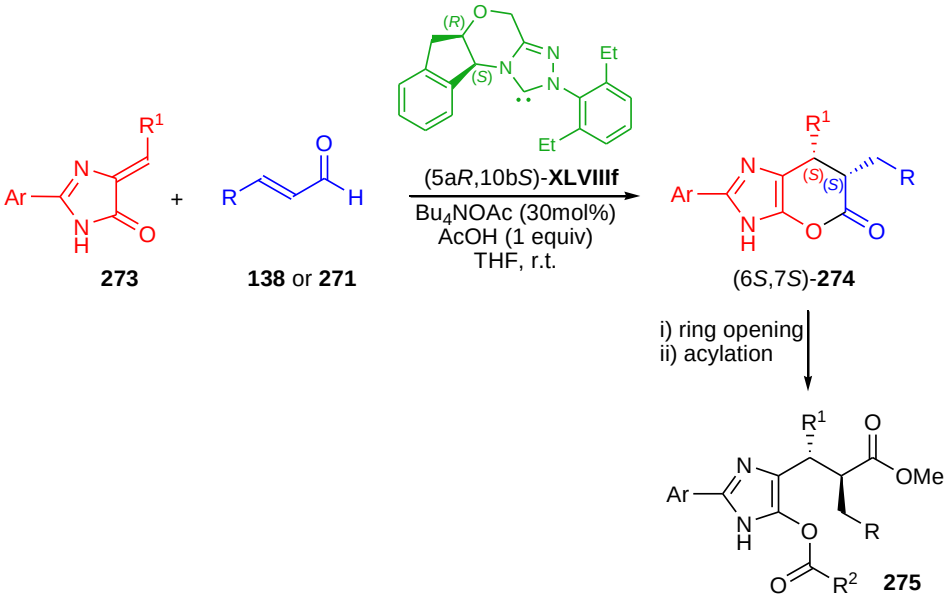
The annulation of aryl-enals **271** with di(enone)s **270** was catalyzed by (5a*R*,10b*S*)-**XLVIIa** to generate the benzotricyclic products **272** with exceptionally high regio- diastereo-, and enantioselectivities (Scheme 96):[108] Over 23 different experiments, the benzo[*f*]isochromen-4-one adducts were indeed obtained within moderate/good reaction yields (average yield, 72 ± 10%), very good diastereoselectivities (average de, 87 ± 3%), and excellent enantioselectivities (average ee, 98 ± 2%), (Table 8, entry 19). When Ar^1 was different from Ar^2, then the observed regioselectivities were in many cases complete (only one regioisomer was observed in the ^{1}H NMR spectra of the unpurified reaction mixtures). The proposed mechanism involves the initial formation of the Breslow intermediate that reacts with one branch of the di(enone) **270** through a cascade sequence involving (i) the Michael addition and then (ii) an intramolecular 1,4-cyclization. The last step is the C–O bond formation to produce **272** with the release of the *N*-HC catalyst **XLVIIa**.

Scheme 96. Asymmetric Cycloaddition Reactions Between Benzodi(enone)s 270 with β-Aryl Substituted α,β-Unsaturated Aldehydes 271 Catalyzed by (5a*R*,10b*S*)-XLVIIa.[108]



The *N*-HC-catalysed reation of alkylidene imidazolidinones **273** with α,β-unsaturated aldehydes (**138** or **271**) afforded enantioenriched bicyclic lactones **274** through a formal [4+2] annulation (Scheme 97).[109] The organocatalyst of choice for this reaction was (5a*R*,10b*S*)-**XLVIIIf**, since it allowed to minimize the competition of the reaction pathway leading to spirocyclic adducts deriving from a formal [3+2] annulation process. Over 24 different experiments, bicyclic lactones **274** were obtained in discrete yields, but with a diastereoselectivity ranging from low (33%) to very good values (de >90%), the highest de being obtained when R or R^1 were alkyl groups. On the contrary, the enantioselectivity was always excellent (the average ee is 96 ± 4%), independently from the reacting substrate structures (Table 8, entry 20). The pyrano[2,3-*d*]imidazole adducts **274** can be readily converted into a second class of 5-oxyimidazoles **275** through acid-catalyzed opening of the lactone followed by acylation.

Scheme 97. Asymmetric Cycloaddition Reactions Between Alkylidene Imidazolidinones 273 with α,β-Unsaturated Aldehydes 138 or 271 Catalyzed by (5a*R*,10b*S*)-XLVIIIf.[109]

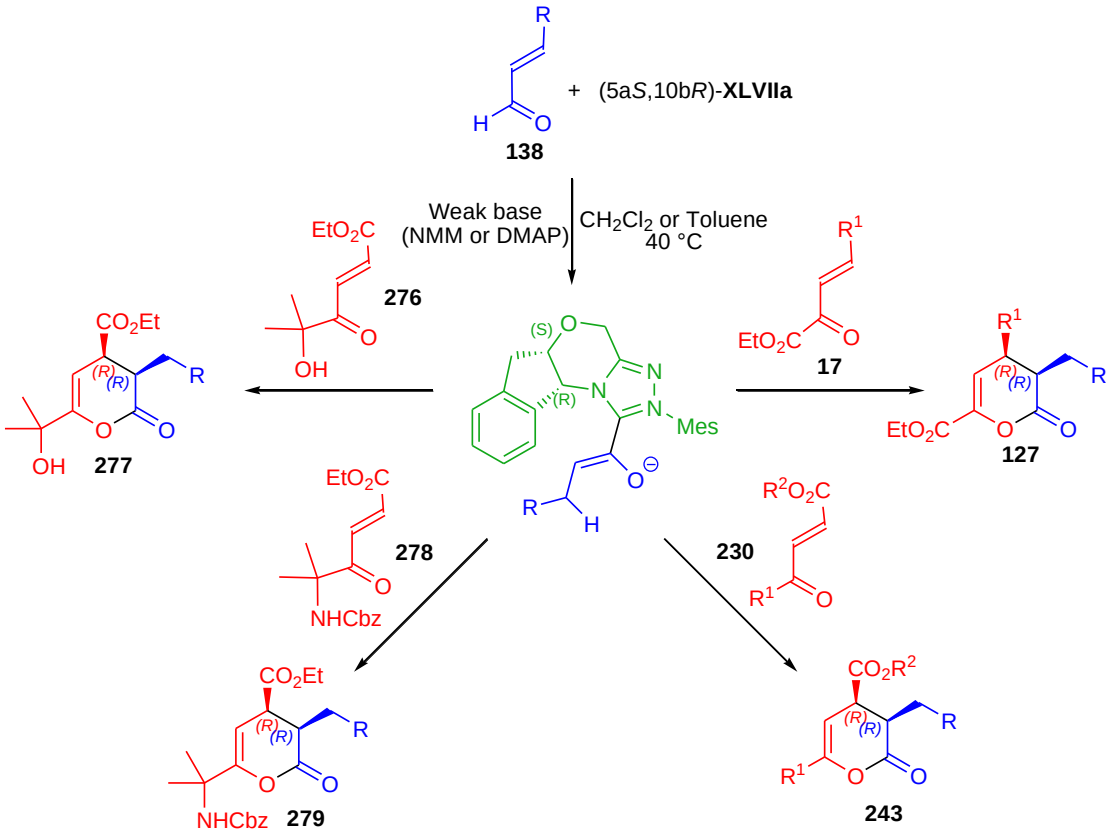


The first pivotal work on the field of *N*-HC catalysed HDA reactions involving activated heterodienes and α,β-unsaturated aldehydes as the 2π components is due to Bode and Kozlowski that investigated the crucial role of the strength of the base in determining the reaction pathways.[110] Strong bases (DBU) favour the formation of cyclopentene derivatives *via* the *homoenolate*

intermediate, while weak bases (DMAP) drive the selectivity toward the formation of HDA products through cycloadditions involving the *enolate* intermediate.

The organocatalyst (5a*S*,10b*R*)-**XLVIIa**, under optimised conditions, catalyzed with excellent results the HDA cycloadditions involving **138** (or **271**) and a series of electron-poor α,β-unsaturated ketones (Scheme 98). The reaction yields were good (average reaction yields, 80 ± 17%), while in all the 26 different experiments the diastereo- and the enantioselectivity were excellent (de >90%; average ee, 99 ± 1%), Table 8, entry 21.[110]

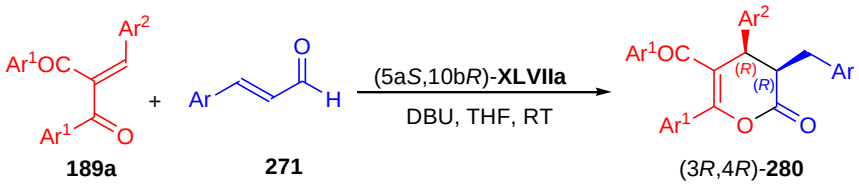
Scheme 98. Asymmetric Cycloaddition Reactions Between Activated Heterodienes 17, 230, 276, and 278 with α,β-Unsaturated Aldehydes 138 Catalyzed by (5a*S*,10b*R*)-XLVIIa.[110]



An electron-withdrawing group was introduced to the α-position of chalcones, and the resulting akylidene diketones **189a** reacted with enals **271** under *N*-HC catalysis. The functionalized dihydropyranones **280** were obtained by the reaction pathway involving the usual enolate equivalent as the reacting intermediate. The organocatalyst of choice was (5a*S*,10b*R*)-**XLVIIa**, which allows the formation of cycloadducts with good yields, high diastereo-, and excellent enantioselectivities

(Scheme 99).[111] Over 21 different experiments, the average yield was 75 ± 10%, the average de was 90 ± 2%, while the ee was always 99% (Table 8, entry 22). The stereochemical outcome of the cycloaddition [(3*R*,4*R*)-**280**] is the same observed for all the reactions in Scheme 98. The only limitation of this catalytic system is that β-aryl-enals are required to run an HDA cycloaddition, while with the corresponding β-alkyl-derivatives only a Stetter type reaction occurred.

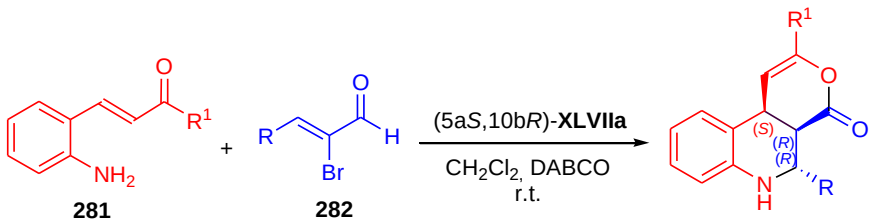
Scheme 99. Asymmetric Cycloaddition Reactions Between Alkylidene Diketones 189a with α,β-Unsaturated Aldehydes 271 Catalyzed by (5a*S*,10b*R*)-XLVIIa.[111]



189a **271** (3*R*,4*R*)-**280**

Some variants of the protocol above described have been reported. The first one involves the use of α-bromo-enals **282** instead of the unsubstituted α,β-unsaturated aldehydes that react with 2′-aminophenylenones **281** to produce pyrano[3,4-*c*]quinoline derivatives (4a*R*,5*R*,10b*S*)-**283** (Scheme 100).[112] The cyclization was efficiently catalysed by (5a*S*,10b*R*)-**XLVIIa**, and the products were obtained in high yields and excellent diastereo- and enantioselectivity. Over 16 different experiments the average yield was 92 ± 13%, the de was >92%, and the average ee was 95 ± 4% (Table 8, entry 23).

Scheme 100. Asymmetric Cycloaddition Reactions Between 2′-Aminophenylenones 281 with 2-Bromoenals 282 Catalyzed by (5a*S*,10b*R*)-XLVIIa.[112]

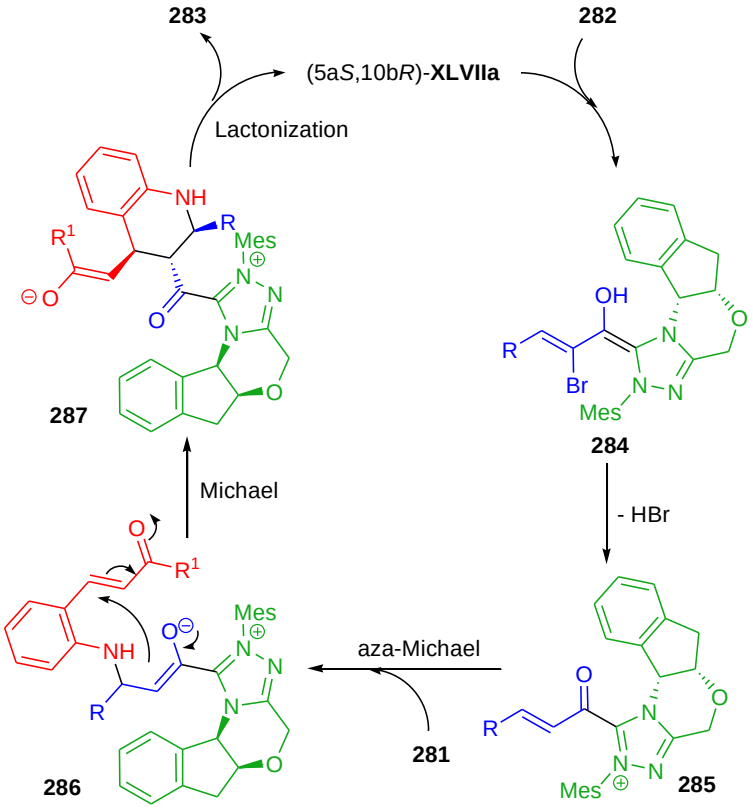


281 **282** (4a*R*,5*R*,10b*S*)-**283**

This process represents the first example of *N*-HC catalysis of a cascade reaction involving an aza-Michael/Michael/lactonization sequence (Scheme 101). Addition of the *N*-HC to the 2-bromoenal **282** forms the Breslow intermediate **284**, which is transformed into **285** through

tautomerization and debromination. The aza-Michael addition of **281** (acting as nucleophile) to **285** provides enolate **286** that undergoes intramolecular Michael addition to give intermediate **287**, which give rise to intramolecular lactonization to furnish the desired product **283** and regenerate the *N*-HC catalyst.[112]

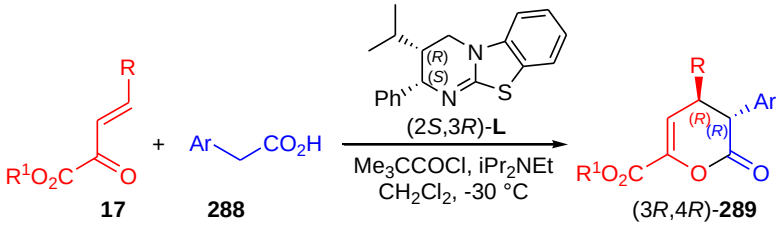
Scheme 101. Proposed Catalytic Cycle of the Cascade Reaction Between 281 and 282 Catalyzed by (5a*S*,10b*R*)-XLVIIa.[112]



The second variant involves the use of carboxylic acids as the 2π nucleophilic component in the cyclization reaction, and it can be considered as an alternative to the use of ketenes discussed at the beginning of this section. For this reason, we discuss this example in this chapter even if it is not strictly connected with *N*-HC organocatalysis.

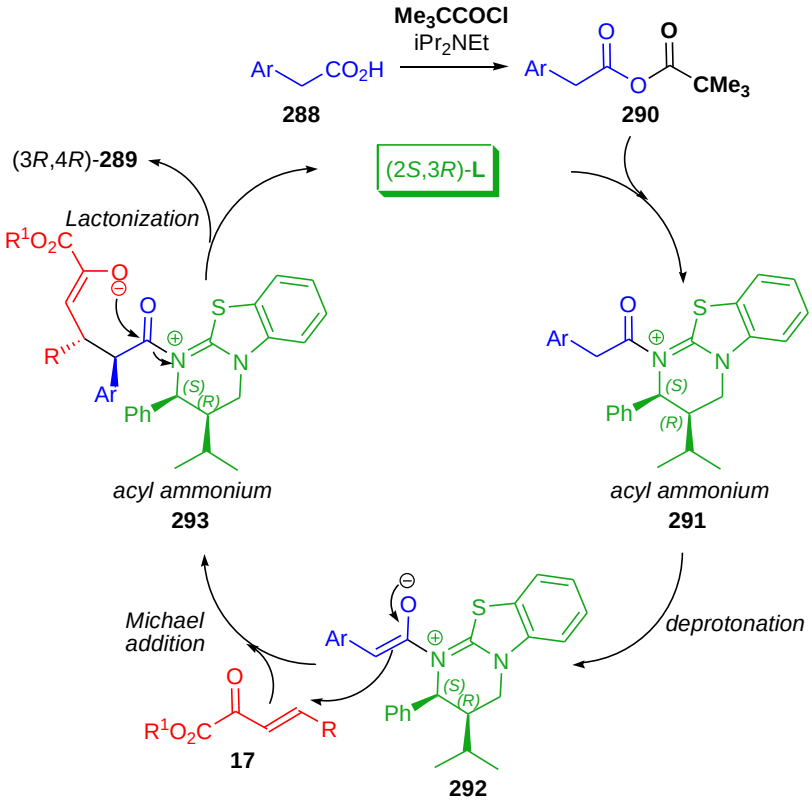
The activated heterodiene **17** was allowed to react with arylacetic acids **288** in the presence of the chiral isothiourea (2*S*,3*R*)-**L**, as the organocatalyst, and pivaloyl chloride, as an activating agent. Under optimized conditions, the 3,4-anti disubstituted pyranone **289** were obtained within good yields and diastereoselectivity and with excellent enantioselectivity (Scheme 102).[113] Twentyone different cyclization reactions were performed with an average yield of 72 ± 7%, an average de of 83 ± 10%, and an average ee of 95 ± 5% (Table 8, entry 24). Among the large number of chiral pyranones discussed in this chapter, this reaction represents the first example of a cyclization process that is anti-selective.

Scheme 102. Asymmetric Cyclization Between α-Keto-β,γ-unsaturated Esters 17 and Arylacetic Acids 288 Catalyzed by (2*S*,3*R*)-L.[113]



The proposed reaction mechanism favors a stepwise Michael addition–lactonization sequence over a concerted [4+2] HDA reaction pathway, although a clear choice between these mechanistic possibilities is difficult. The catalytic cycle involves the initial *in situ* formation of the transient mixed anhydride **290**, which *N*-acylated the isothiourea **L** to give the acyl ammonium species **291**. Deprotonation generates the (*Z*)-ammonium enolate **292** that undergoes an intermolecular asymmetric Michael addition to **17** giving the acyl ammonium intermediate **293**. The last step is the lactonization, which produces the desired product (3*R*,4*R*)-**289** in high de and ee and regenerates the organocatalyst (3*R*,4*R*)-**L** (Scheme 103).[113]

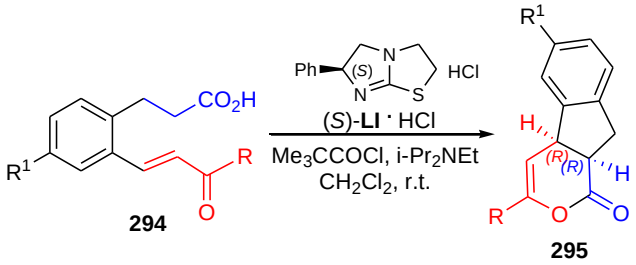
Scheme 103. Proposed Catalytic Cycle for the Michael Reaction/Lactonization Sequence in the [4+2] Cyclization Between 17 and 288 Catalyzed by (2*S*,3*R*)-L.[113]



2.1.2.5.c. N-HC as Organocatalyst of Intramolecular Cycloadditions

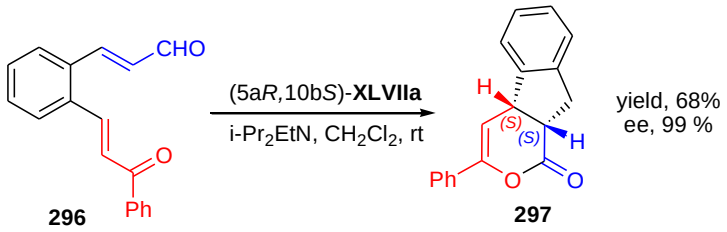
The Michael reaction–lactonization sequence above described was also applied into intramolecular processes involving enone-acids **294** to produce the tricyclic lactones **295** (Scheme 104).[113] The organocatalyst of choice was obtained in situ by deprotonation of the tetramisole hydrochloride (*S*)-**LI**·HCl (the pre-catalyst). (*S*)-**LI** reacted with a mixed anhydride, generated from the reaction between the carboxylic function of **294** and pivaloyl chloride, to give an acyl ammonium intermediate like **291**, which follows the analogous catalytic cycle depicted in Scheme 103 for the intermolecular process to produce the cyclized adducts **295** and to regenerate the organocatalyst (*S*)-**LI**. The domino Michael addition–lactonization process produced adducts syn-**295** within good yields (only in one case over six different experiments the yield was lower than 70%), the diastereo- and the enantioselectivity being excellent (de = 98%; ee = 95 ± 3%, Table 9 entry 1).[113]

Scheme 104. Asymmetric Intramolecular Cyclization of 294 Catalyzed by (*S*)-LI·HCl.[113]



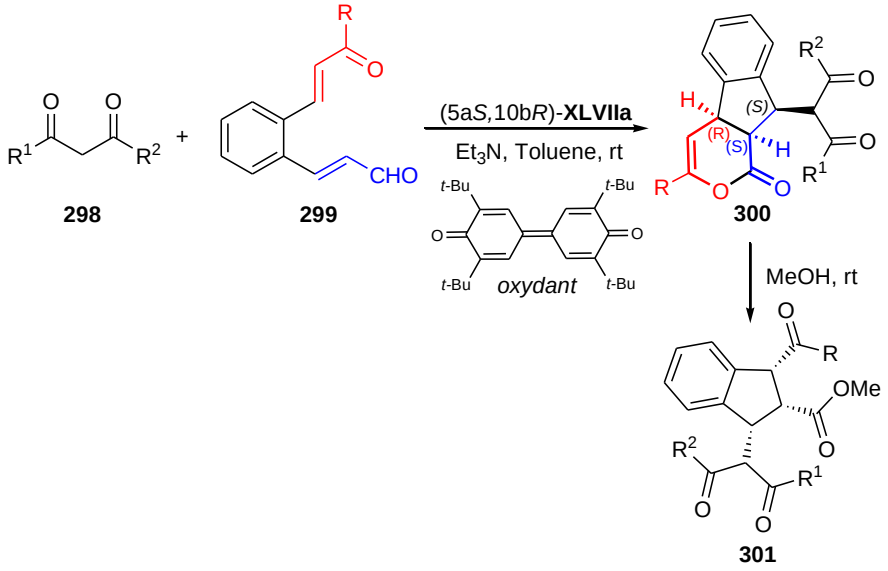
The first example concerning enantioselective intramolecular cyclization processes catalysed by *N*-HC organocatalysts was proposed by Scheidt and co-workers in 2007.[114] The reagent **296**, containing both the heterodiene fragment and the α,β-unsaturated aldehyde function, reacted in the presence of (5a*R*,10b*S*)-**XLVIIa**, the organocatalyst of choice, to produce the tricyclic lactone **297** in good yield (68%) and excellent enantioselectivity (99% ee), Scheme 105.[114]

Scheme 105. Asymmetric Intramolecular Cyclization of 296 Catalyzed by (5a*R*,10b*S*)-XLVIIa.[114]

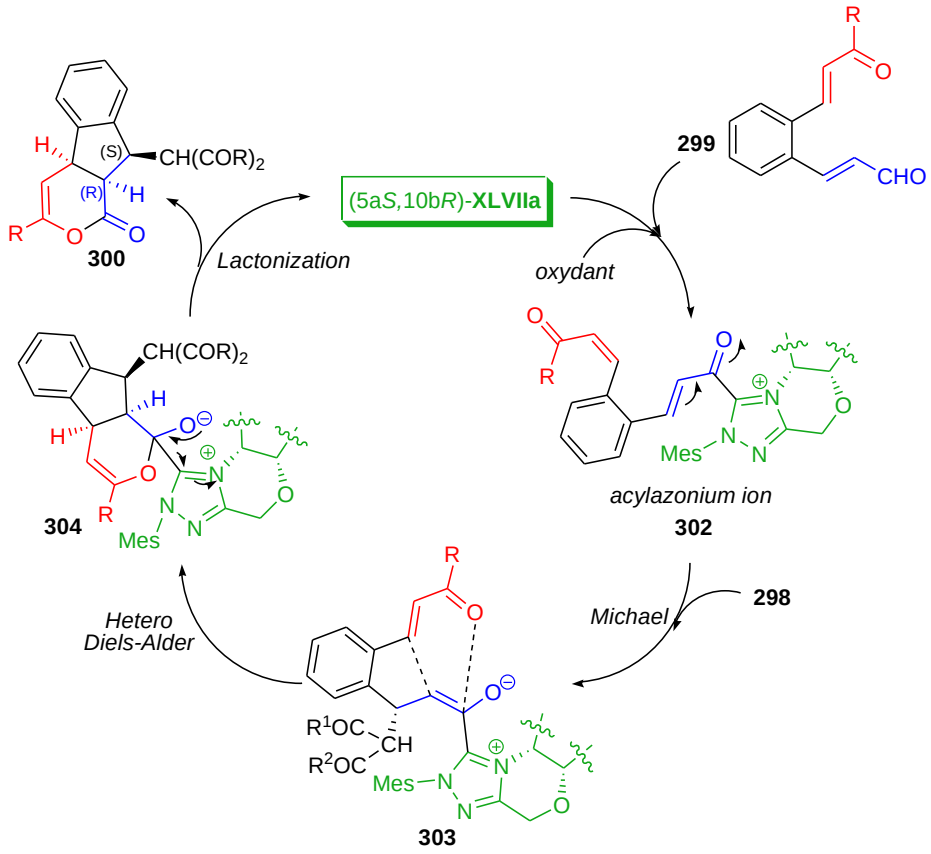


The highly stereoselective synthesis of 1,2,3-trisubstitued indanes was performed by using (5a*S*,10b*R*)-**XLVIIa** as the *N*-HC organocatalyst in Michael addition–HDA reaction–lactonization cascade processes. The reaction of aldehydes **299** with β-diketones **298** was run at r.t. in the presence of the organocatalyst to afford the tricyclic lactones **300** (Scheme 106).[115] The cycloadducts were obtained within moderate yields (average yield, 55 ± 10%), very good diastereoselectivity (average de, 87 ± 16%), and excellent enantioselectivity (average ee, 99 ± 2%), Table 9, entry 2. The cascade products **300** can be converted into the corresponding indane derivatives **301** in quantitative yields by methanolysis under very mild conditions (stirring in MeOH at r.t.).[115]

Scheme 106. Asymmetric Intramolecular Cyclization of 299 Catalyzed by (5a*S*,10b*R*)-XLVIIa.[115]



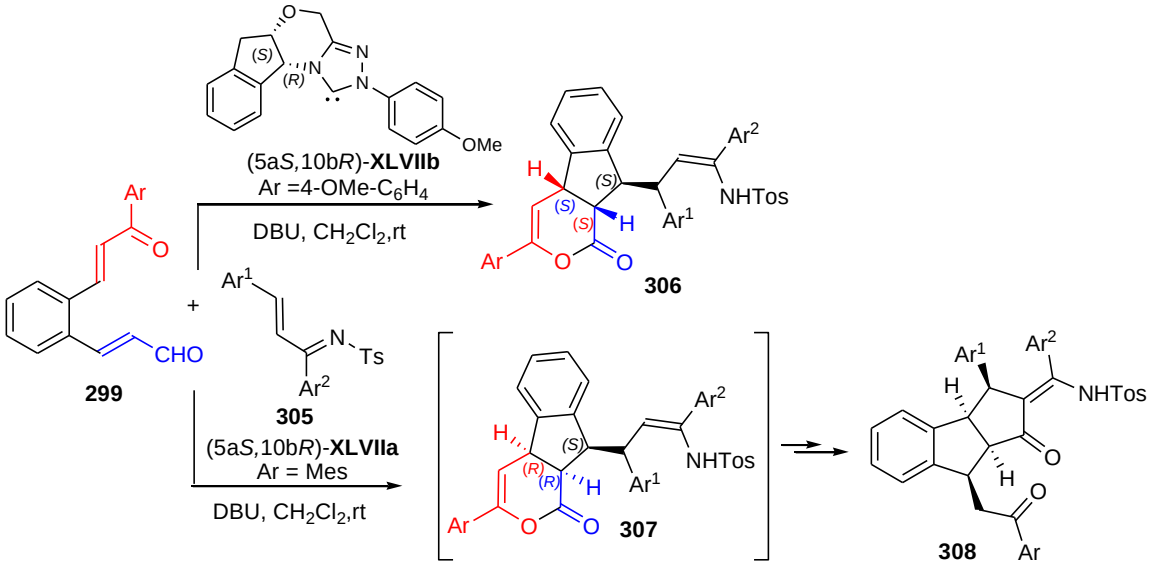
Scheme 107. Proposed Catalytic Cycle for the Cascade Reaction Between 298 and 299 Catalyzed by (5a*S*,10b*R*)-XLVIIa.[115]



The proposed catalytic cycle for the cascade reaction is depicted in Scheme 107. Reaction of enal **299** with the *N*-HC organocatalyst **XLVIIa** in the presence of oxidant generates the acylazolium ion **302**. The intermolecular Michael addition of the likely deprotonated 1,3-dicarbonyl compound **298** to the redox activated Michael acceptor provides the intermediate **303**, which can undergo an endo HDA reaction to furnish **304** (the endo-rule would explain the high cis-selectivity observed). The final lactonization step produces the desired product **300** and regenerates the organocatalyst (5a*S*,10b*R*)-**XLVIIa**.[115]

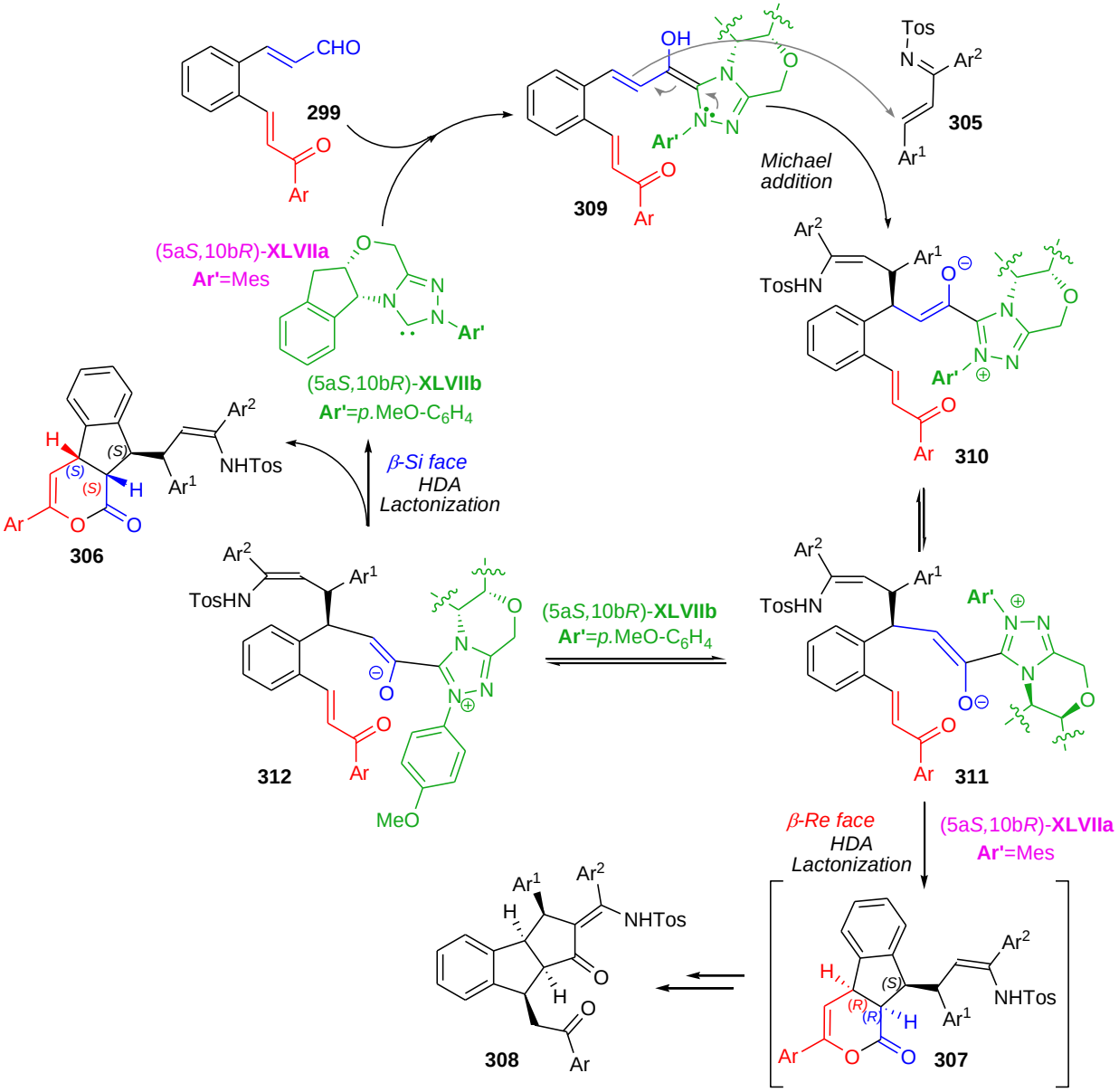
An interesting example of enantioselective intramolecular cyclization to complex polycyclic pyranone structures is the reaction between aldehydes **299** and α,β-unsaturated imines **305** catalyzed by either (5a*S*,10b*R*)-**XLVIIb** (Ar =4-OMe-C_6H_4) or (5a*S*,10b*R*)-**XLVIIa** (Ar = Mes) (Scheme 108).[116] The slight variation of the *N*-substituent on the triazole carbene in the *N*-HC organocatalyst determined a completely different result. When **XLVIIb** was the organocatalyst, then the formation of the indeno[2,1-*c*]pyran-1-ones **306** was observed. The use of **XLVIIa** changed the diastereoselectivity of the process that give rise to the diastereomeric pyranones **307** that in unstable under the reaction conditions being converted into enantiopure indenocyclopentan-1-ones **308** (ee >99%).[116]

Scheme 108. Asymmetric Intramolecular Cyclization of 299 Catalyzed by (5a*S*,10b*R*)-XLVII.[116]



By using the organocatalyst (5a*S*,10b*R*)-**XLVIIb** the HDA adducts **306** were obtained within moderate yields and excellent diastereo- and enantioselectivity: Over 13 different experiments, the average yield was 50 ± 6%, the de was always >95% and the average ee was 94 ± 3% (Table 9, entry 3). To rationalize the selective formation of indeno[2,1-*c*]pyran-1-ones **306** and indenocyclopentan-1-ones **308** two cascade reaction pathways have been proposed (Scheme 109).

Scheme 109. Proposed Catalytic Cycles for the Cascade Reaction Between 299 and 305 Catalyzed by (5a*S*,10b*R*)-XLVII.[116]



The reaction started by an intermolecular Michael addition of the homoenolates **309**, generated from enals **299** and *N*-HC catalyst, to the α,β-unsaturated imines **305**. The resulting enamine anions **310** underwent isomerization and tautomerization to **311**. When the Ar′ substituent in the organocatalyst is the mesityl group, then the intermediates **311**, which is the more stable conformation avoiding the repulsion between the mesityl and 2-aroylvinyl groups, proceed via an HDA reaction–lactonization sequence by attacking the *Re*-face of α,β-unsaturated ketones to afford the unstable dihydropyran-2-one derivatives (4a*R*,9*S*,9a*R*)-**307**, which spontaneously evolve to **308**. When the Ar′ substituent in the organocatalyst is the less sterically demanding anisyl group, the most likely favorable conformation of enolate intermediates is **312** that proceed in the HDA–lactonization sequence by attacking the opposite *Si*-face of α,β-unsaturated ketones to produce indeno[2,1-*c*]pyran-1-ones (4a*S*,9*S*,9a*S*)-**306**.

The last example of this section concerns the synthesis of optically active 3,4-dihydrocoumarins **314** by merging the aminocatalysis, discussed at the beginning of the chapter, with *N*-HC catalysis by a multicatalytic sequence (Scheme 110).[117]

Scheme 110. Asymmetric Intramolecular Cyclization of 313 Catalyzed by (*S*)-XXIIa and LIII Multicatalysis.[117]

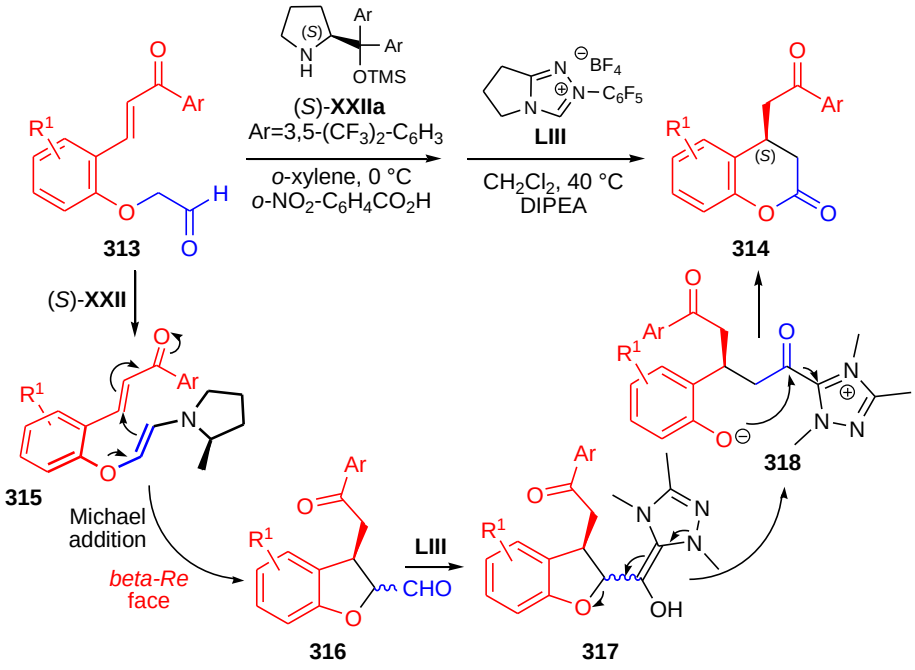


Table 9. Average Values and Standard Deviations (s.d.) of the Reaction Yields, Diastereo-, and Enantioselectivities in the Synthesis of Dihydropyrans by Intramolecular [4+2] Cyclization Processes Catalyzed by *N*-HC Organocatalysts.

Entry	Reagent(s)	Catalyst	n. Exp.	aver. Yield % (s.d.)	aver. de (s.d.)	Reaction Product	aver. ee % (s.d.)	Ref.
1	**294**	(*S*)-**LI**	6	77 (20)	98 (---)	**295**	95 (3)	113
2	**298** + **299**	(5a*S*,10b*R*)-**XLVIIa**	11	55 (10)	87 (16)	**300**	99 (2)	115
3	**305** + **299**	(5a*S*,10b*R*)- **XLVIIb**	13	50 (6)	>95	**306**	94 (3)	116
4	**313**	(*S*)-**XXIIa**/**LIII**	10	64 (15)	---	(*S*)-**314**	86 (12)	117

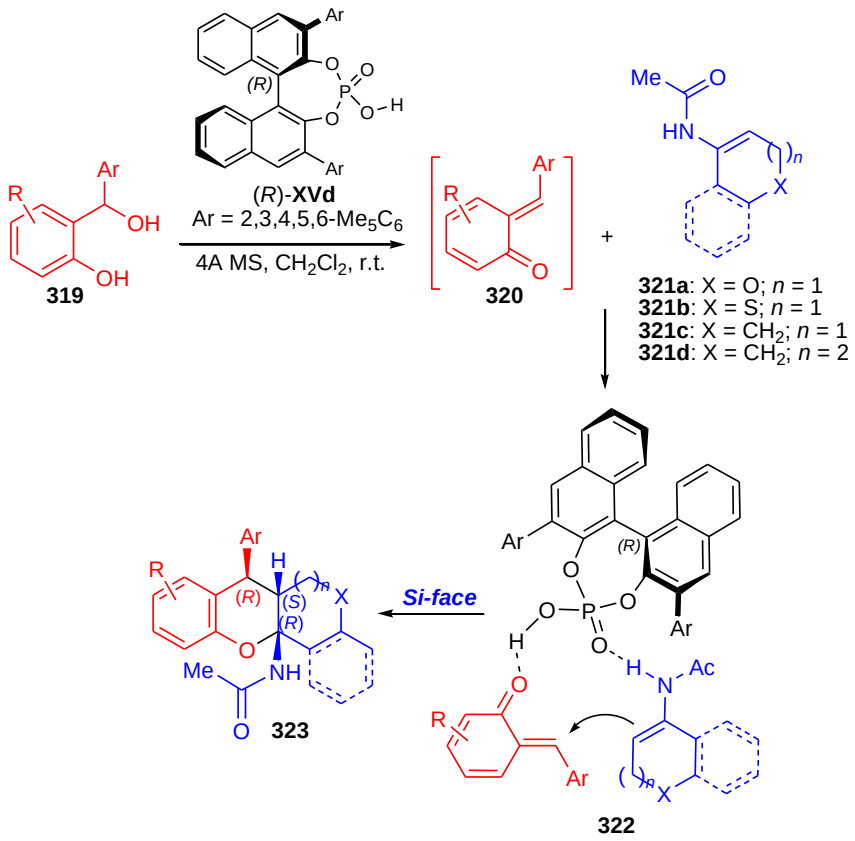
The (*E*)-2-(2-(3-oxo-3-arylprop-1-en-1-yl)aryloxy)acetaldehyde derivatives **313** reacted under optimized conditions with the proline-based organocatalyst (*S*)-**XXIIa** to give the activated enamine **315** that undergo an intramolecular Michael addition to produce the dihydrobenzofurane derivatives **316** as mixture of epimers at the C-2 position. This is the key-step in determining the (*S*) absolute configuration at the C-4 of the final product **314**. Then, the achiral *N*-HC organocatalyst **LIII** was added to the aldehyde to produce the Breslow intermediate **317** that open the ring by eliminating the phenoxide to produce, after tautomerization, the intermediate **318**. The last step is the usual lactonization reaction to produce the final adduct **314** and releasing the *N*-HC catalyst **LIII**. The methodology was applied to 10 different substrates and (*S*)-**314** were obtained within moderate yields (average yield, 64 ± 15%) and encouraging enantioselectivities (average ee, 86 ± 12%), entry 4 in Table 9.[117]

2.1.3. Chiral Brønsted Acids as Catalysts

BINOL-chiral phosphoric acids represent the most recent family of organocatalyst that found useful application in the asymmetric catalysis of [4+2] cyclization processes for the synthesis of enantioenriched 3,4-dihydropyrane structures. The chiral Brønsted acid typically works as a bifunctional catalyst able to activate the electrophilic component (the heterodiene) by hydrogen-bonding and, at the same time, to bound the nucleophilic component by a further H-bond involving the basic phosphoryl oxygen atom.

In all the examples reported in the literature, the heterodienes are the *ortho*-quinone methides **320**, which are generated in situ by acid-catalyzed dehydration of the corresponding *ortho*-hydroxy-benzhydryl alcohols **319**, the dehydrating agent being the chiral Brønsted acid. The following conjugate addition of enamides **321** was efficiently catalysed by the BINOL-based phosphoric acid (*R*)-**XVd** to give the chiral acetamidotetrahydroxanthenes **323** (Scheme 111).[118] During the optimization studies, it was evidenced the importance of the use of 4Å MS to improve the reaction yield, probably due to the trap of the water generated in the first step, and to prevent undesired decomposition reactions.

Scheme 111. Asymmetric Intermolecular Cyclization of 319 and 321 Catalyzed by (*R*)-XVd.[118]



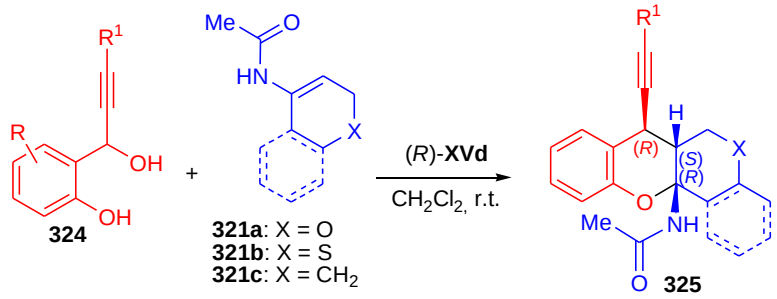
This methodology was tested over 27 different experiments, involving a large variety of acetamido derivatives **321a-d**: the reaction yields were usually good (average yield, 74 ± 7%), and the diastereo- and the enantioselectivity were excellent (average de, 92 ± 12%; average ee, 93 ± 9%), entry 1 in Table 10. The absolute configuration of **323** was determined by X-ray analysis, and it was found consistent with the reacting intermediate **322**, which evidenced the ability of **XV** to organize the reactants in a highly ordered transition state, driving the approach of **321** to less hindered face of **320** (the bottom *Si*-face).

The change of **319** with *o*-hydroxyphenyl-propargylic alcohols **324**, as the quinone methides precursors, allowed to obtain the corresponding alkynyl-xanthenes derivatives **325** (Scheme 112).[119] The reactions of **324** with enamides **321a-c** was catalyzed by (*R*)-**XVd** to furnish, through the same mechanism depicted in Scheme 111, products **325** within good yields and excellent selectivities: Over 21 different experiments the average yield was 73 ± 6%, the average de 91 ± 8%, and the average ee 95 ± 7% (Table 10, entry 2).

Table 10. Average Values and Standard Deviations (s.d.) of the Reaction Yields, Diastereo-, and Enantioselectivities in the Synthesis of Dihydropyrans by [4+2] Cyclization Processes Catalyzed by Chiral Brønsted Acids and Bases as the Organocatalysts.

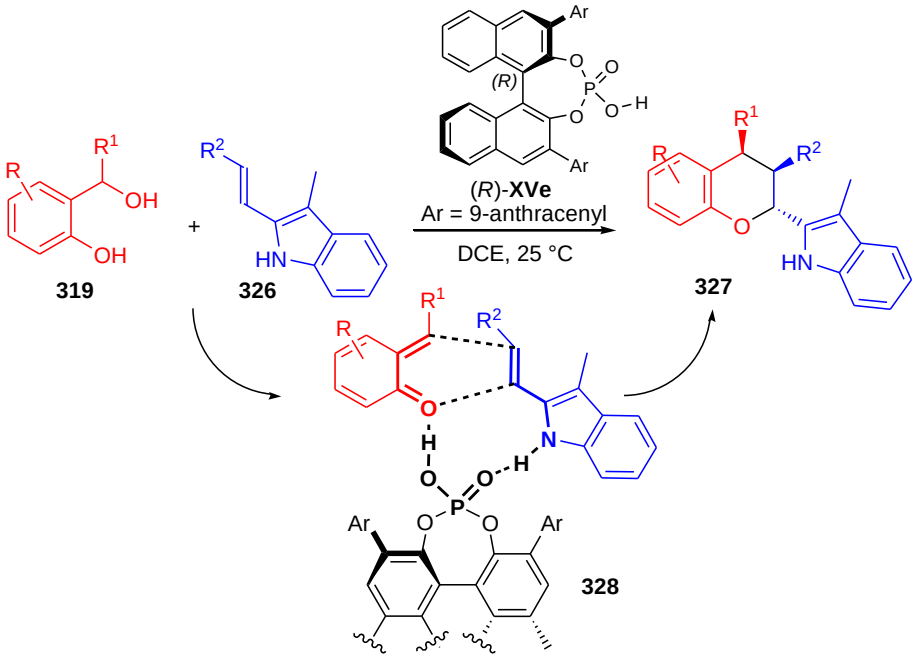
Entry	Reagents	Catalyst	n. Exp.	aver. Yield % (s.d.)	aver. de (s.d.)	Reaction Product	aver. ee % (s.d.)	Ref.
1	**319** + **321**	(*R*)-**XVd**	27	74 (7)	92 (12)	**323**	93 (9)	118
2	**324** + **321**	(*R*)-**XVd**	20	73 (6)	91 (8)	**325**	95 (7)	119
3	**319** + **326**	(*R*)-**XVe**	26	84 (14)	86 (7)	**327**	94 (4)	120
4	**319** + **31**	(*R*)-**LIVa**	18	83 (12)	95 (2)	(2*R*,4*S*)-**332**	91 (4)	121
5	**189** + **334**	(*S*,*S*)-**LV**	32	70 (11)	>95 (---)	(3*S*,4*R*)-**335**	93 (2.5)	122
6	**17** + **334**	(3*R*,8*R*,9*S*)-**LVI**	15	90 (5)	>95 (---)	(3*R*,4*S*)-**338**	91 (4)	123
7	**17** + **334**	(*R*)-**LVII**	9	87 (9)	82 (14)	(3*R*,4*S*)-**338**	82 (7)	124
8	**234** + **334**	**XVIIb**	21	80 (13)	>90 (---)	(3*R*,4*R*)-**342**	91 (4)	125

Scheme 112. Asymmetric Intermolecular Cyclization of 324 and 321 Catalyzed by (*R*)-XVd.[119]



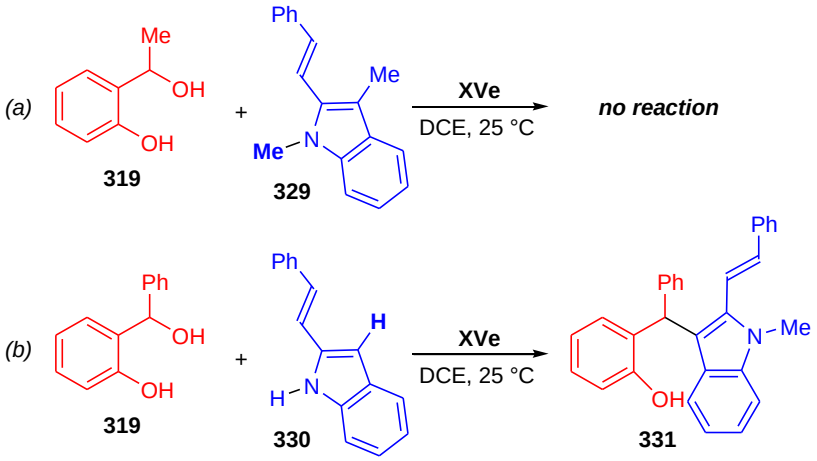
The reaction of **319** with 2-vinyl-indoles **326** was efficiently catalysed by the chiral Brønsted acid (*R*)-**XVe** producing the enantioenriched chroman derivatives **327** bearing three contiguous stereocenters in high yields and excellent selectivities (up to 99% yield, >95% de, 99% ee), Scheme 113.[120] The reactions proceed in a similar manner to those above described. The first step is the in-situ generation of quinone methides by acidic dehydration. Then, the chiral phosphoric acid **XVe** binds by H-bonding both heterodiene and dienophile to give the final adducts **327** by an HDA cycloaddition proceeding through the proposed transition state **328**. Over 26 different experiments, the average yield was 84 ± 14%, the average de 86 ± 7%, and the average ee 94 ± 4% (Table 10, entry 3).

Scheme 113. Asymmetric Intermolecular Cyclization of 319 and 326 Catalyzed by (*R*)-XVe.[120]



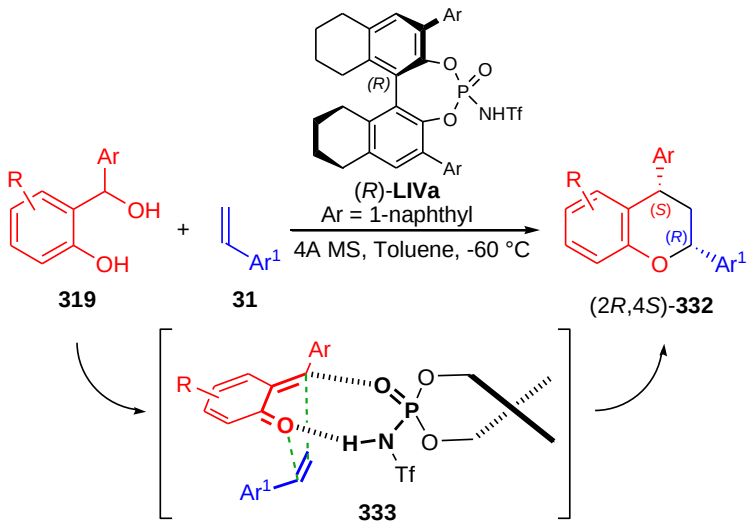
To verify the suggested activation mode, a control experiment using *N*-methyl-protected 3-methyl-2-vinylindole **329** was performed (Scheme 114, eq. *a*). No reaction occurred, thus demonstrating that the N–H group of indole played a crucial role in determining the reactivity of the process. Furthermore, the presence of the methyl substituent on the 3-position of indole was important to drive the reaction toward the HDA pathway: The reaction involving the 3-unsubstituted indole **330** evidenced the formation of the conjugate addition product **331** only, which was obtained within 80% yield and 38% ee (Scheme 114, eq. *b*).[120]

Scheme 114. Control Experiments to Verify the HDA Pathway for the Reaction of 319 with 2-Vinyl Indoles Catalyzed by (*R*)-XVe.[120]



BINOL-based-*N*-triflylphosphoramides **LIV** are more acidic than the corresponding phosphoric acids **XV** and are powerful catalysts for the activation of otherwise unreactive substrates. Hence the organocatalyzed HDA cycloaddition of the *ortho*-quinone methides **320**, generated in situ by the dehydration of **319**, with styrenes **31** produced the enantioenriched chromanes **332**. The catalyst of choice was found to be the octahydro-BINOL-based-triflylphosphoramides (*R*)-**LIVa**, bearing a 1-naphthyl group at the 3-position (Scheme 115),[121] which, under optimized reaction conditions, allowed to obtain syn-2,4-disubstituted chromanes **332** with very good yields and excellent diastereo- and enantioselectivity: In 18 different experiments, the average yield was 83 ± 12%, the average de 95 ± 2%, and the average ee 91 ± 4% (Table 10, entry 4).

Scheme 115. Asymmetric Intermolecular Cyclization of 319 and 31 Catalyzed by (*R*)-LIVa.[121]

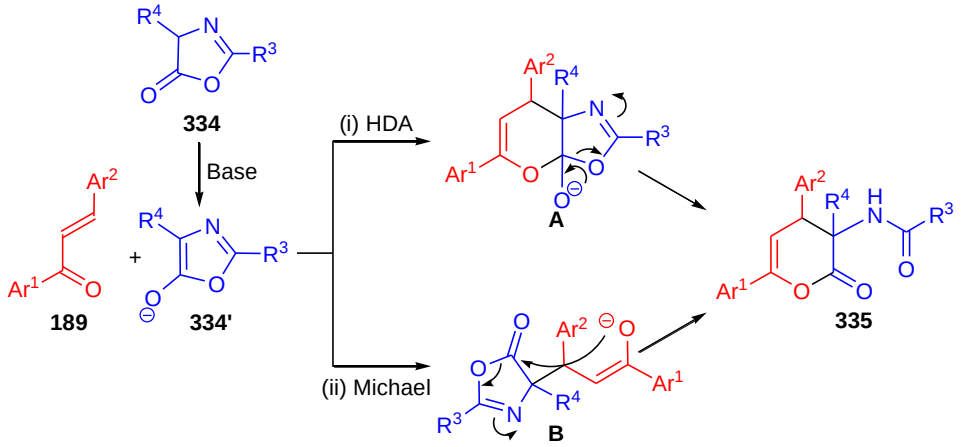


The absolute configuration of **332** was determined to be (2*R*,4*S*) by X-ray analysis and was rationalized by proposing and endo approach of **31** to the less shielded face of *o*-quinone methides coordinated to the catalyst by means of H-bonding and stabilization of the methylene group by the lone pair of the phosphoryl oxygen atom (complex **333**). The formation of the unusual complex **333** was inferred and supported by ^{1}H NMR experiments.[121]

2.1.4. Azlactones as Dienophiles in HDA [4 + 2] Reactions

Azlactones **334** are versatile reactants that are usually employed as Michael donors in the synthesis of potentially bioactive α,α-disubstituted α-amino acids. In some cases, **334** have been shown to act as the 2π component in cyclization processes with heterodienes affording chiral δ-lactones **335** with a quaternary stereocenter. The cyclization may involve two different pathways, as frequently discussed in the present section: (i) a concerted HDA mechanism or (ii) a stepwise reaction beginning with a Michael addition (Scheme 116).[122] Azlactone **334** is initially deprotonated by a base to give the activated reagent **334′**, which can react as an electron-rich dienophile in an HDA reaction with chalcones **189** to produce intermediate **A** that eliminates the good leaving group to give, after protonation, the pyranone **335**. Alternatively, the deprotonated azlactones **334′** acts as a Michael donor at its C-4 position affording intermediate **B** that is converted into **335** by an intramolecular nucleophilic substitution/protonation sequence.

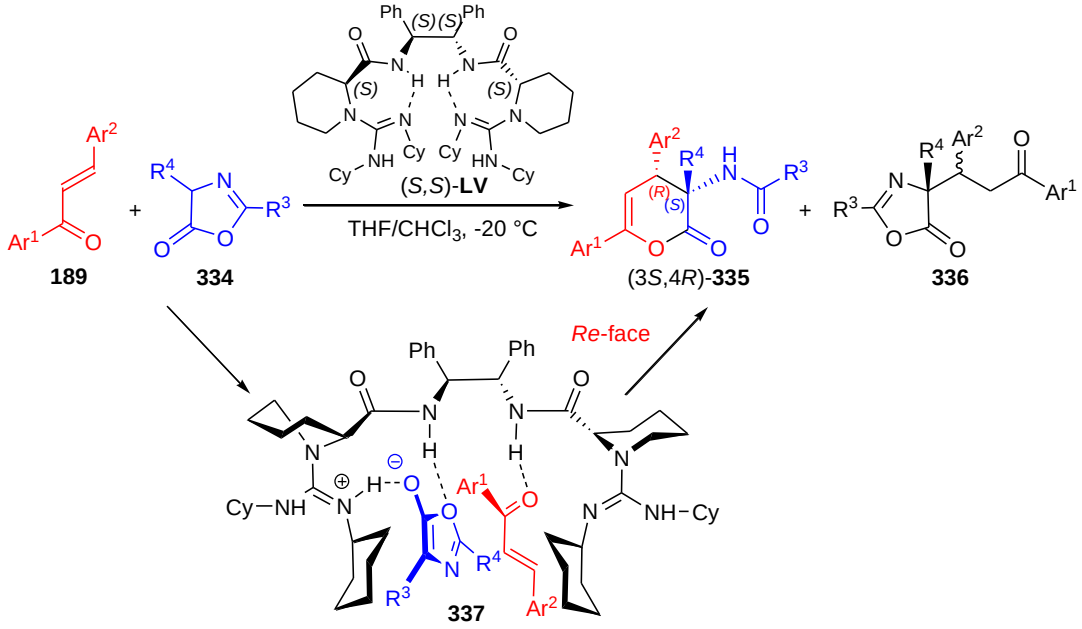
Scheme 116. Proposed Competitive Mechanism for the Base-Catalyzed Cyclization of Heterodienes 189 with Azlactones 334.[122]



The most frequent reaction pathway is the concerted one, and the use of a chiral Brønsted base could allow the enatioselective synthesis of the α-amino δ-lactones with a sugar framework and a quaternary stereocenter. The first efficient synthesis of substrates **335** by following this approach identified the chiral guanidine (*S*,*S*)-**LV**, derived from (*S*,*S*)-1,2-diphenylethylenediamine, as the best chiral Brønsted base to obtain highly selective cycloadditions (Scheme 117).[122] Under optimized conditions, compounds **335** were obtained as the main products together with some traces of **336** (obtained as diastereomeric mixture), products deriving from the protonation of the intermediate **B** in Scheme 116. These side-products were isolated and resubjected to the reaction system, but no conversions into **335** were observed. This evidence strongly supports the concerted HDA cycloaddition as the effective reaction pathway to produce lactones **335**.

δ-Lactones **335** were obtained within good yields as single diastereisomers with excellent enantioselectivity: in 32 different experiments, the average yield was 70 ± 11% and the average ee 93 ± 2.5% (Table 10, entry 5).

Scheme 117. Proposed Transition State for the Asymmetric HDA Reaction of Chalcones 189 and Azlactones 334 Catalyzed by the Chiral Brønsted Base (*S*,*S*)-LV as the Catalyst.[122]

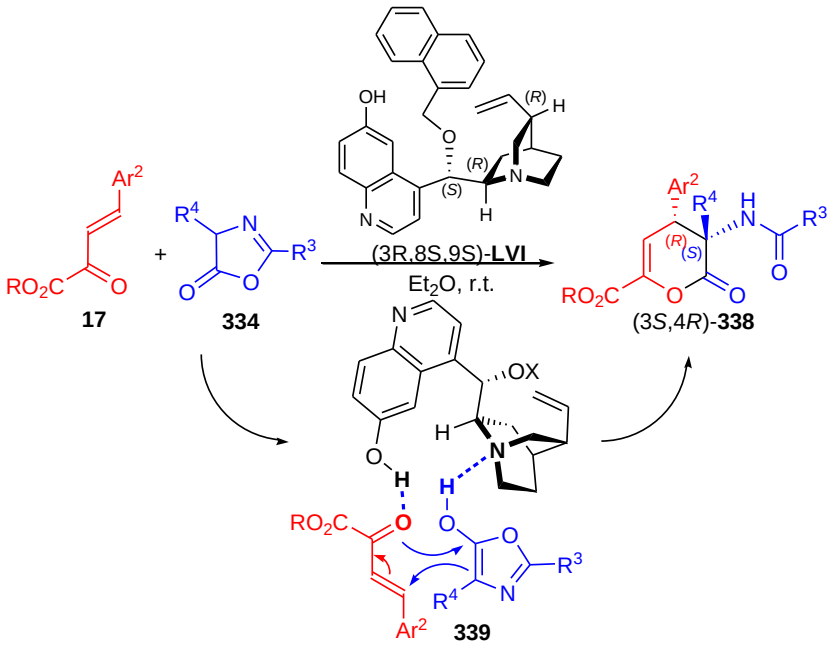


The absolute configuration of the HDA adducts was determined to be (3*S*,4*R*) by X-ray analysis and allowed to propose the bifunctionally activated transition state **337** to rationalize the stereochemical outcome of the HDA cycloaddition (Scheme 117).[122] In the proposed transition state **337** the N-H moiety of the amide could act as a Brønsted acid to activate the chalcone by lowering its LUMO energy through a H-bond. Azlactone **334** could be enolized and recognized by the guanidine moiety, associating with the N-H proton of the amide on the other side via dual intermolecular hydrogen bonds. The enolized azlactone could attach only from the *Re*-face of the chalcone producing the observed (3*S*,4*R*)-**335**.

The cycloadditions between azlactones **334** and activated heterodienes **17** were efficiently catalysed by using cinchona alkaloids as the organocatalysts. After a careful screening of several derivatives, the 6′-hydroxy-cinchonine (3*R*,8*R*,9*S*)-**LVI** was found to be the best catalyst furnishing the δ-lactones **338** as a single diastereoisomer in excellent yields and enantioselectivities (Scheme 118, Table 10, entry 6).[123] The absolute configuration of the adducts was found to be (3*S*,4*R*). Considering the exclusive diastereoselectivity observed in the reaction, the concerted HDA pathway results to be preferred over the stepwise one. The stereochemical outcome of the reaction was

rationalized by considering the transition state **339**, which evidenced the bifunctional action of the catalyst: activation of both heterodiene (by H-bonding) and dienophile (by Brønsted base catalysis).

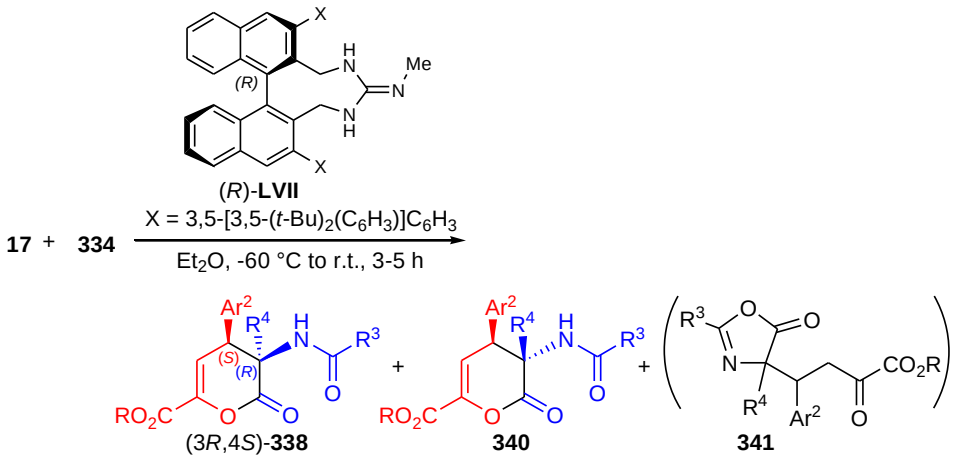
Scheme 118. Asymmetric HDA Reaction of Heterodienes 17 and Azlactones 334 Catalyzed by (3*R*,8*R*,9*S*)-LVI.[123]



The reaction between **17** and **334** was also catalysed by the axially chiral guanidine derivative (*R*)-**LVII** (Scheme 119).[124] After optimization of the reaction conditions (solvent and temperature), the expected cycloadducts **338** were obtained within excellent yields and appreciable enantioselectivities, together with more or less significative amounts of its diastereoisomer **340** (in the previous examples all the reactions were completely diastereoselective), (entry 7 in Table 10).

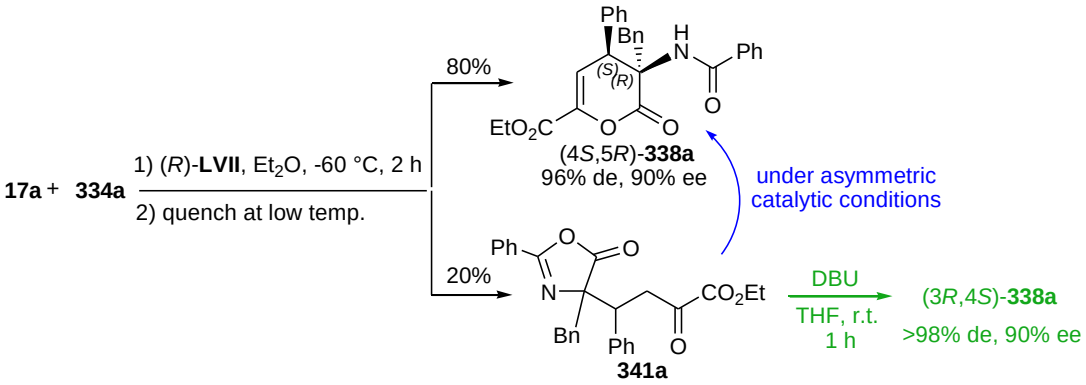
When the reaction was conducted at -60 °C for 2 h, a considerable amount of the acyclic product **341** was detected by ^{1}H NMR spectroscopic analysis of the crude product. Compound **341** corresponds to the Michael addition product resulting from protonation of intermediate **B** (see Scheme 116), and it was transformed to the desired cyclic product **338** by warming the reaction to room temperature. This evidence seems to support a stepwise mechanism for the δ-pyranone formation.

Scheme 119. Asymmetric HDA Reaction of Heterodienes 17 and Azlactones 334 Catalyzed by (*R*)-LVII.[124]



To confirm that the Michael addition was the initial step, the acyclic product **341** was isolated by quenching the reaction at a low temperature and then converted into **338** by using an achiral base as the catalyst (DBU): The cycloadduct was formed with the same de and ee obtained in the catalytic enantioselective reaction (Scheme 120). Hence, these results strongly suggest that **338** is formed via an enolate form of acyclic intermediate **341**, the anionic intermediate **B** in Scheme 116, and the initial Michael addition reaction is the stereo-determining step.

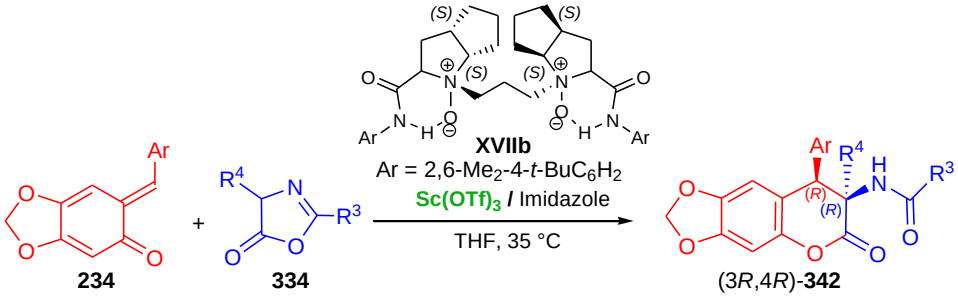
Scheme 120. Mechanistic Investigation of Cycloaddition Reaction of 17 with 334 Catalyzed by (*R*)-LVII.[124]



The HDA reaction between *o*-quinone methides **234** and azlactones **334** was efficiently catalyzed by the complex of $Sc(OTf)_3$ with the *N*,*N*′-dioxide chiral ligand **XVIIb** (Scheme 121).[125] The cycloaddition proceeds under mild reaction conditions to give the expected dihydrocoumarins

342 in high yields and excellent enantioselectivities: Over 21 different experiments the average yield was 80 ± 13%, the de was >90%, and the average ee was 91 ± 4% (Table 10, entry 8). The absolute configuration of the cycloadduct was found to be (3*R*,4*R*) by X-ray analysis, and it was rationalized by an octahedral complex in which Sc(III) coordinates both the reagents allowing an endo approach to the less hindered *Re*-face of **234**. Furthermore, an accurate investigation by IR spectroscopy allowed to exclude any stepwise mechanism for the cyclization process.

Scheme 121. Asymmetric HDA Reaction of Heterodienes 334 and Azlactones 334 Catalyzed by XVIIb.[125]



2.2. 3,4-Dihydropyran Derivatives from Diene and Carbonyl HDA Reactions and Other [4+2] Cyclization Processes

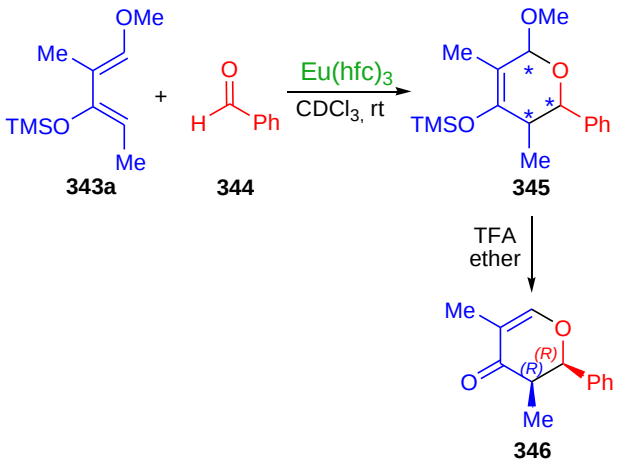
In section 2.1 the [4+2] cyclization processes between oxa-heterodienes and olefins to prepare enantioenriched 3,4-dihydro-2*H*-pyran derivatives (with up to three new contiguous stereocenters), or the corresponding 3,4-dihydro-pyran-2-ones (with up two contiguous chiral carbons), have been discussed. The process may proceed either by a concerted pathway (an inverse electron demand HDA reaction), or by a stepwise mechanism via the initial Michael addition.

The cycloaddition between carbonyl compounds, acting as heterodienophiles, with 1,3-dienes give 3,6-dihydro-2*H*-pyran derivatives, typically from a normal electron demand Diels-Alder reaction. Even if these heterocycles are not in the topic of the present review, the [4+2] cyclizations between either unactivated or activated carbonyl compounds with electron-rich dienes (the Danishefsky's diene) have to be considered since they produce 2,3-dihydro-pyran-4-ones bearing with up to two new stereocenters.[126,127]

2.2.1. Dienes and Aldehydes (an Introduction)

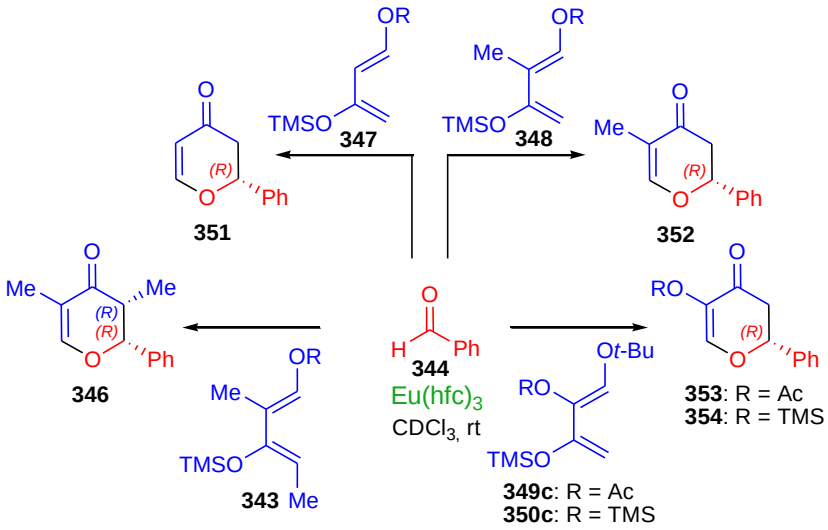
The discovery of the original route to 2,3-dihydro-pyran-4-ones originates from the seminal intuition that the oxophilicity of rare-earth cations should allow their behaviour as mild Lewis acid catalysts in reaction involving aldehydes as the electrophilic reagent. The coordination of the lanthanide cation with the aldehyde should determine a stabilization of the LUMO energy of the carbonyl group, thus allowing a behaviour of the C=O as an electron-poor heterodienophile in HDA reaction with electron rich dienes. After the first experience with $Eu(fod)_3$, which proved to be an efficient catalyst of the reaction between unactivated aldehydes and silyloxydienes, Bednarski and Danishefsky explored the possibility that an europium cation bearing a chiral ligand "*might exhibit topological biases*".[128] The serendipitous choice of tris-[3-(heptafluoropropylhydroxymethylene-*d*-camphorate]europium [(+)-$Eu(hfc)_3$] as the chiral catalyst discovered the potentialities of this method for an asymmetric induction of the reaction between diene **343a** "*the Danishefsky's diene*" and benzaldehyde **344** in the formation of (3,6-dihydro-6-methoxy-3,5-dimethyl-2-phenyl-2*H*-pyran-4-yloxy)trimethylsilane **345**, in which three chiral centers are established through a suprafacial *endo*-cycloaddition process (Scheme 122). The treatment of the crude adduct with TFA in ether gave 2,3-dihydro-3,5-dimethyl-2-phenylpyran-4-one **346**, which was obtained with an encouraging 50% ee (the absolute configuration was later determined to be (2*R*,3*R*)).

Scheme 122. The First Enantioselective HDA Reaction Between the Danishefsky's Diene 343a and Benzaldehyde 344 Catalyzed by $Eu(hfc)_3$.[128]



The methodological investigation of the above findings was immediately developed in two further papers.[129,130] The change of the steric demand in the Danishefsky's diene was tested by using **343** and **347-350** in the $Eu(hfc)_3$ catalyzed HDA with benzaldehyde **344** (Scheme 123).[129]

Scheme 123. Enantioselective HDA Reactions Between Danishefsky's Dienes and 344 Catalyzed by $Eu(hfc)_3$.[129]



The enantioselectivity was always low: in any case the ee was lower than 50%, with an average value of 37 ± 13%. Even if the enantioselectivity cannot be considered satisfactory, these pioneering reports represented one of the corner stones in the developing of asymmetric catalysis.

The reaction mechanism was studied by inferring the effect of the Lewis acid catalyst employed in the cyclization process.[131,132] It was demonstrated that the product of the reaction between diene and aldehyde can be formed through two different pathways: (i) a concerted HDA cycloaddition, and (ii) a Mukaiyama-aldol reaction, whose intermediates were identified and converted into the 2,3-dihydropyran-4-one upon treatment with trifluoroacetic acid.

Obviously, the stereochemistry of the final product depends on the structure of the transition state of the reaction. The HDA reaction may occur through either an *endo* or an *exo* ts, which correspond to an attack to the *Si*- or *Re*-face of the aldehyde, respectively. Analogously, the Mukaiyama-aldol pathway may involve attacks to the *Si*- or to the *Re*-face of the aldehyde. All the possible pathways with the resulting stereochemical outcomes are illustrated in Figure 6. The

configuration of the final products does not depend on the type of reaction, but on the face of the aldehyde involved in the nucleophilic attack. Hence, the discussion in next sections will be more focused on the preferred attacked face than the type of reaction.

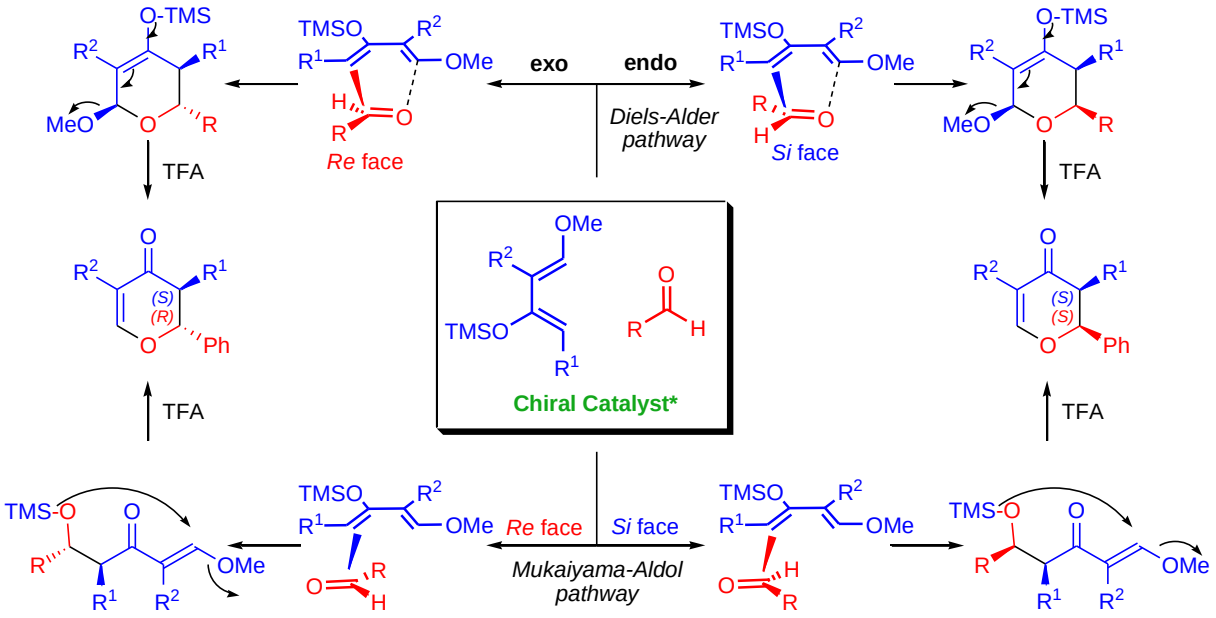


Figure 6. Reaction pathways, preferred attached face, and stereochemical outcome for the reaction between Danishefky's dienes and aldehydes.

This was the seminal research that is again the basis of a useful synthetic route to 2,3-dihydropyran-4-ones, astonishing if one considers that everything starts from $Eu(hfc)_3$ whereas now several clusters of catalysts are usefully employed with the excellent results that will be detailed described in the next sections.

2.2.2. [4+2] Cyclizations between Danishefsky's Dienes and Aldehydes Catalyzed with Chiral Lewis-Acid Complexes

Respect to section 2.1, the enantioselective [4+2] cycloaddition processes to furnish enantioenriched 2,3-dihydropyran-4-ones, involving electron-rich dienes, are mainly obtained by using chiral complexes involving a chiral ligand with the suitable cation acting as a Lewis acid. Among the different possibilities, the most frequently used catalysts are the Ti(IV)-BINOLates, the

Cr(III) with Schiff bases as chiral ligands, and, more recently, the dirhodium(II) carboxamidate catalysts.

2.2.2.1. The BINOL- and BINOL-derivative/Titanium(IV)-based Catalysts

Many reactions employed a [BINOL/Ti(IV)] complex prepared from BINOL (or from a BINOL derivative) and $Ti(OiPr)_4$. Several [BINOLate/Titanium] complexes have been synthesized and characterized by X-ray crystallography. These include the dinuclear $[(BINOLate)Ti(OiPr)_2,Ti(OiPr)_4]$, which contains a bridging naphtholate and isopropoxy group, trinuclear $[(BINOLate)Ti(OiPr)_2,[Ti(OiPr)_4]_2$, and trimeric $[(BINOL)Ti(OiPr)_2]_3$ (Figure 7).[133] The BINOLate-titanium species responsible for the catalytic and stoichiometric asymmetric addition reactions are different, explaining why nonlinear effects are often observed in the catalytic reactions and why complexes containing different BINOL species may give interesting specific catalysts.

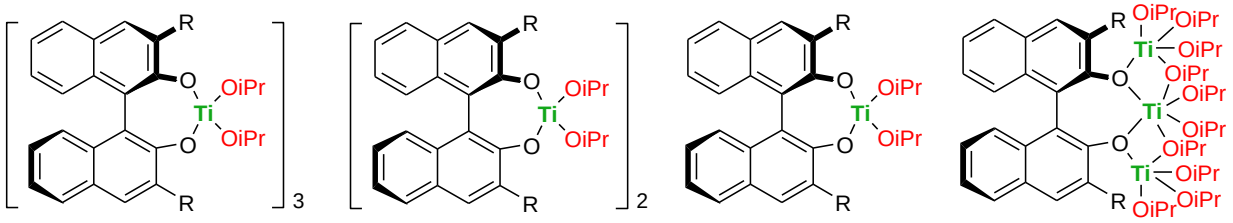
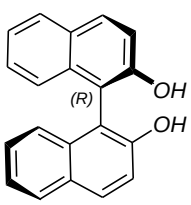


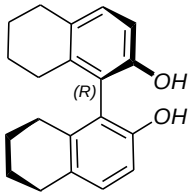
Figure 7. Schematic X-ray structure of different [(*R*)-BINOL/$Ti(OiPr)_4$] complexes whose stability depends on the nature of R (Ref. 133).

Among the different chiral complexes used as enantioselective catalysts in such a kind of process, the BINOL-based complexes are the most frequently used, particularly with Ti(IV) as the Lewis acid. Chart 4 reports the different chiral BINOLs employed, in which the main variations concern the saturation level of the second aromatic ring and the presence of substituents in *ortho* at the hydroxyl group; Chart 5 list the different Danishefsky-type dienes and the carbonyl species whose reactions have been enantioselectively catalysed.

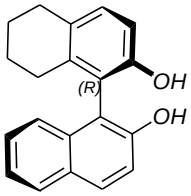
Chart 4. BINOL Ligands Used in Asymmetric Catalysis of HDA Reactions.



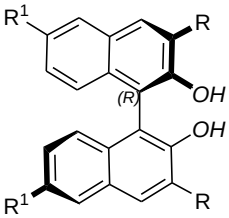
(*R*)-**LVIII**



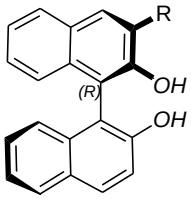
(*R*)-**LIX**



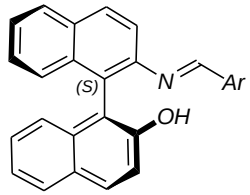
(*R*)-**LX**



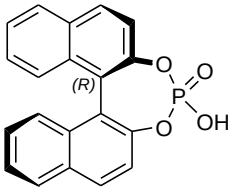
(*R*)-**LXIa**: R = $SiPh_3$; R^1 = H
(*R*)-**LXIb**: R = $Si(3,5\text{-xilyl})_3$; R^1 = H
(*R*)-**LXIc**: R = Ph; R^1 = H
(*R*)-**LXId**: R = $2,5\text{-}(OMe)_2\text{-}C_6H_3$; R^1 = H
(*R*)-**LXIe**: R = $2,5\text{-}(OHex)_2\text{-}C_6H_3$; R^1 = H
(*R*)-**LXIf**: R = $2,5\text{-}(Hept)_2\text{-}C_6H_3$; R^1 = H
(*R*)-**LXIg**: R = Br; R^1 = H
(*R*)-**LXIh**: R = I; R^1 = H
(*R*)-**LXIi**: R = I; R^1 = C_2F_5
(*R*)-**LXIj**: R = I; R^1 = I



(*R*)-**LXII**



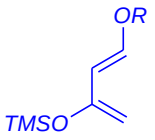
(*S*)-**LXIII**



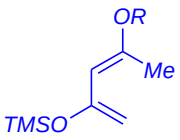
(*R*)-**LXIV**

Chart 5. Electron Rich Dienes and Carbonyl Derivatives Used in Enantioselective HDA Reactions Catalyzed by BINOLate/Titanium Chiral Complexes.

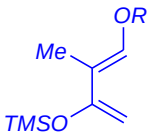
Danishefsky-type Dienes



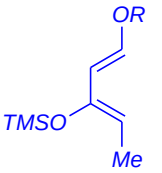
347a: R = Me
347b: R = Et
347c: R = i.Pr
347d: R = *t*-Bu



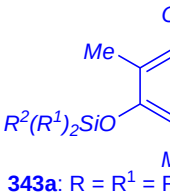
355a: R = Me
355b: R = Et
355c: R = *t*-Bu



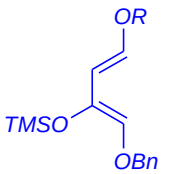
348a: R = Me
348b: R = Et
348c: R = *t*-Bu



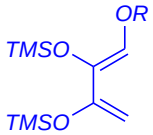
356a: R = Me
356b: R = Et
356c: R = *t*-Bu



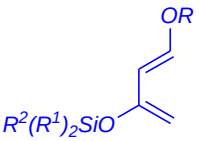
343a: R = R^1 = R^2 = Me
343b: R = Et; R^1 = R^2 = Me
343c: R = *t*-Bu; R^1 = R^2 = Me
343d: R^2 = *t*-Bu; R = R^1 = Me



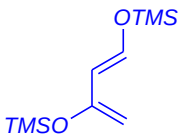
357a: R = Me
357b: R = Et
357c: R = *t*-Bu



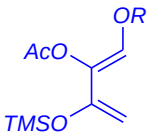
350a: R = Me
350b: R = Et
350c: R = *t*-Bu



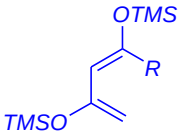
358a: R = R^1 = Me; R^2 = Et
358b: R = Me; R^1 = R^2 = Et
358c: R = *t*-Bu; R^1 = Me; R^2 = Et
358d: R = Me; R^1 = Me; R^2 = *t*-Bu



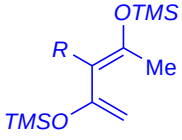
359



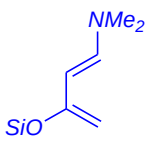
349a: R = Me
349b: R = Et
349c: R = *t*-Bu



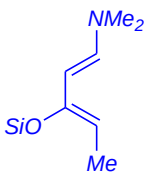
360a: R = Me
360b: R = Ph
360c: R = *t*-Bu



361a: R = Me
361b: R = Et
361c: R = Ph
361d: R = Cl



362a: Si = TMS
362b: Si = TES
362c: Si = TBS



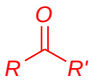
363a: Si = TMS
363b: Si = TES
363c: Si = TBS

Heterodienophiles

Aldehydes

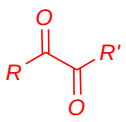
364a: R = aliphatic
364b: R = aromatic
364c: R = heterocyclic

Ketones



365a: symmetric
365b: asymmetric
365c: cyclic

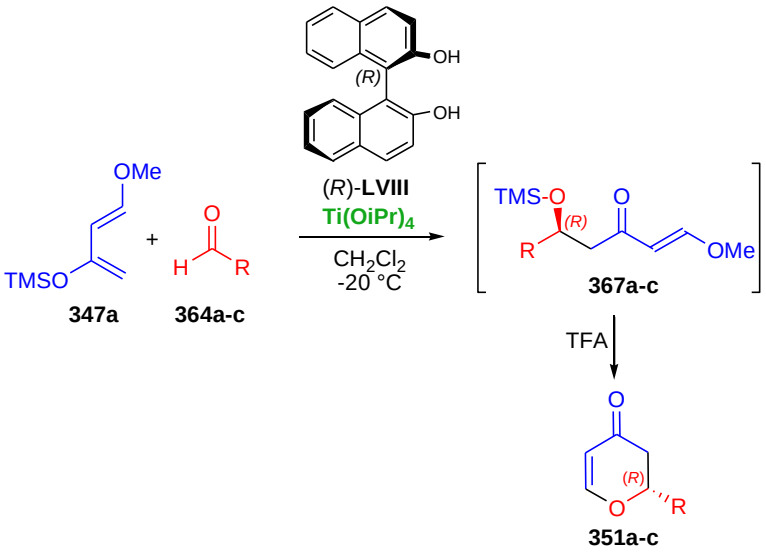
α-dicarbonyls



366a: glyoxylates
366b: 2-oxoaldehydes
366c: ketoesters
366d: diones
366e: cyclic diones

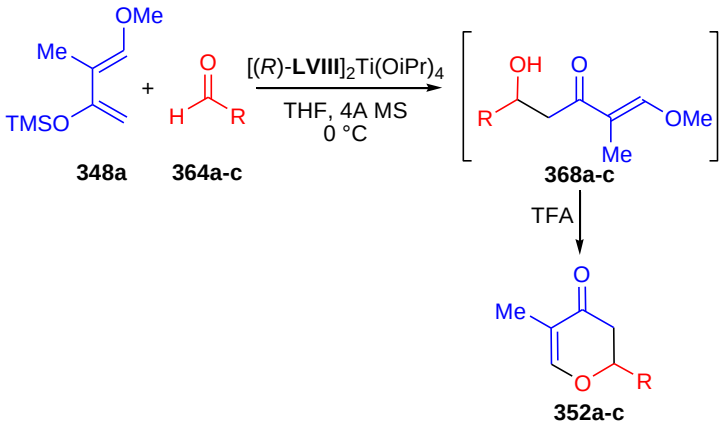
The first report dealing with the use of BINOLate/Ti(IV) as enantioselective catalysts appeared some years after the pioneering Danishefsky's contribution. The chiral BINOL was the simplest (*R*)-**LVIII** and the Ti(IV) source was the classical $Ti(OiPr)_4$ and seven different aldehydes **364a-c** were allowed to react with the Danishefsky's diene **347a** in CH_2Cl_2 at -20 °C (Scheme 124).[134] The isolated crude products were the Mukaiyama-aldol intermediates **367a-c** that, when treated with TFA, cyclized to 4-pyranone **351a-c** with moderate-good yields (from 55 to 88%) and with excellent enantioselectivity (with up to 97% ee), entry 1 in Table 11. The absolute configuration was (*R*), which is consistent with a diene approach to C=O *Re*-face.

Scheme 124. Enantioselective Formal HDA Reactions Between 347a and 364a-c Catalyzed by $Ti(OiPr)_4$[(*R*)-LVIII]$_2$.[134]



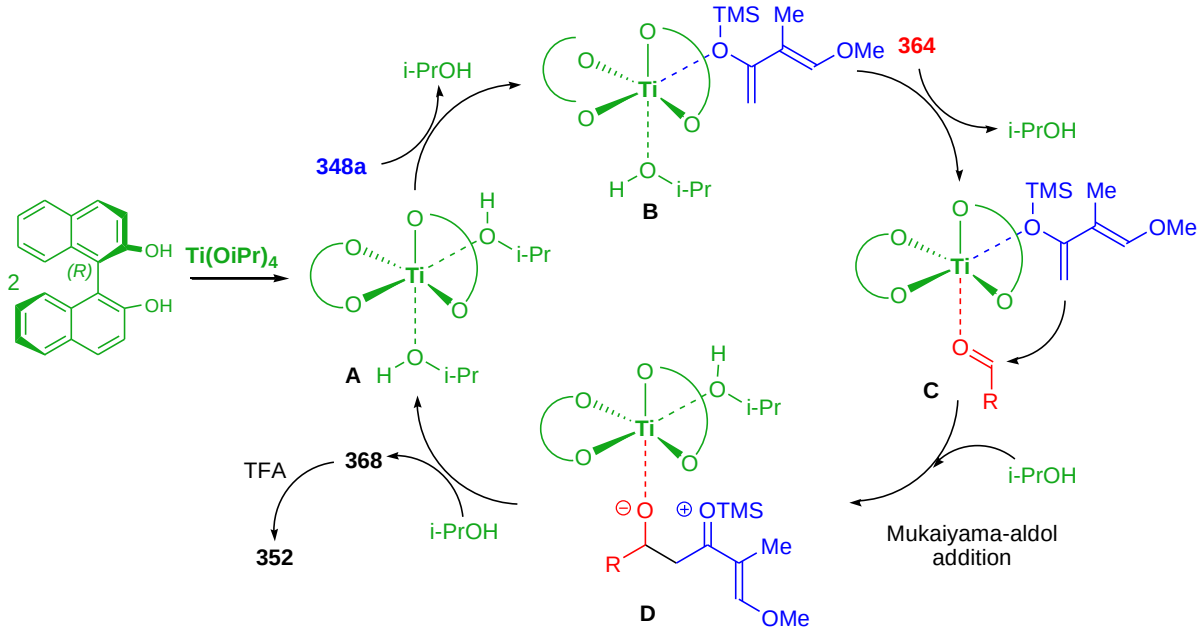
The formal HDA reaction between diene **348a** and aldehydes **364a-c** was efficiently catalysed by Ti(IV)[(*R*)-**LVIII**]$_2$ to produce 2-substituted 5-methyl-2,3-dihydro-pyran-4-ones **352a-c**. The reaction was proved to proceed via Mukaiyama-aldol addition to produce intermediates **368a-c** that could be isolated and characterized by spectroscopic and HRMS analyses. The treatment of crude mixture with TFA furnished cycloadducts **352a-c** with yields ranging from moderate (40-50%) to excellent values (95-99%), and very high enantioselectivities (83-99% ee), Scheme 125.[135,136]

Scheme 125. Enantioselective Formal HDA Reactions Between 348a and 364a-c Catalyzed by Ti(OiPr)$_4$[(*R*)-LVIII]$_2$.[135,136]



22 Different aldehydes were tested and the average results reported in entry 2 of Table 11 evidenced a more important influence of the R substituent on the reactivity (average yield, 77 ± 21%) than on selectivity (average ee, 94 ± 5%). The proposed mechanism for the enantioselectively catalysed cycloadditions is shown in Scheme 126.[136]

Scheme 126. Proposed Mechanism Formal HDA Reactions Between 348a and 364a-c Catalyzed by Ti(OiPr)$_4$[(*R*)-LVIII]$_2$.[136]



The catalyst **A** was prepared in situ by mixing 2 equiv of BINOL (*R*)-**LVIII** with 1 equiv of Ti(OiPr)$_4$. The displacement of one i-PrOH by dienes **348a** produced complex **B** that is rapidly

converted in complex **C** by substitution of the second iPrOH by aldehyde **364**. Hence, the two organized reactants reacted in the Mukaiyama aldol reaction to produce complex **D** that released the condensation product **368** by displacement with i-PrOH regenerating the initial active complex **A**. Finally, treatment of **368** with TFA produced the cycloadducts **352**.

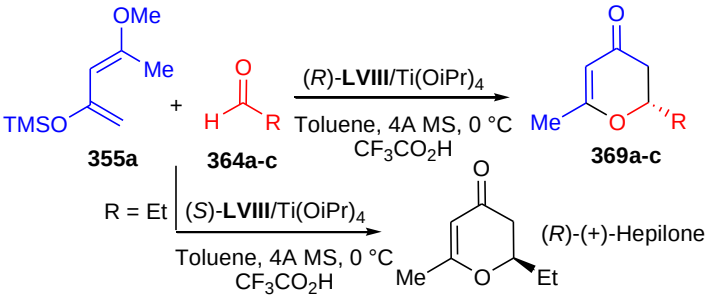
The mechanism depicted in Scheme 126 evidenced the important role of i-PrOH in the catalytic cycle. To infer this specific aspect some control experiments were performed. When $Ti(OiPr)_2Cl_2$ and $TiCl_4$ were used instead $Ti(OiPr)_4$ to generate the catalyst, the yield and the ee of pyranone **352a** (R = Ph) decreased regularly: $Ti(OiPr)_4$, 86% yield and 99% ee; $Ti(OiPr)_2Cl_2$, 62% yield and 87% ee; $TiCl_4$, 26% yield and 82% ee. These decreases, particularly those regarding the reaction yields, were probably due to the fact that the chloride ion was much smaller and more electronegative than the isopropoxide, making more difficult the ligand exchange passages involved in the catalytic cycle.

Also the formal HDA reaction between diene **355a** and aldehydes **364a-c** to give 2-substituted 6-methyl-2,3-dihydro-pyran-4-ones **369a-c** was efficiently catalysed by Ti(IV)/(*R*)-**LVIII** complex, but with a BINOL/Lewis acid ratio of 1:1 (Scheme 127).[137,138] The reaction proceeded again via Mukaiyama-aldol addition followed by cyclization of the adducts by treatment with TFA. The cycloadducts **369a-c** were obtained within good yields (average yield, 79 ± 11%) and excellent enantioselectivities (average ee 95 ± 5%), entry 3 in Table 11.[137,138] This methodology was usefully applied in a direct and convenient synthesis of (*R*)-(+)-Hepilone, a male moth sex pheromone. As expected, the use of (*S*)-BINOL instead of its (*R*) enantiomer allows to obtain the pyranone with the opposite stereochemistry; hence the natural enantiomer of Hepilone was obtained within 88% yield and 94% ee (Scheme 127).[138]

As previously discussed, the use of $TiCl_4$ instead $Ti(OiPr)_4$ was detrimental from both reactivity and selectivity point of view.[136] In order to optimize the results obtainable with $TiCl_4$, the use of sodium alcoholate as additive was tested in the reaction between **355a** and aldehydes **364b**.[139] Hence, the formal HDA cycloadditions were run by using (*R*)-**LVIII**, $TiCl_4$, and *sec*-$ButO^-$

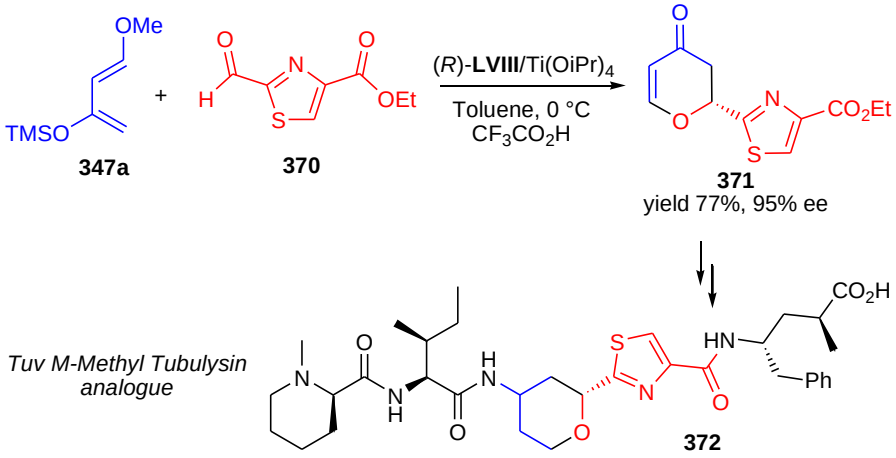
Na^+ in the ratio 1.0:1.2:4.2 as the catalytic system. The use of alcoholates as the additive ameliorates both reactivity and selectivity, but the results were in any case lower respect to those obtained by using $Ti(OiPr)_4$ without any additive (Table 11, entry 4 vs entry 3).

Scheme 127. Enantioselective Formal HDA Reactions Between 355a and 364a-c Catalyzed by $Ti(OiPr)_4$/(*R*)-LVIII.[137,138]



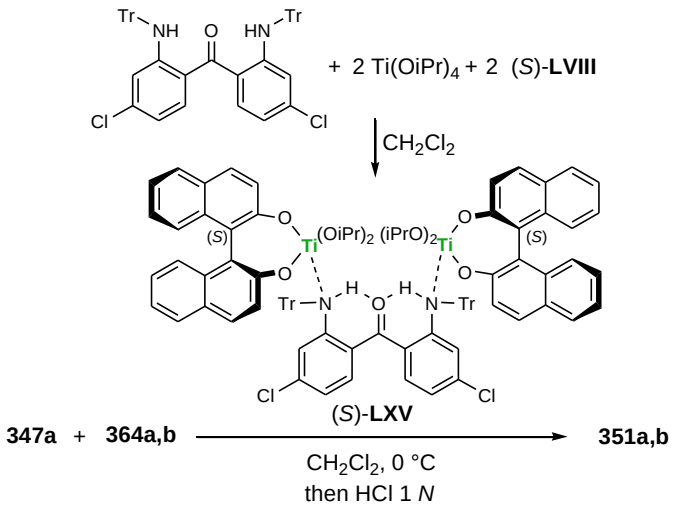
The high efficiency of the Ti(IV)/(*R*)-**LVIII** complex as enantioselective catalyst was the base for an interesting practical application. The reaction between Danishefsky's diene **347a** and the thiazole aldehyde **370** under the usual conditions produced the expected cycloadduct **371** with a very good yield and an excellent enantioselectivity. The functionalised pyran-4-one **371** was the key intermediate in the synthesis of a conformationally rigid Tuv *N*-methyl tubulysin analogue **372** (tubulysins are the most potent antimycotic agents), Scheme 128.[140]

Scheme 128. Enantioselective Formal HDA Reactions Between 347a and 370 Catalyzed by $Ti(OiPr)_4$/(*R*)-LVIII.[140]



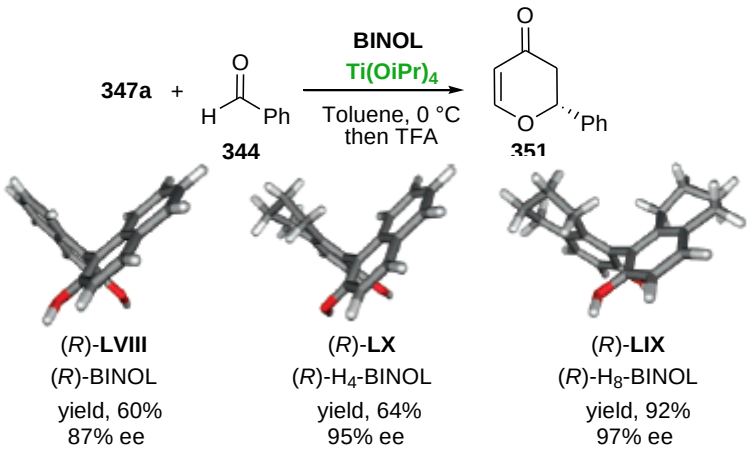
The previously discussed BINOL-base complexes involved 1 equiv of Ti(IV) and either 1 or 2 equivalents of chiral ligand. A variant was developed by Maruoka that proposed a novel bis-titanium(IV) (*S*)-**LXV** as catalyst in formal HDA reactions.[141] It was prepared by simply mixing of 2,2'-bis(tritylamino)-4,4'-dichlorobenzophenone with 2 equiv of $Ti(OiPr)_4$ in CH_2Cl_2 and subsequent treatment with (*S*)-**LVIII** (2 equiv.). The catalysed reaction between Danishefsky's diene **347a** and aldehydes **364a,b** proceeded smoothly to furnish, after acidic hydrolysis, pyran-4-ones **351a,b** (Scheme 129). The adducts were isolated within moderate-good yields and with appreciable enantioselectivities (Table 11, entry 5). Specifically, the best results were obtained for aliphatic aldehydes **364a**, since the products were obtained with up to 78% yield and 97% ee.

Scheme 129. Enantioselective Formal HDA Reactions Between 347a and 364a,b Catalyzed by (*S*)-LXV.[141]



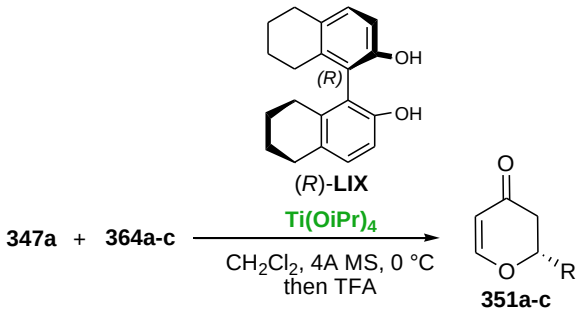
In order to investigate the relationship among catalyst structure and activity, the effect of more or less hydrogenated BINOL ligands on the enantioselective catalysis of the HDA reaction between the Danishefsky's diene **347a** and benzaldehyde **344** was examined (Scheme 130).[142] Among the several ligands tested, the complexes involving (*R*)-BINOL **LVIII**, (*R*)-H_4-BINOL **LX**, and (*R*)-H_8-BINOL **LIX** with Ti(OiPr)4 in a ratio 1:1 evidenced appreciable enantioselectivity level (from 87 to 97% ee), with a regular trend clearly evidencing the improvement of the catalyst efficiency in going from (*R*)-BINOL to (*R*)-H_8-BINOL.

Scheme 130. Enantioselective Formal HDA Reactions Between 347a and 344 Catalyzed by Different BINOL/Ti(OiPr)$_4$ Complexes. [Reproduced from ref. 142. Copyright 2002 American Chemical Society.]



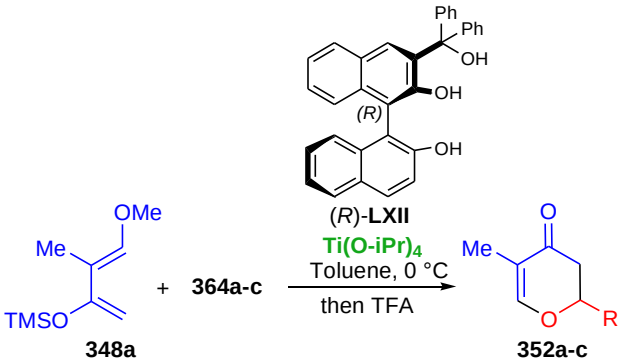
The trends in the change of enantioselectivity and reactivity were rationalized as the result of the steric repulsion between two far-side rings, which determined an analogous trend in the change of the dihedral angle of the axial biaryl groups in the titanium complex in the series (*R*)-H$_8$-BINOL, (*R*)-H$_4$-BINOL, and (*R*)-BINOL (Scheme 130). Hence, the dihedral angle of the axial biaryl group in BINOL ligands was very important to obtain high reactivity and selectivity. This conclusion cannot be generally applied, since analogous experiments with a BINOL:Ti(IV) ratio of 2:1 instead 1:1 evidenced [(*R*)-BINOL]$_2$/Ti(OiPr)$_4$ as the catalyst of choice, while [(*R*)-H$_8$-BINOL]$_2$/Ti(OiPr)$_4$ gave the worse results.[136] Hence, the optimized BINOL (*R*)-**LIX** was exploited in the formal HDA cycloaddition between the Danishefsky's diene and aldehydes **364a-c** to produce pyranone **351a-c** (Scheme 131). Sixteen different aldehydes were tested and the results evidenced good yields and excellent enantioselectivities (Table 11, entry 6).[142,143]

Scheme 131. Enantioselective Formal HDA Reactions Between 347a and 364a-c Catalyzed by (*R*)-LIX/Ti(OiPr)$_4$ Complex.[142-143]



Modifications of the BINOL ligand at either its 3- or 3,3'-positions have been tested in order to improve the catalytic efficiency of the Ti(IV)-based complex, and the catalyst of (*R*)-**LXII** with Ti(OiPr)4 in a ratio 1:1 was found very efficient in the HDA cycloaddition between **348a** and aldehydes **364a-c** (Scheme 132).[144] Under optimized reaction conditions the adducts **352a-c** were obtained in excellent yields and enantioselectivities independently from the nature of R substituent on the aldehyde: Over 20 different experiments with both aliphatic and aromatic or heteroaromatic aldehydes the average yield was 92 ± 7% and the average ee was 93 ± 4% (Table 11, entry 7).

Scheme 132. Enantioselective Formal HDA Reactions Between 348a and 364a-c Catalyzed by (*R*)-LXII/Ti(OiPr)$_4$ Complex.[144]



The mechanism proposed in this example was the traditional Diels-Alder pathway since the open-chain intermediate from the alternative Mukaiyama-aldol addition was not detected. The most intriguing result was obtained by investigating the relation between the ee of the BINOL and the ee of the cycloadduct. The results evidenced both weak positive and strong negative nonlinear effects. The negative deviation was strong since, with a BINOL optical purity of 20% ee, the opposite

enantiomer of **352** was obtained with an incredible 73% ee (Figure 8).[144] This finding was interpreted by proposing that the active species of the HDA reaction might change with the decrease of the ligand optical purity, but more deep investigations are probably required for a more exhaustive rationalization.

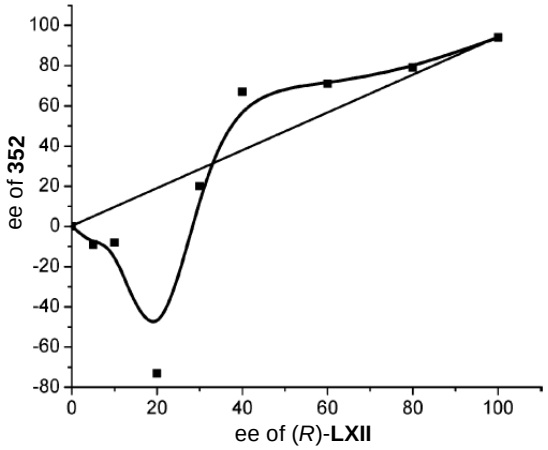


Figure 8. Relationship between enantiomeric purities of the chiral ligand (*R*)-**LXII** and of the product **352**. [Reproduced from ref. 144. Copyright 2008 American Chemical Society.]

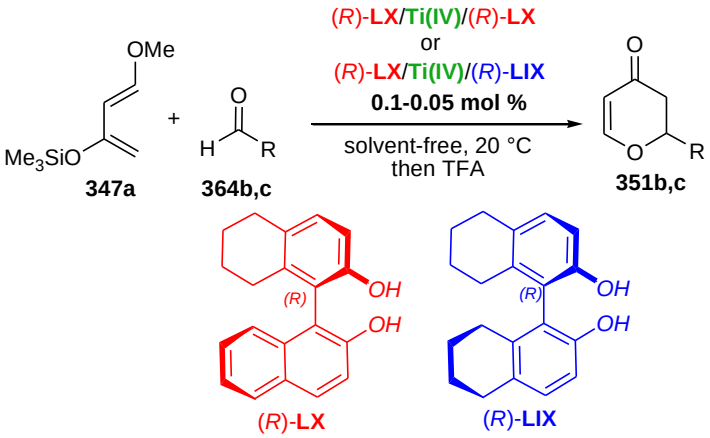
By a combinatorial approach, a catalyst library of 104 members was generated by combining 13 different chiral diols with $Ti(OiPr)_4$ in a ratio of 2:1, which were evaluated in the reaction of Danishefsky's diene with benzaldehyde by using the high throughput chiral HPLC technique.[145] After the initial screening, two ligands were found outstanding from both the reactivity and selectivity point of view: the tetrahydro-BINOL (*R*)-**LX** and the octahydro-BINOL (*R*)-**LIX**. Furthermore, the reaction conditions were optimized in order to decrease the catalyst loading and to run the process under solvent-free conditions (Scheme 133). The final result was the identification of the two best catalysts (*R*)-**LX**/$Ti(OiPr)_4$/(*R*)-**LX** and (*R*)-**LX**/$Ti(OiPr)_4$/(*R*)-**LIX**, which were exploited in the cycloaddition of **247a** with 14 different aldehydes under free-solvent conditions and by using 0.1-0.05 mol % of catalyst. In all cases the cycloadducts were obtained within excellent yields (81-99%) and enantioselectivities (with up to 99.4% ee), see Table 11, entries 8 and 9 respectively.

Table 11. Average Values and Standard Deviations (s.d.) of the Reaction Yields, Diastereo-, and Enantioselectivities for the Formal HDA Reactions Catalyzed by [BINOLate/Titanium(IV)] complexes between Dienes and Aldehydes reported in Chart 5.

Entry	Diene	Hetero-dienophile	Catalyst	n. Exp.	aver. Yield % (s.d.)	Reaction Product	aver. ee % (s.d.)	Attached C=O face	Ref.
1	**347a**	**364a-c**	Ti(IV)[(*R*)-**LVIII**]$_2$	7	67 (14)	**351a-c**	89 (9)	*Re*	134
2	**348a**	**364a-c**	Ti(IV)[(*R*)-**LVIII**]$_2$	22	77 (21)	**352a-c**	94 (5)	---	135, 136
3	**355a**	**364a-c**	Ti(IV)/(*R*)-**LVIII**	25	79 (11)	**369a-c**	95 (5)	*Re*	137, 138
4	**355a**	**364b**	Ti(IV)/(*R*)-**LVIII**[a]	13	79 (8)	**369b**	78 (12)	---	139
5	**347a**	**364a,b**	(*S*)-**LXV**	8	65 (12)	**351a,b**	85 (14)	*Si*	141
6	**347a**	**364a-c**	Ti(IV)/(*R*)-**LIX**	16	64 (15)	**351a-c**	94 (6)	*Re*	142, 143
7	**348a**	**364a-c**	Ti(IV)/(*R*)-**LXII**	20	92 (7)	**352a-c**	93 (4)	---	144
8	**347a**	**364b,b**	(*R*)-**LX**/Ti(OiPr)$_4$/(*R*)-**LX**	14	93 (12)	**351b,c**	95 (7)	*Re*	145
9	**347a**	**364b,c**	(*R*)-**LX**/Ti(OiPr)$_4$/(*R*)-**LIX**	14	91 (15)	**351b,c**	98 (1)	*Re*	145
10	**347a**	**364a-c**	Ti(IV)[(*S*)-**LXIII**]$_2$[b]	11	92 (7)	**351a-c**	86 (8)	*Si*	146
11	**347a**	**364b,c**	Ti(IV)/(*S*)-**LXVII**[c]	12	99 (---)	**351b,c**	91 (9)	*Si*	147

[(a)] *sec*-ButO$^-$Na$^+$ as additive. [(b)] (*S*)-Naproxen **LXVI** as additive. [(c)] Dentritic ligand with (*S*)-Naproxen as additive.

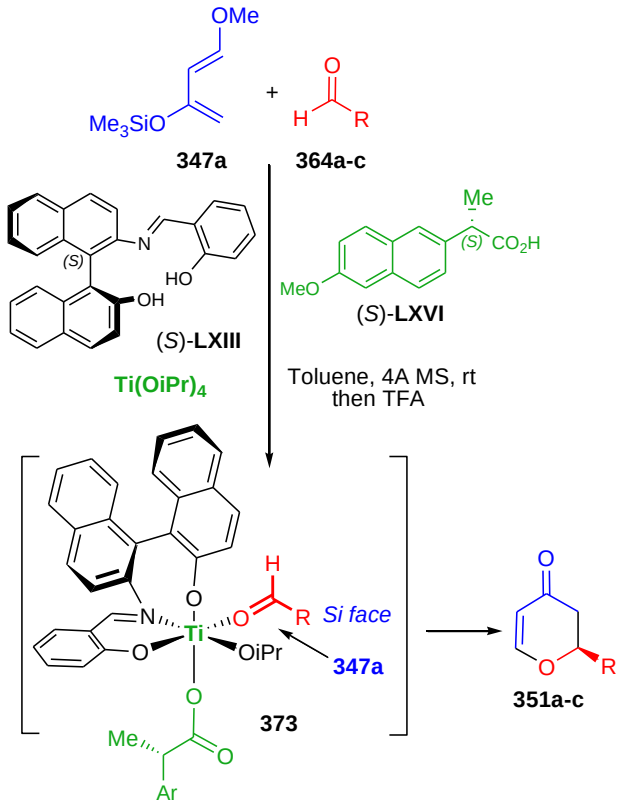
Scheme 133. Enantioselective Formal HDA Reactions Between 347a and 364b,c Catalyzed by (*R*)-LX/Ti(OiPr)$_4$/(*R*)-LX and (*R*)-LX/Ti(OiPr)$_4$/(*R*)-LIX Complexes.[145]



This section closes with a particular non-C_2 symmetric ligand (*S*)-**LXIII**, derived from 2-amino-2′-hydroxy-1,1′-binaphthyl, whose its 2:1 Ti(IV) complex, in the presence of 1 equiv of Naproxen (*S*)-**LXVI** as additive, was identified from a ligand/additive library study as an efficient catalytic system in the reaction between **347a** and aldehyde **364a-c** (Scheme 134).[146] Under the optimized conditions, the newly identified catalytic system was tested in the reactions of 11 different aldehydes and adducts **351a-c** were obtained within excellent yields and very good enantioselectivities (Table 11, entry 10).

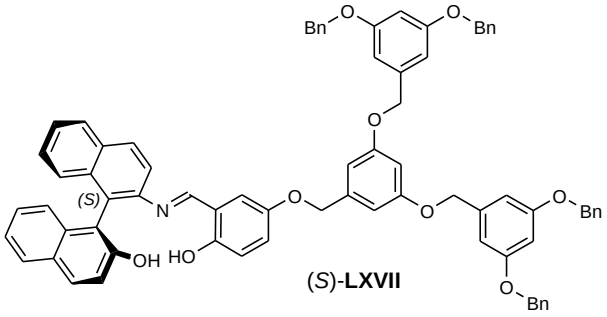
The presence of the Naproxen as the additive significantly enhanced the reaction rate by an order of magnitude, confirming that the added carboxylic acid has to be involved in the reactive intermediate complex. Furthermore, also beneficial effects on selectivity as well as strong non-linear effects were observed, and the combination (*S*)-**LXIII** and (*S*)-**LXVI** was the matched pair to optimize the selectivity. All these findings, together with the preference for a concerted mechanism, allowed to propose the complex **373** as the reactive intermediate. The more favourable coordination of the aldehyde exposed the less hindered *Si*-face to the diene attack leading to cycloadducts with the correct absolute configuration.

Scheme 134. Enantioselective Formal HDA Reactions Between 347a and 364a-c Catalyzed by (*S*)-LXIII/Ti(OiPr)$_4$/(*S*)-LXVI Complex.[146]



Ligand (*S*)-**LXIII** was functionalized by synthetizing the dendritic analogues.[147,148] Among the more or less branched derivatives, (*S*)-**LXVII** was found to be the most efficient ligand (Scheme 135). When used with Ti(OiPr)$_4$ in the presence of (*S*)-Naproxen as the additive, then adducts **351a,b** were obtained within excellent yields and enantioselectivities: Over 12 different experiments, the average yield was 99% and the average ee 91 ± 9% (Table 11, entry 11).[147]

Scheme 135. Dendritic (*S*)-LXVII Ligand.[147]



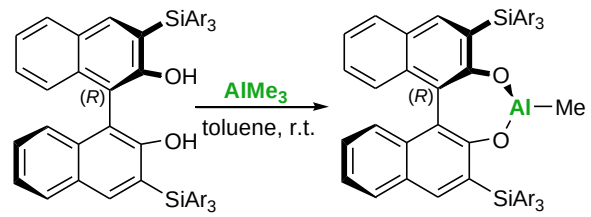
The dendritic catalyst was recovered and reused without any further addition of $Ti(OiPr)_4$ and carboxylic acid for at least three cycles observing the same activity and enantioselectivity. This means that the assembled dendritic titanium catalyst is highly stable, stability attributed to the stabilization effect of the large-sized dendron unit in the catalyst.[147]

2.2.2.2. Other BINOL-based Catalysts

Even if the use of BINOL/Ti(IV) complexes represents the cluster of chiral catalysts more frequently used in enantioselective HDA reactions to enantioenriched 2,3-dihydro-pyran-4-ones (obtainable within excellent yields and enantioselectivities), some catalysts involving different cations acting as a Lewis acid have been tested.

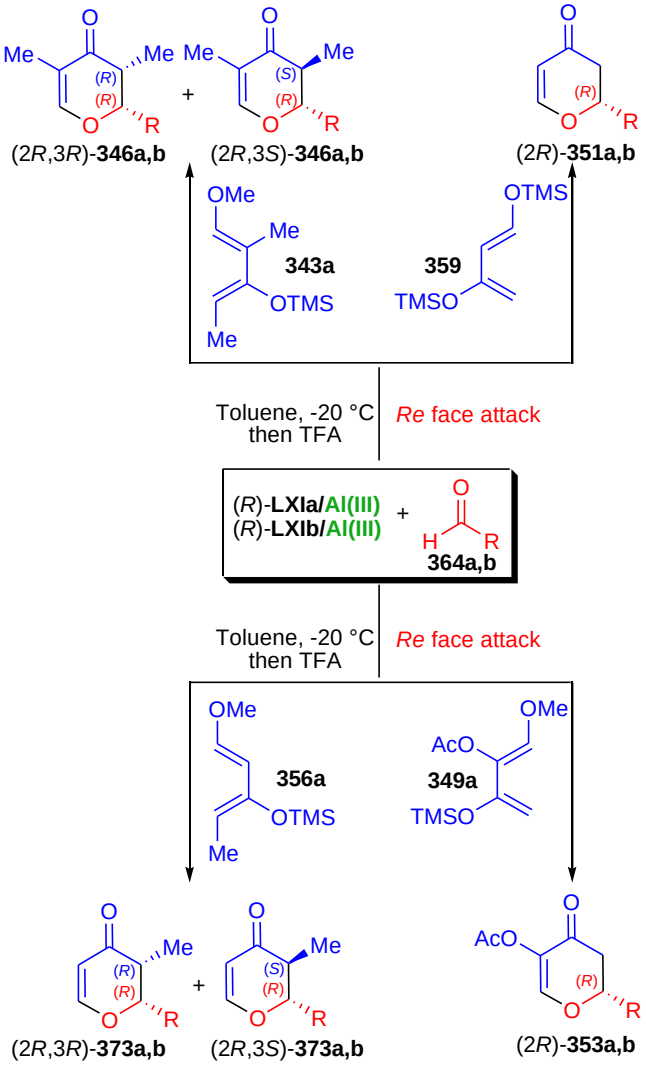
Al(III) was the Lewis acid of choice in one of the first study in this field, published by Yamamoto in 1988, in which the chiral ligand were 3,3'-triarylsilyl-BINOL (*R*)-**LXIa,b**, obtainable from the corresponding 3,3'-dibromo derivative (*R*)-**LXId**.[149] Treatment of the BINOLs with $AlMe_3$ in toluene gave the corresponding chiral Lewis acids **LXI/Al**(III), whose molecular weight, determined by cryoscopical method, was found to closely correspond to value expected for the monomeric species (Scheme 136).[149]

Scheme 136. Synthesis of the (*R*)-LXIa,b/Al(III) Chiral Catalysts.[149]



The effect of (*R*)-**LXIa,b**/Al(III) was then tested on the HDA cycloadditions involving several dienes and aldehydes (Scheme 137).[149] The results were very appreciable, since cycloadducts were isolated with up to 93% yield and 97% ee; when 2,3-disubstituted products can be formed, then also the diastereoselectivity was excellent and the favourite cis-adduct is obtained with up to 95% de.

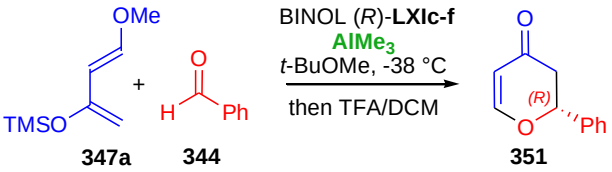
Scheme 137. Enantioselective HDA Reactions Between Danishefsky's Dienes and 364a,b Catalyzed by (*R*)-LXIa,b/Al(III) Complexes.[149]



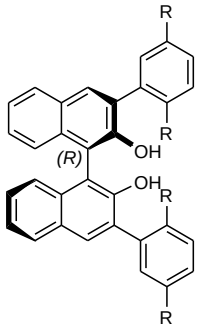
The more sterically hindered ligand (*R*)-**LXIb** gave in general better results than (*R*)-**LXIa**, particularly when diastereoselectivity was considered (Table 12, entry 2 vs 1), and this beneficial effect was consistent with a diene endo-approach to the coordinated aldehyde in order to minimize the steric repulsion between the incoming diene and the proximal triarylsilyl moiety.

The importance of the steric hindrance of the 3,3'-sustituents in BINOLate/Al(III) catalysts was deeply investigated by considering the effects of ligands (*R*)-**LXIc-f** in the HDA cycloaddition between the Danishesfy's diene **347a** and benzaldehyde **344** (Scheme 138).[150]

Scheme 138. Enantioselective HDA Reactions Between Danishefsky's Diene 347a and Benzaldehyde 344 Catalyzed by (*R*)-LXIc-f/Al(III) Complexes.[150]



347a **344** **351**



BINOL	R	% yield	% ee
LXIc	H	29	65
LXId	OMe	56	96
LXIe	OHexyl	97	99
LXIf	Heptyl	95	87

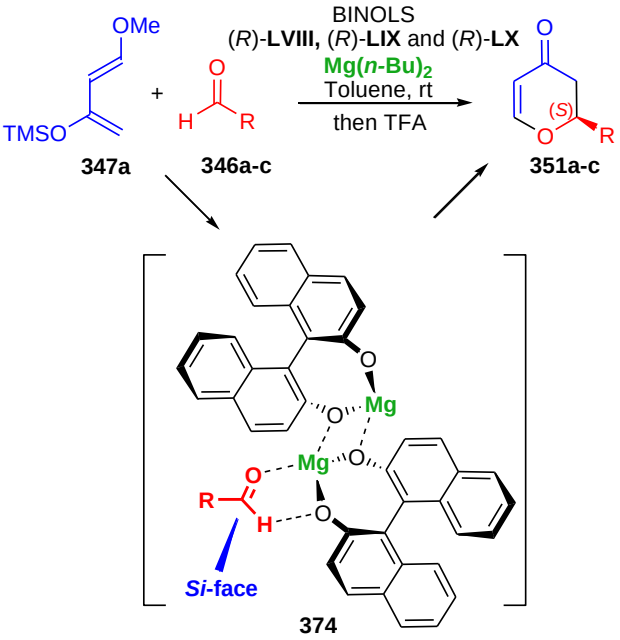
If ligand (*R*)-**LXIc** is taken as the reference compound, ligand **LXId** presents a potential coordinating site (the *ortho*-methoxy group), ligand **LXIf** is characterized by an increased steric demand, while (*R*)-**LXIe** is a potentially coordinating and more sterically hindered ligand than the reference compound **LXIc**. The results evidenced that the increase of only the steric hindrance (**LXIf**) influenced more the reactivity than the selectivity, while the insertion of a coordinating site (**LXId**) had a beneficial effect on the selectivity only. Finally, the use of BINOL **LXIe** in which both the steric and coordinating ability effects are present optimizes both the reactivity (97% yield) and the enantioselectivity (99% ee), Table 12, entry 3.[150]

On the basis of the experimental results it was proposed a reacting complex with a trigonal-bipyramidal geometry, in which the two oxygen atoms from the BINOL ligand and the methyl substituent are located in the equatorial plane, while the two axial positions are occupied by the benzaldehyde oxygen atom and by one ether oxygen atoms of the ligand. The diene approach to the more accessible *Re*-face of the coordinated heterodienophile furnishes the cycloadduct **351** rationalizing the observed (2*R*) absolute configuration.

The BINOL (*R*)-**LVIII** and the corresponding tetrahydro and octahydro derivatives (*R*)-**LIX** and (*R*)-**LX** respectively, where the ligands of choice for Mg(II)-based catalysts, which were

usefully applied in the enantioselective HDA reactions between the Danishefsky's diene **347a** and 14 different aldehydes **346a-c** (Scheme 139).[151] The adducts were obtained with yields and ees going from good, with (*R*)-**LVIII**, to excellent results with (*R*)-**LIX** and (*R*)-**LX** (Table 12, entry 4 vs entries 5 and 6). Hence, these three Mg(II)-based catalysts are more or less efficient than the previously described, but they are the first examples in which (*R*)-BINOL induce a diene approach to the (*Si*)-face of the aldehydes producing adducts with the (2*S*)-absolute configuration.

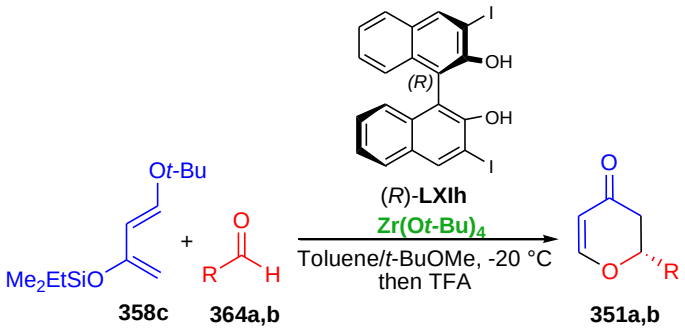
Scheme 139. Enantioselective HDA Reactions Between Danishefsky's Diene 347a and Aldehydes 346a-c Catalyzed by (*R*)-LVIII-LX/Mg(II) Complexes.[151]



Spectroscopic ^{1}H NMR experiments, together with the observed strong positive non-linear effect, evidenced the existence of homo- and hetero-ligand-Mg(II) complexes showing different activities and different aggregation behaviour. The proposed active catalyst species (**374**) possesses an oligomeric zig-zag chain structure. The Mg(II) at the chain ends activate the aldehyde by the usual coordination, with the aldehyde hydrogen involved in an unusual H-bond with one of the BINOL oxygen atoms, a helpful interaction for a better fixing of the aldehyde spatial position. The favoured diene approach is now to the aldehyde *Si*-face producing the cycloadducts **351** with the observed (2*S*) configuration.[151]

3,3′-Diiodio-BINOL derivatives **LXIh-j** were the ligand of choice for Zr(IV)-based chiral catalysts.[152,153] Under optimized conditions, the diene **358c** was allowed to react with aldehydes **364a,b** in the presence of the *in situ* generated catalyst (*R*)-**LXIh**/Zr(O*t*-Bu)$_4$ to produce with excellent yields and enantioselectivities dihydropyran-4-ones **351a,b** deriving from a diene approach to the *Re*-face of the aldehyde (Scheme 140):[152] Over six different experiments, the average yield was 96 ± 3% and the average ee was 92 ± 5% (Table 12, entry 7).

Scheme 140. Enantioselective HDA Reactions Between 358c and Aldehydes 346a,b Catalyzed by (*R*)-LXIh/Zr(IV) Complex.[152,153]



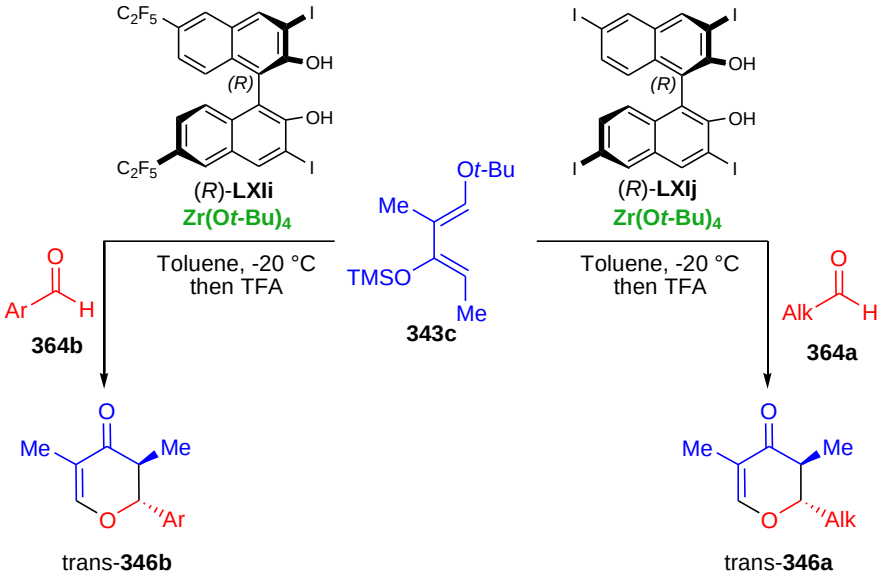
The (*R*)-**LXIh**/Zr(O*t*-Bu)$_4$ catalyst was also prepared and isolated in a powdered and storable form and tested in the HDA reactions in Scheme 140.[153] The pre-formed catalyst showed an activity analogous to that obtained with the *in situ* formed one since the average yield and ee were very close (Table 12, entry 8 vs 7), and it was found to be stable for at least three months.[153]

The use of 2,4-disubstituted-Danishesfky's dienes leads to 2,3,5-trisubstituted pyran-4-one derivatives. The (*R*)-**LXIh**/Zr(O*t*-Bu)$_4$ catalyst was tested in the HDA reaction between diene **343c** and aldehydes, but the results were unsatisfactory, probably due to the lower reactivity of the 4-substituted diene. Hence, an increase in the Lewis acidity of the Zr(IV) was planned by introducing electron-withdrawing groups at the 6,6′-positions of the BINOL derivatives.

The 6,6′-modified BINOLs (*R*)-**LXIi,j** were then synthetized and tested in the HDA reactions between 1-*tert*-butoxy-2-methyl-3-trimethylsiloxy-1,3-pentadiene **343c** and aldehydes **364a,b** by using Zr(O*t*Bu)$_4$ as the Lewis acid source (Scheme 141). The 6,6′-bis(pentafluoroethyl)-substituted BINOL (*R*)-**LXIi** was found the ligand of choice in the reactions involving aromatic aldehydes

364b since the adducts trans-**346b** were obtained with up to quantitative yields, and with good diastereo- and excellent enantioselectivities (Table 12, entry 9). In the case of aliphatic aldehydes **364a**, the BINOL of choice was found the 6,6′-diiodio derivative **LXIj** that allowed to obtain products **346a** with very good yields and selectivities (Table 12, entry 10).[152]

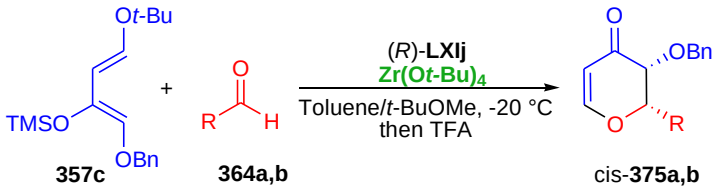
Scheme 141. Enantioselective HDA Reactions Between 343c and Aldehydes 346a,b Catalyzed by (*R*)-LXIi,j/Zr(IV) Complexes.[152]



The favoured diastereoisomers obtained with both catalysts were the 2,3-trans-disubstitued derivatives **346a,b**, and this result was taken as a clear proof that the reaction followed the Mukaiyama-aldol pathway instead the concerted HDA one. In any case the initial attack of the diene is again to the *Re*-face of the reacting aldehyde.

To exploit further the utility of this process, Danishefsky's diene with an oxy substituent at the 4-position was tested, since the obtainable 3-oxygenated-pyran-4-ones are potential precursors of hexose derivatives. The reaction of 4-benzyloxy-diene **357c** with aldehydes was catalysed by the BINOL **LXIj**/Zr(IV) complex to give the adducts cis-**375a,b** within very good yields and selectivities (Scheme 142; Table 12, entry 11).[152] The absolute stereochemistry of the cycloadducts was again consistent with a diene approach to the *Re*-face of the aldehydes.

Scheme 142. Enantioselective HDA Reactions Between 357c and Aldehydes 364b Catalyzed by (*R*)-LXIj/Zr(IV) Complex.[152]



The opposite trans/cis selectivity observed by using the 4-methyl-substituted diene **343c** and the 4-benzyloxy-substituted diene **357c** were rationalized by considering the possibility of the diene substituent to coordinate the Zr(IV) centre. In the case of **343c**, the steric repulsions between the methyl group in the 4-position of the diene and the zirconium catalyst are in accordance with the favoured anti-addition leading to the trans-cycloadduct. In the case of the reaction involving **357c**, the coordination of the oxygen atom of the benzyloxy group to Zr(IV) overwhelmed the unfavourable steric repulsion switching the selectivity toward a syn addition resulting into the preferential formation of cis-cycloadducts.[152]

Cycloadducts **375** are interesting scaffold useful in the synthesis of important natural products. The adduct (2*S*,3*R*)-**375b**, obtained from the reaction between **357c** and benzaldehyde within 95% yield, >94% de, and 97% ee was converted into intermediate **376** by Mukaiyama-Michael addition with silicon enolates followed by the ketone reduction. This intermediate was then converted into (+)-9-deoxygoniopypyrone **377**, a product with cytotoxicity against human tumor cell (Scheme 143).[52]

Scheme 143. Synthetic Application of Cycloadduct (2*S*,3*R*)-375.[152]

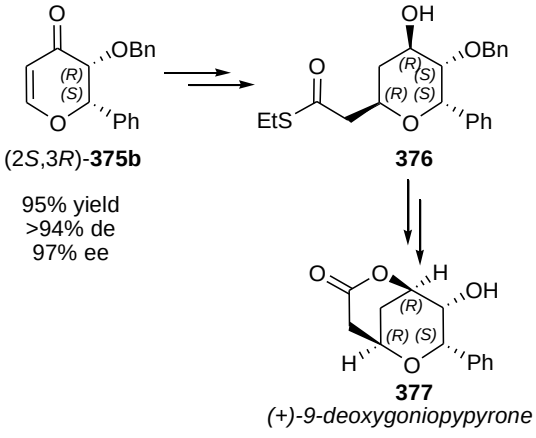


Table 12. Average Values and Standard Deviations (s.d.) of the Reaction Yields, Diastereo-, and Enantioselectivities for the Formal HDA Reactions Catalyzed by [BINOLate/Lewis Acid] Complexes Between Dienes and Aldehydes Reported in Chart 5.

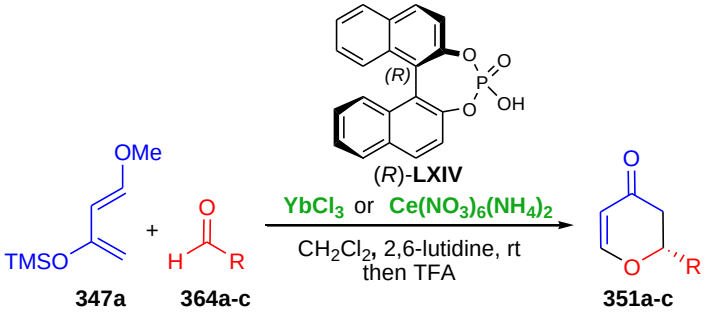
Entry	Diene	Hetero-dienophile	Catalyst	Lewis Acid	n. Exp.	aver. Yield % (s.d.)	Reaction Product	aver. de % (s.d.)	aver. ee % (s.d.)	Attach. CO face	Ref.
1	**343a, 356a, 359**	**364a,b**	(*R*)-**LXIa**	Al(III)	7	83 (12)	**346, 373, 351**	77 (13)	88 (9)	*Re*	149
2	**343a, 349a, 356a, 359**	**364a,b**	(*R*)-**LXIb**	Al(III)	4	88 (7)	**346, 373, 351, 353**	95 (2)	90 (8)	*Re*	149
3	**347a**	**344**	(*R*)-**LXIe**	Al(III)	1	97 (---)	**351**	---	99 (---)	*Re*	150
4	**347a**	**364a-c**	(*R*)-**LVIII**	Mg(II)	14	81 (19)	**351a-c**	---	83 (12)	*Si*	151
5	**347a**	**364a-c**	(*R*)-**LIX**	Mg(II)	14	95 (7)	**351a-c**	---	92 (7)	*Si*	151
6	**347a**	**364a-c**	(*R*)-**LX**	Mg(II)	14	97 (5)	**351a-c**	---	93 (5)	*Si*	151
7	**358c**	**364a,b**	(*R*)-**LXIh**	Zr(IV)	6	96 (3)	**351a,b**	---	92 (5)	*Re*	152
8[a]	**358c**	**364a,b**	(*R*)-**LXIh**	Zr(IV)	6	93 (2)	**351a,b**	---	89 (5)	*Re*	153
9	**343c**	**364b**	(*R*)-**LXIi**	Zr(IV)	8	94 (4)	**346b**	86 (7)[b]	94 (3)	*Re*	152
10	**343c**	**364a**	(*R*)-**LXIj**	Zr(IV)	4	81 (18)	**346a**	81 (1)[b]	90 (4)	*Re*	152
11	**357c**	**364a,b**	(*R*)-**LXIj**	Zr(IV)	6	87 (17)	**375a,b**	87 (9)[c]	92 (6)	*Re*	152

12	**347a**	**364b,c**	(*R*)-**LXIV**	Yb(III)	9	80 (10)	**351b,c**	---	83 (10)	*Re*	154
13	**347a**	**364a,b**	(*R*)-**LXIV**	Ce(IV)	14	68 (23)	**351a,b**	---	81 (18)	*Re*	154
14	**347a**	**364a-c**	(*R*)-**LXIg**	Zn(II)	12	88 (24)	**351a-c**	---	91 (11)	*Re*	155
15	**347a**	**364a-c**	(*R*)-**LXIg**[d]	Zn(II)	12	93 (12)	**351a-c**	---	92 (11)	*Re*	156

[(a)] Reaction run with powdered and storable Zr(IV) catalyst. [(b)] The "exo" adducts trans-(2*R*,3*S*)-**346** are the preferred isomers. [(c)] The "endo" adducts cis-(2*S*,3*R*)-**375** are the preferred isomers. [(d)] (*S*,*S*)-*N*,*N*′-di(4-chlorobenzylidene)cyclohexane **LXVIII** added as activator.

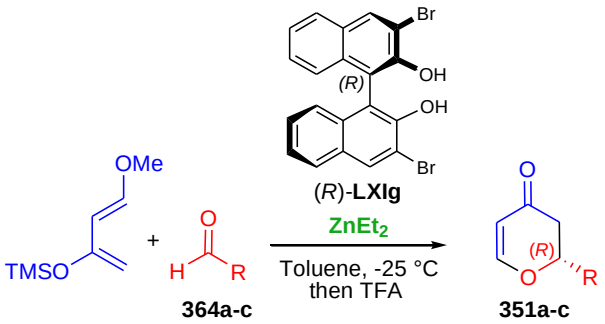
The BINOL derived phosphate complexes with some rare earth cations acting as Lewis acids have been applied in the enantioselective HDA reaction between the Danishefsky's diene **347a** and aldehydes **364a-c** (Scheme 144).[154] Hence the complexes between 3 equiv of BINOL-phosphate (*R*)-**LXIV** and either Yb(III) or Ce(IV) cations were tested in the HDA reaction between **347a** and aldehydes **364a-c**. When aliphatic aldehydes **364a** were used as dienophile, then the results were unsatisfactory, but in the case of aromatic aldehydes the reactions proceeded with satisfactory yields and enantioselectivities, with the Yb(III)-based catalyst working better than the Ce(IV)-based one (Table 12, entry 12 vs 13).[154]

Scheme 144. Enantioselective HDA Reactions Between 347a and Aldehydes 364a-c Catalyzed by [(*R*)-LXIV]$_3$/Yb(III) or Ce(IV) Complexes.[154]



The 3,3′-dibromo-BINOL (*R*)-**LXIg** was the ligand of choice when Zn(II) was the Lewis acid. This complex catalysed HDA reaction between **347a** and aldehydes **364a-c** to produce pyran-4-ones **351a-c** within good yields and excellent enantioselectivities (Scheme 145).[155] Over 12 different experiments, the average yield was 88 ± 24%, while the average ee was 91 ± 11%, with aromatic aldehydes working better than the aliphatic ones (Table 12, entry 14). The system exhibits a correlation between ee of the ligand and those of the adduct that strongly deviated from the linearity, with a trend similar to that showed in Figure 8. The absolute configuration of cycloadducts **351a-c** is again consistent with a diene approach to the *Re*-face of **364**.

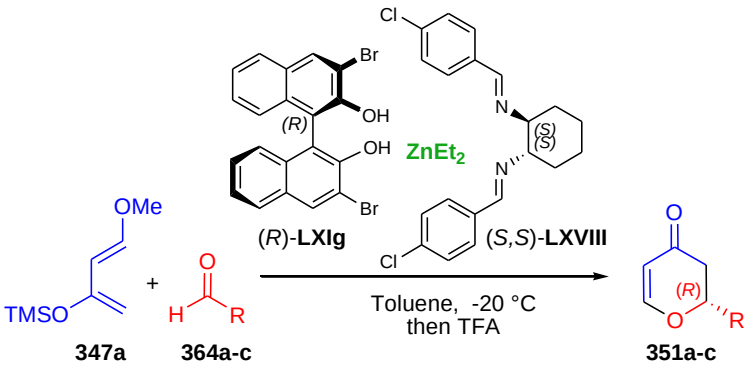
Scheme 145. Enantioselective HDA Reactions Between 347a and Aldehydes 364a-c Catalyzed by (*R*)-LXIg/Zn(II) Complex.[155]



The 3,3′-dibromo-BINOL (*R*)-**LXIg** was identified as the best BINOL ligand for Zn(II)-based catalysts through a combinatorial approach in which 12 different BINOLs were mixed with 20 different chiral diimines used as activators.[156] The better combination involved (*S*,*S*)-*N*,*N*′-di(4-chlorobenzylidene)cyclohexane **LXVIII** as additive which furnished adducts **351a-c** within excellent yields and enantioselectivities (Scheme 146; Table 12, entry 15). The absolute stereochemistry of cycloadducts was again consistent with an approach of the diene to the *Re*-face of aldehydes.

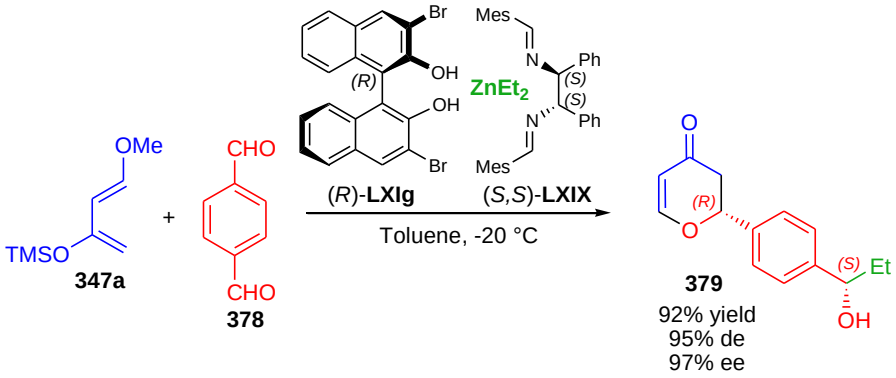
Quite surprisingly the use of the enantiomeric (*R*,*R*)-**LXVIII** as activator did not influence the reactivity nor the selectivity. This evidence is in accordance with the proposed concerted transition state in which only one imino nitrogen atom is involved in the coordination of the Zn(II) cation.[156]

Scheme 146. Enantioselective HDA Reactions Between 347a and Aldehydes 364a-c Catalyzed by (*R*)-LXIg/Zn(II)/(*S*,*S*)-LXVIII Complex.[156]



This new catalytic system found an original application in dialdehyde aromatic derivatives, since a sequential asymmetric HDA reaction and diethylzinc addition was observed allowing to obtain the dihydropyran-4-one fragment and a secondary alcohol moiety in one molecule.[156,157] Thus, terephthalaldehyde **378** was allowed to react with the Danishefsky's diene in the presence of (*R*)-**LXIg**, $ZnEt_2$, and the activator (*S*,*S*)-**LXIX** for 30 h at -20 °C. Subsequently, 3 further equiv of diethyl zinc were directly added, without any workup of the HDA adduct, to run the second-step of the asymmetric addition. Both the asymmetric reactions proceeded efficiently and selectively since the final product **379** was obtained within 92% yield, 95% de, and 97% ee (Scheme 147).[156,157]

Scheme 147. Enantioselective HDA Reactions Between 347a and Aldehydes 364a-c Catalyzed by (*R*)-LXIg/Zn(II)/(*S*,*S*)-LXIX Complex.[156,157]



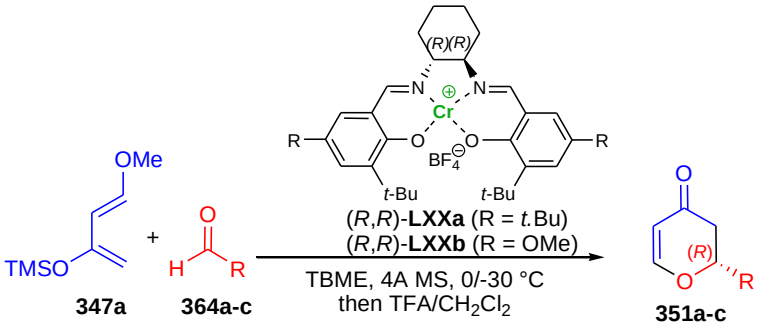
This section has been closed with two examples in which the efficiency of BINOL-based catalysts was increased by the addition of chiral diimines as activators; these chiral Schiff bases will be the ligands of choice for the Cr(III)-based catalysts discussed in the forthcoming section.

2.2.2.3. Chromium (III)-Schiff Base Catalysts

The first application of salen-chromium(III) complexes as enantioselective catalysts in the HDA reaction between the Danishefsky's diene and aldehydes was reported in 1998 by Jacobsen.[158] Salen/Cr(III) complexes (*R*,*R*)-**LXXa,b** were identified as the catalysts of choice and their use in HDA reactions of **347a** with some aldehydes **364a-c** allowed to obtain adducts **351a-c** with up to 98% yield and 93% ee (reaction temperature, from 0 to -30°C; solvent, *t*-butyl methyl ether), Scheme 148. Catalyst **LXXa** was found more selective than **LXXb** (average ee = 82 vs 73%,

respectively), while the effect on reactivity was reversed (average yield = 79 vs 88%, respectively), Table 13, entry 1 vs 2. The reaction mechanism was proposed to follow a concerted HDA pathway and the (*R*) absolute configuration for the 2-phenyl-substituted pyran-4-one was consistent with a diene approach to the *Re*-face of the aldehyde.[158]

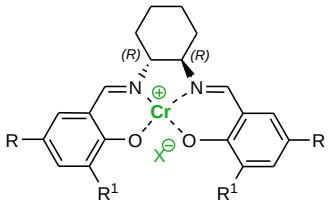
Scheme 148. Enantioselective HDA Reactions Between 347a and Aldehydes 364a-c Catalyzed by (*R*,*R*)-LXXa,b.[158]



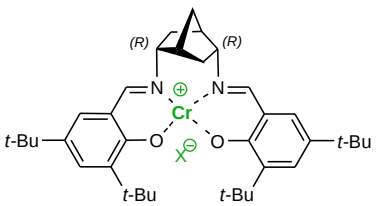
After the Jacoben's paper, several other contributions appeared in the literature, which did not consider the change of the diene (in all examples it is always the Danishefsky's diene **347a** only), but were mainly focussed on the optimization of the ligand structure, whose architecture reached very high levels of complexity. Chart 6 collects all the Cr(III)-salen complexes that have been tested in enantioselective HDA reactions. In the majority of the examples, the chiral spacer is represented by the chiral 1,2-diamino-cyclohexane and the salen ligands are either tetradentate with a C_2-simmetry or, in some cases, tridendate only. Furthermore, axial chirality element has been added in order to test a matching or mismatching behaviour of the new entered chiral information.

The effect of the steric hindrance of the R^1 substituent in (*R*,*R*)-**LXX** salen-based catalysts has been inferred by changing the *t*-butyl group with more steric demanding groups such as $-C(Me)_2Ph$, $-C(Et)_2Ph$, $-C(Pr)_2Ph$.[159] The results (% yield and % ee) obtained by using these catalysts in the HDA reaction between Danishefsky's diene and benzaldehyde under the Jacobens's reaction conditions are shown in Scheme 149.

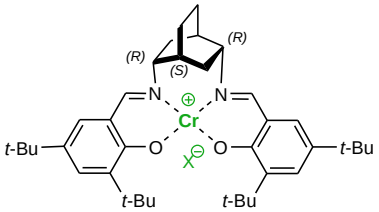
Chart 6. [Chromium(III)-Schiff Base] Catalysts Used in the Asymmetric Catalysis of the HDA Reactions Between Danishefsky's Diene and Aldehydes.



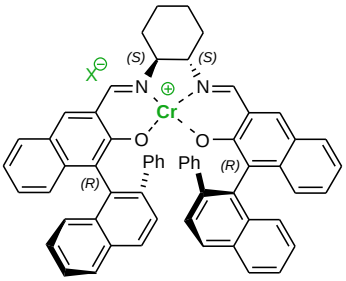
(*R*,*R*)-**LXXa**: R = R^1 = *t*-Bu
(*R*,*R*)-**LXXb**: R =OMe; R^1 = *t*-Bu
(*R*,*R*)-**LXXc**: R = *t*-Bu; R^1 = $C(Me)_2Ph$
(*R*,*R*)-**LXXd**: R = *t*-Bu; R^1 = $C(Et)_2Ph$
(*R*,*R*)-**LXXe**: R = *t*-Bu; R^1 = $C(Pr)_2Ph$



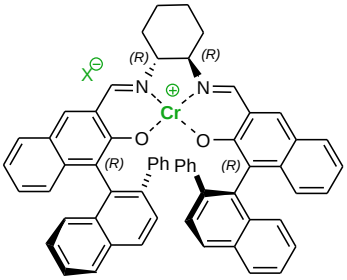
(*R*,*R*)-**LXXI**



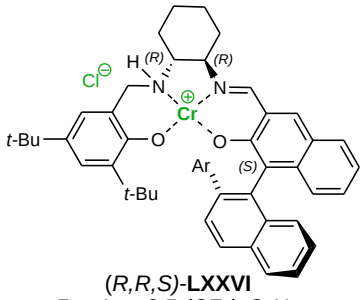
(*R*,*R*)-**LXXII**



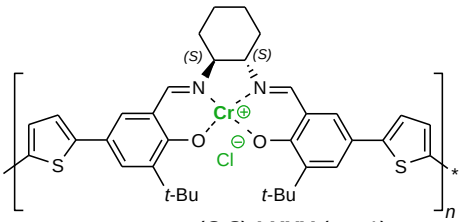
(*R*,*S*,*S*,*R*)-**LXXIIIa**



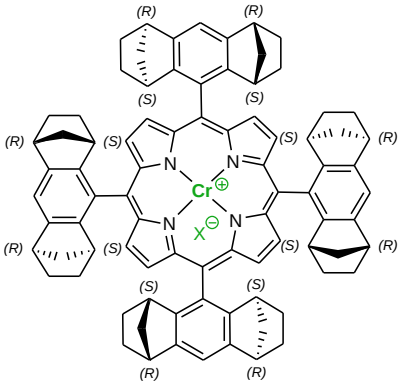
(*R*,*R*,*R*,*R*)-**LXXIVa**



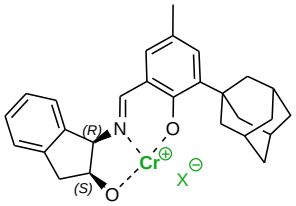
(*R*,*R*,*S*)-**LXXVI**
R = Ar = 3,5-$(CF_3)_2C_6H_3$



mono-(*S*,*S*)-**LXXV** (*n* = 1)
poly-(*S*,*S*)-**LXXV**



(1*S*,4*R*,5*R*,8*S*)-**LXXVIII**

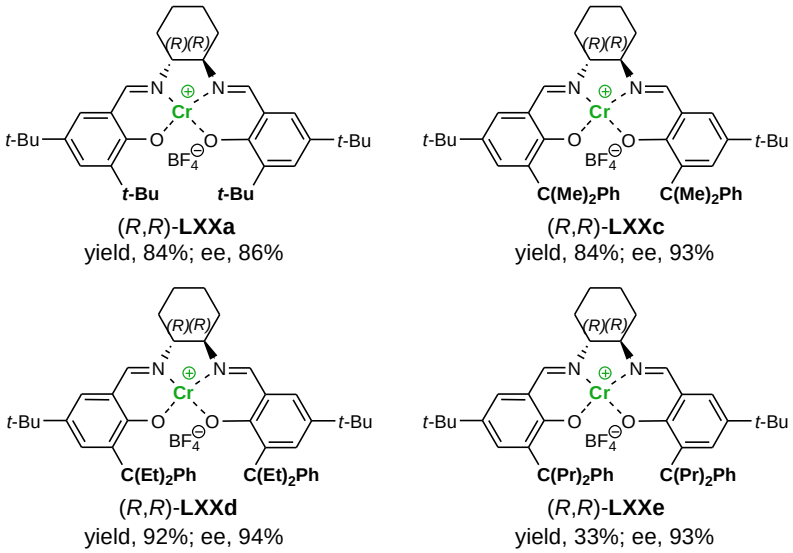


(*R*,*S*)-**LXXVIIa**: X = BF_4
(*R*,*S*)-**LXXVIIb**: X = Cl

The modifications of the substituent at the 3-position of the salicylidene moiety ameliorate the selectivity, since the ee obtained with (*R*,*R*)-**LXXc-e** were better than those obtained with the classic Jacobsen's catalyst (*R*,*R*)-**LXXa**, but only (*R*,*R*)-**LXXd** showed an increase of the reaction yields. On the basis of these evidences, catalysts (*R*,*R*)-**LXXa,d** were tested in the HDA reactions between the Danishefsky's diene and six different aldehydes **364a-c** (Table 13, entries 3 and 4).

The results obtained by using (*R*,*R*)-**LXXa** closely reproduced those previously reported by Jacobsen (Table 13, entry 3 vs entry1), while the use of the more steric demanding (*R*,*R*)-**LXXd** clearly increased both the reactivity and the enantioselectivity (Table 13, entry 4 vs entry 3).

Scheme 149. Results of the Enantioselective HDA Reactions Between 347a and Benzaldehyde Catalyzed by (*R*,*R*)-LXXa,c-e.[159]



(*R*,*R*)-**LXXa**
yield, 84%; ee, 86%

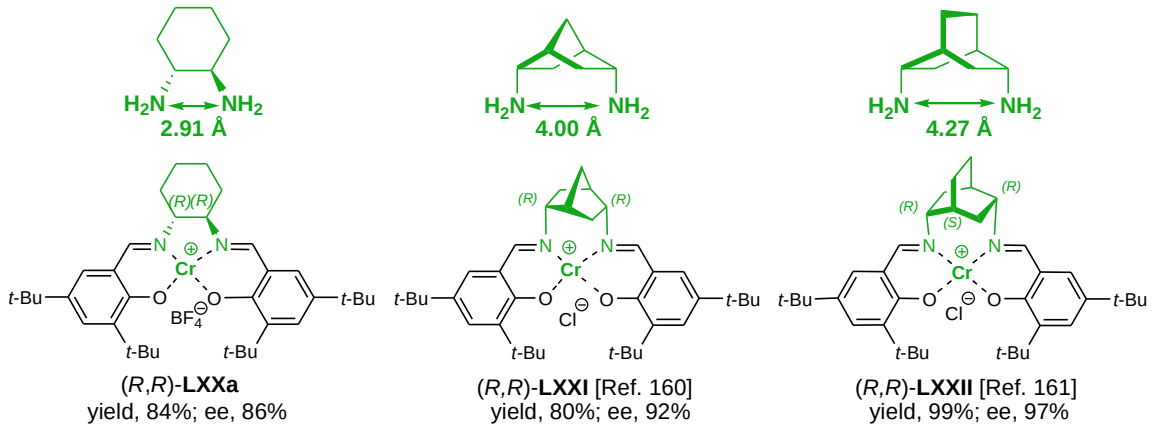
(*R*,*R*)-**LXXc**
yield, 84%; ee, 93%

(*R*,*R*)-**LXXd**
yield, 92%; ee, 94%

(*R*,*R*)-**LXXe**
yield, 33%; ee, 93%

One relevant structural variation concerns the change of the spacer between the two nitrogen atoms. Hence, the cyclohexane scaffold in **LXX** was changed with either the bicycle[2.2.1]heptane or bicycle[2.2.2]octane structures starting from the corresponding chiral 1,3-diamines to give the Cr(III)-based catalysts (*R*,*R*)-**LXXI**[160] and (*R*,*R*)-**LXXII**,[161] respectively (Scheme 150).

Scheme 150. Results of the Enantioselective HDA Reactions Between 347a and Benzaldehyde Catalyzed by (*R*,*R*)-LXXa, (*R*,*R*)-LXXI, and (*R*,*R*)-LXXII.[160,161]



(*R*,*R*)-**LXXa**
yield, 84%; ee, 86%

(*R*,*R*)-**LXXI** [Ref. 160]
yield, 80%; ee, 92%

(*R*,*R*)-**LXXII** [Ref. 161]
yield, 99%; ee, 97%

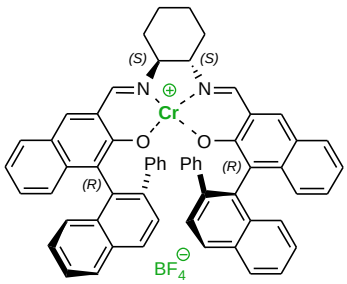
The main structural modification is the lengthening of the distance between the two nitrogen atoms, which can become longer than 4.2 Å. The use of (*R*,*R*)-**LXXI** in the reaction between Danishefsky's diene and benzaldehyde gave a slightly lower yield than that obtained by using the

Jacobsen's catalyst, while the enantioselectivity is significantly ameliorated (Scheme 150).[160] Even better results were obtained by using the more ample catalyst (*R*,*R*)-**LXXII**, since the 2-phenyl-2,3-dihydro-pyran-4-one was obtained with up to 99% yield and 97% ee.[161] In both cases, the absolute configuration of the adduct was found to be (2*S*), which implies a diene approach to the *Si*-face of the benzaldehyde. The extension to reactions of other aldehydes confirmed the trend observed in the benzaldehyde cycloadditions (Table 13, entries 5 and 6).

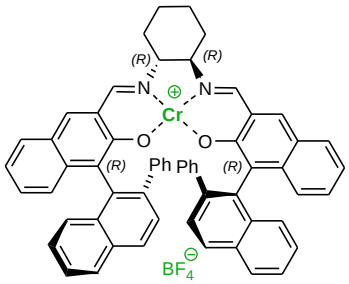
(*R*,*R*)-**LXXI** was tentatively used in a cycloaddition involving a less reactive diene such as 1-methoxy-butadiene. The main product was cis-3,6-dihydro-6-methoxy-2-phenyl-2*H*-pyran (a derivative that does not fit the topic of this review), which was obtained with good diastereoselectivity (90% de), an appreciable enantioselectivity (75% ee), but with too low yield (11%) to make interesting this application.[160]

A second-generation of salen ligands has been synthetized by adding a second chirality element represented by the axial chirality given by the binaphthyl units. Two diastereomeric salen ligands were prepared, (*R*,*S*,*S*,*R*)-**LXXIII** and (*R*,*S*,*S*,*R*)-**LXXIV**, and their complexes with Cr(III) and Mn(III) were applied in the asymmetric catalysis of the HDA reaction between the Danishefsky's diene and some aldehydes (Scheme 151).[162] The cycloadducts were obtained with good yields and moderate-excellent enantioselectivities with the Cr(III) based catalysts giving slightly better results than the corresponding Mn(III)-based ones. Concerning the stereochemical outcome of the cycloadditions, it was evident that the stereochemistry is mainly governed by the configuration of the 1,2-diamino-cyclohexane moiety. The catalysts (*R*,***S***,***S***,*R*)-**LXXIIIa,b** prepared from (*S*,*S*)-diaminocyclohexane produced the (*S*)-**351** as the favoured enantiomer derived from a diene approach to the *Si*-face of the benzaldehyde. The use of the diastereomeric catalysts (*R*,***R***,***R***,*R*)-**LXXIVa** obtained from (*R*,*R*)-diaminocyclohexane reverted the stereochemical outcome.

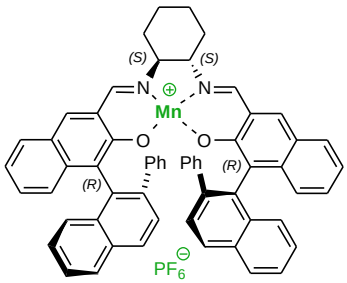
Scheme 151. Results of the Enantioselective HDA Reactions Between 347a and Benzaldehyde Catalyzed by (*R*,*S*,*S*,*R*)-LXXIIIa,b and (*R*,*R*,*R*,*R*)-LXXIVa,b.[162]



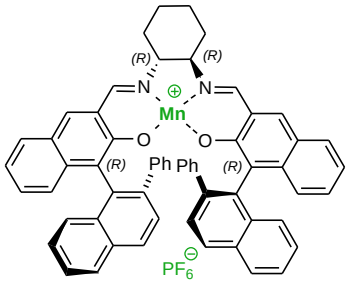
(*R*,*S*,*S*,*R*)-**LXXIIIa**
yield, 96%; ee (*S*)-**351**, 78%



(*R*,*R*,*R*,*R*)-**LXXIVa**
yield, 93%; ee (*R*)-**351**, 93%



(*R*,*S*,*S*,*R*)-**LXXIIIb**
yield, 88%; ee (*S*)-**351**, 60%

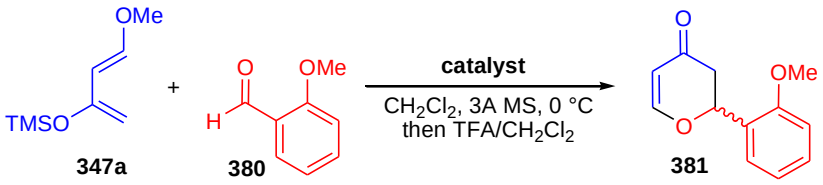


(*R*,*R*,*R*,*R*)-**LXXIVb**
yield, 95%; ee (*R*)-**351**, 88%

The matched combination between the diamine chirality and the axial chirality is meet in catalysts (*R*,*R*,*R*,*R*)-**LXXIVa,b**, since adduct (*R*)-**351** was obtained with enantioselectivities significantly better than those obtained by using the "mismatched" catalysts (*R*,*S*,*S*,*R*)-**LXXIIIa,b** (88-93% ee vs 60-78% ee).

The extensions of these catalysts to other aldehydes gave the results reported in Table 13, entries 7-10.[162,163] Among the different aldehydes tested, a mention is required for 2-methoxy-benzaldehyde, since the introduction of a potentially coordinating function determined a relevant effect on the catalyst efficiency. As shown in Scheme 152, the catalysts giving the best results are those that were the mismatched catalysts in the HDA reaction involving the monocoordinating benzaldehyde, since (*R*,*S*,*S*,*R*)-**LXXIIIa,b** allow to obtain excellent enantioselectivities (96% ee), clearly better than those obtained by using (*R*,*R*,*R*,*R*)-**LXXIVa,b** (63-68% ee). These results suggested that (*R*,*R*,*R*,*R*)-**LXXIVa,b** are the catalysts suitable for the reaction of aldehydes without any coordinating substituent, while (*R*,*S*,*S*,*R*)-**LXXIIIa,b** are the catalysts of choice for reactions involving aldehydes bearing a chelating group.

Scheme 152. Results of the Enantioselective HDA Reactions Between 347a and 2-Methoxy-Benzaldehyde 380 Catalyzed by (*R*,*S*,*S*,*R*)-LXXIIIa,b and (*R*,*R*,*R*,*R*)-LXXIVa,b.[162]



(*R*,*S*,*S*,*R*)-**LXXIIIa** yield, 88%; ee (*S*)-**381**, 96%
(*R*,*R*,*R*,*R*)-**LXXIVa** yield, 90%; ee (*R*)-**381**, 63%

(*R*,*S*,*S*,*R*)-**LXXIIIb** yield, 96%; ee (*S*)-**381**, 96%
(*R*,*R*,*R*,*R*)-**LXXIVb** yield, 97%; ee (*R*)-**381**, 68%

The analogous Ru(II) complexes have been also tested, but the reaction yields were too low to be of practical interest (38-52%).[163]

Catalyst (*R*,*S*,*S*,*R*)-**LXXIIIa** was also tested in HDA reactions involving aldehydes on a solid support (Wang resin) in order to develop an asymmetric synthesis method that would give access to related compound collections in a format amenable to combinatorial synthesis (Scheme 153).[164] The reaction on solid-supported aldehydes required long reaction times (96 h) and the solid supported dihydropyrans **383** were obtained by a mild treatment with TFA for 15 min. The cleavage of the cycloadducts from the resin required a 10% TFA in CH_2Cl_2 for 3 hours at room temperature.

Scheme 153. Enantioselective HDA Reactions Between 347a and Solid Supported Aldehydes 382 Catalyzed by (*R*,*S*,*S*,*R*)-LXXIIIa.[164]

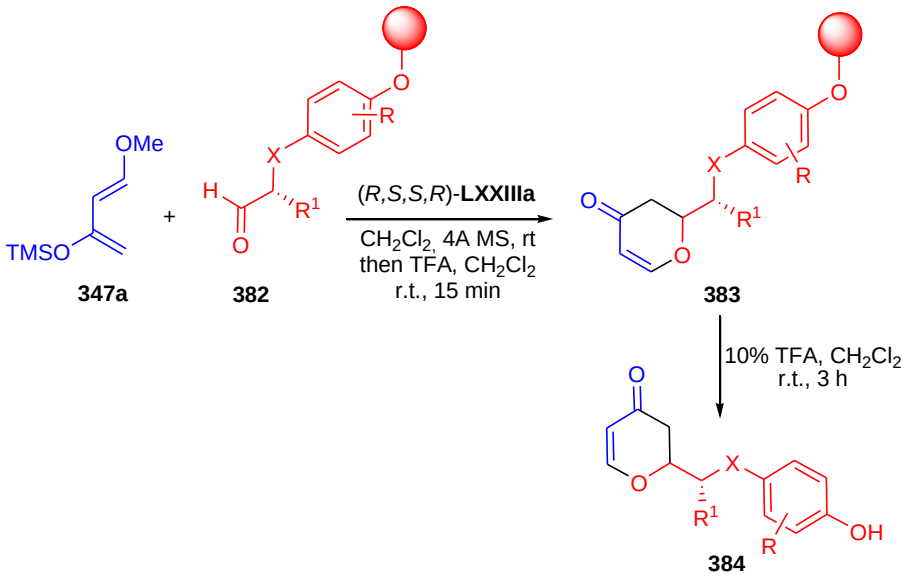


Table 13. Average Values and Standard Deviations (s.d.) of the Reaction Yields, Diastereo-, and Enantioselectivities for the Formal HDA Reactions Between the Danishefsky's Diene **347a** and Aldehydes, Catalyzed by Complexes of Cr(III) and Mn(III) with the Shiff Bases Reported in Chart 6.

Entry	Aldehyde	Catalyst	n. Exp.	aver. Yield % (s.d.)	Reaction Product	aver. ee % (s.d.)	Attach. CO face	Ref.
1	**364a-c**	(*R*,*R*)-**LXXa**	7	79 (11)	(*R*)-**351a-c**	82 (8)	*Re*	158
2	**364a-c**	(*R*,*R*)-**LXXb**	7	88 (8)	(*R*)-**351a-c**	73 (9)	*Re*	158
3	**364a-c**	(*R*,*R*)-**LXXa**	6	73 (12)	(*R*)-**351a-c**	82 (9)	*Re*	159
4	**364a-c**	(*R*,*R*)-**LXXd**	6	80 (10)	(*R*)-**351a-c**	93 (3)	*Re*	159
5	**364a-c**	(*R*,*R*)-**LXXI**	5	70 (26)	(*S*)-**351a-c**	90 (7)	*Si*	160
6	**364a-c**	(*R*,*R*)-**LXXII**	11	98 (2)	(*S*)-**351a-c**	89 (11)	*Si*	161
7	**364b**	(*R*,***S***,***S***,*R*)-**LXXIIIa**	3	92 (4)	(*S*)-**351b**	88 (9)	*Si*	162, 163
8	**364a,b**	(*R*,***R***,***R***,*R*)-**LXXIVa**	6	93 (5)	(*R*)-**351a,b**	89 (13)	*Re*	162, 163
9	**364b**	(*R*,***S***,***S***,*R*)-**LXXIIIb**	5	88 (16)	(*S*)-**351b**	74 (18)	*Si*	162
10	**364a,b**	(*R*,***R***,***R***,*R*)-**LXXIVb**	6	88 (15)	(*R*)-**351a,b**	77 (19)	*Re*	162
11	**382**	(*R*,*S*,*S*,*R*)-**LXXIIIa**	5	18 (12)	**384**	86 (20)	---	164
12	**364a-c**	*mono*-(*S*,*S*)-**LXXV**	10	64 (26)	(*S*)-**351a-c**	69 (6)	*Si*	165

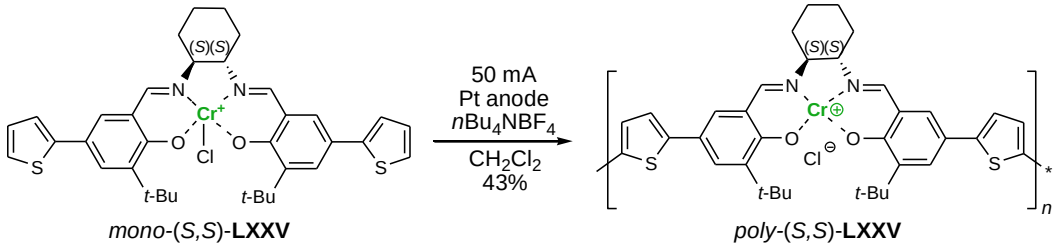
13	**364a-c**	*poly*-(*S*,*S*)-**LXXV**[a]	10	67 (30)	**351a-c**	47 (7)	---	165
14	**364a-c**	*poly*-(*S*,*S*)-**LXXV**[b]	10	54 (19)	**351a-c**	52 (7)	---	165
15	**364a-c**	(*R*,*R*,*S*)-**LXXVI**	9	75 (14)	**351a-c**	92 (4)	*Re*	166
16	**364a-c**	(*R*,*S*)-**LXXVIIa**	10	91 (8)	(*S*)-**351a-c**	89 (3)	*Si*	167
17	**364a-c**	(1*S*,4*R*,5*R*,8*S*)-**LXXVIII**	6	72 (11)	(*R*)-**351a-c**	87 (9)	*Re*	172

[a] First cycle. [b] Second cycle.

After release from the solid support, the desired dihydropyran-4-ones **384** were obtained within 10-40% overall yield over the five synthetic steps starting from the functionalization of the Wang resin. The enantioselectivity was satisfying since the cycloadducts were obtained with up to 99% ee (Table 13, entry 11).[164] Further elaborations on the polymer-bound dihydropyranones **383** allowed the stereoselective synthesis on enantioenriched cis,cis-2,4,6-trisubstituted tetrahydropyrans with almost complete diastereoselectivity.

A further modification concerned the substitution of *t*-butyl groups at the 5,5′-positions of the salen ligand with thiophenes.[165] The corresponding Cr(III) *mono*-(*S*,*S*)-**LXXV** was then prepared and tested in the HDA reaction of the Danishefsky's diene with 10 different aldehydes **364a-c**. The expected adducts were obtained within moderate yields and enantioselectivities (Table 13, entry 12). The stereochemical outcome of the cycloaddition derived from a diene approach to the aldehyde *Si*-face to afford (*S*)-**351a-c**. The monomeric complex was then submitted to electropolymerization to give the chiral polymer *poly*-(*S*,*S*)-**LXXV** as an insoluble powder that was tested as heterogeneous chiral catalyst (Scheme 154). The same batch of *poly*-(*S*,*S*)-**LXXV** was used as catalyst in ten successive HDA reactions run on the ten different aldehydes used in the corresponding homogeneous catalysis. The average reaction yield of these ten experiments was comparable to that obtained by using freshly prepared homogeneous catalysts, while the average enantioselectivity was slightly lower (Table 13, entry 13 vs entry 12). Then, a second sequence of ten reactions was performed by using the recovered catalyst. The recycling procedure was found successful (Table 13, entry 13 vs 14) confirming the promising utility of such heterogeneous catalysts in asymmetric catalysis.[165]

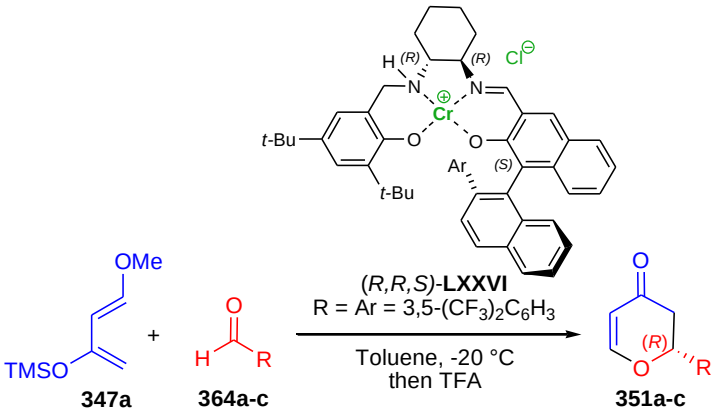
Scheme 154. Anodic Polymerization of Complex *Mono*-(*S*,*S*)-LXXVII in the Synthesis of *Poly*-(*S*,*S*)-LXXV.[165]



mono-(*S*,*S*)-**LXXV** *poly*-(*S*,*S*)-**LXXV**

In all the previously discussed examples, the Cr(III)-based catalysts had a more or less modified structure, but always the C_2-symmetry of the chiral ligand was maintained. Several heterogeneously hybridized salen/salan ligands have been synthetized and their Cr(III) complexes were tested as enantioselective catalysts in the HDA reaction between **347a** and aldehydes **364a-c**.[166] Among them, the chiral complex (*R*,*R*,*S*)-**LXXVI** was found very efficient (Scheme 155), since the cycloadducts were obtained with good yields and excellent enantioselectivities (Table 13, entry 15), even better than those achieved by using the corresponding homogenously hybridized chiral ligands. The stereochemical outcome is the result of a diene approach to the *Re*-face of the aldehyde, and is again dictated by the stereochemistry of the diaminic spacer.

Scheme 155. Enantioselective HDA Reactions Between 347a and Aldehydes 364a-c Catalyzed by (*R*,*R*,*S*)-LXXVI.[166]

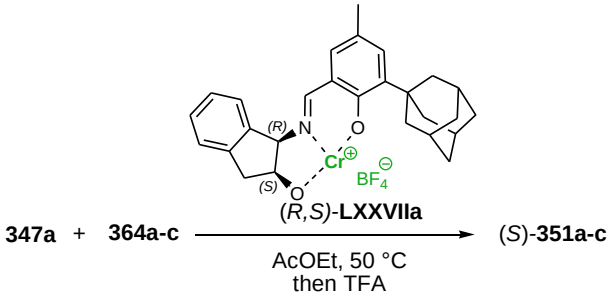


347a **364a-c** **351a-c**

Tridentate Schiff base-Cr(III) complexes, originally introduced by Jacobsen, found several applications in enantioselective synthesis and were also successfully applied with excellent results to the HDA cycloaddition of mono-oxygenated dienes with aldehydes to produce 3,6-dihydro-2*H*-

pyran derivatives (compounds that do not fit the topic of this review). Some applications in cycloadditions involving the Danishefsky's diene have been reported and, in some cases, the enantioselectively catalyzed reaction was one of the key steps in the syntheses of complex natural products. Thus, the Cr(III) complex (*R*,*S*)-**LXXVIIa** was found the catalyst of choice in the HDA reaction between the Danishefsky's diene **347** and aldehydes **364a-c** (Scheme 156).[167]

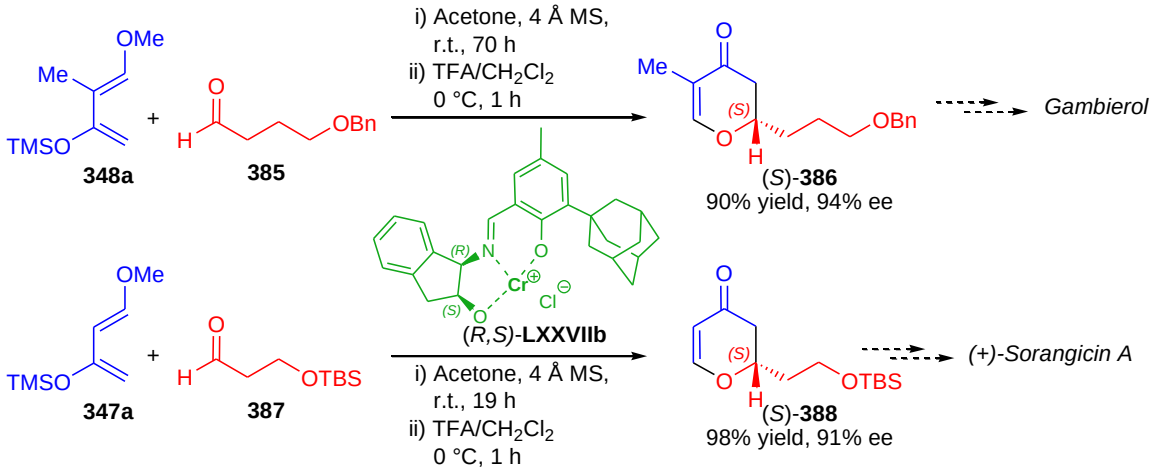
Scheme 156. Enantioselective HDA Reactions Between 347a and Aldehydes 364a-c Catalyzed by (*R*,*S*)-LXXVIIa.[167]



The catalyst was efficient also at high reaction temperature (50 °C) and the cycloadducts (*S*)-**351**, deriving from a diene approach to the *Si*-face of the aldehydes, were obtained within excellent yields and very good enantioselectivities: Ten different aldehydes were tested with an average yield of 91 ± 8%, and an average ee of 89 ± 3% (Table 13, entry 16). The catalytic system exhibited slightly nonlinear effects, positive for catalyst with ee <50% and negative for catalysts with higher ee values. Such double curved plots cannot be explained in terms of a dimeric form of the catalyst, and strongly suggested that a tetrameric form is actually involved in the process.[167]

The high catalytic efficiency of (*R*,*S*)-**LXXVII** was exploited in the enantioselective preparation of some key intermediates involved in the total synthesis of natural products, such as gambierol[168,169] and (+)-sorangicin A (Scheme 157).[170]

Scheme 157. Examples of Application of Catalyst (*R,S*)-LXXVIIb in the Synthesis of Natural Products.[168-170]



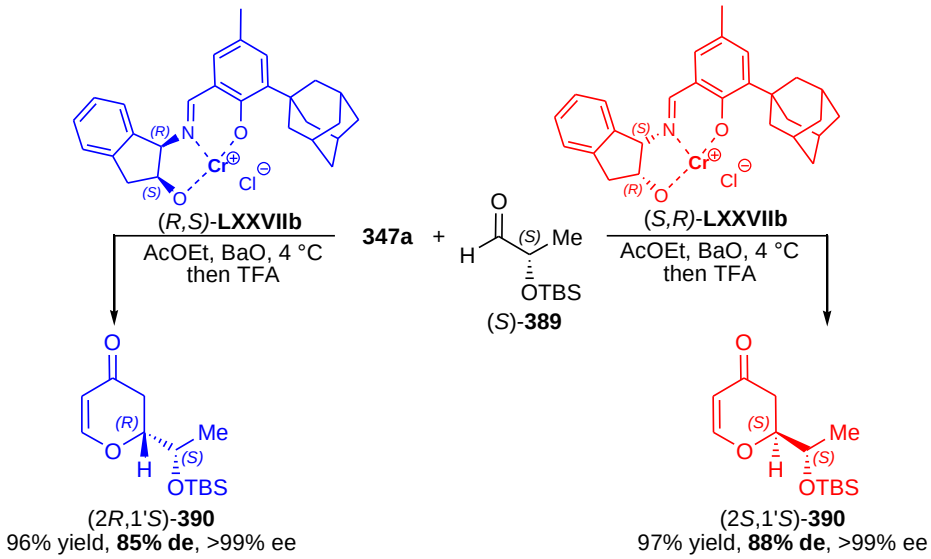
Gambierol, a representative component of the marine ladder toxin, consists of eight ether rings (A-H), 18 stereocenters, and two challenging pyranyl rings (B and C) having methyl groups in a 1,3-diaxial orientation. The 4-pyranone derivative (*S*)-**386** corresponded to the A-ring subunit, and it was obtained in high yields and excellent enantioselectivity from the HDA reaction between **348a** and **385** in the presence of the complex (*R,S*)-**LXXVIIb** as the chiral catalyst (Scheme 157).[168,169]

The same catalyst was effective in the enantioselective synthesis of pyran-4-one (*S*)-**388** obtained from the HDA reaction between the Danishefsky's diene and the β-hydroxy-protected aldehyde **387** (Scheme 157). The cycloadduct was obtained on a multi-gram scale within 98% yield and 91% ee, and was further functionalized in order to build the C(1-15) subtarget to be employed in the total synthesis of (+)-sorangicin A, a macrolide product with a very high antibiotic activity against a broad panel of both Gram-positive and Gram-negative bacteria.[170]

Catalysts (*R,S*)- and (*S,R*)-**LXXVIIb** were also effective to establish chiral catalyst-controlled doubly diastereoselective HDA reactions between Danishefsky's diene and optically active chiral aldehydes.[171] This strategy allowed selective accesses to stereochemically modified dihydropyran-4-one derivatives, which are not easily accessible using substrate-controlled diastereoselective reactions or through enantioselective syntheses starting from achiral substrates.

Thus, (*S*)-lactaldehyde derivative (*S*)-**389** was allowed to react with the Danishefsky's diene **347a** in the presence of enantiomeric tridentate Schiff base catalysts **LXXVIIb** (Scheme 158). Under optimised reaction conditions, the two diastereomeric cycloadducts (2*R*,1'*S*)- and (2*S*,1'*S*)-**390** were selectively obtained within excellent yields (96 and 97%, respectively) and with high diastereoselectivities (85 and 88% de, respectively); in both the cases, the ee of the major diastereoisomer were >99%. The methodology was extended to other optical active chiral aldehydes and enantiomeric salen (*R*,*R*)- and (*S*,*S*)-**LXXa** catalysts were also tested. The results clearly demonstrated the possibility to achieve catalyst-controlled stereoselective HDA reactions, providing selective access to any of the four possible dihydropyran-4-one stereoisomers by judicious choice of aldehyde and catalyst enantiomers.[171]

Scheme 158. Catalyst-Controlled Doubly Diastereoselective HDA Reactions Between 347a and (*S*)-389 with (*S*,*R*)- and (*R*,*S*)-LXXVIIb Complexes.[171]



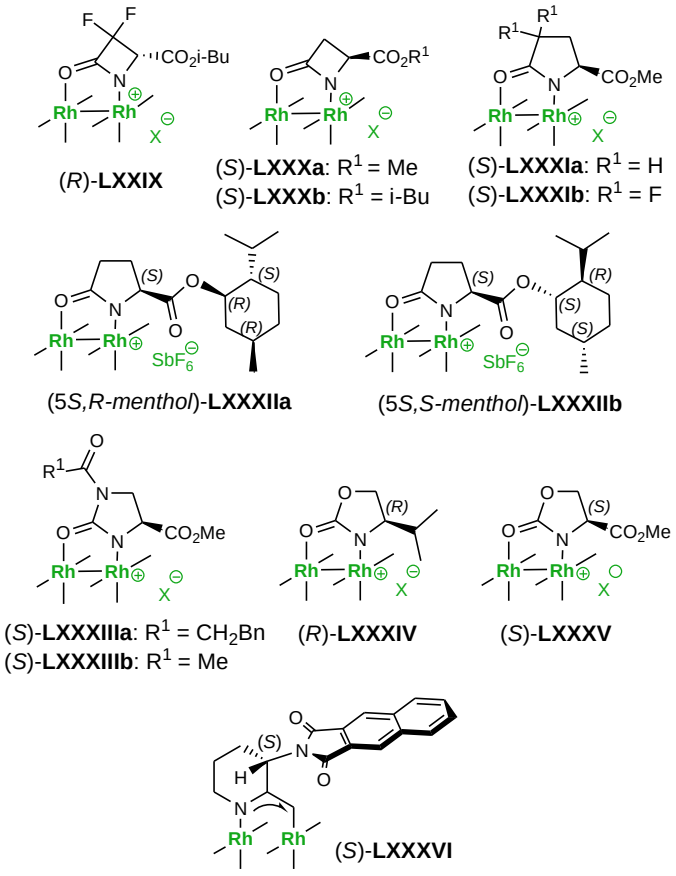
To close this section, a mention has to be made to the first chiral porphyrin used as asymmetric catalyst in HDA reactions.[172] The Cr(III) based complex (1*S*,4*R*,5*R*,8*S*)-**LXXVIII** (Chart 6) was tested in the HDA cycloaddition between the Danishefsky's diene and six different aldehydes **364a-c** to furnish cycloadducts **351a-c** with good yields and good-excellent enantioselectivities (Table 13, entry 17). The adduct stereochemistry derived from a diene approach to the *Re*-face of the aldehydes, and an interesting feature of this particular catalyst was its compatibility with metal-coordinating aldehydes such as pyridine-2-carbaldehyde, which does not inactivate the Cr(III) porphyryn complex.[172]

2.2.2.4. Dirhodium(II) Carboxamidate Catalysts

In many of the above discussed examples, the enantioselectivities observed by using several chiral catalysts were >98%, but with relatively high catalyst loadings (the substrate/catalyst ratio is usually ≤50). To overcome this drawback, chiral dirhodium(II) carboxamidate catalysts, already known for effective and efficient metal carbene transformations, were tested in HDA reactions with substrate-to-catalyst ratio up to 10,000.[173] Chart 7 collects the dirhodium carboxamidate complexes

that have been tested in enantioselective HDA reactions between Danishefsky's dienes and aldehydes.

Chart 7. [Dirhodium(II)-(Carboxamidate)$_4$] Catalysts Used in the Asymmetric Catalysis of the HDA Reactions Between Danishefsky's Diene and Aldehydes.

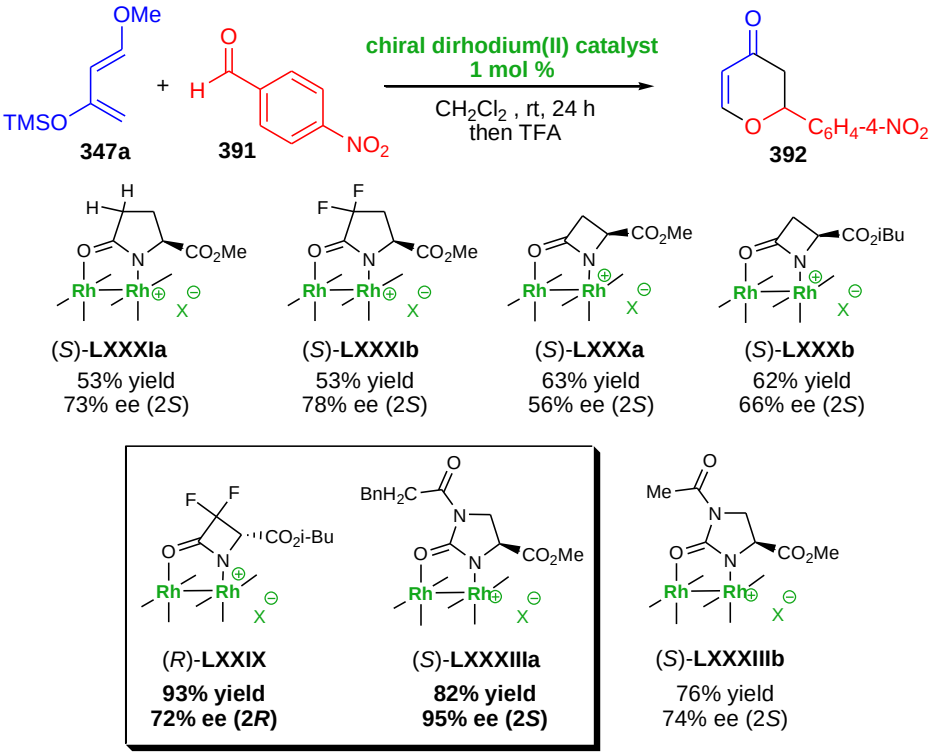


The HDA reaction initially taken as a model involved the Danishefsky's diene **347a** and *p*.nitro-benzaldehyde **391**, which was run in the presence of a broad selection of chiral dirhodium(II) catalysts (1 mol %) for 24 h at room temperature in dichloromethane. Scheme 159 collects the catalysts tested with the corresponding reaction yields and enantioselectivities obtained.[173]

From the comparison of the results collected in Scheme 159, the highest level of enantiocontrol was achieved with the less Lewis acidic (*S*)-**LXXXIIIa**, while (*R*)-**LXXIX** gave the highest reaction yield with a moderate enantioselectivity. These complexes were then chosen as catalysts of choice to screen a series of aromatic and heteroaromatic aldehydes (Table 14, entry 1

and 2). Catalyst (*R*)-**LXXIX** allowed to obtain the higher reaction yields with good enantioselectivities, while (*S*)-**LXXXIIIa** gave excellent level of enantiocontrol even if with lower yields. When the [substrate]/[catalyst] was increased up to 10,000, then only a slight decrease in enantioselectivities was observed, probably due to a background reaction. It was evident that dirhodium(II) catalysts did not have the restrictions for catalyst turnover usually observed for other catalytic systems, since they maintained their activity event at 0.01% of catalyst loading.[173]

Scheme 159. Enantioselective HDA Reactions Between 347a and 4-Nitro-Benzaldehyde 391 Catalyzed by Chiral Dirhodium(II) Complexes.[173]

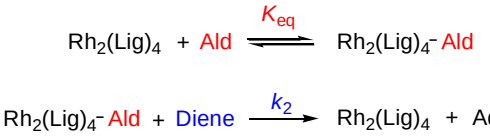


Enantioselectivities (and reaction yields) observed in the *para*-substituted benzaldehydes were significantly related to the electronic effects of the substituent, with the % ee increasing with the increase of the electron-withdrawing character of the *para*-substituent.[173]

The poor reactivities observed in the HDA reactions with the electron-rich aldehydes were ameliorated by running the reaction at higher temperature (60 °C) without markedly affecting enantioselectivity.[174] (*S*)-**LXXXIIIa** (1.0 mol %) was the catalyst of choice used in the cycloadditions of 11 different aromatic aldehydes **364b**. Cycloadducts **351b** were obtained within

high yields and excellent enantioselectivities (Table 14, entry 3). The proposed mechanism was kinetically investigated in order to determine the values of the association constant (K_{eq}) and the rate constant (k_2) for five aromatic aldehydes [(*S*)-**LXXXIIIa** being the catalyst], Scheme 160.

Scheme 160. Proposed Reaction Mechanism of Dirhodium(II)-Catalyzed HDA Reaction and Rate and Equilibrium Constants at 60 °C in Chloroform.[174]



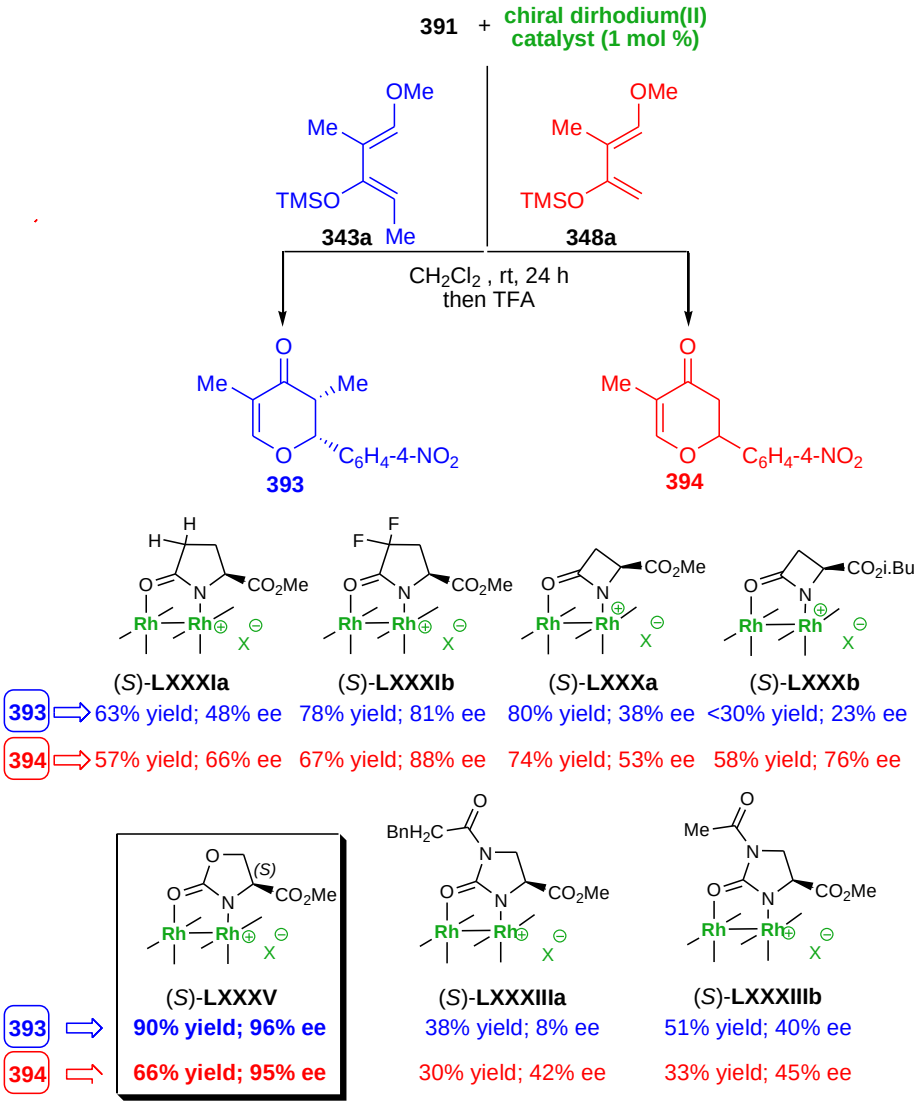
Substituent Ar-CHO	4-NO_2	H	4-Cl	4-Me	4-OMe
K_{eq} [M^{-1}]	6	65	24	62	74
10^{-3} x k_2 [s^{-1} M^{-1}]	133	9.7	6.6	0.87	0.18

Aldehyde (Ald) coordination to catalyst $Rh_2(Lig)_4$ with its carbonyl oxygen lowers its LUMO energy, activating the diene addition to produce the adduct and to regenerate the catalyst. The more electron-poor *p*-nitrobenzaldehyde has a reaction rate (k_2) that is 770 times greater than that of the *p*-anisaldehyde: A Hammett plot vs σ^+ was found to give a ρ value of +1.9 (R^2, 0.97). At the same time, *p*-anisaldehyde is more tightly bound to the catalyst than *p*-nitrobenzaldehyde (K_{eq} is 74 vs 6 M^{-1}, respectively), and it was expected to be an inhibitor for the reaction of *p*-nitrobenzaldehyde with Danishefsky's diene. When equal amounts of both p-nitrobenzaldehyde and p-anisaldehyde were allowed to react together, only the nitro derivative reacted with Danishefsky's diene, but with a rate slower than that observed in the absence of *p*-anisaldehyde. The catalyst inhibition ascribable to the more basic component rationalizes also the effect of Lewis bases, including reactant aldehydes and solvents, in determining a decrease in both the reaction rate and the enantiocontrol,[176] with toluene being identified as the solvent of choice.[177]

The catalysis with chiral dirhodium(II) complexes of the HDA reactions involving less reactive dienes such as **343a** and **348a** was also optimised by screening several catalysts (Scheme 161).[174,175] Catalyst (*S*)-**LXXXIIIa**, which was found one of the most efficient for the HDA

involving the Danishefsky's diene **347a**, now is one of the worse catalysts since cycloadducts **393** and **394** were obtained in low yields and negligible enantioselectivities. The screening identified (*S*)-**LXXXV** has the best catalyst, which allowed to obtain the products in high yields and excellent enantioselectivities.

Scheme 161. Enantioselective HDA Reactions Between Dienes 343a and 348a with 4-Nitro-Benzaldehyde 391 Catalyzed by Chiral Dirhodium(II) Complexes.[174,175]



In the case of cycloadduct **393** the cis-diastereoselectivity was very high (de > 96%), and this finding was taken as a mechanistic proof in favour of the concerted [4+2] cycloaddition pathway. The catalytic efficiency of (*S*)-**LXXXV** was exploited in the HDA reaction of other electron-deficient aldehydes with **343a**.

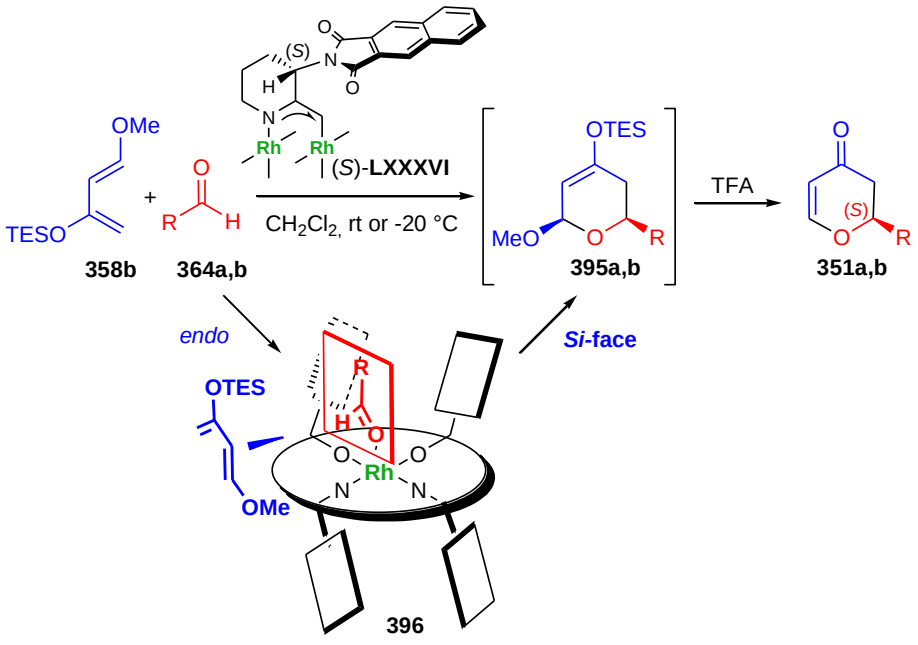
Table 14. Average Values and Standard Deviations (s.d.) of the Reaction Yields, Diastereo-, and Enantioselectivities for the Formal HDA Reactions Between the Danishefsky's Dienes and Aldehydes **364a-c**, Catalyzed by Dirhodium(II) Carboxamidates Complexes Reported in Chart 7.

Entry	Diene	Aldehyde	Catalyst	n. Exp.	aver. Yield % (s.d.)	Reaction Product	aver. ee % (s.d.)	Attach. CO face	Ref.
1	**347a**	**364b,c**	(*R*)-**LXXIX**	6	69 (24)	(2*R*)-**351b,c**	72 (8)	*Re*	173
2	**347a**	**364b,c**	(*S*)-**LXXXIIIa**	3	57 (21)	(2*S*)-**351b,c**	92 (3)	*Si*	173
3	**347a**	**364b**	(*S*)-**LXXXIIIa**	11	82 (14)	(2*S*)-**351b**	92 (4)	*Si*	174
4	**343a**	**364b,c**	(*S*)-**LXXXV**	3	92 (7)	**393**	94 (3)	---	174
5	**347a**	**391**	(5*S*,*R*-menthol)-**LXXXIIa**	2	60 (8)	**392**	87 (4)	*Si*	177
6	**347a**	**391**	(5*S*,*S*-menthol)-**LXXXIIb**	2	92 (5)	**392**	92 (1)	*Si*	177
7	**358b**	**364a,b**	(*S*)-**LXXXVI**	11	90 (8)	**351a,b**	94 (2)	*Si*	178
8	**362c**	**364a-c**	(*S*)-**LXXXVI**	20	77 (6)	**351a-c**	95 (3)	*Si*	179
9	**363c**	**364a-c**	(*S*)-**LXXXVI**	12	88 (7)	**373a-c**	92 (5)	*Si*	180

The cycloadducts **393** were isolated within excellent yields, diastereo- and enantioselectivity by using 1 mol % of catalyst (Table 14, entry 4). These results were confirmed also by using lower catalyst loadings, and excellent stereoselectivities were obtained by using 0.01 mol % of (*S*)-**LXXXV**.[174]

The new dirhodium(II) complex (*S*)-**LXXXVI** has been proved to be an efficient catalyst in HDA reactions involving both aromatic and aliphatic aldehydes (Scheme 162).[178] The new complex, which incorporates (*S*)-3-(benzo-fused-phthalimido)-2-piperidinonate as chiral bridging ligand, was found to be more a general and efficient catalyst for highly endo-enantioselective HDA reactions than other dirhodium(II) complexes. After treatment with TFA, chiral 2,3-dihydro-pyran-4-ones **351a,b** were indeed obtained within excellent yields (from 71 to 97%) and enantioselectivities (91-96% ee), Table 14, entry 7.

Scheme 162. Enantioselective HDA Reactions Between 358b and Aldehydes 364a,b Catalyzed by Chiral Dirhodium(II) Complex (*S*)-LXXXVI.[178]

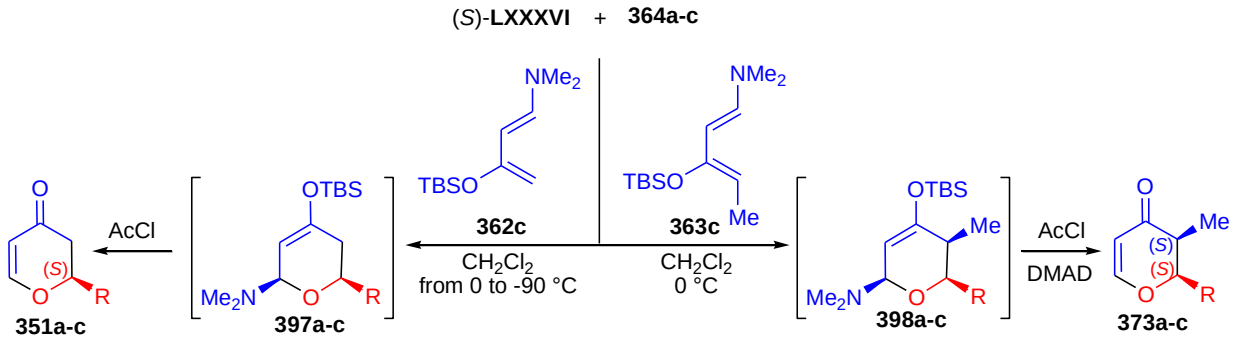


The reaction was demonstrated to follow a concerted [4+2] cycloaddition mechanism. The 2,6-cis-disubstitued dihydropyrans **395a,b** can be isolated prior the treatment with TFA and analysed by ^{1}H NMR spectroscopy. The stereochemical outcome has been rationalized by

proposing complex **396** as the reacting intermediate, in which a favourable H-bond between the formyl hydrogen atom and the carboxamidate oxygen atom is allowed. The less sterically hindered endo approach of the diene to the *Si*-face of the aldehyde is consistent with the (2*S*) absolute configuration of the adducts.[178]

(*S*)-**LXXXVI** is a very robust and active catalyst, which is readily synthesized, air-stable, and easily handled. Reactions with highly reactive aldehydes proceeded smoothly with very low catalyst loadings (0.0075-0.002 mol %) without any decrease in yields and enantioselectivities. The turnover numbers were as high as 48.000, and represent one of the highest value ever reported for Lewis acid catalysed asymmetric reactions.[178]

Scheme 163. Enantioselective HDA Reactions Between Rawal's Dienes 362c-363c and Aldehydes 364a,b Catalyzed by Chiral Dirhodium(II) Complex (*S*)-LXXXVI.[179,180]

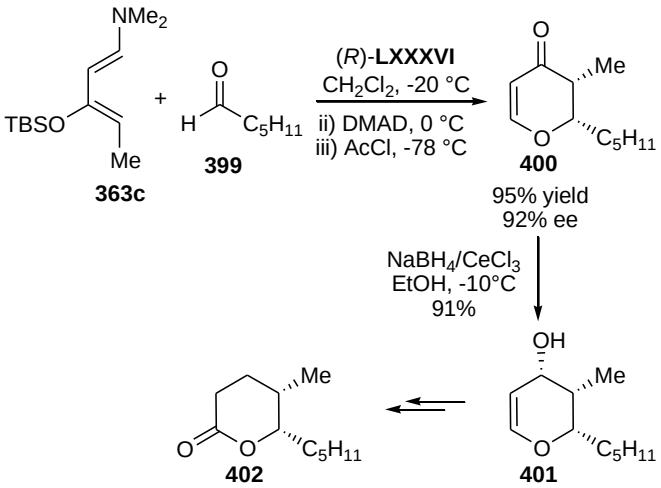


The dirhodium(II) complex (*S*)-**LXXXVI** allowed to run the first example of a chiral Lewis acid-catalyzed HDA reaction between 1-dimethylamino-3-silyloxy-1,3-butadiene **362c** (the Rawal's diene) with aldehydes (Scheme 163).[179] Respect to the previously described protocol, the quenching of the intermediate is now achieved by treatment with acetyl chloride, which converted the dihydropyran intermediates **397a-c** into dihydropyran-4-ones **351a-c**. The reaction proceeded through a concerted pathway with a stereochemical outcome that is in accordance with the intermediate **396** shown in Scheme 162. Cycloadducts were obtained within very good yields and excellent enantioselectivities: Over 20 different aldehydes, the average yield was 77 ± 6% and the average ee 95 ± 3% (Table 14, entry 8).[179]

Furthermore, the more steric demanding diene **363c** was allowed to react under the above described protocol, the only change being the quenching of the intermediates **398a-c** that involved acetyl chloride and DMAD.[180] This latter was required to take away the unreactive (1*E*,3*E*)-**363c** by a fast cycloaddition with DMAD to avoid undesired side-reactions. The cycloadducts **373a-c** were obtained with excellent yields and enantioselectivities (Table 14, entry 9), and only the 2,3-cis-disubstituted pyran-4-ones were observed (de > 99%).

The utility of this catalytic protocol was demonstrated by the asymmetric synthesis of (-)-cis-aerangis lactone **402**, an odoriferous component of *Aerangis* species (Scheme 164). The HDA reaction between diene **363c** and hexanal **399** was catalysed by the enantiomeric complex (*R*)-**LXXXVI** (3 mol %) and produced pyranone **400** as a single diastereoisomer in excellent yield and enantioselectivity. The highly stereoselective $NaBH_4$ reduction furnished the dihydropyran **401** in 91% yield, which was converted in three steps into the final target lactone **402** with a complete control of the stereochemistry.[180]

Scheme 164. Synthetic Application of the Enantioselective HDA Reactions Between Rawal's Diene 363c and Hexanal 399 Catalyzed by (*R*)-LXXXVI to Produce 402.[180]

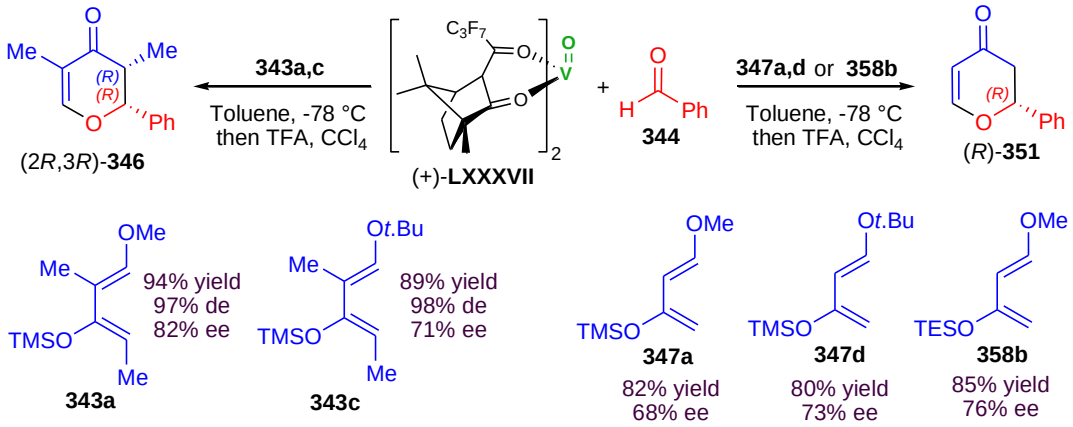


2.2.2.5. Other [Chiral Ligand/Lewis Acid] Catalysts

Chiral complexes involving V(IV) as the Lewis acid have been prepared by using 3-(heptafluorobutyryl)camphor (hfc) as the chiral ligand. Hfc, the ligand already used by Danishefsky in Eu(III)-based chiral catalysts,[128,129] was allowed to react with $VOSO_4 \cdot 5H_2O$ with 1 equiv of Et_3N

in EtOH/H_2O to give the complex (+)-**LXXXVII**, which was isolated in 41% yield.[181] The $VO(hfc)_2$ complex was then used as chiral catalyst in HDA reactions between several Danishefsky's dienes with benzaldehyde **344** (Scheme 165).

Scheme 165. Enantioselective HDA Reactions Between Danishefsky's Dienes and Benzaldehyde 344 Catalyzed by Complex (+)-LXXXVII.[181]



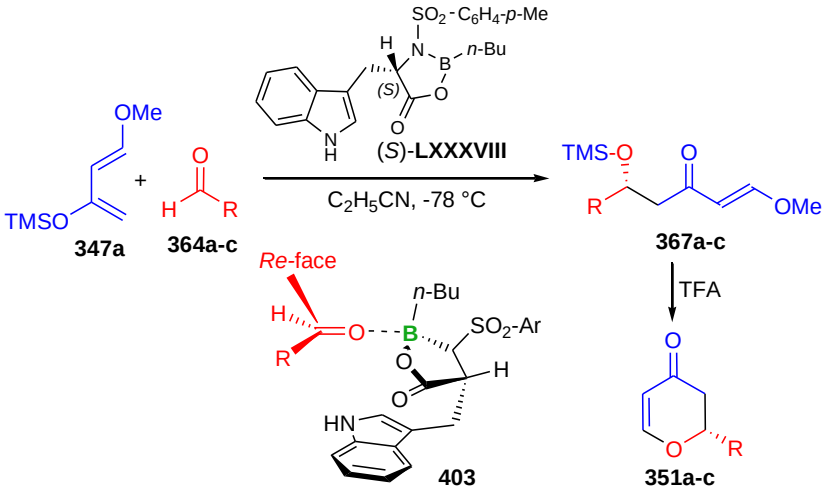
The HDA reaction proceeded with excellent yields and good enantioselectivities to produce dihydropyran-4-ones **346** and **351** with a stereochemistry deriving from a diene approach to the *Si*-face of the aldehyde. When 2,4-dimethyl-substituted diene derivatives **343a,c** were used, then the diastereoselectivity was excellent, and cis-(2*R*,3*R*)-**346** was obtained with up to 98% de.[181]

The catalyst (+)-**LXXXVII** was then exploited in the HDA reaction between diene **343a** and six different aldehydes **364a-c**: the reaction yields were very good and the diastereoselectivities excellent, while the enantioselectivity was only partially satisfactory (average ee, 64 ± 14%), Table 15, entry 1.[181]

In 1992 the borane-derived *N*-*p*-toluenesulphonyl-(*S*)-tryptophan **(*S*)-LXXXVIII** was the catalyst tested by Corey in the enantioselective synthesis of enantioenriched 2,3-dihydro-pyran-4-one derivatives **351a-c**.[182] The reaction of aldehydes **364a-c** with the Danishefsky's diene in the presence of 20 mol % of (*S*)-**LXXXVIII** afforded mainly the Mukaiyama aldol adducts **367a-c**, which were isolated and then converted by treatment with TFA into pyran-4-ones **351a-c** (Scheme 166). The yields were good, but the enantioselectivities were only moderate (Table 15, entry 2). The

stereochemical outcome was rationalized by applying the model (**403**) in which aldehyde is coordinated to the boron by assuming a positioning stabilized by π-stacking interaction, the attack of the Danishefsky diene occurs onto the less shielded *Re*-face of the aldehyde.[182]

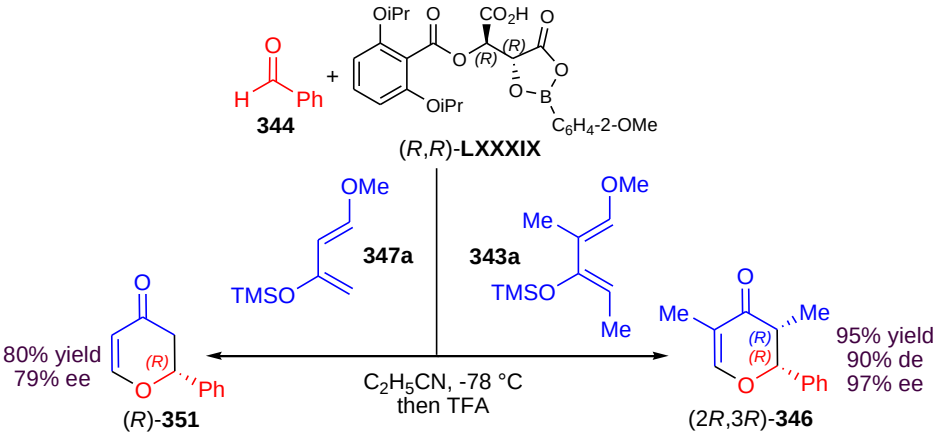
Scheme 166. Enantioselective HDA Reactions Between Danishefsky's Dienes and Aldehydes 364a-c Catalyzed by (*S*)-LXXXVIII.[182]



The same year, Yamamoto successful applied the stable chiral acyloxyborane (CAB), easily prepared by mixing tartaric acid derivatives with arylboric acid, as chiral catalysts in asymmetric HDA reactions.[183] A screening of different arylboric acid evidenced the crucial role of the group at the boron atom in determining the extent of asymmetric induction. Bulky substituents resulted in excellent enantioselectivity, even if overly groups led to a relevant decrease in reactivity. The derivative of choice was found to be (*R*,*R*)-**LXXXIX** bearing an *ortho*-methoxyphenyl substituent (Scheme 167).[183] The HDA reaction between benzaldehyde **344** with Danishefsky's diene **347a** proceeded to afford (*R*)-**351** within good yield and appreciable enantioselectivity. Even better results were obtained with the more sterically demanding diene **343a**, since (2*R*,3*R*)-**346** was obtained with up to 95% yield, 90% de, and 97% ee (Scheme 167). CAB catalyst effectively shielded the *Si*-face of the coordinated carbonyl, and the selective diene approach to the *Re*-face accounted for the stereochemical outcome of the cycloaddition. The efficiency of (*R*,*R*)-**LXXXIX** in HDA reactions involving few other aldehydes **364a-c** has been tested, and the adducts were obtained within good yields and excellent diastereo- and enantioselectivities (Table 15, entry 3).

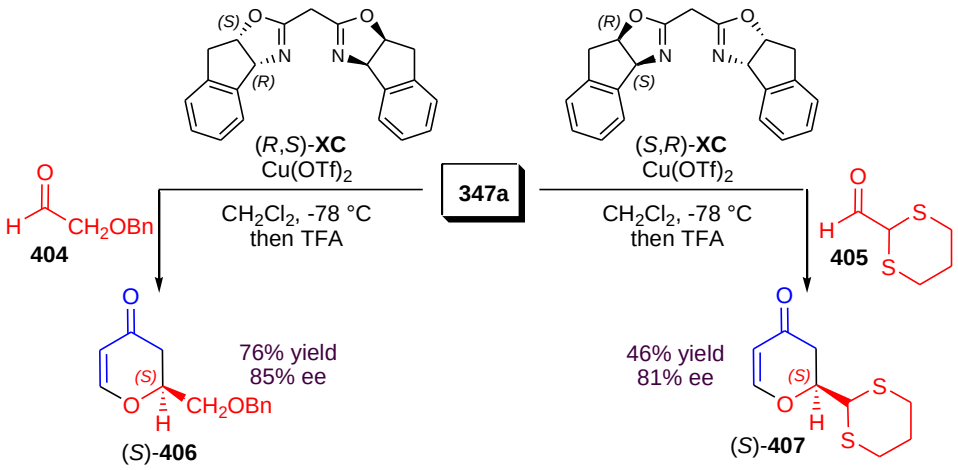
Since optically pure unnatural tartaric acid derivatives are equally available, then the enantiomeric (*S*,*S*)-**LXXXIX** will be easily accessible, allowing the enantioselective synthesis of both antipodal cycloadducts.

Scheme 167. Enantioselective HDA Reactions Between Danishefsky's Dienes 347a and 343a with Benzaldehyde 344 Catalyzed by (*R*,*R*)-LXXXIX.[183]



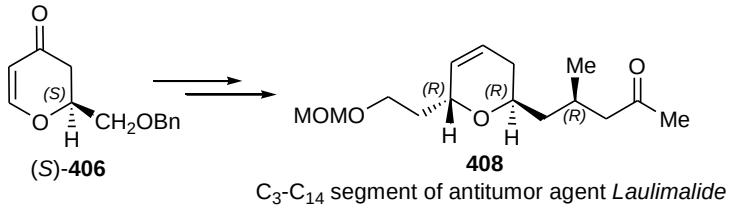
Only few examples of BOX-based chiral catalysts in enantioselective synthesis of pyran-4-one derivatives have been described. In the first report the HDA reaction between Danishefsky's diene **347a** with either benzyloxyacetaldehyde **404** or 1,3-dithianecarboxaldehyde **405** was run in the presence of the complexes between $Cu(OTf)_2$ and either bis(3a*R*,8a*S*) or bis((3a*S*,8a*R*)-8,8a-dihydro-3a*H*-indeno[1,2-*d*]oxazol-2-yl)methane as catalysts [(*R*,*S*)- and (*S*,*R*)-**XC**] (Scheme 168).[184]

Scheme 168. Enantioselective HDA Reactions Between Danishefsky's Dienes 347a and Aldehydes 404, 405 Catalyzed by (*R*,*S*)- and (*S*,*R*)-XC.[184]



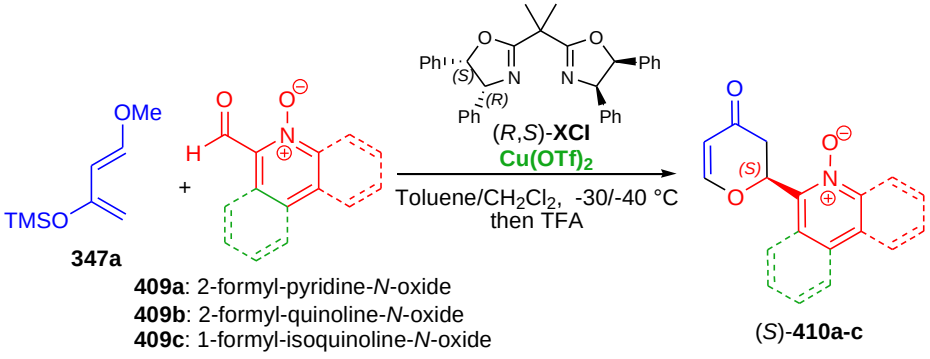
Both adducts **406** and **407** were obtained with good enantioselectivity, while only in the HDA reaction of benzyloxyacetaldehyde **404** the reaction yield was acceptable. The most intriguing point is that cycloadducts have the same (2*S*)-configuration, even if obtained by using the two enantiomeric ligands. This finding may be the result of the different ability of **404** vs **405** to behave as bicoordinating reagents with a change of the geometry of the reacting intermediate, but the point was not further inferred. In any case, cycloadduct (*S*)-**406** was the key intermediate in the synthesis of product **408**, the C_3–C_{14} segment of antitumor macrolide laulimalide (Scheme 169).[184]

Scheme 169. Adduct (*S*)-406 as Key Intermediate in the Synthesis of the 408.[184]



The second report on the use of BOX-based catalysts in the HDA reactions involving carbonyl derivatives as heterodienophile was published ten years later by Jørgensen.[185] The formyl derivatives of pyridine-, quinoline-, and isoquinoline-*N*-oxide **409a-c** were allowed to react with the Danishefsky's diene in the presence of the cis-diphenyl-BOX (4*R*,5*S*)-**XCI** (Scheme 170). The reaction was proposed to proceed *via* a stepwise Mukaiyama-aldol mechanism to give the cycloadducts **410a-c** within moderate yields (42-80%) and good enantioselectivities (55-95% ee), Table 15, entry 4.

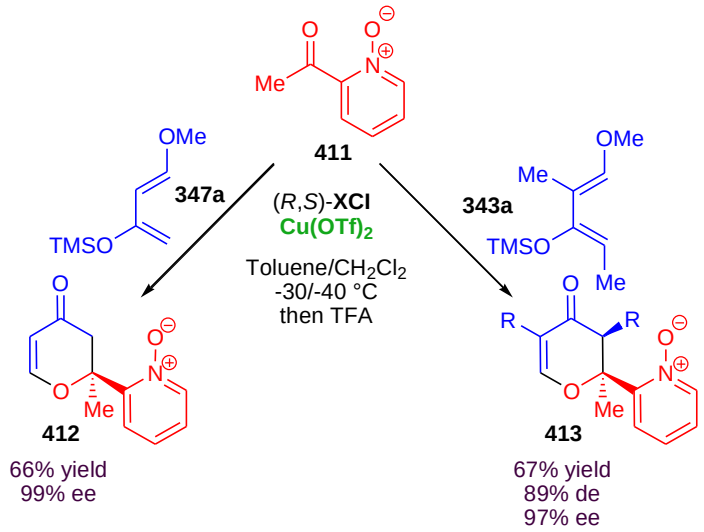
Scheme 170. Enantioselective HDA Reactions Between Danishefsky's Diene 347a and Aldehydes 409a-c Catalyzed by (*R*,*S*)-XCI/Cu(OTf)$_2$ Catalyst.[185]



The (2*S*)-absolute configuration was determined by X-ray crystallographic analysis and it is consistent with a diene approach to the more accessible *Si*-face of **409** bicoordinated to Cu(II) in a square-planar distorted intermediate complex.

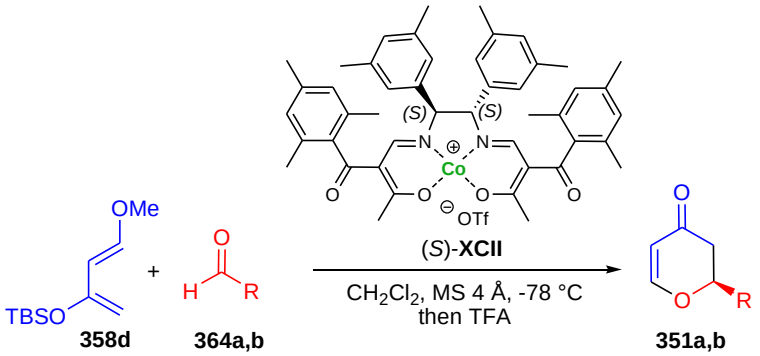
The same catalyst was usefully applied in the HDA reaction involving a ketone instead of an aldehyde as the 2π component. The reaction between 2-acetyl-pyridine-*N*-oxide **411** with dienes **347a** and **343a**, catalyzed by (*R*,*S*)-**XCI** and $Cu(OTf)_2$, furnished 2,3-dihydro-pyran-4-ones **412** and **413** bearing an asymmetric quaternary center in good yields and excellent enantioselectivities, which were even better than those observed with aldehydes **409a-c** (Scheme 171).[185]

Scheme 171. Enantioselective HDA Reactions Between Danishefsky's Dienes 347a and 343a with 2-Acetyl-pyridine-*N*-oxide Catalyzed by (*R*,*S*)-XCI/$Cu(OTf)_2$ Catalyst.[185]



Optically active 3-oxobutylideneaminocobalt(III) complexes have been developed as effective catalysts for the enantioselective HDA reaction between aliphatic and aromatic aldehydes **364a,b** with 3-(*ter*-butyldimethylsilyloxy)-1-methoxy-1,3-butadiene (**358d**). After optimization of the ligand structure, Co(III) counterion, solvent, and reaction temperature, the complex (*S*)-**XCII** was found the catalyst of choice (Scheme 172).[186] Cycloadducts **351a-c**, whose stereochemistry derived from a diene approach to the *Si*-face of the aldehyde, were obtained within very good yields and enantioselectivities (Table 15, entry 5), with *ortho*-substituted benzaldehydes being more reactive, but less selective than the corresponding *para*-substituted derivatives.

Scheme 172. Enantioselective HDA Reactions Between Diene 358d with Aldehydes 364a,b Catalyzed by (*S*)-XCII Complex.[186]



N,*N*′-Dioxide **XVIa**, already used as chiral ligand in either Cu(II)- or Er(III)-based chiral catalysts in the HDA reactions discussed in section 2.1.1.4. (see Schemes 27 and 28), were the chiral ligand in In(III)-based catalyst, which was tested in the HDA reactions between Danishefsky's dienes and aldehydes (Scheme 173).[187] Dienes **348a** and **343a** reacted with benzaldehyde **344** to produce cycloadducts **352** and **346**, respectively with excellent yields (96-99%) and enantioselectivities (98% ee). In the case of diene **343a** the reaction was also highly diastereoselective and the cis-2,3-disubstituted pyran-4-one **346** was obtained with a de >90%; its absolute configuration was found to be (2*S*,3*S*), which was consistent with a diene approach to the *Si*-face of benzaldehyde.

Scheme 173. Enantioselective HDA Reactions Between Dienes 348a and 343a with Benzaldehydes 344 Catalyzed by XVIa/In(III) Complex.[187]

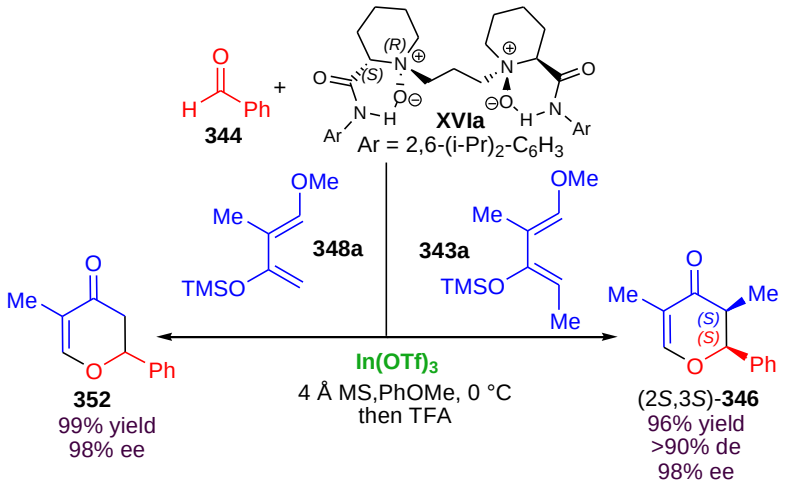


Table 15. Average Values and Standard Deviations (s.d.) of the Reaction Yields, Diastereo-, and Enantioselectivities for the Formal HDA Reactions Between the Danishefsky's Dienes and Aldehydes, Catalyzed by Other [Chiral Ligand/Lewis Acid] Complexes and by Organocatalysts.

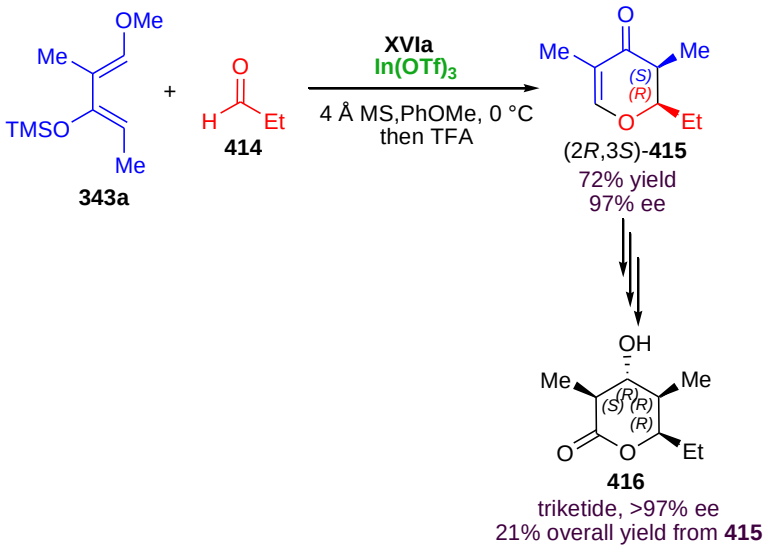
Entry	Diene	Aldehyde	Catalyst/Organocatalyst	n. Exp.	aver. Yield % (s.d.)	Reaction Product	aver. ee % (s.d.)	Attach. CO face	Ref.
1	**343a**	**364a-c**	(+)-**LXXXVII**	6	82 (13)	(2*R*,3*R*)-**346**[a]	64 (14)	*Re*	181
2	**347a**	**364a-c**	(*S*)-**LXXXVIII**	5	81 (16)	**351a-c**	73 (6)	*Re*	182
3	**343a**, **347a**	**364a-c**	(*R*,*R*)-**LXXXIX**	6	79 (20)	(*R*)-**351** or (2*R*,3*R*)-**346**[b]	90 (9)	*Re*	183
4	**347a**	**409a-c**	(*R*,*S*)-**XCI**/Cu(OTf)$_2$	7	61 (17)	(*S*)-**410a-c**	81 (14)	*Si*	185
5	**358d**	**364a,b**	(*S*)-**XCII**	8	86 (8)	**351a,b**	89 (4)	*Si*	186
6	**343a**	**364a-c**	(*S*,*R*)-**XVIa**/In(III)	31	77 (22)	**346a-c**	96 (4)	*Si*	187
7	**348a**	**364a,b**	(*S*,*R*)-**XVIa**/In(III)	9	91 (9)	**352a,b**	88 (7)	*Si*	187
8	**362c**	**364a-c**	(*R*)-**XCIIIa**	8	69 (12)	**351a-c**	95 (4)	*Si*	188
9	**362c**	**364b**	(*R*)-**XCIVa**	6	84 (11)	**351b**	98 (1)	*Si*	192
10	**362c**	**364a**	(*R*)-**XCIVb**	7	76 (19)	**351a**	92 (5)	*Si*	192
11	**362c**	**364b,c**	**XCV**	6	65 (12)	**351b,c**	87 (7)	*Si*	193
12	**360c**	**364b**	(*R*)-**XCVIII**	16	88(11)	**421b**	93 (5)	*Re*	196

[(a)] Average de of the cis-adduct, 94 ± 7%. [(b)] Average de of the cis-adduct, 93 ± 5%.

The HDA reaction of **343a** with a wide range of aromatic, aliphatic, and heterocyclic aldehydes was investigated under the optimized conditions, and the trisubstituted dihydropyranones were obtained within excellent enantioselectivities and high diastereoselectivities (Table 15, entry 6). The reaction yields were, in general, excellent in reactions involving aromatic aldehydes, less satisfactory in the case of aliphatic aldehydes. When the HDA reaction involved **348a** as the diene, then the yields were always excellent for all the aldehydes tested, but the enantioselectivity was slightly decreased. The average ee for **352** was 88 ± 7% respect to the value of 96 ± 4% observed for **346** (Table 15, entry 7 vs entry 6).

One additional advantage of the catalyst **XVIa**/In(III) is its high stability, since it was found to remain unchanged even after more than six months. This methodology was usefully applied to the synthesis of triketide **416**, by elaboration of (2*R*,3*S*)-**415** obtained from the reaction of propanal **414** with **343a** on a sub-gram scale with 72% yield and 97% ee. Triketide **416** was then obtained within 21% overall yield and >97% ee (Scheme 174).[187]

Scheme 174. Synthetic Application of the Enantioselective HDA Reactions Between Diene 343a and Propanal 414 Catalyzed XVIa/In(III) Complex to Produce Triketide 416.[187]

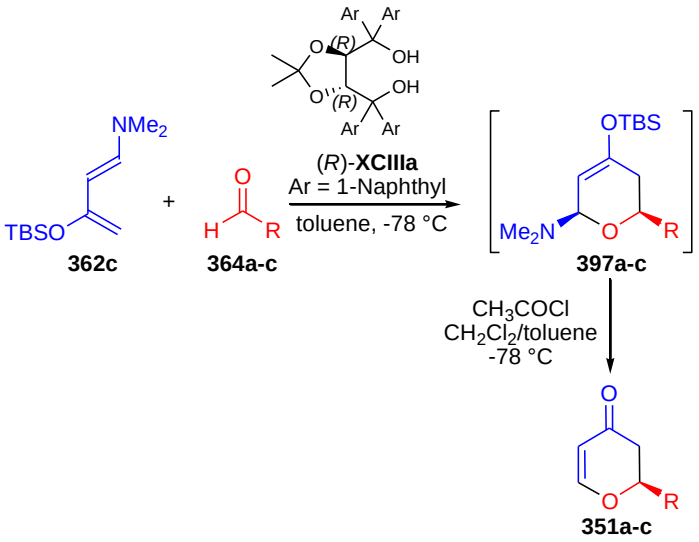


2.2.3. Organocatalyzed [4+2] Cyclization Processes.

In Section 2.1.2., more than 60 papers discussed the application of different families of organocatalysts in successful enantioselective HDA reactions between α,β-unsaturated carbonyl derivatives, acting as electron-poor heterodienes, with electron-rich dienophiles. For evident structural reasons, analogous applications such as those like aminocatalysis are not possible in HDA reactions involving Danishefsky's dienes as the 4π component and aldehyde as the 2π counterpart: The only mechanism of action available is the aldehyde activation through H-bond interaction between the organocatalyst and the carbonyl group.

Among the few examples available, the first contribution appeared as a brief communication in 2003 in which the HDA reaction between the Rawal's diene **362c** and aldehydes **364a-c** was enantioselectively catalyzed by the TADDOL derivative (*R*)-**XCIIIa** (Scheme 175).[188] The analysis of the crude reaction mixture by ^{1}H NMR indicated that the cycloadduct **397** had been formed as a single diastereoisomer, tentatively assigned as the endo stereoisomer. On treatment with acetyl chloride, the intermediates were converted into dihydropyran-4-ones **351a-c** within good-excellent yields (from 52 to 97%) and excellent enantioselectivties (from 86 to 99% ee), Table 15, entry 8.

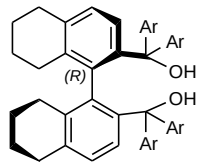
Scheme 175. Enantioselective HDA Reactions Between Rawal's Diene 362c with Aldehydes 364a-c Catalyzed by TADDOL (*R*)-XCIII Organocatalyst.[188]



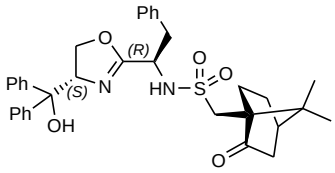
The reaction between a particularly electron-rich diene (1-methoxy-1,3-trimethylsilyloxy-1,3-butadiene, the Chan's diene) with aromatic aldehydes was tentatively catalyzed by (*S*)-**XCIIIa**, but the results evidenced that the HDA pathway is in competition with the vinylogous aldol reaction. The HDA adducts were side products obtained with low yields (from 26 to 64%) and unsatisfactory enantioselectivities (50-60% ee).[189-191]

The efficiency of other organocatalysts acting through H-bond interactions was tested in the HDA reaction between the Rawal's diene and aldehydes. Scheme 176 collects the results obtained by using chiral alcohols/diols as organocatalysts in the cycloaddition between benzaldehyde **344** with diene **362c**.[192-195]

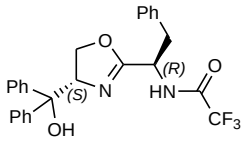
Scheme 176. Results of the Enantioselective HDA Reaction Between Rawal's Diene 362c with Benzaldehyde 344 Catalyzed Organocatalysts XCIV-XCVII.[192-195]



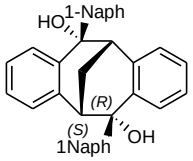
(*R*)-**XCIVa**
Ar = 4-F-3,5-$Et_2C_6H_2$
yield, 84%
ee, 98%
[Ref. 192]



XCV
yield, 62%
ee, 90%
[Ref. 193]



XCVIa
yield, 67%
ee, 91%
[Ref. 194]



XCVII
yield, 50%
ee, 48%
[Ref. 195]

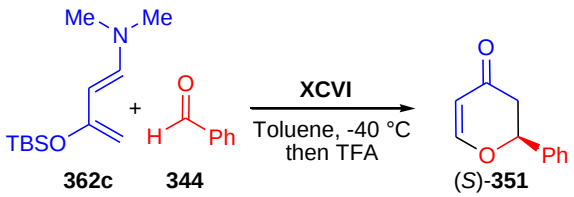
Among the various examples of H-bonding organocatalysts in Scheme 176, the 1,1′-biaryl-2,2′-dimethanol derivative (*R*)-**XCIVa** (Ar = 4-F-3,5-$Et_2C_6H_2$) is the most efficient since both reactivity and selectivity were excellent. It was exploited by running enantioselective HDA reactions mainly involving aromatic aldehydes **364b**, while for cycloadditions involving aliphatic aldehydes **364a** the catalyst of choice was (*R*)-**XCIVb** (Ar = 4-F-3,5-$Me_2C_6H_2$). Reactions yields and enantioselectivities were excellent with both aromatic (>97% ee) and aliphatic aldehydes (>84% ee), entries 9 and 10 in Table 15. The stereochemical outcome derived from a diene approach to the *Si*-face of the aldehyde activated by a single-point H-bonding.[192]

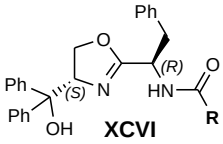
Other organocatalysts are based on a modular oxazoline template, which displays two hydrogen bond donating arms (**XCV** and **XCVI**, Scheme 176). The first HBD group is the tertiary

hydroxy-group bound to the oxazoline ring, the second one being the NH function, whose acidity can be increased by modular change of the NH-substituent.[193,194] Organocatalyst **XCV** was identified as the best one after a careful screening of several analogues structure. From this study it resulted evident that: (a) the relative stereochemistry of the chiral HBD elements was crucial (that in **XCV** was the optimal one); (b) both HBD arms were required for effective turnover. The subsequent investigation focused on the steric and electronic effects of the nitrogen substituent, and the third generation organocatalyst derived from (*S*)-camphor sulfonic acid **XCV** resulted the best one that was exploited in the enantioselective HDA reactions of some aromatic aldehydes. The cycloadducts **351b,c** were obtained within good yields and high enantioselectivities (Table 15, entry 11).[193]

Then, the role of the NH-acidity was carefully examined by evaluation of halogenated acetamido residues in organocatalysts **XCVIa-e** (Scheme 177).[194] It was found that both the reaction rate and enantioselectivity can be directly correlated to the NH acidity, which was quantified by the pK_a of the corresponding acetic acid derivatives. When the log values of the initial reaction rate determined for the five catalysts **XCLIa-e** were plotted vs the pK_a of each acid, a nice linear free energy relationship (LFER) was observed (ρ, -0.46; R^2, 0.99) confirming that the higher the acidity, the faster will be the reaction.

Scheme 177. Results of the Enantioselective HDA Reaction Between Rawal's Diene 362c with Benzaldehyde 344 Catalyzed Organocatalysts XCVIa-e.[194]





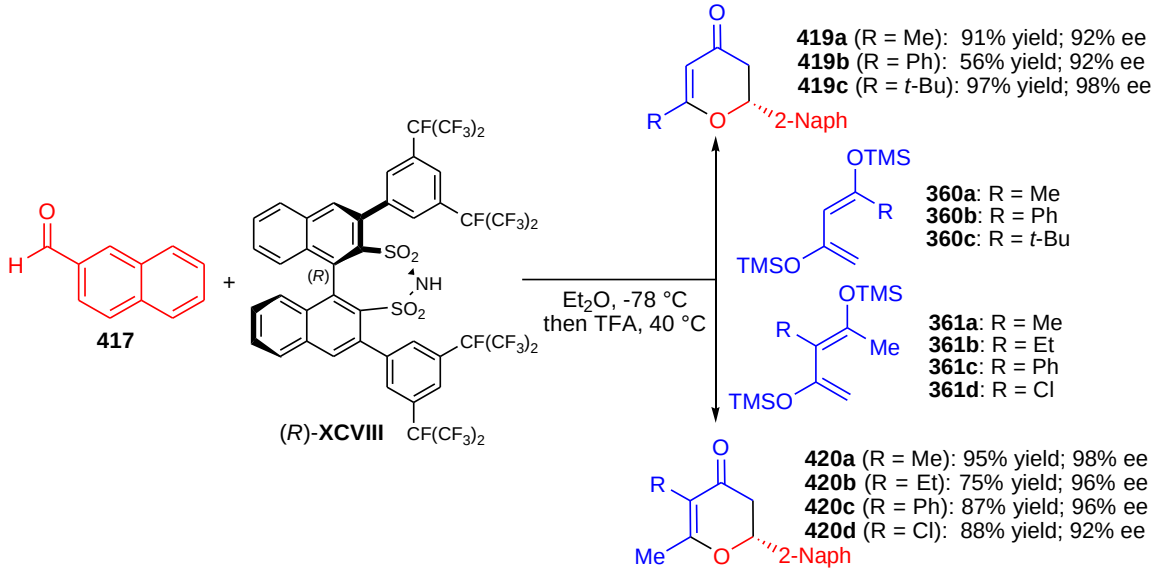
Catalyst:	pK_a RCO_2H	yield %	ee %
a: R = CF_3	- 0.25	67	91
b: R = CCl_3	0.65	61	81
c: R = $CHCl_2$	1.29	53	65
d: R = CH_2F	2.66	17	62
e: R = CH_2Cl	2.86	32	52

A nice LFER was also obtained by plotting the log values of the enantiomeric ratio [(*S*)]/[(*R*)] vs the NH acidity (ρ, -0.24; R^2, 0.97), evidencing that the higher the acidity, the more selective will be the cycloaddition.[194]

A single example using a chiral carbocyclic cleft molecule deriving from 2,3:6,7-dibenzobicyclo[3.3.1]nona-2,6-diene-4,8-dione **XCVII** was also curiously tested.[195] This organocatalyst was applied in the HDA reaction between the Rawal's diene and benzaldehyde, but the results were not comparable with those previously described, probably because the catalysis proceeded by single H-bond activation (cycloadduct (*S*)-**351** was obtained within 50% yield and 48% ee).[195]

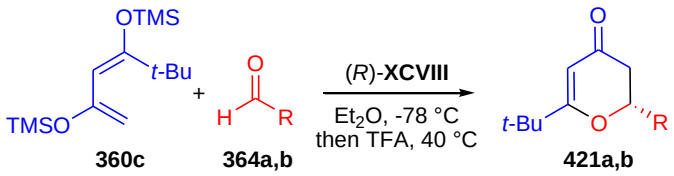
A more efficient organocatalyst acting as chiral Brønsted acid was the binaphthyl-derived chiral cyclic disulfonimides (*R*)-**XCVIII** a more buried acid than the corresponding phosphoric acid **XV**, which was useful applied to the HDA reaction between 1,3-di(trimethylsilyloxy) substituted dienes **360** and **361** with 2-naphthaldehyde **417** (Scheme 178).[196] The cycloadducts **419-420** always bear a substituent at the C-6 position of the dihydropyranones and were obtained within excellent yields and enantioselectivities through a step-wise mechanism (Mukaiyama-aldol addition).

Scheme 178. Enantioselective HDA Reaction Between Dienes 360 and 361 with 2-Naphthaldehyde 417 Catalyzed by (*R*)-XCVIII.[196]



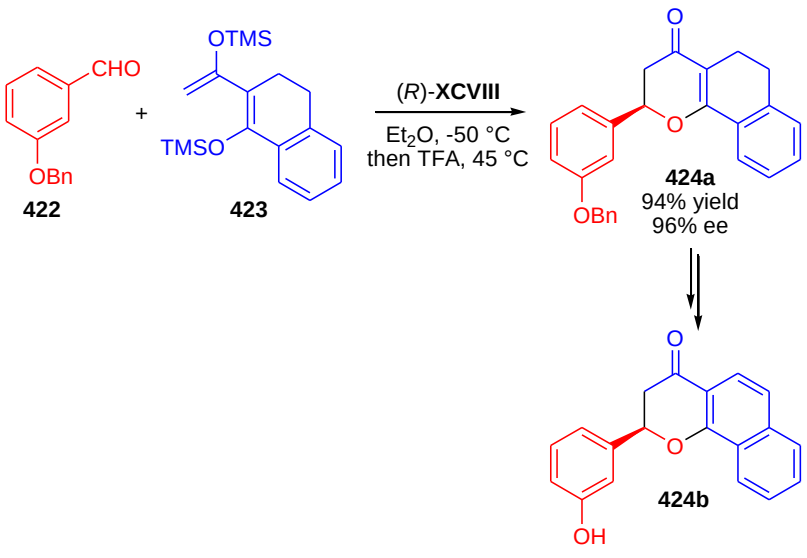
Catalyst (*R*)-**XCVIII** was then exploited in the HDA reaction of **360c** with 16 different aromatic aldehydes **364b** (Scheme 179). The cycloadducts **421b** were always obtained within excellent yields and very high enantioselectivities (Table 15, entry 12), with a stereochemistry deriving from a nucleophilic approach of the diene to the *Re*-face of the protonated aldehyde. When the HDA reaction involved aliphatic aldehydes **364a**, the results were less satisfactory, since adducts **421a** were obtained within very low yields (17-24%) and moderate enantioselectivities (28-74% ee).[196]

Scheme 179. Enantioselective HDA Reaction Between Diene 360c with Aldehyde 364a,b Catalyzed by (*R*)-XCVIII.[196]



The synthetic utility of this methodology was demonstrated by running the first asymmetric synthesis of the 3′-hydroxy-substituted 7,8-benzoflavone **424b**, a potent aromatase inhibitor, by reaction between aldehyde **422** and diene **423** (Scheme 180).[196]

Scheme 180. Synthesis of Aromatase Inhibitor 424 via Enantioselective HDA Reaction Between Diene 423 with Aldehyde 422 Catalyzed by (*R*)-XCVIII.[196]

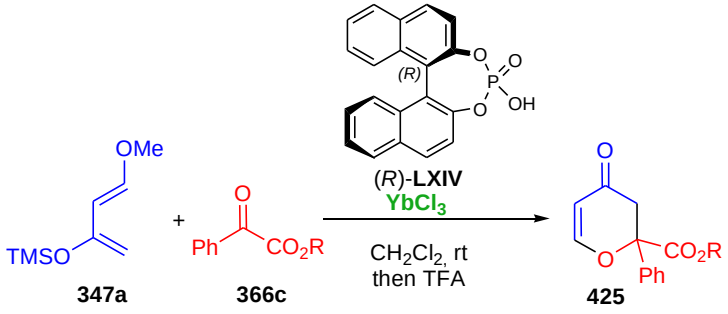


The reaction between 1 mmol of 3-benzyloxybenzaldehyde **422** with diene **423** under optimized conditions in the presence of 1 mol % of (*R*)-**XCVIII** gave the dihydropyran-4-one derivative **424a** in excellent yield and enantioselectivity. Subsequent aromatization by DDQ oxidation, followed by a reduction-oxidation sequence, furnished the target benzoflavone **424b** in good overall yield without any loss in enantiopurity.[196]

2.2.4. Reaction between Dienes and α-Dicarbonyl Derivatives.

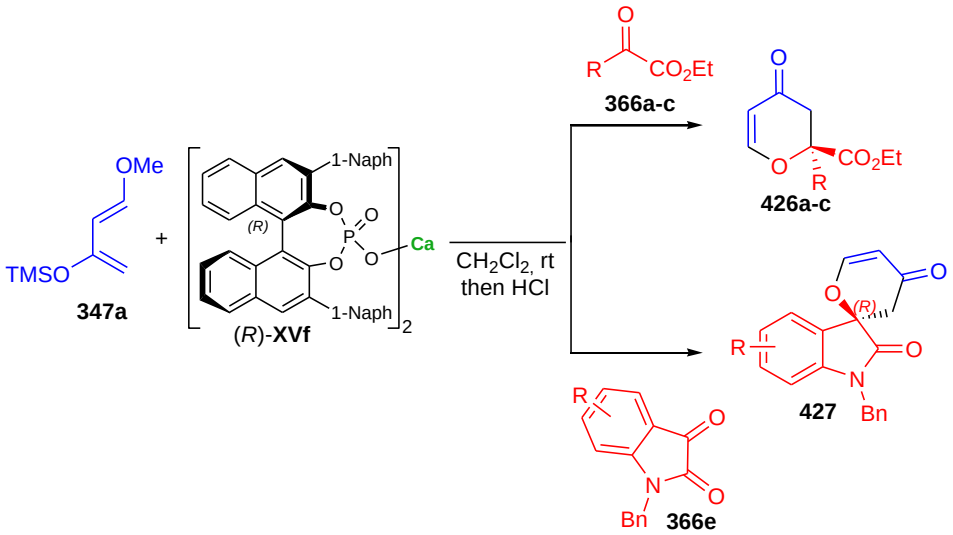
Some reactions between glyoxylates and Danishefsky's dienes have been encountered in previous cited papers, but they do not deserve a specific attention cause the poor results obtained in terms of both reactivity and selectivity.[142,160,173,181] One exception is represented by the BINOL-derived phosphate complexes with Yb(III), which was successfully applied in the enantioselective HDA reaction between **347a** and **364a-c** (Scheme 144). This catalyst gave excellent results also in the HDA reactions between the Danishefsky's diene **347a** α-keto esters **366c** as heterodienophiles (Scheme 181).[154] The (*R*)-**LXIV**/Yb(III)-catalyzed reactions of phenylglyoxylates **366c** (R = Me and Et) proceeded at room temperature under homogeneous conditions to give the cycloadducts **425**, bearing a quaternary stereocenter, within excellent yields (90-99%) and enantioselectivities (98->99% ee). These results suggested that the ketoester might coordinate to the catalyst as a bidentate ligand. The resulting rigid structure may be responsible for such high selectivities.[154]

Scheme 181. Enantioselective HDA Reaction Between Danishefsky's Diene 347a with α-Keto Esters 366c Catalyzed by ((*R*)-LXIV)$_3$Yb(III) Complex.[154]



Several different BINOL-based phosphate calcium salts were evaluated as catalysts in enantioselective HDA reactions between Danishefsky's diene and ketoesters. Among them, the 2:1 complex between (*R*)-**XVf** and Ca(II) was found particularly efficient in the HDA reactions involving either α-keto esters **366a-c** or isatine derivatives **366e** (Scheme 182).[197]

Scheme 182. Enantioselective HDA Reaction Between Danishefsky's Diene 347a with α-Keto Esters 366a-c Catalyzed by ((*R*)-XVf)$_2$/Ca(II) Complex.[197]



After optimization of the reaction conditions, a very wide range of α-keto esters was tested and in any case adducts **426a-c**, bearing a quaternary stereocenter, were obtained in quantitative yields and almost complete enantiocontrol (Table 16, entry 1).

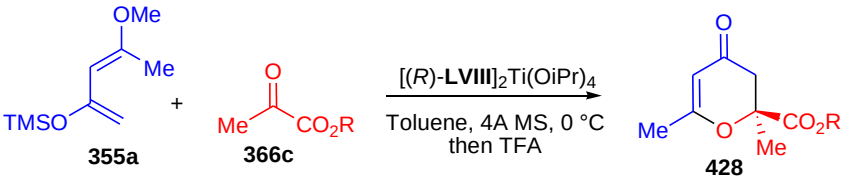
Oxindoles bearing a chiral quaternary carbon center at the 3-position are important structural motif in natural alkaloids and in biologically active derivatives. Hence, given the structural similarity between **366a-c** and oxindoles **366e** these latter were chosen to try to run an enantioselective HDA reactions under [(*R*)-**XVf**]$_2$Ca(II) catalysis (Scheme 182).[197] Also in this case the results were excellent and spiro adducts **427** were again obtained within quantitative yields and almost complete enantiocontrol (Table 16, entry 2). The absolute stereochemistry of the adduct was determined by X-ray analysis to be (3*R*) an it was consistent with a diene approach to the *Si*-face of oxindole bicoordinated to the Ca(II) complex.

Table 16. Average Values and Standard Deviations (s.d.) of the Reaction Yields, Diastereo-, and Enantioselectivities for the Catalyzed HDA Reactions Between the Danishefsky's Dienes and α-Dicarbonyl Derivatives.

Entry	Diene	α-Dicarbonyl Derivative	Catalyst/Organocatalyst	n. Exp.	aver. Yield % (s.d.)	Reaction Product	aver. ee % (s.d.)	Attach. CO face	Ref.
1	**347a**	**366a-c**	[(*R*)-**XVf**]$_2$Ca(II)	16	93 (6)	**426a-c**	98 (2)	---	197
2	**347a**	**366e**	[(*R*)-**XVf**]$_2$Ca(II)	8	96 (1)	(3*R*)-**427**	96 (3)	*Si*	197
3	**358d**	**366a**	(*S*)-**XCIX**	3	86 (9)	(*R*)-**429**	77 (8)	*Re*	198
4	**347a**	**366c**	(*R*,*S*)-**XC**/Cu(OTf)$_2$	4	72 (20)	(*R*)-**426c**	81 (17)	*Re*	199
5	**347a, 348a**	**366a**	(3a*R*,8a*S*)-**C**/InI$_3$	6	66 (8)	(*S*)-**429, 434**	72 (18)	*Si*	200
6	**347a, 348a**	**366c**	(3a*R*,8a*S*)-**C**/InI$_3$	10	64 (13)	**426c, 435c**	85 (28)	---	200
7	**347a**	**366c**	**XVIc**/Mg(ClO$_4$)$_2$	22	89 (7)	**426**	99 (0.5)	---	201
8	**347a**	**17**	**XVIc**/Mg(ClO$_4$)$_2$	9	93 (4)	(*R*)-**436**	99 (1)	*Re*	201
9	**347a**	**366e**	**XVIc**/Mg(ClO$_4$)$_2$	16	95 (3)	(*S*)-**427**	97 (1)	*Re*	201
10	**347a**	**17**	(*S*)-**CI**/Cu(OTf)$_2$	18	93 (5)	(*S*)-**436**	96 (1)	*Si*	202
11	**347a**	**438**	(*S*)-**CI**/Cu(OTf)$_2$	10	88 (6)	(*S*)-**439**	91 (3)	*Si*	202

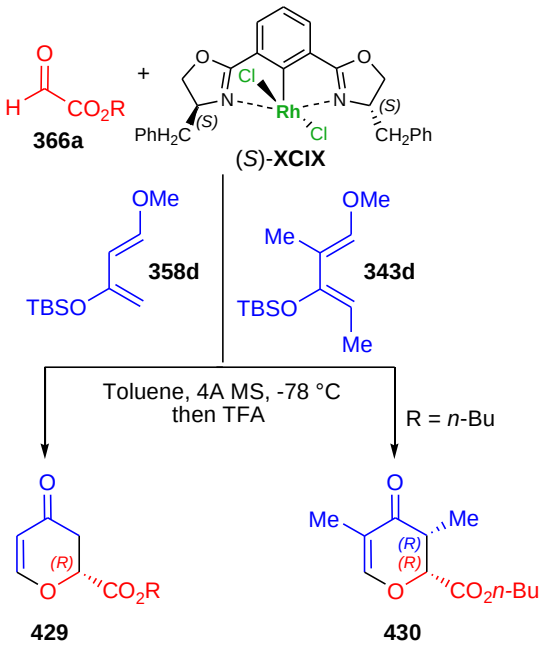
The Ti(IV)/(*R*)-**LVIII** complex already used in enantioselective HDA reactions involving simple aldehydes **364a-c** (Scheme 127), was also tested in the HDA reaction between **355a** and three different pyruvates **366c** (Scheme 183).[138] The adducts **428** were obtained in high yields (76-85%) and excellent enantioselectivities (94-99% ee), but a ratio BINOL:Ti(IV) of 2:1 was required to obtain appreciable the results.

Scheme 183. Enantioselective HDA Reaction Between Diene 355a with Pyruvates 366c Catalyzed by (*R*)-LVIII/Ti(IV) Complex.[138]



In 2001 Nishiyama reported a research entirely dedicated to the study of the HDA reaction catalysed by chiral bis(4*S*)-(oxazolinyl)phenylrhodium(III) aqua complex (*S*)-**XCIX** in which the Danishefsky's dienes **358d** and **343d** were allowed to react with glyoxylates **366a** to produce pyran-4-one derivatives **429** and **430**, respectively (Scheme 184).[198]

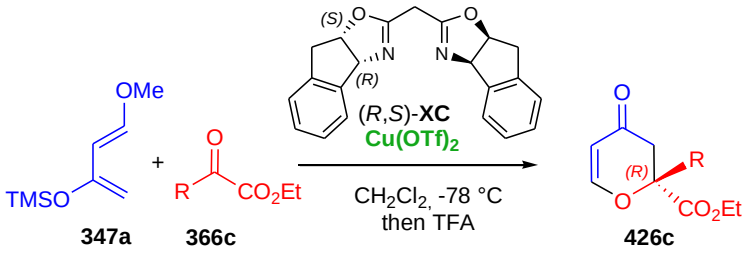
Scheme 184. Enantioselective HDA Reaction Between Dienes 358d and 343d with Glyoxylates 366a Catalyzed by the Rhodium Complex (*S*)-XCIX.[198]



The HDA reactions with **358d** were run in the presence of 2 mol % of complex (*S*)-**XCIX** and furnished (*R*)-**429** within good yields and enantioselectivities (Table 16, entry 3). On the basis of a ^{1}H NMR investigation of the crude product prior the TFA treatment, the reaction was proposed to follow a concerted mechanism. The reaction of the 2,3-dimethyl-substituted diene **343d** produced as major diastereomer the cycloadduct (2*R*,3*R*)-**430** (67% yield, 86% de, 83% ee), which was also proposed to derive from a concerted endo transition state.[198]

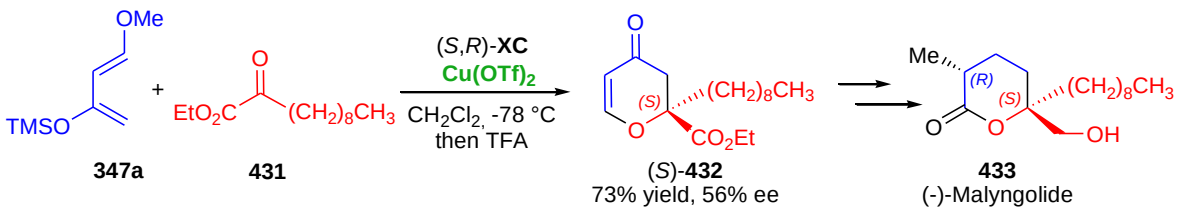
The same year Ghosh studied the reaction between the Danishefsky's diene **347a** with α-ketoesters **366c** catalysed by the complex between bis((3a*R*,8a*S*)-8,8a-dihydro-3a*H*-indeno[1,2-*d*]oxazol-2-yl)methane (*R*,*S*)-**XC** and $Cu(OTf)_2$ (Scheme 185).[199] The reaction proceeded with variable yields (from 52 to 99%) and enantioselectivities (from 56 to 99% ee), Table 16, entry 4, with BOX-based catalyst **XC** working slightly better than *t*-BuBOX/Cu(II) complex (*S*)-**IIIa**.

Scheme 185. Enantioselective HDA Reaction Between Diene 347a with α-Keto Esters 366c Catalyzed by the (*R*,*S*)-XC/$Cu(OTf)_2$ Complex.[199]



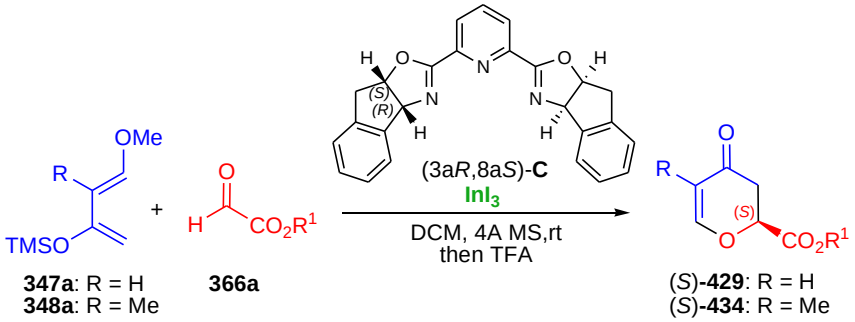
The stereochemistry of the adducts was corroborated by the conversion of cycloadduct (S)-**432**, obtained from the reaction between **347a** with 2-oxoundecanoate **431** in the presence of the enantiomeric (*S*,*R*)-**XC** based catalyst into enantioenriched (–)-*malyngolide* **433** (Scheme 186).[199]

Scheme 186. Stereochemical Correlation Between (*S*)-432 and (–)-Malyngolide 433.[199]



The complex between indeno-PYBOX ligand (3a*R*,8a*S*)-**C** and InI_3 has been demonstrated to catalyse efficiently the HDA reaction involving glyoxylates **366a** and Danishefsky's dienes (Scheme 187).[200] The steric hindrance of the ester group (R^1) was found crucial to obtain good enantioselectivities, the more sterically demanding the substituent, the higher the enantioselectivity. Hence, both yield and enantiomeric excess varied from moderate values (60% yield, 50% ee) to more interesting results (up to 93% ee). In all cases, the (2*S*) absolute configuration of the adducts was consistent with a diene approach to the *Si*-face of the aldehyde with the glyoxylate behaving as a bidentate ligand (Table 16, entry 5).

Scheme 187. Enantioselective HDA Reaction Between Dienes 347a and 348a with Glyoxylates 366a Catalyzed by the (3a*R*,8a*S*)-C/InI_3 Complex.[200]



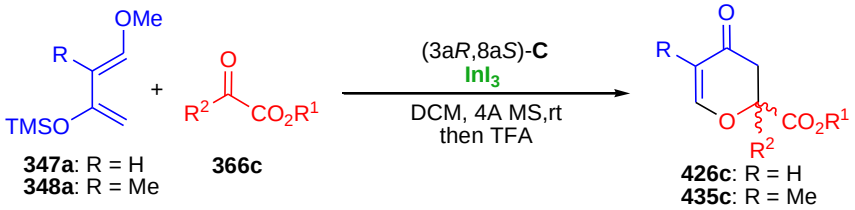
347a: R = H
348a: R = Me

366a

(*S*)-**429**: R = H
(*S*)-**434**: R = Me

When α-keto esters **366c** were used instead glyoxylates (Scheme 188), it was found that the alkyl groups directly attached to the carbonyl group (R^2) had great effects on the reaction efficiency since only pyruvates gave appreciable results (ee 90-94%), while for R^2 = Et no reaction was evidenced (Table 16, entry 6).[200]

Scheme 188. Enantioselective HDA Reaction Between Dienes 347a and 348a with α-Keto Esters 366c Catalyzed by the (3a*R*,8a*S*)-C/InI_3 Complex.[200]



347a: R = H
348a: R = Me

366c

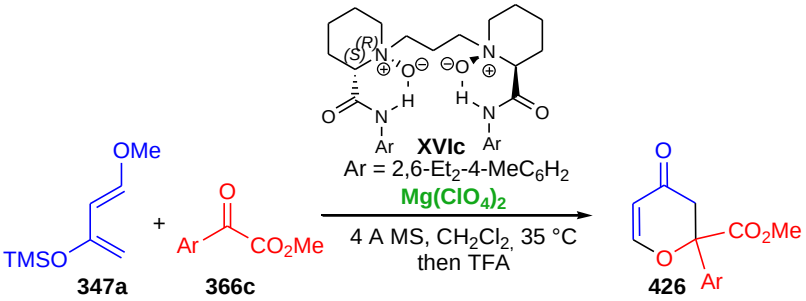
426c: R = H
435c: R = Me

An interesting result was the stereochemistry inversion by changing the ester residue. The catalyzed reaction of i-propyl pyruvate gave (*S*)-**435c** (R^1 = i-Pr, R^2 = Me) within 84% yield and 94% ee, while the corresponding *t*-butyl ester furnished the opposite enantiomer (*R*)-**435c** (R^1 = *t*-Bu, R^2 = Me) within 61% yield and 90% ee. Perhaps this result may be due to a change of the coordination mode of the keto ester to In(III) with a consequent variation of the geometry of the reacting complex. Unfortunately, no further investigation was made on this singular evidence.[200]

Given the relevance of the steric hindrance of the R^2 group, which can negatively influence the reaction efficiency, it was used a linear substituent such as the trimethylsilyl-ethynyl group. The cycloadducts were obtained within moderate yields (50-80%) and with excellent enantioselectivities (87-93% ee); in this case, the absolute stereochemistry of the products was always (2*R*), independently from the ester moiety. On the alkynyl functionality was performed a classical click reaction with tosyl azide to give the corresponding triazole derivative that was obtained in good yield and excellent ee.[200]

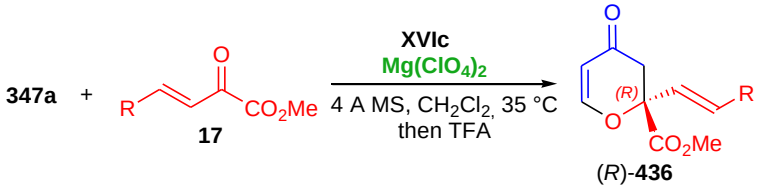
The complex between *N*,*N*-dioxide derivative **XVIc** (Ar = 2,6-Et_2-4-MeC_6H_2) and $Mg(ClO_4)_2$ was found a highly efficient catalyst in the HDA reaction between the Danishefsky's diene and three different typologies of α-dicarbonyl reagents. The cycloaddition between aromatic α-keto esters was efficiently catalyzed by complex **XVIc**/Mg(II) (0.1-0.5 mol %), Scheme 189, and adducts **426** were obtained within excellent yields and enantioselectivities (Table 16, entry 7).

Scheme 189. Enantioselective HDA Reaction Between Diene 347a with α-Keto Esters 366c Catalyzed by the XVIc/$Mg(ClO_4)_2$ Complex.[201]



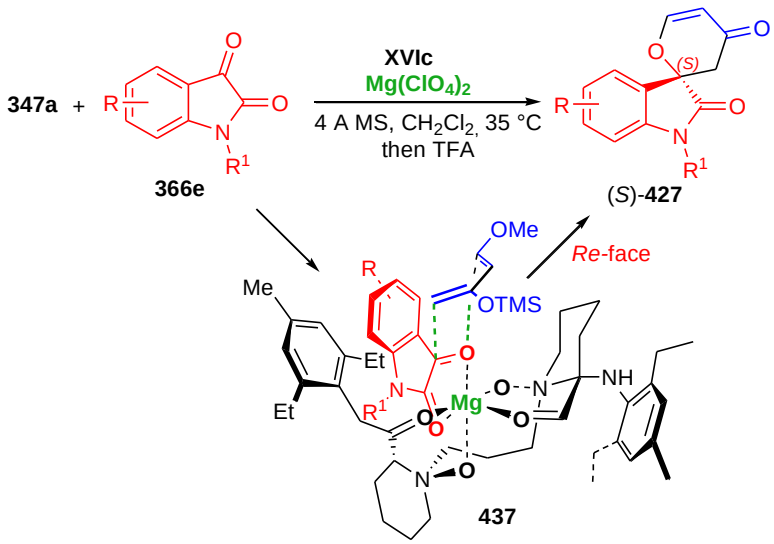
α-Keto β,γ-unsaturated esters **17**, derivatives widely employed as heterodienes and discussed at the beginning of this chapter, found useful applications also as heterodienophile, and their HDA reactions with Danishefsky's diene was successfully catalyzed by **XVIc**/Mg(II) (0.1-0.5 mol %), Scheme 190. The adducts **436** were again obtained with very high yields and excellent enantioselectivities (Table 13, entry 8). The absolute configuration was determined to be (*R*) by X-ray crystallographic analysis.[201]

Scheme 190. Enantioselective HDA Reaction Between Diene 347a with α-Keto-β,γ-unsaturated Esters 17 Catalyzed by the XVIc/Mg(ClO$_4$)$_2$ Complex.[201]



Given the excellent efficiency of the catalyst **XVIc**/Mg(II), the effect on the HDA reaction involving isatins **366e** was tested (Scheme 191). Again, spiro-adducts **427** were efficiently obtained, with yields >90% and ee >95% (Table 13, entry 9).[201]

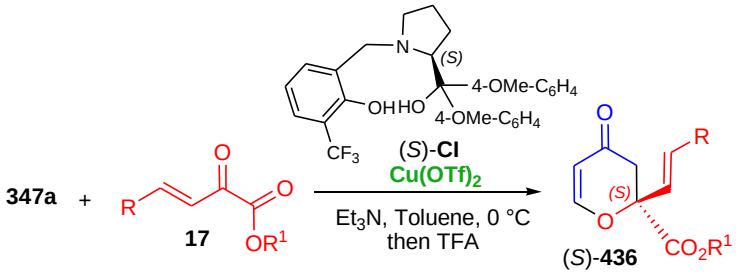
Scheme 191. Enantioselective HDA Reaction Between Diene 347a with Isatins 366e Catalyzed by the XVIc/Mg(ClO$_4$)$_2$ Complex.[201]



The mechanism of the HDA reaction between isatin and Danishefsky's diene was carefully inferred. By monitoring the reaction with *operando* IR experiments, it was verified that the reaction proceeded through a concerted Diels-Alder pathway rather than a Mukaiyama aldol mechanism. The observed linear relationship between the ee of ligand **XVIc** and the ee of the reaction product **427**, allowed to propose a reacting intermediate complex with a ratio Mg(II):**XVIc**:isatin of 1:1:1. This hypothesis was confirmed by HRMS analysis that evidenced the expected peak at *m/z* 880.4866. Since the absolute configuration of the spiro-adducts was found to be (*S*) by X-ray crystallographic analysis, the reacting complex **437** was proposed to take into account all the experimental evidences. Isatin **366e** is coordinated to the Mg(II) cation in a bidentate fashion, which is also coordinated by the four oxygen atoms of the chiral ligand to give an octahedral complex. Since the *Si*-face of the isatin is shielded by the neighbouring 2,6-diethyl-4-methylphenyl group of the ligand, then the diene will approach the *Re*-face of the carbonyl group to produce the spiro-adduct with the observed (*S*) configuration.[201]

Another efficient catalyst for the HDA reaction between Danishefsky diene and α-keto β,γ-unsaturated esters **17** was the $Cu(OTf)_2$-based complex of the prolinol derivative (*S*)-**CI**, Scheme 192. The cycloadducts (*S*)-**436**, deriving from a diene approach to the *Si*-face of the ketonic group, were obtained within excellent yields and enantioselectivities (Table 16, entry 10).[202] The reaction mechanism was demonstrated to follow a concerted HDA cycloaddition.

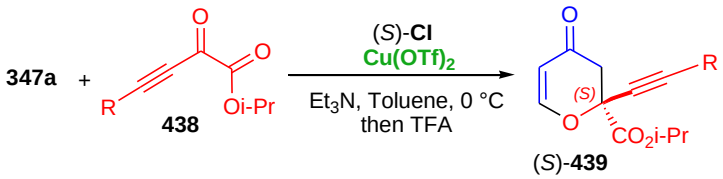
Scheme 192. Enantioselective HDA Reaction Between Diene 347a with α-Keto-β,γ-Unsaturated Esters 17 Catalyzed by the (*S*)-CI/$Cu(OTf)_2$ Complex.[202]



The same catalyst was successfully applied to the analogous HDA reaction involving the corresponding alkynyl derivatives **438** (Scheme 193). The cycloadducts **439** were obtained within

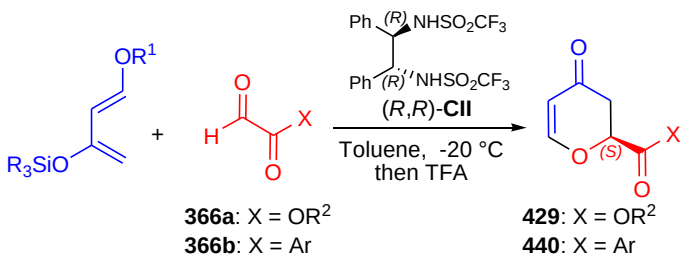
good yields and excellent enantioselectivities (Table 16, entry 11), and the (*S*) configuration of the cycloadduct derived again from the diene approach to the *Si*-face of the heterodienophile.[202] In this case, the reaction mechanism was verified to be a stepwise Michael/aldol reaction. Hence, the reaction mechanism depends on the structure of the ketoester derivative. Furthermore, when the catalyzed HDA reactions of **17** and **438** were performed with the more steric demanding diene **358d** (the TMS was substituted with the TBS group), then both reactions were verified to proceed through a concerted Diels-Alder pathway, evidencing that also the structure of the diene is important to determine the reaction mechanism (adducts **436** and **439** were obtained with 91 and 93% yield, and with 96 and 93% ee, respectively).[202]

Scheme 193. Enantioselective HDA Reaction Between Diene 347a with α-Keto-β,γ-Alkynyl Esters 438 Catalyzed by the (*S*)-CI/Cu(OTf)$_2$ Complex.[202]



Only one example of organocatalyst acting through H-bond activation has been reported. (*R*,*R*)-bis-(trifluoromethanesulfonylamino)-1,2-diphenylethane (*R*,*R*)-**CII** was found to catalyze the HDA reaction between several Danishefsky's dienes with glyoaxylates (two examples) and arylglyoxal derivatives (three examples), but the cycloadducts were obtained within moderate yields (46-80%) and enantioselectivities (23-87% ee), Scheme 194.[203]

Scheme 194. Enantioselective HDA Reaction Between Danishefsky's Dienes with Glyoxylates and Glyoxal Derivatives Catalyzed by the (*R*,*R*)-CII.[203]



2.3. *Ortho*-substituted Phenols as Four-atom Term in [4+2] Cyclizations to 3,4-Dihydro-Benzopyranes

The synthetic route to 3,4-dihydropyran derivatives up to now taken into account was a [4 + 2] cycloaddition that may have different variants: from the Diels-Alder of a diene with a carbonyl group to a hetero-Diels-Alder between an α,β-unsaturated carbonyl derivative and an electron rich double bond, from a synchronous process to a stepwise reaction.

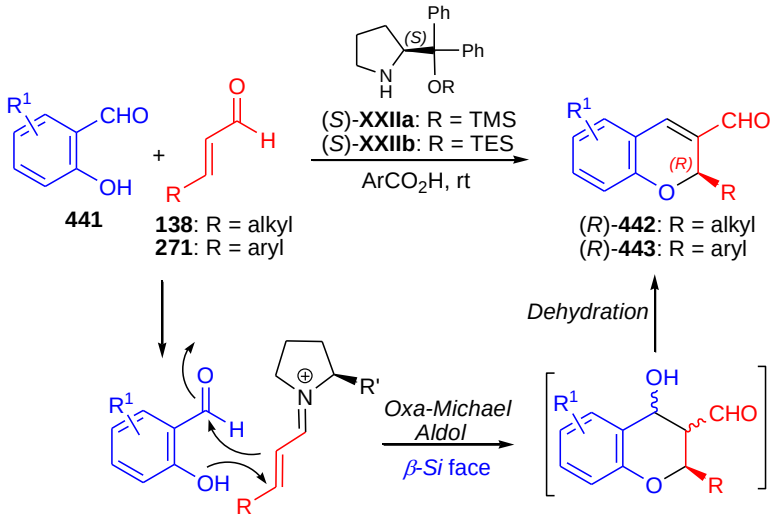
From a retrosynthetic point of view, 3,4-dihydrobenzopyran derivatives can be dissected into an *ortho*-substituted phenol, as four-atom term, and an electron-poor double bond as the two-atom partner. This reaction involves a nucleophile that reacts with an electrophile, with the first step being a Michael-type addition, followed by a ring closure. This basic protocol may have several variants, and this is the topic of the present section.

2.3.1. Through Domino Oxa-Michael/Aldol Reactions

The first protocol considered the asymmetric condensation between salicylic aldehydes derivatives **441** and α,β-unsaturated aldehydes **138** and **271**, with TMS-protected diphenylprolinol (*S*)-**XXIIa** as organocatalyst (Scheme 195).[204] The activation of the α,β-unsaturated aldehydes affords the iminium salt that undergoes the oxa-Michael addition of the phenolic oxygen atom acting as nucleophile, followed by the aldol ring closure. The dehydration step gives adducts (*R*)-**442** or **443** in good yields, whose absolute configuration derives from the attack of the phenol to the *β-Si*-face of the chiral iminium intermediate (Table 17, entry 1).[204]

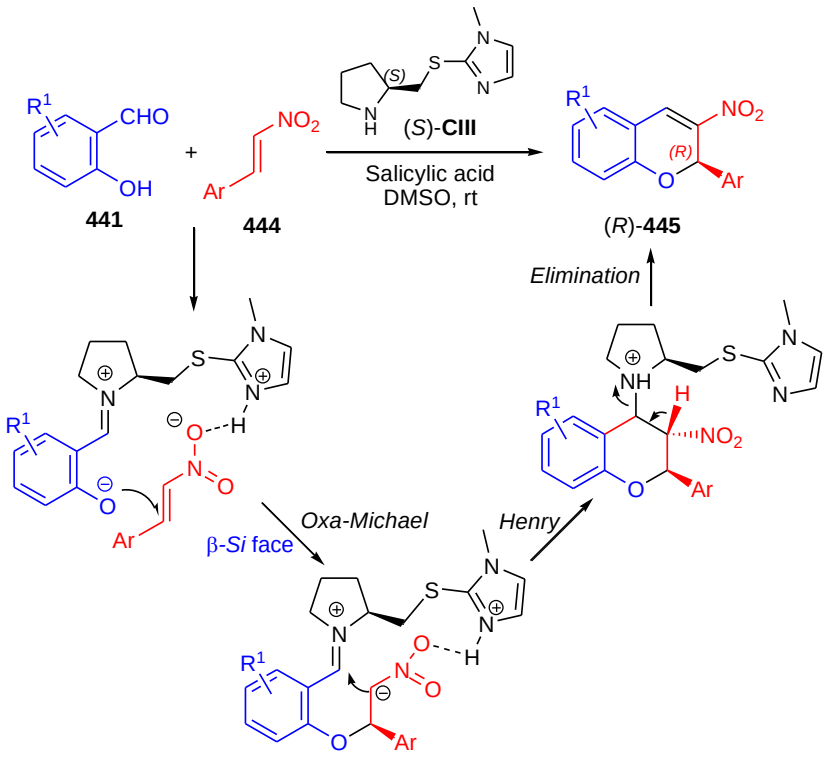
The analogous protocol was followed with the same reagents and TES-protected diphenylprolinol (*S*)-**XXIIb** as the organocatalyst (Scheme 195).[205] The cycloadducts (*R*)-**442** or **443** were obtained in somewhat higher yields than the corresponding TMS-protected organocatalyst (*S*)-**XXIIa**, while the enantioselectivities were the same in favour of the same (*R*) enantiomers (Table 17, entry 2 vs entry 1).

Scheme 195. Enantioselective Domino [Oxa-Michael/Aldol/Dehydration] Reaction between Salicylic Aldehydes Derivatives 441 and α,β-Unsaturated Aldehydes 138 and 271, with (*S*)-XXIIa,b as Organocatalysts.[204,205]



Sometimes the reaction of substituted salicylic aldehydes **441** with electrophilic nitroalkene **444**, gives analogous products, but through a different mechanism. The organocatalyst pyrrolidine-2-thioimidazolepirrolidine (*S*)-**CIII** now gives the iminium-activated salicylaldehyde and coordinates the nitro-olefin by hydrogen bonding. A crucial role was also attributed to the co-catalyst (salicylic acid) in the stabilization through H-bond of the transition state leading to the observed product. Then, the reacting intermediate undergoes an oxa-Michael attack to the *β-Si*-face of the nitro-olefin, followed by the intramolecular Henry reaction (before an aldol reaction), and an elimination process to afford 3-nitro-2*H*-chromenes (*R*)-**445**, with contextual release of the catalyst (Scheme 196).[206] The cyloadducts were obtained within moderate yields, and the enantioselectivities were significantly lower than those previously observed (average ee, 65 ± 14%), see entry 3 in Table 17.

Scheme 196. Enantioselective Domino [oxa-Michael/Henry/Elimination] Reaction between Salicylic Aldehydes Derivatives 441 and β-Nitrostyrenes 444, with (*S*)-CIII as the Organocatalyst.[206]



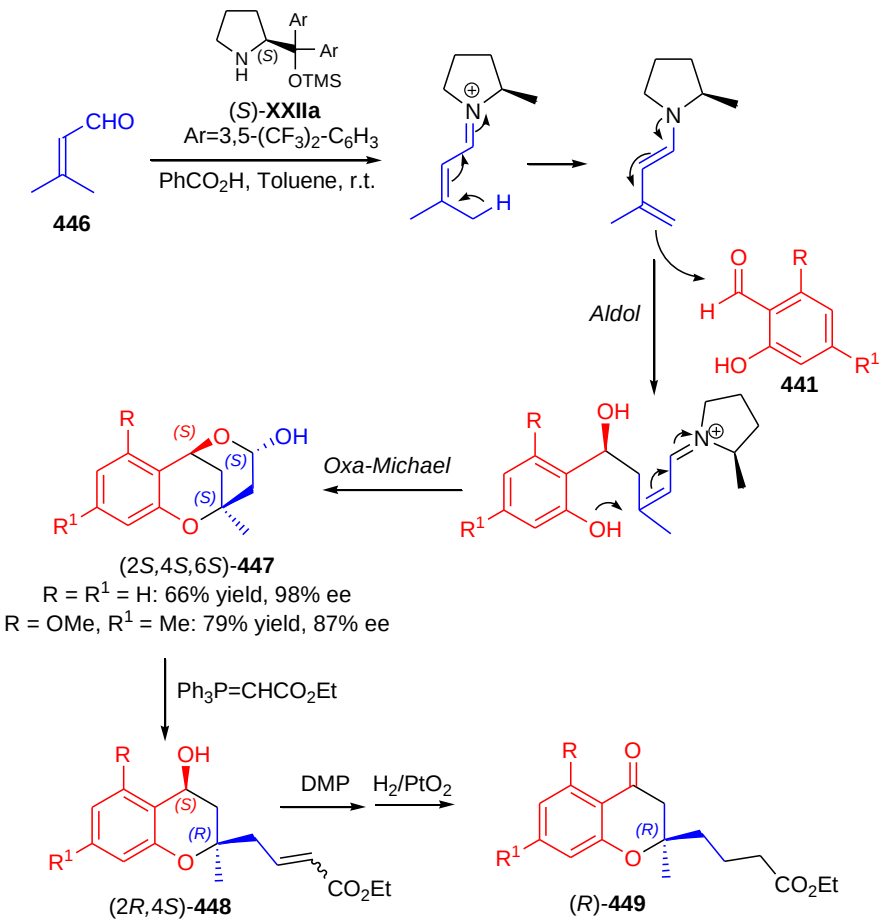
2.3.2. Through Domino Aldol/Oxa-Michael Reactions

In addition to the above variants, the reaction between substituted salicylic aldehydes **441** and α,β-unsaturated aldehydes **446**, with prolinol as the organocatalyst, may follow a different mechanistic pathway if the aldehyde is β,β-dialkylsubstituted.

Using (*S*)-bis-[3,5-bis(trifluoromehtyl)phenyl]-2-pyrrolidinemethanotrimethylsilyl ether [(*S*)-**XXIIa**], the initially produced iminium salt from 3-methylbut-2-enal **446** leads to the dienamine 1-(3-methylbuta-1,3-dienyl)pyrrolidine that with its strong nucleophilic 4-position gave an aldol attack to the salicylic aldehyde group. The following oxa-Michael reaction involving the phenol hydroxy group as the nucleophile afforded the ring closure with release of the prolinol-based organocatalyst and regeneration of the originally protected aldehyde group. The newly formed hydroxyl group at the benzylic position was suitably placed to undergo a further ring closure to give the hemiacetalic tricycle 3,4-dihydro-2-methyl-2,6-methano-2*H*,6*H*-1,5-benzodioxocin-4-ole

(2*S*,4*S*,6*S*)-**447**, whose absolute configuration was determined by X-ray analysis (Scheme 197).[207] This was the useful starting product for further modifications whose usefulness will be emphasized in next examples. By reaction with stabilized ylides, **447** affords the alcohol (2*R*,4*S*)-**448**, whose Dess-Martin periodinane oxidation and subsequent hydrogenation yields chromanone (*R*)-**449**.

Scheme 197. Enantioselective Domino [Aldol/Oxa-Michael/Hemiacetalization] Reaction between Salicylic Aldehydes Derivatives 441 and 3-Methylbut-2-enal 446, with (*S*)-XXIIa as Organocatalyst.[207]

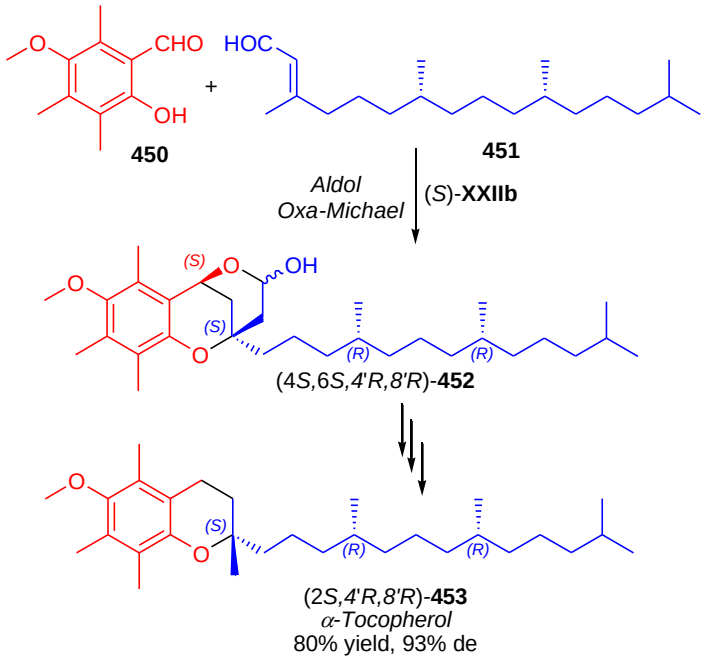


What deserves to be noted is the basic difference between the reactions in Schemes 195 and 197. Both are reactions between salicylic aldehydes and enals. In the former, the salicylic aldehyde is the nucleophile and enal the electrophile. The latter reaction is characterized by the umpolung of both reagents: salicylic aldehyde becomes the electrophile with the enal behaving as the nucleophile.

The methodology described in Scheme 197 was successfully applied to the synthesis of several natural products; the care was the choice of the tailor made salicylic aldehyde derivative and the enal component, with the substituents suitably placed for the targeted product.

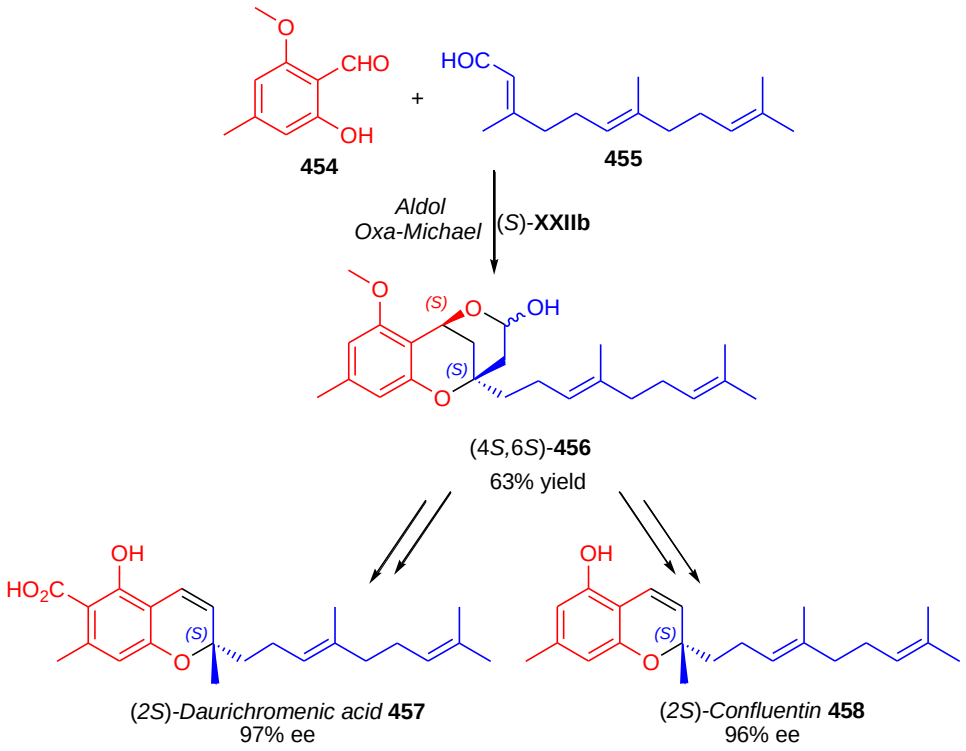
From 2-hydroxy-5-methoxy-3,4,6-trimethylbenzaldehyde (**450**) and phytenal (**451**), with TES-substituted (*S*)-**XXIIb** as organocatalyst, the hemiacetal (4*S*,6*S*,4'*R*,8'*R*)-**452** was obtained with 58% yield and 97% de. Oxidation to lactone, ring opening and few standard reactions gave (*S*,*R*,*R*)-*α-Tocopherol* **453**, a significant member of the vitamin E family which is of leading importance in many biological processes (Scheme 198).[208]

Scheme 198. Enantioselective Domino [Aldol/Oxa-Michael/Hemiacetalization] Reaction, Catalysed by (*S*)-XXIIb as a Short Route to (*S,R,R*)-α-*Tocopherol*.[208]



The same protocol, from 2-hydroxy-6-methoxy-4-methylbenzaldehyde (**454**) and farnesal (**455**), again catalysed by TES-substituted (*S*)-**XXIIb**, afforded the hemiacetal (4*S*,6*S*)-**456**, which was the key intermediate both to (2*S*)-*Daurichromenic acid* (**457**, 97% ee) and (2*S*)-*Confluentin* (**458**, 96% ee), Scheme 199.[209]

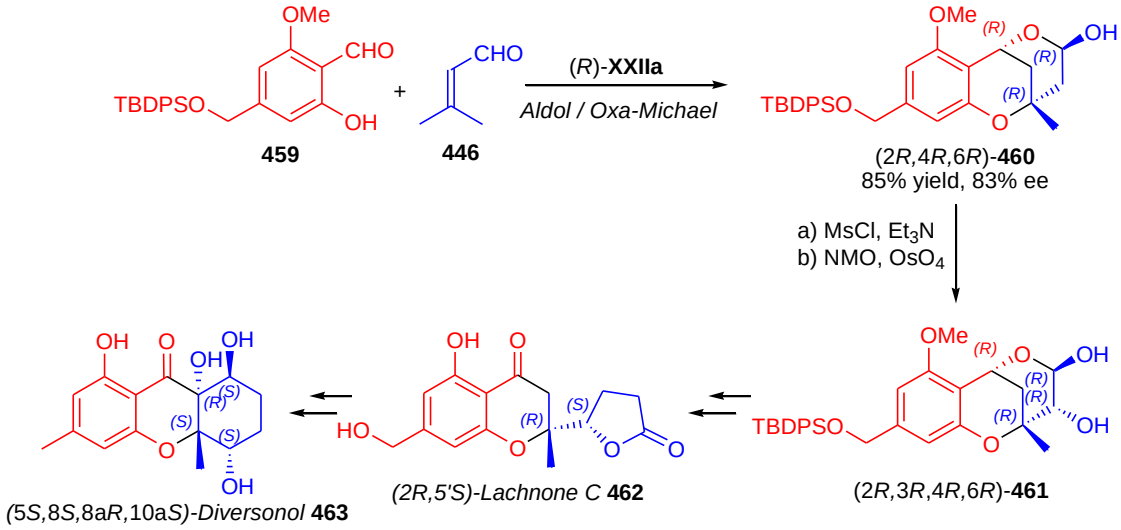
Scheme 199. Enantioselective Domino [Aldol/Oxa-Michael/Hemiacetalization] Reaction, Catalyzed by TES-substituted (*S*)-XXIIb, for the Synthesis of (4*S*,6*S*)-456, Intermediate to *Daurichromenic acid* and *Confluentin*.[209]



From 4-(*t*-butyldiphenylsilyloxymethyl]-2-hydroxy-6-methoxybenzaldehyde (**459**) and 3-methylbut-2-enal (**446**), with (*R*)-**XXIIa** as organocatalyst, (2*R*,4*R*,6*R*)-**460** was obtained with 85 % yield and 83% ee. The introduction of a further chiral center in position 3, obtained by subsequent dehydration and osmylation, afforded (2*R*,3*R*,4*R*,6R)-**461**. This is the starting compound for the synthesis of *Lachnone C* (**462**) and *Diversonol* (**463**), two natural products members of chromone lactone and tetrahydroxanthone families (Scheme 200).[210]

In many of the examples discussed, the β,β-dialkyl substituted aldehyde is 3-methylbut-2-enal, from which the conversion of the initially produced iminium salt to the dienamine does not produce other isomers than the one represented in Scheme 197. When the aldehyde is β,β-unsymmetrically disubstituted, two competitive deprotonations may give rise to two competitive regioselective processes.

Scheme 200. Enantioselective Domino [Aldol/oxa-Michael/Hemiacetalization] Reaction, Catalyzed by (*R*)-XXIIa, for the Synthesis of (2*R*,4*R*,6*R*)-35, Intermediate to the Syntheses of *Lachnone C* (462) and *Diversonol* (463).[210]

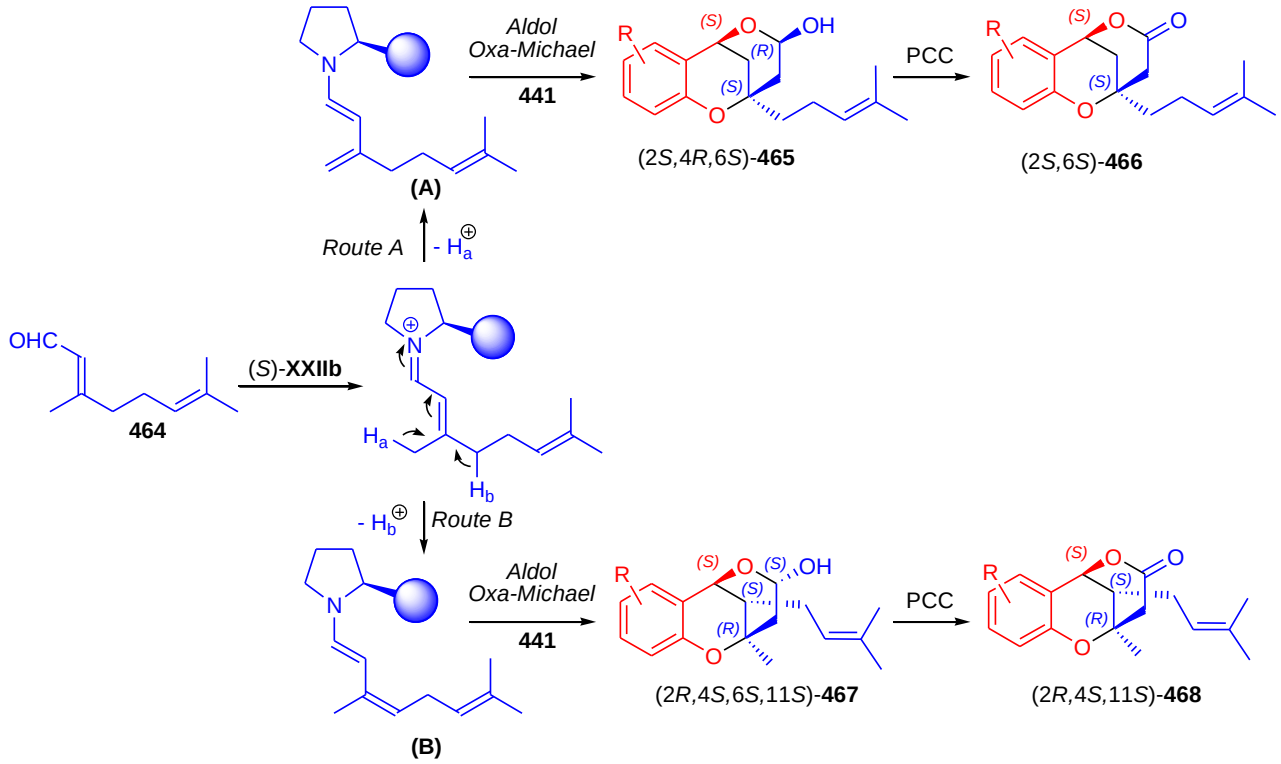


The domino [aldol/oxa-Michael] reactions between different substituted salicylic aldehydes **441** and citral (**464**), catalyzed by TES-substituted (*S*)-**XXIIIb**, were studied in detail. The initially produced iminium salt may give a competitive deprotonation. Losing H_a (route A) gives dienamine (**A**), which reacts with **441** to give (2*S*,4*R*,6*S*)-**465** that can be oxidized by PCC to (2*S*,6*S*)-**466**. If the deprotonation occurs losing H_b (route B), then the dienamine (**B**) is obtained. This latter reacts with **441** to give (2*R*,4*S*,6*S*,11*S*)-**467** (structure and absolute configuration determined by X-ray crystal analysis), which can be oxidized by PCC to give (2*R*,6*S*,11*S*)-**468** (Scheme 201).[211]

The regioisomeric distribution largely depends on the position of the substituents in **441**. When salicylaldehyde presents substituents on both the positions 3 and 6, then the regioisomer **465** is formed with very high selectivity (**465**:**467** > 20:1). If only one of these positions is substituted, adduct **465** is again the favoured one, but its formation is less selective (**465**:**467** from 73:27 to 91:9). When both the positions 3 and 6 are free and the substituent is on the 5-position only, then adduct **467** becomes the favoured one, even if it is obtained with low selectivities (**465**:**467** from 40:60 to 44:56). In any case the reactions yields were satisfactory (from 50 to 82%), while the enantioselectivities were very good, particularly in the case of **468** (Table 17, entries 4 and 4 bis).

Adducts **466** were obtained with an average ee of 91 ± 5%, while the isomeric **468** with an average ee of 98 ± 1.5%.[211]

Scheme 201. Chemoselective and Enantioselective Domino [Aldol/Oxa-Michael/Hemi-acetalization] Reaction Between Salicylic Aldehyde Derivatives 441 and Citral 464, catalyzed by TES-substituted (*S*)-XXIIb.[211]

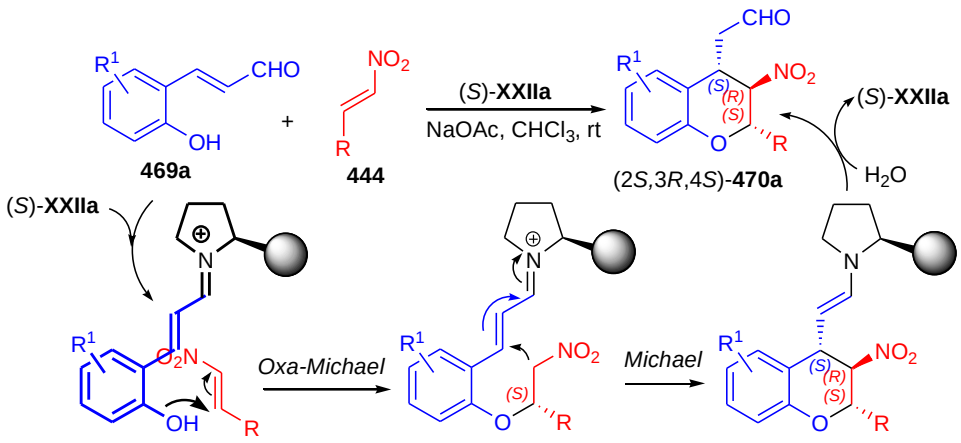


2.3.3. Through Domino Oxa-Michael/Michael Reactions

The reaction between *ortho*-hydroxycynnamaldehyde **469a** and electrophilic nitroalkene **444**, prolinol as organocatalyst, allows to synthesize chromans with three contiguous chiral centers through a catalytic asymmetric [oxa-Michael/Michael] cascade (Scheme 202).[212]

The organocatalyst TMS-substituted (*S*)-**XXIIa** gives the iminium-activated cynnamaldehyde whose OH group affords an oxa-Michael attack to the β-carbon of the nitroolefin, followed by the intramolecular Michael reaction and a hydrolytic process, to provide (2-aryl-3,4-dihydro-3-nitro-2*H*-chromen-4-yl)acetaldehyde (2*S*,3*R*,4*S*)-**470a**, with release of the catalyst. The domino reactions proceeded with good yields and diasteroselectivities, while the ee were excellent (Table 17, entry 5).[212]

Scheme 202. Enantioselective Domino [Oxa-Michael/Michael] Reaction Between 2-Hydroxycynnamaldehyde Derivatives 469a and β-Nitrostyrenes 444, with (*S*)-XXIIa as Organocatalyst.[212]



Other enantioselective domino [oxa-Michael/Michael] reaction have been reported between 3-(2-hydroxyphenyl)prop-2-en-1-ones **469b** and nitro-olefins **444** or *t*-butyl 3-[(ethoxycarbonyl)-methylene]-2-oxoindoline-1-carboxylate **100**. The organocatalysts were 9-amino-epicinconidine squaric acid (3*R*,8*S*,9*S*)-**XLIIIa**,[213] 9-amino-epiquinine-thiourea (3*R*,8*S*,9*S*)-**XXXIV**,[214] and 1-[3,5-bis(trifluoromethyl)phenyl]-3-[(*S*)-3-(diethylamino)-1-methoxy-1,1-diphenylpropan-2-yl]thiourea (*S*)-**CIV**.[215] The reagents and the different products obtained for these reactions are listed in *Chart 8*, while the results in terms of yield, diastereo- and enantioselectivity are reported in Table 17, entries 6-10.

A comparison of the results allows to state that the efficiency is excellent, mainly in terms of enantioselectivity, for all the three organocatalysts, less for the more complicated reaction affording the spiro[chroman-3,3′-indole] derivatives **471**.

The absolute configuration induced by prolinol (*S*)-**XXIIa** derives from the attack of phenol with the less hindered face as reported in Scheme 202. The opposite absolute configuration induced by thiourea- and squaric acid-based organocatalyst (3*R*,8*S*,9*S*)-**XLIIIa** and (3*R*,8*S*,9*S*)-**XXXIV** derives from a mechanism in which the coordination of nitrogroup by two NH activates the electrophile. This is attacked by a nucleophile that is deprotonated by the tertiary amine of

epiquinine and epicinconidine and the resulting quaternary salts coordinate, by electrostatic interaction, the carbonyl of **469b**. The comparison between squaric acid- and thiourea-based organocatalyst is in favour of the former, looking to the results of entries 6 and 9 in Table 17 in terms of diastereoselectivity.

The mechanism of the catalyst (*S*)-**CIV** involves the two NH that coordinate the indolic carbonyl, and the tertiary amine that deprotonates and subsequently coordinates **469b**. A small difference can be pointed out for the formulae of the organocatalysts in Chart 8. The different configuration of the chiral center adjacent to NH, is enough to induce opposite enantioselectivities in the product **471**.

Chart 8. Reagents, Organocatalysts, and Products of Enantioselective Domino [Oxa-Michael/Michael] Reactions.[213-215]

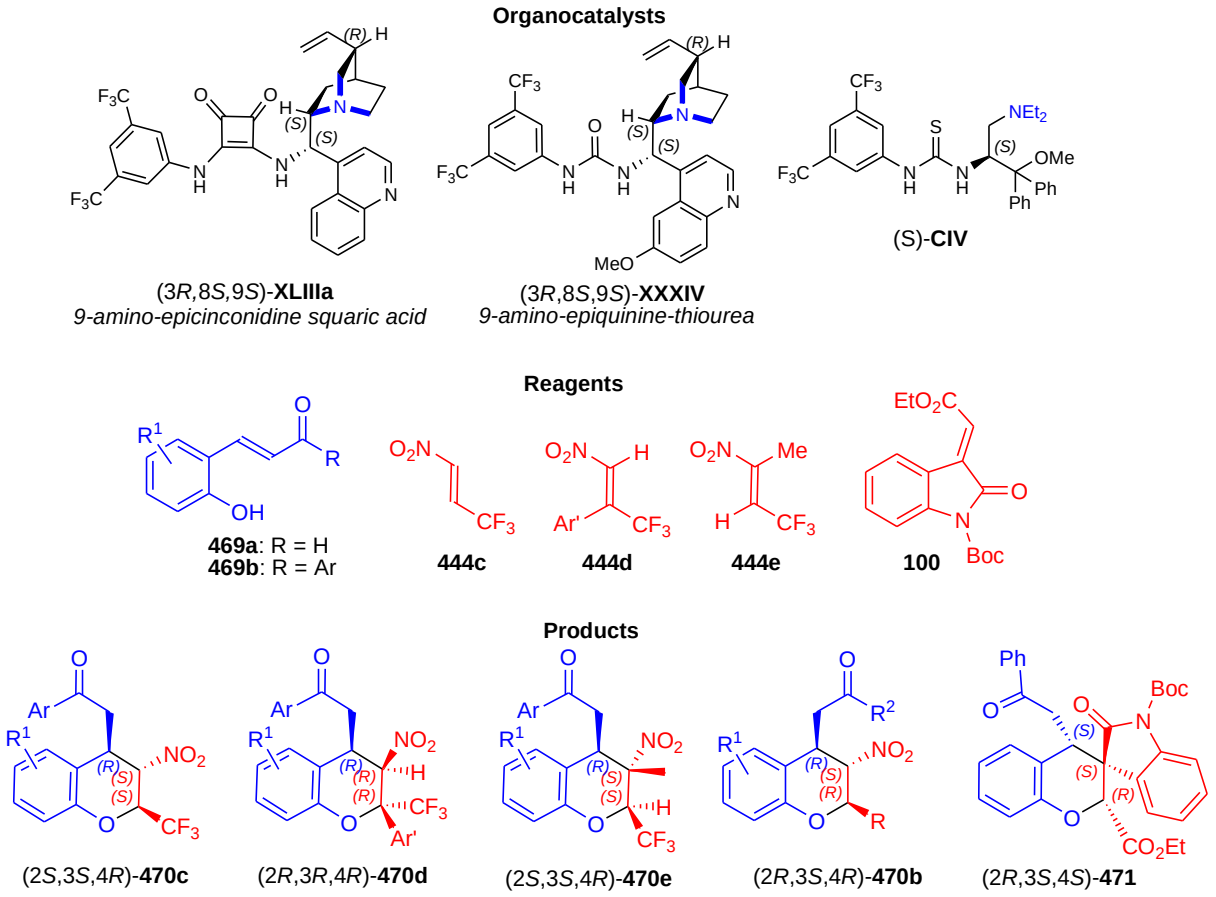


Table 17. Average Values and Standard Deviations (s.d.) of the Reaction Yields, Diastereo-, and Enantioselectivities in [4+2] Cyclizations to 3,4-Dihydro-Benzopyranes Through Domino Reactions.

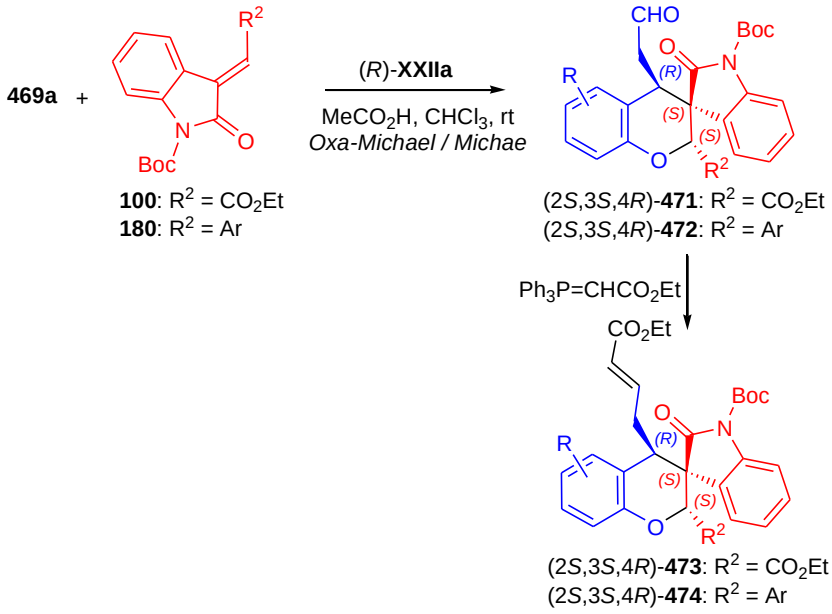
Entry	Nucleophile	Electrophile	Catalyst/ Organocatalyst	n. Exp.	aver. Yield % (s.d.)	Reaction Product	aver. ee % (s.d.)	Attach. face	Ref.
1	**441**	**138** and **271**	(*S*)-**XXIIa**	23	65 (20)	(*R*)-**442, 443**	90 (5)	β-*Si*	204
2	**441**	**138** and **271**	(*S*)-**XXIIb**	12	85 (15)	(*R*)-**442, 443**	89 (7)	β-*Si*	205
3	**441**	**444**	(*S*)-**CIII**	14	58 (18)	(*R*)-**445**	65 (14)	β-*Si*	206
4[a]	**441**	**464**	(*S*)-**XXIIb**	8	49 (14)	(2*S*,6*S*)-**466**	91 (5)	---	211
4 bis[a]	**441**	**464**	(*S*)-**XXIIb**	8	22 (20)	(2*R*,6*S*,11*S*)-**468**	98 (1.5)	---	
5	**469a**	**444**	(*S*)-**XXIIa**	12	73 (8)	(2*S*,3*R*,4*S*)-**470a**[b]	96 (2)	---	212
6	**469b**	**444c**	(3*R*,8*S*,9*S*)-**XLIIIa**	11	75 (7)	(2*S*,3*S*,4*R*)-**470c**[c]	99 (1)	---	213
7	**469b**	**444d**	(3*R*,8*S*,9*S*)-**XLIIIa**	7	76 (2)	(2*R*,3*R*,4*R*)-**470d**[d]	>99	---	213
8	**469b**	**444e**	(3*R*,8*S*,9*S*)-**XLIIIa**	2	96 (1)	(2*S*,3*S*,4*R*)-**470e**[e]	>99	---	213
9	**469b**	**444a**	(3*R*,8*S*,9*S*)-**XXXIV**	19	71 (17)	(2*R*,3*R*,4*R*)-**470b**[f]	96 (4)	---	214
10	**469b**	**100**	(*S*)-**CIV**	15	74 (13)	(2*R*,3*S*,4*S*)-**471**[g]	87 (4)	---	215
11	**469°**	**100** or **180**	(*R*)-**XXIIa**	23	65 (15)	(2*S*,3*S*,4*R*)-**473** or	91 (14)	---	216

11bis[h]	**469a**	**180**	(*R*)-**XXIIa**			(2*S*,3*S*,4*R*)-**474**[i]			
12	**475**	**147**	(1*R*,2*R*)-**CV**	20	89 (22)	(2*R*,3*R*,4*R*)-**476**[j]	91 (9)	β-*Re*	217
13	**475**	**100**	(3*R*,8*S*,9*S*)-**XLIII**	17	69 (6)	(2*R*,3*S*,4*S*)-**477**[k]	96 (3)	β-*Re*	218
14	**475**	**478**	(*S*)-**CVI**	17	90 (11)	(4a*S*,10*R*,10a*R*)-**479**[l]	96 (2)	β-*Si*	219
15	**475**	**480**	(*S*)-**CVI**	18	67 (16)	(2*R*,3*R*,4*R*)-**481**[m]	93 (4)	β-*Si*	219
16	**475**	**271** and **446**	(*S*)-**XXIIa**	10	60 (10)	(6a*S*,9*R*,10*R*,10a*S*)-**482**[n]	>99%	β-*Si*	220
17	**475**	**232** and **446**	(*S*)-**XXIIa**	17	56 (10)	(1*S*,2*R*,3*S*,4*S*,4a*R*,10b*S*)-**483**[o]	98 (2.5)	---	221
18	**469a**	**488**	(*R*)-**XXIIa**	12	64 (8)	(2*R*,4a*R*,5*R*,10b*R*)-**489**[p]	96 (4)	---	223
19	**469b**	**271**	(*S*)-**XXIIa**	8	55 (19)	(6*R*,6a*S*,9*S*,10*S*,10a*S*)-**490**	>99	β-*Si*	224

[a] Entries 4 and 4bis refer to the reaction between **441** and **464**, catalyzed by (*S*)-**XXIIb**, which gives two products (2*S*,6*S*)-**466** and (2*R*,6*S*,11*S*)-**468** in an overall average yield of 72±10%. [b] The average de was 70 ± 15%. [c] The de was always >90%. [d] The average de was 91 ± 1%. [e] The average de was 83 ± 12%. [f] The average de was 57 ± 12%. [g] The average de was 79 ± 19%. [h] The average de was 84 ± 15%. [i] Entries 11 and 11bis refer to the reaction between **469** and **100** or **180**, catalyzed by (*R*)-**XXIIa**, which gives (2*S*,3*S*,4*R*)-**473** or (2*R*,6*S*,11*S*)-**474**. [j] The average de was 51 ± 21%. [k] The de was >90%. [l] The de was >90%. [m] The average de was 89 ± 8%. [n] The de was >93%. [o] The average de was 81 ± 4%. [p] The average de was 49 ± 12%.

The reactions involving the indole derivatives **100** and **180** were run with the enantiomeric catalyst (*R*)-**XXIIa** and the products were one-pot submitted to the Wittig reaction with very good results (Scheme 203, Table 17 entry 11).[216] The absolute configuration of the adducts **473** and **474** was determined by X-ray structure analysis to be (2*S*,3*S*,4*R*), and this means that the [oxa-Michael/Michael] intermediates are (2*S*,3*S*,4*R*)-**471** and **472**, respectively, with the configuration of the chiral center in position 4 opposite to that of (2*S*,3*R*,4*S*)-**470** in Scheme 202.

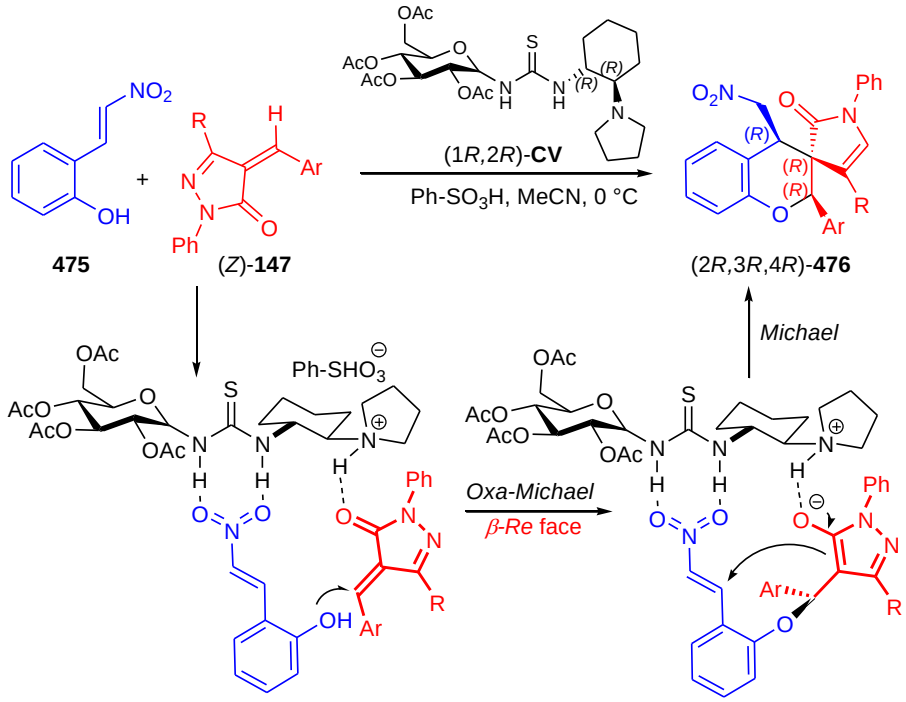
Scheme 203. Enantioselective Domino [Oxa-Michael/Michael] Reaction Between 469a and 180, with (*R*)-XXIIa as Organocatalyst.[216]



An interesting variant consists in the reaction of 2-(2-nitrovinyl)phenol (**475**), which bears both a Michael donor and a Michael acceptor and the cascade of reactions depends on the second reagent involved. The reaction with 5-substituted 4-benzylidene-2-phenylpyrazolone **147** in the presence of the bifunctional [carbohydrate/cyclohexane-1,2-diamine] thiourea (1*R*,2*R*)-**CV** as the organocatalyst and benzene sulfonic acid is paradigmatic. In the reacting intermediate, reported in Scheme 204, the Authors propose that **475** is activated by the thiourea through the double hydrogen bonding between two NH and the nitro group, while the protonated tertiary amine activates **147**. The cascade sequence is hence an intramolecular oxa-Michael attack to the *β-Re* face of the α,β-

unsaturated enone fragment, followed by the Michael ring closure that gives (2*R*,3*R*,4*R*)-**476** (Scheme 204).[217] The spiro[chroman-3,3′-pyrazol] derivatives **476** were obtained with very good reaction yields (usually >85%) and high enantioselectivities (in many examples ee >95%), but the diastereoselectivity of the domino process was frequently unsatisfactory (Table 17, entry 12).

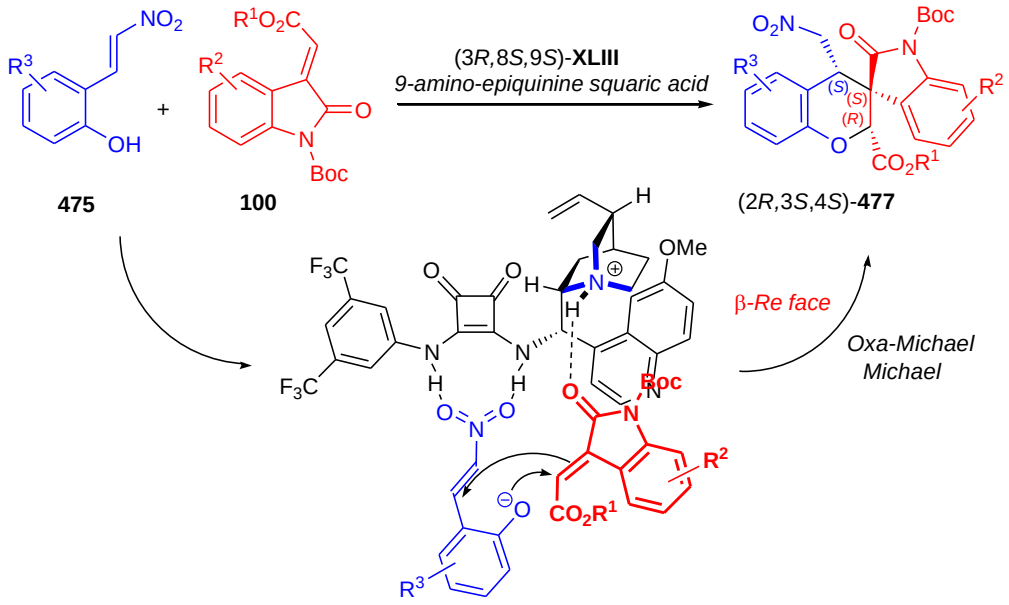
Scheme 204. Enantioselective Domino [Oxa-Michael / Michael] Reaction Between 475 and 147, with Bifunctional [Carbohydrate/Cyclohexane-1,2-diamine] Thiourea (1*R*,2*R*)-CV as Organocatalyst.[217]



The reaction between nitrovinylphenol **475** and Boc-protected 3-[(methoxycarbonyl) methylene]-2-oxoindole **100** has many analogies with the example above reported. The organocatalyst is the 9-*amino-epiquinine*-based squaric acid (3*R*,8*S*,9*S*)-**XLIII** that again activates **475** through the double hydrogen bonding between two NH and the nitro group, while the protonated tertiary amine of epiquinine activates **100** (Scheme 205). The cascade sequence is again an intramolecular oxa-Michael attack to the *β-Re* face of 3-[(methoxycarbonyl)methylene]-2-oxoindole, followed by the Michael addition to the β-position of the nitrovinyl group. The spiro derivatives (2*R*,3*S*,4*S*)-**477** containing three contiguous stereocenters were obtained within

moderate-good yields (from 53 to 80%) and with excellent diastereo- and enantioselectivities (>90% de; 92-99% ee), Table 17, entry 13.[218]

Scheme 205. Enantioselective Domino [Oxa-Michael/Michael] Reaction Between 475 and 100, with 9-*Amino-epiquinine*-based Squaric Acid (3*R*,8*S*,9*S*)-XLIII as Organocatalyst.[218]

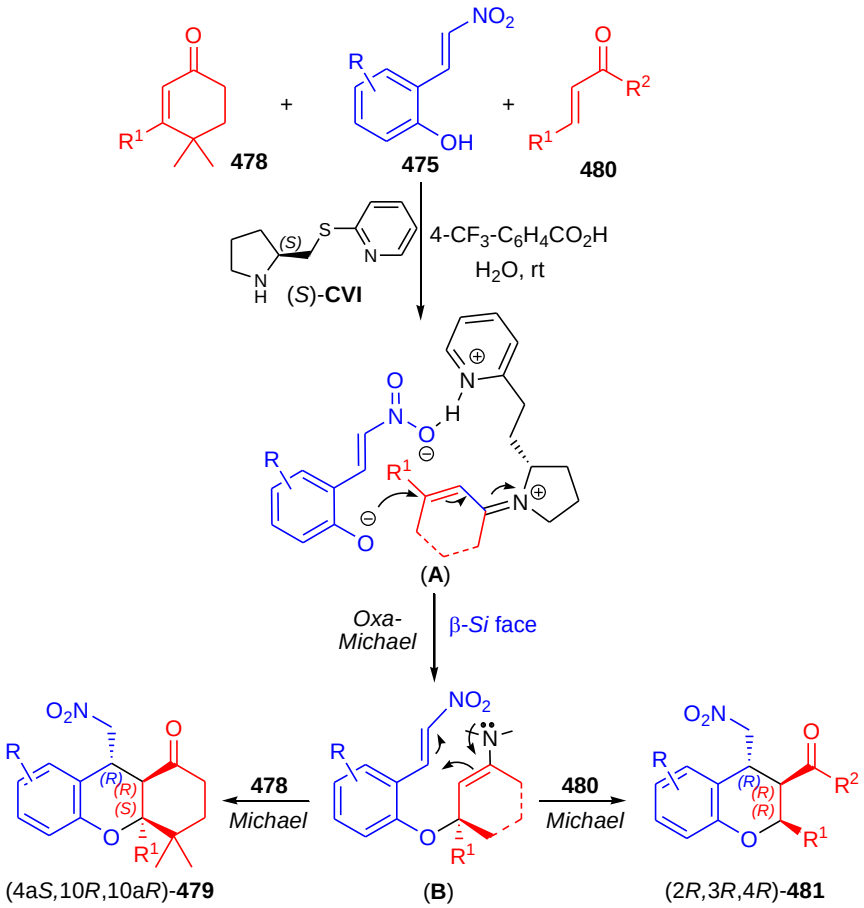


An interesting case is the reaction of nitrovinylphenol **475** with simple cyclic or acyclic enones, using (*S*)-2-[(pyrrolidin-2-yl)methylthio]pyridine (*S*)-**CVI** as bifunctional organocatalyst.

Taking first 3-substituted 2-cyclohexenones **478** as electrophiles, these are activated by the catalyst to form the reactive chiral iminium ion (**A**) that has a pyridinium ion residue able to activate the nucleophilic nitrovinylphenol by hydrogen bonding (Scheme 206). This gives rise to an ideal reacting intermediate in which the two reagents are activated, approached and correctly oriented. Now the intramolecular oxa-Michael reaction occurs through attack of the phenolic OH to the *β-Si* face of the enone to give the (4a*S*) chiral center of the developing product **479**. The Michael ring closure is the second step of the cascade and, after hydrolytic release of the organocatalyst, gives (4a*S*,10*R*,10a*R*)-**479** with three contiguous stereocenters in excellent yield, diastereo- and enantioselectivity (Table 17, entry 14).[219]

The same Authors experienced the same catalyst in the reaction between **475** and simple enones **480** with formation of (2*R*,3*R*,4*R*)-**481**, again result of an [oxa-Michael/Michael] cascade (Scheme 206).[219] In this case, the reaction yields were only moderate, but again diastereo- and enantioselectivities were excellent (Table 17, entry 15).

Scheme 206. Enantioselective Domino [Oxa-Michael/Michael] Reaction of 475 with 478 or with 480, and with (*S*)-CVI as Bifunctional Organocatalyst.[219]



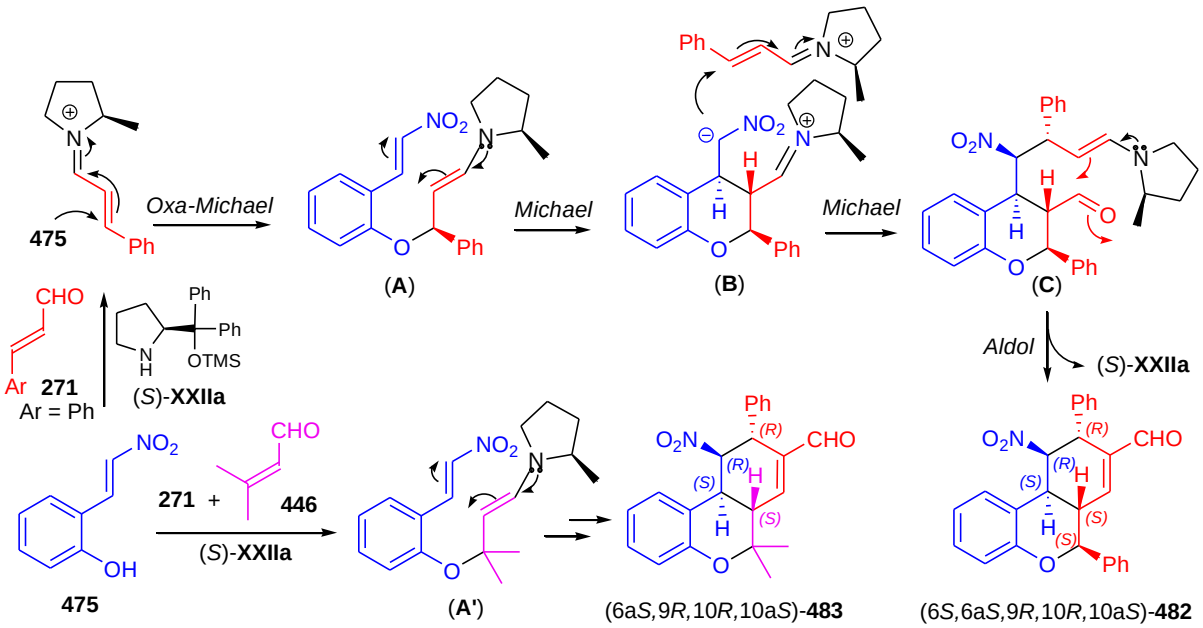
2.3.3.1 Through Oxa-Michael/Michael Introducing Multiple Cascade Reaction

Organocatalytic domino/cascade reactions rapidly became a sequence of complicated reactions; from the simplest protocol that puts together two reagents through two consecutive reactions, in which the selectivity of the second step is increased taking advantage from the synergistic effect with the first step. Playing with the Rubik cube, each with a different color, you

plan one movement, and expect a series of authomatic subsequent movements that you are convinced will afford to the monochrome face. The fantastic thing is that sometimes it happens!

Some organocatalytic cascade reactions start with an *oxa-Michael step* and one example is the reaction of nitrovinylphenol **475** with an excess of cynnamaldehydes **271**, with simple prolinol (*S*)-**XXIIa** as organocatalyst. The reaction begins with the catalyst that activates the electrophile **271** to form the reactive chiral iminium ion that is attached by nitrovinylphenol through an *oxa-Michael* attack to the *β-Si* face affording the (*S*) chiral center of the first reacting intermediate (**A**) (Scheme 207).[220] Its ring closure involves an intramolecular *Michael* reation between enamine and nitroalkene to provide the second reacting intermediate (**B**) with three chiral centers. Its carbanion is stable enough to be trapped by a second equivalent of the reactive chiral iminium ion through an intermolecular *Michael* reaction that gives the five-chiral-centers reacting intermediate (**C**), whose intramolecular *aldol* reaction provides (6*S*,6a*S*,9*R*,10*R*,10a*S*)-**482** (yield 70% and ee >99%).

Scheme 207. Enantioselective Domino [Oxa-Michael/Michael/Michael/Aldol] Reaction of 475 with 271 and 446, with (*S*)-XXIIa as Organocatalyst.[220]

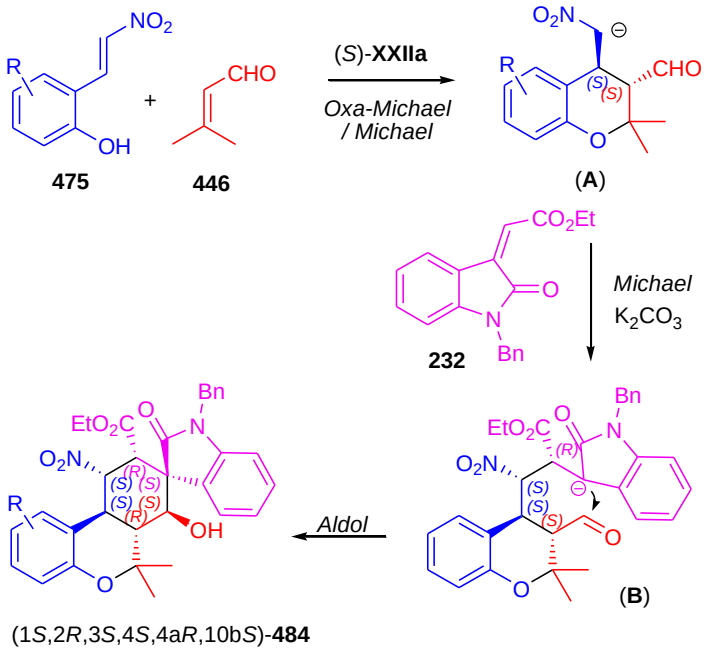


To increase the complexity of the system one can put together a *black* (*S*)-**XXIIa**, a *mauve* **446**, a *blue* **475**, and a *red* **271**. The *black* holds the *mauve*, the ordered couple of colours takes the

blue, and triple strip of colors takes at last the *red* to form the highly ordered (6a*S*,9*R*,10*R*,10a*S*)-**483** in appreciable yields and excellent diastereo- and enantioselectivities (>93% de, >99% ee; entry 16 in Table 17).[220] Yes, things sometime happen.

Another example of enantioselective domino [*oxa-Michael*/*Michael*/*Michael*/*Aldol*] reaction is obtained from nitrovinylphenol **475** with 3-methylbut-2-enal (**446**) and ethyl 2-(1-benzyl-2-oxoindolin-3-ylidene)acetate (**232**), with prolinol (*S*)-**XXIIa** as organocatalyst (Scheme 208).[221] The *oxa-Michael*/*Michael* steps give the reacting intermediate (**A**) with two chiral centers and the anion suitable to give the second *Michael* reaction with **232**. The anion of the resulting four chiral center intermediate (**B**) promotes an *aldol* reaction to the carbonyl of the former aldehyde affording (1*S*,2*R*,3*S*,4*S*,4a*R*,10b*S*)-**484** with six chiral centers, one of them being related to the spiro-structure, and with an average enantioselectivity of 98 % over 17 experiments (Table 17, entry 17).[221]

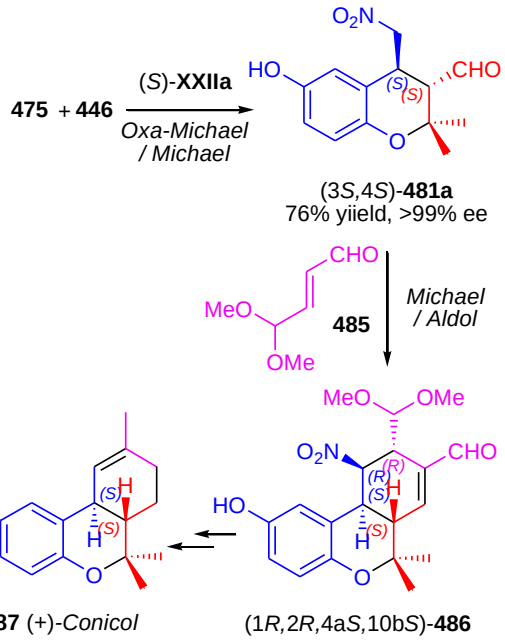
Scheme 208. Enantioselective Domino [Oxa-Michael/Michael/Michael/Aldol] Reaction of 475 with 232 and 446, with (*S*)-XXIIa as Organocatalyst.[221]



A third example may be defined as a domino [*oxa-Michael*/*Michael*] plus a domino [*Michael*/*Aldol*] reaction between 2-(2-nitrovinyl)benzene-1,4-diol (**475**) and 3-methylbut-2-enal

(**446**), catalyzed by (*S*)-**XXIIa**, because the product of the first two-step (3*S*,4*S*)-**481a**, the protonated form of the already mentioned intermediate (**A**) (Scheme 208), was isolated and made to react with 4,4-dimethoxybut-2-enal (**485**). The result of the [*Michael*/*Aldol*] step was (1*R*,2*R*,4a*S*,10b*S*)-**486** that was converted (with loss of two chiral centers) into (+)-*Conicol* **487**, a meroterpenoid isolated from a marine invertebrate, the ascidian *Aplidium conicum* (Scheme 209).[222]

Scheme 209. Enantioselective Synthesis of (+)-*Conicol* from Multistep Cascade Began with an Oxa-Michael Reaction.[222]

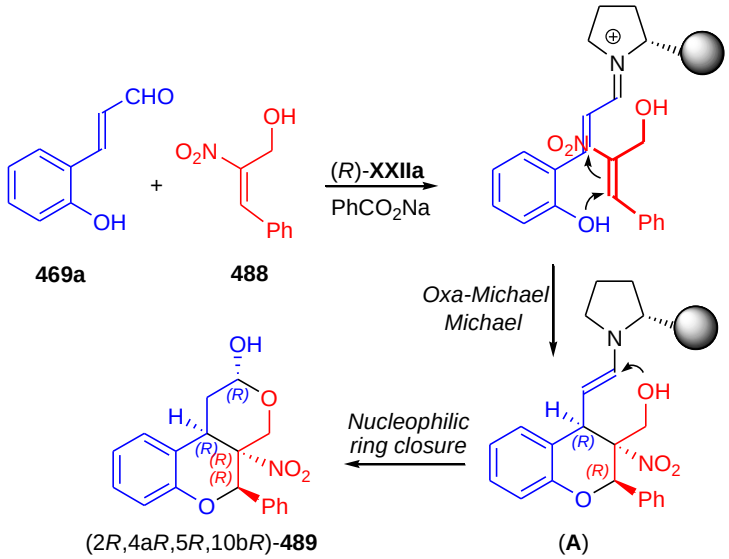


As seen before, the oxa-Michael reaction may initiated with a reaction between *ortho*-hydroxycynnamaldehyde **469a** or 3-(2-hydroxyphenyl)prop-2-en-1-ones **469b** and an electrophilic alkene. Here, few examples in which this reaction is followed by further steps will be discussed.

The reaction between **469a** and 2-nitro-3-phenylprop-2-en-1-ol (**488**), catalysed by (*R*)-**XXIIa**, begins with the catalyst that forms with **469a** the reactive chiral iminium ion, which attacks the β-position of nitroalkenol through an *oxa-Michael* reaction that is followed by the *Michael* step to afford the reacting intermediate (**A**). A nucleophilic ring closure concludes the cascade reaction to afford (2*R*,4a*R*,5*R*,10b*R*)-**489** (Scheme 210).[223] The reaction yields were good, while the

diastereoselectivities were low, but over 12 experiments the average ee was excellent (96 ± 4%), Table 17, entry 18.

Scheme 210. Enantioselective Domino [Oxa-Michael/Michael/Nucleophilic Ring Closure] Reaction Between *ortho*-Hydroxycynnamaldehyde 469a and 488, with (*R*)-XXIIa as Organocatalyst.[223]

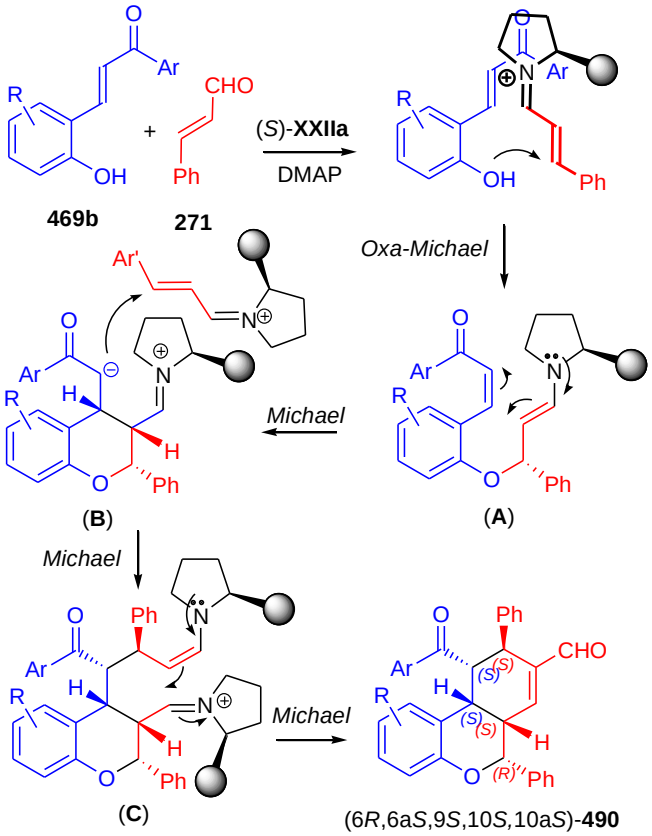


We close this section with a further example in which the starting step is an oxa-Michael reaction involving 3-(2-hydroxyphenyl)prop-2-en-1-ones **469b**, where the second reagent, an unsaturated aldehyde, enters in the cascade more than one time.

The simple reaction between 2-hydroxychalcones **469b** and cinnamaldehydes **271**, catalysed by (*S*)-**XXIIa**, begins with the catalyst that activates the electrophile **271** to form the reactive chiral iminium ion, which is attached by the phenolic OH through an *oxa-Michael* attack to the *β-Si* face affording the (*R*)-chiral center of the first reacting intermediate (**A**) (Scheme 211).[224] Its *Michael* ring closure affords the three chiral centers intermediate (**B**) whose anion intercepts, through a second *Michael* attach the second reactive imminium ion of **271** providing the five chiral centers intermediate (**C**). The last *Michael* ring closure with loss of catalyst and water gives the final product (6*R*,6a*S*,9*S*,10*S*,10a*S*)-**490** whose absolute configuration was unambiguously determined by X-ray crystal analysis. This is one of the few article in which the unsuccesful reactions are reported

together with the succesful ones. Over 13 experiments with different reagents, five gave only traces of product, but 8 gave good yields of enantiomerically pure products (>99% ee), Table 17, entry 19.

Scheme 211. Enantioselective Domino [Oxa-Michael/Michael/Michael/Michael] Reaction Between 2-Hydroxychalcones 469b and Cinnamaldehydes 271, with (*S*)-XXIIa as Organocatalyst.[224]



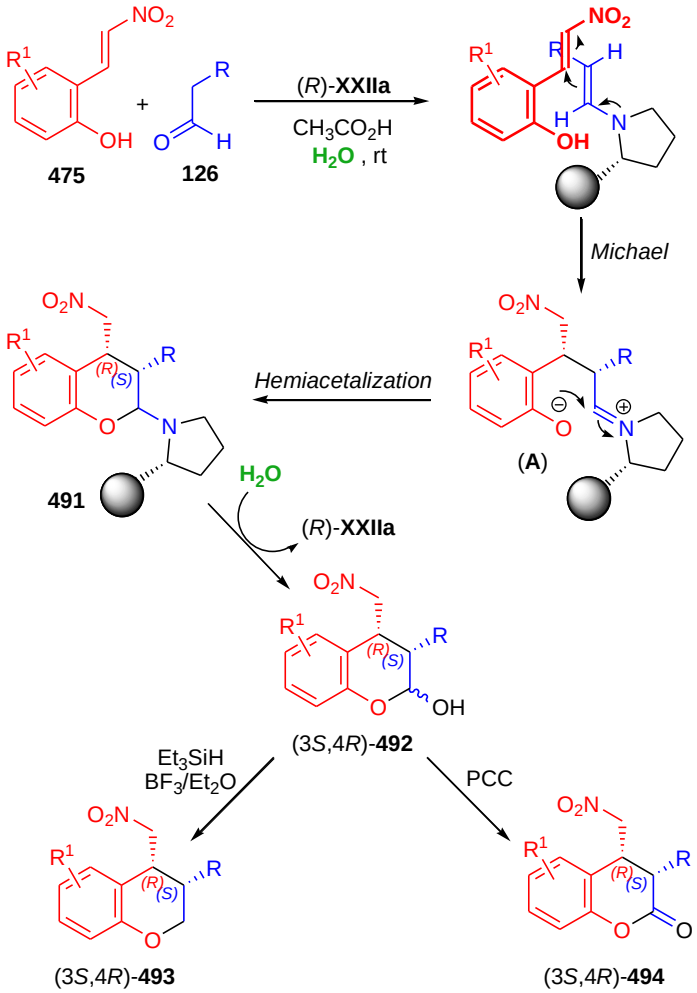
2.3.4. Through Domino Michael/Hemiacetalization Reactions

In the previous section it was discussed in detail the reaction between *ortho*-nitrovinylphenols **475** and aldehydes that give domino processes in which the first step is an oxa-Michael reaction. Another pathway may be preferred, mainly with saturated aldehydes **126**, activated by protected diphenylprolinol. The resulting enamine gives a *Michael* attach to the nitrovinyl group of **475** giving rise to an intermediate whose ring closure to chromanols occurs through an hemiacetalization followed by hydrolytic cleavage that recycle the organocatalyst.

This protocol was first followed by Enders with the reaction between **475** and aliphatic aldehydes **126**, with (*R*)-**XXIIa** as organocatalyst (Scheme 212).[225] The *Michael* step gives the *cis*

substituted reacting intermediate (**A**), whose absolute configuration (3*S*,4*R*) depends on the organocatalyst, which determines the sense of the approach to the less sterically encumbered face. The *hemiacetalization* to **491** is followed by the hydrolytic cleavage of the catalyst and chromanols (3*S*,4*R*)-**492** are isolated in excellent yields. These are easily converted by dihydroxylation to chromans (3*S*,4*R*)-**493**, or oxidised with pyridinium chlorochromate to 3,4-dehydrocoumarins (3*S*,4*R*)-**494**, both with excellent diastereo- and enantioselectivity (Table 18, entries 1 and 2).

Scheme 212. Enantioselective Domino [Michael/Hemiacetalization] Reaction between *ortho*-Nitrovinylphenols 475 and Aldehydes 126, with (*R*)-XXIIa as Organocatalyst.[225]



What deserves attention is a fundamental difference between domino [Michael/hemiacetalyzation] and domino [oxa-Michael/Michael] reactions. Both can involve *ortho*-nitrovinylphenols **475**, but in the former reactions it behaves as an electrophile, in the latter ones it is the nucleophilic counterpart.

Several enantioselective domino [Michael/hemiacetalization] reactions have been reported between *ortho*-nitrovinylphenols **475** and different aldehydes with different organocatalysts. Chart 9 reports the catalysts, the reagents and the different products obtained (either chromanols, or chromans, or 3,4-dihydrocoumarins), while Table 18 collects the results in terms of yield, diastereo- and enantioselectivity.

Chart 9. Reagents, Organocatalysts, and Products of Enantioselective Domino [Michael/Hemiacetalization] Reactions.

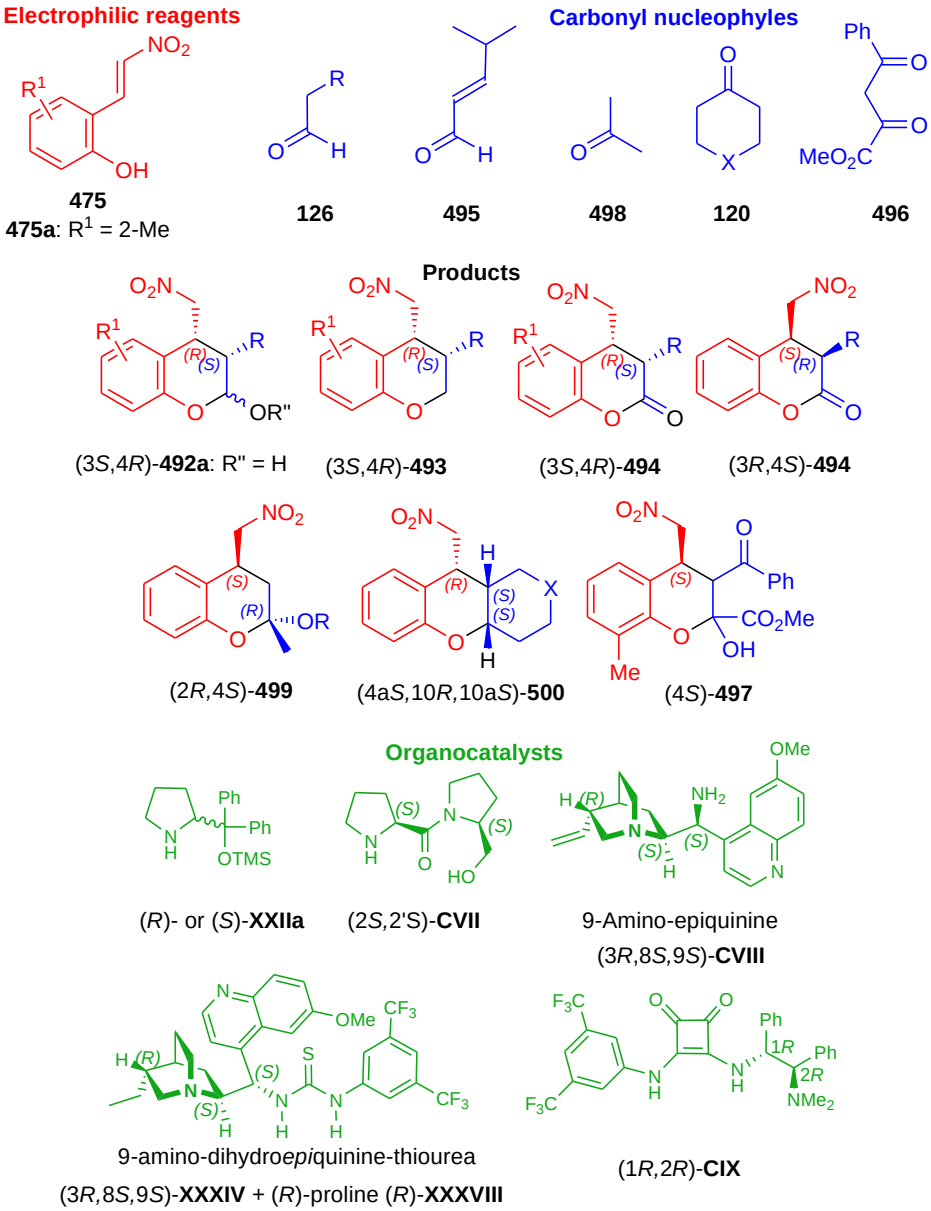


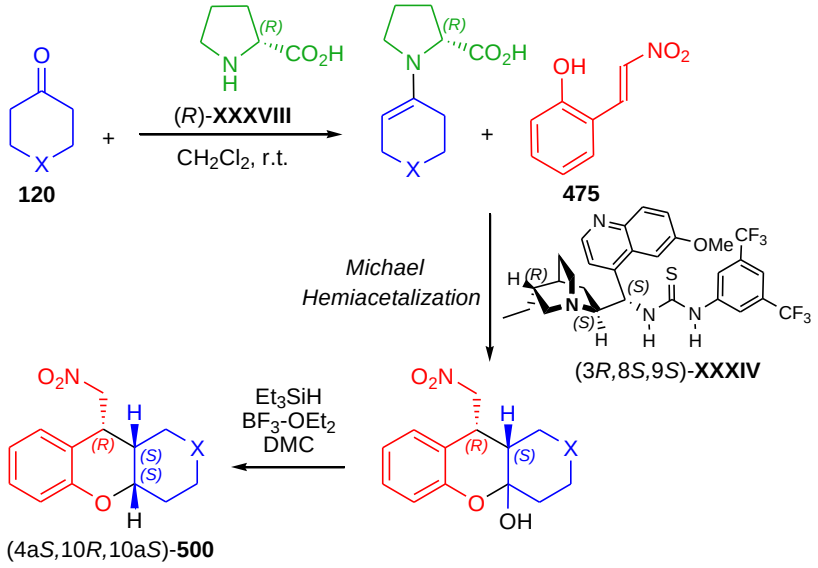
Table 18. Average Values and Standard Deviations (s.d.) of the Reaction Yields, Diastereo-, and Enantioselectivities of Domino [Michael/Hemiacetalization] Reactions for Reagents, Organocatalysts, and Products in Chart 9.

Entry	Electrophile	Nucleophile	Organocatalyst (Additive)	n. Exp.	aver. Yield % (s.d.)	Reaction Product	aver. de % (s.d.)	aver. ee % (s.d.)	Ref.
1	**475**	**126**	(*R*)-**XXIIa** (Et_3SiH)	11	76 (13)	(3*S*,4*R*)-**493**	91 (9)	98 (1)	225
2	**475**	**126**	(*R*)-**XXIIa** (PCC)	5	76 (7)	(3*S*,4*R*)-**494**	>98	>99	225
3	**475**	**495**	(*R*)-**XXIIa** (PCC)	9	74 (9)	(3*S*,4*R*)-**494**	67 (23)	97 (2)	226
4	**475**	**126**	(*S*)-**XXIIa** (PCC)	13	74 (7)	(3*R*,4*S*)-**494**	57 (9)	99 (0.5)	227
5	**475**	**126**	(2*S*,2'*S*)-**CVII** (PCC)	13	88 (4)	(3*R*,4*S*)-**494**	95 (3)	84 (4)	227
6	**475a**	**496**	(1*R*,2*R*)-**CIX**	1	76	(2*R*,4*S*)-**499**	18	85	228
7	**475**	**498**	(3*R*,8*S*,9*S*)-**CVIII** (ROH)	14	42 (9)	(2*R*,4*S*)-**499**	0	84 (7)	229
8	**475**	**120**	(3*R*,8*S*,9*S*)-**XXXIV** (Et_3SiH)[(a)]	11	78 (9)	(4a*S*,10*R*,10a*S*)-**500**	94 (4)	97 (3)	230
9	**319**	**501**	(*R*)-**XVg** ($Rh_2(OAc)_4$)	25	69 (9)	(2*S*,3*S*,4*S*)-**503**	>98	90 (5)	231

[(a)] In the presence of (*R*)-proline ((*R*)-**XXXVIII**).

Besides different prolinol-based organocatalysts (Table 18, entries 1-5),[225-227] other organocatalysts were: the squaramide-based derivative bound to 3,5-trifluomothylbenzene group and to a fragment with two chiral centers, (1*R*,2*R*)-**CIX** (Table 18, entry 6),[228] 9-amino-*epi*quinine (3*R*,8*S*,9*S*)-**CVIII** (Table 18, entry 7),[229] and 9-amino-dihydro*epi*quinine-thiourea (3*R*,8*S*,9*S*)-**XXXIV** in admixture with (*R*)-proline (Table 18, entry 8).[230] About the mechanism by which the above organocatalysts transmit the chiral information to the products, in addition to what reported in Scheme 212 for prolinol derivatives, we wish to discuss the reaction between *ortho*-nitrovinylphenols **475** and cyclic ketones **120**, catalyzed by 9-amino-dihydroepiquinine-thiourea (3*R*,8*S*,9*S*)-**XXXIV** in the admixture with (*R*)-proline [(*R*)-**XXXVIII**] (Scheme 213).[230]

Scheme 213. Enantioselective Domino [Michael/Hemiacetalization] Reaction between *ortho*-Nitrovinylphenols 475 and Ketones 120, with a Self-assembly of (3*R*,8*S*,9*S*)-XXXIV with (*R*)-Proline [(*R*)-XXXVIII] as Organocatalyst.[230]

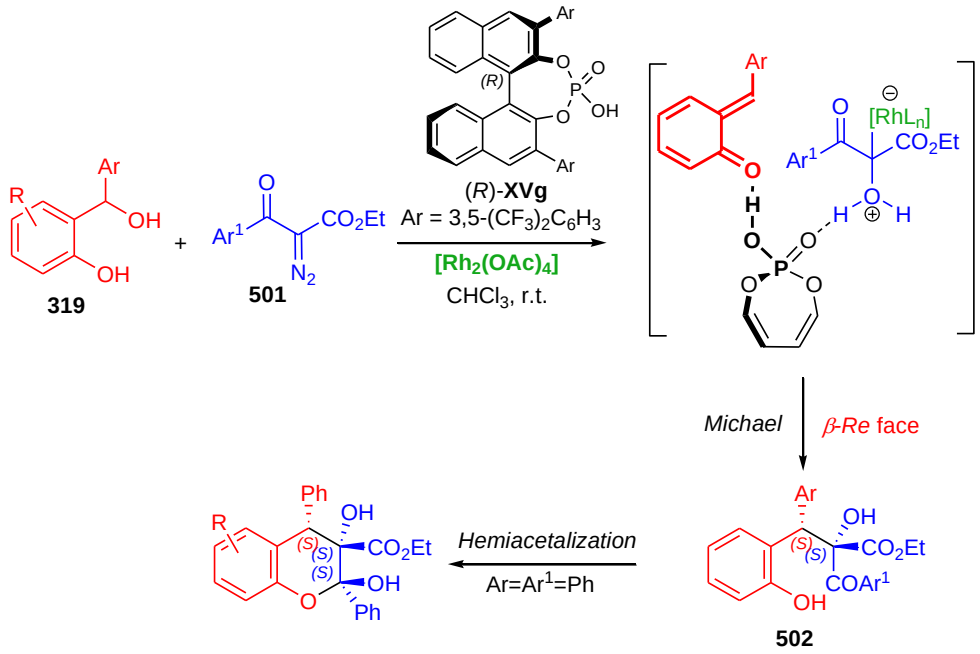


The first step is the formation of the (*R*) enamino-acid between **120** and proline. The organocatalyst 9-amino-dihydro*epi*quinine-thiourea (3*R*,8*S*,9*S*)-**XXXIV** activates **475** through the double hydrogen bonding, while the protonated tertiary amine of dihydro*epi*quinine activates the nucleophilic anion. The Michael attack is followed by the hemiacetalization and hydrolytic loss of

the catalyst. This gives the three chiral centers of (4a*S*,10*R*,10a*S*)-**500** with excellent diastereo- and enantioselectivities. β

A reaction that formally belongs to this section, but in which phenol is simply the starting material of a different reacting species, is the one involving *ortho*-hydroxy benzhydryl alcohols **319** and ethyl 2-diazo-3-oxo-3-arylpropanoates **501**. The catalyst is the BINOL-based phosphoric acid (*R*)-**XVg** acting with [$Rh_2(OAc)_4$] (Scheme 214).[231]

Scheme 214. Enantioselective Domino [Michael/Hemiacetalization] Reaction between Phenols 319 and Diazo Derivatives 501, Catalyzed by (*R*)-XVg and [$Rh_2(OAc)_4$].[231]



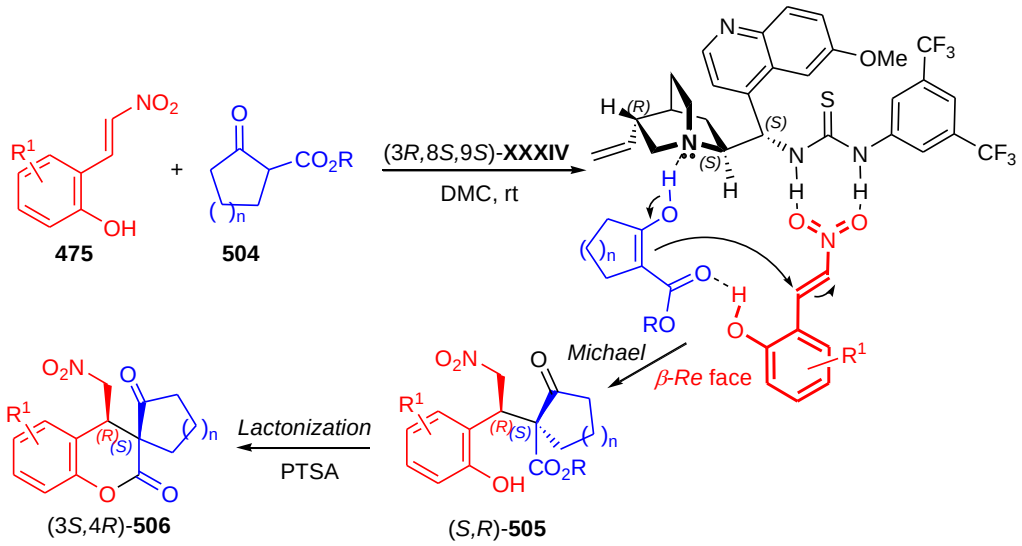
The reaction begins with the acid-catalyzed dehydration of **319** that produces *ortho*-quinone methydes which are the true reagents of the reaction. The water formed from the above dehydration traps the rhodium carbene produced from **501**. The so-formed nucleophilic oxonium ylide undergoes a conjugate addition to the electrophilic quinone methydes via a reacting intermediate with the phosphoric acid bound to both reagents through hydrogen bonding. The Michael attack occurs on the *β-Re* face of the electrophile affording (*S*,*S*)-**502**, whose hemiacetalization provides chromans (2*S*,3*S*,4*S*)-**503** with complete diastereo- and excellent enantioselectivities (Table 18, entry 9).

2.3.5. Through Different Sequential Michael Cascade Reactions

As seen in previous sections, the Michael reaction is often a step of a cascade sequence whose target is the enantioselective syntheses of 3,4-dihydropyran derivatives. We have just discussed the domino [*Michael/Hemiacetalization*], now different cascade reactions in which the Michael addition is the first step will be considered.

As shown above, the reaction between *ortho*-nitrovinylphenols **475** and α-ketoesters **504**, catalysed by 9-amino-epiquinine-thiourea (3*R*,8*S*,9*S*)-**XXXIV**, has a *Michael* reaction as the first step of the cascade (Scheme 215).[232]

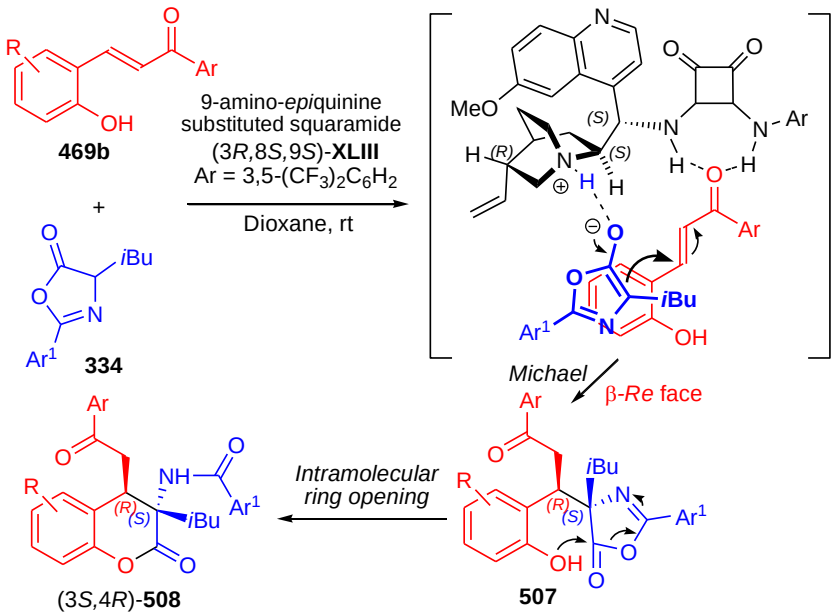
Scheme 215. Enantioselective Domino [Michael/Lactonization] Reaction Between Nitrophenols 475 and α-Ketoesters 504, Catalyzed by (3*R*,8*S*,9*S*)-XXXIV.[232]



The organocatalyst activates the electrophilic **475** through the double hydrogen bonding between two NH and the nitro group, while the tertiary amine of *epi*quinine activates the nucleophile. The neighbouring group participation in organocatalysis favours a further hydrogen bonding between the phenolic OH and the carbonyl group of **504** and participates to determine the configuration of a reacting intermediate in which the *Michael* attack occurs "*bottom/up*" to the *β-Re* face of *ortho*-nitrovinylphenol. The resulting (*S*,*R*)-**505** intermediate undergoes *lactonization* that affords the spirodihydrocoumarins (3*S*,4*R*)-**506** in good yields and with excellent diastereo- and enantioselectivities (Table 19, entry 1).

The role of the neighbouring group, affording a specific reacting intermediate having a fundamental effect on the absolute configuration of the product, can be appreciated in the comparison between the reaction above described and the reaction between 2-hydroxychalcones **469b** and azlactones **334** catalyzed by (3*R*,8*S*,9*S*)-**XLIII** (Scheme 216).[233]

Scheme 216. Enantioselective Domino [Michael/Ring Opening] Reaction Between 2-Hydroxychalcones 469b and Azlactones 334, Catalyzed by (3*R*,8*S*,9*S*)-XLIII.[233]



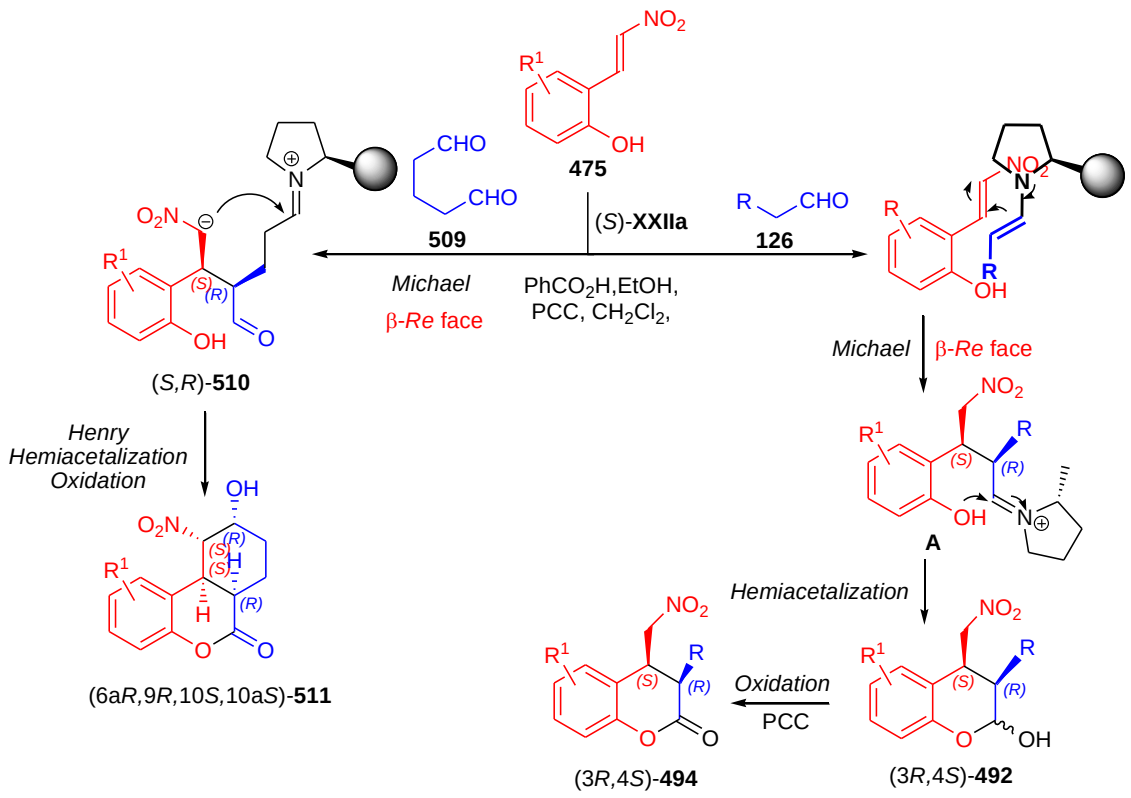
The absolute configuration of the products, unambiguously determined to be (3*S*,4*R*)-**508**, suggests a specific reacting intermediate, derived from the bifunctional squaramide catalyst, which activates 2-hydroxychalcone **469b** by the H-bonding interactions, and the azlactone **334** via deprotonation to give a chiral ion pair. Furthermore, a π-stacking interaction between aromatic moieties on the azlactone and 2-hydroxychalcone favors the *Michael* attack "*top/down*" to the *β-Re* face of *ortho*-nitrovinylphenol. The reaction cascade is terminated by the intramolecular *azlactone ring-opening* of the intermediate product (*R*,*R*)-**507** that affords (3*S*,4*R*)-**508**, which were obtained within good yields and appreciable selectivities (Table 19, entry 2).[233]

Ortho-nitrovinylphenols **475** are very diffused starting products for the enantioselective syntheses of 3,4-dihydropyran derivatives for their specific characteristic to have together a nucleophilic and an electrophilic center. Both are involved in two reactions in which **475** reacts with

aldehydes with TMS-diphenylprolinol (*S*)-**XXIIa** as organocatalyst. With aldehydes **126** the organocatalyst gives the chiral enamine whose *Michael* addition is the starting step of a cascade through **A**, followed by *hemiacetalization* to (3*R*,4*S*)-**492** and oxidation (with PCC) to (3*R*,4*S*)-**494** (Scheme 217).[234] The final adducts **494** were obtained within excellent yields and enantioselectivities, while the diastereoselectivity was only moderate (Table 19, entry 3).

Much more interesting is the reaction of **475** with glutaraldehyde **509**, under the same catalytic conditions (Scheme 217). The enaminoalehyde gives a cascade involving successively the *Michael* addition to give **510**, the *Henry* reaction and the *hemiacetalization*, and finally an oxidation to produce tetrahydro-6*H*-benzo[*c*]chromenones (6a*R*,9*R*,10*S*,10a*S*)-**511**. The adducts containing four chiral centers are formed in three experiments within moderate yields and diastereoselectivities, while enantioselectivity was again excellent (>99% ee), Table 19, entry 4.[234]

Scheme 217. Enantioselective Domino [Michael/Hemiacetalization] and [Michael/Henry/Hemiacetalization] Reactions Between *ortho*-Nitrovinylphenols 475 and Aldehydes, with TMS-diphenylprolinol (*S*)-XXIIa as Organocatalyst.[234]



When the above reaction of *ortho*-nitrovinylphenols **475** involved acetaldehyde and (*R*)-**XXIIa** as catalyst, the *Michael* step is the same and gives (*R*)-**512**. However, the aldehyde, that previously originated the nucleophile, behaves now as an electrophile, undergoing an *aldol* addition with (*R*)-**512** to produce (*R*)-**513**. This latter gives dehydration and then a ring closure through an *oxa-Michael* reaction to furnish the valuable intermediate (2*S*,3*R*,4*R*)-**514** (Scheme 218).[235] Using the in situ formed triple domino chromane, in a sequential one-pot procedure, it undertakes a Wittig reaction with **515** to afford (2*S*,3*R*,4*R*)-**516**, and the Wittig-Horner reaction with **517**, which provides (6*S*,6a*R*,10*S*,10a*R*)-**528**: Over four experiments: 98% d.e. and >99% ee! (Table 19, entries 5 and 6).

Scheme 218. Enantioselective Domino [Michael/Aldol/oxa-Michael] Between *ortho*-Nitrovinylphenols 475 and Acetaldehyde, with (*R*)-XXIIa as Organocatalyst.[235]

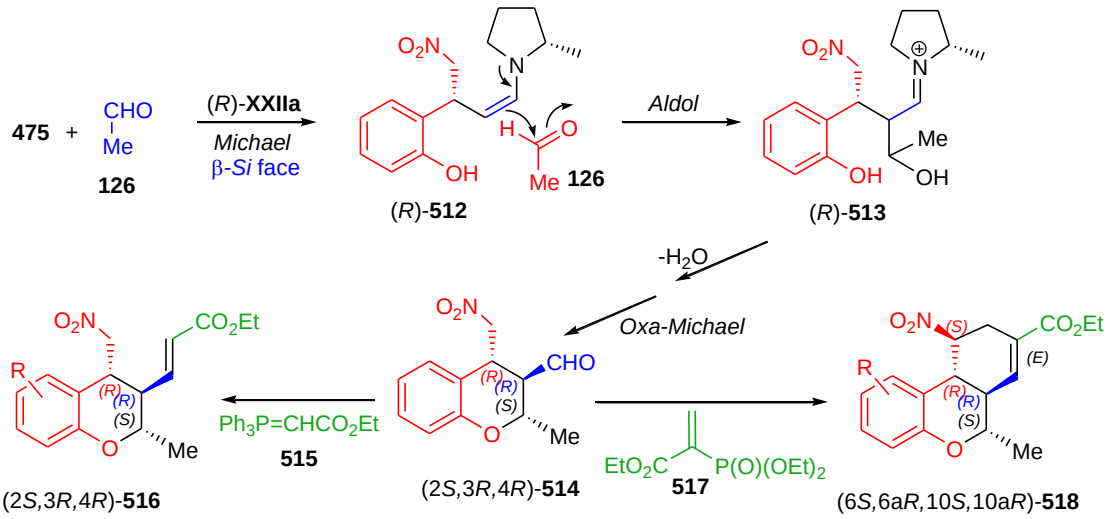


Table 19. Average Values and Standard Deviations (s.d.) of the Reaction Yields, Diastereo-, and Enantioselectivities in [4+2] Cyclizations to 3,4-Dihydro-Benzopyranes Through Sequential Michael Cascade and Other Sequential Cascade Reactions.

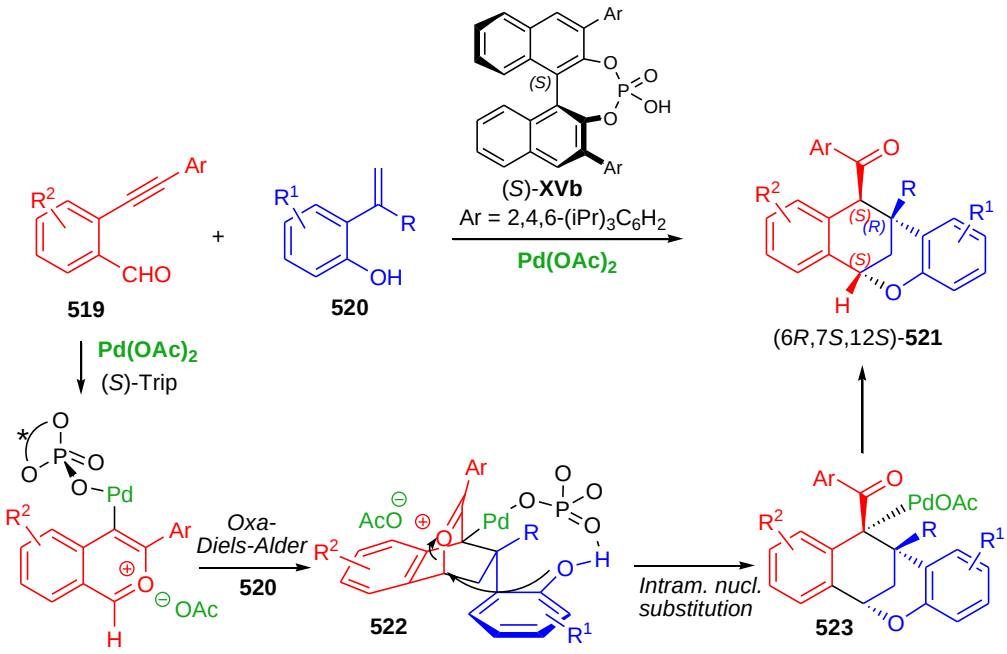
Entry	Nucleophile	Electrophile	Catalyst/ Organocatalyst	n. Exp.	aver. Yield % (s.d.)	Reaction Product	aver. ee % (s.d.)	Attach. face	Ref.
1	**504**	**475**	(3*R*,8*S*,9*S*)-**XXXIV**	15	73 (9)	(3*S*,4*R*)-**506**[a]	93 (8)	*β-Re*	232
2	**334**	**469b**	(3*R*,8*S*,9*S*)-**XLIII**	20	72 (12)	(3*S*,4*R*)-**508**[b]	82 (11)	*β-Re*	233
3	**126**	**475**	(*S*)-**XXIIa**	12	83 (5)	(3*R*,4*S*)-**492**[c]	95 (6)	*β-Re*	234
4	**509**	**475**	(*S*)-**XXIIa**	3	59 (8)	(6a*R*,9*R*,10*S*,10a*S*)-**511**[d]	>99	*β-Re*	234
5	**126**	**475** and **126**	(*R*)-**XXIIa**	10	81 (4)	(2*S*,3*R*,4*R*)-**516**[e]	>99	*β-Si*	235
6	**126**	**475** and **126**	(*R*)-**XXIIa**	4	71 (3)	(6*S*,6a*R*,10*S*,10a*R*)-**518**[f]	>99	*β-Si*	235
7	**520**	**519**	$Pd(OAc)_2$/(*S*)-**XVb**	40	71 (13)	(6*R*,7*S*,12*S*)-**521**	82 (22)	---	236
8	**10** or **21**	**524**	(*S*)-**LIVb**	26	71 (13)	(3a*R*,4*R*,9a*S*)-**256**[g]	88 (5)	*β-Re*	238
9	**498**	**441**	(*S*)-**XXXVIII**	12	67 (14)	(2*R*,4*R*)-**528**	77 (19)	*β-Re*	239
10	**529**	**271**	(*S*)-**XXIIa**	21	85 (5)	(4*S*,4a*S*,5*S*,10b*S*)-**532**[h]	>99	*β-Re*	240
11	**529**	**271**	(*S*)-**XXIIa**	16	91 (3)	(6*S*,6a*S*,9*R*,10*R*,10a*R*)-**535**[h]	>99	*β-Re*	240
12	**529**	**271** and **271a**	(*S*)-**XXIIa**	17	91 (6)	(6*S*,6a*S*,9*R*,10*R*,10a*R*)-**535a**[h]	>99	*β-Re*	240

[(a)] The de was always >99%. [(b)] The de was always >91%. [(c)] The average de was 60 ± 22%. [(d)] The average de was 66 ± 9%. [(e)] The average de was 60 ± 2%. [(f)] The de was 98%. [(g)] The average de was 46 ± 26%. The absolute configuration refers to products in which n=1. [(h)] The de was always >91%.

2.3.6. Through Different Sequential Cascade Reactions

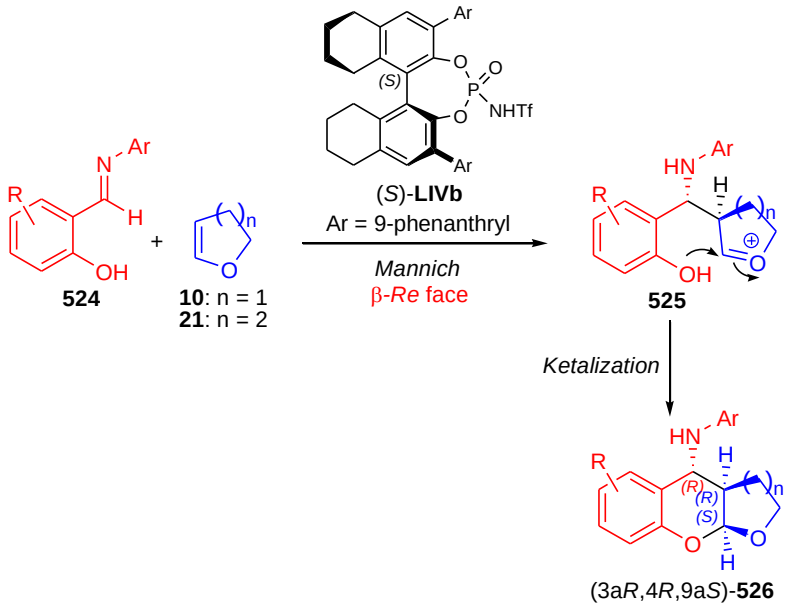
Complex cascade reaction in which phenols behave either as nucleophiles or electrophile were achieved in enantioselective syntheses of 3,4-dihydropyran derivatives. One example is the cascade annulation between 2-alkynylbenzaldehydes **519** and 2-hydroxystyrenes **520**, using the cooperative binary catalysis of $Pd(OAc)_2$ and BINOL-derived phosphoric acid (*S*)-**XVb** (Scheme 219).[236] The 2-alkynylbenzaldehyde, with $Pd(OAc)_2$ and (*S*)-**XVb** affords the chiral cationic oxa-diene which gives an *oxa-Diels-Alder* with the electron rich double bond of **520** as dienophile. The reacting intermediate **522** affords the second step of the cascade because the phenolic OH gives **523** through an intramolecular nucleophilic substitution. The release of the catalyst provides (6*R*,7*S*,12*S*)-**521**, with discrete enantoselectivity, through a protocol that was tested on 40 experiments with reagents characterized by different decorations (Table 19, entry 7).[236] The same identical reaction was also performed changing $Pd(OAc)_2$ with AgOAc, and the results may be considered comparable to those above reported.[237]

Scheme 219. Enantioselective Domino [Oxa-Diels-Alder/Intramolecular Substitution] Between 2-Alkynylbenzaldehydes 519 and 2-Hydroxystyrenes 520, with [$Pd(OAc)_2$/(*S*)-XVb] as Catalyst.[236]



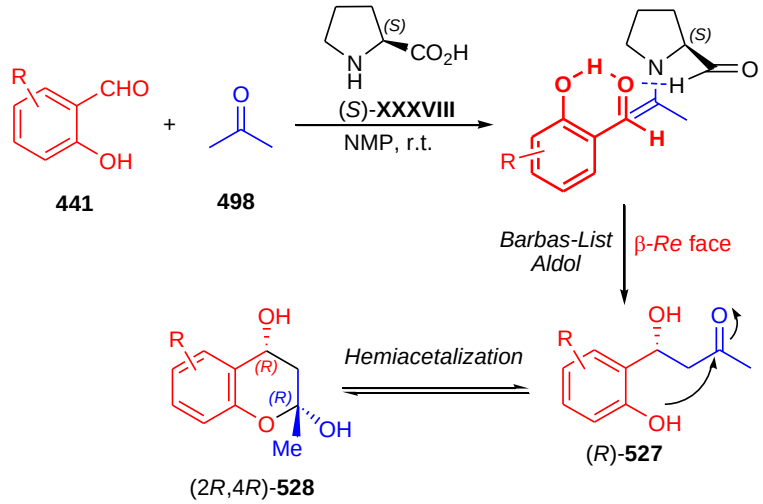
In the presence of highly acidic *N*-triflyphosphoramide (*S*)-**LIVb**, derived from (*S*)-BINOL, 2-hydroxybenzaldimines **524** undergo an enantioselective domino [*Mannich/ketalization*] with electron-rich alkenes **10** and **21** (Scheme 220).[238] The first step gives **525**, followed by the ring closure to (3a*R*,4*R*,9a*S*)-**256** (when n=1), which is obtained with good yields, low diastereoselectivities, and appreciable enantioselectivity (Table 19, entry 8).

Scheme 220. Enantioselective Domino [Mannich/Ketalization] between 2-Hydroxybenzaldimines 524 and 2,3-Didydro-2*H*-furane 10 or -pyran 21, with (*S*)-LIVb as Catalyst.[238]



An amino acid catalyzed variant of intramolecular aldol reaction was recently developed by Barbas, List and co-workers and this process was applied to the reaction of 2-hydroxybenzaldehyes **441** and acetone **498**, with L-Proline [(*S*)-**XXXVIII**], or *trans*-4-hydroxy-L-proline, as the catalyst (Scheme 221).[239] The formation of enamine from proline and acetone gives a nucleophile whose carboxylic acid coordinates and activates the aldehyde group of **441** favouring the *Barbas-List-aldol* formation of (*R*)-**527**. The research enters in the details of the *lactolization* affording (2*R*,4*R*)-**528** or its diastereoisomer, seldom as a mixture, within moderate yields and enantioselectivities (Table 19, entry 9). Curiously, the reaction with 2-hydroxy-naphthalene-1-carbaldehyde furnished the (2*R*,4*R*)-diastereoisomer with 98% de, while, from the process involving 2-hydroxy-5-nitrobenzaldehyde, the favoured diastereoisomer is (2*S*,4*R*)-**528** obtained with 98% de.[239]

Scheme 221. Enantioselective Domino [Barbas-List Aldol/Lactolization] Between 2-Hydroxy-benzaldehyes 441 and Acetone 498, with L-Proline [(*S*)-XXXVIII] as Catalyst.[239]



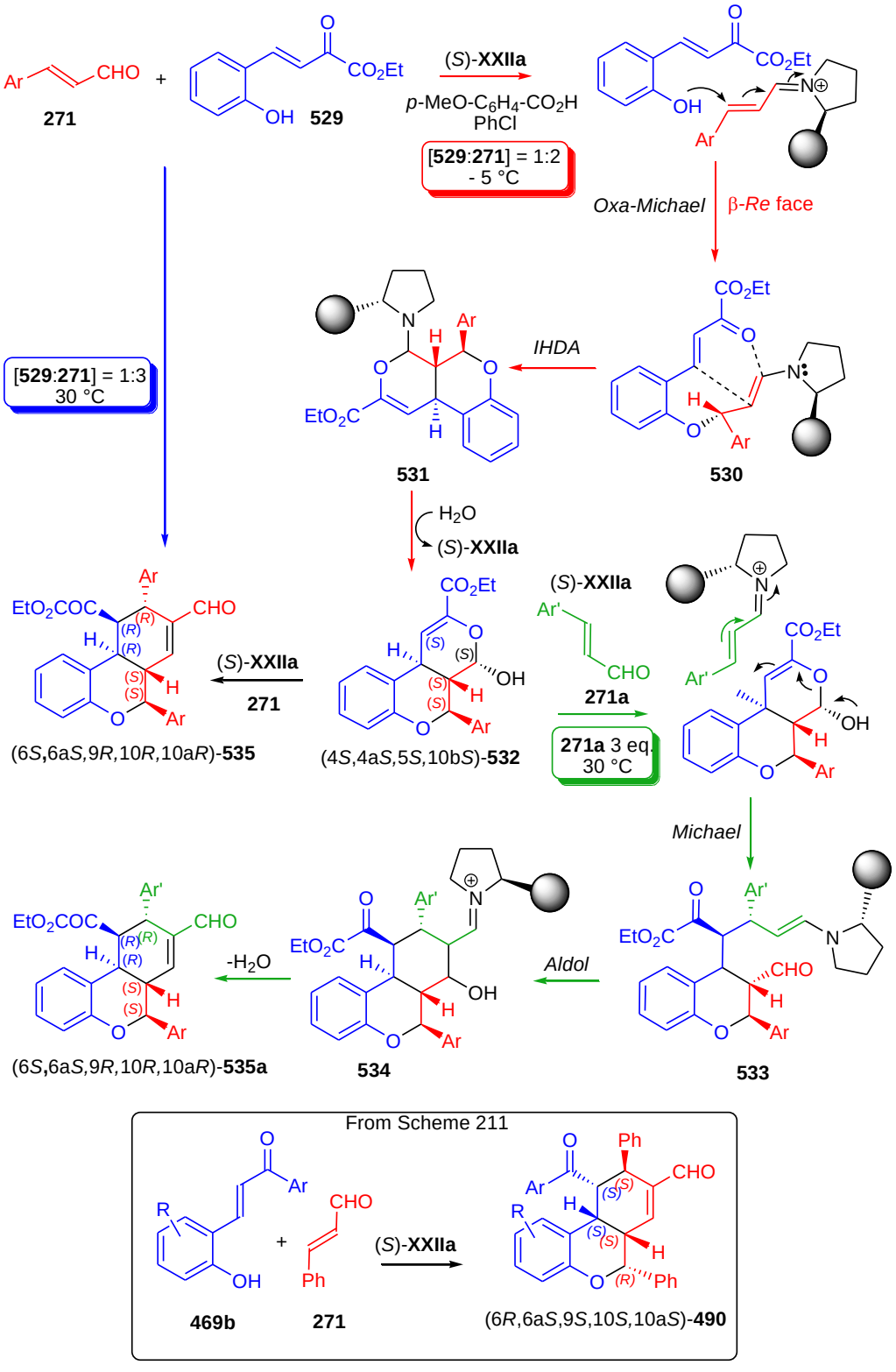
A cascade of fireworks that allows the asymmetric syntheses of tricyclic chroman derivatives concludes this section. The reaction between (*E*)-2-hydroxyaryl-2-oxobut-3-enoate derivatives **529** with enals **271** has been run in the presence of (S)-**XXIIa** as organocatalyst under controlled conditions: ratio [**529**:**271**] = [1:2] and -5 °C temperature. The process begins with the formation of the chiral iminium ion that undergoes the *oxa-Michael* addition of **529** to afford **530**. This is suitably organized for an *intramolecular Hetero-Diels-Alder* which affords **531**, with three chiral centers, to which the fourth one is added in (4*S*,4a*S*,5*S*,10b*S*)-**532** by the hydrolytic release of the catalyst (Scheme 222).[240]

This may become the starting product of a further cascade by adding three equiv. **271a** with Ar ≠ Ar′ at 30 °C. Then, a *Michael reaction*, on which **532** becomes the nucleophile that attacks the chiral iminium ion from **271a**, gives **533** which undergoes an *aldol reaction* to afford **534**, whose *dehydration* gives the five chiral centers tricyclic chroman (6*S*,6a*S*,9*R*,10*R*,10a*R*)-**535a**.

When the reaction between **529** and **271** is run in the presence of (*S*)-**XXIIa** as organocatalyst with the reagents ratio [**529**:**271**] = [1:3] and at 30 °C temperature, then **532** is by-passed and (6*S*,6a*S*,9*R*,10*R*,10a*R*)-**535** is directly obtained as the reaction product.

The potentiality of the above reaction can be appreciated if the reader considers that the enantioselectivity of the different products, run under three different conditions, on a total of 54 different experiments, with two exceptions, is always >99 % ee (Table 19, entries 10-12).[240]

Scheme 222. Diversity Oriented Asymmetric Syntheses of Tricyclic Chroman Derivatives.[240]

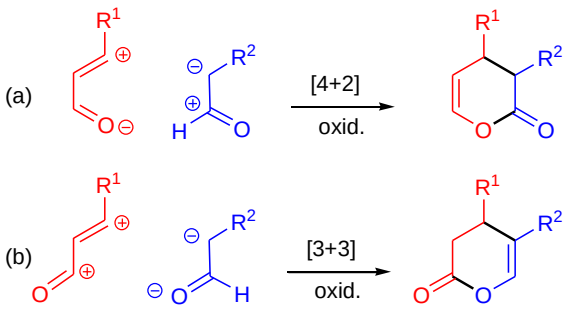


This result deserves a further comment. If the absolute configuration of (6*S*,6a*S*,9*R*,10*R*,10a*R*)-**535** is compared with that of the product of the reaction reported in Scheme 211, between 2-hydroxychalcones **469b** (which has many points in common with **529**) and cinnamaldehydes **271**, again catalysed by (*S*)-**XXIIa**,[224] one immediately notes a discrepancy in the absolute configuration of the product (6*R*,6a*S*,9*S*,10*S*,10a*S*)-**490** of this reaction which is not so simple to rationalize.

3. The Enantioselective Acceptor/Donor [3+3] Cyclization to 3,4-Dihydropyran Derivatives.

In the previous chapters the [4+2] cyclization strategy involving α,β-unsaturated carbonyl derivatives (more or less activated) and aldehydes was discussed. In this approach, the natural synthons were combined to give, after oxidation, 3,4-disubstituted pyran-2-ones (Scheme 223, eq. a). A different combination of the two natural synthons may produce regioisomeric adducts such as 4,5-disubstituted pyran-2-ones (Scheme 223, eq. b). The analysis of these reactions will be the scope of this chapter.

Scheme 223. Different Reaction Modes Between α,β-Unsaturated Carbonyl Derivatives and Aldehydes.



3.1. Competition Between [3+3] and [4+2] Cycloadditions: the *Oxidative N*-HC-Catalyzed [4+2] Cycloadditions Between Aldehydes and Enones

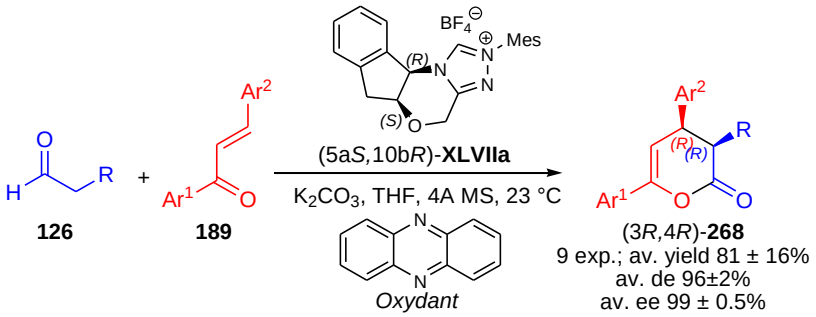
The successful preparation and characterization of stable chiral *N*-Heterocyclic Carbenes (*N*-HC) and their application to the homogeneous asymmetric catalysis, first developed by Sheehan and Hunneman,[241] had an important seminal effect on different enantioselective reactions.[91] Among

them, the enantioselective syntheses of 3,4-dihydropyran derivatives gained tumultuous developments from this class of catalysts.

In a previous section of this review we have discussed several examples of the application of *N*-HC as organocatalysts for [4+2] HDA reaction. Besides these examples, optically active 3,4-dihydropyran derivatives can be obtained through the *oxidative N*-HC-catalyzed [4+2] cycloaddition between aldehydes and enones.[242,243]

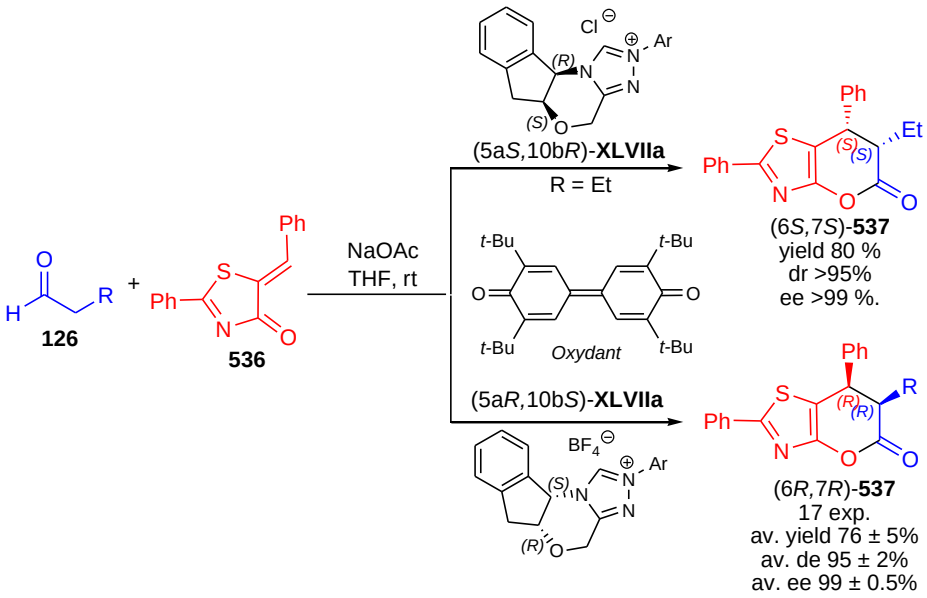
The reaction between α,β-unsaturated carbonyl compounds **189** and aldehydes **126** with phenazine as oxidant, was catalyzed by the mesityl triazolium salt (5a*S*,10b*R*)-**XLVIIa** as precatalyst (converted into the *N*-HC catalyst by K_2CO_3) gives (3*R*,4*R*)-disubstituted-6-substituted-3,4-dihydropyran-2-ones [(3*R*,4*R*)-**268**] (Scheme 224), which were obtained within very good yields and excellent selectivities (with up to >95% de and >99% ee).[242]

Scheme 224. The *Oxidative N*-HC-Catalyzed [4+2] Cycloaddition Between Aldehydes 126 and Enones 189 Catalyzed by (5a*S*,10b*R*)-XLVIIa.[242]



The same catalyst from (5a*S*,10b*R*)-**XLVIIa**, in the presence of NaOAc and 3,3′,5,5′-(*t*-Bu)$_4$-diphenoquinone as oxidant, was later used to catalyze the reaction between aldehydes **126** and 5-alkenyl thiazolones **536**. This catalyst gives the adduct (6*S*,7*S*)-**537**, whereas the products with the opposite configuration (6*R*,7*R*)-**537** are obviously obtained by using the enantiomeric catalyst (5a*R*,10b*S*)-**XLVIIa**, which were obtained within excellent yields and selectivities (Scheme 225).[243] The absolute configuration of both enantiomeric products have been unambiguously determined by X-ray analysis.

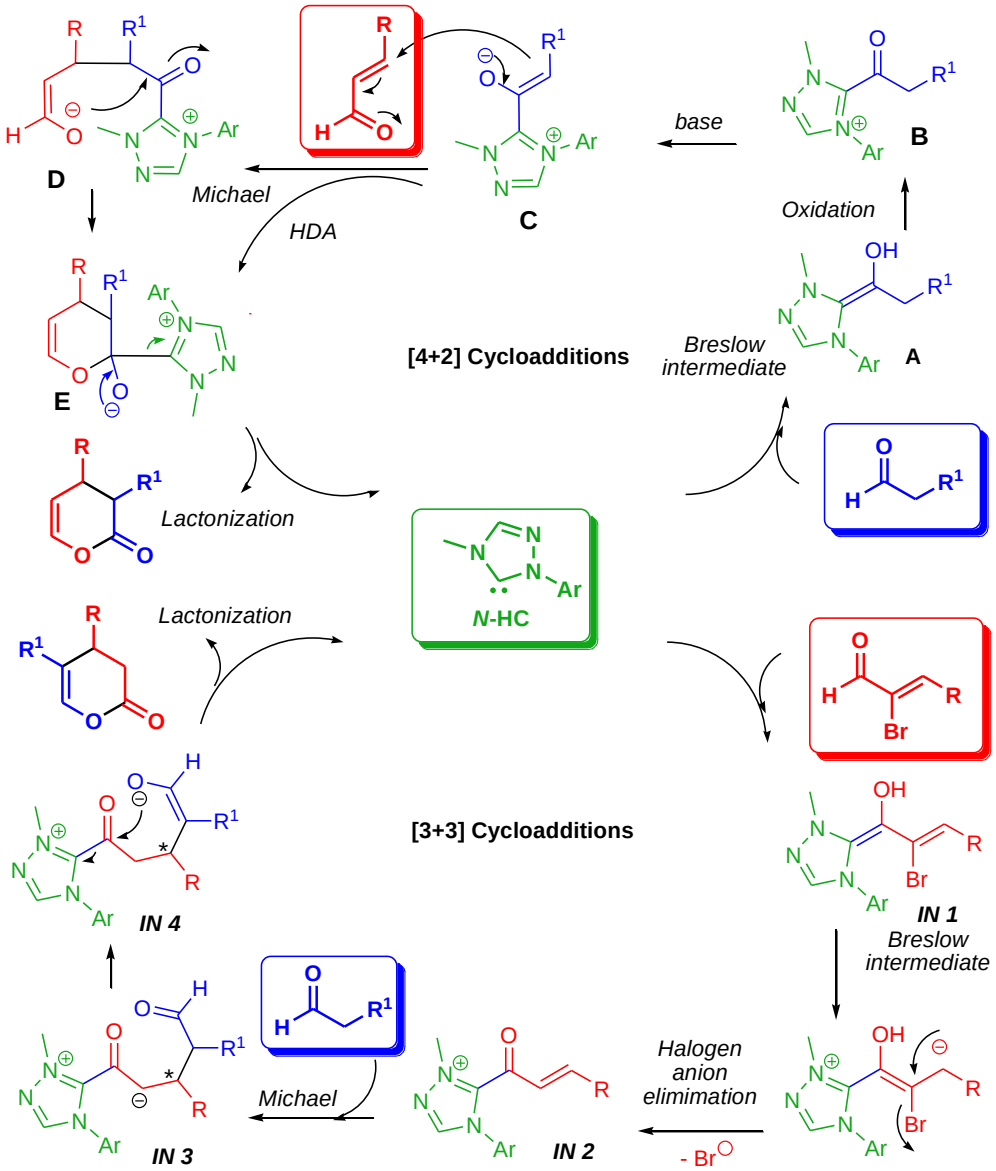
Scheme 225. The *Oxidative N*-HC-Catalyzed [4+2] Cycloaddition Between Aldehydes 126 and 5-Alkenyl Thiazolones 536 Catalyzed by (5a*S*,10b*R*)-XLVIIa.[243]



Even if the products of the [4+2]-cycloaddition are always obtained with excellent diastereo- and enantioselectivity, there is a clear unexpected discrepancy in the induced absolute configuration of the products by using the same catalyst in the reactions involving **189** and **536** as the electrophile.

The mechanism of the [4+2]-cycloaddition between α,β-unsaturated carbonyl compounds and aldehydes, already discussed in Scheme 85, is proposed in the upper part of Scheme 226.

Scheme 226. Mechanisms of [4+2]-Cycloadditions Between α,β-Enones and Aldehydes (up) *versus* [3+3] Cyclization Between Aldehydes and α-Halo-enals (bottom).



The free carbene reacts with the aldehyde to give the Breslow intermediate **A**, which is oxidized to the acyl azolium **B**. Its deprotonation gives the enolate **C** whose reaction with the α,β-

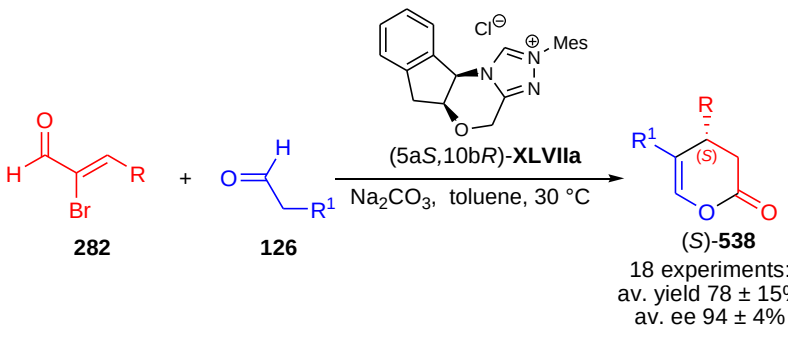
unsaturated carbonyl compounds may occur through a Michael intermediate **D** that cyclize to **E**, or directly to this via a HDA reaction. The carbene is released from **E** to give the lactam product.

If the α,β-unsaturated carbonyl compound is an α-halo-enal, the reaction takes a different pathway. The above pathway is in competition with cycloadditions in which both the acceptor and the donor reagents act as three-atoms partners of a [3+3] cycloaddition (see Scheme 226, bottom). The mechanism now involves the nucleophilic addition of the *N*-HC catalyst that affords the Breslow intermediate ***IN 1***. This is deprotonated by the base and the loss of bromine leads to the α,β-unsaturated acylazolium key intermediate ***IN 2***, which undergoes the Michael addition of the nucleophilic carbonyl derivative to its β-position with formation of a chiral center in the addition product ***IN 3***. The subsequent lactonization through the intermediate ***IN 4*** yields the final 3,4-dihydro-4,5-disubstituted pyran-2-one. The next section is devoted to this alternative pathway.

3.2. The *N*-HC-Catalyzed [3+3] Cycloaddition Between α-Haloenals and Carbonyl Derivatives.

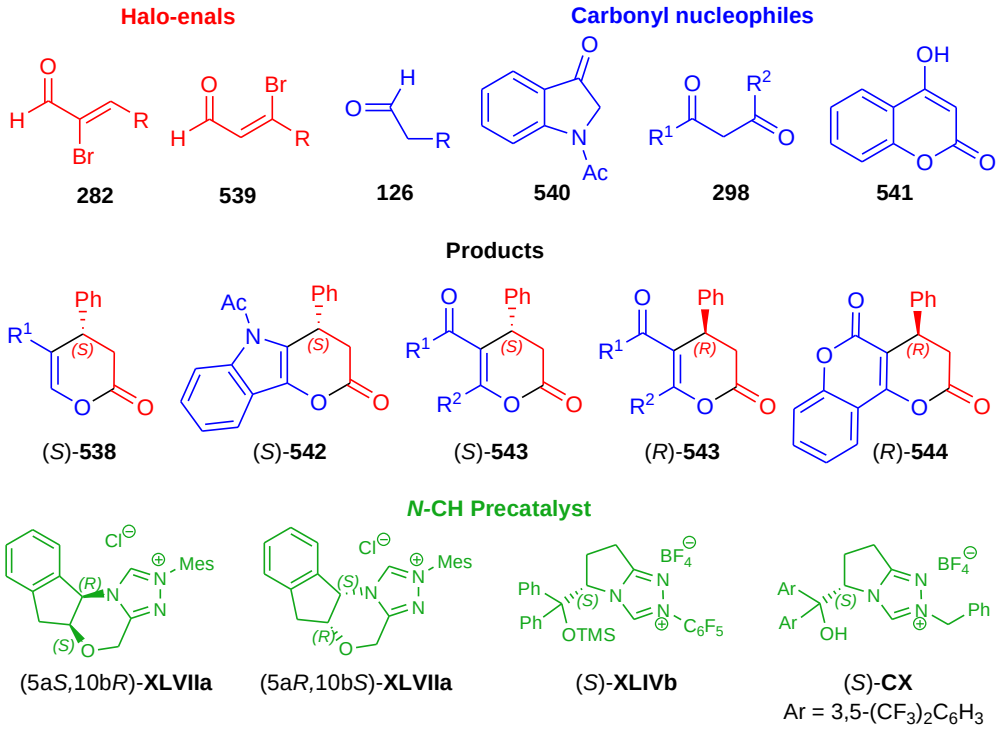
The reaction of α-bromo-enals **282** and aldehydes **126** can be usefully catalyzed by the triazolium *N*-CH precursors (5a*S*,10b*R*)-**XLVIIa** in the presence of Na_2CO_3 as a base. The reaction, through a highly enantioselective [3+3] cyclization, gives 4,5-disubstituted dihydropyran-2-ones (*S*)-**538** within very good yields and excellent enantioselectivities, whose absolute configuration was determined by single-crystal X-ray analysis (Scheme 227).[244]

Scheme 227. The *N*-HC-Catalyzed [3+3] Cyclization Between Aldehydes 126 and α-Bromo-enals 282 Catalyzed by (5a*S*,10b*R*)-XLVIIa.[244]



In recent years several reactions with α-bromo-enals **282** and different carbonyl nucleophiles, catalyzed by *N*-CHs, have been reported in the literature and the reagents, the catalysts, and the products are reported in Chart 10, while Table 20 collects the results in terms of yields and enantioselectivity.[244-249] In general, all reactions involve the participation of α-bromo-enal **282** as the electrophilic component. However, in one case the reaction is run also on β-bromo-enal **539**, which reacts with β-dicarbonyl compounds **298** as the nucleophilic component. The results obtained with both the bromo-enals **282** and **539** are reported in Table 20, entries 3 and 5.[246,248]

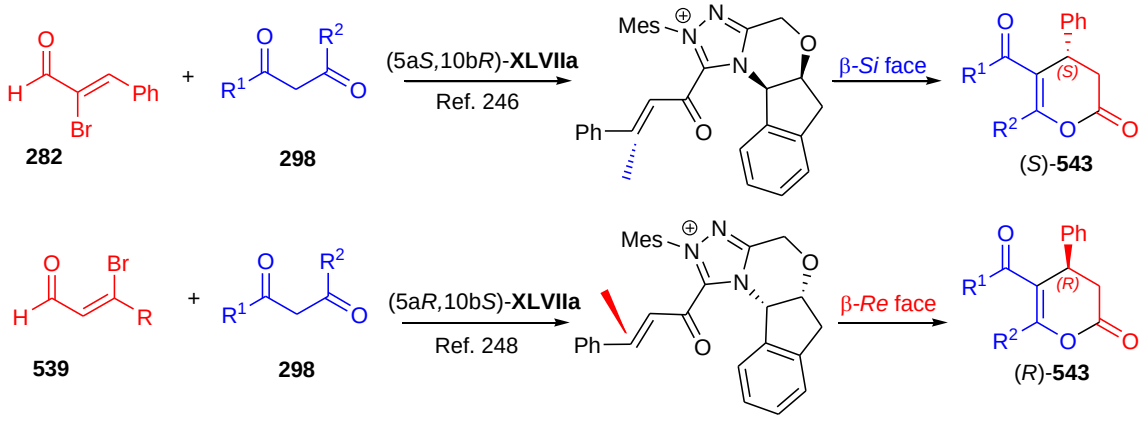
Chart 10. Reagents, Organocatalysts, and Products of the *N*-HC-Catalyzed [3+3] Cyclizations Between α-Halo-enals and Carbonyl Derivatives.



Both reactions give the same adduct **543**, even if the reactions involving β-bromo enals **539** proceeds with yields and enantioselectivity slightly lower than those obtained starting from the α-bromo derivatives **282**. In any case, the opposite stereochemistry obtained by using the enantiomeric catalysts **XLVIIa**, (5a*S*,10b*R*)-**XLVIIa** for the reaction of **282** and (5a*R*,10b*S*)-**XLVIIa** for that of **539**, is fully consistent with a mechanism involving the same intermediate ***IN 2***

independently from the α- or β-position of the bromine in the electrophilic component. The steric-controlled addition of **298** to the enantiomeric intermediate ***IN 2*** will obviously furnish the opposite enantiomers of the same adduct, (*S*)-**543** and (*R*)-**543**, respectively (Scheme 228).

Scheme 228. The [3+3] Cyclization Between Bromo-enals 282 and 539 with 298 Catalyzed by (5a*S*,10b*R*)- and (5a*R*,10b*S*)-XLVIIa, with Their Respective Cinnamoyl-triazolium Intermediates.[246,248]



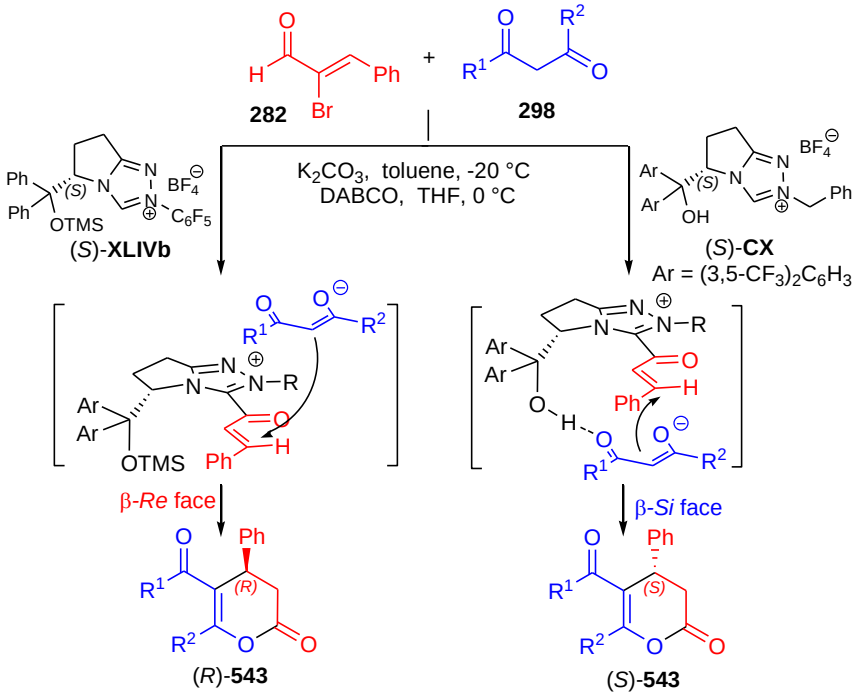
The reaction of α-bromo-enals **282** and β-dicarbonyl derivatives **298** can be usefully catalyzed by two (*S*)-pyrrolo[2,1-*c*][1,2,4]triazolium *N*-CH precursors (*S*)-**XLIVb** and (*S*)-**CX** (Scheme 229). The reactions, through a highly enantioselective [3+3] cyclization, give the (*R*)- and (*S*)-5-acyl-3,4-dihydro-4,6-disubstitutedpyran-2-ones (*R*)- and (*S*)-**543**, respectively, in very good yields and enantioselectivities (Table 1, entries 6 and 7).[249]

It seems important to point out that two *N*-CH chiral catalysts with the same (*S*) configuration give opposite stereochemical induction. This is due to the TMS protection of the hydroxyl group in (*S*)-**XLIVb** that induces the attack of the nucleophile from the less sterically hindered *β-Re* face of the azolium intermediate. On the other hand, the free OH of (*S*)-**CX** binds the nucleophile **298** to the azolium intermediate with hydrogen bonding, hence forcing the attack to occur intramolecularly, on the *β-Si* face giving (*S*)-**543**.[249]

Table 20. Average Values and Standard Deviations (s.d.) of the Reaction Yields, Diastereo-, and Enantioselectivities of the *N*-HC-Catalyzed [3+3] Cyclizations between α-Halo-enals and Carbonyl Derivatives for Reagents, Organocatalysts, and Products in Chart 10.

Entry	α-Halo-enals	Carbonylic Nucleophile	*N*-HC Organocatalyst	n. Exp.	Reaction Product	aver. Yield % (s.d.)	aver. ee % (s.d.)	Attached Face	Ref.
1	**282**	**126**	(5a*S*,10b*R*)-**XLVIIa**	18	(*S*)-**538**	78 (15)	94 (4.0)	β-*Si*	244
2	**282**	**540**	(5a*S*,10b*R*)-**XLVIIa**	12	(*S*)-**542**	66 (4)	91 (8)	β-*Si*	245
3	**282**	**298**	(5a*S*,10b*R*)-**XLVIIa**	16	(*S*)-**543**	86 (6)	93 (5.5)	β-*Si*	246
4	**282**	**541**	(5a*S*,10b*R*)-**XLVIIa**	4	(*R*)-**544**	79 (10.5)	80.5 (5.5)	β-*Re*	247
5	**539**	**298**	(5a*R*,10b*S*)-**XLVIIa**	12	(*R*)-**543**	71 (14)	87 (9)	β-*Re*	248
6	**282**	**298**	(*S*)-**XLIVb**	12	(*R*)-**543**	75 (17)	89 (7)	β-*Re*	249
7	**282**	**298**	(*S*)-**CX**	12	(*S*)-**543**	78 (19)	84.5 (13)	β-*Si*	249

Scheme 229. The [3+3] Cyclization Between α-Bromo-enals and β-Dicarbonyl Compounds Catalyzed by *N*-CHs (*S*)-XLIVb and (*S*)-CX.[249]

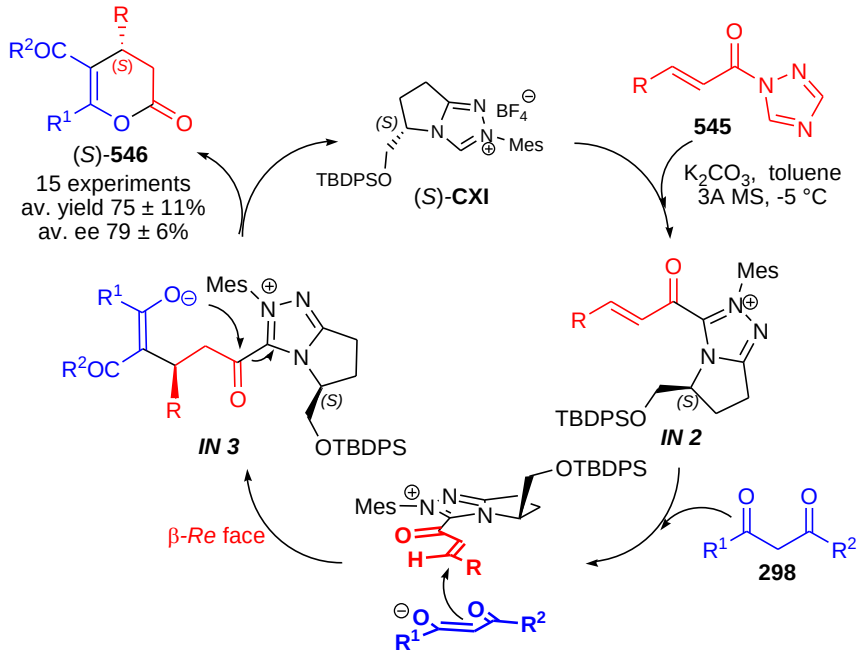


Recently, the *N*-HC activation of α,β-unsaturated *N*-acyltriazoles **545** has been described (Scheme 230).[250] This interesting reaction is mechanistically related to that described in the left part of Scheme 229. The reaction between **545** and the β-dicarbonyl compound **298**, catalyzed by *N*-CH derived by (*S*)-**CXI** occurs through the formation of the acylazolium intermediate (***IN 2***), which undergoes the Michael addition of **298** on the less hindered *β-Re* face to give (***IN 3***) with an (*S*) configuration that is transferred by intramolecular lactonization to furnish the target product (*S*)-**546** within good yields and moderate enantioselectivities. The absolute configuration of **546** was unambiguously determined by X-ray crystal-structure analysis.[250]

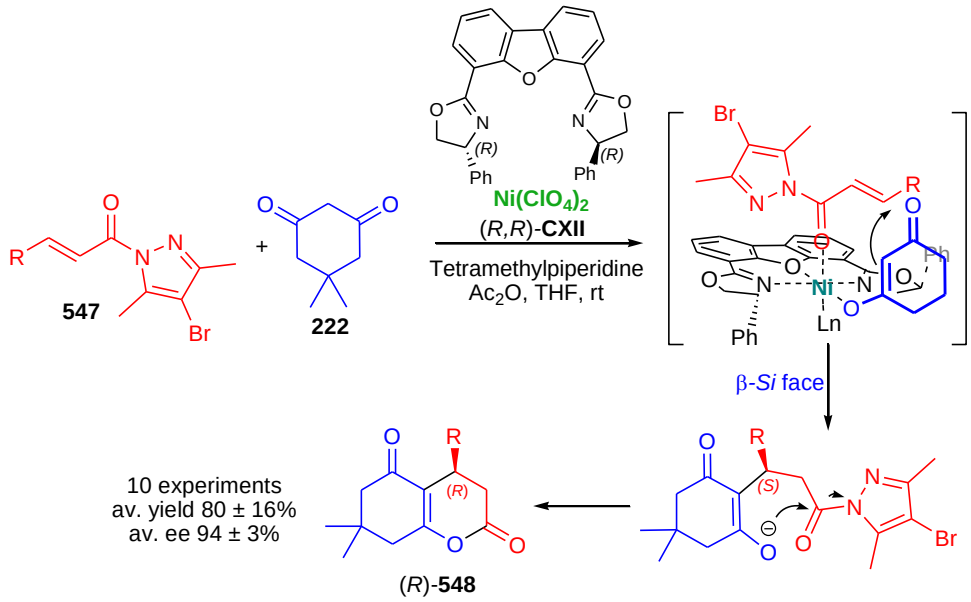
The pathway reported in Scheme 230 has strong analogies with that of the [(*R*,*R*)-diPh-DBFOX/Ni(ClO_4)$_2$]-catalyzed reaction of dimedone **222** with 1-(4-bromo-3,5-dimethyl-1*H*-pyrazol-1-yl)-3-phenylprop-2-en-1-one **547** that gives 3,4,7,8-tetrahydro-7,7-dimethyl-4-phenyl-6*H*-chromene-2,5-dione (*R*)-**548** (Scheme 231).[251] Two "*small details*" differentiate this Michael reaction from that in Scheme 230: The chiral induction derives from that of the reacting

intermediate [(*R*,*R*)-diPh-DBFOX/Ni/**547**/**222**] instead of that belonging to ***IN 2***, and the leaving group is 4-bromo-3,5-dimethyl-1*H*-pyrazole instead of *N*-HC.

Scheme 230. The [3+3] Cyclization Between α,β-Unsaturated *N*-Acyltriazoles 545 and β-Dicarbonyl Compounds 298 Catalyzed by *N*-HC (*S*)-CXI.[250]



Scheme 231. The DBFOX/Ni-catalyzed [3+3] Cyclization Between α,β-Unsaturated *N*-Acylpyrazole 547 and Dimedone 222.[251]



3.3. The *Oxidative N*-HC-catalyzed [3+3] Cyclization of Enals with Carbonyl Nucleophiles and Phenols.

In the previous section we discussed the [3+3] cyclization between α-bromo-enals **282** and aldehydes **126** catalyzed by *N*-HC precursor (5a*S*,10b*R*)-**XLVIIa** to give (*S*)-**538** in very good yields and excellent enantioselectivities.[244] The bromine atom behaves as a leaving group whose elimination furnishes the cinnamoyl-triazolium intermediate. The same result can be obtained if the reaction between cinnamaldehyde (**271**) and phenylacetaldehyde (**126**), catalyzed by (5a*S*,10b*R*)-**XLVIIa**, is run in the presence of 3,3',5,5'-(*t*-Bu)-4-diphenoquinone as the *oxidant*.[244] The oxidative step in the mechanism transforms the Breslow intermediate ***IN 1*** into the acylazolium intermediate ***IN 2***; then, a Michael addition to its *β-Si* face determines the absolute configuration of the product (***IN 3*** that tautomerizes to ***IN4***), and the final lactonization affords (*S*)-**538**, which is obtained in low yield (33%), but with an excellent 98% ee (Scheme 232).[244]

Scheme 232. The Oxidative [3+3] Cyclization Between Cinnamaldehyde 271 and Phenylacetaldehyde 126 Catalyzed by (5a*S*,10b*R*)-XLVIIa.[244]

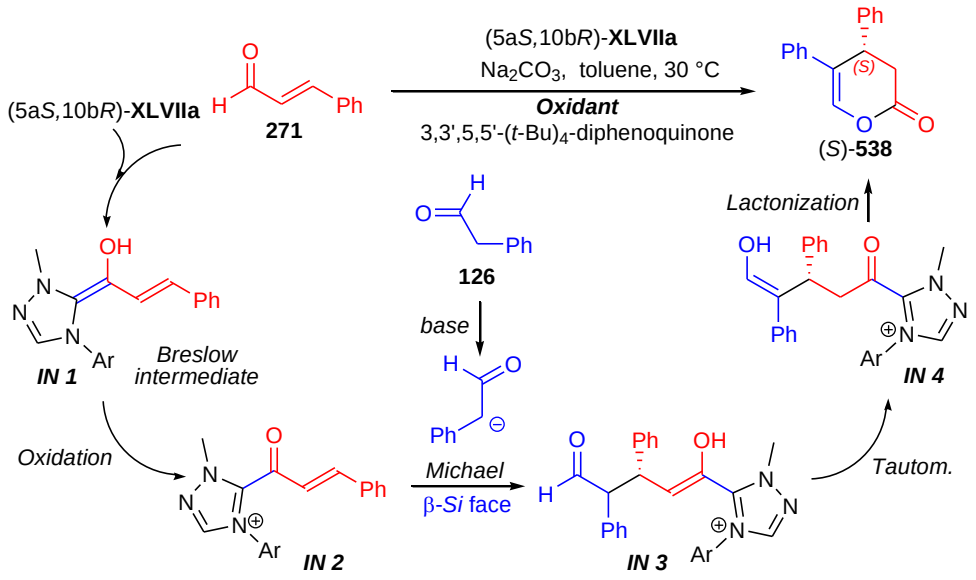
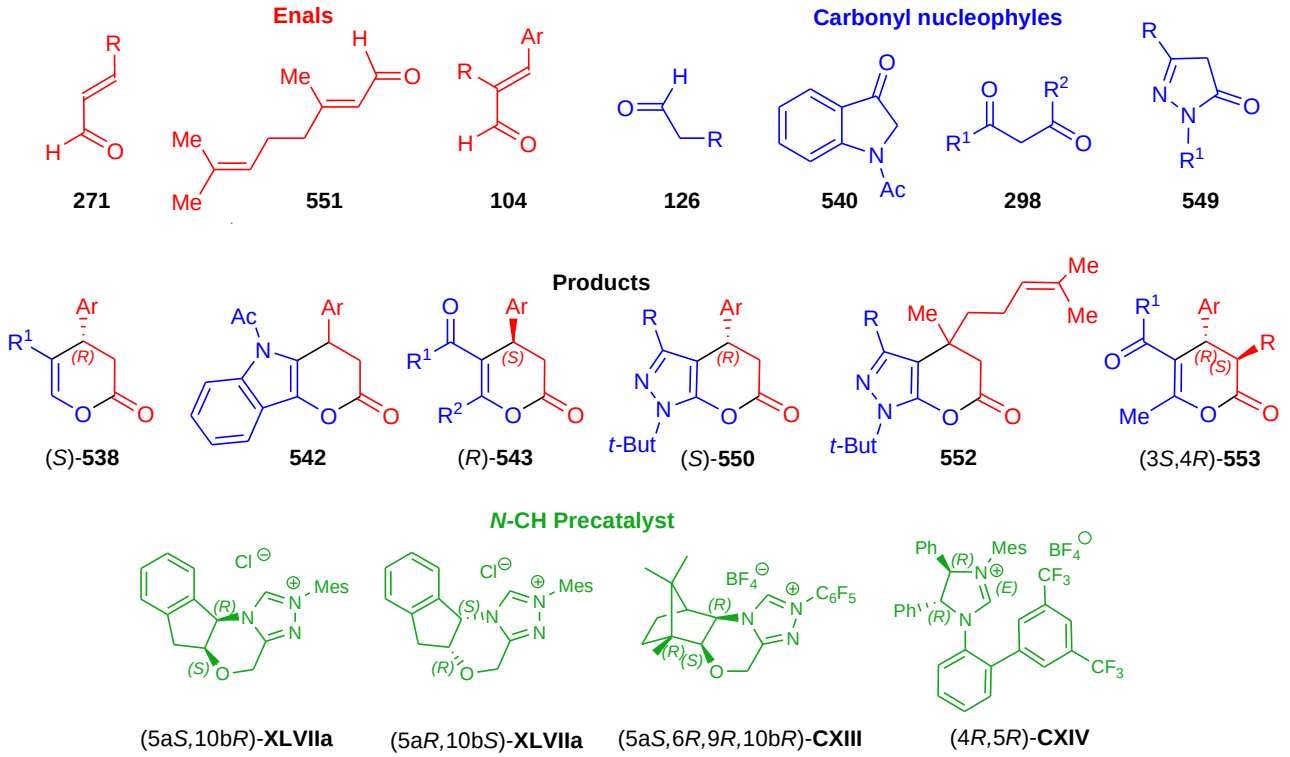


Chart 11 reports reagents, products, catalysts, while Table 21 collects the results for several examples of oxidative reactions between α,β-enals and different carbonyl nucleophiles that were catalyzed by *N*-CHs and reported in recent literature.

Chart 11. Reagents, Organocatalysts, and Products of the *N*-HC-Catalyzed [3+3] Cyclizations between Enals and Carbonyl or Naphthol Derivatives.



The reaction was also tested with various 1- and 2-naphthols **554a,b** as nucleophiles, which adds to the acylazolium intermediate ***IN 2*** derived from α,β-unsaturated aldehyde **271** and the precatalyst (5a*R*,10b*S*)-**XLVIIa**, in the presence of oxidant, to give 3,4-dihydro-4-phenylbenzo [*h*]chromen-2-ones (*R*)-**555a** and 1,2-dihydro-1-phenylbenzo[*f*]chromen-3-ones (*R*)-**555b**, respectively (Scheme 233). Sometimes by products were observed leading to diminished chemical yields.[256]

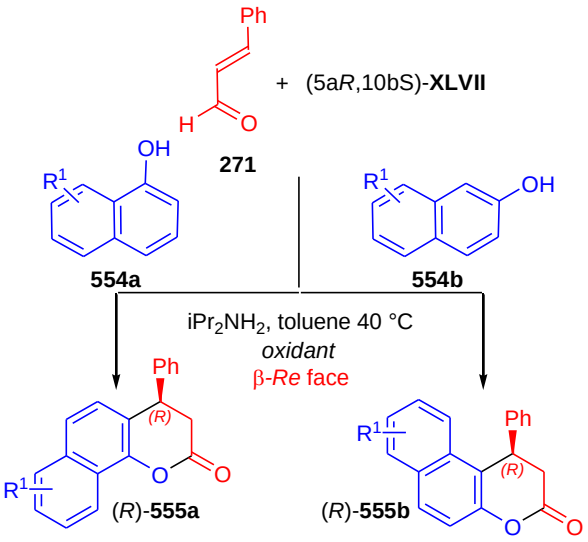
In addition to several experiments performed with (5a*S*,10b*R*)- and (5a*R*,10b*S*)-**XLVIIa** as precatalysts of indeno-oxazinetriazolium *N*-CHs, which are by far the most popular carbene catalysts tested, the reactions described deserve attention because two new heterocyclic carbenes were used. The camphor-derived triazolium salt (5a*S*,6*R*,9*R*,10b*R*)-**CXIII** and the imidazolium-based salt (*R*,*R*)-**CXIV,** which were the precatalysts for the reactions described in entries 5 and 6 of Table 21 and the enantioselectivities resulted excellent for both the reactions.[254,255]

Table 21. Average Values and Standard Deviations (s.d.) of the Reaction Yields, Diastereo-, and Enantioselectivities of the *N*-HC-Catalyzed [3+3] Cyclizations between Enals and Carbonyl or Naphthol Derivatives for Reagents, Organocatalysts, and Products in Chart 11.

Entry	Enals	Carbonylic Nucleophile	*N*-HC Organocatalyst	n. Exp.	Reaction Product	aver. Yield % (s.d.)	aver. ee % (s.d.)	Attached Face	Ref.
1	**271**	**126**	(5a*S*,10b*R*)-**XLVIIa**	1	(*S*)-**538**	33	98	β-*Si*	244
2	**271**	**549**	(5a*S*,10b*R*)-**XLVIIa**	22	(*S*)-**550**	66 (12)	87.5 (6)	β-*Si*	252
3	**551**	**549**	(5a*S*,10b*R*)-**XLVIIa**	1	**552**	93	24	---	252
4	**271**	**540**	(5a*R*,10b*S*)-**XLVIIa**	1	**542**	76	74	---	253
5	**271**	**298**	(5a*S*,6*R*,9*R*,10b*R*)-**CXIII**	16	(*R*)-**543**	65 (25)	91 (8.5)	β-*Re*	254
6	**104**	**298**	(4*R*,5*R*)-**CXIV**	24	(3*S*,4*R*)-**553**[a]	83 (8)	92 (6)	β-*Si*	255
7	**271**	**554**[b]	(5a*R*,10b*S*)-**XLVIIa**	6	(*R*)-**555**	66 (21)	68 (8)	β-*Re*	256

[(a)] The average de was 71 ± 15%. [(b)] The nucleophiles are α- and β-naphthols.

Scheme 233. Catalytic Enantioselective Oxidative Reactions Between Naphthols 554 and Enals 271 Catalyzed by (5a*R*,10b*S*)-XLVIIa.[256]

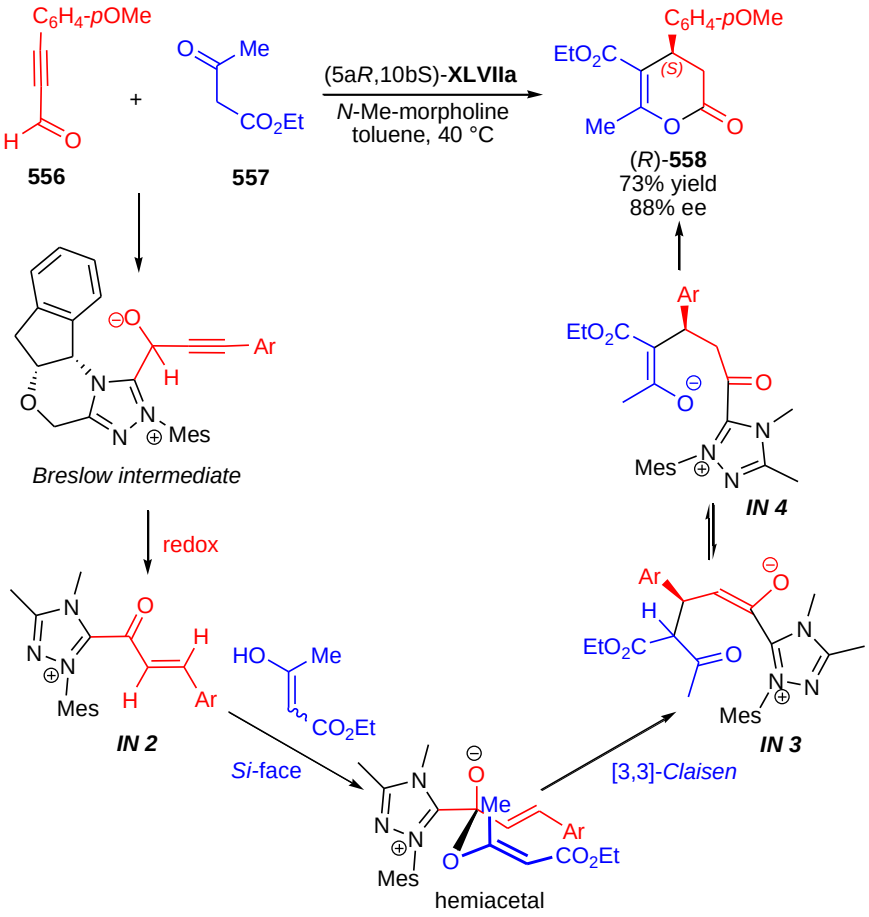


3.4. The [3+3] *N*-HC-Catalyzed Reaction of Ynaldehydes with Enols

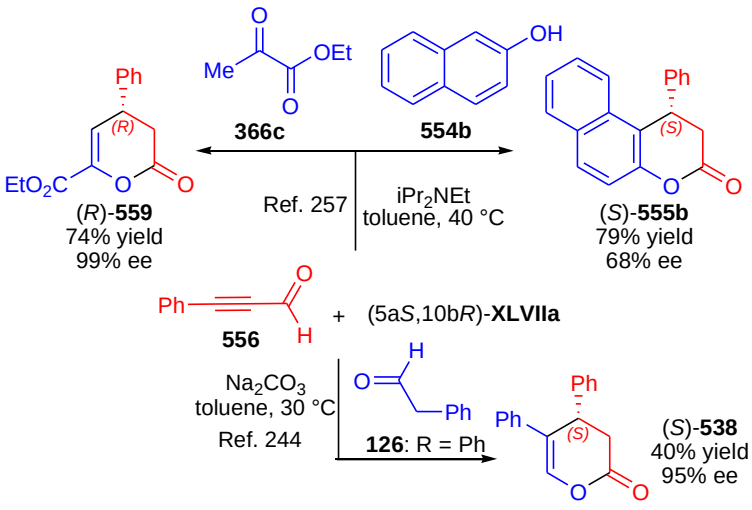
The α,β-unsaturated acyl acylazolium intermediate ***IN 2*** can also be generated from 3-arylpropiolaldehydes **556**, *N*-HC, and a base, through a redox reaction.[256,257] The mechanism of the reaction with ethyl acetacetate **557** acting as nucleophile, catalyzed by (5a*R*,10b*S*)-**XLVIIa**, is reported in Scheme 234 and the absolute configuration of the product **558** is (*R*). The mechanism demonstrated by the authors involves first the formation of the Breslow intermediate that gives the α,β-unsaturated acyl azolium intermediate ***IN 2***. The addition of the enol to the *Si*-face of the carbonyl group gives the hemiacetal that undergoes a [3,3]-Claisen rearrangement, followed by tautomerization and lactonization to give (*R*)-ethyl 5,6-dihydro-2-methyl-6-oxo-4-phenyl-4*H*-pyran-3-carboxylate (*R*)-**558**.

The same mechanism rationalizes the different reactions involving 3-phenylpropiolaldehyde **556** reported in Scheme 235: The reactions with ethyl glyoxylate (**366c**) and 2-naphthol (**554b**),[257] and the reaction with 2-phenylacetaldehyde (**126**).[244] All products, independently from the (*R*) or (*S*) absolute configuration, which depends on the substituent priority, derive from the attack to the *Re*-face of ***IN 2***, which is consistent with that in Scheme 234 if the opposite absolute configuration of the *N*-CH precatalysts involved in the respective reactions is considered.

Scheme 234. Catalytic Enantioselective Reactions Between Ynals 556 and Enols Catalyzed by (5a*R*,10b*S*)-XLVIIa.[256]



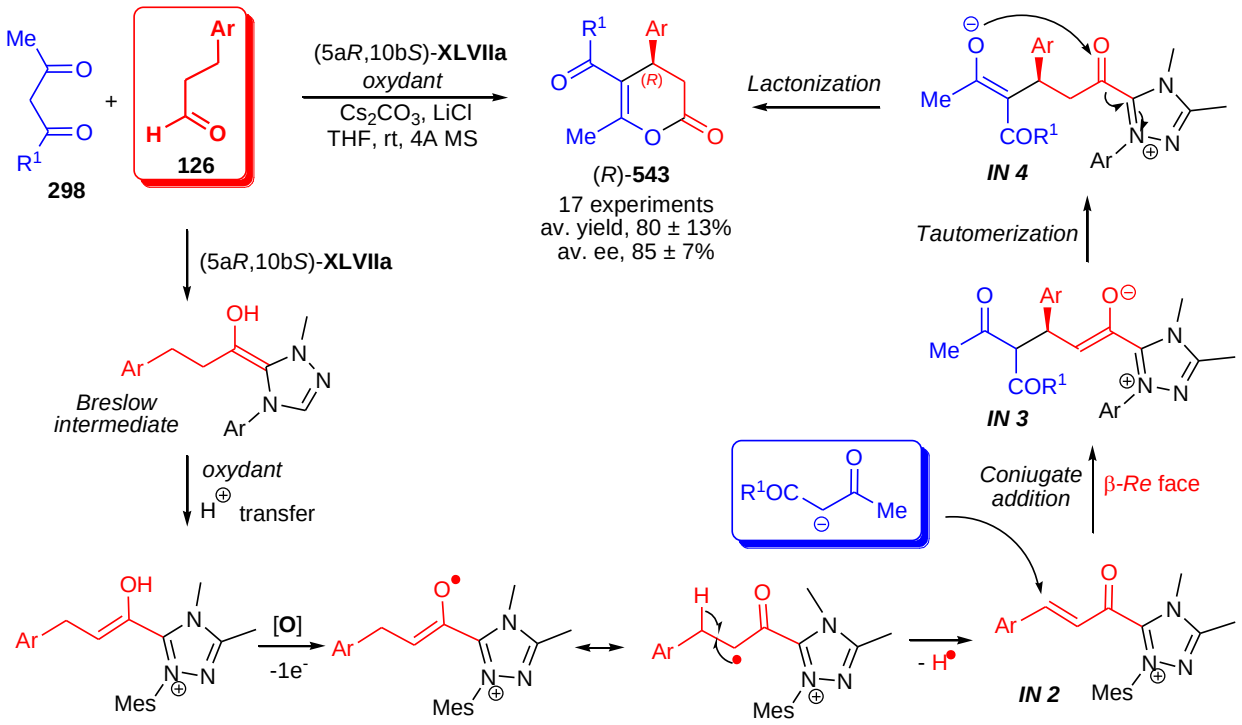
Scheme 235. Catalytic Enantioselective Reactions Between Phenylpropiolaldehyde 556 and Different Nucleophiles Catalyzed by (5a*R*,10b*S*)-XLVIIa.[244,257]



3.5. The *Oxidative* [3+3] *N*-HC-catalyzed Reaction Between Saturated Aldehydes and Carbonyl Nucleophiles

As a further possibility, the α,β-unsaturated acylazolium intermediate ***IN 2*** can also be generated from 3-phenylpropionaldehyde (**126**: R = CH_2Ar) in the presence of (5a*R*,10b*S*)-**XLVIIa**, a base and 3,3',5,5'-(*t*.Bu)-4-diphenoquinone as *oxidant* (Scheme 236)[258]. With ***IN 2*** in hands, the reaction proceeds with different nucleophiles whose anions give a conjugate addition followed by tautomerization and lactonization. As expected, the absolute configuration of the product (*R*)-**543** derives from the attack to the *β-Re* face of ***IN 2*** and several experiments were performed with very good yields and enantioselectivities, suggesting the use of this reaction in a wide range of applications.

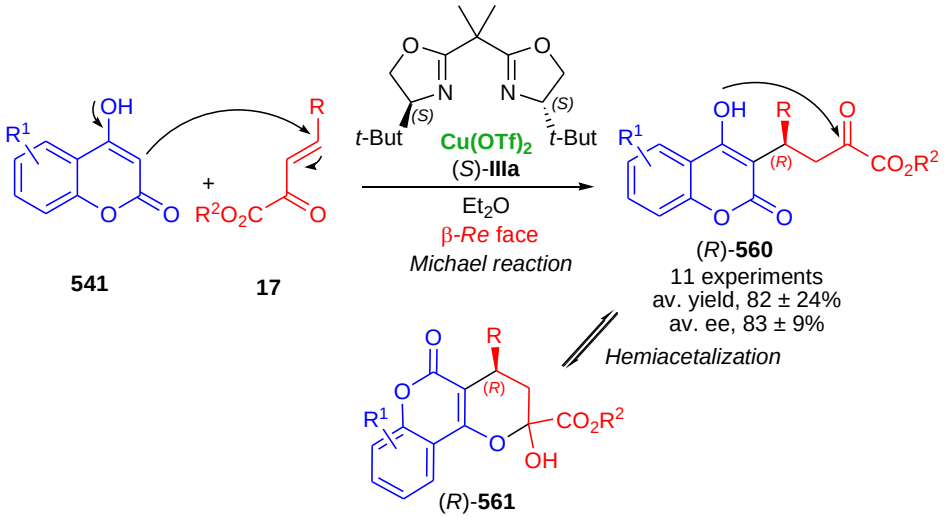
Scheme 236. Catalytic Enantioselective Oxidative Reactions Between Saturated Aldehydes 126 and β-Dicarbonyl Nucleophiles 298 Catalyzed by (5a*R*,10b*S*)-XLVIIa.[258]



3.6. The Enantioselective [3+3] Cyclization to 3,4-Dihydropyrans via [Michael Reaction/Hemiacetalization]

In 2003, Jørgensen *et al.* reported the enantioselective Michael reaction between cyclic 1,3-dicarbonyl compounds and β,γ-unsaturated α-keto esters **17**, catalysed by chiral [BOX-Cu(II)] complex (*S*)-**IIIa** with good yield and enantioselectivity (Scheme 237).[259] The reaction was studied in detail with 4-hydroxycoumarins **541** whose Michael addition products **560**, with an (*R*) absolute configuration, derived from the attack of the nucleophile to the *β-Re* face of the electrophile. Compounds **560** are in equilibrium with the cyclic hemiketals, 2,3,4,5-tetrahydro-2-hydroxy-5-oxo-4-phenylpyrano[3,2-*c*]chromene-2-carboxylates (*R*)-**561**, structures that fit the topic of this review.

Scheme 237 [BOX/Cu(II)]-complex Catalyzed [Michael Reaction/Hemiacetalization] Between 4-Hydroxycoumarins 541 and β,γ-Unsaturated α-Keto Esters 17 Catalyzed by (*S*)-IIIa.[259]

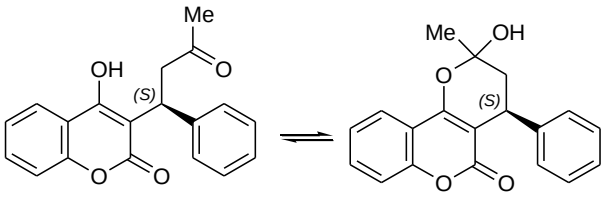


The composition of the tautomeric equilibrium between **560** and **561** is determined by spectroscopic methods and it is a function of solvent, temperature and several other factors. Furthermore, **561** is in general formed as a mixture of two diastereoisomers. We want to point out that this and all other similar adducts will be considered as a single product whose yield is the sum of the different isomers. Their ee and absolute configuration (*the important datum*) refers to the configuration of the chiral center in position 4 of the pyrano[3,2-*c*]chromene subunit that is determined from the Michael attack and is retained in the subsequent equilibrium.

3.6.1. The Enantioselective [3+3] [Michael Reaction/Hemiacetalization] Between 4-Hydroxycoumarin Derivatives and α,β-Unsaturated Carbonyl Derivatives

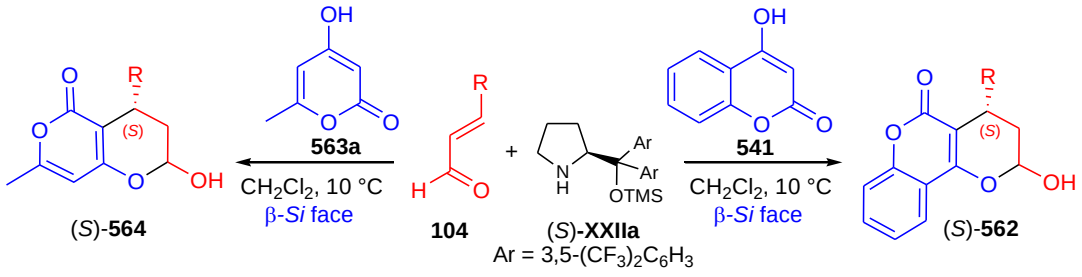
The tautomeric mixtures of the cyclic products obtained from these reactions are *Warfarin* analogues, compound used as anticoagulant for more than half a century, and this explain the interest generated by the reaction (Scheme 238).

Scheme 238. The Tautomeric Equilibrium of *Warfarin*



Among the large number of catalysts tested in order to improve reactivity and enantioselectivity, few years after the Jørgensen's contribution, the reaction of 4-hydroxycoumarin (**541**) and 4-hydroxy-6-methyl-2*H*-pyran-2-one (**563a**) with α,β-unsaturated aldehydes (**104**), with diaryl[(*S*)-pyrrolidin-2-yl]methoxy]trimethylsilane (*S*)-**XXIIa** (Ar=3,5-$(CF_3)_2$-C_6H_3), as organocatalyst was published (Scheme 239).[260] After the Michael addition, the acetalization gave the 3,4-dihydro-2-hydroxy-4-substituted-pyrano[3,2-*c*]chromen-5(2*H*)-ones (**562**) and 3,4-dihydro-2-hydroxy-4-substituted-pyrano[3,2-*c*]pyran-5(2*H*)-ones (**564**), both with the (*S*) absolute configurations, and with excellent enantioselectivities.

Scheme 239. Organocatalyzed [Michael Reaction/Acetalization] of 4-Hydroxycoumarin (541) and 4-Hydroxy-6-methyl-2*H*-pyran-2-one (563a) with α,β-Unsaturated Aldehydes 104 Catalyzed by (*S*)-XXIIa.[260]



In addition to the synthetic protocols above reported, several other reactions were performed involving γ,δ-unsaturated α-keto esters **17** or arylidene-2-acetylpyridine-*N*-oxide **20**, with 4-hydroxycoumarins (**541**) or 4-hydroxy-2*H*-pyran-2-ones (**563a**), catalyzed by either the chiral complexes or organocatalysts (**CXV-CXXI**) reported in Chart 12. The results in terms of number of examples, average yields and average enantioselectivity are listed in Table 22. Few different enolic nucleophiles have also been tested, somewhat related to **541** or **563a**: **563b**, **568**, and **570**, whose reaction products are reported in Chart 12 and the results, of not leading importance, are also listed in Table 22. Depending on the reaction conditions, the products isolated from these reactions are described as Michael adducts or cyclic hemiketals. As emphasized before, both products have one defined chiral center, having the same absolute configuration in both structures. When the absolute configuration is determined by X-ray analysis and the product has the hemiketalic structure, the second chiral center is sometimes defined, although it is irrelevant in the discussion of the chirality induction. Hence, the reaction adducts can be considered a single product, the Michael adduct in equilibrium with its cyclic hemiketal.

It is interesting to note that the reactions listed in entries 9, 10, and 14-16 (Table 22) gave products having an (*R*) absolute configuration, deriving from the attack of **17** to the *β-Re* face of **541**.

Concerning the organocatalysts, all the thiourea- or squaric acid-derivatives have a common (*S*) configuration of the carbon atom adjacent to the NH that is involved in the hydrogen bonding with the carbonyl group of the ester.[268] Hence, it seems reasonable to consider this chiral center of the catalyst as the responsible of the transmission of the chirality to the products.

Cyclic enones **572** are a special α,β-unsaturated system with a rigid structure and their reaction with 4-hydroxycoumarin **541** follows the same sequence of reactions, but with a different structural result.

Chart 12. Reagents, Organocatalysts, and Products of the Enantioselective Catalyzed [3+3] [Michael Reaction/Hemiacetalization] of 4-Hydroxycoumarins, 4-Hydroxy-2*H*-pyran-4-ones, and Some Derivatives, with α,β-Unsaturated Carbonyl Derivatives.

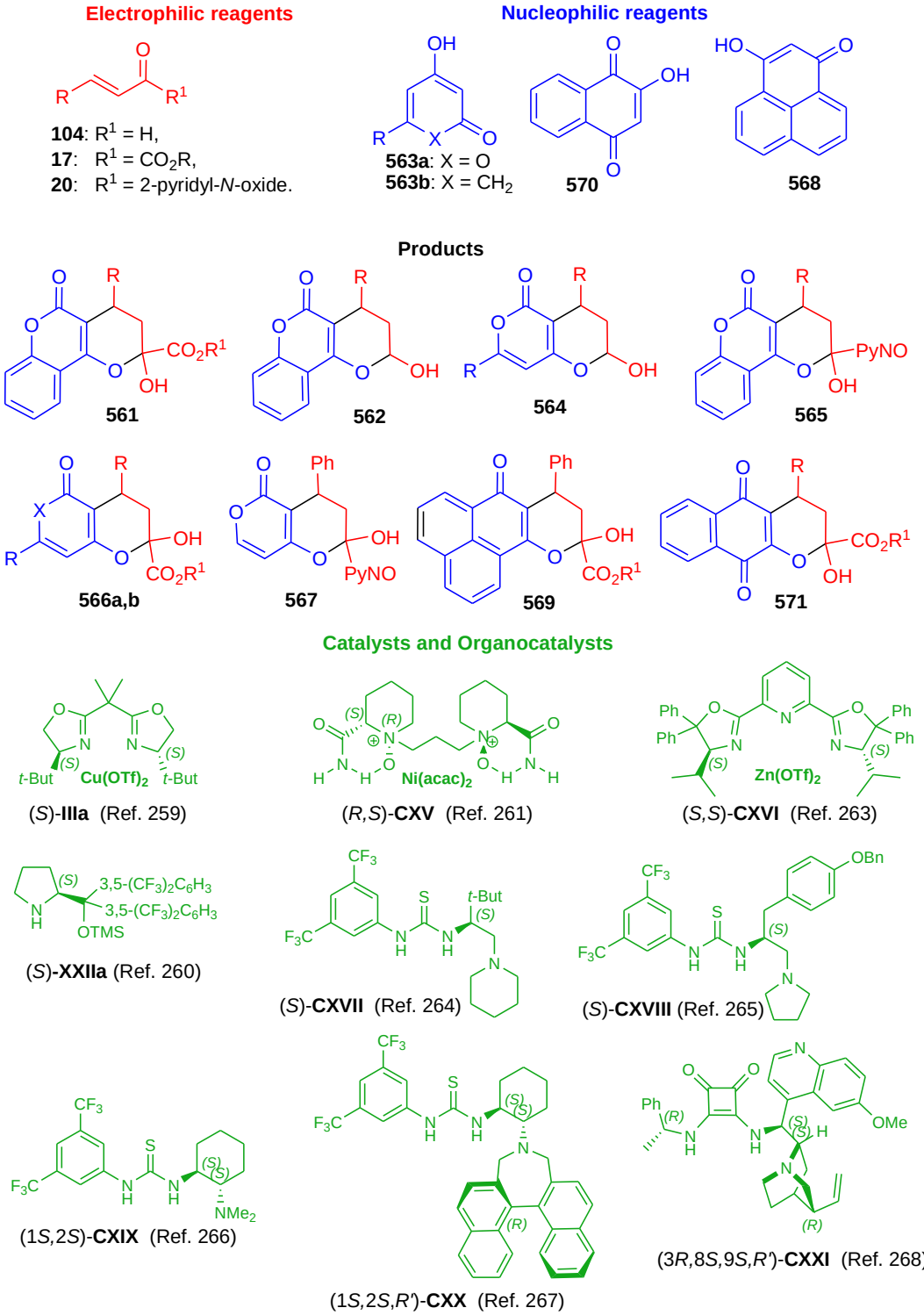


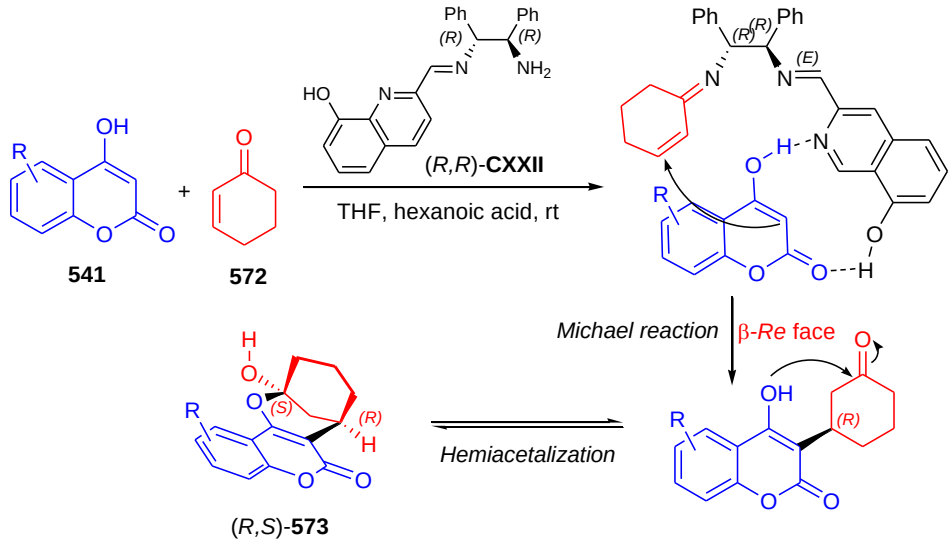
Table 22. The Enantioselective [3+3] [Michael Reaction/Hemiacetalization] of 4-Hydroxycoumarins, 4-Hydroxy-2*H*-pyran-4-ones, and Some Derivatives, with α,β-Unsaturated Carbonyl Derivatives Catalyzed by Chiral Complexes or Organocatalysts Reported in Chart 12.

Entry	Electrophile	Hydroxy Nucleophile	Catalyst	n. Exp.	Reaction Product	aver. Yield % (s.d.)	aver. ee % (s.d.)	Attached Face	Ref.
1	**17**	**541**	(*S*)-**IIIa**	11	(*R*)-**561**	82 (24)	83 (9)	*β-Re*	259
2	**17**	**563a**	(*S*)-**IIIa**	2	**566a**	87 (2)	77 (8)	---	259
3	**17**	**568**	(*S*)-**IIIa**	2	**569**	75 (28)	63 (19)	---	259
4	**104**	**541**	(*S*)-**XXIIa**	9	(*S*)-**562**	71 (18)	93 (2)	*β-Si*	260
5	**104**	**563a**	(*S*)-**XXIIa**	9	(*S*)-**564**	67 (19)	87 (4)	*β-Si*	260
6	**17**	**541**	(*R,S*)-**CXV**	13	(*S*)-**561**	95 (5)	88 (1)	*β-Si*	261
7	**547**	**541**	(*S,S*)-**CXVI**	12	(*R*)-**561**	93 (6)	81 (12)	*β-Re*	263
8	**547**	**563a**	(*S,S*)-**CXVI**	1	**566a**	90	96	---	263
9	**17**	**541**	(*S*)-**CXVII**	17	(*R*)-**561**	96 (2)	95 (2)	*β-Re*	264
10	**17**	**541**	(*S*)-**CXVIII**	13	(*R*)-**561**	95.5 (5)	91 (4)	*β-Re*	265
11	**17**	**563a**	(*S*)-**CXVIII**	2	**566a**	99	93.5 (0.5)	---	265
12	**17**	**563b**	(*S*)-**CXVIII**	2	**566b**	98.5 (0.5)	90.5 (0.5)	---	265

13	**17**	**570**	(*S*)-**CXVIII**	1	**571**	96	77	---	265
14	**17**	**541**	(1*S*,2*S*)-**CXIX**	14	(*R*)-**561**	96 (7)	76 (2)	*β-Re*	266
15	**17**	**541**	(1*S*,2*S,R'*)-**CXX**	11	(*R*)-**561**	87 (11)	90 (49	*β-Re*	267
16	**17**	**541**	(3*R*,8*S*,9*S,R'*)-**CXXI**	32	(*R*)-**561**	82 (8)	94 (3)	*β-Re*	268
17	**572**	**541**	(*R*,*R*)-**CXXII**	18	(*R*,*S*)-**573**	88 (8)	94 (2)	*β-Re*	269

The reaction run in the presence of 2-(*E*)-[(1*R*,2*R*)-2-amino-1,2-diphenylethylimino methyl]quinolin-8-ol [(*R*,*R*)-**CXXII**] as the organocatalyst occurs through an intermediate in which the cyclohex-2-enone forms the imine and 4-hydroxycoumarin is coordinated by a double hydrogen bonding (Scheme 240).[269] The intramolecular Michael attack gives product **573** in very good yields and excellent enantioselectivities (Table 22, entry 17). Its X-ray crystal structure allowed to determine the (*R*) absolute configuration deriving from the attack to the *β-Re* face, and the last hemiacetalization step gives the tetracyclic product with the (*R*,*S*) absolute configuration.

Scheme 240. The Enantioselective [3+3] [Michael Reaction/Hemiacetalization] of 4-Hydroxycoumarin 541 and Cyclic Enones 48 Catalyzed by (*R*,*R*)-CXXII.[269]

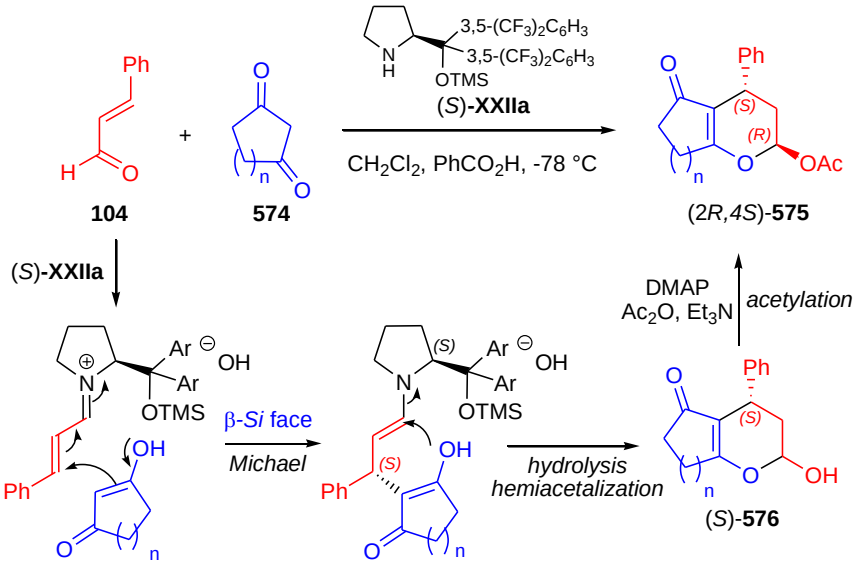


3.6.2. The Enantioselective [3+3] [Michael Reaction/Hemiacetalization] Between 1,3-Dicarbonyl Nucleophiles and α,β-Unsaturated Carbonyl Derivatives.

The already mentioned Michael reaction reported by Jørgensen[259] between α,β-unsaturated carbonyl compounds and 4-hydroxycoumarin was seminal to develop a more general reaction, again based on the sequence *Michael reaction/hemiacetalization*, but with a variety of nucleophiles.

A paradigmatic example is the reaction, developed again by Jørgensen in 2008, between α,β-unsaturated aldehydes **104** and cyclic β-diketones **574** with (*S*)-**XXIIa** (Ar=3,5-$(CF_3)_2$-C_6H_3) as organocatalyst (Scheme 241).[270]

Scheme 241. The Enantioselective [3+3] [Michael/Hemiacetalization] of Enals 104 and Cyclic β-Diketones 574 with (*S*)-XXIIa as Organocatalyst.[270]



The reaction of the enal with the catalyst gives the planar iminium ion that undergoes the Michael addition by β-diketones to the *β-Si* face, which is favoured from the bulk of the C2-substituent in the pyrrolidine ring. The ring closure, followed by hydrolysis, releases the organocatalyst and gives the hemiacetal (*S*)-**576** that, for separation purposes, is acetylated with formation of (2*R*,4*S*)-**575** as the major stereoisomer. The final adducts were obtained within good yields, moderate de, and very good ee (Table 23, entry 1).

In the same years, the analogous reaction between 1,3-cyclohexanone **574a** and enals **104**, with the same organocatalysts (*S*)-**XXIIa** (Ar=Ph or 3,5-$(CF_3)_2$-C_6H_3), was studied by the Rueping′s group (Scheme 242).[271] The results coincide with those reported by Jørgensen since (*S*)-**576** were obtained with good yields and excellent enantioselectivities (Table 23, entry 2).

Scheme 242. The Enantioselective [Michael/Hemiacetalization] Reaction of 104 and 574a Catalysed by (*S*)-XXIIa.[271]

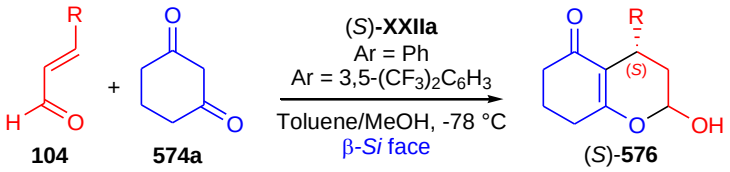
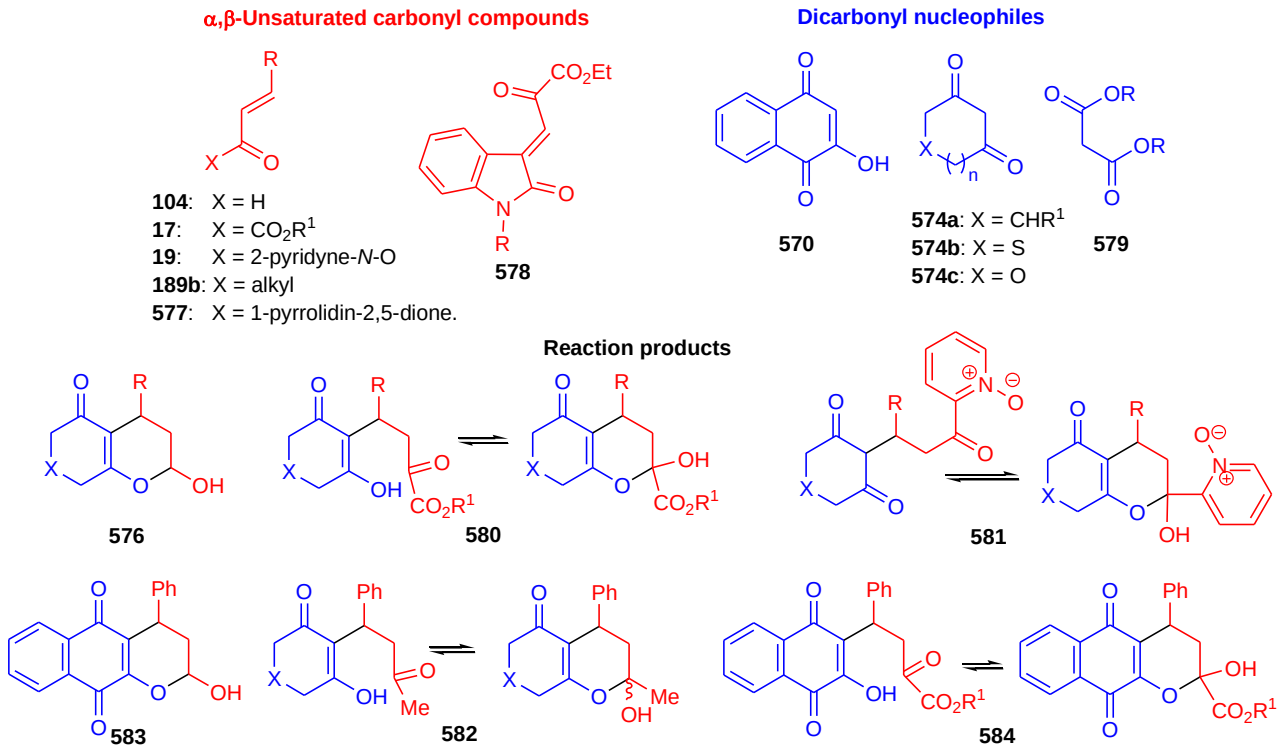


Chart 13. Reagents and Reaction Products of the Enantioselective [3+3] [Michael Reaction/Hemiacetalization] of 1,3-Dicarbonyl Nucleophiles with α,β-Unsaturated Carbonyl Derivatives.

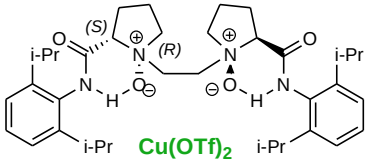


Later, the same reaction between **104** and **574a**, again catalysed by (*S*)-**XXIIa**, was performed under slightly different experimental conditions, and not only (*S*)-**576** was again obtained,[272] but yields and enantioselectivities were again nearly identical (Table 23, entry 3 vs entries 1 and 2).

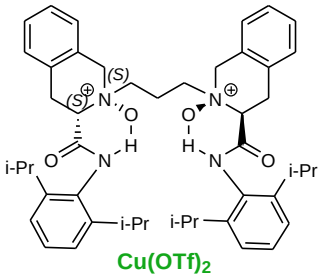
This was the beginning of a series of researches that involved different α,β-unsaturated-carbonyl compounds, with several β-dicarbonyl nucleophiles, either cyclic or acyclic, catalysed by either chiral complexes or organocatalysts. The various starting reagents and the reaction products are summarized in Chart 13, while the catalysts and organocatalysts are shown in Chart 14. The results of the concerned reactions are listed in Table 23, and they deserve a comment. Some catalysts [(*S*)-**XXIIa**, (*S,S*)-**CXVI**, and (*S,S,R*)-**CXX**] have already been tested in the reaction with 4-hydroxycoumarin derivatives (Table 22): The absolute configurations induced are always the same. Whereas the *N,N′*-dioxide Cu(II) complex (*R,S*)-**CXXIII** induces the attack of the nucleophile to the *β-Re* face of **17** (Table 23: entry 5),[273] the similar *N,N′*-dioxide Ni(II) complex

(*R*,*S*)-**CXV** induce the attack of 4-hydroxycoumarin to the *β-Si* face always of **17** (Table 22: entry 6).[261]

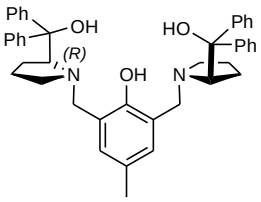
Chart 14. Catalysts and Organocatalysts of the Enantioselective [3+3] [Michael Reaction/Hemiacetalization] of 1,3-Dicarbonyl Nucleophiles with α,β-Unsaturated Carbonyl Derivatives.



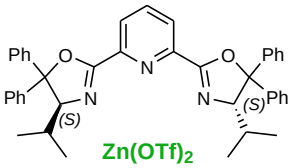
(*R*,*S*)-**CXXIII** (Ref. 273)



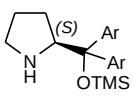
(*S*,*S*)-**CXXIX** (Ref. 274)



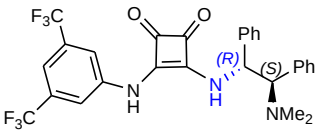
(*R*)-**CXXV** (Ref. 275)



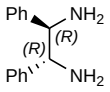
(*S*,*S*)-**CXVI** (Ref. 276)



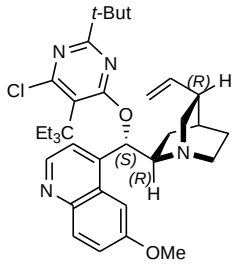
(*S*)-**XXIIa**
Ar = Ph
Ar = 3,5-$(CF_3)_2C_6H_3$
(Ref. 270, 271, 272, 281)



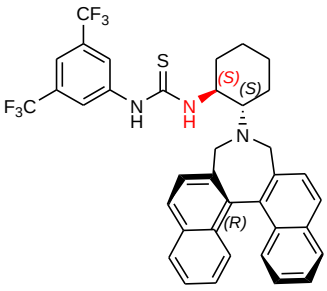
(1*R*,2*R*)-**CIX** (Ref. 277)



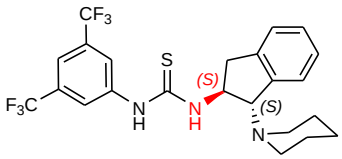
(*R*,*R*)-**CXXVI** (Ref. 279)



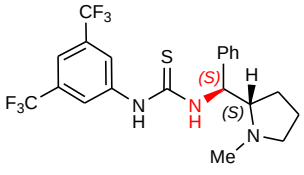
(3*R*,8*R*,9*S*)-**CXXVII** (Ref. 278)



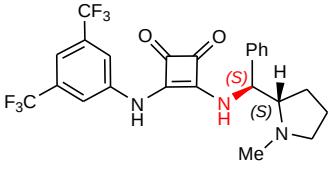
(1*S*,2*S*,*R*')-**CXX** (Ref. 280, 282)



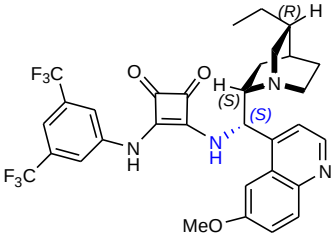
(1*S*,2*S*)-**CXXVIII** (Ref. 283)



(1*S*,2*S*)-**CXXIX** (Ref. 284)



(1*S*,2*S*)-**CXXX** (Ref. 286)



(3*R*,8*S*,9*S*)-**XLIII** (Ref. 285)

Table 23. The Enantioselective [3+3] [Michael Reaction/Hemiacetalization] between 1,3-Dicarbonyl Nucleophiles and α,β-Unsaturated Carbonyl Derivatives Catalyzed by Chiral Complexes or Organocatalysts Reported in Charts 13 and 14.

Entry	Electrophile	Dicarbonyl Nucleophile	Catalyst	n. Exp.	Reaction Product	aver. Yield % (s.d.)	aver. ee % (s.d.)	Attached Face	Ref.
1	**104**	**574**	(*S*)-**XXIIa**	14	(2*R*,4*S*)-**575**[a]	75 (12)	90 (4)	*β-Si*	270
2	**104**	**574a**	(*S*)-**XXIIa**	20	(*S*)-**576**	69 (12)	93 (3)	*β-Si*	271
3	**104**	**574a**	(*S*)-**XXIIa**	8	(*S*)-**576**	71 (8)	93 (6)	*β-Si*	272
4	**104**	**574b**	(*S*)-**XXIIa**	1	(*S*)-**576**[b]	66	>99	*β-Si*	272
5	**17**	**574a**	(*R*,*S*)-**CXXIII**	18	(*R*)-**580**	92 (9)	98 (2)	*β-Re*	273
6	**17**	**574a**	(*S*,*S*)-**CCXXIV**	8	**580**	81 (9)	78 (6)	---	274
7	**17**	**574a**	(*R*)-**CXXV**	23	(*R*)-**580**	79 (20)	82 (22)	*β-Re*	275
8	**19**	**574a**	(*S*,*S*)-**CXVI**	14	(*R*)-**581**[c]	91 (5)	93 (6)	*β-Re*	276
9	**17**	**574a**	(1*R*,2*R*)-**CIX**	23	(*S*)-**580**	85 (6)	96 (4)	*β-Si*	277
10	**189b**	**574a**	(*R*,*R*)-**CXXVI**	23	(*S*)-**582**	84 (11)	93 (3)	*β-Si*	279
11	**17**	**574a**	(3*R*,8*R*,9*S*)-**CXXVII**	7	(*R*)-**580**	88 (13)	97 (2)	*β-Re*	278
12	**17**	**574a**	(1*S*,2*S,R'*)-**CXX**	7	(*R*)-**580**	93 (2.5)	92 (3)	*β-Re*	280
13	**104**	**570**	(*S*)-**XXIIa**	15	(*S*)-**583**	61 (15)	96 (3)	*β-Si*	281

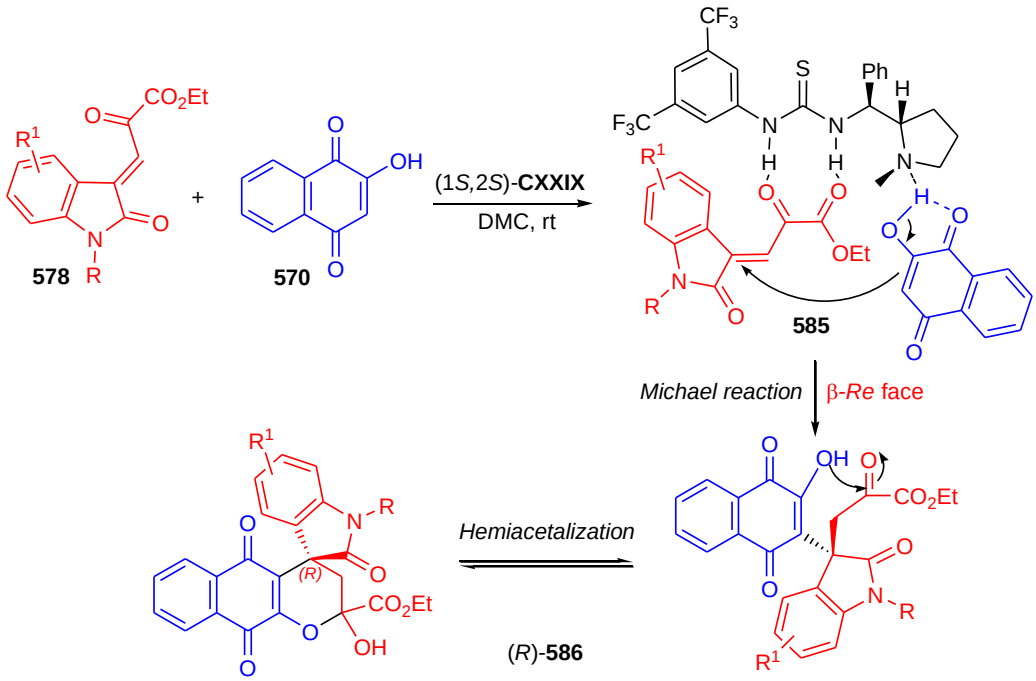
14	**17**	**570**	(1*S*,2*S,R'*)-**CXX**	10	(*R*)-**584**	90 (7)	95 (3)	*β-Re*	282
15	**17**	**570**	(1*S*,2*S*)-**CXXVIII**	16	(*R*)-**584**	97 (1.5)	94 (3)	*β-Re*	283
16	**578**	**570**	(1*S*,2*S*)-**CXXIX**	18	(*R*)-**586**	85 (4)	92 (11)	*β-Re*	284
17	**577**	**574a**	(3*R*,8*S*,9*S*)-**XLIIIb**	10	(*R*)-**588**	84 (12)	77 (11)	*β-Re*	285

[(a)] The average de was 51 ± 15%. [(b)] X = S. [(c)] The configuration refers to the hemiacetalic tautomer.

2-Hydroxy-1,4-naphthoquinone (**570**) can be regarded as a cyclic 1,2,4-tricarbonyl compound whose reaction, in accordance to that of 1,3-dicarbonyl compounds described above, should give 3,4-dihydro-2-hydroxy-2*H*-benzo[*g*]chromene-5,10-dione derivatives. This is what was obtained with α,β-unsaturated aldehydes **104** and (*S*)-**XXIIa** (Ar=3,5-$(CF_3)_2C_6H_3$) as the organocatalyst (Table 23, entry 13).[281] The reaction has several analogies with that illustrated in Scheme 240. It begins with the formation of the intermediate iminium ion that undergoes Michael addition of **570** to its *β-Si* face, acetalization, and hydrolysis to give the expected product (*S*)-**583**. The yields are somewhat poor, but the enantioselectivities are excellent.

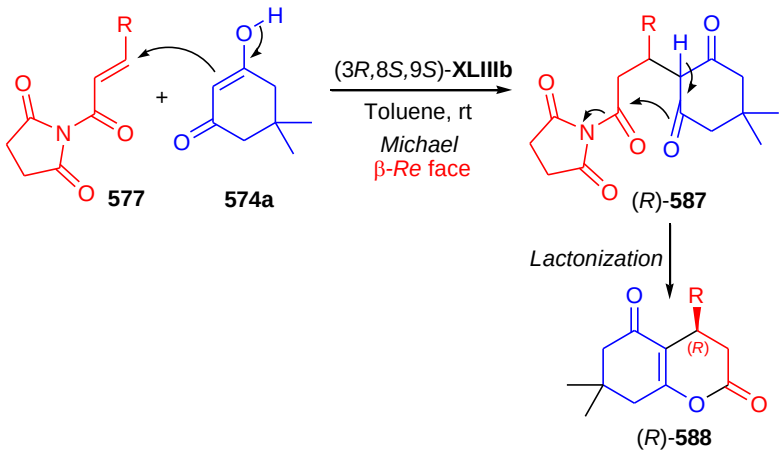
The same reaction with the β,γ-unsaturated α-ketoesters **17** was performed with (1*S*,2*S*)-**CXXVIII** and the already mentioned (1*S*,2*S*,*R'*)-**CXX** as the organocatalysts.[282,283] Both catalysts give excellent yields and enantioselectivities of (*R*)-**584** as resulting from the attach of **570** to the *β-Re* face of **17**, an expected result from two thiourea-based organocatalysts that have the same (*S*) configuration of the carbon atom adjacent to the NH, involved in hydrogen bonding the carbonyl group of the ester (Table 23, entries 14 and 15).[268] A simple comparison of data in Table 23 indicate that the best catalysts for the reaction between **104** and **17** with **574a** are (*R,S*)-**CXXIII** and (3*R*,8*R*,9*S*)-**CXXVII** (Table 23, entry 5, a metal complex, and entry 11, an organocatalyst), whereas for the reaction between **17** and **570** the best organocatalysts are (1*S*,2*S*,*R'*)-**CXX** and (1*S*,2*S*)-**CXXVIII** (Table 23, entries 14 and 15). For these four reactions the extraordinary average enantioselectivity is in the range 94-98% ee. When the α,β-unsaturated carbonyl derivative is ethyl 3-(1-methyl-2-oxoindolin-3-ylidene)-2-oxopropanoate (**578**), 2-hydroxy-1,4-naphthoquinone (**570**) behaves again as an electrophile but, among the different position to be attacked, it prefers that at 3-oxindole giving the Michael adduct reported in the Scheme 243. Then, the hemiacetalization step occurs at the ketonic carbonyl group and the final product is the *spiro* derivative (*R*)-**586**.[284] The absolute (*R*) configuration is consistent with the Michael attack to the *β-Re* face of **578** through the illustrated reacting intermediate **585** in which the organocatalyst (1*S*,2*S*)-**CXXIX** coordinates both reagents. The results are summarized in Table 23 (entries 16).

Scheme 243. Enantioselective [Michael/Hemiacetalization] Reaction of 2-(Oxoindolin-3-ylidene)-2-oxopropanoate (578) and 570 Catalyzed by (1*S*,2*S*)-CXXIX.[284]



All reactions described above, independently from the structure of the α,β-unsaturated carbonyl derivative, occurs through a Michael addition followed by the hemiacetalization step that gives a 3,4-dihydro-2*H*-pyran-2-ol derivative. The reaction between 5,5-dimethyl-1,3-cycloheandione (**574a**) and 1-(3-substituted-acryloyl)pyrrolidin-2,5-dione (**577**), with (3*R*,8*S*,9*S*)-**XLIIIb** as organocatalyst, has a different behaviour (Scheme 244).[285]

Scheme 244. Enantioselective [Michael/Lactonization] Between 1-(3-Substituted-acryloyl) pyrrolidin-2,5-dione (577) and 574a Catalyzed by (3*R*,8*S*,9*S*)-XLIIIb.[285]



After the Michael step, the product **587** undergoes an intramolecular acylic substitution, favoured by the presence of pyrrolidine-2,5-dione acting as a good leaving group, and the product of the reaction is a 3,4-dihydro-4-phenylpyran-2-one derivative (*R*)-**588** whose absolute configuration derives from the attack to the *β-Re* face of **577** during the Michael step. Yields and enantioselectities are listed in entry 17 of Table 23.

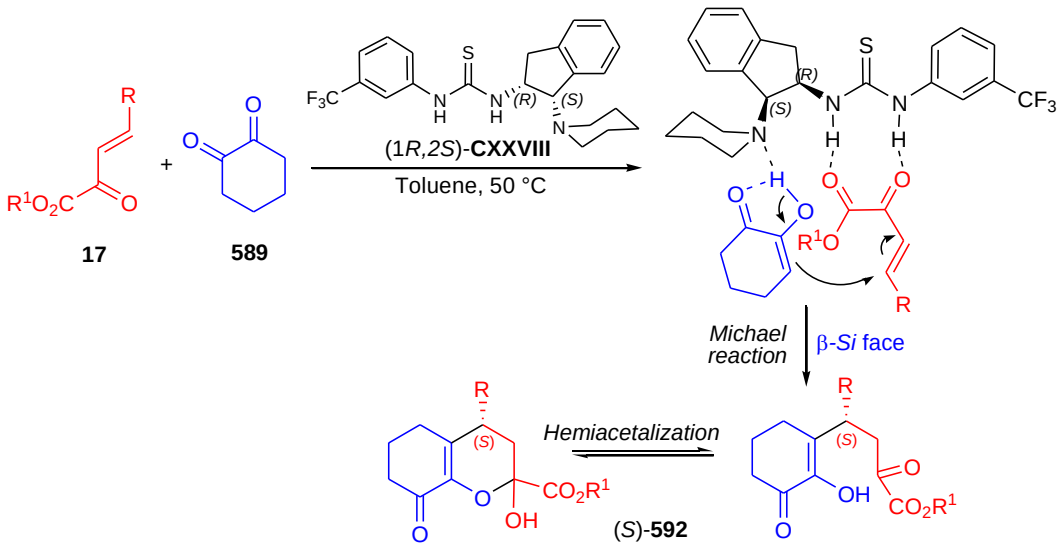
3.6.3. The Enantioselective [3+3] [Michael Reaction/Hemiacetalization] Between 1,2-Dicarbonyl Nucleophiles and α,β-Unsaturated Carbonyl Derivatives

The sequence Michael/hemiacetalization was later extended to 1,2-cyclohexa- and cyclopentadione derivatives (**589**) since the functionality of the products offers a good starting point for additional transformations. The first step of the reaction is the Michael addition, followed again by the hemiacetalization step in which the intramolecular cyclization of the enolic group to the carbonyl gives the final product.

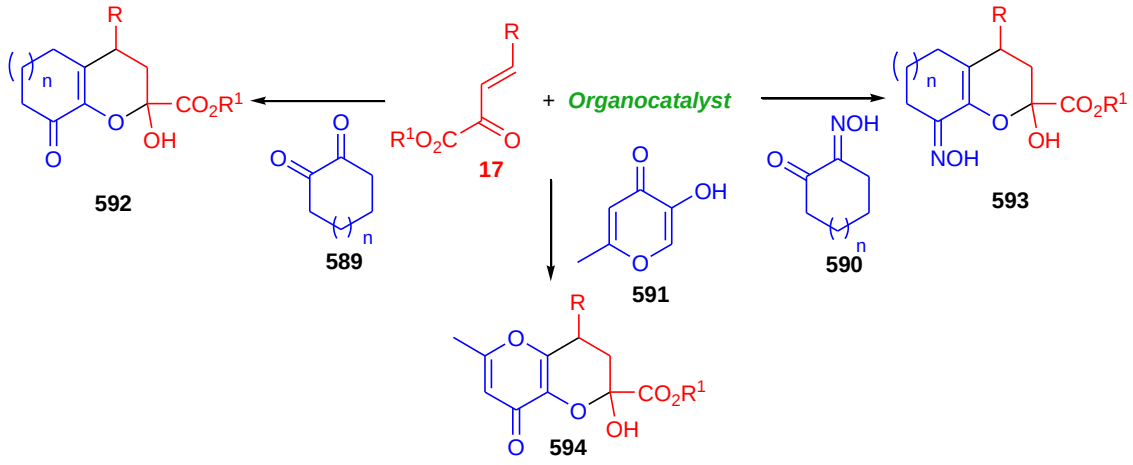
The first example concerns the reaction between 1,2-cyclohexandione (**589**) and unsaturated α-ketoester **17**, with the indane skeleton-based thiourea (1*S*,*2R*)-**CXXVIII** as the organocatalyst (Table 24: entry 1).[287] This is suitable for the bifunctional activation of both reagents: the tautomer of **589** binds through hydrogen bond the pyrrolidine group of the catalyst, while the α-dicarbonyl groups of **17** are coordinated by the thiourea hydrogens. The reacting intermediate illustrated in Scheme 245 promotes an "*intramolecular*" Michael addition to the *β-Si* face of **17**. The subsequent hemiacetalization gives (*S*)-**592** in very good yields and excellent enantioselectivity. Similarly, the reaction between 1,2-cyclopentandione (**589**) and **17** was catalysed by (1*S*,2*S*)-**CXIX** and the product was again (*S*)-**592** (Table 24: entry 2).[288]

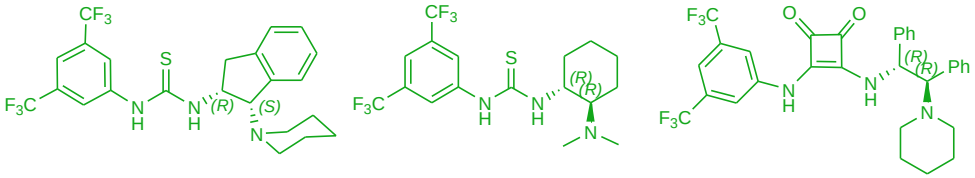
Then the reaction with **17** was extended to the α-hydroxyimino derivative of cyclic 1,2-diketones (**590**) and was catalysed by (1*R*,2*R*,1'*R*,4a'*S*,10a'*R*)-**XXXVI**, affording the product (*S*)-**593** (Scheme 246) (Table 24: entry 3).[289]

Scheme 245. Organocatalyzed [3+3] [Michael Reaction/Hemiacetalization] Between 589 and Unsaturated α-Ketoester 17 Catalyzed by (1*S*,2*R*)-CXXVIII.[287]

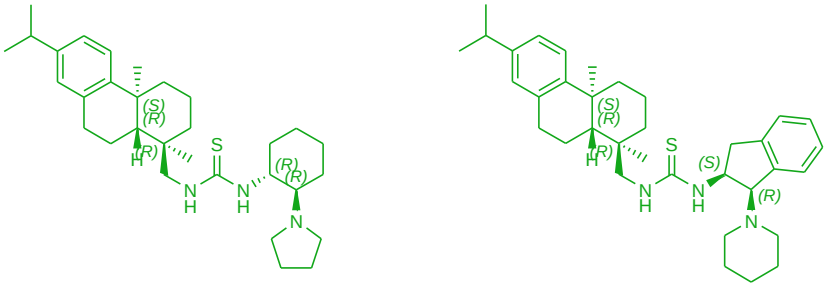


Scheme 246. Enantioselective [3+3] [Michael Reaction/Hemiacetalization] Between 17 and α-Diketones 589-591 Catalyzed by Several Organocatalysts.





(1*R*,2*S*)-**CXXVIII** (Ref. 287) (1*R*,2*R*)-**CXIX** (ref. 288) (1*R*,2*R*)-**CXXXI** (Ref. 290)



(1*R*,2*R*,1'*R*,4a'*S*,10a'*R*)-**XXXVI** (Ref. 289) (1*S*,2*R*,1'*R*,4a'*S*,10a'*R*)-**CXXXII** (Ref. 291)

Table 24. The Enantioselective [3+3] [Michael Reaction/Hemiacetalization] between 1,2-Dicarbonyl Nucleophiles and α,β-Unsaturated Carbonyl Derivatives Catalyzed by the Organocatalysts Reported in Scheme 246.

Entry	Electrophile	Dicarbonyl Nucleophile	Catalyst	n. Exp.	Reaction Product	aver. Yield % (s.d.)	aver. ee % (s.d.)	Attached Face	Ref.
1	**17**	**589**	(1*R*,2*S*)-**CXXVIII**	17	(*S*)-**592**	89 (6)	95 (1.5)	*β-Si*	287
2	**17**	**589**	(1*R*,2*R*)-**CXIX**	10	(*S*)-**592**	70 (17)	92 (3)	*β-Si*	288
3	**17**	**590**	(1*R*,2*R*,1′*R*,4a′*S*,10b′*R*)-**XXXVI**	17	(*S*)-**593**	84 (13)	99 (0.5)	*β-Si*	289
4	**17**	**591**	(1*R*,2*R*)-**CXXXI**	22	(*S*)-**594**	63 (7)	90 (18)	*β-Si*	290
5	**17**	**591**	(1*S*,2*R*,1′*R*,4a′*S*,10b′*R*)-**CXXXII**	15	(*R*)-**594**	93 (2)	94 (4)	*β-Re*	291

The further step was the reaction of **17** with *Allomaltol* (**591**), the enolic form of a cyclic 1,2-diketone whose interest is the strong relationship with bioactive *Kojic acid* derivatives. Two organocatalysts were tested: (1*R*,2*R*)-**CXXXI** and (1*S*,2*R*,1'*R*,4a'*S*,10a'*R*)-**CXXXII** and the products were (*S*)-**594** and its enantiomer (*R*)-**594**, respectively.[290,291] The reagents, catalysts, and products of these reactions are illustrated in Schemes 245 and 246, while the corresponding yields and enantioselectivities are listed in Table 24. The average reaction yields ranged from moderate (63%) to very good values (93%), while the average ee was always excellent (with up to 99%).

As we noted in previous section 3.6.1, the reactions catalyzed with thiourea- and squaric acid-based organocatalysts showed a relationship between the configuration of the carbon atom adjacent to the NH, which is involved in hydrogen bonding with the CO_2R of the electrophile,[268] and the absolute configuration of the reaction product. If the configuration of the mentioned above carbon atom of the organocatalyst is (*S*), then the product has an (*R*) absolute configuration deriving from an attack to the *β-Re* face of the reacting intermediate. The reactions in Table 24 have **17** as electrophile and are all catalysed by the above types of thiourea- and squaric acid organocatalysts (Scheme 246): (1*R*,2*S*)-**CXXXVIII**, (1*R*,2*R*)-**CXIX**, (1*R*,2*R*)-**CXXXI**, and (1*R*,2*R,4'R,4a'R,10b'S*)-**XXXVI** (Table 24, entries 1-4) have all the crucial chiral center (1*R*), all reactions occur through an attack to the *β-Si* face of **17**, and all the products have an (*S*) absolute configuration. Adversely, (1*S*,2*R,4'R,4a'R,10b'S*)-**CXXXII** (Table 24, entry 5) has the chiral center with configuration (1*S*), the reactions occur through an attack to the *β-Re* face of **17**, and the product is (*R*)-**594**.

These relationships require further supports, but homogeneous results, even with very complicated structures, do not happen by chance.

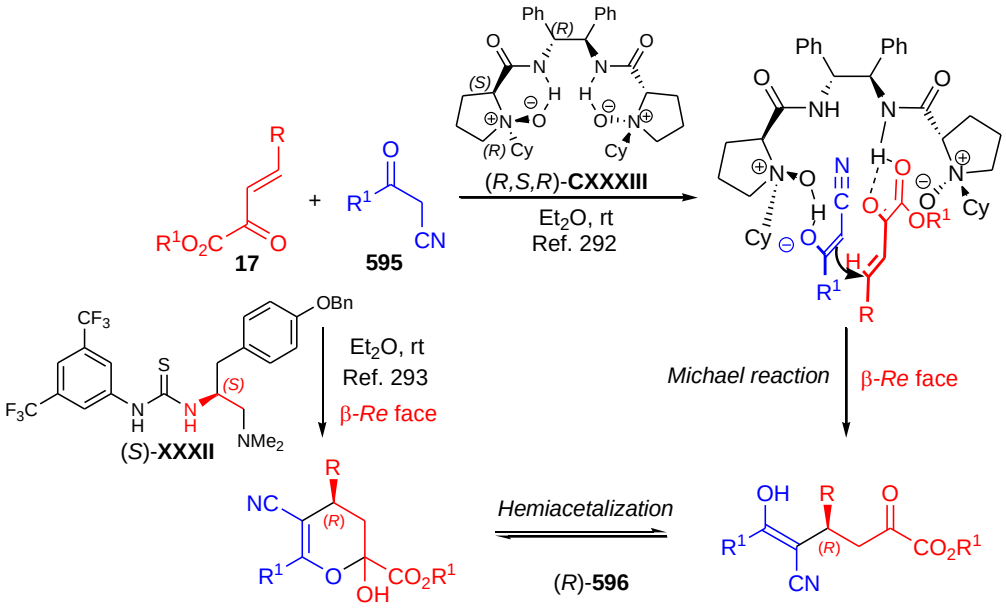
3.6.4. The Enantioselective [3+3] [Michael Reaction/Hemiacetalization] Between α,β-Unsaturated Carbonyl Derivatives and Other Nucleophiles

The reaction between α-substituted cyanoketones **595** and β,γ-unsaturated α-ketoesters **17** has been catalysed with bifunctional *N,N*-dioxide (1*R*,2*R*)-1,2-diphenyldiaminoethane-(*S*)-prolinamide-*N,N'*-dioxide [(*R,S,R*)-**CXXXIII**],[292] which is able to coordinate both reagents through hydrogen

bonding, giving the reacting intermediate illustrated in Scheme 247. The *Si*-face of the ketoester is shielded by the cyclohexyl moiety and the cyanoketone attacks the *β-Re* face, giving product **596** with the (*R*) configuration. Several substrates have been tested with very good yields and enantioselectivities (Table 25, entry 1).

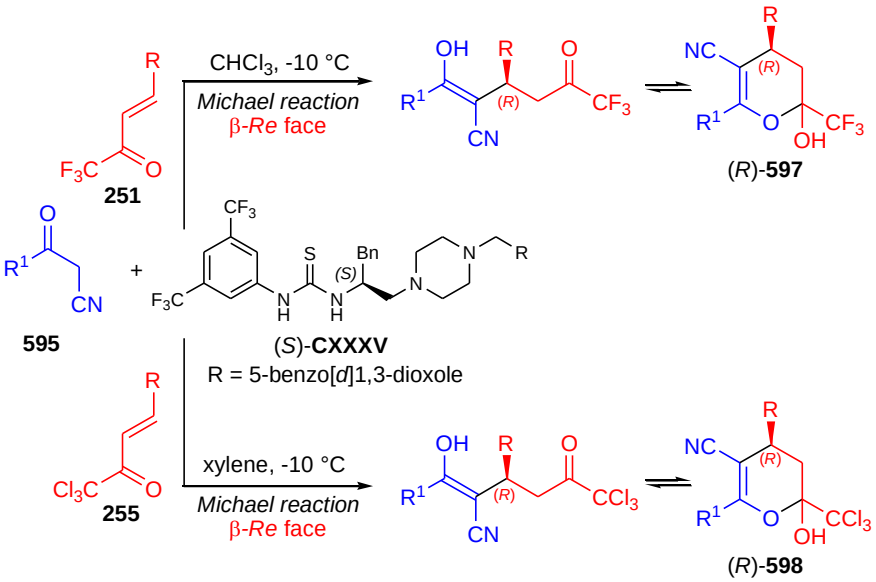
The same reaction was catalysed, under the same experimental conditions, by the thiourea-based organocatalyst (*S*)-**CXXXIV** (Scheme 247).[293] As expected, the attack occurred on the *β-Re* face affording (*R*)-**596** with very good yields and ee. It is astonishing how two deeply different organocatalysts gave nearly overlapping results (Table 25, entry 1 vs entry 2).

Scheme 247. Enantioselective [Michael Reaction/Hemiacetalization] of Cyanoketones 595 and 17 Catalyzed by (*R,S,R,*)-CXXXIII and (*S*)-CXXXIV.[292,293]



α,β-Unsaturated trifluoromethyl **251** and trichloromethyl ketones **255** were also tested in the reaction with **595**, in the presence of the same organocatalyst (*S*)-**CXXXV** (Scheme 248).[294,295] As expected, the attack occurred on the *β-Re* face of both trihalomethyl ketones giving (*R*)-**597** and (*R*)-**598**, respectively. The results were very similar in both the reactions, and the products were obtained within excellent yields and very good enantioselectivities (Table 25, entries 3 and 4).

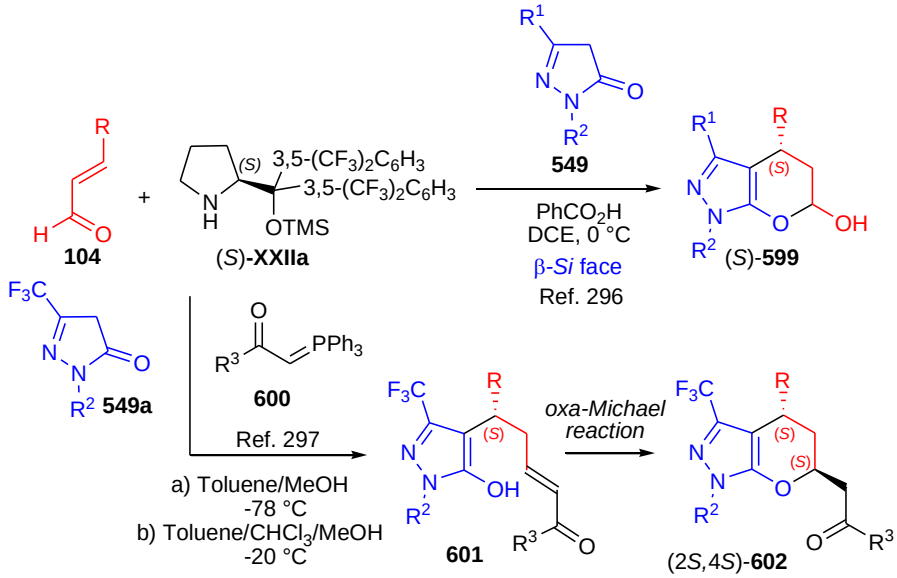
Scheme 248. Enantioselective [Michael Reaction/Hemiacetalization] of Cyanoketones 595 with α,β-Unsaturated Trifluoromethyl 251 and Trichloromethyl Ketones 255 Catalysed by (*S*)-CXXXV.[294,295]



The Michael reaction/hemiacetalization sequence was applied to the synthesis of pyrazole-tetrahydropyran scaffolds through the reaction between α,β-unsaturated aldehydes **104** and pyrazol-5-ones **549**, catalysed by prolinol derivative (*S*)-**XXIIa** (Scheme 249).[296] The reaction follows the usual protocol and the nucleophile adds to the *β-Si* face of the planar iminium ion that undergoes the Michael addition, followed by hemiacetalization, to give (*S*)-**599**, obtained within good yields and enantioselectivities (Table 25 entry 5).

If the reaction with 3-trifluoromethyl-5-pyrazolone **549a** is performed "*one pot*" in the presence of phosphorous ylide **600** under hydrolytic conditions, the Michael oxyaldehyde gives a Wittig reaction with **600** to afford **601** (Scheme 249). This undergoes an oxa-Michael intramolecular addition providing (2*S*,4*S*)-**602** within good yields, moderate diastereoselectivities, but excellent enantioselectivities (Table 25, entry 6).[297]

Scheme 249. Enantioselective [Michael Reaction/Hemiacetalization] of Pyrazol-5-ones 549 with Enals 104 Catalysed by (*S*)-XXIIa.[296,297]



When the enal is substituted by ethyl 3-(2-oxoindolin-3-ylidene)-2-oxopropanoates **578**, the Michael/hemiacetalization reaction with **549** follows a different pathway (Scheme 250).[286] With the organocatalyst (1*S*,2*S*)-**CXXX** coordinating both the reagents, the pyrazolone attack occurs to the *β-Re* face of **578** to afford the Michael adduct **603**. Then, the hemiacetalization step occurs at the ketonic carbonyl group, and the final products are the *spiro* derivatives (*S*)-**604**, which were obtained within excellent yields and enantioselectivities (Table 25, entry 7).

Scheme 250. Enantioselective [Michael/Hemiacetalization] Between 549 and 578 Catalyzed by (1*S*,2*S*)-CXXX.[286]

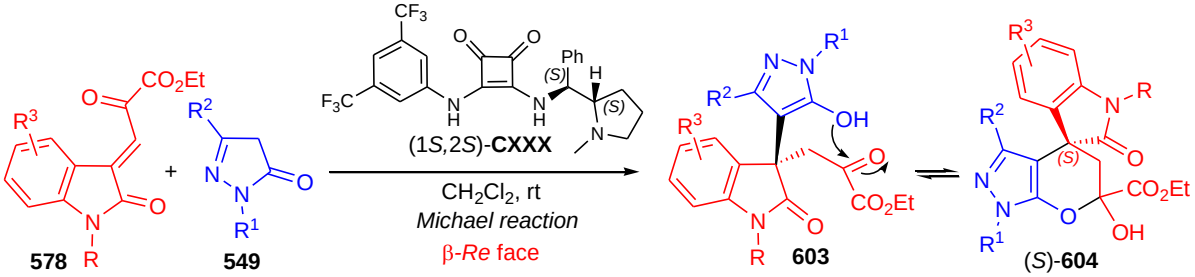


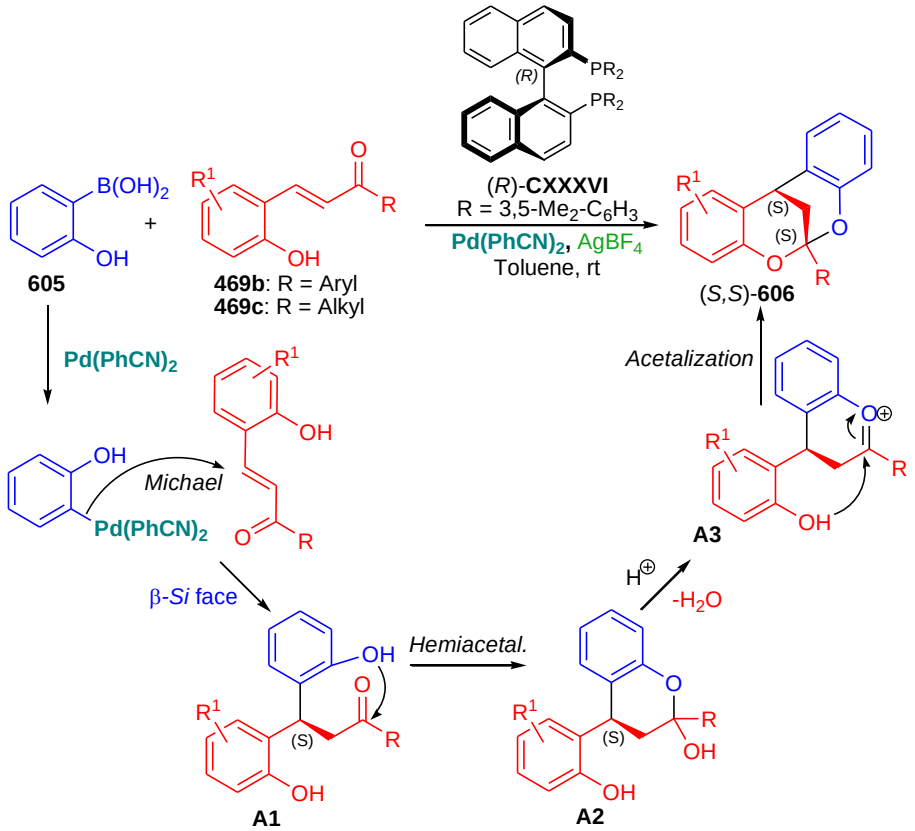
Table 25. The Enantioselective [3+3] [Michael Reaction/Hemiacetalization] between α,β-Unsaturated Carbonyl Derivatives and Other Nucleophiles Catalyzed by Different Organocatalysts

Entry	Electrophile	Nucleophile	Catalyst	n. Exp.	Reaction Product	aver. Yield % (s.d.)	aver. ee % (s.d.)	Attached Face	Ref.
1	**17**	**595**	(*R*,*S*,*R*)-**CXXXIII**	30	(*R*)-**596**	92 (7)	89 (6)	*β-Re*	292
2	**17**	**595**	(*S*)-**CXXXIV**	20	(*R*)-**596**	93 (5)	92 (2)	*β-Re*	293
3	**251**	**595**	(*S*)-**CXXXV**	15	(*R*)-**597**	96 (10)	92 (2)	*β-Re*	294
4	**255**	**595**	(*S*)-**CXXXV**	16	(*R*)-**598**	91 (11)	88 (5)	*β-Re*	295
5	**104**	**549**	(*S*)-**XXIIa**	14	(*S*)-**599**	80 (7)	87 (23)	*β-Si*	296
6[a]	**104**	**549a**	(*S*)-**XXIIa**	10	(2*S*,4*S*)-**602**[b]	79 (6)	92 (6)	*β-Si*	297
7	**578**	**549**	(1*S*,2*S*)-**CXXX**	19	(*S*)-**604**	87 (4)	95 (5)	*β-Re*	286
8	**469b,c**	**605**	(*R*)-**CXXXVI**	15	(*S*,*S*)-**606**[b]	70 (23)	93 (3)	*β-Si*	298

[(a)] The reaction is performed one pot in the presence of the Wittig reagent **600**. [(b)] The average de was 52 ± 18%.

We close this section with the interesting reaction between 1-substituted 3-(2-hydroxyphenyl)-prop-2-en-1-one (**469b,c**) and 2-hydroxyphenylboronic acid (**605**), which reacts with $Pd(PhCN)_2$ to give the nucleophile for the Michael reaction. The catalyst is 3,5-xylyl-BINAP (*R*)-**CXXXVI** and the addition occurs to the *β-Si* face of **469b,c** giving the Michael adduct (*S*)-**A1**, suitable for the hemiacetalization to (*S*)-**A2** (Scheme 251).[298] Up to now we have discussed this type of reactions; however, the hemiacetal compound can undergo dehydration to furnish the oxocarbenium ion intermediate (*S*)-**A3** in which the phenolic hydroxide promotes an intramolecular nucleophilic attack affording 6-substituted 12*H*-6,12-methano-dibenzo[*d,g*][1,3]dioxocin (**606**), whose absolute (*S,S*) configuration was determined by X-ray analysis. The products were obtained within high yields and excellent enantioselectivities (Table 25, entry 8).

Scheme 251. Enantioselective [Michael/Hemiacetalization] Between 469b,c and 2-Hydroxyphenylboronic Acid 605 Catalyzed by (*R*)-CXXXVI.[298]



In summary, this is a sequence of reactions in which four consecutive steps harmoniously generate new functionalities in the reacting molecules, suitably placed to promote other steps, up to generate the final 3,4-dihydropyran derivatives. Everything being accurately planned to obtain the final result. This is not an exception, it is the beginning of the next chapter.

3.7. 3,4-Dihydropyrans via Cascade Reactions

This section develops the concept illustrated above. The sequence of reactions becomes a consecutive process, a cascade that incorporates multiple bond-forming events, at the end of which an optically active 3,4-dihydropyran derivative is synthetized through a mixing of creativity and fantasy applied to the art of organic synthesis.

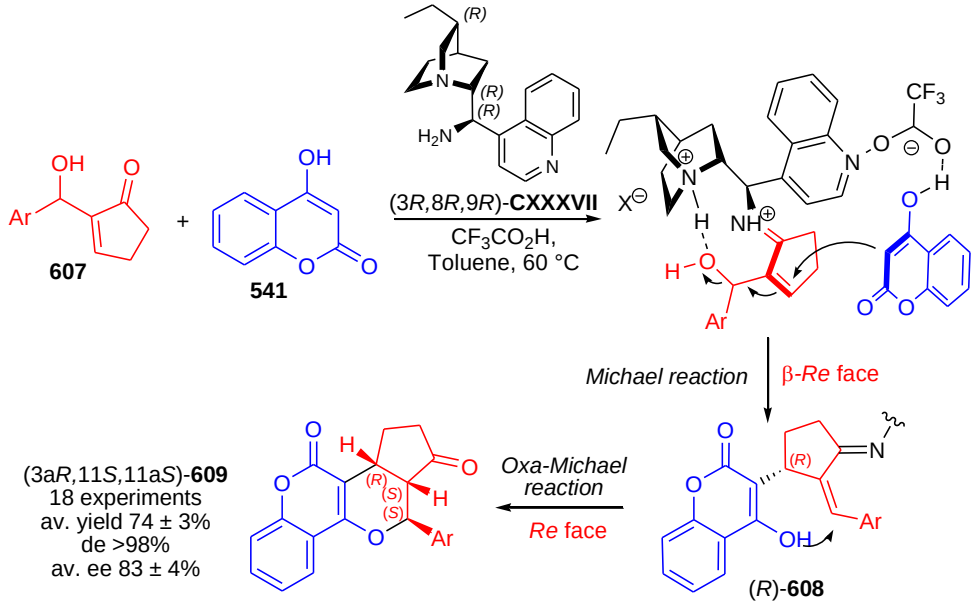
3.7.1. The Enantioselective [3+3] Cycloadditions to 3,4-Dihydropyrans through [Michael/Oxa-Michael] Cascade Reactions

A reaction involving a synthesis of 3,4-dihydropyrans through a Michael/oxa-Michael cascade has been shown in Scheme 249: The reaction between enals **104** and 3-trifluoromethyl-5-pyrazolone **549a**, performed in the presence of phosphorous ylide **600**, which gives a *cascade* sequence *Michael*/*Wittig*/*oxa-Michael* reactions to afford (4*S*,6*S*)-**602**.[297] This cascade was already discussed, but other examples have been reported in the literature and will be considered here.

The reactions between 4-hydroxycoumarin (**541**) and different cyclic enones have been described in Section 3.3.1. and give the Michael adducts in equilibrium with their cyclic hemiketals.[269] When the electrophile is 2-(hydroxy(phenyl)methyl)cyclopenten-2-enone (**607**) the destiny of the *Michael* product is less trivial. The organocatalyst is 9-amino-dihydrocinchonine [(3*R*,8*R*,9*R*)-**CXXXVII**], in combination with a Brønsted acid, able to activate both reagents by formation of an active iminium ion and through hydrogen bonding. The attack to the *β-Re* face of the electrophile affords the Michael product (*R*)-**608**, whose hydroxyl group is suitably placed for an intramolecular *oxa-Michael* reaction that generates two further chiral centers (Scheme 252).[299] The tetracyclic final products **609** have three adjacent chiral centers with the (3a*R*,11*S*,11a*S*)

absolute configuration, and are formed within good yields and enantioselectivities, while diastereoselectivity is excellent (de >98%).

Scheme 252. Enantioselective [Michael/Oxa-Michael] Cascade Reaction Between 607 and 541 Catalyzed by (3*R*,8*R*,9*R*)-CXXXVII.[299]

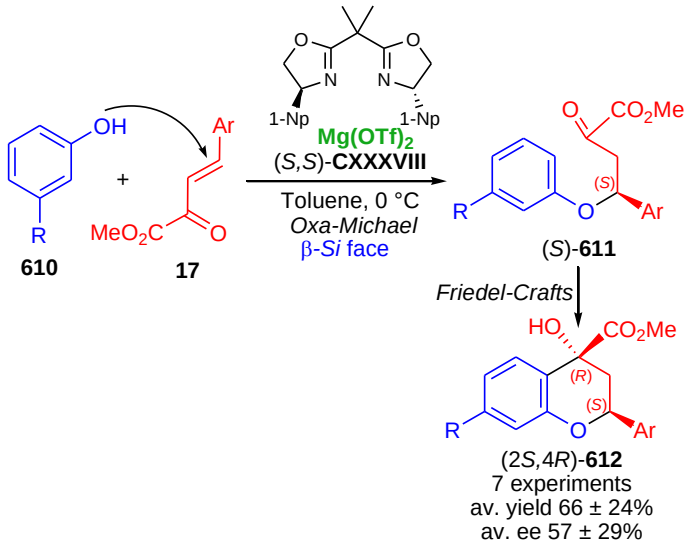


3.7.2. The Enantioselective [3+3] Cycloadditions to 3,4-Dihydropyrans through [Oxa-Michael/Friedel-Crafts] Cascade Reactions

With *O*-nucleophiles, basically electron rich substituted phenols **610**, the attack on the β position of α,β-unsaturated carbonyl derivatives **17** is the result of an *oxa-Michael* reaction and the product, in the presence of a Lewis acid, is suitable to give an intramolecular *Friedel-Crafts* reaction on the aromatic ring.

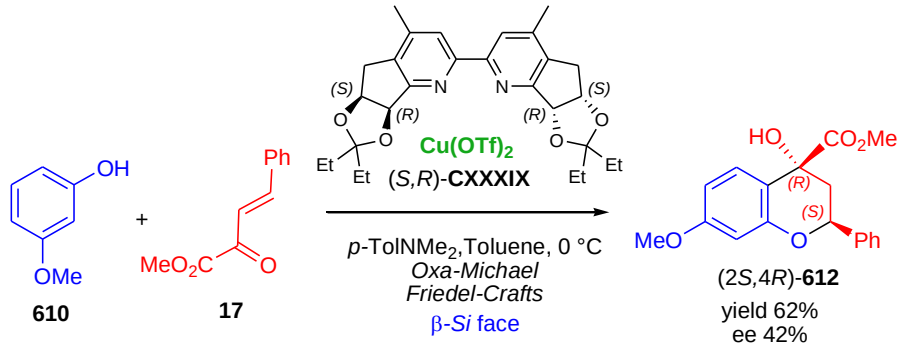
The first enantioselective reaction was run several years ago by Jørgensen *et al.* with (*S*,*S*)-**CXXXVIII**, a [Box/Mg(OTf)$_2$] complex, as the catalyst.[300,301] The phenol attacks the *β-Si* face of **17** to afford the *oxa-Michael* adduct (*S*)-**611**, which undergoes the *Friedel-Crafts* ring closure to produce methyl 4-hydroxy-2-phenylchroman-4-carboxylates (2*S*,4*R*)-**612**, which are obtained with enantioselectivities up to 81% ee (Scheme 253).

Scheme 253. Enantioselective [Oxa-Michael/Friedel-Crafts] Cascade Reaction Between 610 and 17 Catalyzed by (*S*,*S*)-CXXXVIII.[300,301]



The same reactions sequence involving **17** and 3-methoxyphenol **610** was later run in the presence of the C_2-symmetric 2,2′-bipyridyl Cu(II) complex (*S*,*R*)-**CXXXIX**.[302] (2*S*,4*R*)-**612** was obtained in moderate yield and low enantioselectivity through the attack to the *β-Si* face of **17** (Scheme 254).

Scheme 254. Enantioselective [Oxa-Michael/Friedel-Crafts] Cascade Reaction Between 3-Methoxyphenol 610 and 17 Catalyzed by (*S*,*R*)-CXXXIX.[302]

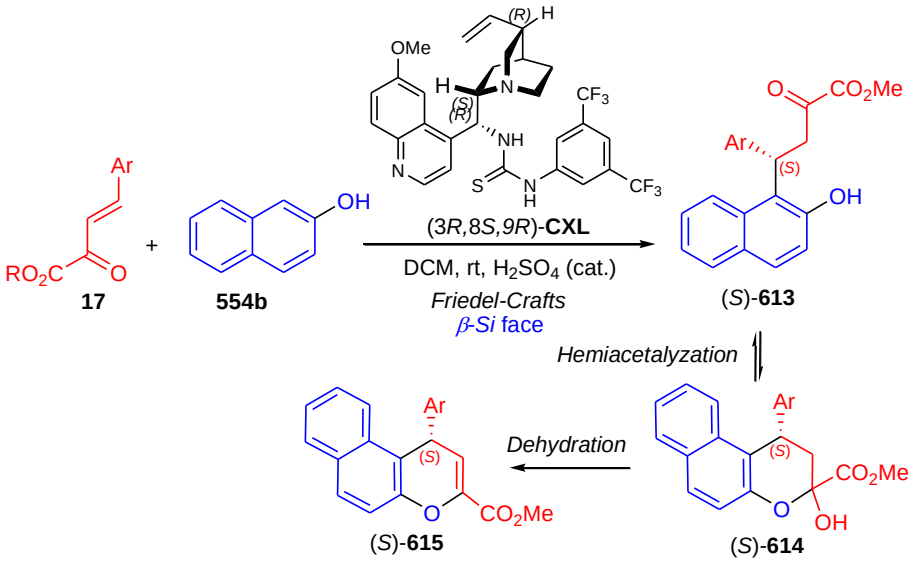


3.7.3. The Enantioselective [3+3] Cycloadditions to 3,4-Dihydropyrans through [Friedel-Crafts/Hemiacetalization] Cascade Reactions.

In the previous section we have discussed the reaction of electron rich substituted phenols **610** whose hydroxyl group attacks the β-position of **17** to give an *oxa-Michael*, followed by a *Friedel-Crafts* reaction.

When the nucleophile is 2-naphthol **554b**, the attack derives from the 1-position of naphthol, giving rise to a Friedel-Crafts reaction as the first step of the cascade. This reaction is catalysed by a bifunctional thiourea-9-aminoquinine organocatalyst (3*R*,8*S*,9*R*)-**CXL**, which can coordinate both reagents by hydrogen bonding, **17** by the thiourea fragment and **554a** as ammonium ion (Scheme 255).[303] The Friedel-Crafts step occurs by attack to the *β-Si* face of **17** to afford (*S*)-**613** that is acetalized to (*S*)-**614**. This structure belongs to the 3,4-dihydropyran family, the subject of this review, but the Authors submitted it to dehydration with a catalytic amount of H_2SO_4 and the isolated product of this reaction was **615**.

Scheme 255. Enantioselective [Friedel-Crafts/Hemiacetalization] Cascade Reaction Between 2-Naphtol 554b and 17 Catalyzed by (3*R*,8*S*,9*R*)-CXL.[303]

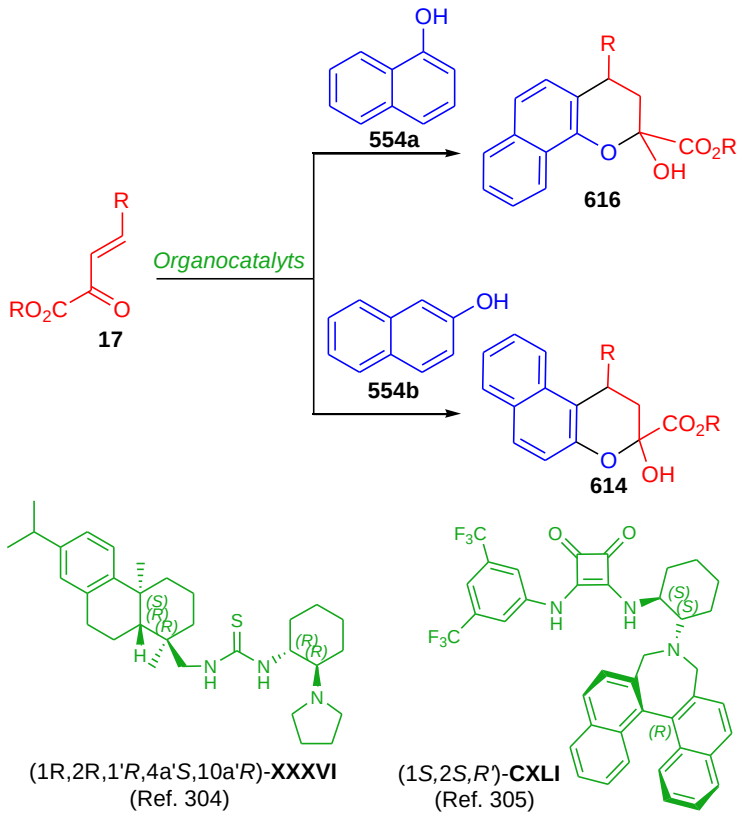


The methyl 1-substituted-1*H*-benzo[*f*]chromene-3-carboxylate thus obtained, has the absolute configuration (*S*)-**615** determined by X-ray crystallographic analysis, and the determination of its

enantioselectivity is the mode we have to evaluate the results in terms of stereochemistry and efficiency of the cascade reaction (Table 26, entry 1).

The Friedel-Crafts/hemiacetalization cascade reaction was the topic of an extended research testing the behaviour of different α,β-unsaturated carbonyl compounds with several nucleophiles. The α-keto esters **17** were allowed to react with 1- and 2-naphthols **554a,b** in the presence of the thiourea- or squaramide-derived organocatalysts (1*R*,2*R*,1'*R*,4a'*S*,10a'*R*)-**XXXVI** and (1*S*,2*S*,*R'*)-**CXLI**, respectively (Scheme 256).[304,305] The products **616** and **614** were obtained within very good yields and enantioselectivities (Table 26, entry 2-4)

Scheme 256. Enantioselective [Friedel-Crafts/Hemiacetalization] Cascade Reaction Between Naphthols 554a,b and 17.[304,305]



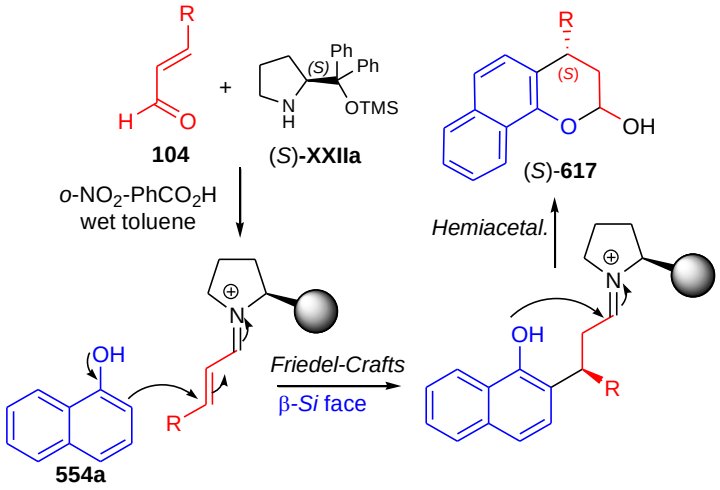
The enal **104**, activated by diphenylprolinol-TMS derivative (*S*)-**XXIIa** that affords the iminium derivative reported in Scheme 257, reacts with 1-naphthol **554a** in the Friedel-Crafts step with the attack on the *β-Si* face, and the hemiacetalization product (*S*)-**617** is obtained in good yields and enantioselectivities (Table 26, entry 5).[306]

Table 26. The Enantioselective [3+3] [Friedel-Crafts/Hemiacetalization] between α,β-Unsaturated Carbonyl Derivatives and Naphthols Catalyzed by Different Organocatalysts.

Entry	Electrophile	Nucleophile	Catalyst	n. Exp.	Reaction Product	aver. Yield % (s.d.)	aver. ee % (s.d.)	Attached Face	Ref.
1	**17**	**554b**	(3*R*,8*S*,9*R*)-**CXL**	15	(*S*)-**615**[a]	70 (14)	81 (10)	*β-Si*	303
2	**17**	**554a**	(1*R*,2*R*,1'R,4a'*S*,10a'*R*)-**XXXVI**	15	(*S*)-**616**	82 (2)	91 (5)	*β-Si*	304
3	**17**	**554b**	(1*R*,2*R*,1'*R*,4a'*S*,10a'*R*)-**XXXVI**	3	**614**	88 (2)	89 (3)	nd	304
4	**17**	**554a**	(1*S*,2*S,R'*)-**CXLI**	12	(*R*)-**616**	77 (9)	93 (4)	*β-Re*	305
5	**104**	**554a**	(*S*)-**XXIIa**	16	(*S*)-**617**	80 (9)	83 (5)	*β-Si*	306
6	**572**	**554a**	(3*R*,8*S*,9*S*)-**CVIII**	6	(2*R*,4*S*,6*S*)-**618**	62 (30)	92 (3)	*β-Re*	307
7	**572**	**554b**	(3*R*,8*S*,9*S*)-**CVIII**	7	(1*R*,2*R*,5*R*)-**619**	67 (26)	75 (8)	*β-Re*	307

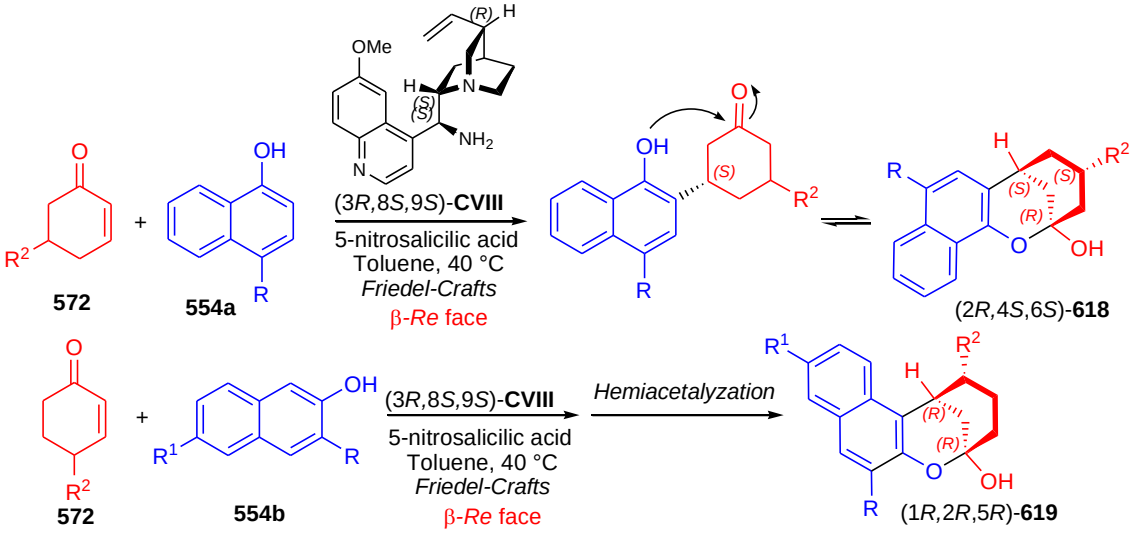
[(a)] The results in terms of yields and enantioselectivity were determined from the dehydration products (S)-**615** (Scheme 255).

Scheme 257. Enantioselective [Friedel-Crafts/Hemiacetalization] Cascade Reaction Between 1-Naphtol 554a and 104 Catalyzed by (*S*)-XXIIa.[306]



When the reaction is performed with an α,β-unsaturated carbonyl in which the *cisoid* configuration is inhibited, the pathway gives different fall-out after the Friedel-Crafts step. An example is the reaction of 1- and 2-naphthols **554a,b** with 2-cyclohexenones **572**. The organocatalyst is 9-amino-epiquinine (3*R*,8*S*,9*S*)-**CVIII** that coordinates both the reagents, one as iminium ion, the other one by hydrogen bonding. Following the convention applied in this review that assumes a *β*-phenyl substituent at the enone, the Friedel-Crafts attack of **554a** occurs on the *β*-*Re* face of **572** to give (*S*)-3-(1-hydroxynaphthalen-2-yl)cyclohexanones as reported in Scheme 258.[307] The cascade is accomplished with the hemiacetalization to form two new stereocenters and gives the methanonaphtho[1,2-*b*]oxocin-2-ols (2*R*,4*S*,6*S*)-**618** in discrete yields and excellent enantioselectivities (Table 26, entry 6). The reaction with 2-naphthol **554b** follows the same pathway and he final product are the methanonaphtho[2,1-*b*]oxocin-5-ols (1*R*,2*R*,5*R*)-**619**, which are obtained with comparable yields, but with lower enantioselectivities (Table 26, entry 7).

Scheme 258. Enantioselective [Friedel-Crafts/Hemiacetalization] Cascade Reactions of 2-Cyclohexenones 572 with 1- and 2-Naphthols 554a,b Catalyzed by (3*R*,8*S*,9*S*)-CVIII.[307]

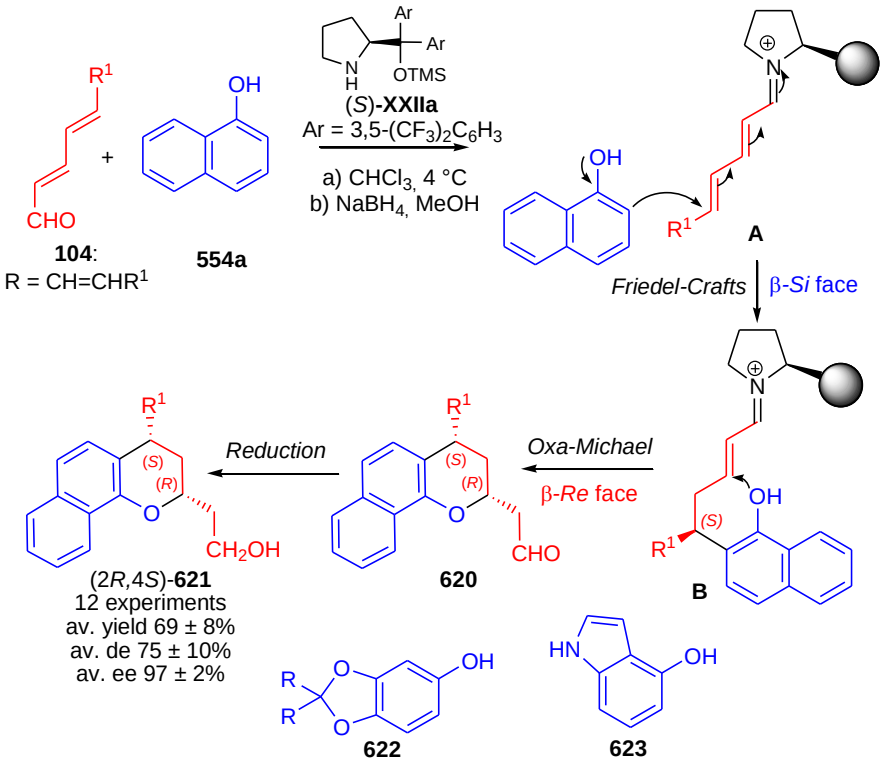


3.7.4. The Enantioselective [3+3] Cycloadditions to 3,4-Dihydropyrans through [Friedel-Crafts/Oxa-Michael] Cascade Reactions.

In the previous section we discussed the reaction of α,β-unsaturated aldehydes **104** with 1-naphthol **554a**, catalysed by (*S*)-prolinol derivative (*S*)-**XXIIa** (Ar=Ph), which occurs through a Friedel-Crafts followed by hemiacetalization reaction.[306]

The reaction of the electrophilic 2,4-dienal **104** (R= CH=CHR[1]), catalyzed by (*S*)-**XXIIa** (Ar=3,5-$(CF_3)_2$-C_6H_3), proceeds selectively through the *1,6-Friedel-Crafts* reaction path in which the 1-naphthol attacks the *β-Si* face of the iminium ion intermediate **A** to give the adduct **B** (Scheme 259).[308] On the basis of computational studies, this preferred pathway follows the *Oxa-Michael* intramolecular cyclization to the *β-Re* face to give, out of the four possible regioisomers, only (2*R*,4*S*)-**620**. After reduction, the final product is the 2-[(2*R*,4*S*)-4-substituted-3,4-dihydro-2*H*-benzo[*h*]chromen-2-yl]ethanol (**621**), obtained with good yield and diastereoselectivity, and an average ee of 97% from 12 experiments. The same reaction was successfully accomplished with the 2,2-dimethylbenzo[*d*][1,3]dioxol-5-ol (**622**) and 1*H*-indol-4-ol (**623**) to demonstrate the flexibility of the protocol.

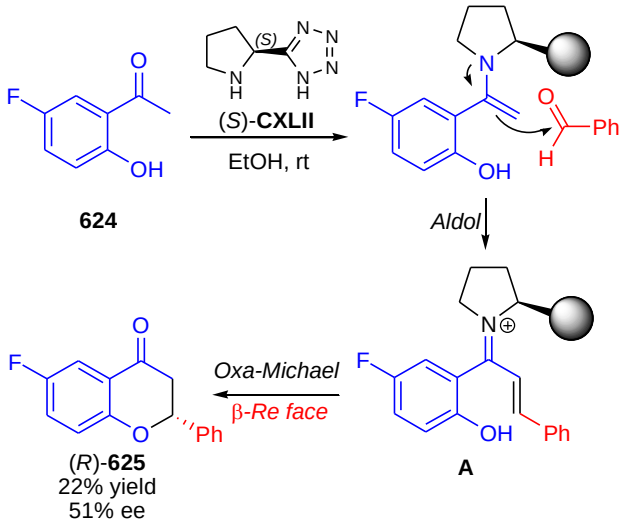
Scheme 259. Enantioselective [Friedel-Crafts/oxa-Michael] Cascade Reactions of 2,4-Dienals 104 with 1-Naphthol 554a Catalyzed by (*S*)-XXIIa.[308]



4. The Enantioselective Acceptor/Donor [5+1] Cyclization

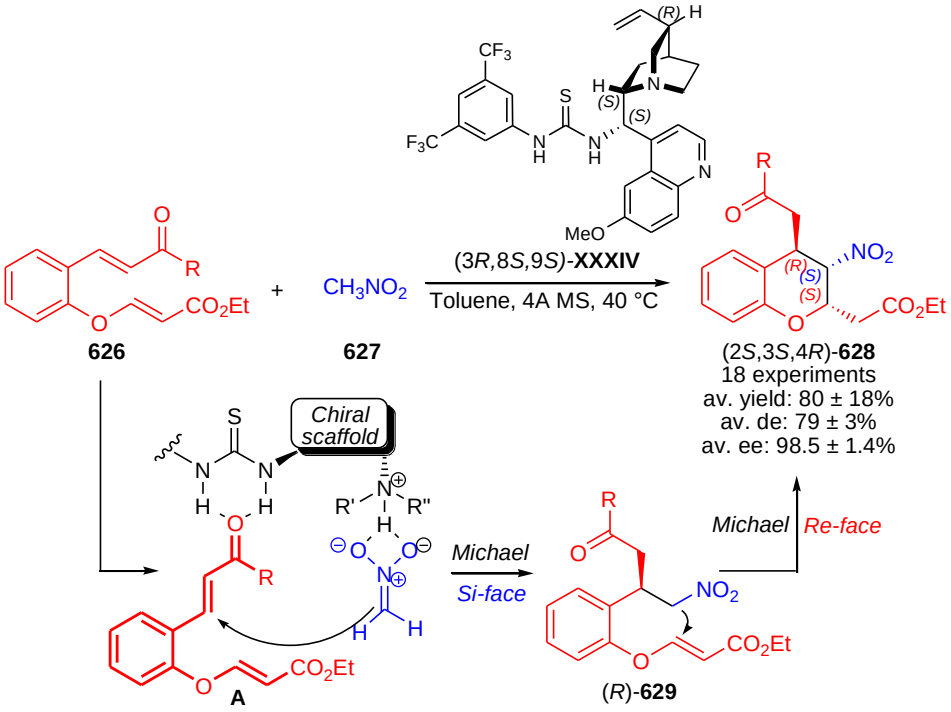
An unusual approach to 3,4-dihydropyran derivatives is the cyclization between a five-atoms and a one-atom partners; hence, a [5+1] cyclization (see Scheme 1). The first example is the reaction between 5-fluoro-2-hydroxyacetophenone (**624**) and benzaldehyde, catalysed by 5-[(*S*)-pyrrolidin-2-yl]-1*H*-tetrazole [(*S*)-**CXLII**] (Scheme 260).[309] Acetophenone is activated by the pyrrolidinyl organocatalyst and the resulting nucleophile gives an aldol reaction to benzaldehyde, followed by the intramolecular oxa-Michael attack to the β-*Re* face of the intermediate **A** with formation of the O(1)-C(2) bond of flavanone (*R*)-**625**, which was obtained within low yield and moderate enantioselectivity.

Scheme 260. Enantioselective [5+1] Cyclization Reaction of 2-Acylphenol 635 with Benzaldehyde Catalyzed by (*S*)-CXLII.[309]



The reaction between **626** and nitromethane **627**, with the 9-amino-epiquinino-thiourea-based organocatalyst (3*R*,8*S*,9*S*)-**XXXIV**, gives polysubstituted chromans **628** (Scheme 261).[310] This catalyst allows to coordinate the ketonic group of **626** by hydrogen bonding and to activate nitromethane through the nitrogen quaternary ion.

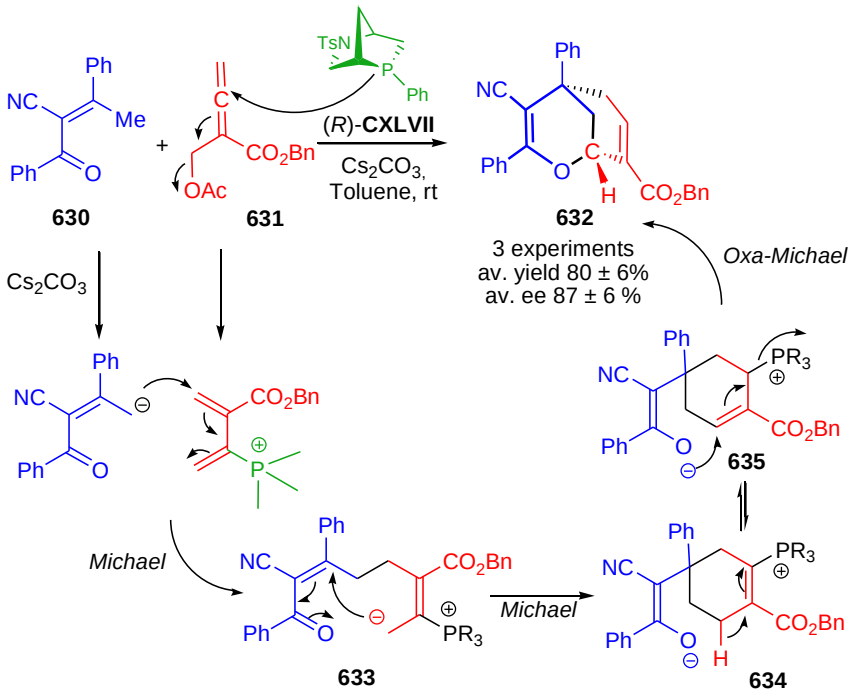
Scheme 261. Enantioselective [Michael/Michael] Cascade Reaction Between 626 and Nitromethane 627 Catalyzed by (3*R*,8*S*,9*S*)-XXXIV.[310]



The reacting complex (**A**) is therefore harmoniously oriented to give an "*intramolecular*" *Michael* attack of the nitromethane enolate to the *β-Si* face of the enone fragment. The cascade proceeds with the second *Michael* attach of the new nitromethane anion to the *β-Re* face of the acrylate fragment of the intermediate (*R*)-**629**, and with the ring closure and the formation of chromans **628** whose three contiguous stereocenters have the (2*S*,3*S*,4*R*) absolute configuration. Yields and diastereoselectivities are good and the excellent enantioselectivities determine the added value of these reactions (on 18 different experiments the average ee is 98.5%).

Recently, an original approach to the [5+1] cyclization reaction has been proposed. The addition/cycloaddition domino reaction of 2-benzoyl-3-methylacrylonitrire (**630**) to benzyl β-acetoxyallenoate (**631**) was performed with the Kwon's phosphine [(*R*)-**CXLIII**] and Cs_2CO_3 (Scheme 262).[311]

Scheme 262. The Kwon's Phosphine-Catalyzed [5+1] Cyclization Between 2-Benzoyl-3-methyl-acrylonitrire (630) and Benzyl β-Acetoxyallenoate (631) Catalyzed by (*R*)-CXLIII.[311]



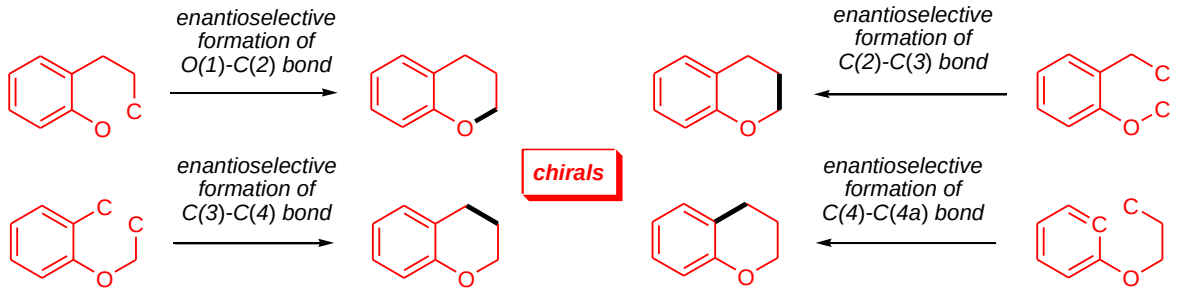
The phosphine adds to **631**, followed by acetate elimination, and gives the electrophile that undergoes the *Michael* addition with the anion of **630** to form the first zwitterionic intermediate **633**. The second *Michael* reaction gives the enolate intermediate **634** that, after a hydrogen shift

process to **635** and an *oxa-Michael* ring closure, affords the bicyclic product (1*R**,5*R**)-5-substituted benzyl-6-cyano-7-phenyl-8-oxa-bicyclo[3.3.1]nona-2,6-diene-2-carboxylate (**632**) with good yield and enantioselectivity. This is a preliminary note (3 experiments) in which the absolute configuration was not determined, but it is an exciting new approach that deserves further studies.

5. Enantioselective Cyclization to 3,4-Dihydro-2*H*-Chromenes.

A pathway to chiral 3,4-dihydro-2*H*-chromenes involves the formation, under enantioselective catalysis, of a bond in the pyran ring from a suitably substituted benzene derivative. The diagram of the different bonds formed through this approach is shown in Scheme 263 and each class of reactions, with the possible different approaches, will be discussed separately in next sections.

Scheme 263. **Intramolecular Cyclization to 3,4-Dihydro-2*H*-chromenes.**

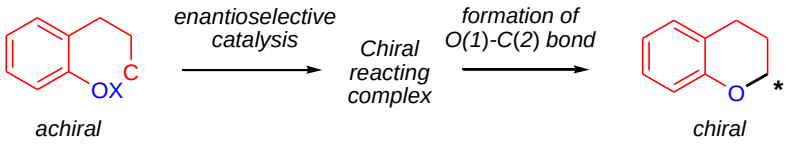


5.1. Formation of the O(1)-C(2) Bond.

The formation of the O(1)-C(2) bond to obtain 3,4-dihydro-2*H*-chromenes can be easily imagined to be performed from an *ortho*-substituted phenol by ring closure of the OH on a suitable electrophilic center placed at the end of a three-carbon chain. The process will require first the formation of the chiral complex with interaction of the substrate with the enantioselective catalyst, followed by the ring closure with formation of the O(1)-C(2) bond, as exemplified in Scheme 264.

The key step is the formation of the electrophilic center that may be a carbonyl group or an electrophilic double bond. Both must be adequately activated and placed in the correct geometrical position to undergo the attack of the nucleophilic OH.

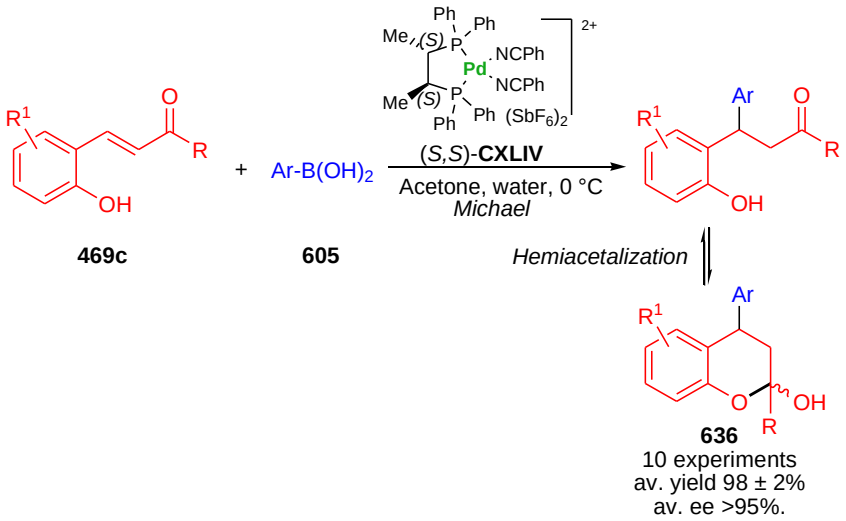
Scheme 264. Intramolecular Ring Closure with Formation of the O(1)-C(2) Bond



5.1.1. Formation of the O(1)-C(2) Bond via [Michael/Hemiacetalization] Reaction.

The first example is based on β-(2-hydroxyaryl)-enones **469c** that have the suitable reacting groups, hydroxyl and carbonyl, although not placed in the correct position. However, the induction of the chirality was obtained with the β-addition of arylboronic acids **605**, catalysed by the Pd(II)-chiraphos complex (*S*,*S*)-**CXLIV**. The Michael addition introduces the chiral center (whose absolute configuration was not determined) with excellent yield and enantioselectivity, giving compounds **636** that are in a rapid equilibrium with the cyclic hemiketals, the 2-hydroxy-4-aryl-4*H*-chromenes, whose structures fit the subject of this review (Scheme 265).[312]

Scheme 265. Intramolecular Cyclization of β-(2-Hydroxyaryl)-enones 469c with Arylboronic Acids 605 via Pd(II)-(*S*,*S*)-Chiraphos Catalyzed [Michael/Hemiacetalization] Reactions.[312]

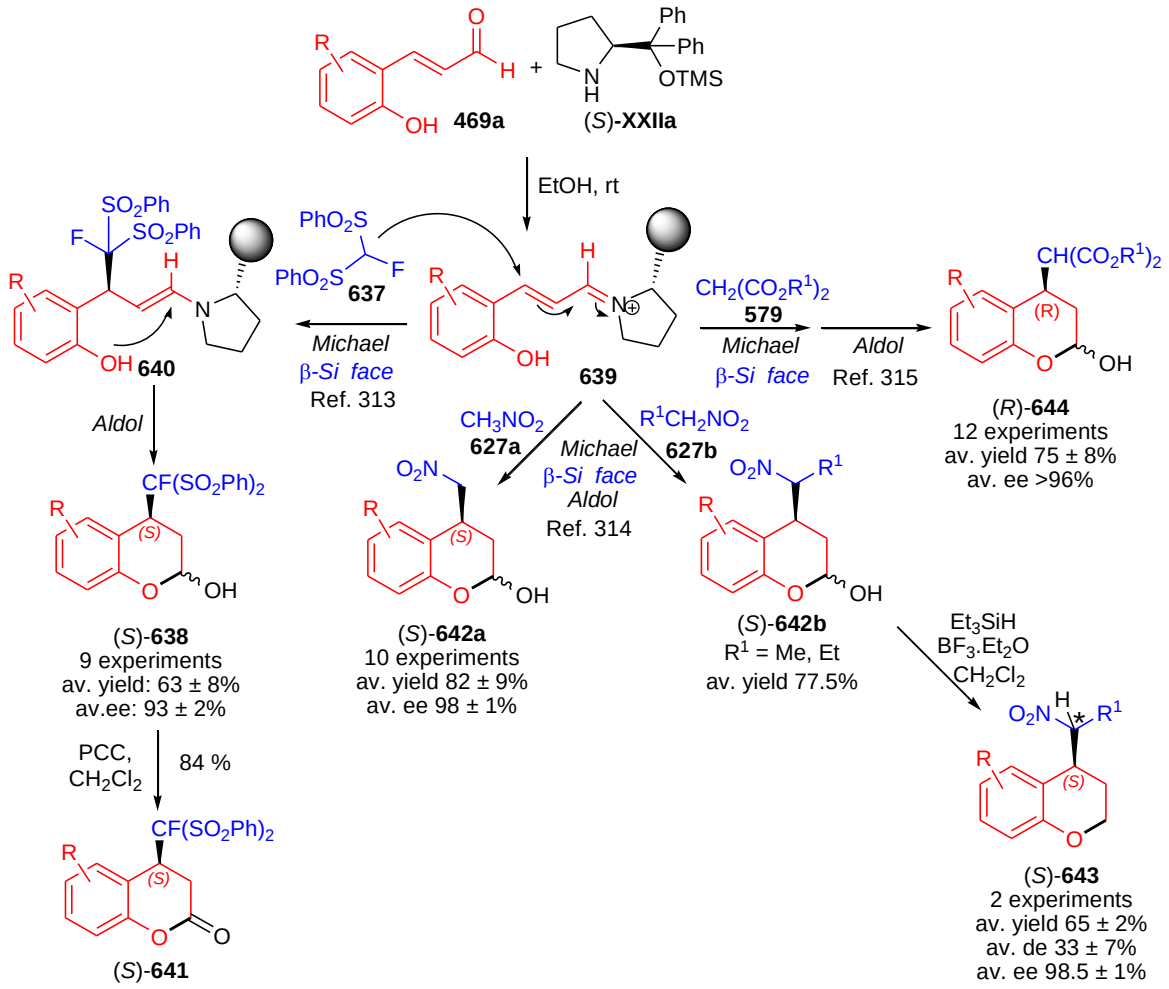


5.1.2. Formation of the O(1)-C(2) Bond via [Michael/Aldol] Reaction.

The development of the reaction above reported is based on the use of prolinol derivatives as organocatalysts, which introduce a formal change in the reaction sequence. After the Michael addition, an aldol step substitutes the hemiacetalization, but the reaction product remains the same after the hydrolytic cleavage of the proline residue.

The addition of fluorobis(phenylsulfonyl)methane **637** to 3-(2-hydroxyphenyl)-acrylaldehydes **469a**, catalysed by TMS-derivative of diphenylprolinol (*S*)-**XXIIa** as the organocatalyst is a paradigmatic example of [Michael/Aldol] cascade synthesis of fluorochroman-2-ol derivatives **638** (Scheme 266).[313] The organocatalyst activates the acrylaldehyde by forming the iminium ion **639** that undergoes the Michael attack of **637** to the less sterically hindered *β-Si* face affording the enamine intermediate **640**. The intramolecular aldol reaction followed by hydrolytic cleavage gives (*S*)-**638** with moderate yields and excellent enantioselectivities, allowing the recycle of the catalyst. The Authors reported a further oxidation step with PCC to fluorochroman-2-one (S)-**641** to emphasize the reaction utility.

Scheme 266. Enantioselective Intramolecular Cyclization of 3-(2-Hydroxyphenyl) acrylaldehyde 469a with Different Nucleophiles Catalyzed by (*S*)-XXIIa.[313-315]



An analogous pathway is that followed in the intramolecular cyclisation of the same aldehyde **469** with nitroalkanes **627**, again catalysed by (*S*)-**XXIIa** (Scheme 266).[314] The intermediate iminium ion **639** undergoes the Michael attack of **627** to the *β-Si* face, followed by the aldol reaction. With nitromethane **627a** the products are 3,4-dihydro-4-(nitromethyl)-2*H*-chromen-2-ols (*S*)-**642a** and the average enantioselectivity in 10 experiments is an astonishing 98% ee. With nitro-ethane and -propane (**627b**) the average yield of (*S*)-**642b** is 77.5%, and these products can be reduced to chromans (*S*)-**643** with Et_3SiH/BF_3 to give two diastereoisomers, which retain the excellent enantioselectivity of **642b**.

The third example of reaction that follows the previously reported pathway is the intramolecular cyclisation of the same aldehyde **469a** with malonates **579** catalysed by (*S*)-**XXIIa** (Scheme 266).[315] The products are 2-(3,4-dihydro-2-hydroxy-2*H*-chromen-4-yl)malonates (*R*)-**644**, which are formed again by the attack of the nucleophile to the *β-Si* face of **639**.

One short comment to the above three examples of [Michael/Aldol] cascade reactions between **469a** and different nucleophiles, all catalysed by (*S*)-**XXIIa**. The Michael attack occurs always on the same *β-Si* face of the common iminium ion intermediate **639**, and the induced average enantioselectivity is always above 95% ee.

5.1.3. Formation of the O(1)-C(2) Bond. via Oxa-Michael or via [Oxa-Michael/Decarboxilation] Tandem Reaction

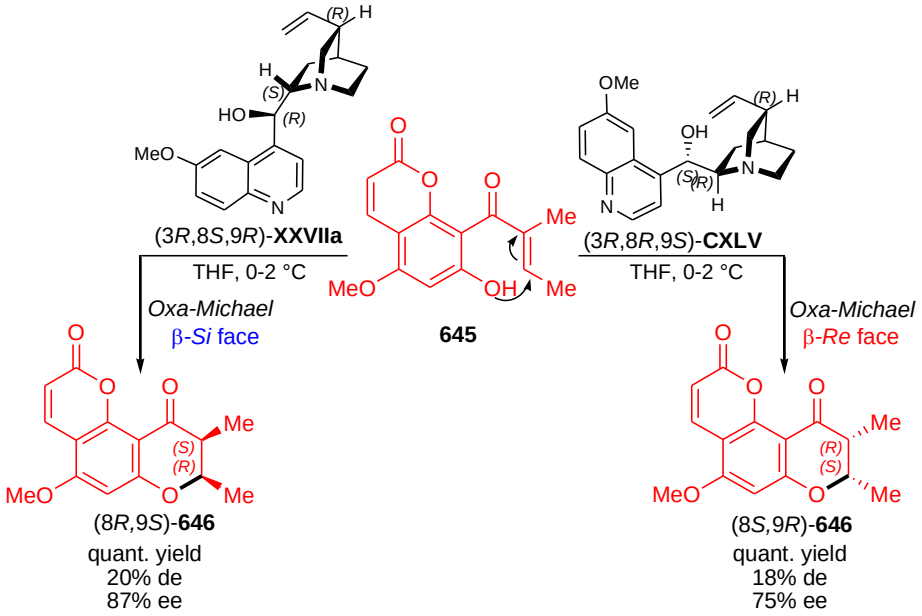
The formation of the O(1)-C(2) bond by ring closure of the OH onto either a carbonyl group or an analogue function acting as the electrophilic center, has been discussed in the above sections. In an interesting variant, the β-position of the electrophilic double bond is the site of the oxa-Michael attack.

This pathway was first proposed by Ishikawa as an easy and useful approach to anti-HIV-1 active *Calophillum* coumarins through the intramolecular oxa-Michael addition of the *o*-tigloyphenol **645** that cyclises to the tricyclic chromanone **646** in the presence of a tertiary amine.[316] The use of (-)-quinine (3*R*,8*S*,9*R*)-**XXVIIa** instead of TEA, and the consequent asymmetric

induction, was fundamental for the development of the asymmetric oxa-Michael synthesis and led to (8*R*,9*S*)-**646** in quantitative yield and with very good enantioselectivity (Scheme 267) through the *β-Si* face attack (in accordance to the convention described in Figure 4).

The same reaction, catalysed by (+)-quinidine (3*R*,8*R*,9*S*)-**CXLV**, led to the enantiomeric product (8*S*,9*R*)-**646** through the *β-Re* face attack, again in a quantitative yield and with good enantioselectivity (Scheme 267).[316] The main limit of these cyclizations is the low diastereoselectivity observed, which is due to the formation of significant amounts of *trans* products during the protonation following the attack.

Scheme 267. Enantioselective Intramolecular Oxa-Michael Cyclization of 645 Catalyzed by Quinine or Quinidine.[316]

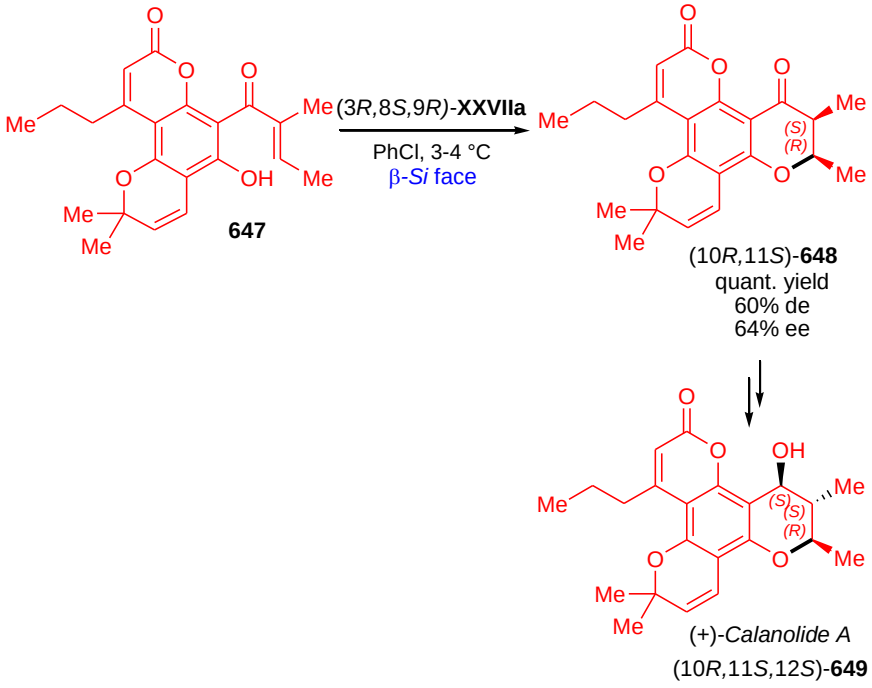


Since the above protocol immediately appeared an attractive route to biologically active products characterized by chromanone structures, Ishikawa went in the depth of the enantioselective intramolecular oxa-Michael cyclization with *Cinchona alkaloids.*

The first target was the synthesis of anti HIV-1 (+)-*Calanolide A*.[317] The intramolecular oxa-Michael cyclization of *o*-tigloylphenol derivative **647**, catalysed by quinine (3*R*,8*S*,9*R*)-**XXVIIa**, affords quantitatively a cyclization product, in which the major product is (10*R*,11*S*)-**648** in 60% de and 94% ee. Since (+)-*Calanolide A* has a *trans* configuration, **648** was treated with MgI_2 to convert

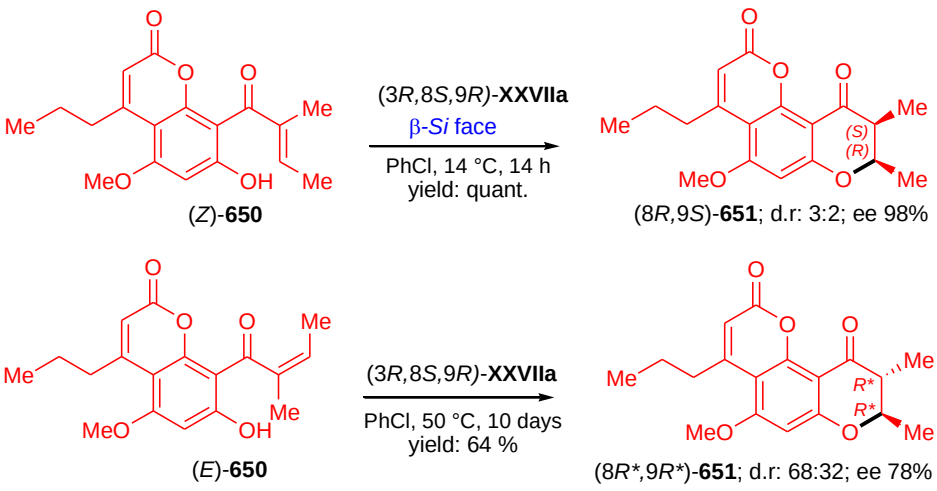
the *cis* structure to the *trans* one and submitted to reduction with LiAl(O-*t*-But)$_3$H that afforded the target (10*R*,11*S*,12*S*)-**649** (Scheme 268).[317]

Scheme 268. Enantioselective Intramolecular Oxa-Michael Synthesis of (+)-*Calanolide A*.[317]



In the light of the above results, the solvent and temperature effects were investigated on the quinine-catalysed intramolecular oxa-Michael cyclization of *o*-tigloylphenol derivative (*Z*)-**650**. The best solvent was found to be the chlorobenzene, and the attack to the *β-Si* face, gave (8*R*,9*S*)-**651** with the best stereoselectivity at 14 °C (Scheme 269).[318]

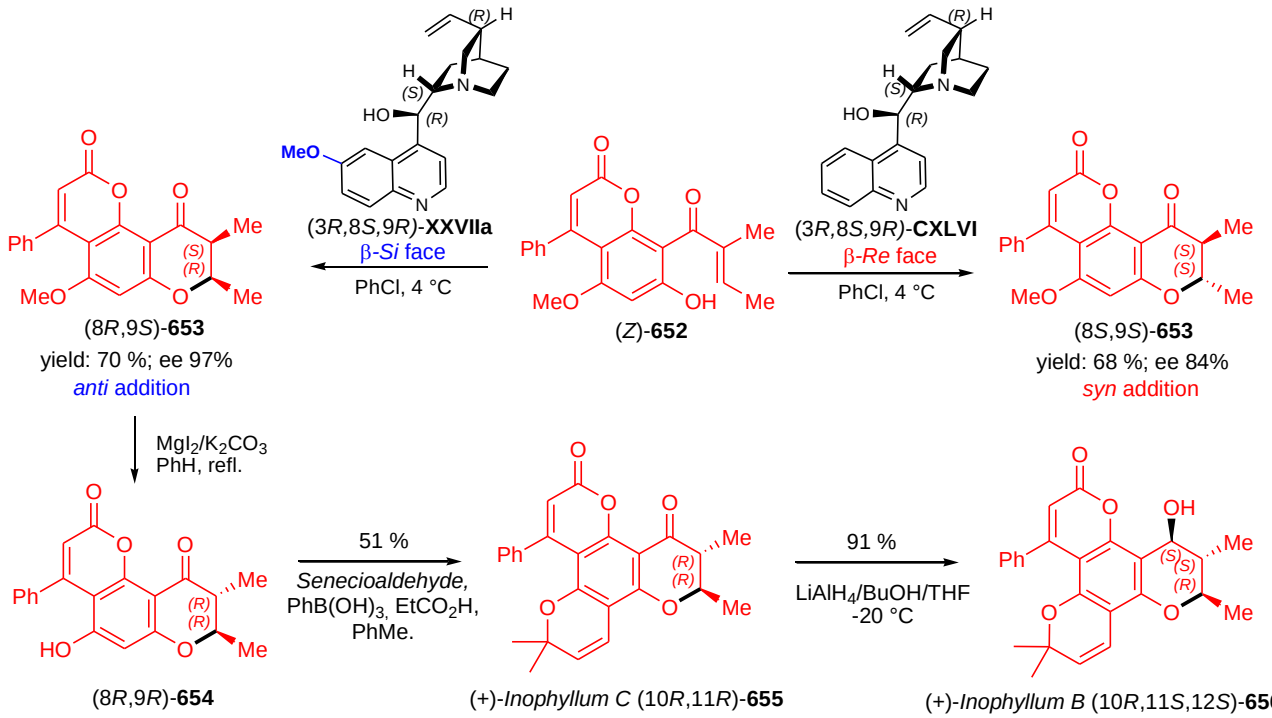
Scheme 269. Solvent and Temperature Effect on the Oxa-Michael Cyclization of (*Z*) and (*E*)-650 Catalyzed by (3*R*,8*S*,9*R*)-XXVIIa.[318]



As a comparable experiment, the same protocol was applied to *o*-angeloylphenol (*E*)-**650**. Heating at 50 °C for 10 days the oxa-Michael cyclization afforded a 68:32 mixture of *trans* and *cis* **651**, with the former obtained in 78% ee (Scheme 269).[318]

The wide possibilities of the intramolecular oxa-Michael cyclization protocol can be evaluated from the total syntheses of (+)-*Inophyllum B* and *C*, the most active components for inhibition against HIV-reverse trascriptase isolated from *C. inophillum*.[319] The oxa-Michael cyclization of (*Z*)-7-hydroxy-5-methoxy-4-phenyl-8-tigloylcoumarin (**652**) with (-)-quinine (3*R*,8*S*,9*R*)-**XXVIIa**, under the above described protocol, gives (8*R*,9*S*)-**653** through a *β-Si* face attack and the sequential *anti* addition. This product was treated with MgI_2 to convert the *cis* structure to *trans* (8*R*,9*R*)-**654** that was cyclized with senecioaldehyde to the tetracyclic (+)-*Inophyllum C* (10*R*,11*R*)-**655**, and then reduced to (+)-*Inophyllum B* (10*R*,11*S*,12*S*)-**656** (Scheme 270).[319]

Scheme 270. Influence of the Methoxy Substituent of (-)-Cinchona Alkaloid on the Stereochemistry of the Intramolecular Oxa-Michael of 652 in the Synthesis of (+)-*Inophyllum C* and *B*.[319]

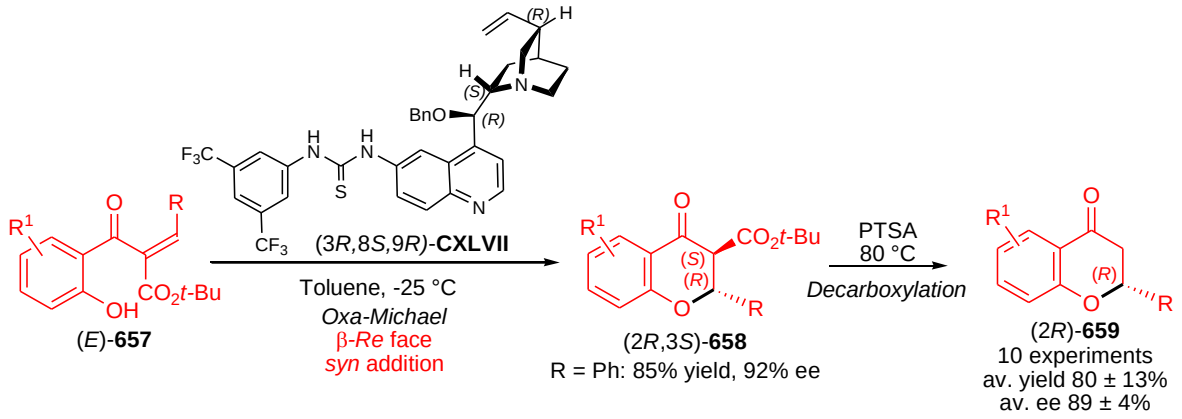


The investigation of the influence of different commercially available *cinchona* alkaloids on the stereoselectivity of the reaction led to the very interesting observation that the cyclization of (*Z*)-**652**

with (-)-cinchonidine (3*R*,8*S*,9*R*)-**CXLVI** gives (8*S*,9*S*)-**653** through a *β-Re* face attack and the sequential *syn* addition. This suggests the importance of the organocatalyst methoxy substituent on the overall reaction pathway that will have useful fallout when fully cleared (Scheme 270).[319]

Other catalysts have been used to perform the intramolecular oxa-Michael cyclization and we wish to discuss now the reaction with chiral 9-benzyloxy-cinchonidin-thiourea (3*R*,8*S*,9*R*)-**CXLVII**.[320] The reaction was first optimized on *t*-butyl 3-(2-hydroxyphenyl)-3-oxo-2-benzylidenpropanoate (*E*)-**657** that afforded *t*-butyl 3,4-dihydro-4-oxo-2-phenyl-2*H*-chromene-3-carboxylate (2*R*,3*S*)-**658** through an oxa-Michael attack to the *β-Re* face and the sequential *syn* addition. Then, the reaction was run under the conditions that led to the decarboxylation product (*R*)-**659** (Scheme 271).[320] Considering the structure of the cinchona fragment of the catalyst and the stereochemical outcome, the reader will be certainly surprised by the analogies of this reaction with the reaction described in Scheme 270 from (*Z*)-**652** to (8*S*,9*S*)-**653**.

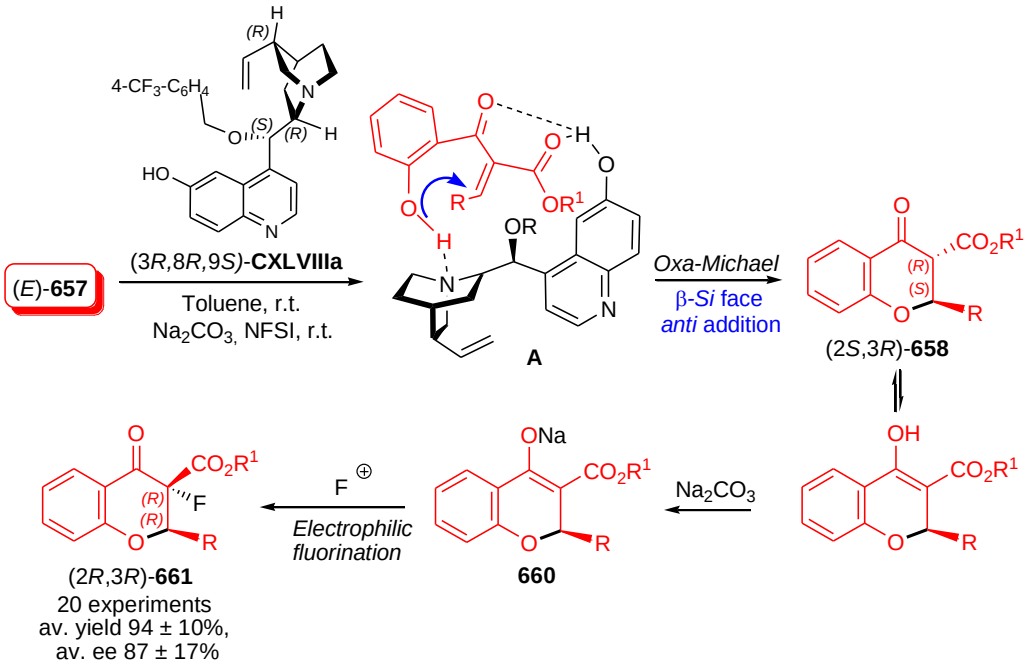
Scheme 271. Enantioselective Intramolecular Oxa-Michael Cyclization of (*E*)-657 Catalyzed by 9-Benzyloxy-cinchonidin-thiourea (3*R*,8*S*,9*R*)-CXLVII.[320]



This interesting result can be compared with that obtained from the tandem intramolecular [oxa-Michael cyclization/electrophilic fluorination] reaction, again from (*E*)-**657**, with the 9-OH-protected-6′-desmethyl quinidine derivative (3*R*,8*R*,9*S*)-**CXLVIIIa** as the organocatalyst.[321] The concurrent deprotection of 6-hydroxyquinolyl and the protection of 3-hydroxy groups make the bifunctional organocatalyst suitable to coordinate the phenoxy group of **657** with the tertiary amino

group and both carbonyl groups with the free OH group of the organocatalyst by hydrogen bonding. Thus, the proposed reacting intermediate **A** has a structure suitable to direct the oxygen nucleophile to attack the *β-Si* face of the double bond to form (2*S*,3*R*)-**658** after the hydrogen *anti*-addition. The formation of the sodium salt of the oxa-Michael product **660** makes this product appropriate to undergo electrophilic fluorination with *N*-fluorobenzenesulfonimide to afford the desired product (2*R*,3*R*)-**661** (Scheme 272).[321]

Scheme 272. Enantioselective Intramolecular [Oxa-Michael Cyclization/Electrophilic Fluorination] of (*E*)-657 with 9-OH-Protected-6′-desmethyl Quinidine Derivative (3*R*,8*R*,9*S*)-CXLVIIIa as organocatalyst.[321]

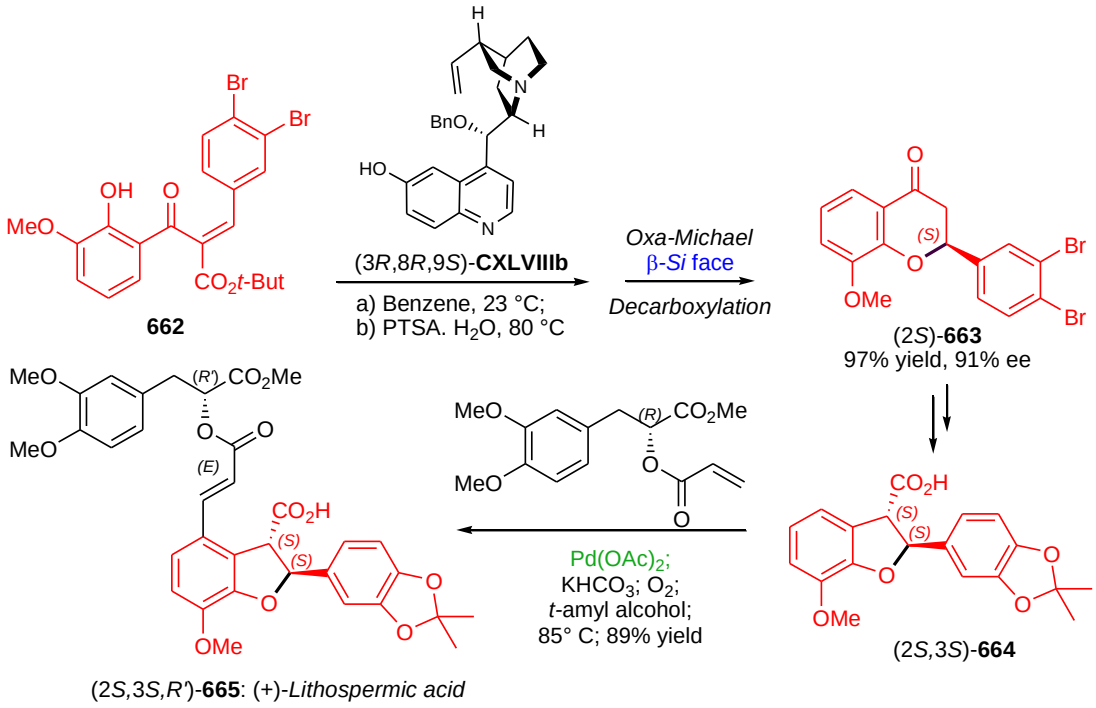


The relationship derived from the structure of the catalyst and the stereochemical outcome, illustrated from intermediate **A**, suggests that the configuration at the centers in 8 and 9 of the organocatalyst (3*R*,8*R*,9*S*)-**CXLVIIIa** induce the rear attack of the OH to the *β-Si* face of the double bond of (*E*)-**657**. It seems now reasonable that (3*R*,8*S*,9*R*)-**CXLVII** could afford a product with the opposite absolute configurations with the same reagent (Scheme 271).

The result of the tandem intramolecular oxa-Michael cyclization/electrophilic fluorination reaction catalysed by 9-OH-protected-6′-desmethyl quinidine derivative (3*R*,8*R*,9*S*)-**CXLVIIIa** is

confirmed in the [oxa-Michael cyclization/decarboxylation] catalyzed by the 9-benzyloxy-6′-desmethyl quinidine derivative (3*R*,8*R*,9*S*)-**CXLVIIIb** that differs for the benzylic protecting group. This reaction is applied to the enantioselective synthesis of (+)-*lithospermic acid*, a potent anti-HIV agent, and features the intramolecular oxa-Michael reaction of **662** under the conditions that causes the decarboxylation of the primary compound and the isolation, with excellent yield and enantioselectivity, of 2-(3,4-dibromophenyl)-2,3-dihydro-8-methoxychromen-4-one (*S*)-**663** that satisfactorily corresponds to the attack of the OH to the *β-Si* face of the double bond of **662** (Scheme 273).[322] (*S*)-**663** was submitted to rearrangement to dihydrobenzofuran (2*S*,3*S*)-**664** employing phenyliodine bis(trifluoroacetate) as the oxidant and anhydrous formic acid in the presence of H_2SO_4. The addition of the suitably designed chiral acrylate derivative functionalizes the position 4 affording the targeted (+)-*Lithospermic acid* (2*S*,3*S,R′*)-**665**.

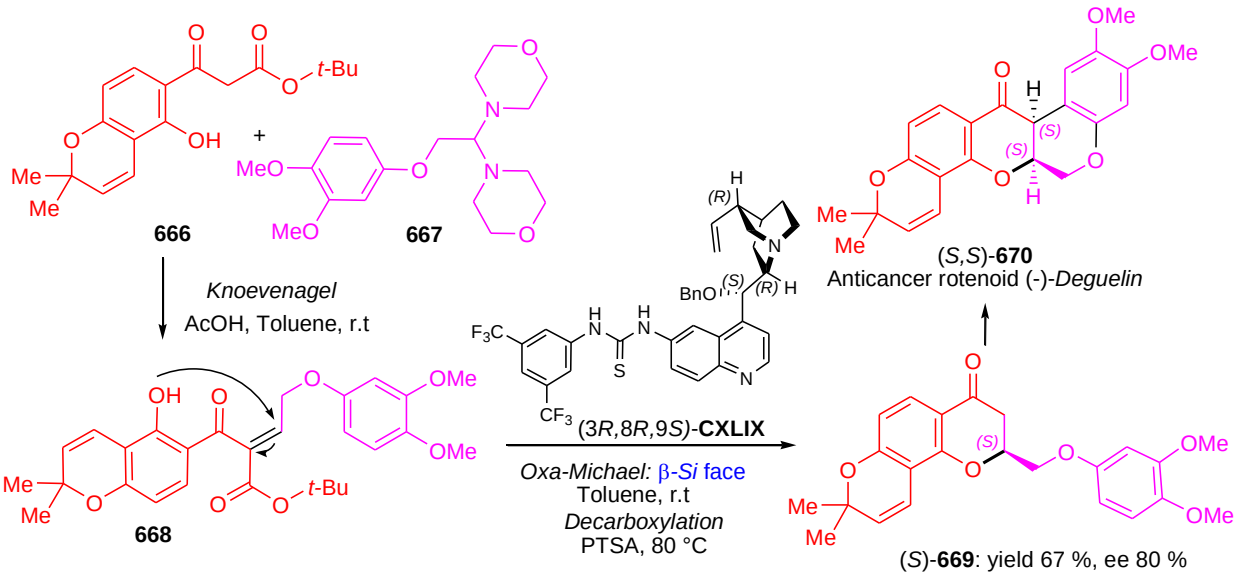
Scheme 273. Enantioselective Intramolecular [Oxa-Michael Cyclization/Decarboxylation] of 662 with 9-Benzyloxy-6′-desmethyl Quinidine Derivative (3*R*,8*R*,9*S*)-CXLVIIIb as Organocatalyst.[322]



The enantioselective intramolecular [oxa-Michael cyclization/decarboxylation] tandem reaction with *cinchona* alkaloids-based catalysts was discussed in detail above because the authors of this review were fascinated by the intriguing elegance of the relationship between structure of the catalyst and stereochemistry of the products. Moreover, this protocol can be usefully applied to the synthesis of biologically interesting natural products.

(-)-*Deguelin* is a rotenoid natural product with specific potential as chemopreventive agent. A concise enantioselective synthesis can be realized starting from *t*-butyl 3-(5-hydroxy-2,2-dimethyl-2*H*-chromen-6-yl)-3-oxopropanoate (**666**) and 4-(2-(3,4-dimethoxyphenoxy)-1-morpholinoethyl)morpholine (**667**), whose Knoevenagel reaction gives **668**. This undergoes "one pot" [oxa-Michael cyclization/decarboxylation] to afford the chromanone precursor (*S*)-**669** (Scheme 274).[323] The last step of the synthesis is an oxidative arylation with copper(II) triflate that stereoselectively leads to the *cis*-fused natural product (*S*,*S*)-**670**, with no evidence of the *trans*-fused isomer.

Scheme 274. Enantioselective Synthesis of (-)-*Deguelin* via Intramolecular [Oxa-Michael Cyclization/Decarboxylation] Tandem Reaction.[323]

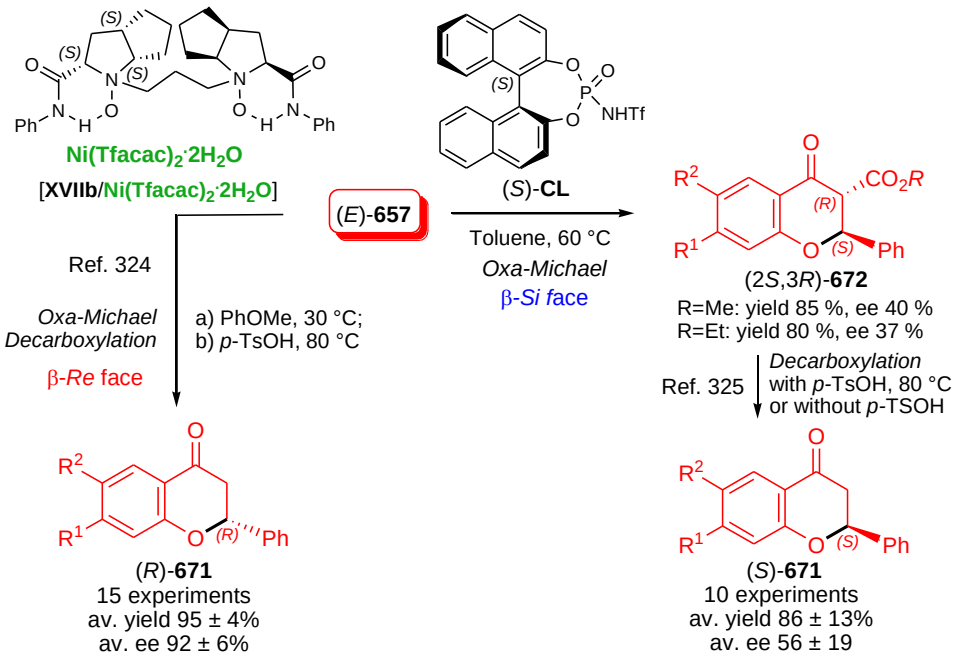


From the synthetic point of view, in this reaction the thiourea cinchona-based organocatalyst (3*R*,8*R*,9*S*)-**CXLIX** affords (*S*)-**669** through a *β-Si* face attack. Its diastereoisomer (3*R*,8*S*,9*R*)-

CXLII gives (*R*)-**669** through a *β-Re* face attack. This result demonstrates the importance of the configuration of the stereocenters at the positions 8 and 9 to determine the chirality transmission.

The enantioselective intramolecular oxa-Michael cyclization of (*E*)-**657** can be also performed with catalysts that do not have the structure based on *cinchona* alkaloids. The chiral *N,N'*-dioxide Nickel(II) complex (2*S*,3a*S*,6a*S*)-**XVIIb** belongs to a catalyst family already encountered in previous chapters and gives a "one pot" [oxa-Michael/decarboxylation] reaction, affording (*R*)-**671** with broad substrate scope since the chiral flavanones are obtained with excellent yields and very good enantioselectivities over 15 experiments (Scheme 275).[324] Worse results are obtained with chiral *N*-triflylphosphoramide (*S*)-**CL** because both the oxa-Michael products (2*S*,3*R*)-**672**, and the products of the "one pot" [oxa-Michael/decarboxylation] reaction (*S*)-**671** are obtained with good yields, but unsatisfactory enantioselectivities (Scheme 275).[325]

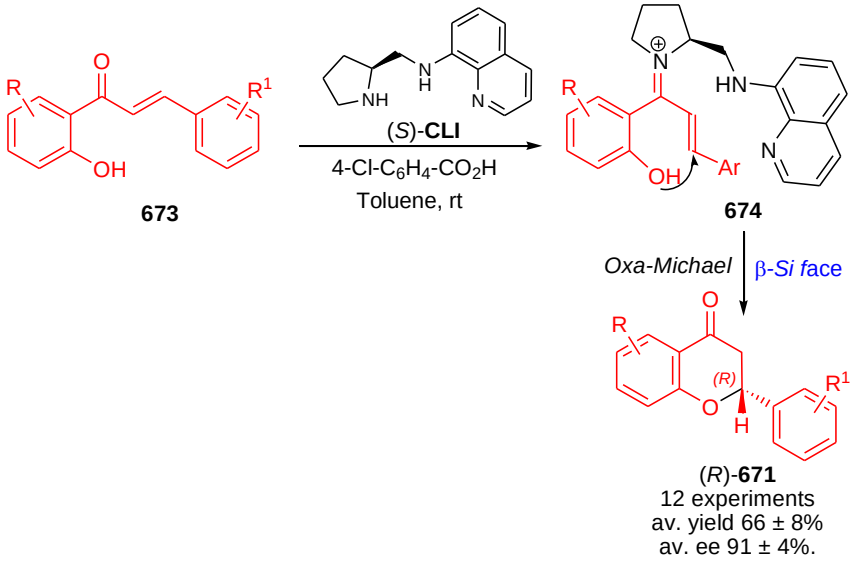
Scheme 275. Enantioselective Intramolecular [Oxa-Michael Cyclization/Decarboxylation] of (*E*)-668 with Different Catalysts.[324,325]



The intramolecular oxa-Michael cyclization was also applied to different classes of reagents. Simple 1-(2-hydroxyaryl)-3-arylprop-2-en-1-ones **673** are activated by the organocatalyst (*S*)-*N*-[(pyrrolidin-2-yl)methyl]quinolin-8-amine [(*S*)-**CLI**] through the formation of the iminium ion

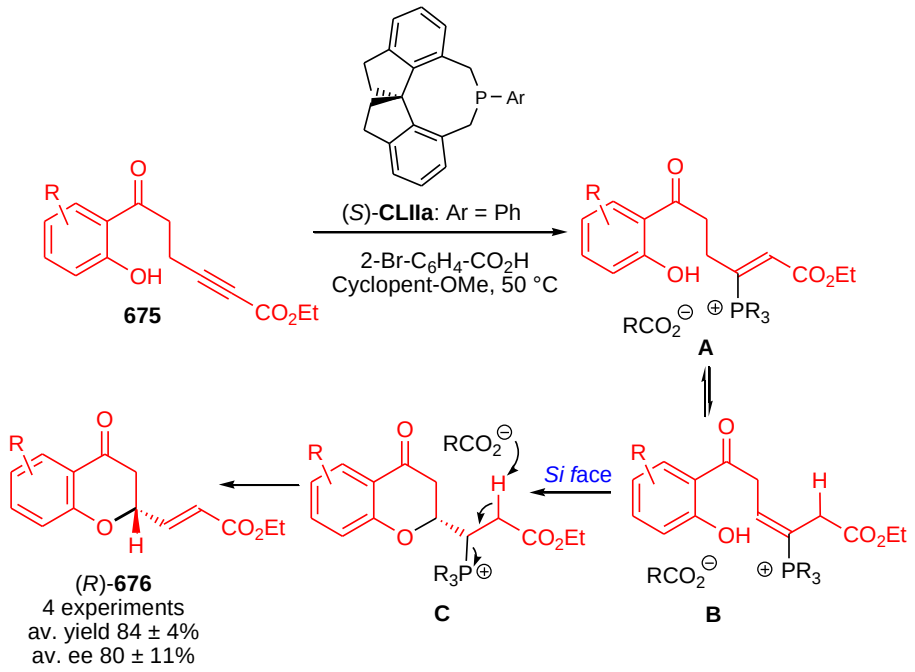
intermediate **674**, and the result of the oxa-Michael cyclization is (*R*)-**671** through the attack to the less hindered *β-Si* face of the former enone (Scheme 276).[326]

Scheme 276. Enantioselective Intramolecular Oxa-Michael Cyclization (*E*)-673 Catalyzed by (*S*)-CLI.[326]



To close this section, we report the enantioselective phosphine-catalyzed synthesis of ethyl 3-(3,4-dihydro-4-oxo-2*H*-chromen-2-yl)acrylates [(*R*)-**676**] from ethyl 6-(2-hydroxyphenyl)-6-oxohex-2-ynoates (**675**), which cyclize with the chiral spiro-phosphine (*S*)-**CLIIa** (Ar = Ph) as the catalyst. This is a quite unusual example because the triple bond is not the direct site of reaction, but it is the critical site that promotes the formation of the electrophilic center on which the hydroxy group will determine the O(1)-C(2) bond formation (Scheme 277).[327] A mechanistic rationale has been proposed by Trost and Li[328] where the phosphine adds the triple bond giving the phosphonium ion **A** that isomerizes to **B**, generating the electrophilic center. The ring closure occurs through the nucleophilic attack of the hydroxy group to the *Si* face of the double bond inducing the chirality in **C** that loses the catalyst to afford (*R*)-**676** (Scheme 277).[327]

Scheme 277. Enantioselective Intramolecular Cyclization of 675 Catalyzed by (*S*)-CLIIa.[327,328]



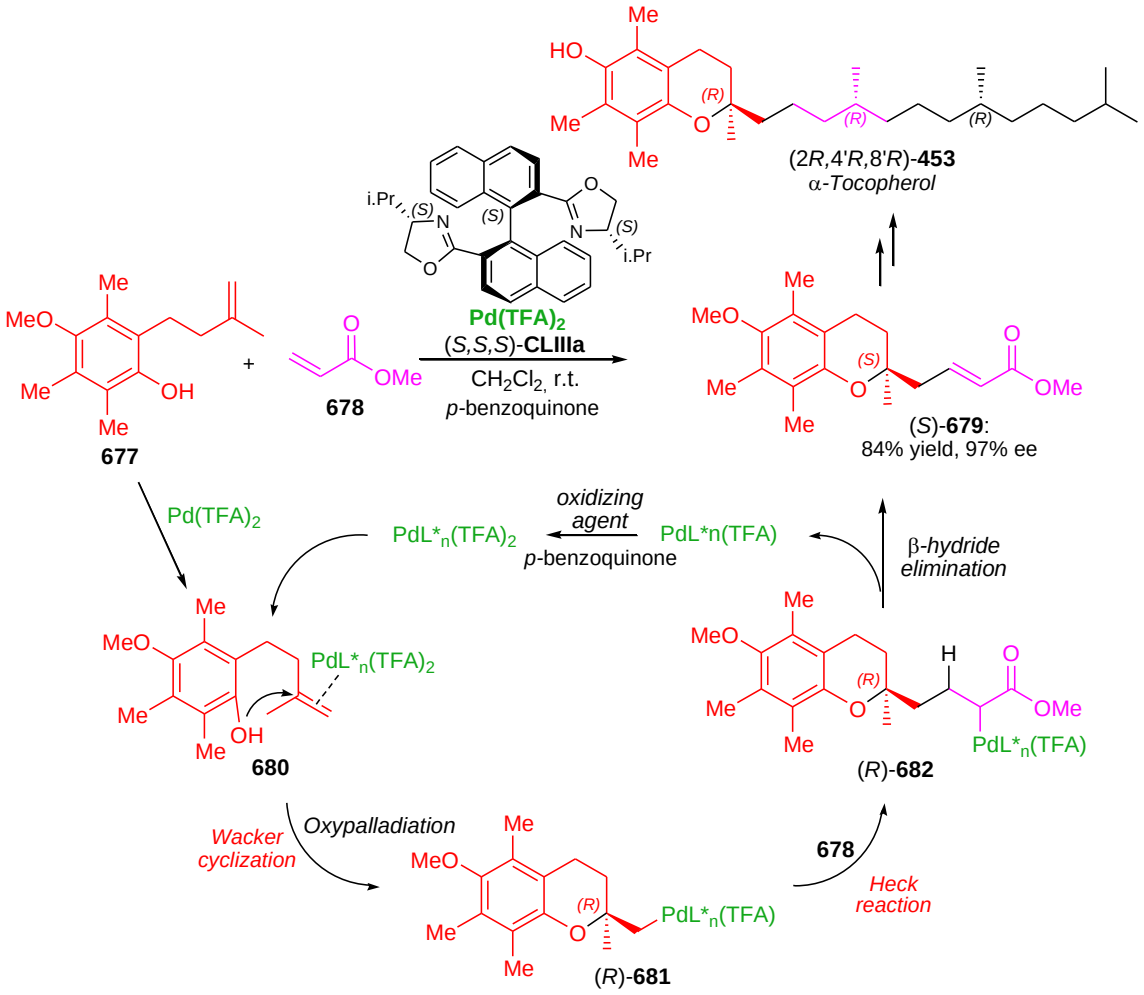
5.1.4. Intramolecular Formation of the O(1)-C(2) Bond via [Wacker/Carbonylation] and [Wacker/Heck] Tandem Reaction

In the above sections we have discussed the formation of the O(1)-C(2) bond by ring closure of the OH onto electrophilic double bond as the site of the oxa-Michael attack. Another approach, widely applied to the synthesis of natural products, was introduced by Tietze in 2005 and deals with the palladium-catalysed domino reaction in which the chiral Pd(II) complex activates the double bond. The reaction allows the formation of the chiral chromane framework by a Wacker cyclization, with the possible concurrent introduction of part of the side chain through a Heck reaction.

This enantioselective domino reaction was first applied to the synthesis of (*R*,*R*,*R*)-α-*Tocopherol* (**453**), one of the eight *natural* compounds of the vitamin E family. The reaction between 4-methoxy-2,3,5-trimethyl-6-(3-methylbut-3-enyl)phenol (**677**) and methyl acrylate (**678**), with *p*-benzoquinone as the oxidant, catalysed by the complex [Pd(OCOCF$_3$)$_2$/(*S*,*S*,*S*)-iPr-BOXAX] (*S*,*S*,*S*)-**CLIIIa**, gives "one pot" the chroman (*S*)-**679** that is the result of the sequel of reactions outlined in Scheme 278.[329,330] The first step is the coordination of the Pd(II) chiral catalyst to the

double bond of **677**. The Waker oxypalladiation affords the intermediate **680** that cyclizes enantioselectively to the chroman (*R*)-**681**. This palladium species reacts in accordance to the Heck reaction with **678** and the addition product (*R*)-**682** leads, by β-hydride elimination, to (*S*)-**679** and Pd(0) that undergoes reoxidation by *p*-benzoquinone to Pd(II), allowing to start a new catalytic cycle. The product (*S*)-**679**, obtained with excellent yield and 96%ee, is the key intermediate easily converted with standard protocols to *α-tocopherol* (2*R*,4′*R*,8′*R*)-**453**.

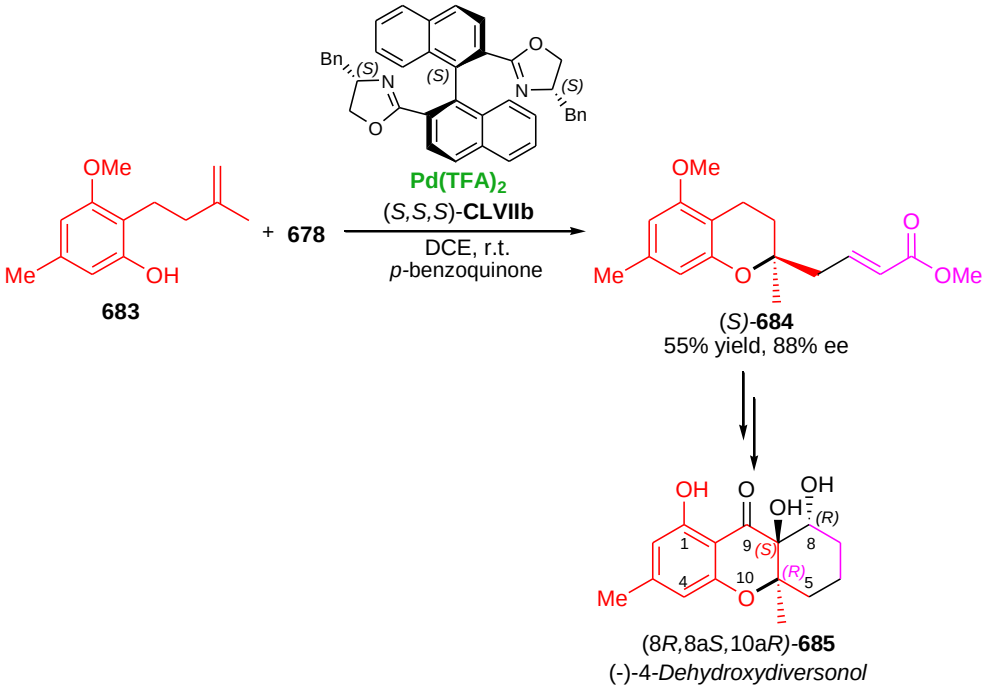
Scheme 278. Palladium-Catalyzed Enantioselective Wacker/Heck Domino Reaction to Afford (*S*)-679, Intermediate for the Synthesis of *α-Tocopherol* (2*R*,4′*R*,8′*R*)-453.[329,330]



The reaction pathway, above described and discussed in detail, is the protocol followed by the Tietze group for the synthesis of an important series of natural products, always with excellent results. The specific syntheses will be reported below, putting in evidence reagents, catalysts, chiral products, with a final mention to the natural target.

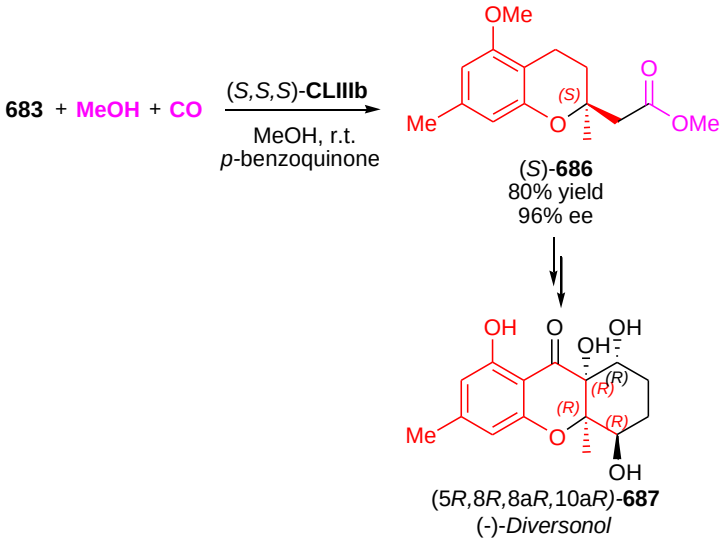
The second target was the synthesis of *4-Dehydroxydiversonol*, a tetrahydroxanthenone structurally related to the fungal metabolite diversonol and to secalonic acids. The reaction between 3-methoxy-5-methyl-2-(3-methylbut-3-enyl)phenol (**683**) and methyl acrylate (**678**), in the presence of *p*-benzoquinone and catalysed by the complex [Pd(OCOCF$_3$)$_2$/(*S*,*S*,*S*)-Bn-BOXAX] (*S*,*S*,*S*)-**CLIIIb**, gives "one pot" the chroman (*S*)-**684** in 88% ee, the key intermediate to (8*R*,8a*S*,10a*R*)-**685**, the *4-Dehydroxydiversonol* (Scheme 279).[331]

Scheme 279. Synthesis of *4-Dehydroxydiversonol* via the Palladium-Catalysed Enantioselective Wacker/Heck Domino Reaction to Afford (*S*)-684.[331]



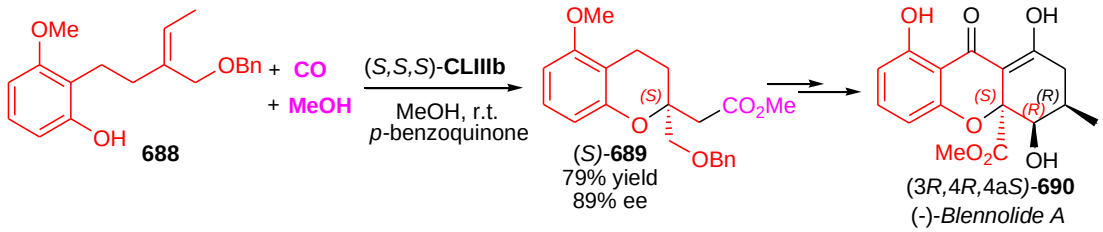
The above synthesis was integrated with the more sophisticated synthesis of (-)-*Diversonol*, the enantiomer of the fungal metabolite isolated from *Penicillum diversum* and *Microdiplodia sp.* The protocol includes an interesting variant because the reaction of **683**, instead to involve methyl acrylate, is based on the domino [Wacker/carbonylation/methoxylation] in the presence of carbon monoxide and methanol. The product (*S*)-**686** was obtained in 80% yield and 96% ee and this was converted through a multistep process into the 1,4,8,9a-tetrahydroxy-4a,6-dimethyl-2,3,4,4a-tetrahydro-1*H*-xanthen-9(9a*H*)-one [(5*R*,8*R*,8a*R*,10a*R*)-**687**], the expected (-)-*Diversonol* (Scheme 280).[332]

Scheme 280. Palladium-Catalyzed Enantioselective Domino Wacker/Carbonylation/Methoxylation Reaction Affording (*S*)-686, Intermediate for the Synthesis of (-)-*Diversonol*.[332]



The research around the fungal metabolites continued with the synthesis of *Blennolide A*, isolated from endophytic fungus *Blennoria* sp. The protocol is based on the domino [Wacker/carbonylation/methoxylation] and the reaction between the 2-[(*Z*)-3-((benzyloxy)methyl) pent-3-enyl]-3-methoxyphenol **688** with carbon monoxide and methanol, catalysed by (*S*,*S*,*S*)-**CLIIIb**, gave (*S*)-**689** in 79%yield and 89%ee. A multistep process converted the product into (3*R*,4*R*,4a*S*)-**690**, the targeted product (-)-*Blennolide A* (Scheme 281).[333]

Scheme 281. Palladium-Catalyzed Enantioselective Domino [Wacker/Carbonylation/Methoxylation] Reaction Affording (*S*)-689, Intermediate for the Synthesis of (-)-*Blennolide A*.[333]

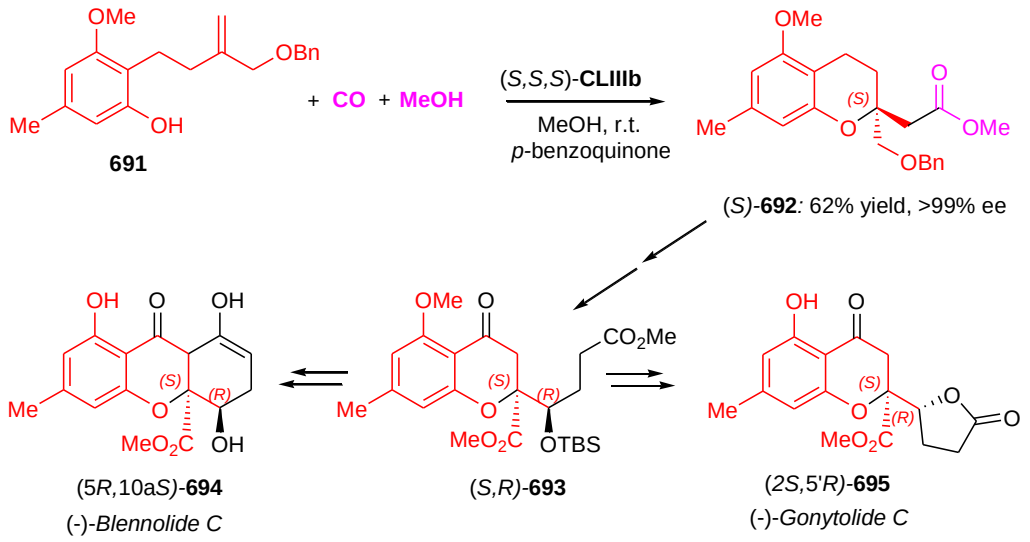


The synthesis of fungal metabolites derived from endophytic fungus *Blennoria sp*. was completed by the preparation of a second metabolite from the same species, the *Blennolide C*. Due

to some structural analogies, the entire research found its completion in the synthesis of the (-)-*Gonytolide C*, isolated from the fungus *Genytrichum sp.*

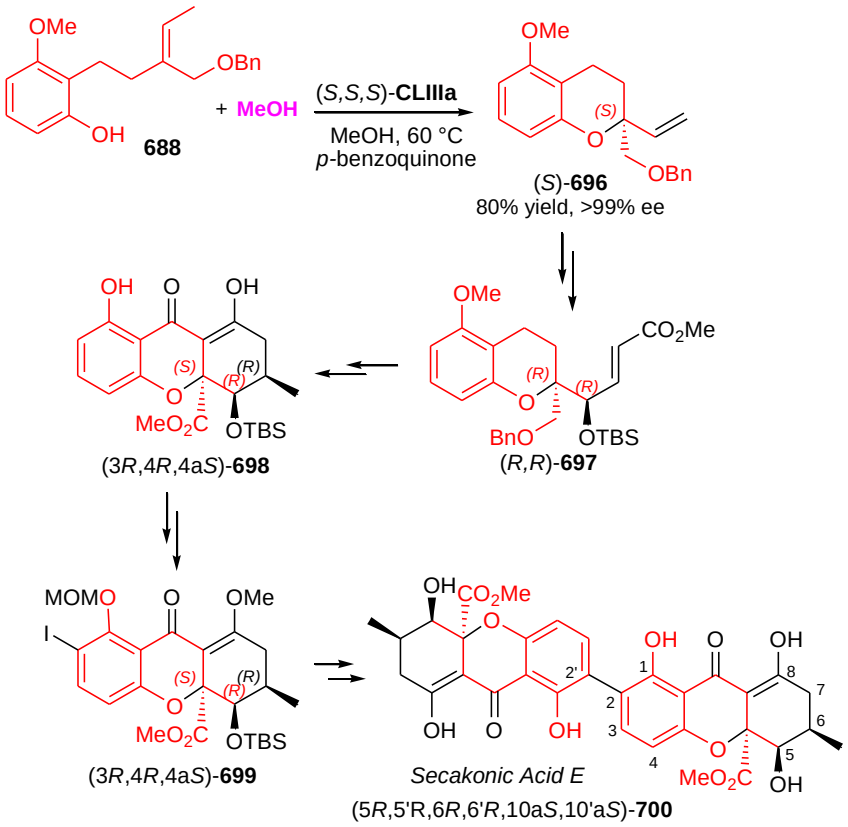
The protocol is again based on the domino [Wacker/carbonylation/methoxylation] in which the reaction of 2-[3-((benzyloxy)methyl)but-3-enyl]-3-methoxy-5-methylphenol (**691**) with carbon monoxide and methanol, catalyzed by (*S,S,S*)-**CLIIIb**, gave (*S*)-**692** in 62% yield and ee >99%. This product, having the (*S*) chiral center of the targeted natural products, was submitted to a reaction sequence: reduction, elimination, Sharpless dihydroxylation of the double bond, protection and selective deprotection, chain elongation by Wittig-Horner reaction, modification of the angular CH_2OBn group into a carbomethoxy group. At the end of the sequence of reactions (*S,R*)-**693** was obtained, which is the key intermediate for the syntheses of both metabolites (Scheme 282).[334] By trichlorotitanium isopropoxy-induced ring closure, the tetrahydroxanthenone scaffold was obtained and easily converted into (5*R*,10a*S*)-**694**, the (-)-*Blennolide C*. The treatment of (*S,R*)-**693** with triethylamine trihydrofluoride induced the γ-lactone formation that was demethylated to give (2*S*,5′*R*)-**695**, the (-)-*Gonytolide C*.[334]

Scheme 282. Palladium-Catalyzed Enantioselective Domino [Wacker/Carbonylation/Methoxylation] Reaction to (S)-692, Intermediate for the Synthesis of (-)-*Blennolide C* and (-)-*Gonytolide C*.[334]



Another Wacker-type cyclization, the domino methylation variant, proved to be fruitful for the synthesis of natural product and was applied to the preparation of a member of the family of Secalonic acids, natural mycotoxins with a dimeric tetrahydroxanthenone skeleton. The main research was directed to the synthesis of *Secakonic Acid E*, which bears two units linked by a 2,2′ biphenol linkage.[335] The reaction of the already mentioned **688** with methanol, catalysed by (*S,S,S*)-**CLIIIa** gave the enantiomerically pure [(benzyloxy)methyl]-3,4-dihydro-5-methoxy-2-vinyl-2*H*-chromene [(*S*)-**696**]. The Sharpless dihydroxylation was the first step of a sequence of standard reactions, which gave (*R,R*)-**697** that was cyclized to (3*R*,4*R*,4a*S*)-**698** with three contiguous stereocenters in the correct configuration. The iodination with $BnNMe_3ICl_2$ afforded the monomer (3*R*,4*R*,4a*S*)-**699** suitable to be dimerized to (5*R*,5′*R*,6*R*,6′*R*,10a*S*,10′a*S*)-**700**, the targeted *Secakonic Acid E* (Scheme 283).[335]

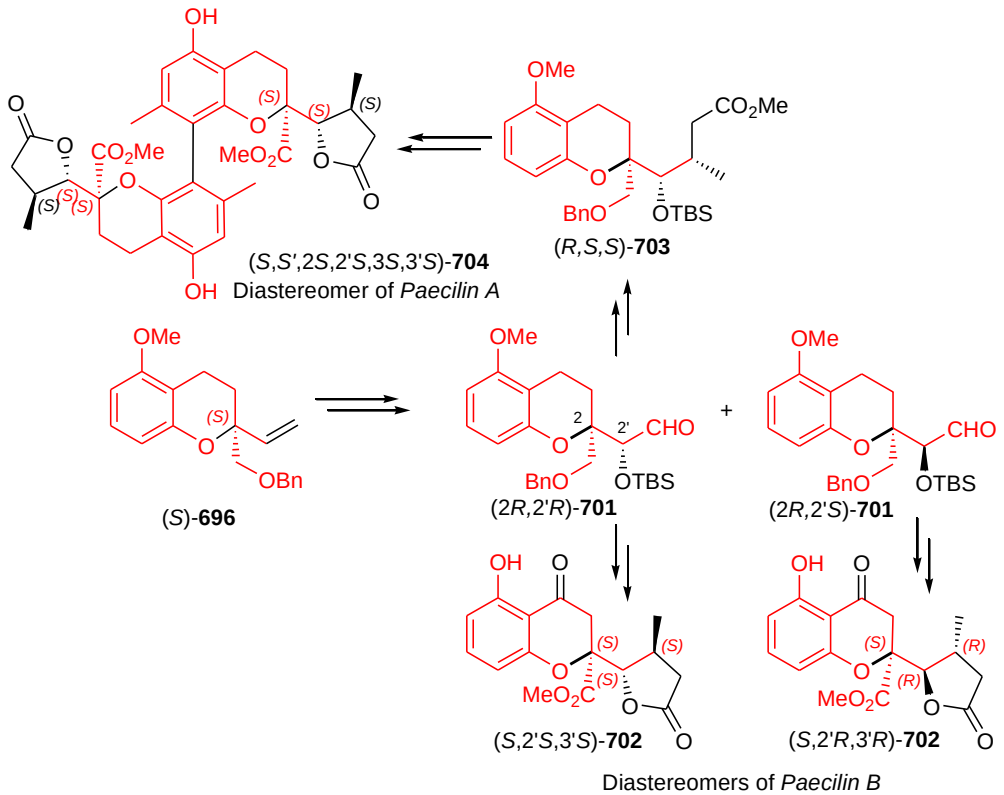
Scheme 283. Palladium-Catalyzed Enantioselective Domino Wacker/Methoxylation Reaction to (*S*)-696, Intermediate for the Synthesis of *Secakonic Acid E*.[335]



The product of the above domino [Wacker/methoxylation] [(benzyloxy)methyl]-3,4-dihydro-5-methoxy-2-vinyl-2*H*-chromene [(S)-**696**] was the key to focus the structure of two metabolites of endophytic fungus *Paecilomyces sp.*: *Paecilin A* and *B* whose absolute and relative configurations are still unknown.

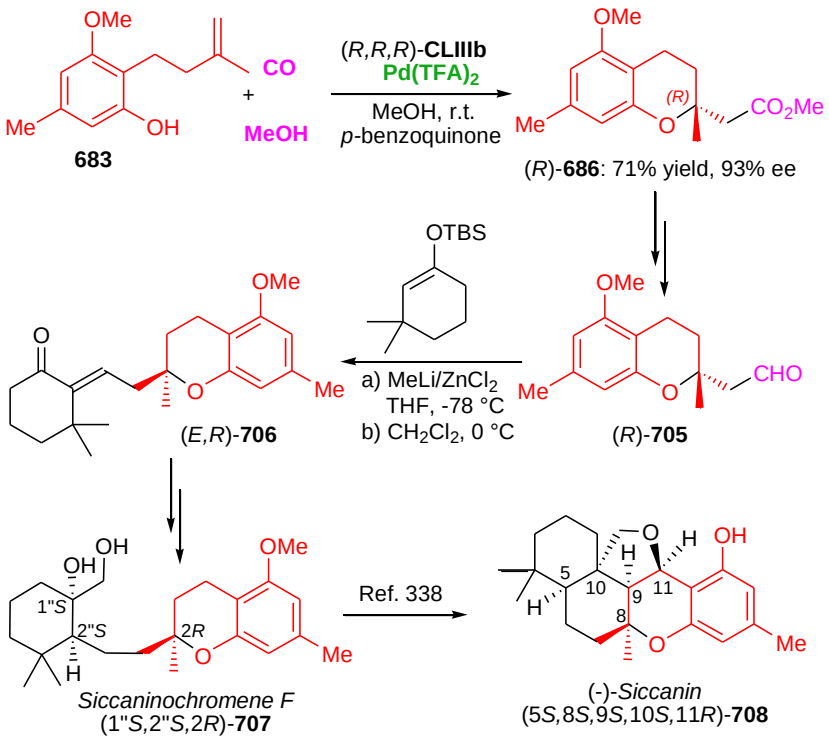
The "*Paecilin puzzle*" started with the Sharpless dihydroxylation of (*S*)-**696** that, after protection and oxidation, gave the two diastereomeric aldehydes, (*R*,2′*R*)-**701** and (*R*,2′*S*)-**701**, converted into two of the four possible diastereoisomers of *Paecilin B*: (*S*,2′*S*,3′*S*)-**702** and (*S*,2′*R*,3′*R*)-**702**. Furthermore, (2*R*,2′*R*)-**701** was converted into (*R*,*S*,*S*)-**703** that, after proper modifications, dimerized to (*S*,*S*′,2*S*,2′*S*,3*S*,3′*S*)-**704**, one of the several possible diastereoisomers of *Paecilin B* (Scheme 284).[336] These synthetic efforts had a disappointing end because the spectroscopic data of all the new compounds did not match those of the isolated natural products. Hence, absolute and relative configurations of *Paecilin A* and *B* are still unknown.

Scheme 284. The "*Paecilin Puzzle*" from the Palladium-Catalyzed Enantioselective Domino [Wacker/Methoxylation] of Product (*S*)-699.[336]



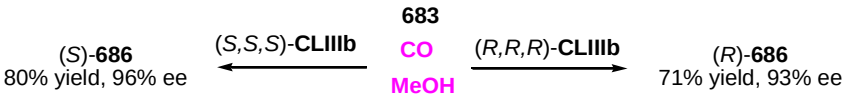
We close this section with a domino [Wacker/carbonylation/methoxylation] reaction, showing how flexible is this protocol to plan the synthesis of complex natural products and also to allow shedding some light on the transmission of the chirality from the catalyst to the product. *Siccanin* and different structurally related *Siccanochromenes* are fungal metabolites isolated from the culture broth of *Helminthosporium siccans*. The enantioselective domino [Wacker/carbonylation/methoxylation] of the already mentioned **683** was now catalysed by (*R*,*R*,*R*)-**CLIIIb** and gave (*R*)-**686** (Scheme 285).[337] The ester is reduced to aldehyde **705** and the aldol condensation with (3,3-dimethylcyclohex-1-enyloxy)(tert-butyl)dimethylsilane gave (*E*,*R*)-**706** under the conditions reported in Scheme 285. This product is ready to be converted in the targeted *Siccanochomenes F* with the configuration (1"*S*,2"*S*,2*R*)-**707**. It is important to remember that this diol is a late intermediate in the synthesis of *Siccanin* (*S*,*S*,*R*,*R*,*S*,*S*)-**708** developed by Trost.[338]

Scheme 285. Palladium-Catalyzed Enantioselective Domino [Wacker/Carbonylation/Methoxylation] Reaction to (*R*)-686, Intermediate for the Synthesis of *Siccaninochromene F* and (-)-*Siccanin*.[337]



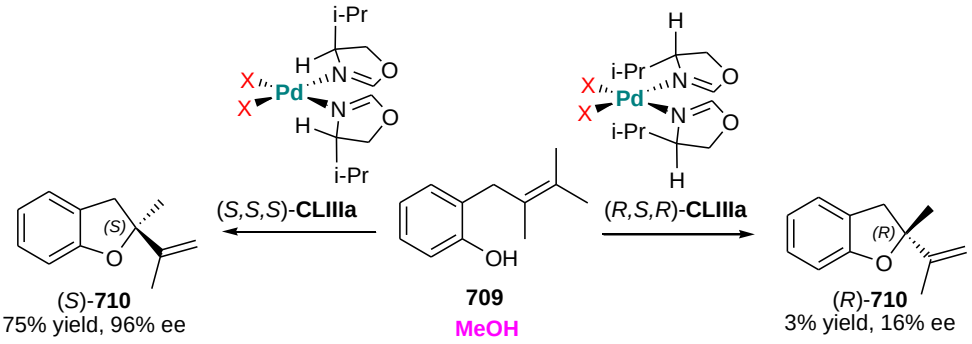
Scheme 286 allows to compare the above result [(*R*,*R*,*R*)-**CLIIIb** gives (*R*)-**686**] with that in Scheme 280 in which the same reagent **683**, under the same experimental conditions with (*S*,*S*,*S*)-**CLIIIb**, gives the enantiomer (*S*)-**686**. As expected, two catalysts that are enantiomers give enantiomeric products with nearly identical yields and opposite enantioselectivity.

Scheme 286. Schematic Structure of the [Wacker/Carbonylation/Methoxylation] of 683 catalyzed by (*S*,*S*,*S*)- and (*R*,*R*,*R*)-CLIIIb.



What should be the result changing the configuration of the stereogenic carbon of the peripheral oxazolines from *S* to *R*, maintaining the configuration of the central binaph moiety? An answer can be derived from an interesting paper in which two data are reported: the X-ray structure of the complex (*S*,*S*,*S*)-**CLIIIa** and the [Wacker/methoxylation] of 2-(2,3-dimethylbut-2-enyl)phenol (**709**) catalysed by (*S*,*S*,*S*)- and (*R*,*S*,*R*)-**CLIIIa**.[339] The complex (*S*,*S*,*S*)-**CLIIIa** adopts a square planar structure in which two nitrogen of the oxazoline ring and two oxygen of triflate are attached to palladium, with the isopropyl groups as the axial substituents. Whereas the [Wacker/methoxylation] of **709**, catalyzed by (*S*,*S*,*S*)-**CLIIIa**, affords the (*S*) enantiomer of 2,3-dihydro-2-methyl-2-(prop-1-en-2-yl)benzofuran [(*S*)-**710]** in 80 % yield and 96% ee, the (*R*,*S*,*R*)-**CLIIIa** catalyst gives (*R*)-**710** with 3 % yield and 16 ee (Scheme 287).[339]

Scheme 287. Schematic Representation of the [Wacker/Methoxylation] Reactions of 709 catalyzed by (*S*,*S*,*S*)- and (*R*,*S*,*R*)-CLIIIa.[339]



The first step of the reaction is the coordination of the Pd(II) to the double bond. This is the process already observed in Scheme 278 with the same catalyst, which affords the intermediate **680** that cyclizes enantioselectively to the chroman **682**. A schematic structure of the reacting intermediates based on computer modelling of the X-ray data have been suggested and this allowed to propose the respective reacting intermediates of (*S,S,S*)- and (*R,S,R*)-**CLIIIa** shown in Scheme 287.[339] The presence of two equatorial i-Pr groups makes more difficult and less selective the further step and rationalise the lower performance of the catalyst

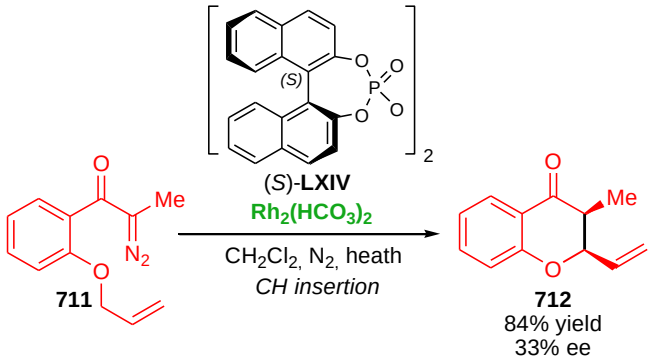
In conclusion, an efficient transmission of the chirality from [Pd(II)/BOXAX] catalyst to the product requires a careful coordination between the stereogenic chiral centers of oxazoline and binaph.

5.2. Formation of the C(2)-C(3) Bond

The formation of the C(2)-C(3) bond to obtain 3,4-dihydro-2*H*-chromenes is an unusual reaction because it is not simple to imagine an electrophilic carbon atom adequately placed to undergo the attack of a nucleophilic carbon atom located in the suitable position for the required bond formation.

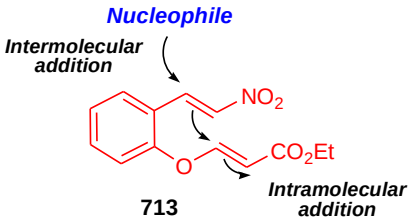
An "*old*" research successfully explored this option by synthesizing the diazoketone **711** that was submitted to diazo decomposition and chiral C-H insertion, catalysed by the rhodium(II) complex of (*S*)-(+)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate (*S*)-**LXIV**.[340] The reaction proceeds smoothly and the C-H insertion gives *cis*-**712** as major product in a very good yield, although with poor enantioselectivity. For this reason, the above synthetic route to 3,4-dihydro-2*H*-chromenes is only a reaction with an historical interest (Scheme 288).[340]

Scheme 288. Synthesis of 3,4-Dihydro-2*H*-chromene Derivative 713 by Formation of the C(2)-C(3) Bond.[340]



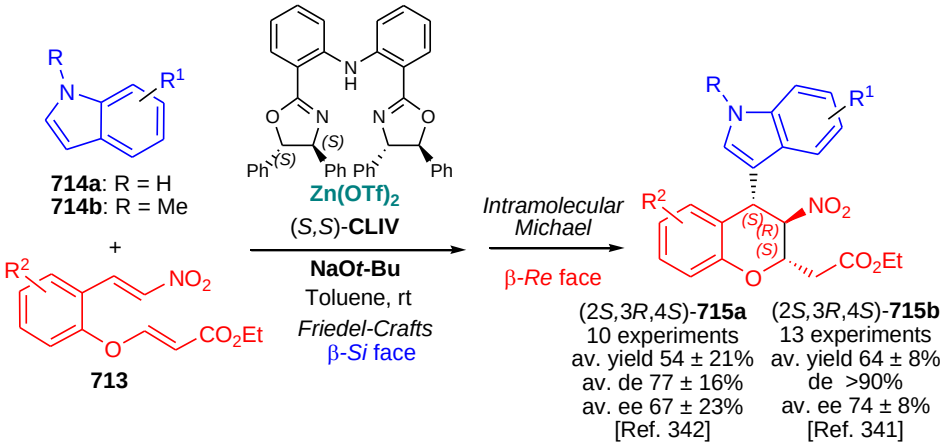
Much more important are the applications of ethyl 3-(2-nitrovinyl)phenoxy)acrylate **713**, a molecule that seems to be born to undergo *intermolecular/intramolecular* cascade reactions. The β-position of its nitro-olefinic part is appropriate to undergo an intermolecular nucleophilic addition that produces the anionic center suitably placed to add intramolecularly to the electrophilic β-position of the acrylate moiety (Scheme 289).

Scheme 289. Intermolecular/Intramolecular Nucleophilic Addition Cascade Reactions on 713.



Two recent papers deal with the nucleophilic addition of indoles **714** to ethyl 3-(2-nitrovinyl)phenoxy)acrylates **713**, catalysed by a diphenylamine-linked [bis(oxazoline)/$Zn(OTf)_2$] complex (4*S*,5*S*,4'*S*,5'*S*)-**CLIV**.[341,342] The reaction run with 1-methylindoles **714b** begins with the Friedel-Crafts attack of indole to the *β-Si* face of the nitroalkene fragment of **713**, followed by the intramolecular Michael addition of the anion to the *β-Re* face of the unsaturated ester affording the (2*S*,3*R*,4*S*)-substituted 2*H*-chromens **715**. From 13 experiments, yields and enantioselectivities are satisfactory, and the diastereomeric ratio is always greater than [95:5] (Scheme 290).[341] If the reaction is performed with *NH* indoles **714a**,[342] under the same experimental conditions and with the same catalyst, yields, diastereo- and enantioselectivities are significantly decreased.

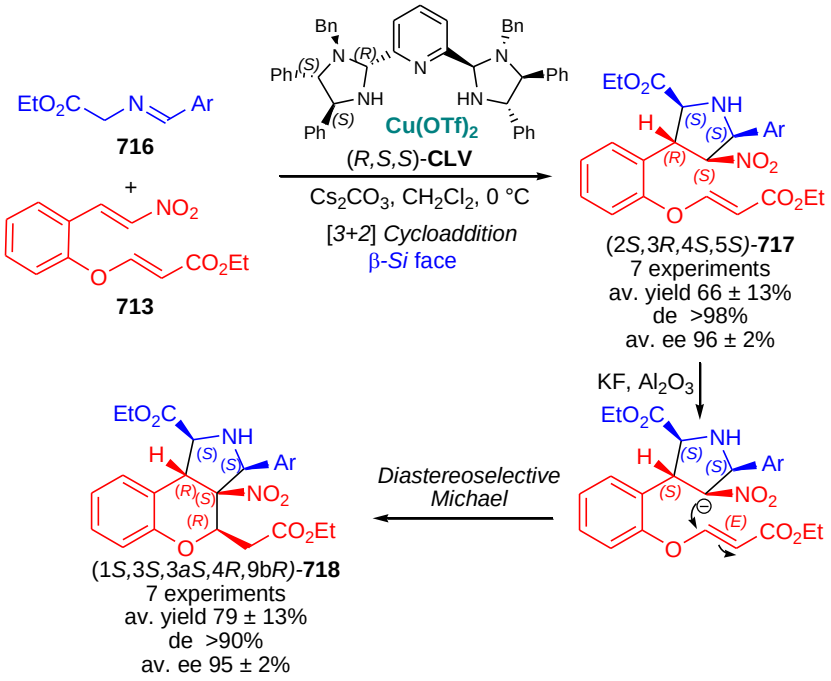
Scheme 290. Enantioselective [Intermolecular Friedel-Crafts/Intramolecular Michael] Cascade Reactions between 713 and Indoles 714 Catalyzed by (4*S*,5*S*,4'*S*,5'*S*)-CLIV/Zn(OTf)$_2$ Complex.[341,342]



Interestingly, the reaction between **713** and iminoesters **716**, catalysed by the chiral bis(imidazolidine)pyridine-Cu(II) complex (2*R*,4*S*,5*S*)-**CLV**, gives an intermolecular 1,3-dipolar cycloaddition through an *endo ts* that involves the attack to the *β-Si* face of **713** affording ethyl 3-[2-[(*E*)-2-(carbethoxy-eth-1-enoxyphenyl]-4-nitro-5-aryl-pyrrolidine-2-carboxylates (2*S*,3*R*,4*S*,5*S*)-**717** (Scheme 291).[343] The products were obtained within moderate yields, but with excellent diastereo- (de >98%) and enantioselectivity.

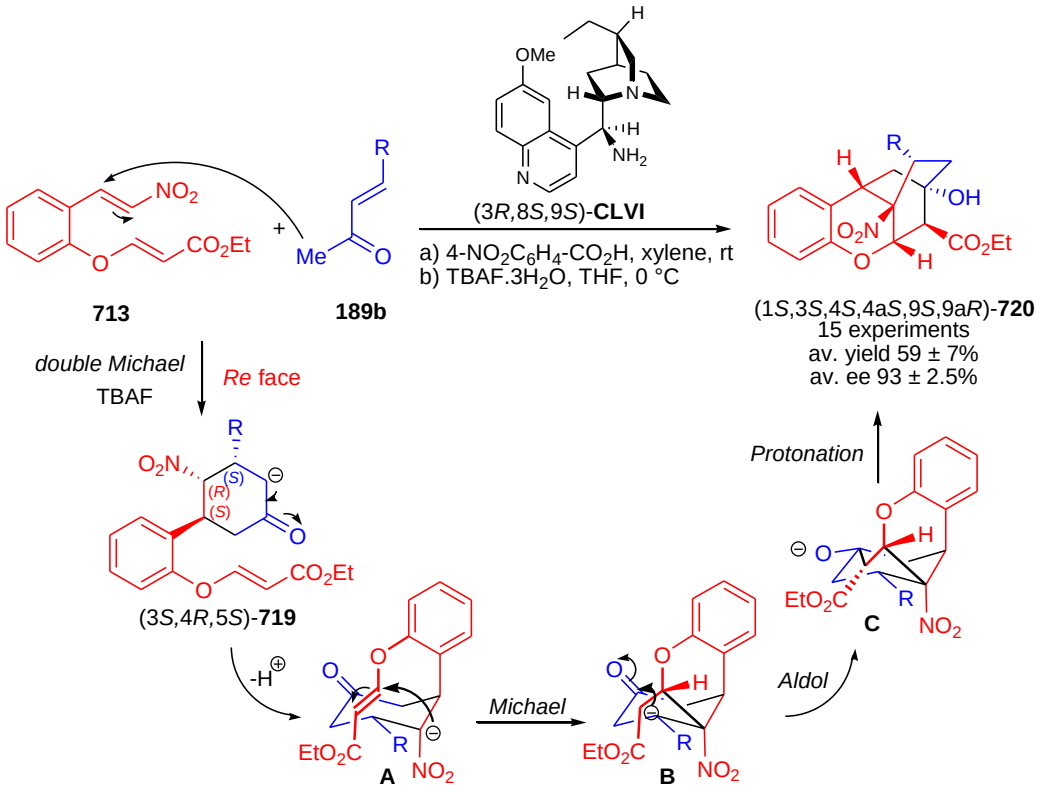
In the presence of a base (KF/Al_2O_3), the 1,3-dipolar cycloadducts generate the corresponding anions that give rise to an intramolecular Michael ring closure leading to the (1*S*,3*S*,3a*S*,4*R*,9b*R*)-1*H*-chromeno[3,4-*c*]pyrrole derivatives **718**, with a further new chiral center formed with a complete control of diastereoselectivity.

Scheme 291. Enantioselective Intermolecular-1,3-Dipolar Cycloaddition/Intramolecular Michael Cascade Reactions Between 713 and Iminoesters 716 Catalyzed by (2*R*,4*S*,5*S*)-CLV/Cu(OTf)$_2$ Complex.[343]



When the same electrophile **713** reacts with methyl stiryl ketones **189b**, which here behave as nucleophiles, in the presence of dihydro-9-amino-epiquinine derivative (3*R*,8*S*,9*S*)-**CLVI** as the organocatalyst, the cascade reaction begins with the intermolecular *Michael* attack of the anionic **189b** on the *β-Re* face of nitroalkene to afford, through the *Michael* ring closure, the first intermediate **719** whose three chiral centers have the (3*S*,4*R*,5*S*) absolute configuration (Scheme 292).[344]

Scheme 292. Enantioselective Intermolecular-Intramolecular [Michael/Michael/Michael/ Aldol] Cascade Reactions Between 713 and Methyl Stiryl Ketones 189b Catalyzed by (3*R*,8*S*,9*S*)-CLVI.[344]



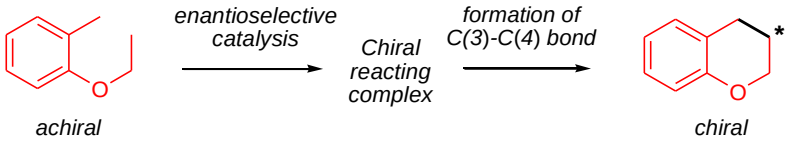
In the presence of TBAF, cyclohexanone (3*S*,4*R*,5*S*)-**719** is deprotonated and the nitro-anion **A** gives the intramolecular step, the *Michael* attack to the *β-Si* face of the stiryl group, affording **B**. This intermediate undergoes an intramolecular *aldol* attack to the *Re* face of the carbonyl group to form the intermediate **C**, whose protonation gives the tetracyclic product ethyl 1-substituted-3-hydroxy-9a-nitro-2,3,4,4a,9,9a-hexahydro-1*H*-3,9-methanoxanthene-4-carboxylates (1*S*,3*S*,4*S*,4a*S*,9*S*,9a*R*)-**720**, with moderate yields, but with excellent enantioselectivities.

A *one-pot reaction* that gives a product with *six chiral centers*, precisely obtained with 93% average ee in 15 different experiments, through a sequence of intermolecular and intramolecular steps, proves that phantasy applied to organic synthesis makes easy to build a bond between an electrophilic C(2) and a nucleophilic C(3) to obtain optically active 3,4-dihydro-2*H*-chromene derivatives.

5.3. Formation of the C(3)-C(4) Bond

The intramolecular ring closure to 3,4-dihydro-2*H*-chromenes can be performed through the formation of the C(3)-C(4) bond. Different routes can be planned, but the key step is always the formation of an electrophilic carbon atom suitably placed to undergo the attack by another carbon behaving as a nucleophile. The carbon that will became the future C(4) must belong to a substituent *ortho* to the oxygen of a suitably substituted aryl ether. The process requires first the formation of the chiral reacting complex by interaction of the reagent with the enantioselective catalyst. This reacting complex develops both the nucleophilic and the electrophilic centers, then the ring closure, exemplified in Scheme 293, will afford the chiral 3,4-dihydro-2*H*-chromene. As in many of the previous intramolecular ring closure reactions, normally these processes occur between a carbonyl group and a double bond. The different variants will be described below.

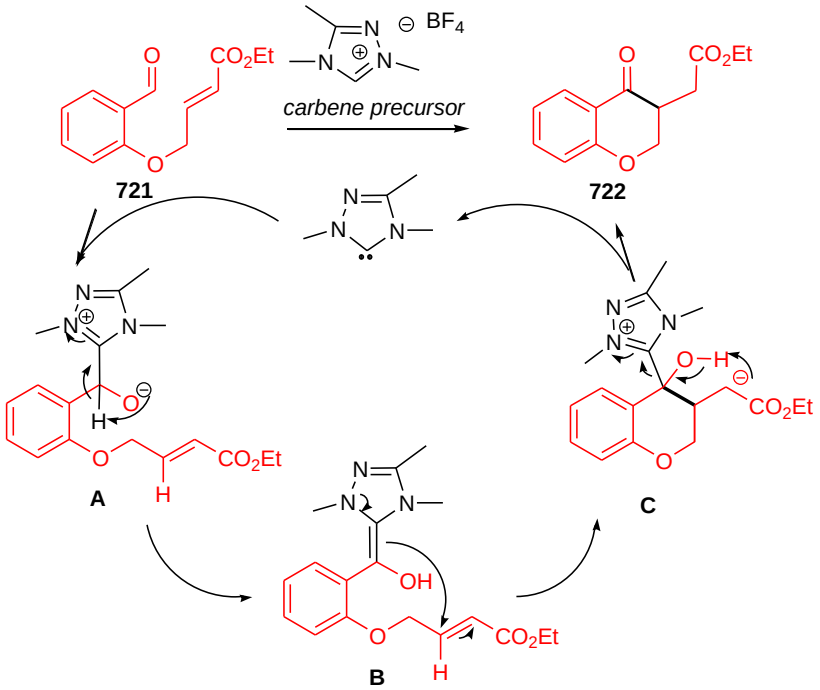
Scheme 293. Intramolecular Ring Closure with Formation of the C(3)-C(4) Bond



5.3.1. Formation of the C(3)-C(4) Bond via Intramolecular Stetter Reaction

The most efficient pathway accounting the planed synthesis is the intramolecular ring closure between the carbonyl group and the double bond of ethyl 4-(2-formylphenoxy)but-2-enoate (**721**), which gives ethyl 2-(3,4-dihydro-4-oxo-2*H*-chromen-3-yl)acetate (**722**).[345] Noteworthy, both carbon atoms are electrophilic and an *umpolung* procedure is required. This is the core of the *Stetter* reaction in which the electrophilic carbonyl group becomes an acyl-carbanion equivalent (Scheme 294).

Scheme 294. Mechanism of the Intramolecular *Stetter* Reaction from 721 to Chroman-4-one 722.[345]

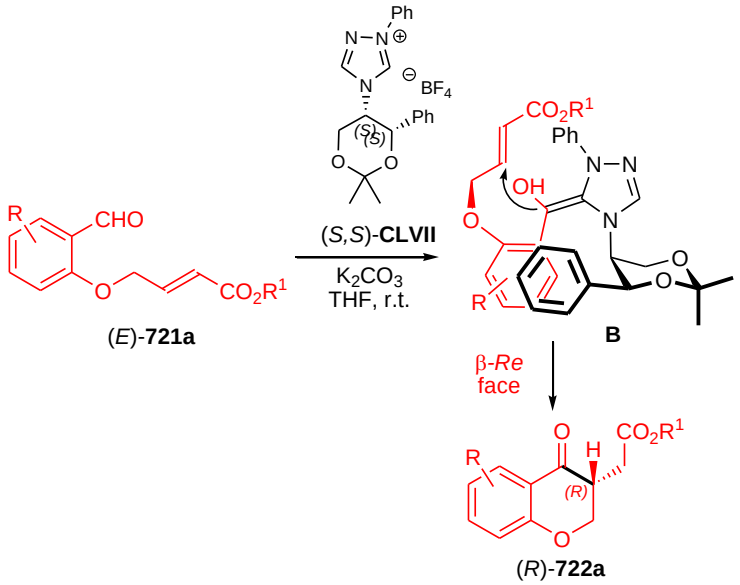


The reaction is catalyzed by a heterocyclic carbene, formed *in situ* by base deprotonation of the corresponding azolium pre-catalyst, which adds to the aldehyde carbonyl group of **721** to afford the tetrahedral oxy-anion **A** (Scheme 294). A proton transfer gives rise to the acyl anion equivalent **B** (the Breslow intermediate) in which the addition to the electrophilic carbon of the double bond forms the C-C bond of **C**. A second proton transfer gives the final product **722** accompanied by the recycling of the carbene catalyst. This mechanism is supported by an accurate study that determined rate law and kinetic isotope effect of the reaction of **721**. The reaction was found to be first order in aldehyde and carbene precursor (or free carbene) and these results suggest that the proton transfer from **A** to **B** is the first irreversible step.[345]

The first asymmetric intramolecular *Stetter* reaction was reported by Enders and co-workers in 1996 on (*E*)-**721a**, utilizing the chiral triazolic carbene derived from the precursor (*S*,*S*)-**CLVII**, and product (*R*)-**722a** was obtained with discrete yield and enantioselectivity (Scheme 295 Table 27;, entry 1).[346] The observed absolute configuration of the product suggests that the attack of the

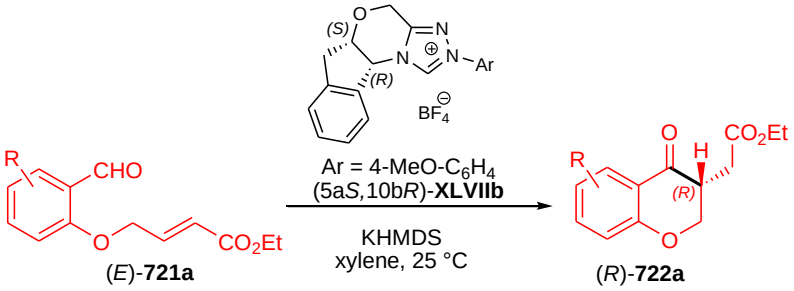
nucleophilic anion of the Breslow intermediate **B** occurs on the *β-Re* face of the double bond, unshielded by the Ph group of the dioxane moiety.

Scheme 295. The First Asymmetric Intramolecular *Stetter* Reaction from (*E*)-721a to Chroman-4-one (*R*)-722a Catalyzed by the Carbene Formed from the Precursor (*S,S*)-CLVII.[346]



An important progress was obtained when the reaction of (*E*)-**721a** was performed using carbene (5a*S*,10b*R*)-**XLVIIb** (Ar = 4-MeO-C_6H_4) having the indane[1',2'-*e*]-1,2,4-triazolo[3,4-*c*][1,4]oxazine moiety, in which the methoxy substituted benzene should make the complex more nucleophilic, and would facilitate the attack to the electron poor alkene in **B** (Scheme 296).[347] As expected the reaction occurs under mild conditions and (*R*)-**722a**, in four experiments, was obtained with excellent yields and enantioselectivities (Table 27, entry 2).

Scheme 296. Asymmetric Intramolecular *Stetter* Reaction from (*E*)-721a to (*R*)-722a Catalyzed by the Carbene Formed from the Precursor (5a*S*,10b*R*)-XLVIIb.[347]



The *Stetter* reaction can be performed on different 4-(2-formylphenoxy)propene derivatives with electron-withdrawing substituents such as esters, ketones, nitriles as in (*E*)-**721a-c**. The results are similar, and the most important factor is the carbene catalyst and its chirality.[348-350] In some circumstances, excellent yields were obtained although with less satisfactory enantioselectivities. Other protocols can be preferred because of the excellent enantioselectivities. The chirality of the catalyst and its relationship with the face attack on the Breslow intermediate **B**, as well as the efficiency of the catalyst, can be appreciated from the data reported in Chart 15 and Table 27, in which reagents, products, pre-catalysts, and results are reported. The substrates are always benzaldehydes with in position *ortho* a O-CH_2-C=C-C=O fragment variably substituted, and the results of the *Stetter* reaction are often excellent.[351,352]

Another important point that has a great influence on the enantioselectivity is the configuration of the double bond of the substrate. The (*Z*) reagents may give very good yields of chroman-4-ones, whereas the resulting enantioselectivity is always very poor.[349,352]

An unusual source of chirality in the heterocyclic carbene was proposed by Miller for the reaction of (*E*)-**721a** catalyzed by (*S*)-**CLX**. He described the reaction as "*peptide-catalyzed*", but it is simply a [*peptide*-substituted *N*-CH]-*catalyzed Stetter* reaction that affords the chroman-4-ones **722a** in low yields but good enantioselectivities. The efficiency of the catalyst is not increased for more sophisticated structures in which the substituent has more than one aminoacid residue.[354]

Chart 15. *N*-CH Precatalyst, Reagents, and Products of Asymmetric Intramolecular *Stetter* Reactions.

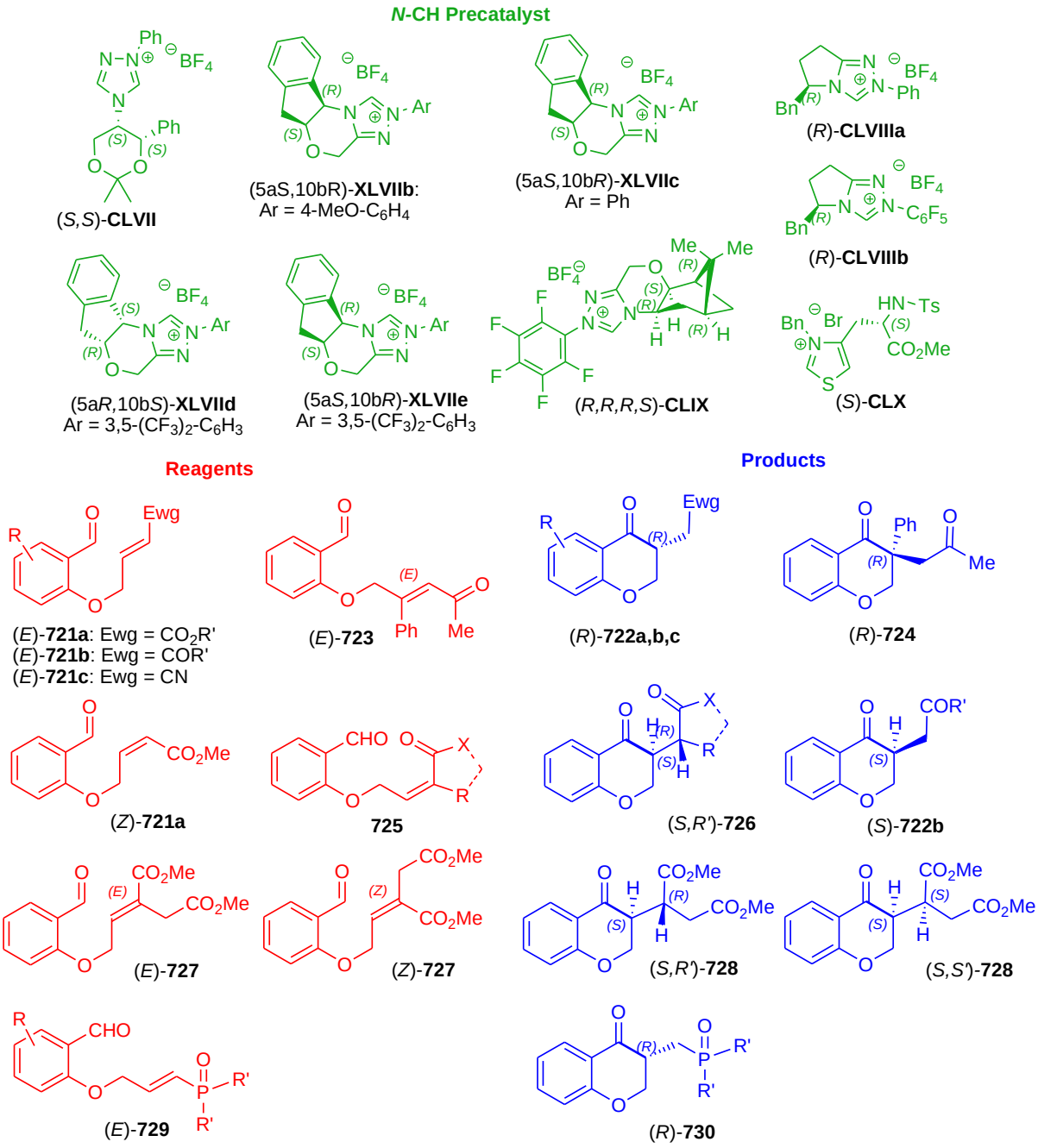


Table 27. Asymmetric Intramolecular *Stetter* Reactions with Reagents and Products, Catalyzed with the *N*-HC Pre-catalyst, whose Formulae are Reported in Chart 15.

Entry	Reagent	Catalyst	n. Exp.	Reaction Product	aver. Yield % (s.d.)	aver. ee % (s.d.)	Attached Face	Ref.
1	(*E*)-**721a**	(*S,S*)-**CLVII**	8	(*R*)-**722a**	54 (17)	61 (9)	*β-Re*	346
2	(*E*)-**721a**	(5a*S*,10b*R*)-**XLVIIb**	4	(*R*)-**722a**	93 (6)	93 (5)	*β-Re*	347
3	(*E*)-**721a**	(5a*S*,10b*R*)-**XLVIIc**	1	(*R*)-**722a**	58	95	*β-Re*	348
4	(*E*)-**721b**	(5a*S*,10b*R*)-**XLVIIc**	1	(*R*)-**722b**	90	92	*β-Re*	348
5	(*E*)-**721c**	(5a*S*,10b*R*)-**XLVIIc**	1	(*S*)-**722c**	78	75	*β-Re*	348
6	(*E*)-**723**	(5a*S*,10b*R*)-**XLVIId**	1	(*R*)-**724**	55	99	(*β-Re*)[a]	351
7	**725**	(*R*)-**CLVIIIa**	7	(*S,R'*)-**726**	85 (14)[b]	94 (3)	*β-Si*	352
8	(*E*)-**727**	(*R*)-**CLVIIIa**	1	(*S,R'*)-**728**	80[c]	92	*β-Si*	353
9	(*Z*)-**727**	(*R*)-**CLVIIIa**	1	(*S,S'*)-**728**	70	38	-	353
10	(*E*)-**721a**	(5a*S*,10b*R*)-**XLVIIb**	5	(*R*)-**722a**	87 (13)	84 (16)	*β-Re*	349
11	(*E*)-**721a**	(*R*)-**CLVIIIb**	7	(*S*)-**722a**	87 (19)	87 (5)	*β -Si*	349
12	(*E*)-**721a**	(*R*)-**CLVIIIa**	6	(*S*)-**722a**	85 (15)	93 (2)	*β -Si*	349

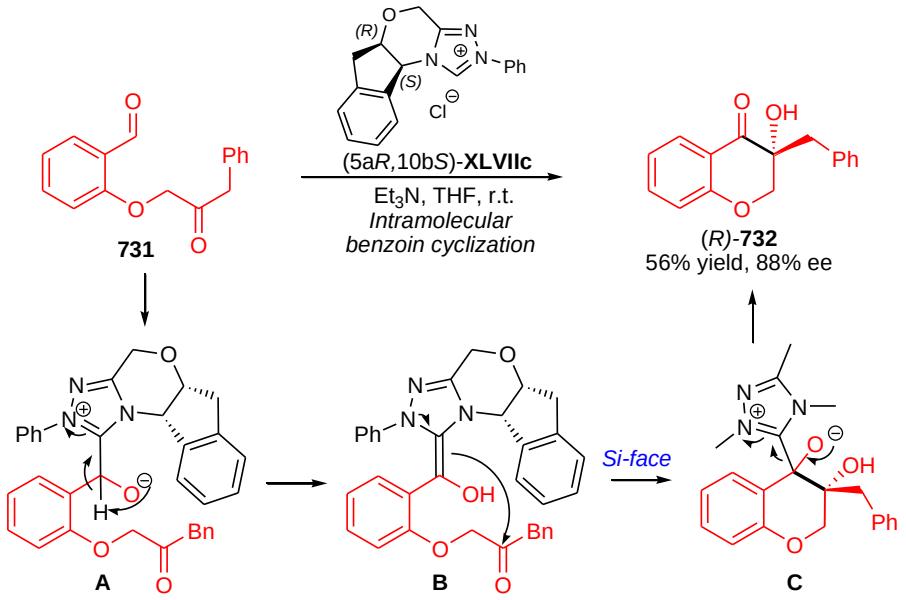
13	(*E*)-**721a**	(5a*R*,10b*S*)-**XLVIId**	8	(*S*)-**722a**	87 (15)	81 (23)	*β-Si*	349
14	(*Z*)-**721a**	(5a*R*,10b*S*)-**XLVIId**	1	(*S*)-**722a**	85	22	*β-Si*	349
15	(*E*)-**729**	(5a*S*,10b*R*)-**XLVIId**	6	(*R*)-**730**	85 (6)	91.5 (4)	*β-Re*	353
16	(*E*)-**721a**	(5a*R*,6*R*,8*R*,9a*R*)-**CLIX**	12	(*R*)-**722a**	98 (1.5)	82 (21)	*β-Re*	350
17	(*E*)-**721a**	(*S*)-**CLX**	1	(*R*)-**722a**	40	80	*β-Re*	354

[a] Change of the priority face. [b] Average de = 86.5 ± 14%. [c] 99% de.

5.3.2. Formation of the C(3)-C(4) Bond via Different Cyclizations

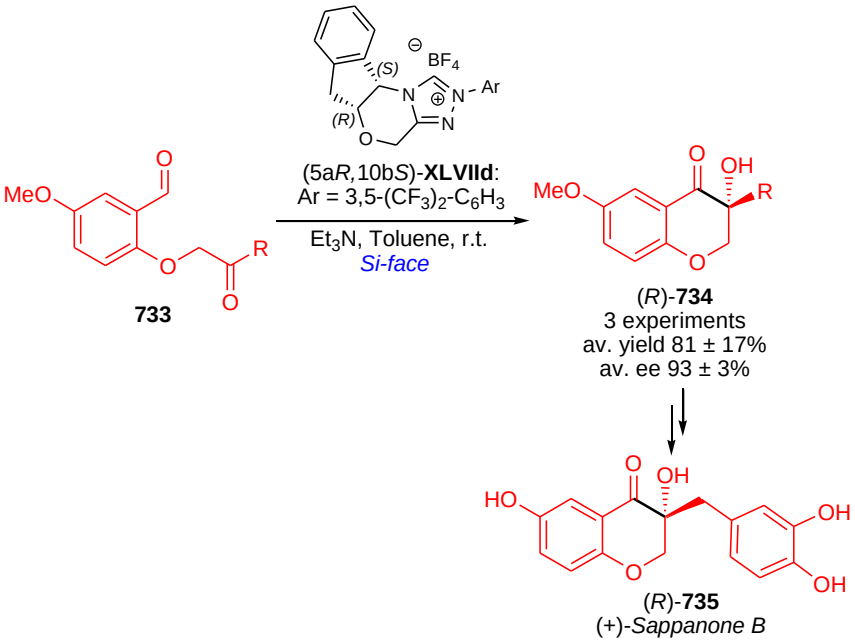
Chiral *N*-heterocyclic carbenes have occupied, in the last decade, an outstanding position in the field of enantioselective catalysts, and a proof of this is their application to the old-fashioned *benzoin reaction*. In its intramolecular form a ketoaldehyde compound gives the cyclization to an α-hydroxyketone in the presence of a base. The 2-(2-oxo-3-phenylpropoxy)benzaldehyde (**731**) reacts with the pre-catalyst (5a*R*,10b*S*)-**XLVIIc** with chlorine as anion, and gives the 3-benzyl-2,3-dihydro-3-hydroxychromen-4-one [(*R*)-**732**] in moderate yield, but with good enantioselectivity. The mechanism of this reaction is analogous to that of the above discussed *Stetter* reaction, with a base-promoted carbene formation, whose attack to the aldehyde gives first the tetrahedral intermediate **A**, and then the Breslow intermediate **B**. The pathway differs only because an *aldol* reaction substitutes the *Michael* step of the *Stetter* reaction with the attack to the less hindered *Si*-face of the carbonyl group that rationalizes the (*R*) absolute configuration of the product (Scheme 297).[355]

Scheme 297. Enantioselective Intramolecular Aldehyde-Ketone *Benzoin* Cyclization from 731 to (*R*)-732 with (5a*R*,10b*S*)-XLVIIc as Pre-catalyst of *N*-HC.[355]



With the aim to ameliorate the catalytic efficiency of *N*-HC, several new triazolium salts possessing fluorine atoms or trifluoromethyl substituents on the *N*-aryl group were prepared. The best was (5a*R*,10b*S*)-**XLVIId** [Ar = 3,5-$(CF_3)_2$-C_6H_3] that was tested on the intramolecular *benzoin* cyclization on **733** with excellent enantioselectivity since (*R*)-**734** was obtained with an average ee of 93% on three experiments (Scheme 298).[356] With this catalyst in hands, the synthesis of (+)-*Sappanone B*, a homoisoflavanoid with xanthine oxidase inhibitory activity, was planned and, starting from **733** with R = CH_2-3,4-$(MeO)_2$-C_6H_3, the corresponding (*R*)-**734** was isolated (92% yield and 95% ee). This intermediate was deprotected in two steps and the targeted (*R*)-**735** was obtained.

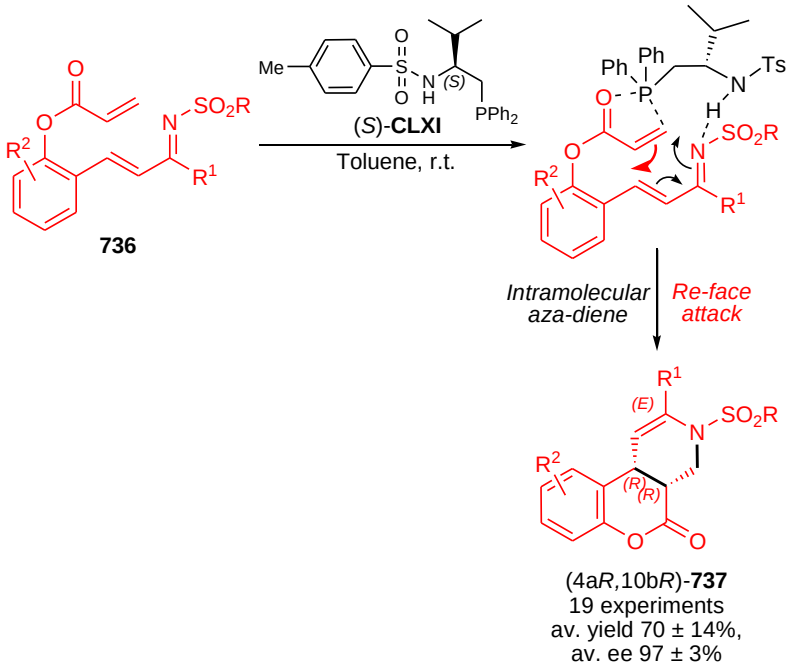
Scheme 298. Synthesis of (+)-*Sappanone B* via Asymmetric Intramolecular *Benzoin* Cyclization.[356]



The variety of reactions tested to synthetize 3,4-dihydro-2*H*-chromen derivatives is so various that the authors cannot avoid discussing some of them. The first chiral phosphine-catalyzed *intramolecular* formal [4+2] cycloaddition between an acrylate and an unsaturated imine is an example to mention. The starting product is **736** that cyclizes in the presence of the simple phosphine catalyst (*S*)-**CLXI** at ambient temperature to give (4a*R*,10b*R*)-**737** with a remarkable

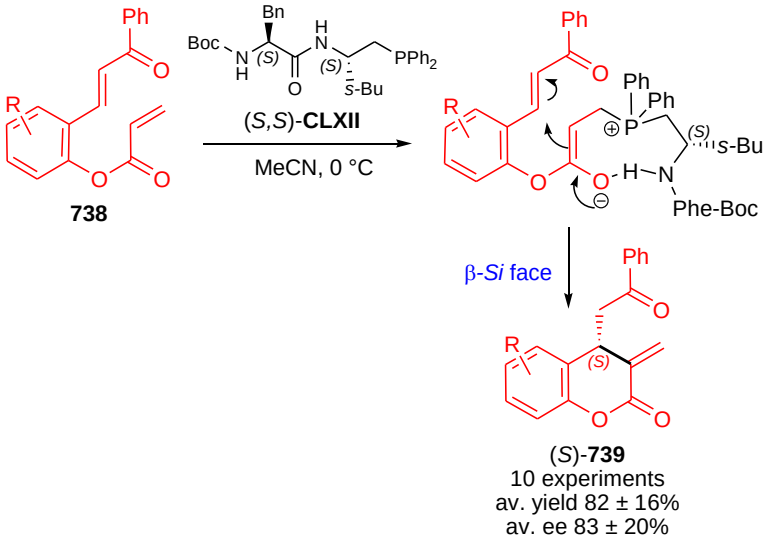
high average ee of 97% over 19 experiments.[357] This impressive result derives from the control of a very selective *Re*-face attack exploited by a simple isopropyl group in the reacting intermediate as reported in Scheme 299.

Scheme 299. Enantioselective Intramolecular Formal [4+2] Cycloaddition of 736 Catalyzed by Phosphine (*S*)-CLXI.[357]



The *Rauhut-Currier* reaction is one of the oldest phosphane-catalyzed reactions and consists in the dimerization of two Michael acceptors with the formation of a new C-C bond. The intramolecular variant has been applied to the synthesis of optically active chromanones via the formation of the C(3)-C(4) bond in **738**, catalyzed by the Boc-protected phenylalanine-isoleucine derived phosphane (*S*,*S*)-**CLXII**. Its nucleophilic attack to the most reactive terminal double bond of **738** gives a zwitterion in which the enolate is stabilized by hydrogen bonding. In this conformation, the *β-Re* face is protected, and the intramolecular Michael addition gives enantioselectively (*S*)-**739** (Scheme 300).[358]

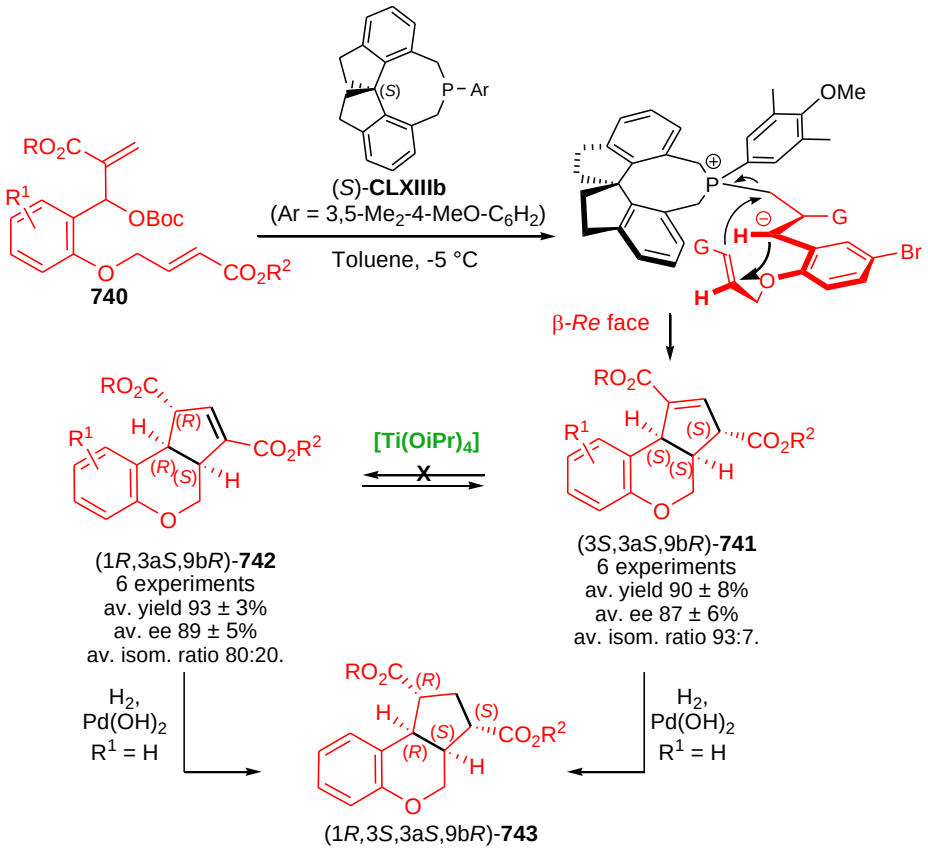
Scheme 300. Enantioselective *Rauhut-Currier* Intramolecular Reaction of 738 Catalyzed by (*S*,*S*)-CLXII Phosphane.[358]



A catalytic asymmetric version of the intramolecular ylide annulation has been developed on the substituted derivatives of 4-(2-allylphenoxy)but-2-enoates **740** with the spiro bi-indane-based chiral phosphine (*S*)-**CLXIIIb**, with or without titanium tetraisopropilate (Scheme 301).[359]

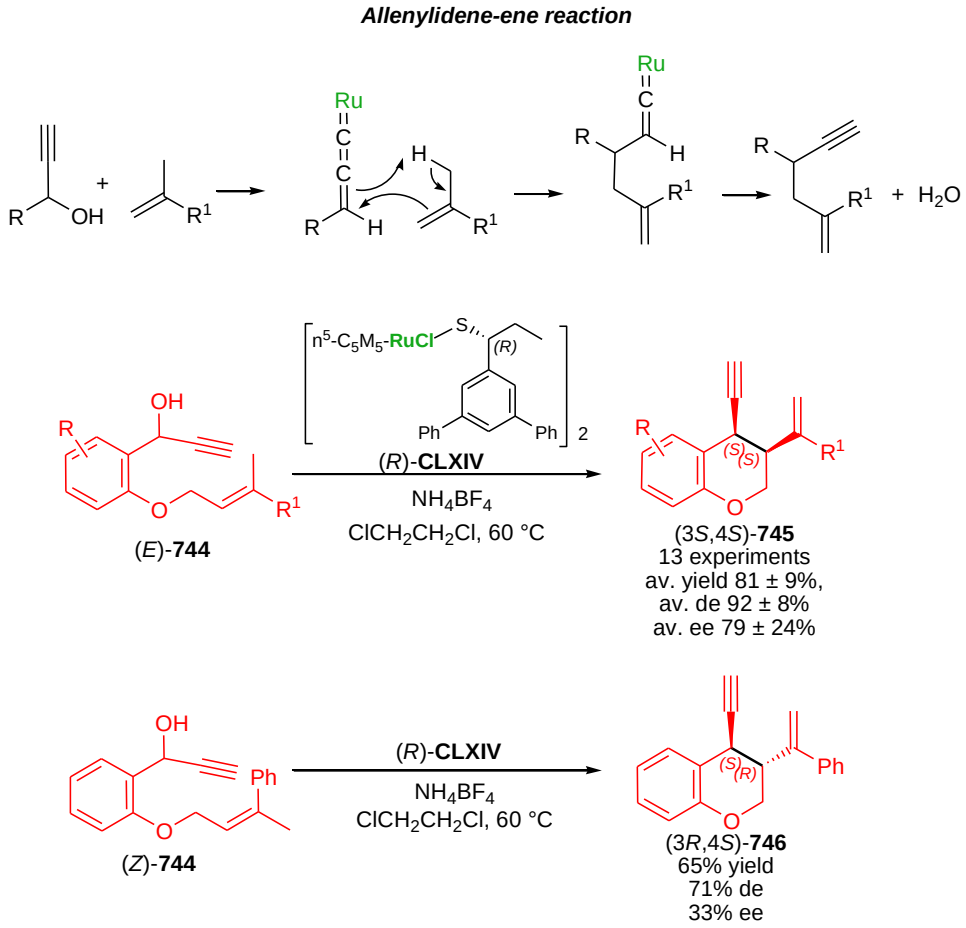
In the absence of the titanium alkoxy derivative, the reaction gives two regioisomeric 1,3a,4,9b-tetrahydrocyclopenta[*c*]chromene-1,3-dicarboxylates (3*S*,3a*S*,9b*S*)-**741** and its regioisomer (1*R*,3a*S*,9b*R*)-**742** in a ratio of about 20:80. Compound (3*S*,3a*S*,9b*S*)-**741** becomes the main product (average ratio 97:3) if the reaction is run in the presence of $Ti(OiPr)_4$, whose role is to slow down the isomerization of the primary reaction product **741** to **742**, allowing its isolation with high selectivity (Scheme 301).[359] This process can be considered a formal intramolecular [3+2] cycloaddition on the reaction intermediate derived from the nucleophilic attack of the chiral phosphine on the most reactive terminal double bond of **740**. The attack to the less hindered *β-Re* face rationalizes the stereochemical outcome. Both these tetrahydrocyclopenta[*c*]chromenes with three adjacent stereocenters can undergo a stereoselective hydrogenation to (1*R*,3*S*,3a*S*,9b*R*)-**743**, having four stereocenters; yields and enantioselectivities are the same starting either from **741** or **742**.

Scheme 301. Enantioselective Formal Intramolecular [3+2] Cycloaddition of 740 Catalyzed by (*S*)-CLXIIIb Phosphine.[359]



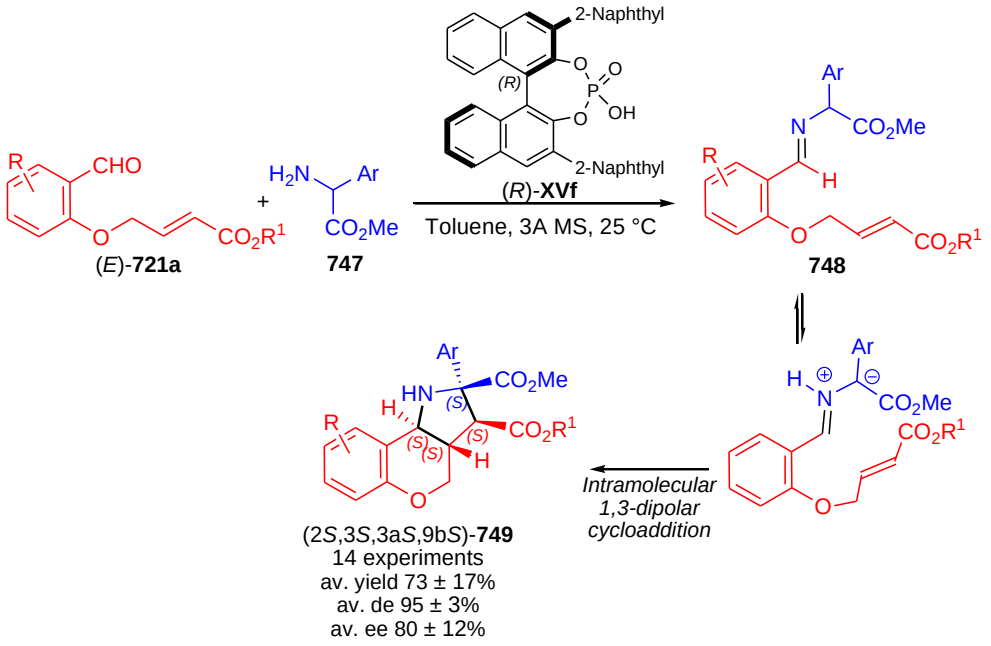
The recently disclosed Ruthenium-catalyzed intermolecular C-C bond formation from propargylic alcohols and alkenes, through an intermolecular allenylidene ene-type reaction (Scheme 302, upper part)[360] has been applied to substituted 1-[2-(but-2-enyloxy)phenyl]prop-2-yn-1-ol (*E*)-**744** (Scheme 302, lower part).[361] Heating the propargylic alcohol in the presence of the optically active thiolate-bridged diruthenium complex (*R*)-**CLXIV** and NH_4BF_4, the C(3)-C(4) bond is formed by intramolecular *allenylidene ene-type* reaction and the 4-ethynyl-3,4-dihydro-3-(1-phenylvinyl)-2*H*-chromenes [(3*S*,4*S*)-**745**] are formed, as main *syn* isomers, with good yields and good diastereo- and enantioselectivities over 13 experiments. These excellent results are strongly connected with the configuration of the double bond of the reagent because the same reaction run with (*Z*)-**744** gives the diastereoisomeric (3*R*,4*S*)-7**46**, with discrete yield and diastereomeric excess, although the enantioselectivity was disappointing (33% ee) (Scheme 302).[361]

Scheme 302. Enantioselective Intramolecular *Allenylidene Ene-type* Reaction of 744 Catalyzed by Diruthenium Complex (*R*)-CLXIV.[360,361]



The list of the unusual reactions used to build the C(3)-C(4) bond includes the intramolecular *1,3-dipolar cycloaddition* performed on the product of the reaction between 4-(2-formylphenoxy)but-2-enoates **721a** and aminoesthers **747**.[362] The Schiff base **748** interacts with the chiral phosphoric acid (*R*)-**XVf** giving an azomethine ylide whose intramolecular 1,3-dipolar cycloaddition to the double bond gives multiply substituded hexahydrochromeno[4,3-*b*]pyrrolidine derivatives (2*S*,3*S*,3a*S*,9b*S*)-**749** in high optical purity (Scheme 303).[362]

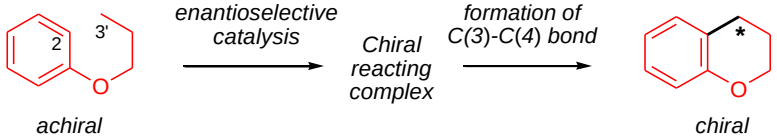
Scheme 303. Enantioselective Intramolecular Azomethine Ylide [3+2] Cycloaddition of 748 Catalyzed by Chiral Phosphoric Acid (*R*)-XVf. [362]



5.4 Formation of the C(4)-C(4a) Bond of 3,4-Dihydro-2*H*-Chromenes

The intramolecular ring closure to 3,4-dihydro-2*H*-chromenes can be performed through the formation of the C(4)-C(4a) bond. The basic pathway is the intramolecular ring closure of at least an aryl propyl ether between the positions (2) and (3′). Since the aryl ring has intrinsically an electron-releasing group, this fact makes easier the ring closure through an electrophilic attack, *e.g.* an intramolecular Friedel-Crafts reaction, which should be favoured if the aryl group has further electron releasing groups and the propyl has an electron attracting group in position 3′. The process requires first the formation of the chiral complex with interaction of the substrate with the enantioselective catalyst, then the ring closure as exemplified in Scheme 304. The different variants will be described below.

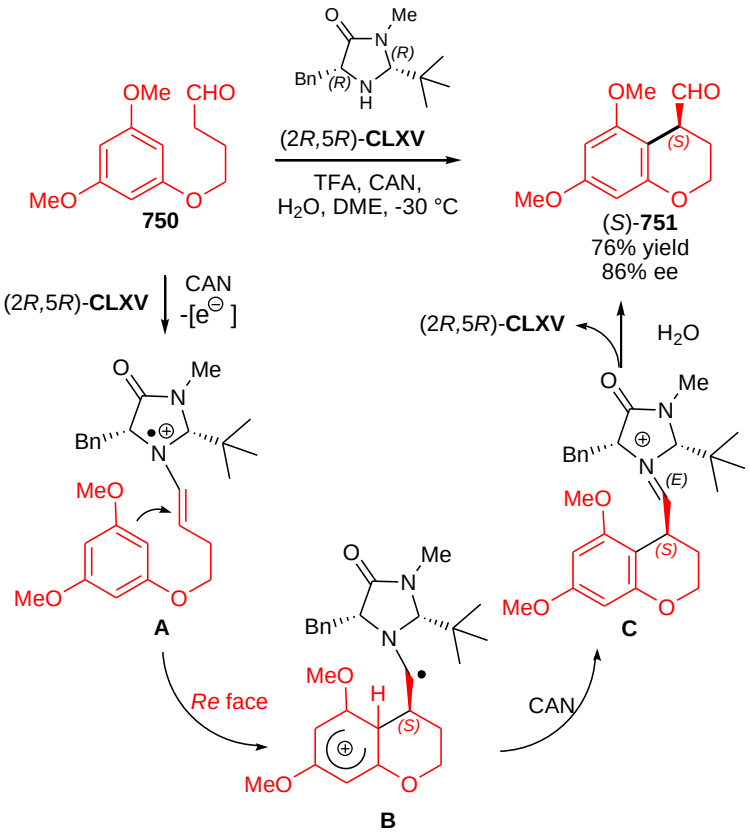
Scheme 304. Intramolecular Ring Closure with Formation of the C(4)-C(4a) Bond.



5.4.1. Formation of the C(4)-C(4a) Bond via Intramolecular Friedel-Crafts Reaction

A paradigmatic example is the intramolecular *Friedel-Crafts* cyclization of 4-(3,5-dimethoxyphenoxy)butanal (**750**) with 2-*t*-butyl-5-benzyl-3-methylimidazolidin-4-one (2*R*,5*R*)-**CLXV** as the organocatalyst, in the presence of cerium(IV) ammonium nitrate (CAN) as the oxidant. The first step involves reagent, catalyst, and oxidant to produce the highly reactive radical cation **A** that rapidly collapses intramolecularly through the nucleophilic attack to the less shielded *Re*-face, leading to the formation of the (*S*) chiral center of the Friedel-Crafts intermediate **B**. This latter loses a proton and undergoes a second single-electron transfer oxidation with CAN to afford the iminium ion **C**, whose hydrolysis affords the 3,4-dihydro-5,7-dimethoxy-2*H*-chromene-4-carbaldehyde (*S*)-**751** and the recycling of the catalyst (Scheme 305).[363] Due to the suitably placed substituents, good yields and high enantioselectivities are obtained under mild reaction conditions (Table 28: enrty 1).

Scheme 305. Enantioselective Intramolecular Friedel-Crafts Cyclization of 750, with (2*R*,5*R*)-CLXV as Organocatalyst.[363]



Other enantioselective organocatalyzed intramolecular Friedel-Crafts cyclizations have been reported in the literature, sometimes with a Brønsted acid as additive. Reagents, catalysts and products are reported in Chart 16 and the results are listed in Table 28.

Chart 16. Catalysts, Substrates, and Products of Asymmetric Intramolecular *Friedel-Crafts* Reactions.

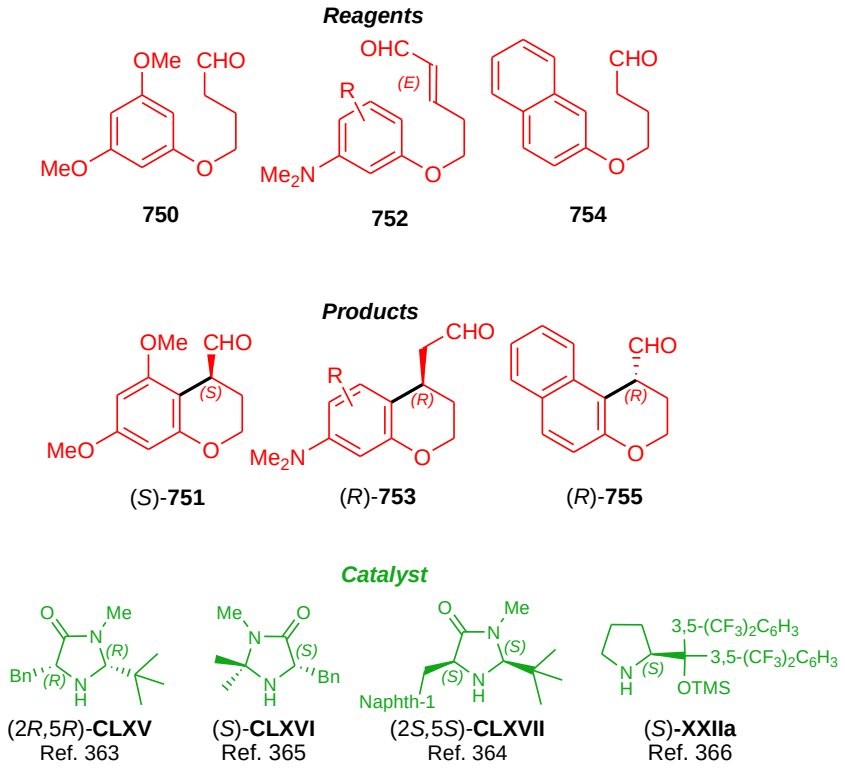


Table 28. Asymmetric Intramolecular *Friedel-Crafts* Reactions with Catalysts, Substrates, and Products, Reported in Chart 16.

Entry	Substrate	Catalyst[a]	n. Exp.	Reaction Product	av. Yield % (s.d.)	av. ee % (s.d.)	Ref.
1	**750**	(2*R*,5*R*)-**CLXV**	1	(*S*)-**751**	76	86	363
2	**752**	(*S*)-**CLXVI**	1	**753**	88	90	365
3	**752**	(*S*)-**XXIIa**[b]	3	(*R*)-**753**	67 (15)	94 (4)	366
4	**754**	(2*S*,5*S*)-**CLXVII**	1	(*R*)-**755**	70	95	364

[a] The presence of oxidants or additives is required. [b] Ar=3,5-$(CF_3)_2$-C_6H_3.

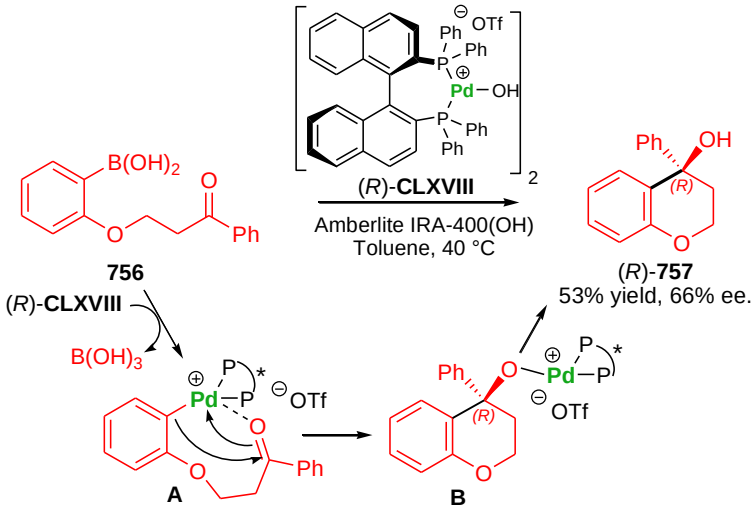
The results are always very good mainly in terms of enantioselectivity. It is worth to note the extremely limited variety of substrates tested in the experiments with each organocatalyst. This fact strongly inhibits the friendliness of a reaction that could have a wide application due to the mild experimental conditions required for a straightforward access to optically active 4-substituted 3,4-dihydro-5,7-dimethoxy-2*H*-chromenes.

5.4.2. Formation of the C(4)-C(4a) Bond via Different Intramolecular Cyclizations.

In addition to the Friedel-Crafts reaction discussed in the previous section, other pathways have been applied to get the formation of the C(4)-C(4a) bond, which not always compete in terms of efficiency with the above route.

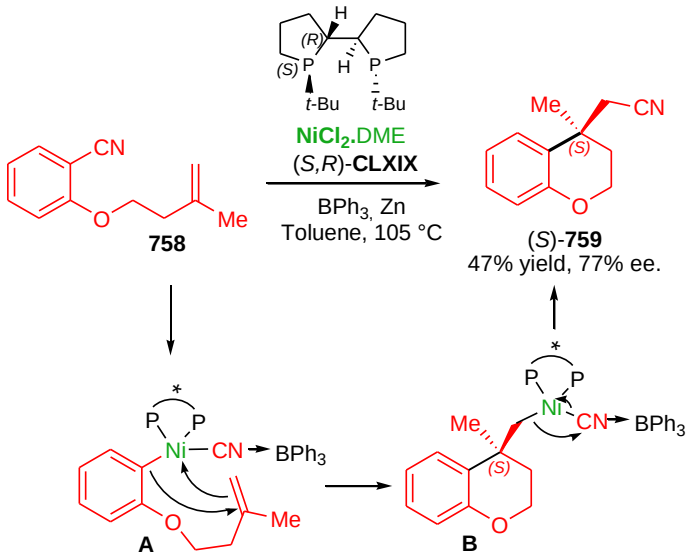
An original approach is the intramolecular version of the addition of arylboronic acid to ketone in which **756** cyclizes to (*R*)-**757** in the presence of the cationic Pd(II) complex of BINAP (*R*)-**CLXVIII**. The first step is the trans-metalation with elimination of boric acid to generate the intermediate **A** in which the Lewis acid acidity of the cationic palladium activates the carbonyl group, making easy the attack of the aryl group and the formation of **B**. The cleavage of the Pd-O bond gives the product and allows the catalyst recycling (Scheme 306).[367]

Scheme 306. Enantioselective Intramolecular Cyclization of Arylboronic Acid 759, Catalyzed by the Cationic Pd(II) Complex of BINAP (*R*)-CLXVIII.[367]



Somewhat similar to the above reaction is the intramolecular phenylcyanation of 2-(3-methylbut-3-enyloxy)benzonitrile (**758**), catalyzed by the complex of Ni(II) and (*S*,*R*)-TangPHOS [(*S*,*R*)-**CLXIX**], leading to the synthesis of 2-(3,4-dihydro-4-methyl-2*H*-chromen-4-yl)acetonitrile [(*S*)-**759**]. The rationale, proposed in Scheme 307, involves as first step the trans-metalation of the substrate, in which nitrile is coordinated by BF_3, and affords the intermediate **A**. The reaction proceeds with the stereoselective migratory insertion leading to the intermediate **B**, and the reductive elimination that forms the C-CN bond of (*S*)-**759** and allows the catalyst release.[368]

Scheme 307. Enantioselective Intramolecular Arylcyanation of 758, with the Ni(II)/Phosphine Complex (*S*,*R*)-CLXIX.[368]

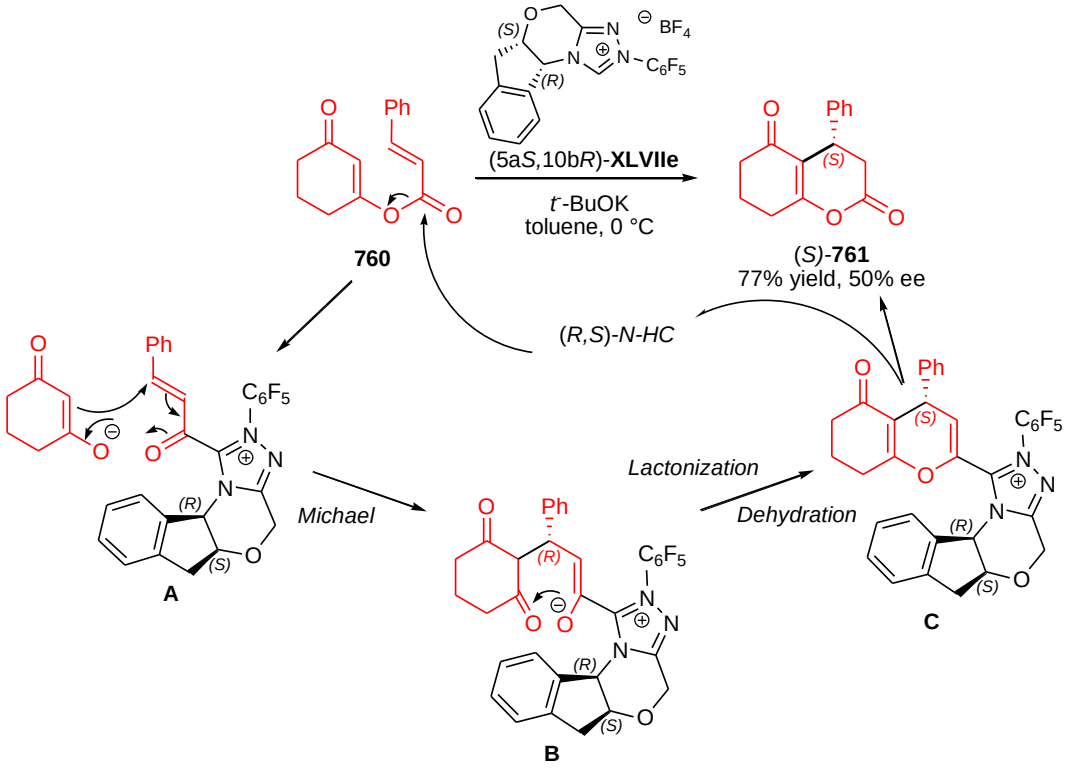


The reader has certainly noted the low enantioselectivities, escorted by disappointing yields, that were obtained from both the reactions above reported. However, this is balanced by the fact that both **756** and **758** have the aryl rings without any activating substituents, which were the characteristics of the substrates in the Friedel-Crafts reactions described in the previous section.

We conclude with a reaction that does not strictly fit the topic of this section, however, it deals with the formation of a C(4)-C(4a) bond for the synthesis of the optically active 3,4,5,6,7,8-hexahydro-4-phenyl-2*H*-chromene.

3-Oxocyclohex-1-enyl cinnamate (**760**), in the presence of (5a*S*,10b*R*)-**XLVIIe** (Ar = C_6F_5) (the precursor of an already mentioned *N*-HC) undergoes a ring closure to afford 3,4,7,8-tetrahydro-4-phenyl-6*H*-chromene-2,5-dione (**761**) (Scheme 308).[369] This is the only enantioselective example in a research focussed to test the non-chiral version of the reaction, and even if yield and enantioselectivity are the result of a single and non-optimized experiment, the reaction illustrates the enormous possibilities of the *N*-HC-catalyzed synthesis of chiral heterocycles.

Scheme 308. Enantioselective Intramolecular Cyclization of 760 with the *N*-HC Derived from (5a*S*,10b*R*)-XLVIIe.[369]



This reaction is the *intramolecular variant* of some reactions we discussed in the previous section 3.3 and the rationale that can be proposed relies upon the nucleophilic attach of the *N*-HC to the ester group with formation of the [enolate/acyltriazolium] ion pair **A** that undergoes the Michael addition affording **B**. The [lactonization/dehydration] gives **C** that loses the catalyst and forms **761** (Scheme 308). The authors of this review would be stunned if the absolute configuration of this product would be different from (*S*).

6. Syntheses by Introduction of Asymmetric Centers in Pyran or Benzopyran Derivatives

All previous chapters of this review, dedicated to the synthesis of optically active 3,4-dihydropyran derivatives, discussed the different modes to build the chiral six-membered heterocyclic ring. While many of these methods require multistep reactions, it would be easier to employ the ready available heterocycle, pyran or benzopyran derivative, as the substrate on which to introduce the chiral center in any of the 2-4 positions.

These transformations, from the 2,3-dehydro or 3,4-dehydro heterocycles, are perhaps the most straightforward pathways for targeting the enantio-enriched molecules and will be the topic of some of the following sections.

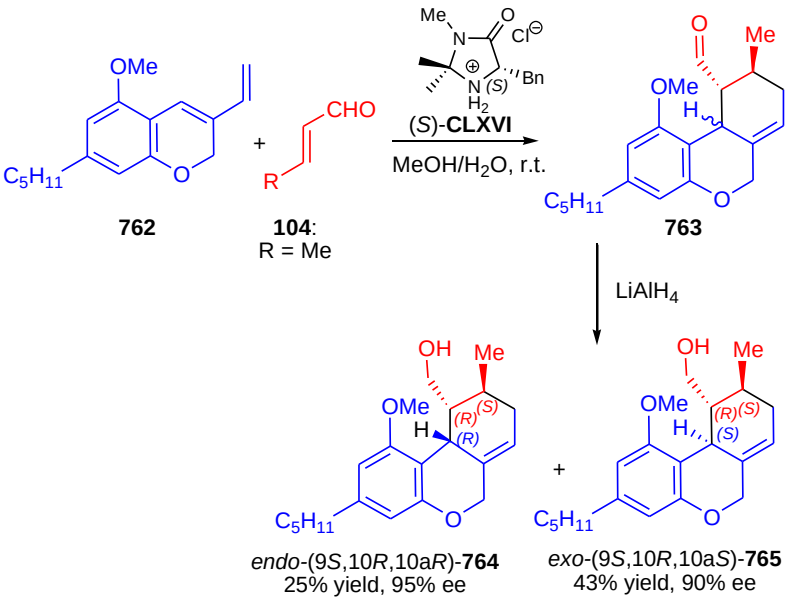
6.1. Chirality Induced in 3,4-Dihydropyran Derivatives through Cycloaddition Reactions

6.1.1. Diels-Alder with Dihydropyran Derivatives Behaving as a Diene

If the 3,4-dehydropyran derivative has a vinyl group in position 3, the resulting diene system may react with an electron-poor dienophile in a Diels-Alder reaction. If the catalyst, suitable to lower the MO energy separation between the HOMO diene and the LUMO dienophile, is a chiral catalyst, the cycloaddition introduces three chiral centers in one step into the benzo[*c*]chromene derivative. This process is of great potential value because benzo[*c*]chromene is the basic structure of *cannabinoids*, a well-known group of psychotropic compounds. Most strategies have been designed to the formation of this tricyclic system, but the Diels-Alder approach appears to be an appealing and straightforward pathway to *cannabinoids*.

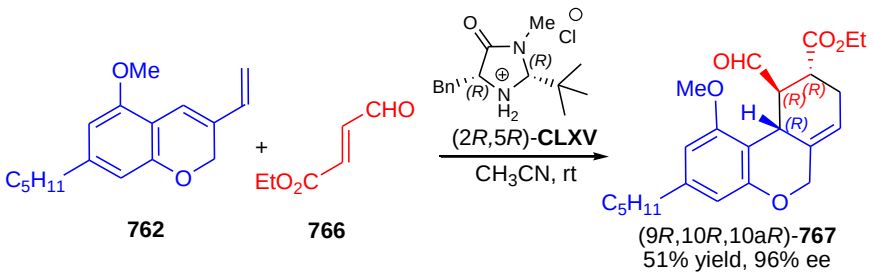
Within this strategy, one of the first examples is the reaction between 5-methoxy-7-pentyl-3-vinyl-2*H*-chromene (**762**) and crotonaldehyde (**104**: R=Me), catalyzed by (5*S*)-benzyl-2,2,3-trimethylimidazolidin-4-one hydrochloride [(*S*)-**CLXVI**]. The product is the (9*S*,10*R*)-8,9,10,10a-tetrahydro-1-methoxy-9-methyl-3-pentyl-6*H*-benzo[c]chromene-10-carbaldehyde (**763**) that can be reduced with $LiAlH_4$ to give the copy of diastreoisomers *endo* (9*S*,10*R*,10a*R*)-**764** and *exo* (9*S*,10*R*,10a*S*)-**765**, both with excellent enantioselectivity (Scheme 309).[370]

Scheme 309. Enantioselective Diels-Alder Reaction Between 762 and 104 Catalyzed by (*S*)-CLXVI.[370]



The Diels-Alder reaction between **762** and ethyl 3-formylacrylate (**766**) catalysed by (2*R*)-*t*-butyl-(5*R*)-benzyl-2,2-dimethylimidazolidin-4-one hydrochloride [(2*R*,5*R*)-**CLXV**] is much more stereoselective since the *endo* (9*R*,10*R*,10a*R*)-**767** is the only adduct obtained, in very good yield and with excellent enantioselectivity (Scheme 310).[371]

Scheme 310. Synthesis of (9*R*,10*R*,10a*R*)-767 by Enantioselective Diels Alder Reaction of 762 with 766, Catalyzed by (2*R*,5*R*)-CLXV.[371]

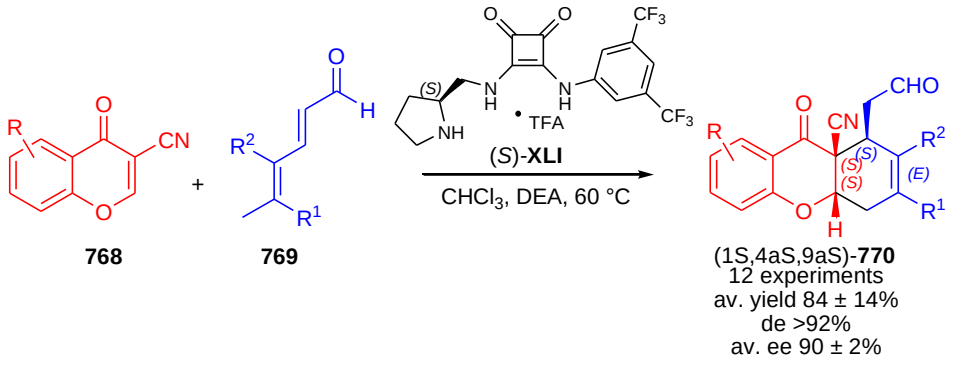


6.1.2. Diels-Alder with Dihydropyran Derivative Behaving as Dienophile

An original approach to 3,4-dihydropyran derivatives consists in introducing the chiral centers through a Diels-Alder reaction in which the dienophile is the double bond of a chromene that has an electron-attracting group in the positions (2) or (3).

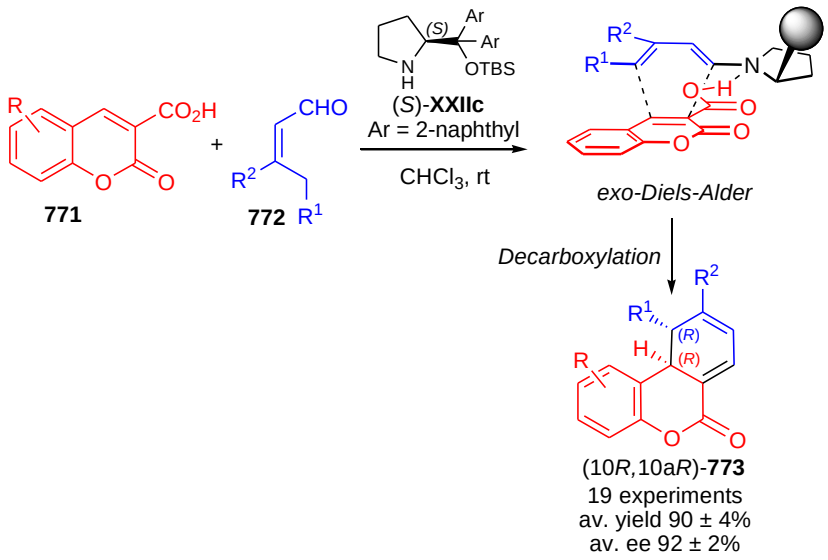
A beautiful example of this approach is the reaction between 3-cyanochromones (**768**) and substituted hexa-2,4-dienals (**769**), with bifunctional squaramide (*S*)-**XLI** as organocatalyst, in which the squaramide framework activates **768** by hydrogen bonding and the pyrrolidinium 2,2,2 trifluoroacetate acts both as a sterically demanding group and as the activator of the diene fragment (Scheme 311).[372] The products of 12 experiments are the (1*S*,4a*S*,9a*S*)-9a-cyano-9-oxo-1-(2-oxoethyl-4,4a,9,9a-tetrahydro-1*H*-xanthenes (**770**), obtained in excellent yields, and whose three contiguous stereocenters are formed with de >92% and with an average ee of 90%.

Scheme 311. Enantioselective Diels-Alder Reaction Between 768 and 769, Catalyzed by (*S*)-XLI.[372]



Another nice example is the reaction between coumarin-3-carboxylic acids (**771**) and unsaturated aldehydes **772**, catalysed by dinaphthyl-prolinol TBS derivative (*S*)-**XXIIc** (Scheme 312).[373] The Diels-Alder reaction occurs through an *exo* TS induced by the coordination of the carboxylic acid to the pyrrolidine nitrogen atom and, under the experimental conditions, the reaction gives rise to the decarboxylation of the early adduct. Hence, the final products are (10*R*,10a*R*)-dihydro-6*H*-benzo[*c*]chromen-6-ones **773**, obtained in excellent yields and enantioselectivities with a wide range of reagents.

Scheme 312. Enantioselective Diels-Alder Reaction Between 771 and 772, Catalyzed by (*S*)-XXIIc.[373]

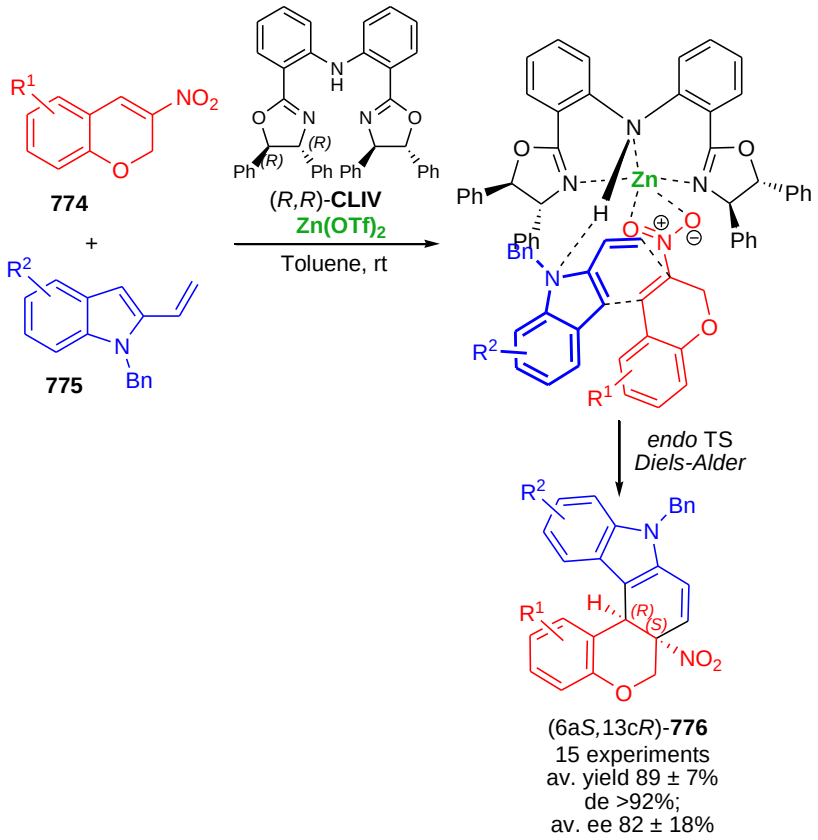


Also 3-nitro-2*H*-chromene (**774**) is suitable to behave as electron-poor dienophile in the Diels-Alder reaction with the electron-rich 1-benzyl-2-vinyl-1*H*-indole (**775**), in the presence of the Zn(II) complex of diphenylamine-tethered bis (4*R*,5*R*)-Box ligand (*R*,*R*)-**CLIV** as the catalyst (Scheme 313).[374] The bifunctional activation, in which Zn(II) acts as the Lewis acid that coordinates the nitro group of **774**, and the NH group is the donor binding the nitrogen of **775**, promotes an *endo*-selective Diels-Alder reaction providing the tetracyclic adduct (6a*S*,13c*R*)-**776** in good ee and with a diastereomeric ratio that in 15 experiments is always >95:5.

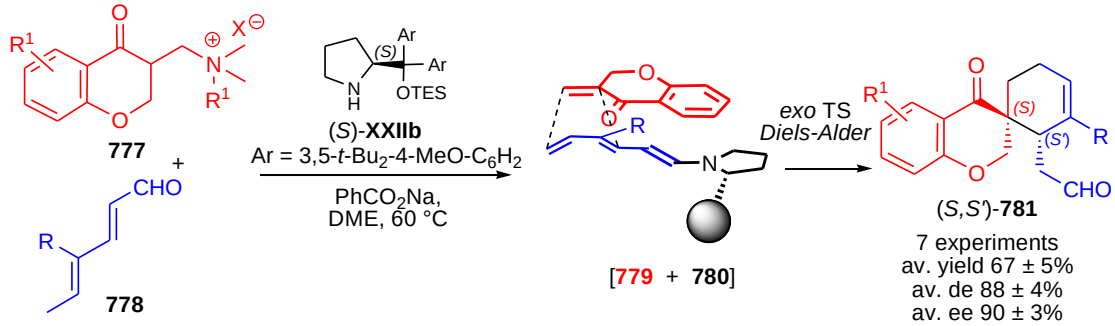
The above examples have always the dienophile with an *endo*-cyclic double bond. Quite unusual is the Diels-Alder reaction in which the dienophile has an *exo*-cyclic double bond. An example is the reaction between the methiodide salt of the Mannich base derived from 4-chromanone **777** and 2,4-hexadienal **778**, catalyzed by prolinol-TES-derived organocatalyst (*S*)-**XXIIb** (Ar = 3,5-(*t*-Bu)$_2$-4-MeO-C$_6$H$_2$) (Scheme 314).[375] Compound **777** is the precursor of 2,3-dihydro-3-methylenechromen-4-one (**779**) with an *exo*-cyclic double bond, while the aldehyde **778**, in the presence of the organocatalyst, gives an electron rich hexatriene **780**. The Diels-Alder reaction may follow two pathways: a normal DA process under [HOMO (diene **780**)/LUMO (dienophile **779**)] control, or an inverse electron demand DA reaction controlled by the interaction

[LUMO (heterodiene **779**)/HOMO (dienophile **780**)]. The first pathway is the preferred one; the dienophile is the *exo*-cyclic double bond and the *exo* TS affords (*S,S'*)-**781** with very good diastereo- and enantioselectivities.

Scheme 313. Enantioselective Diels-Alder Reaction Between 774 and 775, Catalyzed by Tethered bis (4*R*,5*R*)-Box Ligand (*R,R*)-CLIV.[374]



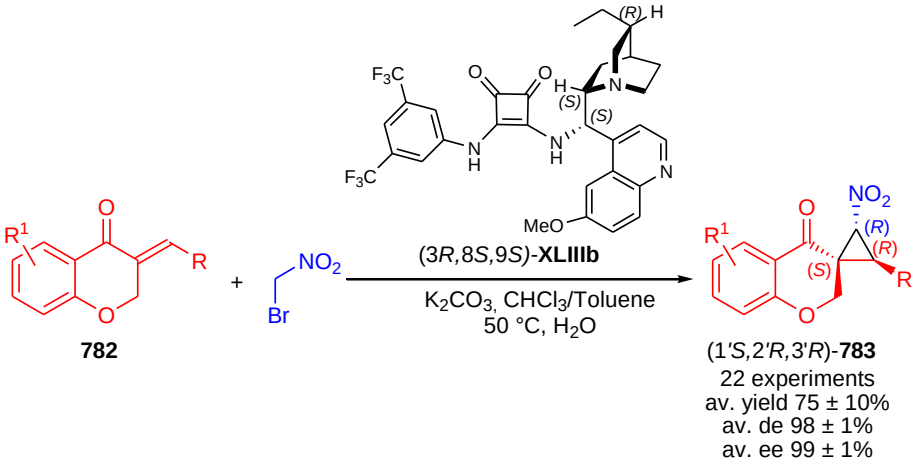
Scheme 314. Enantioselective Diels-Alder Between 779 and 780, Derived from the Reaction Between 777 and 778 Catalyzed by (*S*)-XXIIb.[375]



6.1.3. Functionalization through Cyclization Reactions

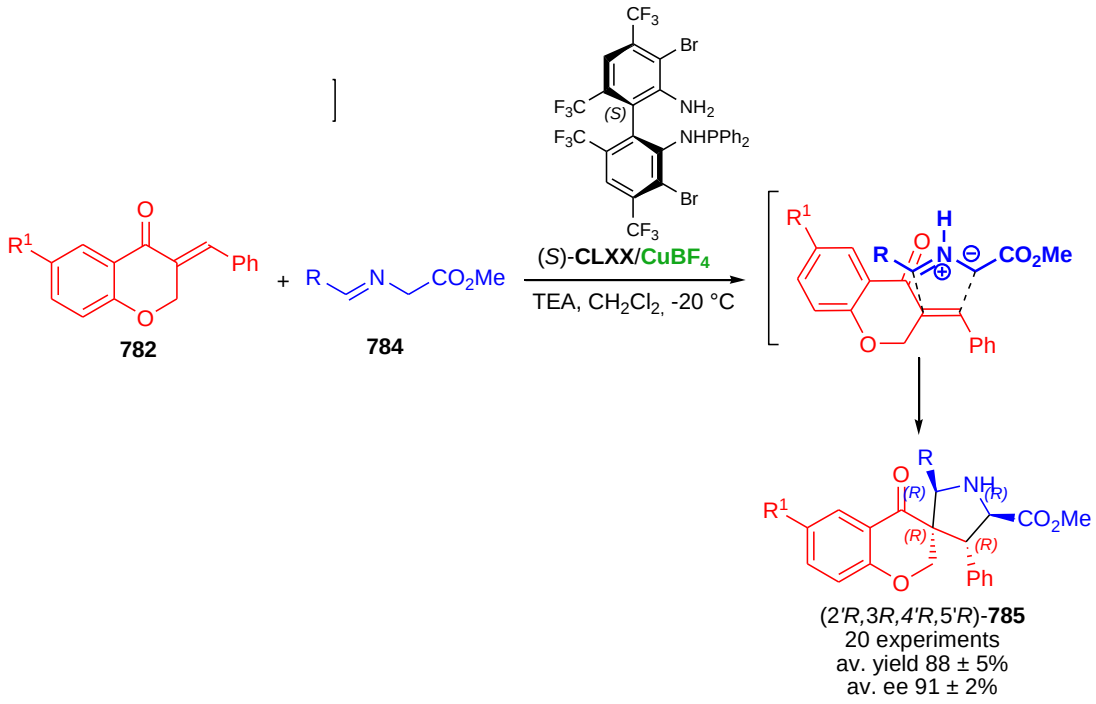
An interesting diastereoselective and enantioselective cyclopropanation reaction was accomplished by employing the *Michael* alkylation between the 3-arylidenechroma-4-ones **782** and bromonitromethane. The organocatalyst is the chiral squaramide based on 9-amino-dihydroepiquinine, (3*R*,8*S*,9*S*)-**XLIIIb**, and the result is the formation of nitro-spirocyclopropanes (1′*S*,2′*R*,3′*R*)-**783** with three contiguous stereocenters, obtained in moderate yields but with an excellent diastereo- and enantioselectivity, whose absolute configuration was determined by X-ray analysis of the derivative in which R is the *ortho*-bromophenyl group (Scheme 315).[376]

Scheme 315. Enantioselective Cyclopropanation Reaction Between 782 and Bromonitromethane, Catalyzed by Squaramide Derivative of 9-Aminodihydroepiquinine (3*R*,8*S*,9*S*)-XLIIIb.[376]



A nice example of enantioselective 1,3-dipolar cycloaddition in which azomethine ylides, generated from imino esters **784**, add to the exocyclic double bond of the (*E*)-3-benzylidene-2,3-dihydrochromen-4-ones (**782**) in the presence of [$Cu(CH_3CN)_4BF_4$] as metal source and [TF-BinphamPhos] as the chiral ligand of the catalyst [(*S*)-**CLXX**] (Scheme 316).[377] The spirocyclic 4-thiochromanone-3,3′-pyrrolidines (2′*R*,3*R*,4′*R*,5′*R*)-**785**, with four contiguous stereocenters, are obtained in excellent yields and enantioselectivities.

Scheme 316. Enantioselective 1,3-Dipolar Cycloaddition Reaction Between 782 and Imino Esters 784, Catalyzed by Cu(I)/BiphamPhos Complex (*S*)-CLXX.[377]

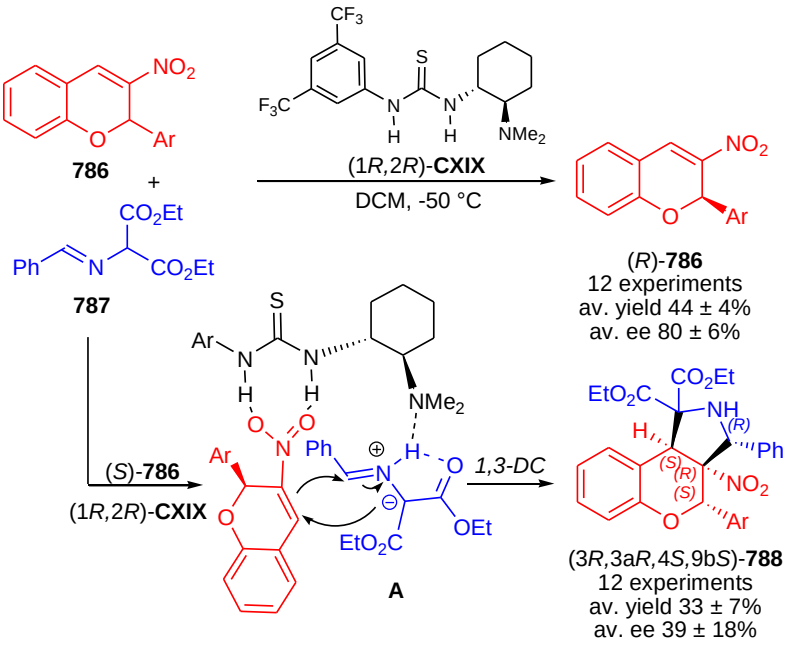


3-Nitro-2-aryl-2*H*-chromenes (**786**) are electrophilic reagents in which it should be intrinsically easy to introduce chirality with different addition reactions. Due to their racemic structure, each one of the above-described reactions should be preliminary submitted to a kinetic resolution of the racemate, a protocol that does not fit the topic of this review. However, if the resolution and the introduction of further chiral centers are conducted in a "*one pot reaction*", this protocol may become an excellent "*diastereoselective pathway to chiral dihydrochromene derivatives from optically inactive reagents*". For this reason, we will discuss some examples.

The original scope of the research in ref. 378 was the kinetic resolution of **786**, which was allowed to react with diethyl 2-(benzylideneamino)-malonate **787** in the presence of the Takemoto's organocatalyst (1*R*,2*R*)-**CXIX**. In 12 different experiments (*R*)-**786** was isolated in average 44% yield and 80% ee. Interestingly, the rest of the reaction was the tricyclic product (3*R*,3a*R*,4*S*,9b*S*)-**788** even if the average yield was 33% and the enantioselectivity was quite low. This benzopyran[3,4-*c*]pyrrolidine derivative with four vicinal chiral carbon centers is the result of the

coordination of both reagents to the bifunctional organocatalyst that activates the electrophile by hydrogen-bonding and promotes the deprotonation of the nucleophile, affording the reacting intermediate **A**. The azomethine ylide [3+2] dipolar cycloaddition involves the *β-Re* face of the nitro olefin and provides **788** (Scheme 317).[378] In conclusion, a protocol set up for the kinetic resolution of a racemate becomes the seminal result of a new route for the enantioselective functionalization of benzopyran derivatives through cyclization reactions.

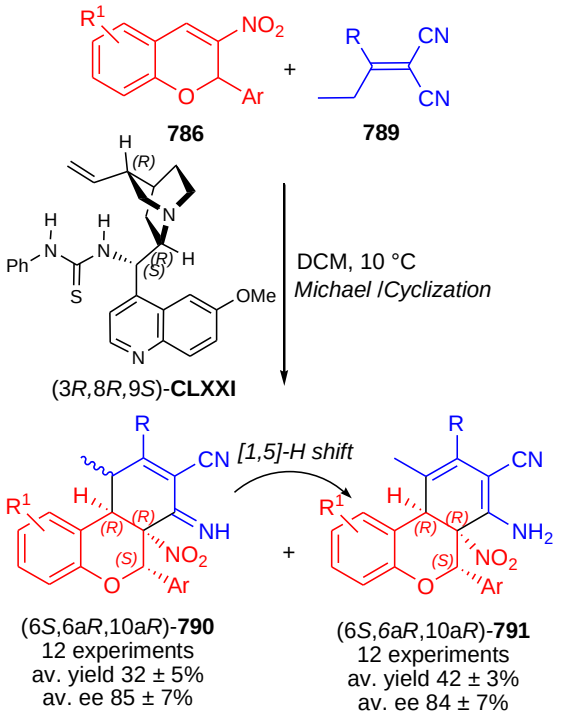
Scheme 317. 1,3-Dipolar Cycloaddition between Azomethinylides 787 and Nitroaryl-chromenes 786 Catalyzed by (1*R*,2*R*)-CXIX.[378]



A further development of the above-described protocol is the asymmetric domino reaction of nitroarylchromenes **786** with different dicyanoolefins **789**, catalysed by the *cinchona*-derived thiourea (3*R*,8*R*,9*S*)-**CLXXI** (Scheme 318).[379] The tertiary aminic center of the organocatalyst deprotonates **789** affording the anion suitable for a *Michael* reaction on **786**, activated by the thiourea moiety through double hydrogen bonding**.** Hence the *Michael* step occurs with the attack of the nucleophile to the nitroalkene, followed by the attack to the proximate cyano group and the ring closure to (6*S*,6a*R*,10a*R*)-**790**. This product nearly represents the half part of the reaction

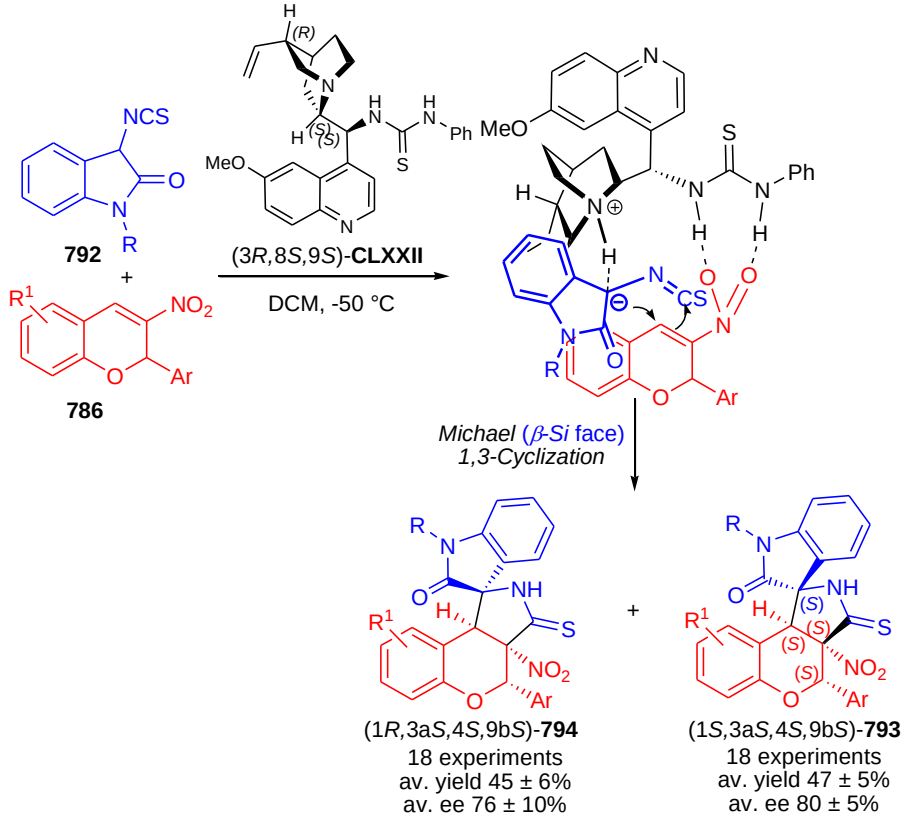
mixture. The second half is (6*S*,6a*R*,10a*R*)-**791**. Looking with accuracy to the enantiomeric purity of each couple of products performed in the 12 experiments, within the determination limits, the enantiomeric purities of **790** and **791** are identical. Therefore, it seems reasonable to assume a 1,5-hydrogen shift that correlates these products.

Scheme 318. Domino [Michael/Cyclization/Tautomerization] Reaction Between α,α-Dicyano Olefins 789 and Nitroarylchromenes 786 Catalyzed by (3*R*,8*R*,9*S*)-CLXXI.[379]



The analogous organocatalytic domino [*Michael/cyclization*] reaction was performed between **786** and 1-substituted 3-isothiocyanatoindolin-2-one **792**, with the *epiquinine*-derived thiourea (3*R*,8*S*,9*S*)-**CLXXII** as the organocatalyst. Again, the first step is a *Michael* attack of deprotonated **792** to the *β-Si* face (according the convention of this review) of the nitroalkene, followed by the cyclization with ring closure on the carbon atom of the isocyanato group and formation of two diastereoisomeric tetracyclic spiroindoles, both with good enantioselectivities. The structure and the absolute configuration of these stereoisomers was determined by X-ray diffraction analysis and resulted to be (1*S*,3a*S*,4*S*,9b*S*)-**793** and (1*R*,3a*S*,4*S*,9b*S*)-**794**, respectively (Scheme 319).[380]

Scheme 319. Domino Reaction Between 786 and 3-Isothiocyanatoindolin-2-one 792 Catalyzed by (3*R*,8*S*,9*S*)-CLXXII.[380]

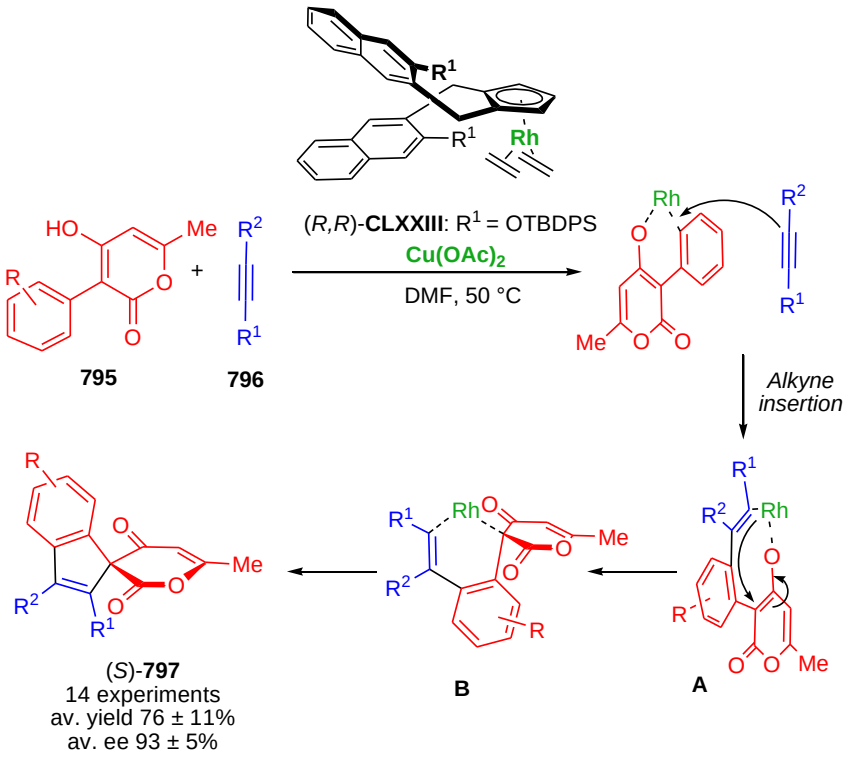


However, one short comment is required. The reaction yields seem not to fit within this collection of excellent results. The sum of the product yields for **790** and **791** in the reaction of Scheme 318 is 76%, while that for **793** and **794** in the reaction of Scheme 319 is 92%. The reader must remember that the reactions involve only the enantiomer (*S*)-**786** of the racemic reagent.

To complete this section, the enol-directed C-H functionalization of 4-hydroxy-6-methyl-3-phenyl-2*H*-pyran-2-ones **795** with alkynes **796**, promoted by the chiral cyclopentadienyl Rhodium complex (*R*,*R*)-**CLXXIII**, is discussed (Scheme 320).[381] The cyclorhodanation of **795**, by the rhodium diacetate complex, the coordination and the migratory insertion of alkyne **796** give the rhodacycle **A**. The subsequent step is the isomerization of the O-bound enolate into the C-bound isomer through a rotation of the alkoxypyranone moiety, directed away from the steric interaction with the ligand, and affording **B**. The last step is the reductive elimination of Rh(I), oxidized by $Cu(OAc)_2$ to regenerate the catalyst, which leads to the spiroindene containing all-carbon

quaternary stereocenters (*S*)-**797**, whose enantioselectivity was excellent (93% ee) from over 14 experiments.

Scheme 320. Enantioselective Synthesis of Spiroindenes (*S*)-797 by Rhodium(III)-catalyzed C-H Functionalization and Spiroannulation.[381]



6.2. Syntheses via Enantioselective Intramolecular and Intermolecular Addition of Reagents to Chromones

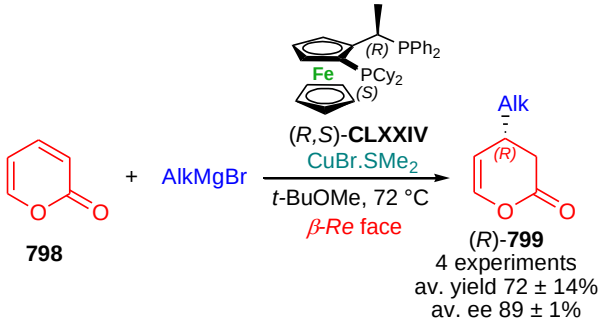
6.2.1. Intermolecular Addition of Reagents to Pyranones and Chromones

Pyranones and chromones have electrophilic positions suitable for the attack of a nucleophile and these reactions, under catalytic asymmetric conditions, promote the formation of a chiral center in the substrate.

The asymmetric conjugate addition of alkyl Grignard reagents to 2-pyrone **798** was performed for the first time in the presence of $CuBr \cdot SMe_2$ and the commercially available reverse-Josiphos ligand (*R,S*)-**CLXXIV**. The attack to the *β-Re* face gave 4-alkyl-substituted-3,4-dihydropyran-2-ones, (*R*)-**799**, in an average 72% yield and with 89% enantioselectivity over 4 experiments (Scheme 321).[382] These products have significant synthetic interest because they can be further

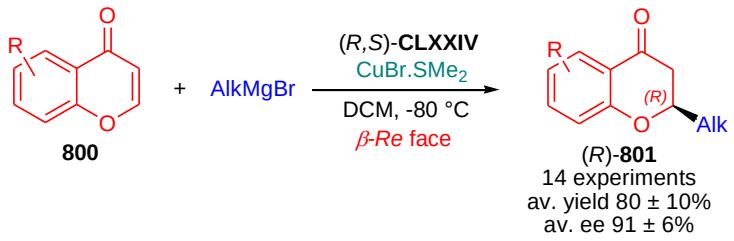
converted *in-situ* to highly versatile building blocks such as β-alkyl substituted aldehydes or β-bromo-γ-alkyl substituted alcohols.

Scheme 321. Enantioselective Conjugate Addition of Grignard Reagents to Pyranones 788 Catalyzed by (*R,S*)-CLXXIV.[382]



The same CuBr·SMe$_2$ and Josiphos ligand (*R,S*)-**CLXXIV** was the catalyst for a highly regio- and enantioselective conjugate addition of Grignard reagents to chromones **800**. The methodology tolerates a broad scope of alkyl Grignard reagents and functionalized chromones (14 experiments), and the resulting 2-substituted-2,3-dihydrochromen-4-ones (*R*)-**801** are obtained in very good yield (average 80%) and excellent enantioselectivity (average ee 91%), again from the attack of the *alkyl* nucleophile to the *β-Re* face of enone (Scheme 322).[383]

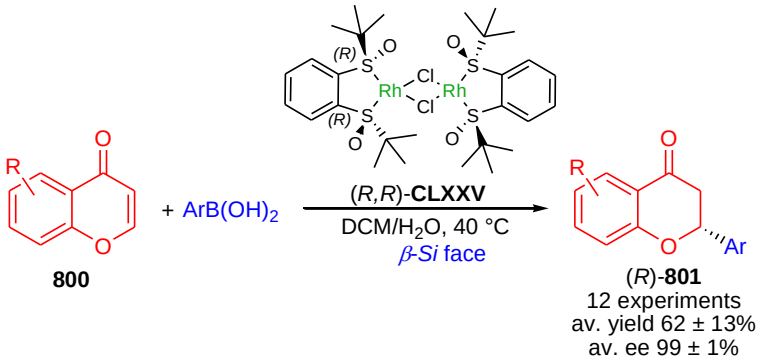
Scheme 322. Enantioselective Conjugate Addition of Grignard Reagents to Chromones 800 Catalyzed by (*R,S*)-CLXXIV.[383]



The asymmetric addition of arylboronic acids to chromones **800** is complementary to the above catalytic asymmetric conjugate addition of alkyl groups. The first experiment (Scheme 323)[384] was performed with the Rhodium complex of (*R,R*)-1,2-bis(*tert*-butylsulfinyl)benzene and the structure of the catalyst (*R,R*)-**CLXXV**, determined by X-ray analysis, shows it is a dimer with the bis-sulfoxide ligand acting as a rigid pincer, and the Rhodium atom clamped by the sulfur atoms into a

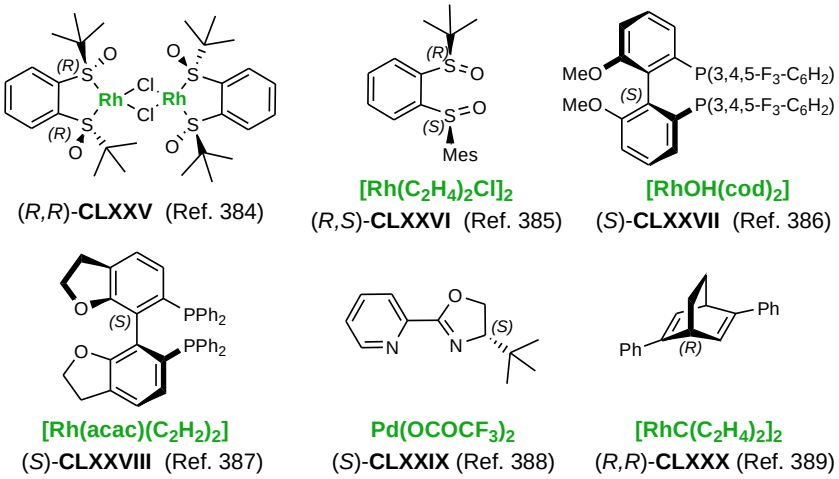
five-membered ring. The result of 12 experiments deserves attention because, despite the moderate yields (average yield 62%), the enantioselectivity is always excellent (average ee 99%) (Table 29: entry 1). The absolute configuration of (*R*)-**801** results from the attack of the *aryl* nucleophile to the *β-Si* face of the enone fragment.

Scheme 323. Enantioselective Conjugate Addition of Arylboronic Acids to Chromones 800 Catalyzed by (*R,R*)-CLXXV.[384]



The reactions between arylboronic acids and chromones have been tested with different catalysts (Chart 17), beginning with a modified heterodisulfoxide ligand again complexed with Rh[385] that did not improve the above reported results. Table 29 gathers the obtained results.

Chart 17. Catalysts for the Enantioselective Addition of Arylboronic acids to Chromones 800.



Noteworthy, three catalysts (*R,R*)-**CLXXV**,[384] (*S*)-**CLXXVII**,[386] and (*R,R*)-**CLXXX**[389] (Table 29, entries 1, 3, and 7, respectively) gave the products with an average 99% enatiomeric purity, and the yields for the reactions run with the second and third catalysts were excellent.

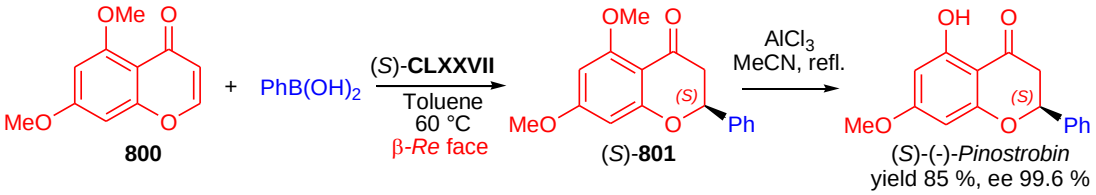
Table 29. Asymmetric Addition of Arylboronic acids to Chromones **800** Catalyzed by Chiral Complexes Reported in Chart 17.

Entry	Catalyst	n. Exp.	Av. Yield % (s.d.)	Av. ee % (s.d.)	**801** *Abs. config.* (attacked face)	Ref.
1	(*R*,*R*)-**CLXXV**	12	62 (13)	99 (1)	(*R*) (*β-Si*)	384
2	(*R*,*S*)-**CLXXVI**	13	59 (9)	94 (1)	(*R*) (*β-Si*)	385
3[a]	(*S*)-**CLXXVII**	11	85 (4)	99	(*S*) (*β-Re*)	386
4	(*S*)-**CLXXVIII**	1	31	99	(*S*) (*β-Re*)	387
5[a]	(*S*)-**CLXXIX**	12	61 (16)	90 (7)	(*S*) (*β-Re*)	388
6[b]	(*S*)-**CLXXIX**	17	74 (14)	91 (4)	(*S*) (*β-Re*)	388
7	(*R*,*R*)-**CLXXX**	12	84 (8.5)	99 (1)	(*R*) (*β-Si*)	389

[(a)] Experiments on unsubstituted chromone and different arylboronic acids. [(b)] Experiments on substituted chromones and different arylboronic acids.

In conclusion, this is a useful route to enantioenrichede flavones and the synthesis of (*S*)-(-)-*Pinostrobin*, an anti-leukemic flavonoid from *Polygonum lapathifolium* (Scheme 324),[389] makes the method promising for an easy preparation of bioactive chiral flavanones from commercially available products.

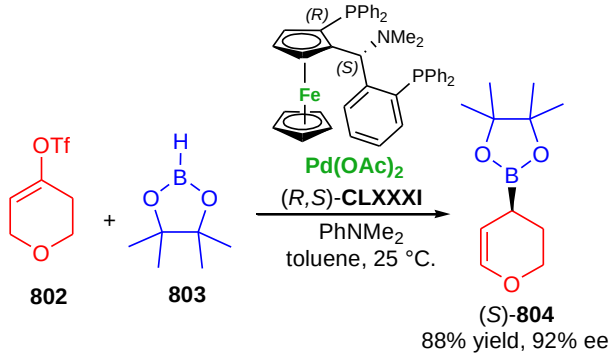
Scheme 324. Synthesis of Optically Pure (-)-Pinostrobin through Asymmetric Conjugate Addition of Phenylboronic Acid to 5,7-Dimethoxy-4*H*-chromen-4-one (800).[389]



Pinacolborane (**803**) was the reagent for an efficient catalytic enantioselective borylation of 3,4-dihydro-2*H*-pyran through a formal asymmetric isomerization of 3,6-dihydro-2*H*-pyran-4-yl trifluoromethanesulfonate (**802**), the protected form of tetrahydropyran-4-one, with diphosphine

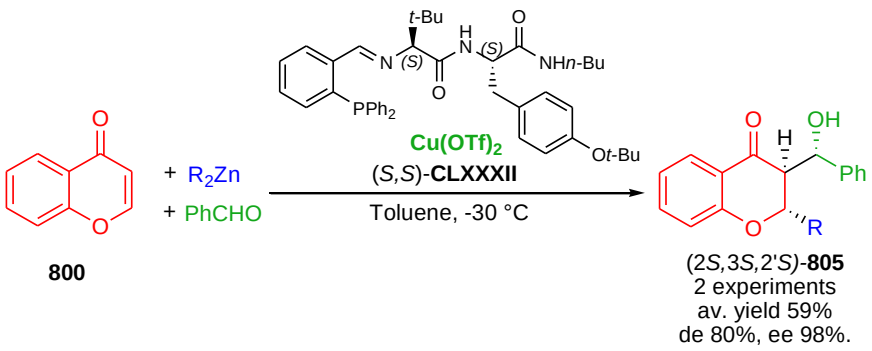
TANIAPHOS and $Pd(OAc)_2$ [(*R*,*S*)-**CLXXXI**] as catalyst (Scheme 325).[390] Beside a small amount of allylboronate, the product 2-[(*S*)-3,4-dihydro-2*H*-pyran-4-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane [(*S*)-**804**] was obtained with an excellent yield and 92% ee. Applications and extensions of this original method are expected.

Scheme 325. Enantioselective Borylation/Isomerization of 802 Catalyzed by (*R*,*S*)-CLXXXI.[390]



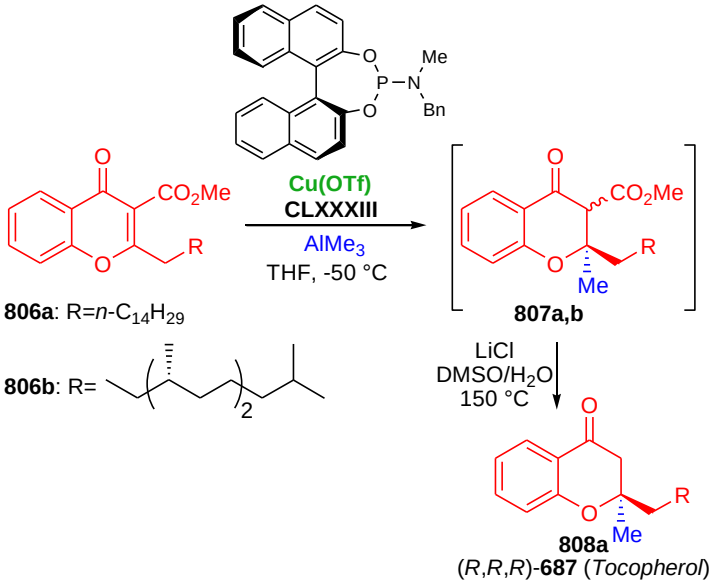
The asymmetric conjugate addition of dialkylzinc regent and benzaldehyde to 4*H*-chromen-4-one **800**, catalysed by the Cu(II) complex of the optically pure peptide phosphane (*S*,*S*)-**CLXXXII**, occurs through the alkyl addition with formation of the enolate intermediate, which affords the aldol attack to the aldehyde. The result is the formation of three chiral centers and the final products, whose absolute configuration was not determined, are the (2*S**,3*S**)-2-alkyl-2,3-dihydro-3-[(*S**)-hydroxy(phenyl) methyl]chromen-4-ones (**805**), which were obtained with excellent stereoselectivity (Scheme 326).[391]

Scheme 326. Enantioselective Addition of Dialkylzinc and Benzaldehyde to 4*H*-Chromen-4-one 800 Catalyzed by (*S*,*S*)-CLXXXIII.[391]



The addition of $AlMe_3$ to chromenones **806a,b** was usefully catalyzed by the Cu(I) complex of phosphoramidite **CLXXXIII** (Scheme 327).[392] The 1,4-addition of the nucleophile to **806a** was run at -50 °C and the intermediate **807a** was directly submitted to decarboxylation to furnish **808a** in excellent yield and enantioselectivity (94% yield and 96% ee). Starting from the optically pure chromenone **806b**, the natural stereoisomer of α-*Tocopherol* (*R*,*R*,*R*)-**687** was obtained with high yield (83%) and very good diastereoselectivity (94% de).

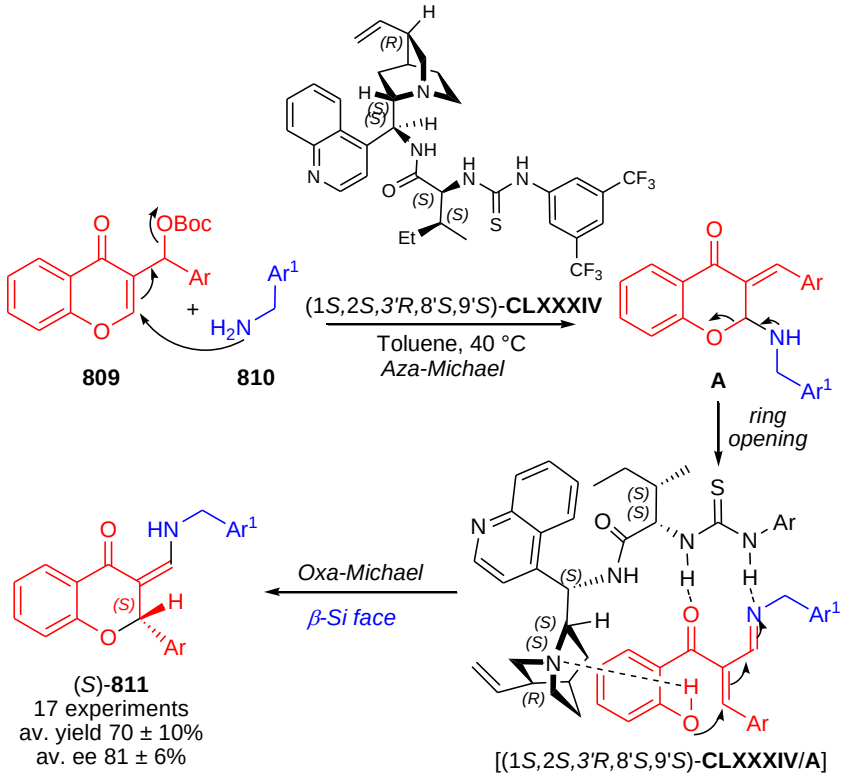
Scheme 327. The Syntheses of 808a and α-*Tocopherol* (*R*,*R*,*R*)-687 by Enantioselective Addition of $AlMe_3$ to Chromen-4-one Derivatives 806a,b Catalyzed by Cu(I)-CLXXXIII.[392]



An unusual approach to chiral 3-aminomethylene-flavanones, interesting pharmaceutical molecules with aromatase inhibition activity, was performed starting from chromenones **809** with suitably placed leaving groups (OBoc). The starting reagents undergo an *aza-Michael* addition of benzylamines **810**, catalysed by the trifunctional organocatalyst with cinchonidine-amine-thiourea functions (1*S*,2*S*,3'*R*,8'*S*,9'*S*)-**CLXXXIV**, to give the intermediate **A.** This chromanone undergoes the *ring opening* and the resulting imino-ketone binds through hydrogen bonding its imino, carbonyl and hydroxyl groups to the organocatalyst to give the reacting complex [(1*S*,2*S*,3'*R*,8'*S*,9'*S*)-**CLXXXIV**/**A**] (Scheme 328).[393] The chiral step of the cascade is the *oxa-Michael* attack of the hydroxyl group to the *β-Si* face (*β-Re* in accordance to the convention of this

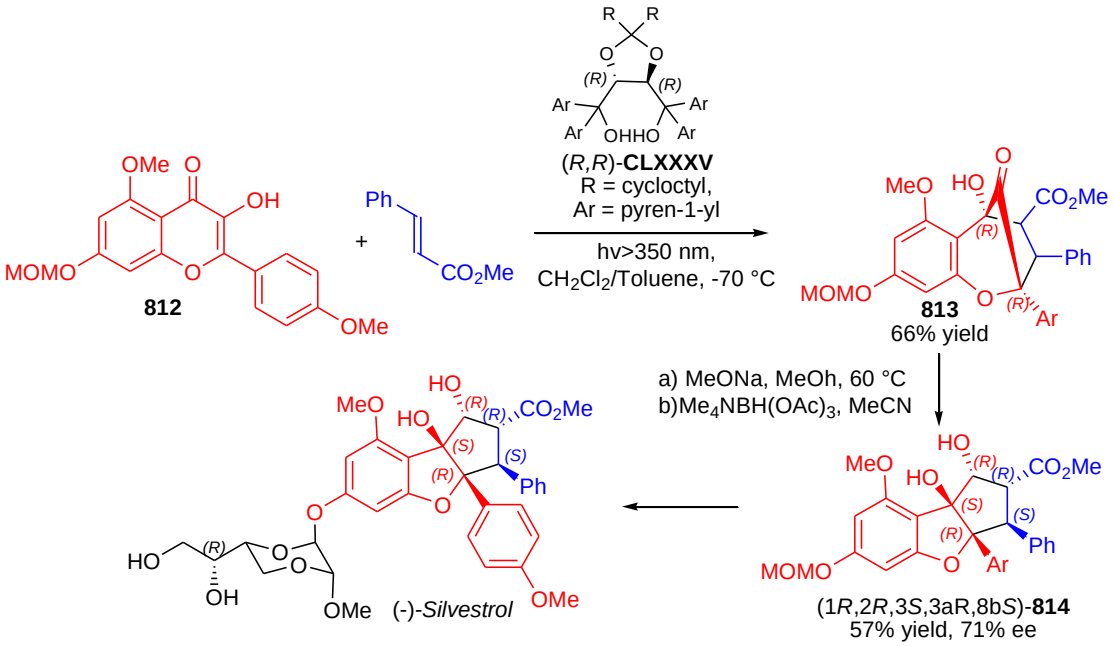
review) of the styrenic fragment to give 3-[(benzylamino)methylene]-2-arylchroman-4-ones [(*S*)-**811**] that, over ten experiments, are formed in good yields and enantioselectivities.

Scheme 328. Enantioselective [Aza-Michael/Ring Opening/Oxa-Michael] Cascade Reactions of Chromones 809 with Amines 810 Catalyzed by (1*S*,2*S*,3'*R*,8'*S*,9'*S*)-CLXXXIV.[393]



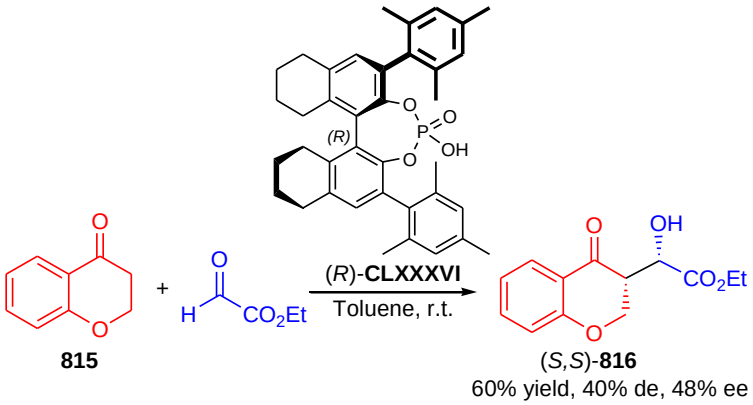
The synthesis of (-)-*Silvestrol*, a rocaglate natural product and antitumor agent, is an example of the fantasy that is sometimes required for the synthetic studies in the field of this review. The unusual enantioselective [3+2] photocycloaddition between the protected hydroxyflavone **812** and methyl cinnamate, catalysed by TADDOL (*R*,*R*)-**CLXXXV**, led to the formation of cycloadduct **813** (Scheme 329).[394] After an [α-ketol rearrangement/hydroxyl-directed reduction] sequence, the *endo*-rocaglate derivative (1*R*,2*R*,3*S*,3a*R*,8b*S*)-**814** was isolated in 57% yield and 71% ee. The Mitsonobu reaction between compound **814** and dioxanol gave the desired (-)-*Silvestrol* whose structure was found to be methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-6-({(2*S*,3*R*,6*R*)-6-[(1*R*)-1,2-dihydroxyethyl]-3-methoxy-1,4-dioxan-2-yl}oxy)-1,8b-dihydroxy-8-methoxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-benzo[*b*]cyclopenta[*d*]furan-2-carboxylate by X-ray analysis (Scheme 329).

Scheme 329. Enantioselective Synthesis of (-)-*Silvestrol*.[394]



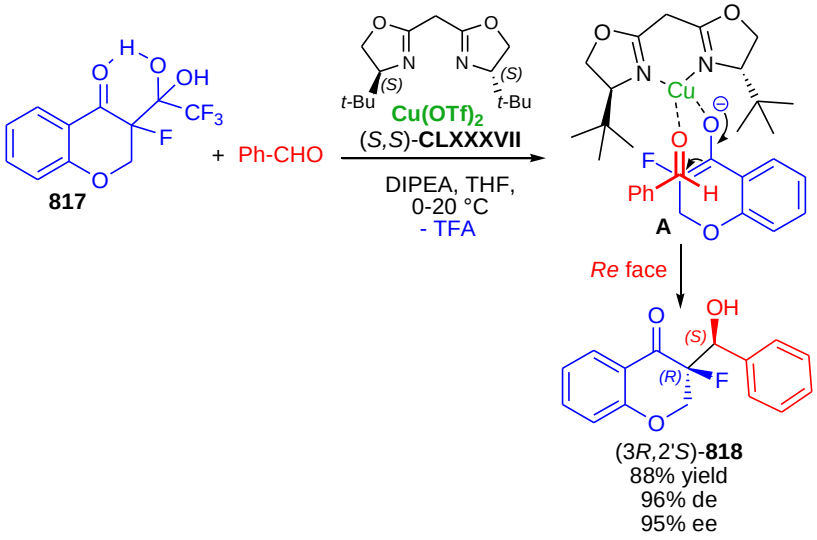
The reported examples are based on the formation of a chiral center by addition to the double bond of 2,3- or 3,4-chromanones. Since the 2,3-dihydrochromen-4-one (**815**) has acidic hydrogens at the 3-position, the chirality may be induced by transforming enantioselectively one of them into a chiral center. A *syn*-enantioselective aldol reaction with ethyl glyoxylate can be developed using the chiral Brønsted acid (*R*)-**CLXXXVI** (Scheme 330).[395] One single interesting exploratory example was reported, and the result was (*S*,*S*)-**816**.

Scheme 330. Brønsted Acid Catalyzed Asymmetric Aldol Reaction Between 815 and Ethyl Glyoxylate Catalyzed by (*R*)-CLXXXVI.[395]



We close this section with an example of [(*S*,*S*)-BOX/Cu(II)]-catalyzed asymmetric synthesis of a C-F quaternary stereogenic center through detrifluoroacetylative aldol addition. The reaction between 3-fluoro-3-(2,2,2-trifluoro-1,1-dihydroxyethyl)-2,3-dihydrochromen-4-one (**817**) and benzaldehyde, catalyzed by (*S*,*S*)-**CLXXXVII**, occurs first by loss of trifluoroacetic acid and generation of the enolate that is coordinated, together with benzaldehyde, by the Cu(II)/BOX complex to give the reacting intermediate **A**. Its chair-like stereochemistry locates the enolate moiety in a favourable position and the phenyl in the opposite direction to minimize the interactions with the *t*-butyl groups of the ligand. The aldol addition of the enolate occurs to the *Re* face of benzaldehyde and affords (*R*)-3-fluoro-2,3-dihydro-3-[(*S*)-hydroxy(phenyl)methyl]chromen-4-one [(3*R*,2′*S*)-**818**] containing the C-F quaternary stereogenic center, in a very good yield and excellent diastereo- and enantioselectivity (Scheme 331).[396]

Scheme 331. Enantioselective Synthesis of Fluorinated Quaternary Stereogenic Center through Detrifluoroacetilative Aldol Reaction Catalyzed by (*S*,*S*)-CLXXXVII.[396]

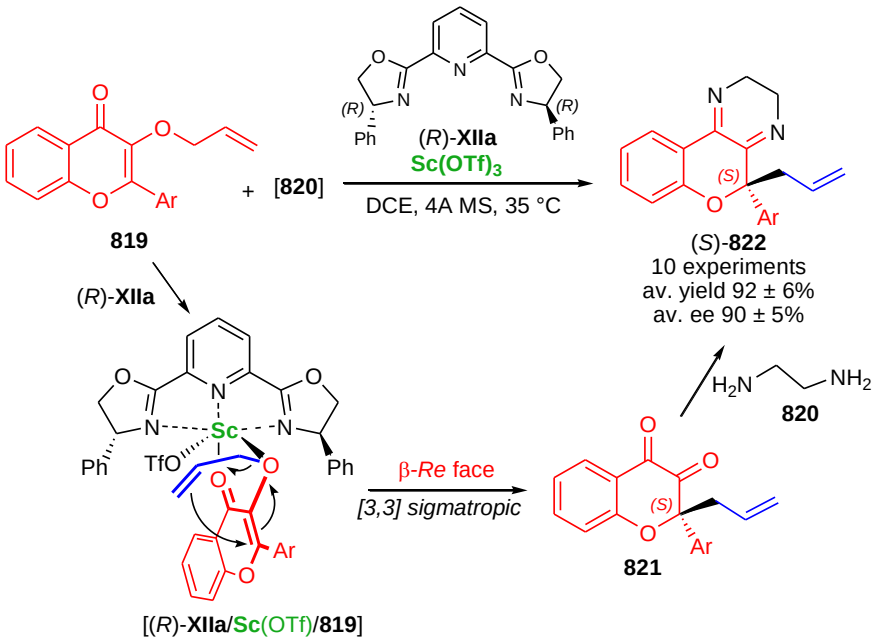


6.2.2. Intramolecular Addition of Reagents to Chromones.

If a 2,3- or 3,4-chromenone has a suitably placed substituent behaving as a nucleophile, its attack to the electrophilic position of the enone may promote the formation of a chiral center in the substrate under catalytic asymmetric conditions. This is the simplified frame of a chirality-induced reaction in chromenone through an intramolecular addition.

The asymmetric rearrangement of 3-(allyloxy)-2-aryl-4*H*-chromen-4-one (**819**), catalysed by the [Sc(III)/(*R*,*R*)-Pybox] complex [(*R*)-**XIIa**/Sc(OTf)$_3$], is a paradigmatic example of this route to generate a chiral center by intramolecular addition. The reaction, run in the presence of ethylendiamine **820** that participates in a late marginal step, starts with the octahedral Sc(III) complex that coordinates **819** with the carbonyl group axial and the oxygen of the allyloxy group equatorial to give the reacting complex [(*R*)-**XIIa**/Sc(OTf)/**819**]. The subsequent step is a [3,3] sigmatropic rearrangement, confirmed by the Authors with deuterium labelling experiments, in which the allyl group migrates to the position 2 of chromenone to attack the *β-Re* face of this specific enone, affording (*S*)-2-allyl-2-aryl-2*H*-chromene-3,4-diones **821**. This finally reacts with ethylendiamine and gives, with excellent yields and enantioselectivities, (*S*)-5-allyl-5-aryl-3,5-dihydro-2*H*-chromeno[3,4-*b*]pyrazines [(*S*)-**822**] whose absolute configuration was determined by X-ray crystallography, (Scheme 332).[397]

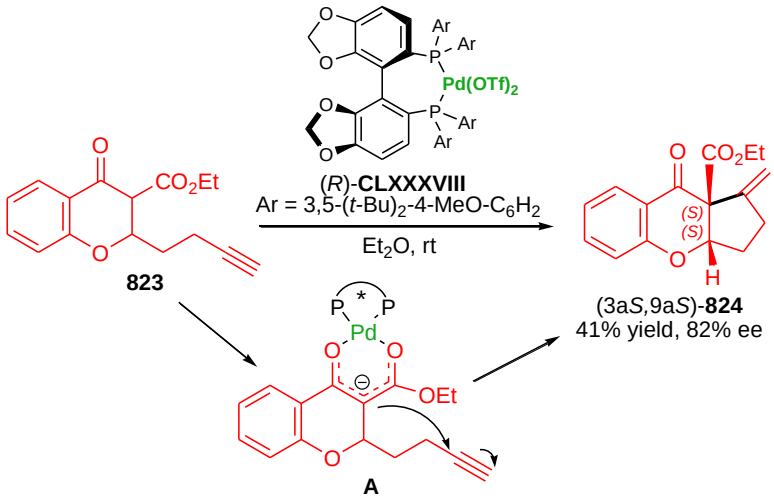
Scheme 332. Enantioselective Synthesis of 3,4-Chromanediones Through Intramolecular Rearrangenent of 3-(Allyloxy)-chromen-4-ones Catalyzed by (*R*)-XIIa/Sc(OTf)$_3$.[397]



The generation of chiral palladium enolates from 1,3-dicarbonyl compounds with palladium complex and its application to catalytic enantioselective Michael reactions is an useful synthetic route for the asymmetric synthesis of all-carbon quaternary stereocenters.[398] Its intramolecular

version is the enantioselective *Conia-ene* reaction in which β-dicarbonyl compounds bound to alkynes afford methylene cyclopentanes. This reaction, catalyzed by DTBM-Segphos-Pd(II) complex (*R*)-**CLXXXVIII**, was applied to ethyl 2-(but-3-ynyl)-3,4-dihydro-4-oxo-2*H*-chromene-3-carboxylate (**823**) and proceeds with the generation of the palladium enolate **A** that undergoes a Brønsted acid-promoted intramolecular addition to the alkyne which results in the enantioselective synthesis of ethyl 1,2,3,3a,9,9a-hexahydro-1-methylene-9-oxocyclopenta[*b*]chromene-9a-carboxylate [(3a*S*,9a*S*)-**824**] in 82% ee at 41% conversion (Scheme 333).[399]

Scheme 333. Synthesis of 9-Oxocyclopenta[*b*]chromene-9a-carboxylate Derivative (3a*S*,9a*S*)-824 through Enantioselective Conia-Ene Reaction Catalyzed by (*R*)-CLXXXVIII.[399]



7. The Enantioselective Multicomponent [m+n+o] Syntheses of Pyran Derivatives

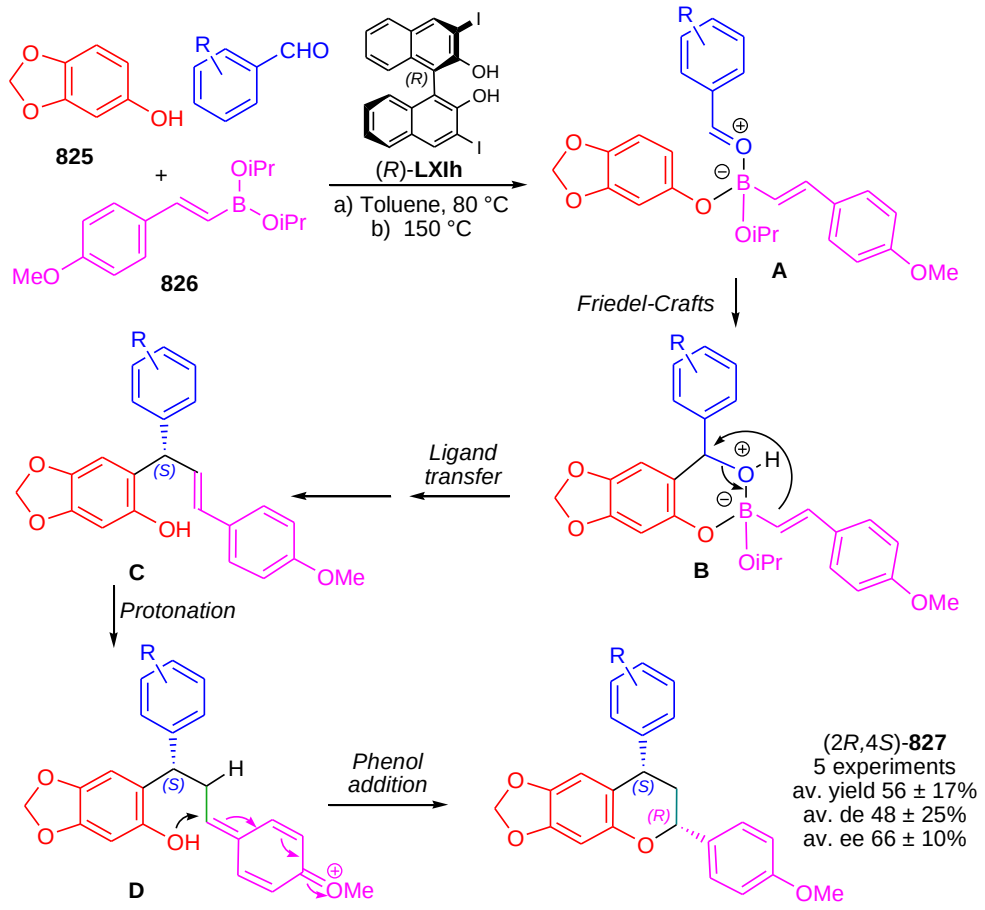
As encountered in previous sections, the discovery of new reactions for the synthesis of dihydropyrans is a major focus of current research and the topic of this review. Within this scope, cycloaddition reactions are prominent methods for the construction of cyclic compounds with structural and functional complexity. The two-component [m+n] mode is the most typical cycloadditions but the assembly mode requires a catalyst to bring together two reagents for the correct stereochemical gathering to afford the final product. If the components to be assembled are more than two, the difficulty is strongly increased and the most common [2+2+1] (the Paulson-

Khand reaction) and the [2+2+2] cycloadditions require a transition-metal complex that acts as a template for the unsaturated substrates, bringing the reagents around the metal center in the correct way required for the cycloaddition. The difficulty in performing the enantioselective multicomponent [m+n+o] syntheses of pyran derivatives is to find three reagents that accept to melt into the heterocycle, a chiral catalyst that has sympathy for each of them; a result that corresponds to a chiral pyran derivative. The great development of organocatalysis made somewhat simpler this hard task.

7.1. The [3+2+1] Cyclo-condensation

The first example is an organocatalytic domino [*Friedel-Crafts/ligand transfer/protonation/ phenol addition*] reaction performed with benzaldehydes, electron rich phenols **825**, and styrenyl boronates **826**, catalysed by the 3,3′-diiodo-BINOL (*R*)-**LXIh** (Scheme 334).[400]

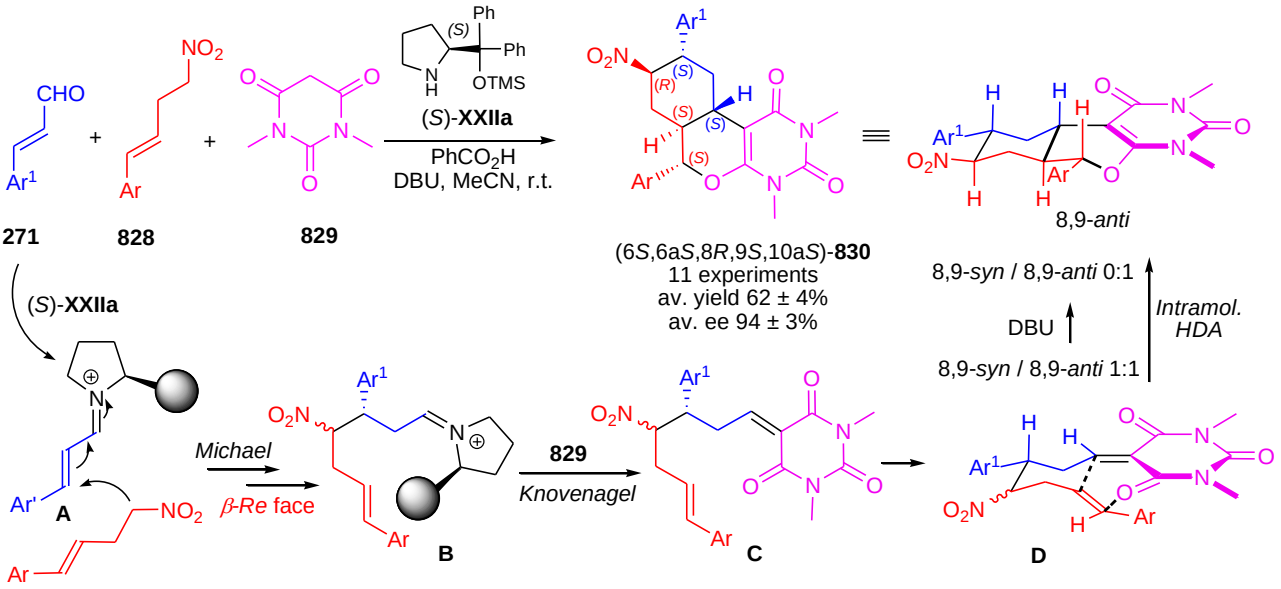
Scheme 334. Enantioselective Multicomponent Cyclization of Phenols, Aldehydes and Boronates.[400]



The stepwise pathway begins with the condensation of phenol to boronate that coordinates the aldehyde to give the Lewis complex **A**. The boron-mediated Friedel-Crafts generates the C(4)-C(4a) bond and affords the boronate complex **B** that provides the chiral intermediate **C** in the enantiodetermining step with the ligand transfer and loss of boric ester. The final protonation gives **D** that undergoes the phenol intramolecular ring closure to afford (2*R*,4*S*)-**827**. The reader can be satisfied for yields, diastereomeric- and enantiomeric excess obtained in five experiments, which confirm the flexibility of a protocol that allows to generate one product, with two defined stereocenters, from three reagents.

The reaction from α,β-unsaturated aldehydes **271**, olefinic nitroalkanes **828**, and 1,3-dimethylbarbituric acid **829**, catalysed by prolinol-TMS-derived organocatalyst (*S*)-**XXIIa**, may be taken as paradigmatic example of the power that a simple organocatalyst has to determine, from the first step, the result of a highly ordered multicomponent reaction (Scheme 335).[401]

Scheme 335. Organocatalyzed Enantioselective Multicomponent Cyclization of α,β-Unsaturated Aldehydes, Olefinic Nitroalkanes, and 1,3-Dimethylbarbituric Acid.[401]



The iminium derivative **A**, derived from proline and α,β-unsaturated aldehyde, undergoes the initial Michael attack of olefinic nitroalkane to the *β-Re* face to afford the enamine intermediate that is transformed into the iminium ion **B**. This latter reacts with the barbituric acid via a Knovenagel

condensation to give the barbituric acid derivative **C** that has a C=C-C=O system and a double bond suitably placed to behave, respectively, as heterodiene and dienophile in the intramolecular HDA transition state **D**. The product is an equimolar mixture of [8,9-*syn*] and [8,9-*anti*] adducts, in which the former is isomerized by DBU to the 8,9-*anti* isomer. This reaction defines the last of the five stereocenters and (6*S*,6a*S*,8*R*,9*S*,10a*S*)-**830** is obtained as a single enantiomer with an average enantioselectivity of 94% in eleven experiments.

8. Relationship between Different Organocatalysts and the Stereochemical Outcome

This section deals with the relationship between chiral catalyst and stereochemical outcome, shortly discussed for 3,4-dihydropyran derivatives synthetized from 2-oxo-3-butenoates in our previous review on this topic.[402]

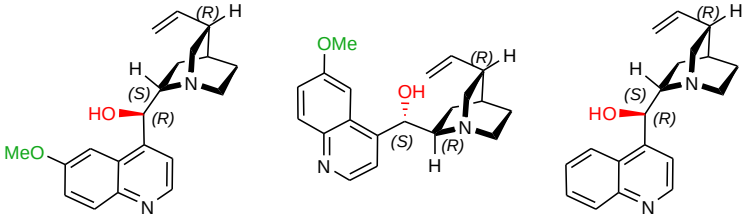
It was certainly noted that some [chiral ligand/inorganic cation] complexes or some organocatalysts were used and discussed several times throughout the text because they were successfully applied in several reactions. If the chiral activator and different reactants give the reacting complexes involved as the key intermediates in the chirality transmission, is the stereochemical outcome of the reactions always the result of the same facial approach to the coordinated reagents?

Due to the enormous development of organocatalysis, this discussion will be limited to few clusters of organocatalysts, taking the most significant reactions in which these catalysts are involved, and trying to find common links between some specific chiral centers shared with the members of the cluster and the stereochemical result.

8.1. *Cinchona* Alkaloids

Three basic *Cinchona* alkaloids (Chart 18): *Quinine, Quinidine* and *Cinchonidine*, have been used as organocatalysts, mainly in the formation of the O(1)-C(2) bond in 4-chromanones by ring closure of the phenolic OH on the β-position of an electrophilic double bond as the site of the oxa-Michael attack.

Chart 18. Basic *Cinchona* Alkaloids as organocatalysts for Enantioselective Syntheses of 3,4-Dihydropyran Derivatives.



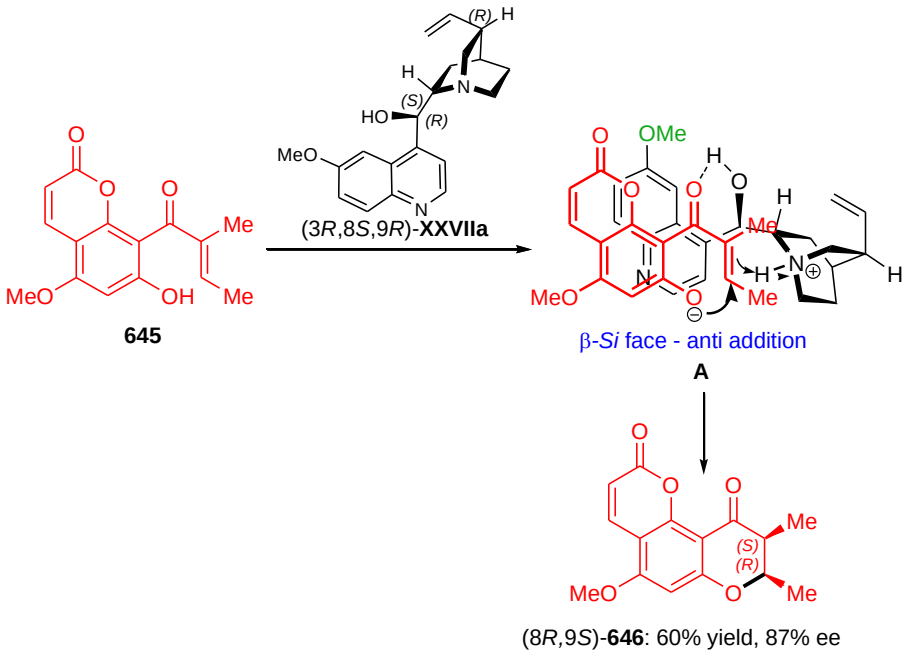
Quinine
(3*R*,8*S*,9*R*)-**XXVIIa**
(Ref. 316-319)

Quinidine
(3*R*,8*R*,9*S*)-**CXLV**
(Ref. 316)

Cinchonidine
(3*R*,8*S*,9*R*)-**CXLVI**
(Ref. 319)

This protocol was first proposed by Ishikawa with the reaction of *o*-tigolyphenol **645** that, in the presence of quinine (3*R*,8*S*,9*R*)-**XXVIIa**, affords (8*R*,9*S*)-**646** (Scheme 336).[316] For the major reaction product, the asymmetric induction of *Quinine* can be rationalized through the reacting intermediate **A** in which the hydroxy function of the catalyst binds the carbonyl group of the tigolyl moiety by hydrogen bonding, the tertiary amino group is protonated by phenol, and the resulting sandwich structure is stabilized by non-bonding π-π stacking interactions between electron-rich and electron-poor aromatic rings.

Scheme 336. Chirality Transfer by using *Quinine* (3*R*,8*S*,9*R*)-XXVIIa as Organocatalyst.[316]



645

(3*R*,8*S*,9*R*)-**XXVIIa**

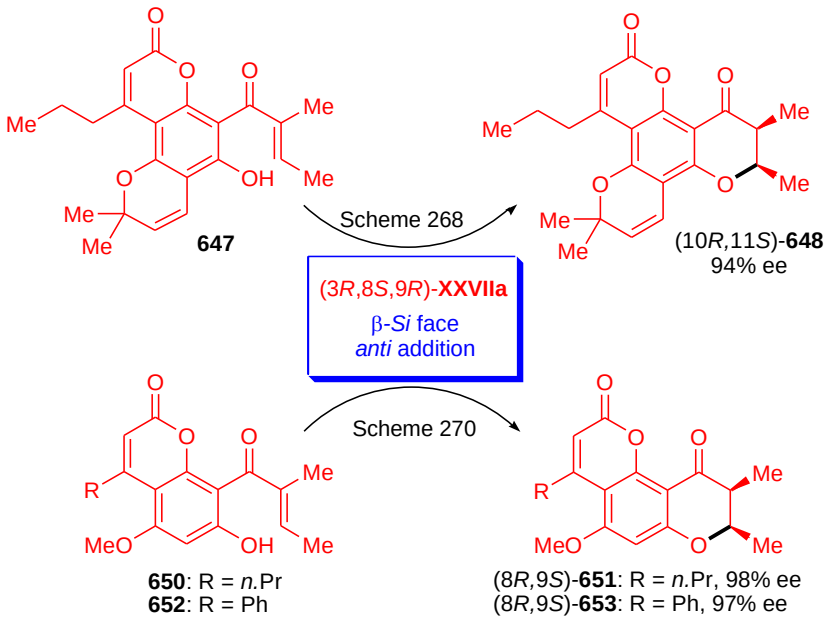
β-*Si* face - anti addition

A

(8*R*,9*S*)-**646**: 60% yield, 87% ee

This arrangement forces the oxa-Michael attack to the *β-Si* face (in accordance to the convention described in Figure 4) and the result is the *R* configuration of the early formed chiral center, followed by an *anti*-addition of the proton affording to the *S* configuration in the second chiral center. Other reacting intermediates could be invoked for the minor products. The same model can be applied to the ring closure of 1-(2-hydroxyphenyl)-2-methylbut-2-en-1-ones **647**, **650** and **652** to give (10*R*,11*S*)-**648**, (8*R*,9*S*)-**651** and (8*R*,9*S*)-**653** by using the same *Quinine* (3*R*,8*S*,9*R*)-**XXVIIa** as the organocatalyst.[316,317,319] In all cases the cyclized products are obtained within excellent enantioselectivities (Scheme 337).

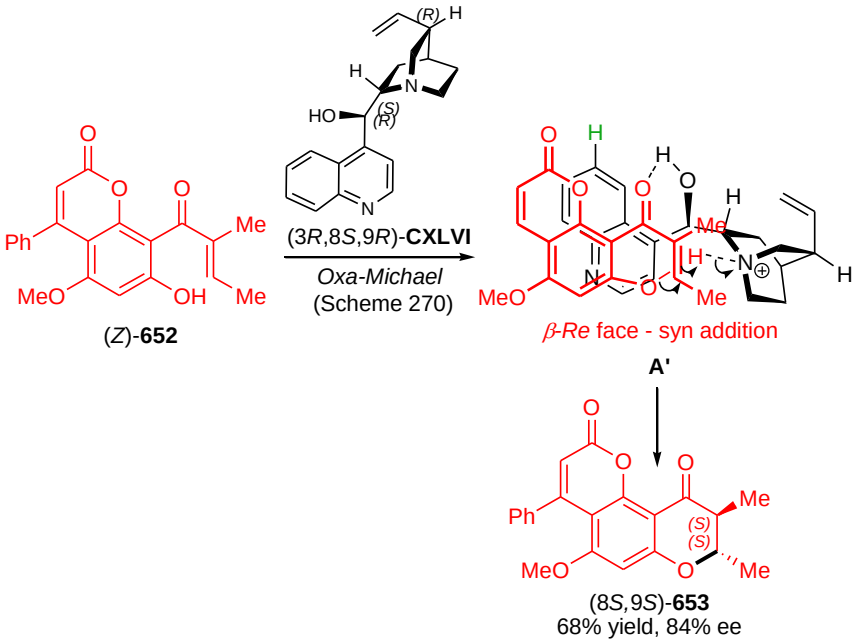
Scheme 337. Chirality Transfer by using *Quinine* (3*R*,8*S*,9*R*)-XXVIIa as Organocatalyst.[316,317,319]



When the reaction described above on 1-(2-hydroxyphenyl)-2-methylbut-2-en-1-one **652** is catalysed with *Cinchonidine* (3*R*,8*S*,9*R*)-**CXLVI** that differs from *Quinine* simply for the absence of the 6′-OMe, the result is surprising because the product (8*S*,9*S*)-**653** is the diastereoisomer of that obtained with *Quinine*, and the enantioselectivity is somewhat lower (Scheme 338).[319] This result derives from an oxa-Michael attack to the *β-Re* face of the enone that affords an (*S*) configuration to the chiral center in position 8, and a *syn*-addition of the proton. The Authors suggest that the change of the stereochemical result from *Quinine* to *Cinchonidine* is due to the absence of the methoxy

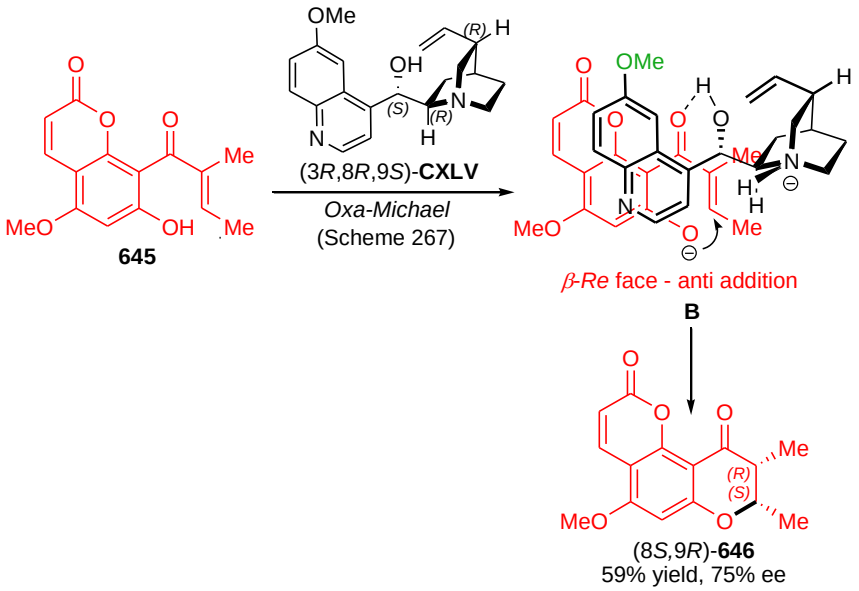
group on the quinoline skeleton in the catalyst that gives to the conjugated acid of the former a more acidic character than that of the latter. Thus, *Quinine* induces the oxa-Michael attack through the ion-pair reacting intermediate **A** in Scheme 336 whereas *Cinchonidine* promotes the oxa-Michael attack in a reacting intermediate **A′** with of a less polarized hydroxy group.

Scheme 338. Chirality Transfer by using *Cinchonidine* (3*R*,8*S*,9*R*)-CXLVI as Organocatalyst.[319]



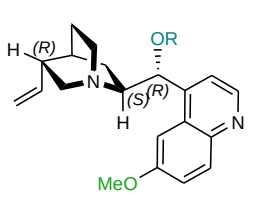
When the organocatalyst is *Quinidine* (3*R*,8*R*,9*S*)-**CXLV**, as reported in the reaction with the 1-(2-hydroxyphenyl)-2-methylbut-2-en-1-one **645** (Scheme 267),[321] the reacting intermediate **B** has the hydroxy function of the catalyst that binds the carbonyl group of the tigolyl moiety by hydrogen bonding, the tertiary amino group protonated by phenol, and the sandwich structure stabilized by non-bonding π-π stacking interactions between electron-rich and electron-poor aromatic rings. Thus, the oxa-Michael attack occurs to the *β-Re* face, followed by an *anti*-addition of the proton to produce (8*S*,9*R*)-**646** (Scheme 339).[316]

Scheme 339. Chirality Transfer by using *Quinidine* (3*R*,8*R*,9*S*)-CXLV as Organocatalyst.[342]

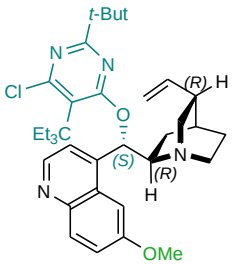


The basic structure of the *Cinchona* alkaloids is sometimes modified for a supposed better activity as organocatalyst. Those above can be modified by protecting the 9-hydroxy group, or by demethylating the 6′-methoxy (Chart 19). Four examples are the modified *Quinine* (3*R*,8*S*,9*R*)-**XXVIIc**,[69] *Quinidines* (3*R*,8*R*,9*S*)-**CXXVII**,[278] (3*R*,8*R*,9*S*)-**CXLVIIIb**,[322] and (3*R*,8*R*,9*S*)-**CXLVIIIa**.[321]

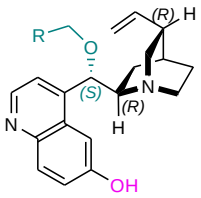
Chart 19. Modified Basic *Cinchona* Alkaloids as Organocatalysts for Enantioselective Syntheses of 3,4-Dihydropyran Derivatives.



(3*R*,8*S*,9*R*)-**XXVIIb**: R=Bn (Ref. 68)
(3*R*,8*S*,9*R*)-**XXVIIc**: R=Me (Ref. 69)



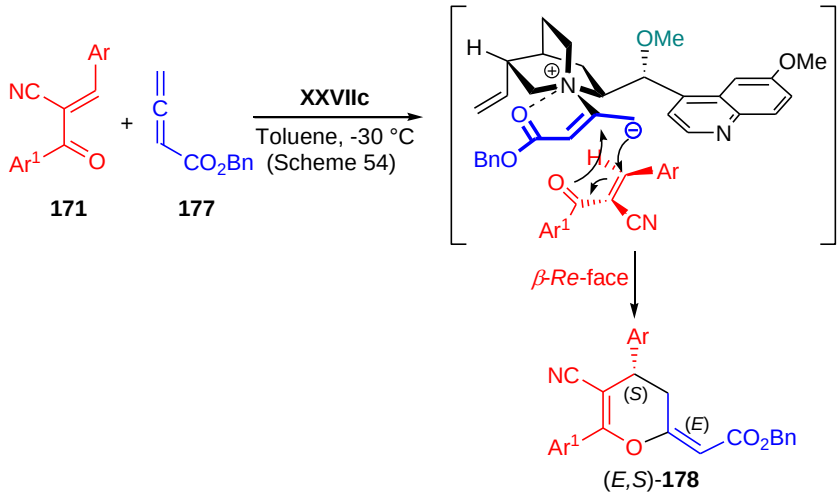
(3*R*,8*R*,9*S*)-**CXXVII** (Ref. 278)



(3*R*,8*R*,9*S*)-**CXLVIIIa**: R=4-F_3C-C_6H_4 (Ref. 321)
(3*R*,8*R*,9*S*)-**CXLVIIIb**: R=Ph (Ref. 322)

The *Quinine*-derived (3*R*,8*S*,9*R*)-**XXVIIc** was the organocatalyst of the reaction between α-cyano-α,β-unsaturated ketones **171** with allenoate **177** to give adducts (*E*,S)-**178**.[69] The Authors suggest that the organocatalyst tertiary amine coordinates the allene and shields its upper face, thus guiding the attack from the bottom face to the *β-Re* face of the oxodiene **171** (Scheme 340).

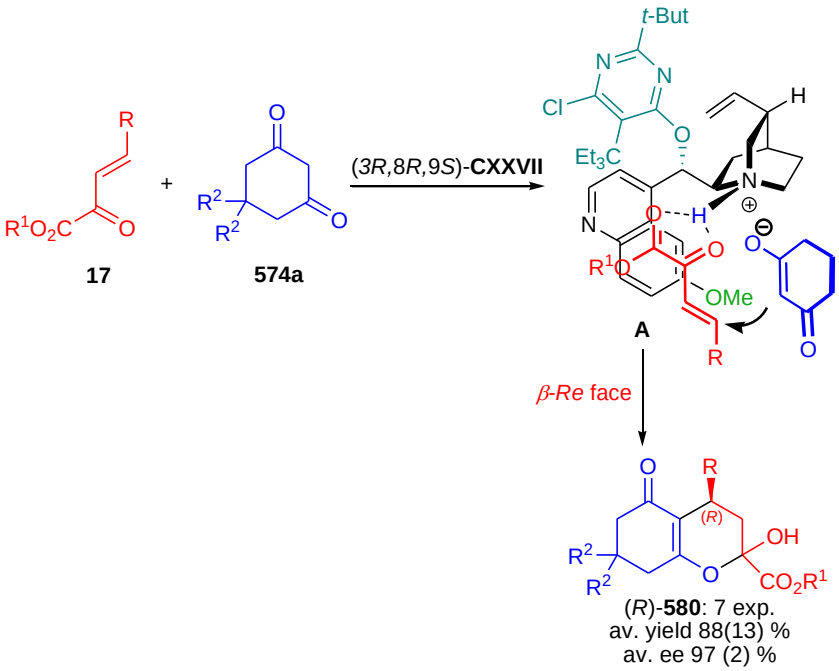
Scheme 340. Enantioselective [4+2] Annulations of 171 with Allenoates 177 Catalyzed by XXVIIc.[69]



It would be easy to emphasize the different stereochemical outcome of **XXVIIc** in Scheme 340 compared to that of *Quinine* (3*R*,8*S*,9*R*)-**XXVIIa** in Schemes 336 and 337, but these logic connections have a rigorous sense when derived from reactions involving similar reagents under comparable conditions, because different reagents may involve different coordinations. Taking this into account, *Quinine* **XXVIIa** is a bifunctional organocatalyst while **XXVIIc** is a monofunctional one.

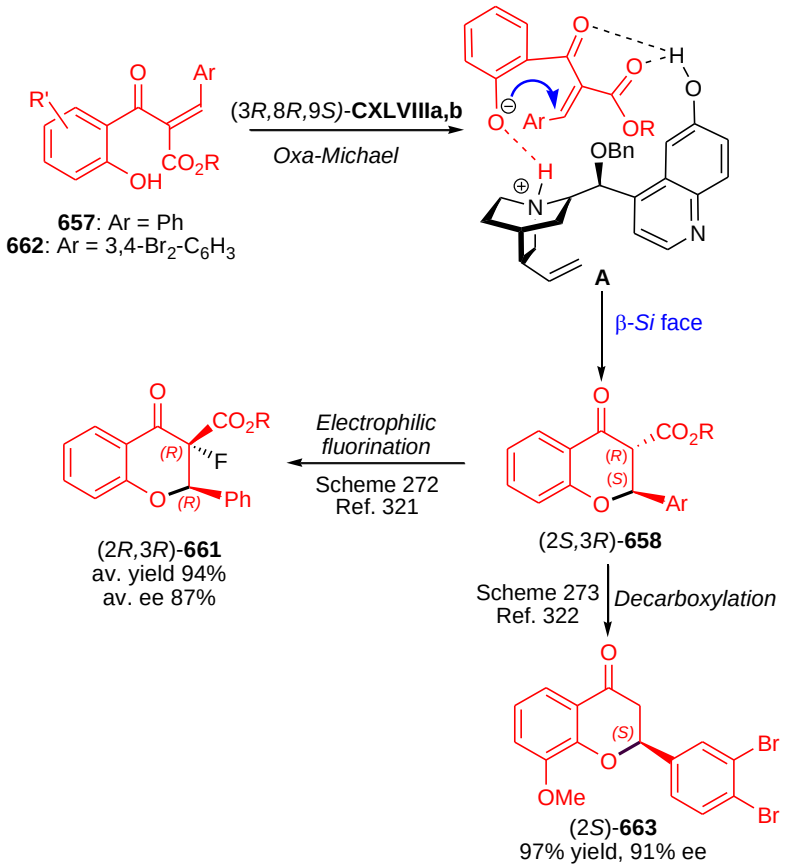
The *Quinidine*-derived organocatalyst (3*R*,8*R*,9*S*)-**CXXVII**, in which the 9-hydroxy group is protected by 4-[2-*tert*-butyl-6-chloro-5-(3-ethylpentan-3-yl)]pyrimidine, is the organocatalyst of the [Michael reaction/hemiacetalization] between 1,3-cyclohexandiones **574a** and β,γ-unsaturated α-ketoesters **17**. The product is (*R*)-**580** (in equilibrium with the cyclic tautomer) that is obtained with excellent enantioselectivity (Table 23, entry 11).[278] This is the result of the addition of the nucleophile to the *β-Re* face of the enone, but even if the result is the same induced above by *Quinidine*, the reacting intermediate must be very different. As an exercise, we propose that the reacting intermediate **A** results from the tertiary amino group protonated by **574a** with formation of an ion pair, the hydrogen-bonding coordination of α-ketoesters **17**, which is suitably placed to undergo the *β-Re* face addition of the anionic nucleophile. (Scheme 341).

Scheme 341. Chirality Transfer by using Pyrimidine-protected *Quinidine* (3*R*,8*R*,9*S*)-XXIII as Organocatalyst.[278]



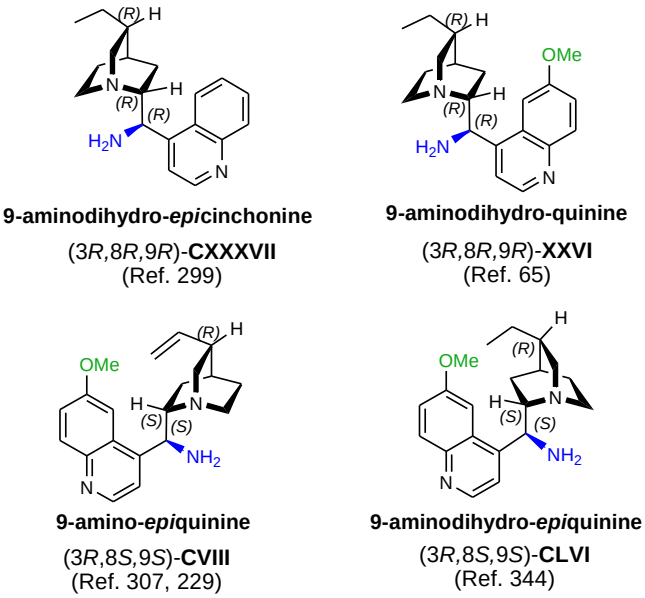
Two *Quinidine*-derived organocatalyst, (3*R*,8*R*,9*S*)-**CXLVIIIb**[322] and (3*R*,8*R*,9*S*)-**CXLVIIIa**,[321] with both the 9-hydroxy group protected by benzyl-type group and the 6′-hydroxy function unprotected, are the organocatalysts of cascade reactions in which an oxa-Michael is the first step. Both reactions were run on 2-hydroxy-β-oxo-α-(arylmethylene)-phenylpropenoic esters **657** and **662** and, after the *oxa-Michael* that is the enantio-discriminating step affording (2*S*)-**658**, the former was followed by an electrophilic fluorination that gave (2*R*,3*R*)-**661**, the latter by a decarboxylation providing (*S*)-**663**. The Authors propose a reacting intermediate **A** in which the bifunctional catalyst activates both the nucleophile and the electrophilic acceptor by hydrogen bonding, the former through coordination with the tertiary amine, the latter by coordinating the carbonyl groups with 6′-hydroxy function that assumes a crucial role in the configuration of the reacting intermediate. Therefore, both reactions have a stereo-determining attack to the *β-Si* face of the enone. The examples with the organocatalysts reported in Scheme 342 show the importance that a tailored modification of the basic structure of *Cinchona* alkaloid has in the stereochemical result.

Scheme 342. Chirality Transfer by Using 9-Benzyl-protected and 6′-Hydroxy *Quinidine* (3*R*,8*R*,9*S*)-CXLVIIIa,b as Organocatalysts.[321,322]



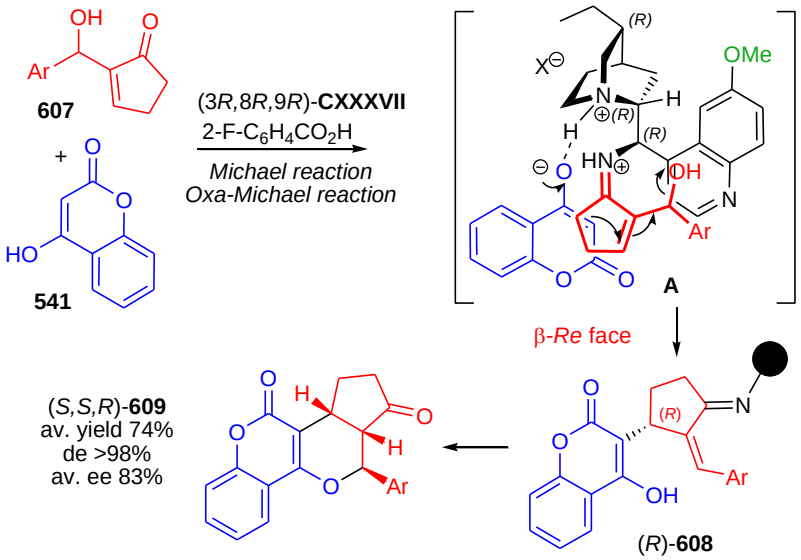
An important class of *Cinchona* alkaloids have a 9-amino function instead of the 9-hydroxy group. This modification opens new horizons to the organocatalysis because the amino group can react with a carbonyl reagent (the field of organocatalysis was opened by proline derivatives) giving a reacting intermediate built not only on hydrogen bonding or on the electrostatic forces of an ion pairs, but based on the definite structure of an iminium ion also. Four organocatalysts with this feature have been tested: (3*R*,8*R*,9*R*)-**CXXXVII** with the 9-amino-3-dihydro-*epicinchonine* framework,[229] (3*R*,8*R*,9*R*)-**XXVI** with the 9-amino-3-dihydro-*quinine*,[65] (3*R*,8*S*,9*S*)-**CVIII**,[229,307] and (3*R*,8*S*,9*S*)-**CLVI**,[344] both with 9-amino-epiquinine framework, the latter as a 3-dihydro derivative (Chart 20).

Chart 20. 9-Amino *Cinchona* Alkaloids as Organocatalysts for Enantioselective Syntheses of 3,4-Dihydropyran Derivatives.



9-Amino-*epicinchonine* (3*R*,8*R*,9*R*)-**CXXXVII** is the organocatalyst of the [Michael/oxa-Michael] cascade reaction between **607** and **541** and a reacting intermediate **A** can be proposed, which involves the formation of the activated iminium ion from **607** with the primary amine, and the hydroxycoumarin anion bound, without any linking with the anion of trifluoroacetic acid, by hydrogen bonding to protonated tertiary amine of the catalyst (Scheme 343).[299]

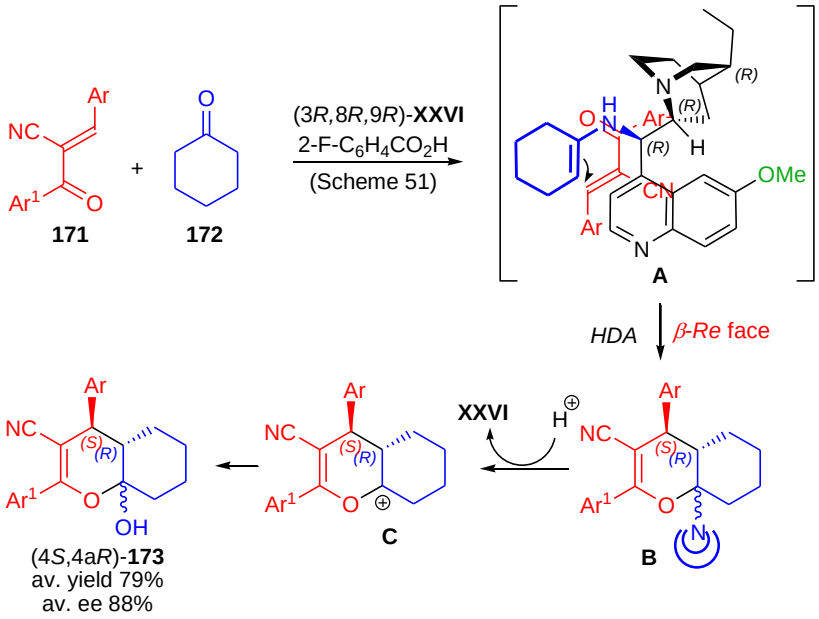
Scheme 343. Chirality Transfer by using 9-Amino-*epicinchonine* (3*R*,8*R*,9*R*)-CXXXVII as Organocatalyst.[299]



This favours the attach of **541** to the γ-position of **607**, in this specific case from the *β-Re* face, to afford the intermediate (*R*)-**608** with the first chiral center of the final adduct (3a*R*,11*S*,11a*S*)-**609**.

9-Amino-3-dihydro-*quinine* (3*R*,8*R*,9*R*)-**XXVI** catalyses the reaction between diaryl-α-cyano-α,β-unsaturated ketones **171** with cyclohexanone **172** to give adducts **173** (Scheme 51).[65] Being very similar to the above organocatalyst (same absolute configuration), we could expect the same stereochemical result through a close catalytical behaviour. But amino *Cinchona* alkaloids, which have a complex and flexible framework, may behave as a large sterically hindering substituent, and they have several functions that may interact with the reagents. Now, the primary amine of the catalyst reacts with **172** to give an enamine that, in the reacting intermediate **A**, undergoes an attack of the electron poor heterodiene **171** from the less hindered face (Scheme 344).[65]

Scheme 344. Chirality Transfer by Using 9-Amino-3-dihydro-*quinine* (3*R*,8*R*,9*R*)-XXVI as Organocatalyst.[65]

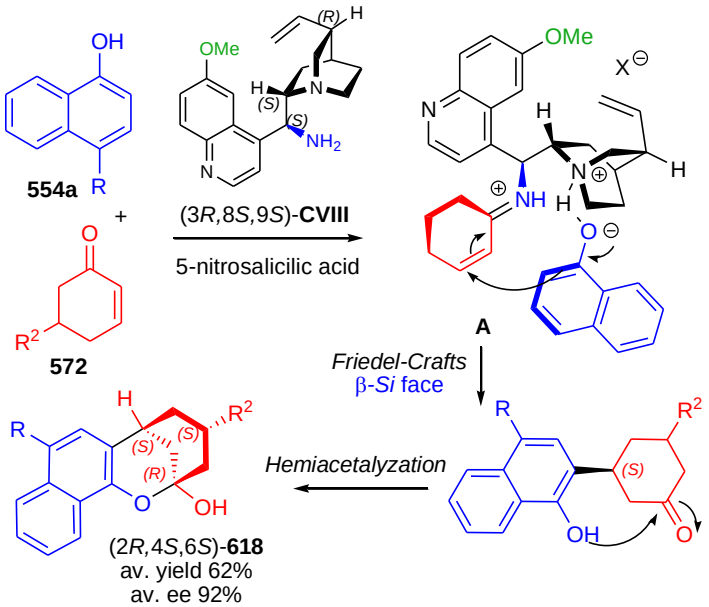


This may be considered a HDA reaction with an attack to the *β-Re* face of the specific enone and the formation of the adduct **B** having the (4*S*,4a*R*) configuration. The acidic recycling of the catalyst and the hydration of the carbocation **C**, affords **173** in which the absolute configuration of the quaternary C-atom bearing the OH group is preferentially (*R*).

The above two 9-amino *Cinchona* alkaloids, with the same absolute configuration (3*R*,8*R*,9*R*)-**CXXXVII** and (3*R*,8*R*,9*R*)-**XXVI**, behave as organocatalysts with two reacting intermediates in which the first step is the reaction of NH_2 with the carbonyl group of a reagent to give an enamine or an iminium ion. Given the above mechanisms for organocatalysts with a (3*R*,8*R*,9*R*)-configuration, which will be the model suitable to rationalize the reactions of other 9-amino-*cinchona* alkaloids? 9-Amino-*epiquinine* (3*R*,8*S*,9*S*)-**CVIII** is the organocatalyst of two reactions: the [Friedel-Crafts/ hemiacetalization] cascade reactions of 2-cyclohexenones **572** with 1- and 2-naphthols **554a** and **554b** (Table 26, entries 6 and 7),[307] and the [Michael/acetalization] between 2-(2-nitrovinyl)phenol **475** and acetone **498** (Table 18, entry 7).[229]

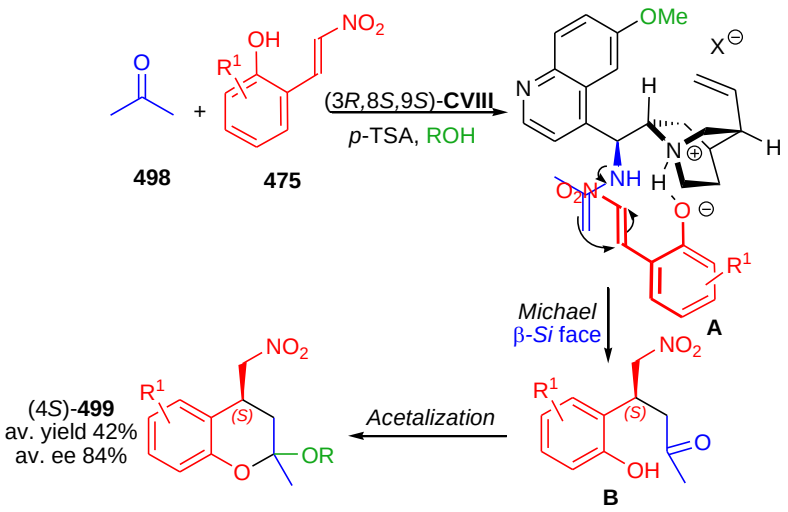
For a rationale of the stereochemical outcome of the first reaction, the intermediate **A** can be proposed in which the activated iminium ion derived from **572** and the primary amine is faced to the naphtholate bound by hydrogen bonding to the protonated tertiary amine of *epiquinine*. This favours the attack of the electron-rich α-carbon of **554a** to the β-position of **572**, in this specific case from the *β-Si* face, to afford the first (*S*) chiral center of the final adduct (2*R*,4*S*,6*S*)-**618**. This model is represented in Scheme 345 for 1-naphthol, but the result is the same for **554b**.

Scheme 345. Chirality Transfer in the Reaction between 554a and 572 by Using 9-Amino-*epiquinine* (3*R*,8*S*,9*S*)-CVIII as Organocatalyst.[307]



The same catalyst in the [Michael/acetalization] reaction promotes the formation of the enamine between the primary amine of the catalyst and acetone, and the coordination of 2-(2-nitrovinyl)phenol **475** through hydrogen bonding to the *epiquinine* tertiary amine, which provide the reacting intermediate **A**.[229] The intramolecular Michael attack of the electron rich enamine to the electrophile **475** involves its *β-Si* face with formation of the intermediate (*S*)-**B**. This configuration is retained in the final product (*S*)-**499** after the ring closure by acetalization with the suitable alcohol in the acidic medium (Scheme 346).

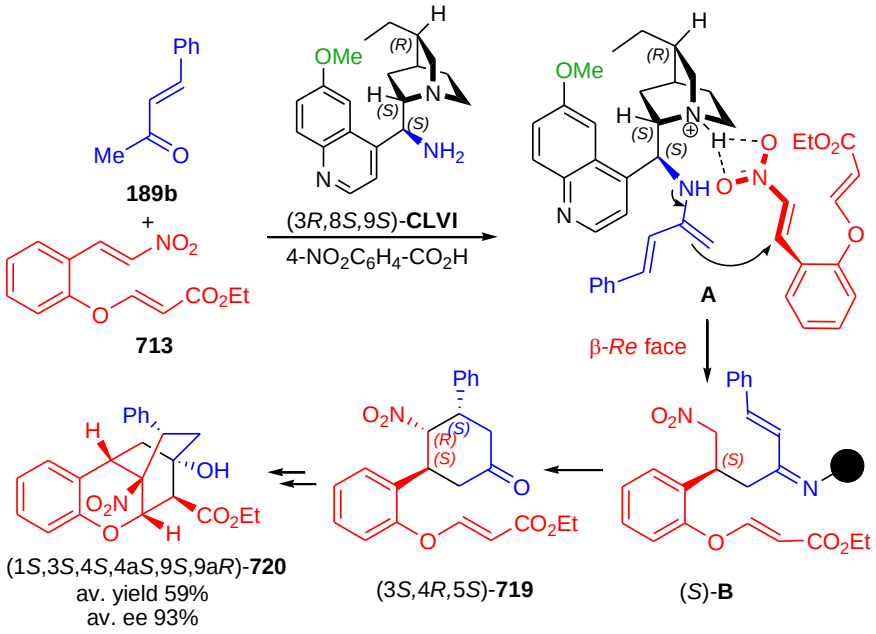
Scheme 346. Chirality Transfer in the Reaction Between 475 and 498 by Using 9-Amino-*epiquinine* (3*R*,8*S*,9*S*)-CVIII as Organocatalyst.[229]



Finally, 9-amino-*dihydroepiquinine* (3*R*,8*S*,9*S*)-**CLVI** is the organocatalyst of the intermolecular-intramolecular [Michael/Michael/Michael/Aldol] cascade reaction between **713** and methyl stiryl ketone **189b**.[344] The cascade begins with the intermolecular Michael attack of the enamine derived from **189b** on nitroalkene to afford the first intermediate (*S*)-**B**. This can be rationalized through the reacting intermediate **A**, from reaction of methyl stiryl ketone with the primary amino group to afford a bound enamine, and the coordination by hydrogen bonding of the nitro group of **713** with the protonated tertiary amine of the catalyst. The attack of the former methyl group of **189b** to the *β-Re* face of the electrophilic double bond gives (*S*)-**B**. Then, the Michael ring closure affords the intermediate with three chiral centers (3*S*,4*R*,5*S*)-**719** that

undergoes, through deprotonation, Michael and aldol reactions affording the tetracyclic product (1*S*,3*S*,4*S*,4a*S*,9*S*,9a*R*)-**720** (Scheme 347).

Scheme 347. Chirality Transfer by Using 9-Amino-*dihydroepiquinine* (3*R*,8*S*,9*S*)-CLVI as Organocatalyst.[344]



The above examples represent the homogeneous model by which 9-amino-*cinchona* alkaloids act as organocatalysts. The NH_2 group reacts with the carbonyl of one reagent to give the enamine or the activated iminium ion, which are bound to the catalyst. The second reagent is coordinated by hydrogen bonding with the protonated tertiary amine of the catalyst. However, the specificity of the reagents involved give a difference in the reacting intermediates because the enamine (or the activated iminium ion) may behave as the electrophile (Schemes 343 and 345) or the nucleophile (Schemes 344, 346, and 347). Obviously, the second reagent, coordinated by hydrogen bonding to the protonated tertiary amine acts respectively as the nucleophile or as the electrophile in the further step of the reaction.

It is not necessary to emphasize the importance of this step where the chirality of the catalyst is transferred to the product, because this is clearly illustrated by two reactions.

9-Amino-*epicinchonine* (3*R*,**8*R*,9*R***)-**CXXXVII** catalyzes the [Michael/oxa-Michael] reaction between hydroxycoumarin **541** and enone **607**, and the attack of the former to the *β-Re* face of **607**

gives (*R*)-**608** (Scheme 343). 9-Amino-*epiquinine* (3*R*,**8*S*,9*S***)-**CVIII** catalyse the [Michael/acetalization] reaction between naphthols **554** and 2-cyclohexenones **572**, and the attack of the former to the *β-Si* face of **572** gives (*S*)-**618** (Scheme 345). These 9-amino-*cinchona* alkaloids behave as two *organocatalyst enantiomers*, and the common (3*R*) chiral center does not influence the transmission of chirality.

8.2. Chiral Squaramide Derivatives

Squaramide is a class of organocatalysts that had a great success for their structural characteristics: it has a rigid flat structure with two NH groups able to give hydrogen bonding with reagents with a carbonyl functionality. Their behaviour has been supported by *ab initio* calculations at the HF/6-31+G(d,p) level, and the transition state structure, linking ethyl 2-oxo-4-phenylbut-3-enoate **17** to squaramide simplified organocatalysts, was located (Figure 9).

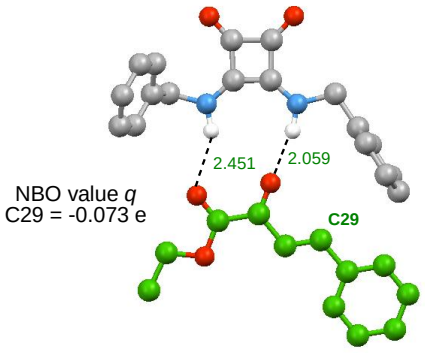
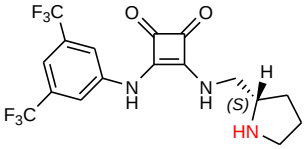


Figure 9. Natural bond orbital (NBO) analysis of optimized transition state structure that link **17** to squaramide simplified organocatalyst.[268,402]

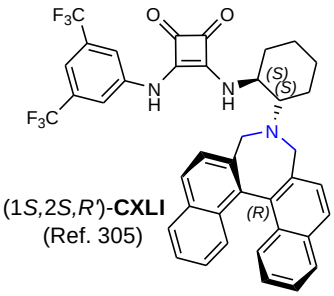
Natural bond orbital (NBO) analyses were carried out, and the NBO values (q) at C29 (−0.073 e) showed that C29 is strongly electrophilic, a fact that rationalizes the catalytic efficiency of this organocatalyst (Figure 9).[268,402]

Ten chiral squaramide derivatives have been used as organocatalyst for the reactions discussed above, whose structures are reported in Chart 21.

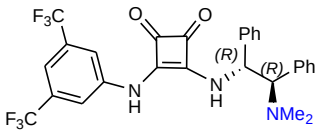
Chart 21. Chiral Squaramides as Organocatalysts of the Reactions Discussed in This Review.



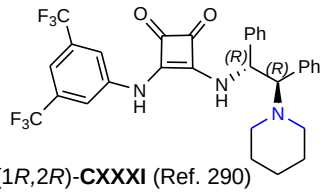
(*S*)-**XLI** (Ref. 86, 87, 372)



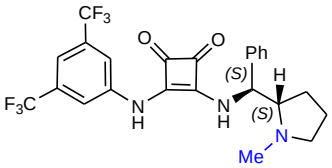
(1*S*,2*S*,*R*')-**CXLI** (Ref. 305)



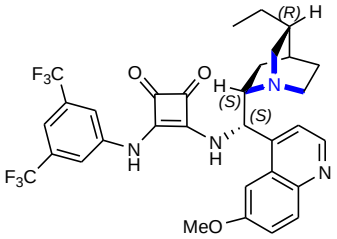
(1*R*,2*R*)-**CIX** (Ref. 277)



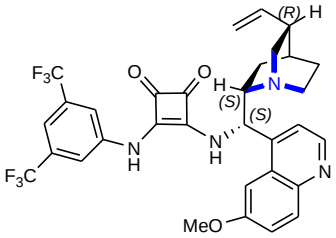
(1*R*,2*R*)-**CXXXI** (Ref. 290)



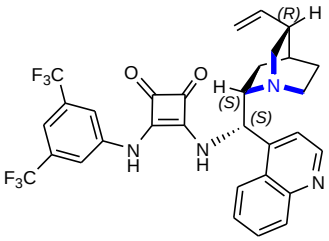
(1*S*,2*S*)-**CXXX** (Ref. 286)



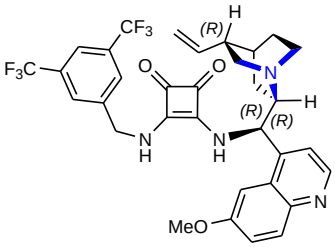
Epiquinine-dihydro (3*R*,8*S*,9*S*)-**XLIIIb** (Ref. 205, 376)



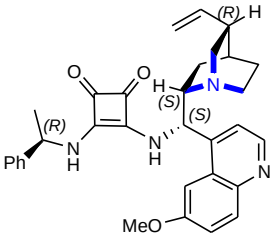
Epiquinine (3*R*,8*S*,9*S*)-**XLIII** (Ref. 89, 376)



Epicinconidine (3*R*,8*S*,9*S*)-**XLIIIa** (Ref. 213)



Epiquinidine (3*R*,8*R*,9*R*)-**XLII** (Ref. 88)



Epiquinine (3*R*,8*S*,9*S*,*R*')-**CXXI** (Ref. 268)

From a structural point of view the above chiral squaramide derivatives have a common framework, with the exception of (*S*)-**XLI** which will be considered separately: The NH which carries the chiral substituent has in the β-position a tertiary amino group. Thus, two N-H hydrogen bond donors and one protonable NR_3 group can bind the electrophilic (El) and the nucleophilic (Nu) reagents respectively, with different modes of bifunctional activation. Among these, DFT calculations located the two lowest energy TSs,[403,404] which are shown in Figure 10. In the **Type A** TS the deprotonated nucleophile is coordinated by monodentate hydrogen bond to the side chain alkylammonium group and attacks the electrophile, which is activated by bidentate hydrogen

bonding to the squaramide fragment. In **Type B** TS the deprotonated nucleophile is bound by hydrogen bonding to squaramide and oriented to attack the electrophile that is activated by the alkylammonium of the protonated catalyst.

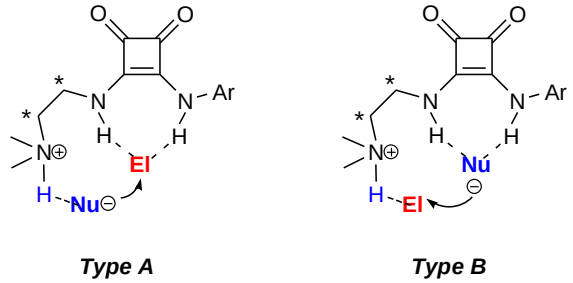


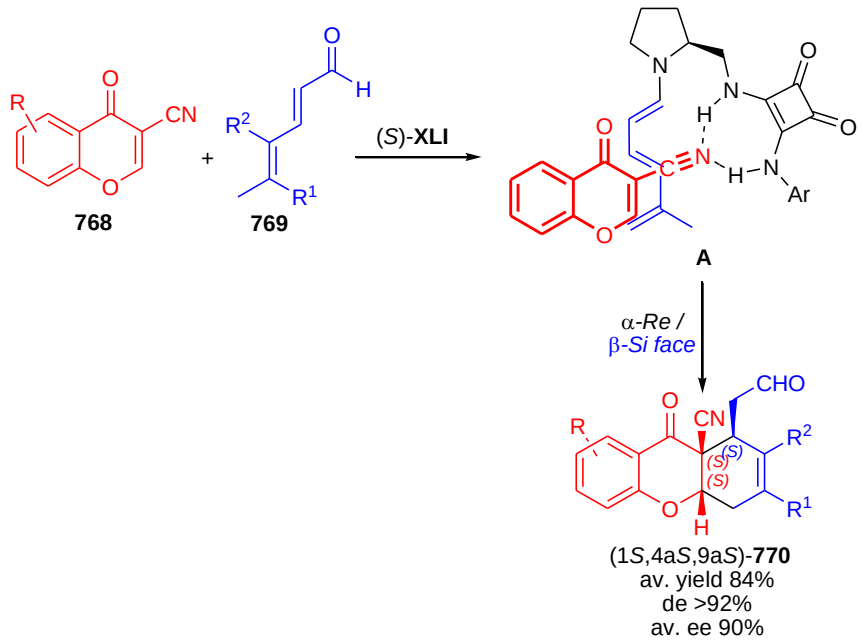
Figure 10. Lowest energy TSs, as determined by DFT calculations, of a bifunctional activated reaction between an electrophile (El) and a nucleophile (Nu) catalyzed by a chiral squaramide derivative.[403,404]

From a structural point of view, these molecules can be divided into two clusters: (*S*)-**XLI** belongs to the first one and has a (*S*)-pyrrolidine as chiral center; the remaining nine structures belong to the second cluster, all having a tertiary amine in the β-position of the chiral chain.

First, we discuss (*S*)-**XLI**, used as organocatalyst in three different reactions: The DA reaction between **768** and **769**,[372] and two HDA reactions discussed in Section 2.1.2.4.[86,87] The catalyst may give a reacting intermediate characterized by the enamine formation from the reactions between the proline residue and different aldehydes.

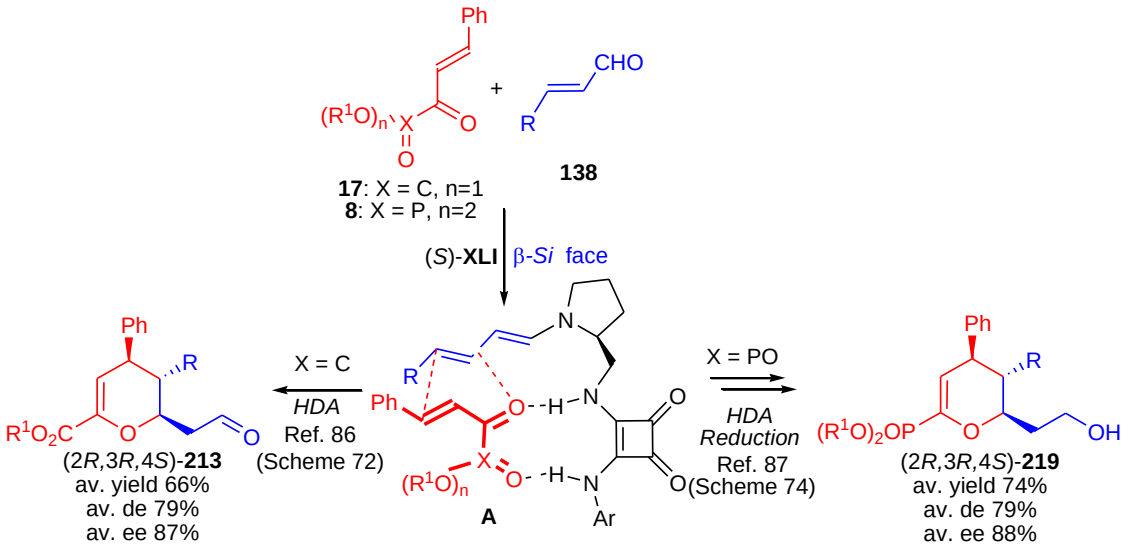
The reaction between 3-cyanochromones (**768**) and substituted 5-methylhexa-2,4-dienals (**769**) is catalysed by (*S*)-**XLI**, and gives the reacting intermediate **A** in which the squaramide framework acts as hydrogen bonding donor and activates **768**, whereas pyrrolidinium 2,2,2 trifluoroacetate reacts with **769** giving the 1-(5-methylhexa-1,3,5-trienyl)pyrrolidine fragment (Scheme 348).[372] Thus, the reacting intermediate has an electron-rich diene and an electron-poor dienophile positioned in a close spatial proximity suitable to give an *exo*-DA reaction through the attack of the diene on the [*α-Re*/*β-Si*] face, and the resulting product is (1*S*,4a*S*,9a*S*)-**770**.

Scheme 348. Chirality Transfer by Using Squaramide (*S*)-XLI as Organocatalyst of DA Reaction.[372]



The same (*S*)-**XLI** is the organocatalyst of two hetero-Diels-Alder reactions in which the heterodienes are either 2-oxo-4-phenylbut-3-enoates **17** (Scheme 72)[86] or enoylphosphonates **8** (Scheme 74),[87] which react with α,β-unsaturated aldehydes **138** (Scheme 349).

Scheme 349. Chirality Transfer by Using Squaramide (*S*)-XLI as Organocatalyst of HDA Reaction.[86,87]

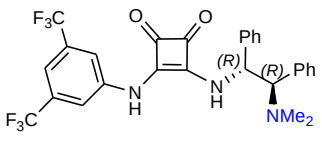


The reaction of aldehydes with the pyrrolidine fragment of the catalyst leads to the formation of the bound dienamine, whereas the heterodienes, reacting in the *s-trans* conformation, are coordinated by hydrogen bonding. Hence, both reagents are activated, **138** through HOMO activation, **17** or **8** through LUMO lowering. Furthermore, the optimal proximity facilitates the cycloaddition step that occurs for both reactions through attack of dienophile to the *β-Si* face of enone and gives (2*R*,3*R*,4*S*)-**213** and (2*R*,3*R*,4*S*)-**219**, with similar yields, diastereo- and enantioselectivities.

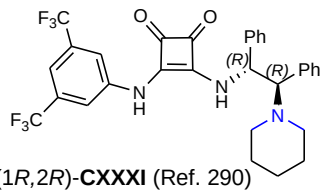
In conclusion, squaramide (*S*)-**XLI** is a bifunctional organocatalyst that activates both the electron-rich and the electron-poor cycloaddend and it is structurally constructed in such a way that the chirality transfer is the same, independently from the $HOMO_{diene}$ or $LUMO_{heterodiene}$ cycloaddition control.

Four squaramide-based molecules, used as organocatalyst for the enantioselective [3+3] [Michael reaction/hemiacetalization], have the squaramide core bound to a shared 3,5-trifluomethylbenzene group and to a fragment with two chiral centers. (1*R*,2*R*)-**CIX** and (1*R*,2*R*)-**CXXXI** are structurally and enantiomerically very similar (NMe_2 and piperidine are the tertiary amines). (1*S*,2*S*,*R*')-**CXLI** and (1*S*,2*S*)-**CXXX** are structurally different and enantiomerically opposite, the former because in addition to the chiral centers it has an axial chirality conveyed by the 4,5-dihydro-3*H*-naphtho[7,6,1,2-*cde*]azepine, the latter because the second chiral center is a pyrrolidine group (Chart 22).

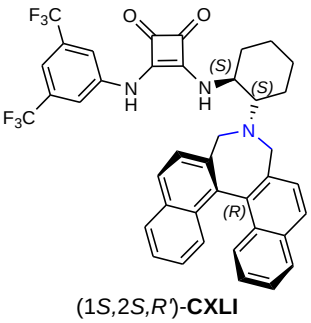
Chart 22. Chiral Squaramides as Organocatalysts with Two Chiral Centers.



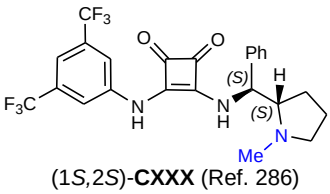
(1*R*,2*R*)-**CIX** (Ref. 277)



(1*R*,2*R*)-**CXXXI** (Ref. 290)



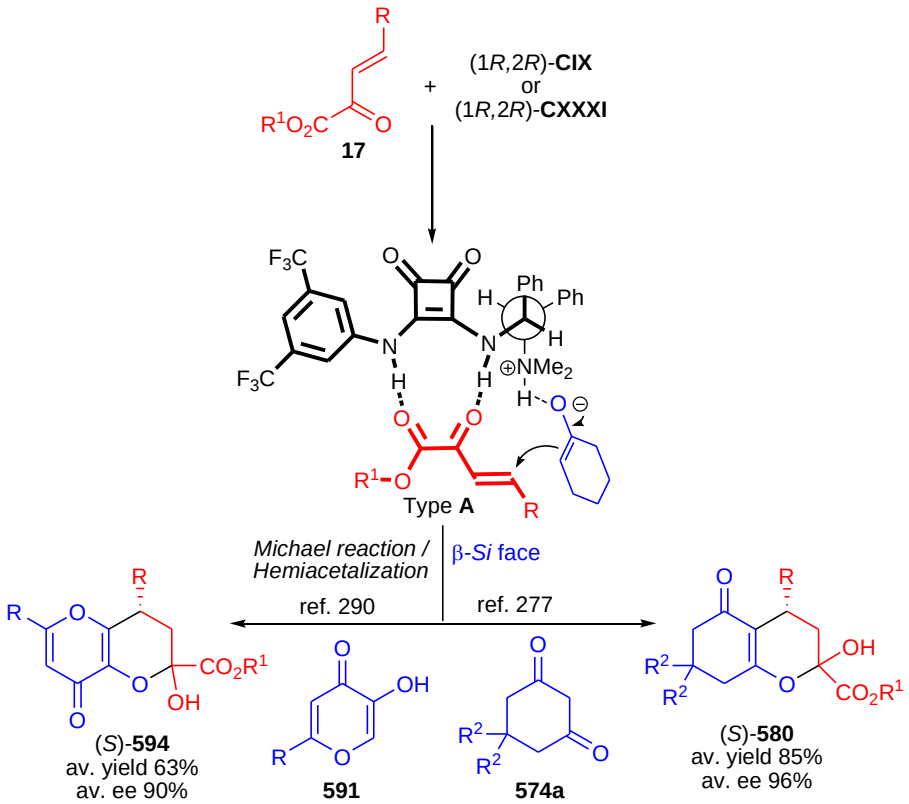
(1*S*,2*S*,*R*')-**CXLI**
(Ref. 305)



(1*S*,2*S*)-**CXXX** (Ref. 286)

Squaramides (1*R*,2*R*)-**CIX** and (1*R*,2*R*)-**CXXXI** are the organocatalyst of the reactions of 2-oxo-4-phenylbut-3-enoates **17** with cyclic 1,3-diketones **574a**[277] or **591**, the enolic form of a cyclic 1,2-diketone.[290] These reactions occur through the reacting intermediate Type **A** reported in Scheme 350, in which the bifunctional organocatalyst coordinates both the C=O groups of **17** by a double hydrogen bonding, while the protonated tertiary amine binds the nucleophile anion. The structure of the bifunctional organocatalyst brings the nucleophile to approach the *β-Si* face of the electrophile, rationalizing the formation of (*S*)-**580** and (*S*)-**594** respectively (Scheme 350).

Scheme 350. Chirality Transfer by using as Organocatalyst Squaramides with Two (1*R*,2*R*) Chiral Centers.[277,290]

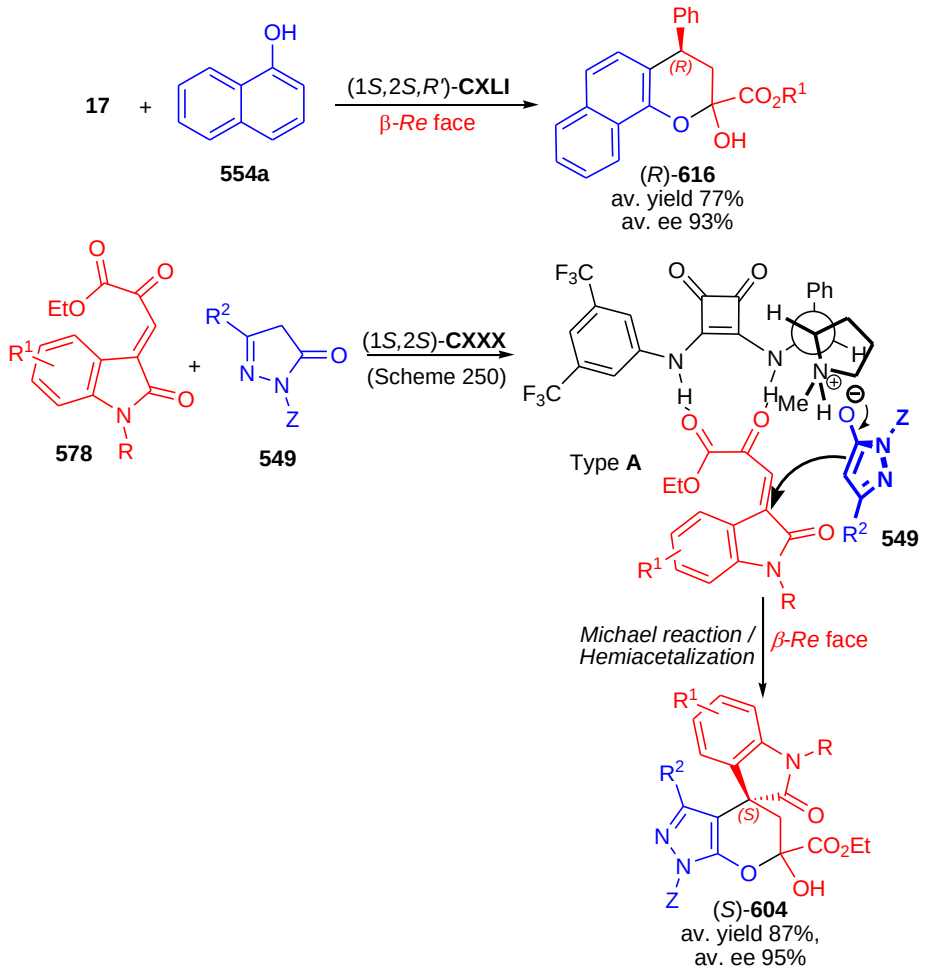


(1*S*,2*S*,*R*')-**CXLI** is the organocatalyst of the [3+3] [Friedel-Crafts/hemiacetalization] cascade reactions between 2-oxo-4-aryl-but-3-enoates **17** and 1-naphthol **554a** (Scheme 351).[305] The reaction product is (*R*)-**616** whose formation can be rationalized through a Type **A** reacting intermediate with a configuration opposite to that of the TS reported in Scheme 325, leading to an

attack to the *β-Re* face of bound **17**. This means that the chirality transfer is basically induced by the (1*S*,2*S*) configuration of the organocatalyst.

Squaramide (1*S*,2*S*)-**CXXX** catalyzes the [Michael reaction/hemiacetalization] sequence between ethyl 3-(2-oxoindolin-3-ylidene)-2-oxopropanoates **578** and 3-substituted-5-pyrazolones **549** (Scheme 250).[286] The reaction occurs through the Type **A** reacting intermediate reported in Scheme 351, in which the different stereochemistry of the bifunctional organocatalyst brings the nucleophile **549** to approach the *β-Re* face of the bicoordinated **578**, affording (*S*)-**604**.

Scheme 351. Chirality Transfer by Using as Squaramide-based Organocatalysts with Two (1*S*,2*S*) Chiral Centers.[286, 305]

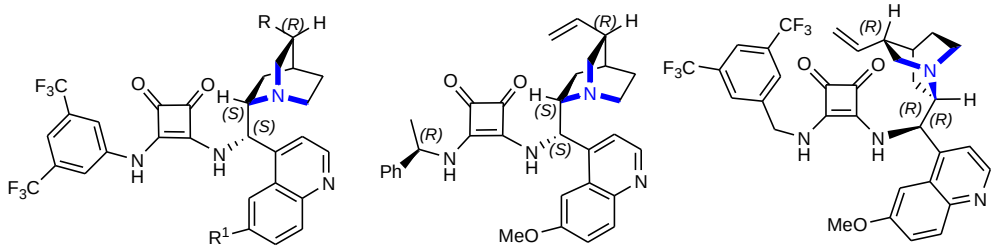


The rest of the squaramide-based organocatalysts, molecules in which one substituent is a *Cinchona* alkaloid residue attached in position 9, belongs to the sub-cluster characterized by a

tertiary amine in the β-position of the chiral chain, and the tertiary amine is in the position 8 of the *Cinchona* substituent (Chart 23).

The *Cinchona* alkaloid residue is not a simple substituent, it is flexible, it may assume several conformations, it may behave as a large sterically hindering substituent, but it has a heterocyclic aromatic ring that may give π-interactions, and its tertiary amine may be protonated by the nucleophile. Among these different modes to consider the structure, the behaviour as a tertiary amine located in a defined space is critical.

Chart 23. Squaramides as Organocatalyst with Three Chiral Centers Behaving to a *Cinchona* Alkaloid Residue



(3*R*,8*S*,9*S*)-**XLIIIb**: R=ethyl, R'=OMe
Epiquinine-dihydro (Ref. 285, 376)
(3*R*,8*S*,9*S*)-**XLIII**: R=vinyl, R'=OMe
Epiquinine (Ref. 89**,** 218, 233)
(3*R*,8*S*,9*S*)-**XLIIIa**: R= vinyl, R'=H
Epicinchonidine (Ref. 213)

(3*R*,8*S*,9*S*,*R'*)-**CXXI**
Epiquinine (Ref. 268)

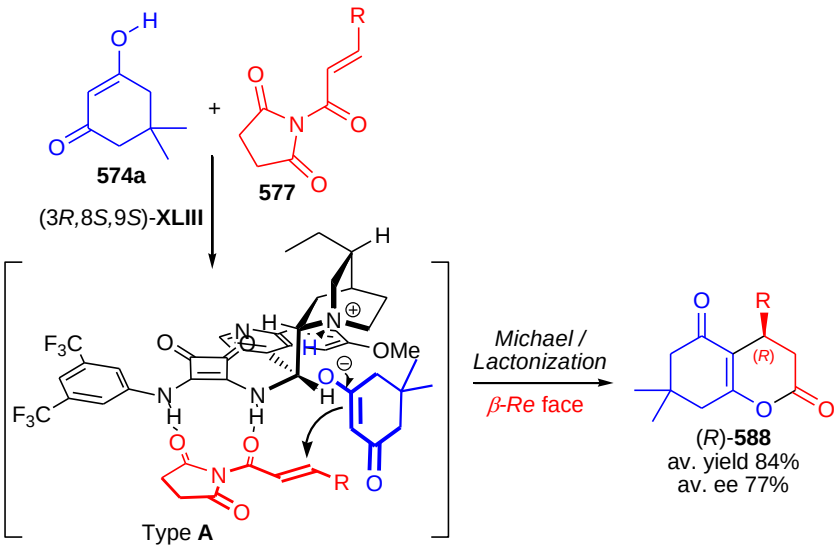
(3*R*,8*R*,9*R*)-**XLII**
Epiquinidine (Ref. 88)

(3*R*,8*S*,9*S*)-**XLIIIb** is a *dihydro-Epiquinine* squaramide derivative and is the catalyst of two reactions: the [Michael/lactonization] cascade reaction between **577** and 1,3-cyclohexanone **574a** (Table 23, entry 17),[285] and the cyclopropanation reaction between 3-arylidenechroma-4-ones **782** and bromonitromethane (Scheme 315).[376] (3*R*,8*S*,9*S*)-**XLIII** is an *Epiquinine*-substituted derivative and is the organocatalyst of three reactions: the cyclization reaction of *ortho*-quinone methides and Meldrum's acid **222**;[89] the domino [Michael/ring opening] reaction between 2-hydroxychalcones **469b** and azlactones **334** (Scheme 216);[233] the [oxa-Michael/Michael] reaction between nitrovinylphenol **475** and Boc-protected 3-[(methoxycarbonyl) methylene]-2-oxoindole **100** (Scheme 205).[218] (3*R*,8*S*,9*S*)-**XLIIIa** is an *epicinchonidine*-substituted squaramide tested as catalyst of the domino [oxa-Michael/Michael] reaction between 3-(2-hydroxyphenyl)prop-2-en-1-ones **469b**

and 3,3,3-trifluoro-1-nitroalkenes **444** (Table 17, entries 6-8).[213] Finally, (3*R*,8*R*,9*R*)-**XLII** is an epiquinidine-substituted squaramide that is the organocatalyst of the [Michael/hemiacetalyzation/acetylation] cascade reaction between β,γ-unsaturated α-keto esters **17** and β-oxo aldehydes **186** (Table 7, entry 10).[88]

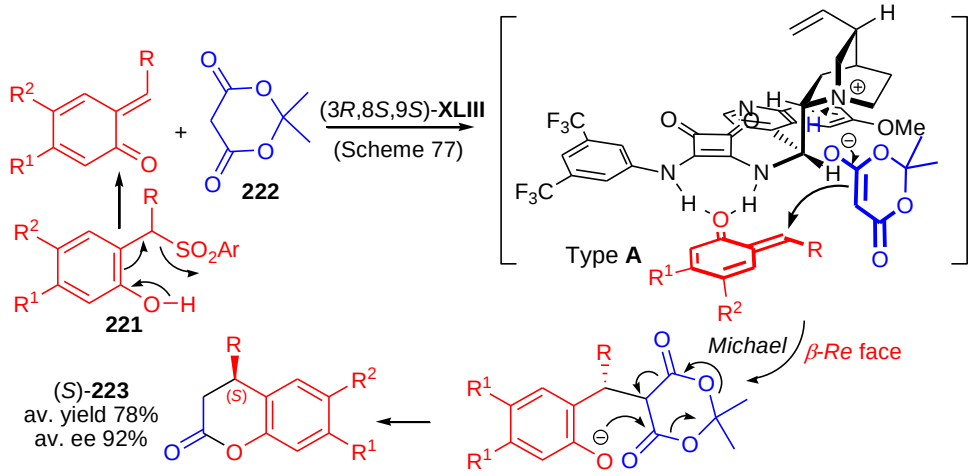
The reaction catalyzed by (3*R*,8*S*,9*S*)-**XLIIIb** between enone **577** and 1,3-cyclohexanone **574a** is shown in Scheme 352 in which the carbonyl groups of **577** are coordinated by hydrogen bonding to the squaramide moiety, **574a** protonates the tertiary amine and the anionic nucleophile is bound to it.[285] The resulting Type **A** reacting intermediate has the nucleophile suitably placed to attack to the *β-Re* face of **577** to give the Michael product that after lactonization affords to (*R*)-**588**.

Scheme 352. Chirality Transfer by Using *Dihydro-Epiquinine*-based Squaramide (3*R*,8*S*,9*S*)-XLIIIb as Organocatalyst.[285]



The model applied to *dihydro-Epiquinine* derivative (3*R*,8*S*,9*S*)-**XLIIIb** should also rationalize the catalytic effect of the analogue *Epiquinine*-squaramide (3*R*,8*S*,9*S*)-**XLIII**, which catalyzes the reaction between *ortho*-quinone methides (from 2-(arylsulfonyl)alkyl phenols **221**) and Meldrum's acid **222**.[89] Scheme 353 reports the Type **A** reacting intermediate in which the carbonyl group of quinone methides is coordinated by double hydrogen bonding, and the anion of **222**, bound to the protonated tertiary amine of epiquinine attacks the *β-Re* face of quinone methide to afford the Michael product that gives (*S*)-**223** through ring closure.[89]

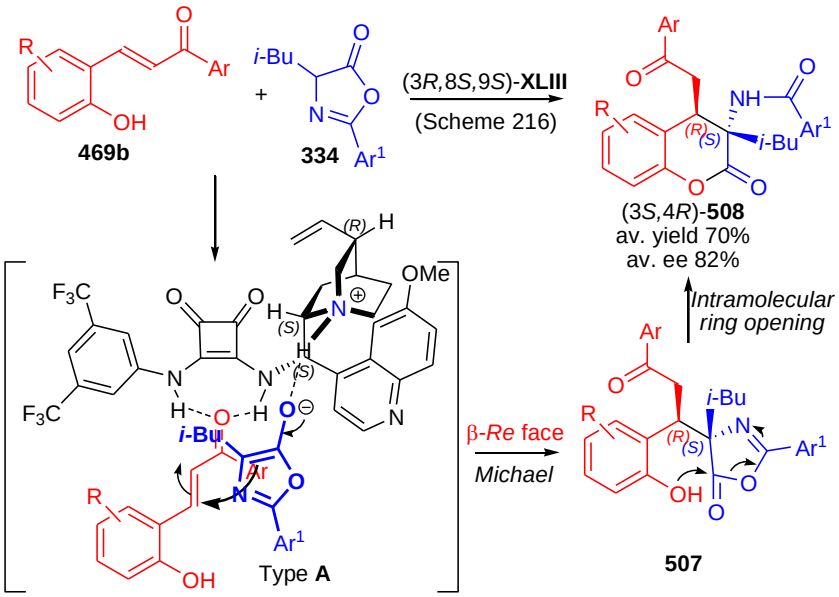
Scheme 353. Chirality Transfer by Using *Epiquinine*-based Squaramide (3*R*,8*S*,9*S*)-XLIII as Organocatalyst.[89]



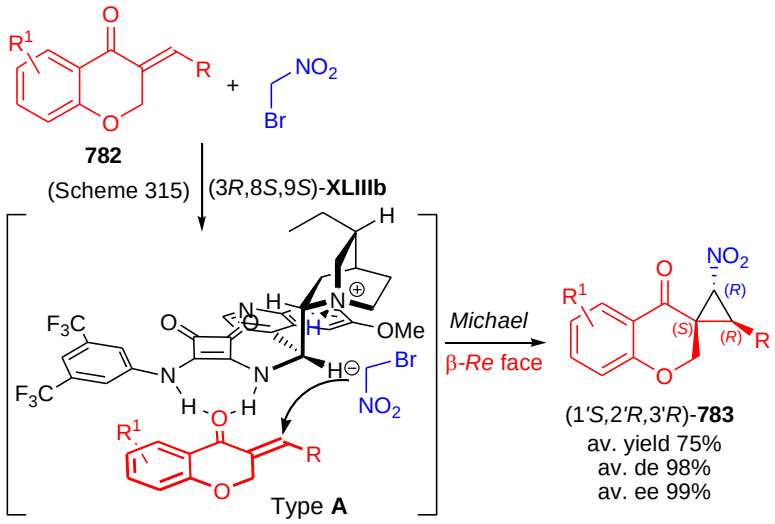
The same organocatalyst (3*R*,8*S*,9*S*)-**XLIII** was applied to the of the domino [Michael/ring opening] reaction between 2-hydroxychalcones **469b** and azlactones **334** (Scheme 216).[233] Again, the organocatalyst activates through the squaramide double hydrogen bonding the carbonyl group of **469b**, while the protonated tertiary amine of *epiquinine* activates the azalactone **334** giving the Type-**A** reacting intermediate.[233] The former is the electrophile and suffers the Michael attack of the bound nucleophile **334** to its *β-Re* face affording the product **507**. This is not stable and, through ring opening, gives the stable product (3*S*,6*R*)-**508** (Scheme 354).

The above mentioned *dihydro-Epiquinine*-based squaramide (3*R*,8*S*,9*S*)-**XLIIIb** was also the organocatalyst of the cyclopropanation reaction accomplished through the *Michael* alkylation of 3-arylidenechroma-4-ones **782** with bromonitromethane (Scheme 315).[376] The interaction between reagents and organocatalyst leads to the Type-**A** reacting intermediate represented in Scheme 355, in which the carbonyl of **782** is coordinated by double hydrogen bonding. The deprotonated bromonitromethane attacks again the *β-Re* face, now of the coordinated **782**, and the stereochemical outcome of the intramolecular Michael attack is the formation of the stereocenter (1′*S*), the first of the tree contiguous stereocenters of the nitro-spirocyclopropane product (1′*S*,2′*R*,3′*R*)-**783**.

Scheme 354. Chirality Transfer by Using *Epiquinine*-based Squaramide (3*R*,8*S*,9*S*)-XLIII as Organocatalyst of the Domino [Michael/Ring opening] Reaction Between 2-Hydroxychalcones 469b and Azlactones 334.[233]



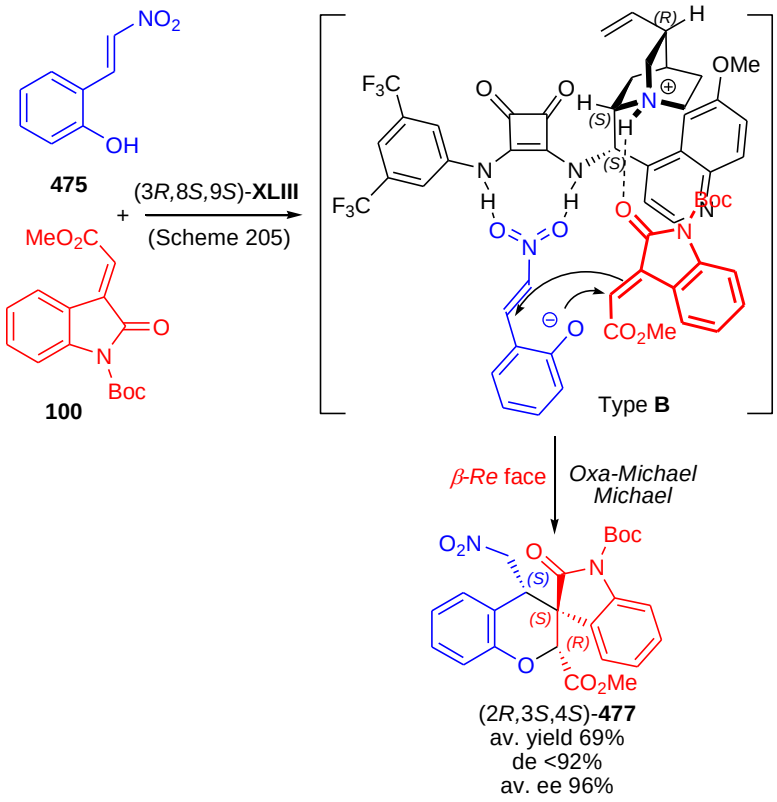
Scheme 355. Chirality Transfer by using *dihydro-Epiquinine*-based Squaramide (3*R*,8*S*,9*S*)-XLIIIb as Organocatalyst of the Cyclopropanation Reaction between 782 and Nitrobromomethane.[376]



The reaction between 2-nitrovinylphenol **475** and Boc-protected 3-[(methoxycarbonyl) methylene]-2-oxoindole **100** is catalysed by the 9-*amino-epiquinine*-based squaramide (3*R*,8*S*,9*S*)-**XLIII** (Scheme 205).[218] The mode of activation of the reagents is somewhat different because the

phenol protonates the epiquinine tertiary amine, which coordinates the carbonyl group of the electrophilic oxindole **100** by hydrogen bonding. The squaramide fragment activates by double hydrogen bonding the nitro group of nitrovinylphenolate and the Type **B** reacting intermediate (different by those discussed above) has as suitable structure to promote an intramolecular oxa-Michael attack to the *β-Re* face of 3-[(methoxycarbonyl)methylene]-2-oxoindole (Scheme 356). The cascade proceeds with the Michael addition to the β-position of the nitrovinyl group to afford the spiro derivatives (2*R*,3*S*,4*S*)-**477** containing three contiguous stereocenters in moderate-good yields and with excellent diastereo- and enantioselectivities.[218]

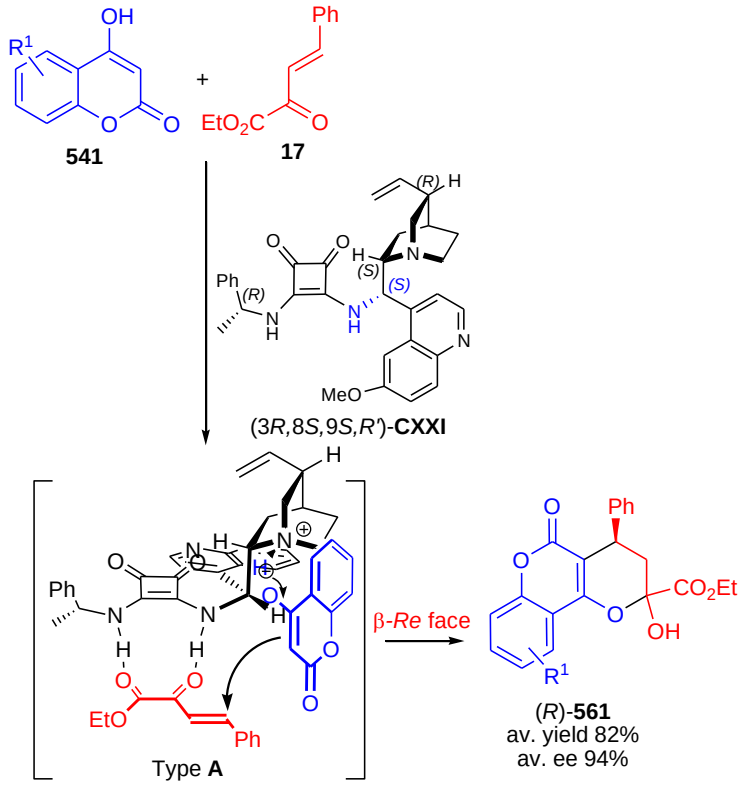
Scheme 356. Chirality Transfer by Using *Epiquinine*-based Squaramide (3*R*,8*S*,9*S*)-XLIII as Organocatalyst for the Domino [Oxa-Michael/Michael] Reaction Between 100 and 475.[218]



(3*R*,8*S*,9*S*,*R'*)-**CXXI** is again an *Epiquinine* derivative, but the second substituent has a further (*R*) chiral center. It is the organocatalyst of the [Michael reaction/hemiacetalyzation] sequence between **17** and 4-hydroxycoumarins **541** (Table 22, entry 16),[268] and it is a good model to test if the chirality transmission derives from the *Cinchona* alkaloid residue or if it is influenced by other

factors. The reaction between **17** and 4-hydroxycoumarins **541** affords (*R*)-ethyl 4-aryl-4-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-2-oxobutanoate [(*R*)-**561**], whose structure was determined by X-ray crystallography. This result can be rationalized through a Type-**A** reacting intermediate in which the carbonyl groups of **17** are coordinated by hydrogen bonding to the squaramide moiety, while the anion of 4-hydroxycoumarins is bound to the protonated tertiary amine of *epiquinine*. The result is again the intramolecular attack of the nucleophile **541** to the *β-Re* face of the coordinated electrophilic enone **17** with excellent results in terms of yields and enantioselectivities.

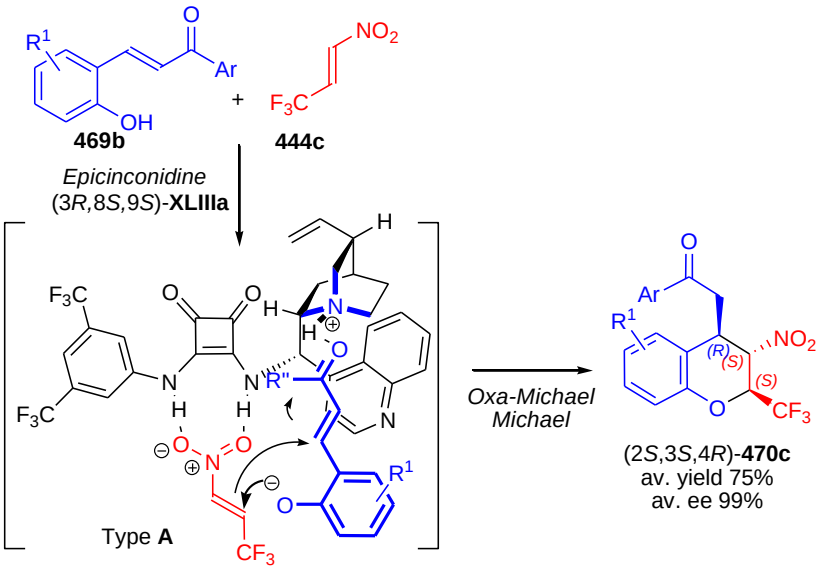
Scheme 357. Chirality Transfer by Using (3*R*,8*S*,9*S*,*R'*)-CXXI *Epiquinine*-Based Squaramide as Organocatalyst.[268]



The domino [oxa-Michael/Michael] reaction between 3-(2-hydroxyphenyl)prop-2-en-1-ones **469b** and 3,3,3-trifluoro-1-nitroalkenes **444** (Table 17, entries 6-8),[213] is catalysed by the *epicinchonidine*-substituted squaramide (3*R*,8*S*,9*S*)-**XLIIIa**: The squaramide fragment activates the electrophile, the nitro-olefin, through a double hydrogen bonding between the two NH and the nitro group (Scheme 358 for **444c**). The acidic phenol of **469b** protonates the *epicinchonidine* tertiary

amine that is therefore suitable to coordinate the phenolate through its carbonyl group. The Type-**A** reacting intermediate has now the phenolic anion suitably placed for the "*top/down*" attack to the nitro-olefin *β-Re* face through the *oxa-Michael* reaction, which is followed by the *Michael* ring closure to afford (2*S*,3*S*,4*R*)-**470c**.[213]

Scheme 358. Chirality Transfer by Using the *Epicinchonidine*-based Squaramide (3*R*,8*S*,9*S*)-XLIIIa as Organocatalyst.[213]



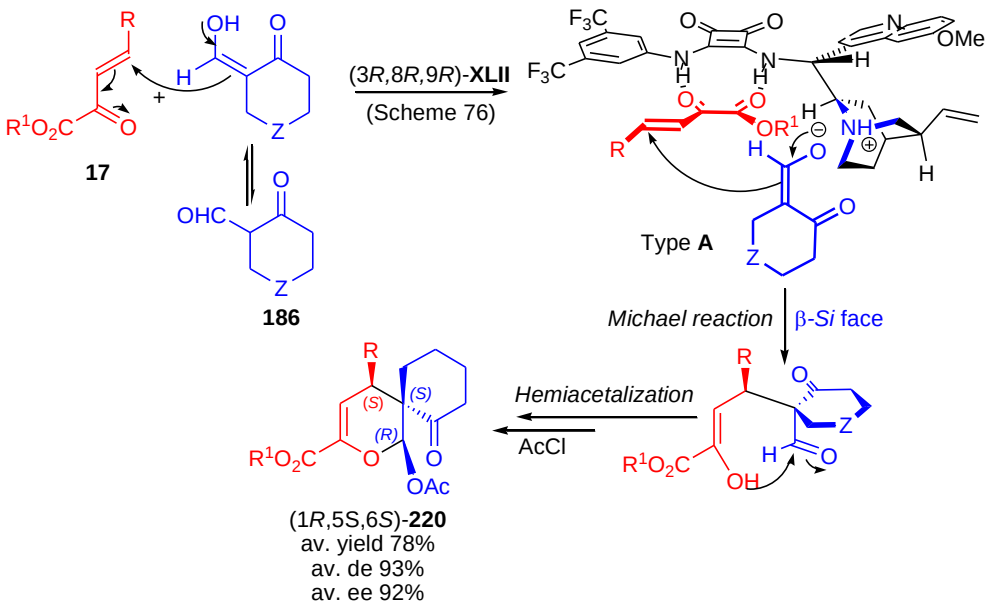
Above, we have discussed several reactions catalysed by squaramides substituted by a *Cinchona* alkaloid with (3*R*,8*S*,9*S*) configuration. All examples, except one reaction (Scheme 356),[218] are characterized by Type **A** reacting intermediates in which the NH groups of the squaramide coordinate the electrophile by a double hydrogen bonding. To our opinion, there are several analogies between all these reacting intermediates. Independently from the different reactions, the different electrophile, and the different functional groups of the coordinated electrophile, the nucleophilic attack occurs "*top/down*" to the electrophile. This is either an α,β-enone or a nitro-olefin, and *the attack occurs to its β-Re face.*

The last squaramide to be discussed is (3*R*,8*R*,9*R*)-**XLII**, which has an *Epiquinidine*-residue as substituent. It is the organocatalyst of the [Michael/hemiacetalyzation/acetylation] cascade reaction between **17** and β-oxo aldehydes **186** that affords (1*R*,5*S*,6*S*)-**220** (Scheme 76).[88]

If the (3*R*,8*R*,9*R*) configuration of **XLII** is compared with the (3*R*,8*S*,9*S*) configuration of the organocatalysts discussed above, which enantioselectivity is transmitted from a catalyst whose absolute configuration is the same for the the 3-position (3*R*), but opposite for the 8 and 9 chiral centers?

A model of reaction intermediate may be proposed in which, again, the carbonyl groups of **17** are coordinated by hydrogen bonding to the squaramide moiety, the enolate of β-oxo aldehydes **186** protonates the tertiary amine and the anionic nucleophile is bound to it. The absolute configuration of the catalyst gives now rise to the Type **A** reacting intermediate reported in the Scheme 359 that induces the anion of **186** to attack "*bottom/up*" the *β-Si* face of **17**. This arrangement affords the Michael product that undergoes hemiacetalization and, in the presence of acetyl chloride, leads to (1*R*,5*S*,6*S*)-**220**. Consequently, the above organocatalyst with (3*R*,**8*R*,9*R***) configuration behaves as enantiomer of all those with the (3*R*,**8*S*,9*S***) configuration.

Scheme 359. Chirality Transfer by Using *Epiquinidine* Derivative Squaramide (3*R*,8*R*,9*R*)-XLII as Organocatalyst.[88]



8.3. Chiral Thiourea Derivatives

Thiourea derivatives belong to a class of organocatalysts with an excellent catalytic activity that have a close analogy to squaramides. They have two NH groups able to give hydrogen bonding with reagents with a carbonyl functionality, the main difference being a less rigid structure that allows the possibility for thiourea derivatives to assume conformations impossible for squaramides. This suggests that squaramides and thioureas, in some circumstances, may transmit a different induction of chirality to the products.

As squaramides, thioureas behaviour has been supported by *ab initio* calculations at the HF/6-31+G(d,p) level, and the transition state structure, linking ethyl 2-oxo-4-phenylbut-3-enoate (**17**) to thiourea simplified organocatalysts, was located (Figure 11). Natural bond orbital (NBO) analyses were carried out, and the NBO values (q) at C25 (−0.082 e) showed that C25 is again considerably electrophilic.[268,402]

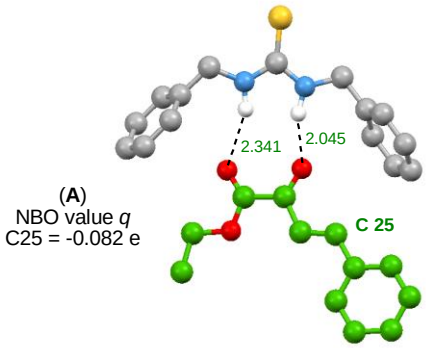
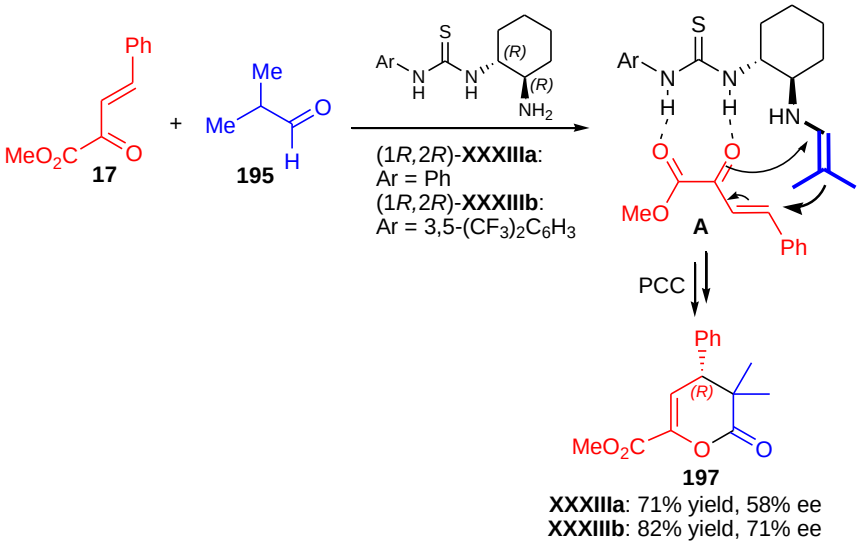


Figure 11. Natural bond orbital (NBO) analysis of optimized transition state structure that bound **17** to thiourea simplified organocatalyst.[268,402]

Several dozens of thiourea-based structures have been encountered along the previous sections and it will be considered different clusters of structures characterized by homogeneous characters. One group is characterized by a primary amino group at the β position of one substituent: *N*-[(1*R*,2*R*)-2-aminocyclohexyl]-3-phenylthiourea [(1*R*,2*R*)-**XXXIIIa**], and the analogue 3-(3,5-trifluoromethyl)phenyl (1*R*,2*R*)-**XXXIIIb**, which are the organocatalysts of the reaction between methyl 2-oxo-4-phenylbut-3-enoate (**17**) and isobutylaldehyde **195** (Scheme 63).[76]

The thiourea framework, as seen for squaramide in Scheme 348, acts as hydrogen bonding donor and activates **17**, and NH_2 reacts with **195** giving the enamine fragment in the reacting intermediate **A**. This has a close spatial proximity suitable to afford the nucleophilic attack to the electrophilic β-position, followed by the ring closure (and oxidation by PCC) to give **197** (Scheme 360). The best enantioselectivity is obtained with the catalyst that possesses the most acidic pk_a (13.1) and, even if the absolute configuration was not assigned to **197**, an (*R*)-**197** product should be expected.

Scheme 360. Chirality Transfer by Using NH_2-Substituted Thiourea-derived (1*R*,2*R*)-XXXIIIa,b as Organocatalysts.[76]



The majority of thiourea organocatalysts have an aryl, or better a 3,5-bis(trifluoromethyl)phenyl substituent, to increase the NH acidity, whereas the second substituent has at least one chiral center in position α and a tertiary amine in β.

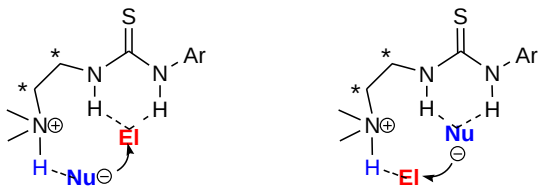


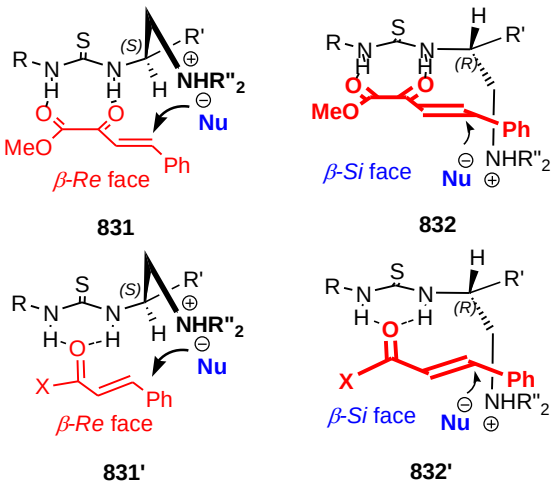
Figure 12. Lowest energy TSs, as determined by DFT calculations, of a bifunctional activated reaction between an electrophile (El) and a nuceophile (Nu) catalyzed by a chiral thiourea derivative.[403,404]

These compounds behave as bifunctional organocatalysts and density functional theory calculations individuates the two lowest energy TSs (Figure 12).[403,404] In Type **A** TS the deprotonated nucleophile is coordinated by a monodentate hydrogen bond to the side chain alkylammonium group and attacks the electrophile, which is activated by bidentate hydrogen bonding to the thiourea fragment. In Type **B** TS the deprotonated nucleophile is bound by hydrogen bonding to squaramide and oriented to attack the electrophile that is activated by the alkylammonium moiety of the protonated catalyst.

Applying the type **A** TS represented in Figure 12 to an (*S*)- and an (*R*)-substituted thiourea, two reacting intermediates can be considered. The former gives **831** in which the nucleophile approaches the *β-Re* face of the electrophile, the latter gives **832** that induces the attack of the nucleophile to the opposite *β-Si* face (Scheme 361).

If the electrophile is an enone with one carbonyl group only [*e.g.* 1,1,1-trifluoro-4-phenylbut-3-en-2-one; Scheme 361: X = CF_3], this coordinates to the thiourea fragment by a double hydrogen bonding, which gives the reacting intermediates **831′** or **832′** depending on the configuration of the adjacent chiral center (Scheme 361).

Scheme 361. Reacting Intermediates for Thiourea-based Organocatalysts with (*S*) and (*R*) Configuration.



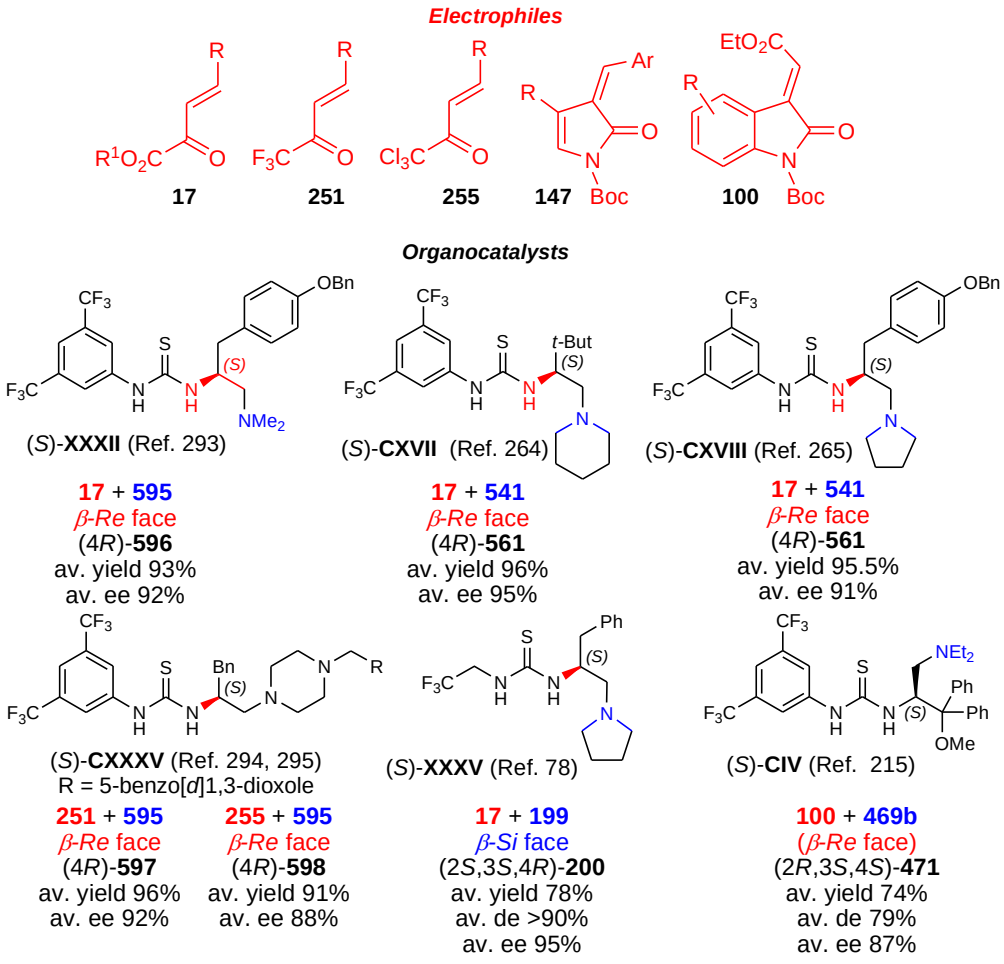
831 **832**

831' **832'**

The different thiourea-based structures that have been encountered in the previous sections form two clusters depending on the chirality of the α-chiral center, with sub-classes for number and type of the chiral centers in the substituents. The discussion will start from the cluster in which the first chiral center adjacent to nitrogen has the (*S*) configuration.

Scheme 362 summarizes seven reactions with six different thiourea-based organocatalysts having a single chiral center with the (*S*) configuration. Five reactions occur through the attack of the nucleophile to the *β-Re* face of the coordinated electrophile, hence through the expected **831** or **831′** reacting intermediates in Scheme 361, and give a product with a single defined chiral center.

Scheme 362. Enantioselectivity Observed by Using Different Thiourea-based Organocatalysts with a Single Chiral Center Having the (*S*) Configuration.

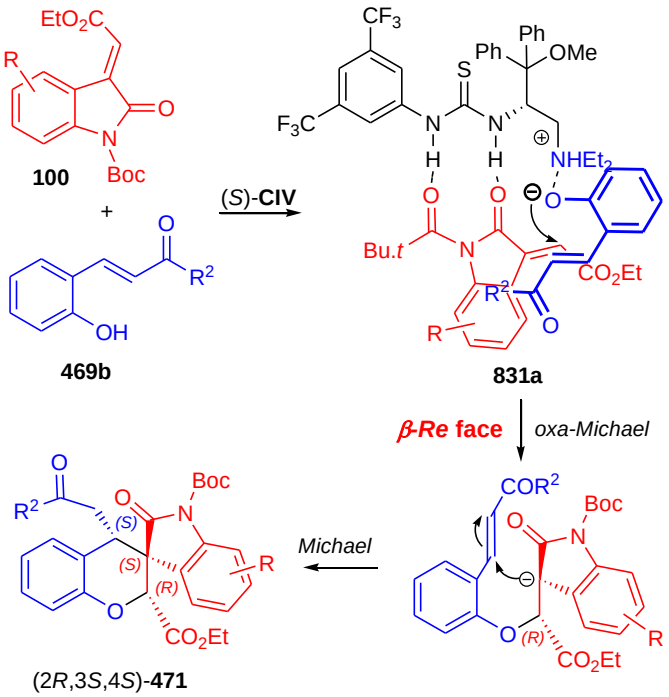


The exception is (*S*)-**XXXV** whose thiourea has a substituent less sterically encumbered (and less electrophilic) than the more usual 3,5-bis(trifluoromethyl)phenyl, and hence one cannot exclude the opposite binding of the electrophile.

The most intrigued case is the seventh reaction catalysed by (*S*)-**CIV** because (*E*)-*tert*-butyl 3-[(ethoxycarbonyl)methylene]-2-oxoindoline-1-carboxylate (**100**) reacts with 3-(2-hydroxyphenyl)-1-substituted-prop-2-en-1-ones (**469b**) through an [oxa-Michael/Michael] cascade reaction to afford (2*R*,3*S*,4*S*)-**471** (Table 17, entry 10), a product with three chiral centers, with excellent stereoselectivity (Scheme 363).[215]

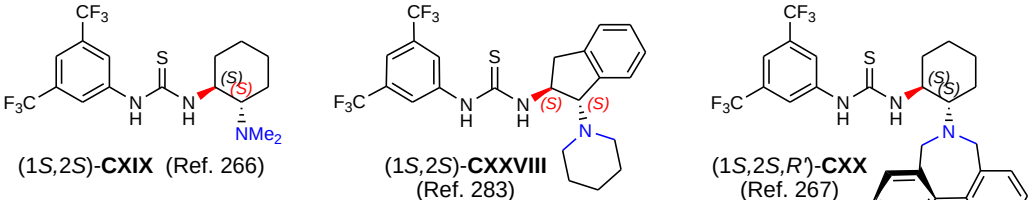
In accordance to the model of transmission of the chirality illustrated in Scheme 361, the reacting intermediate **831a** can be proposed in which **100** is bound to the thiourea fragment by two hydrogen bonding with two CO groups, and the phenolate of **469b** is coordinated to the ammonium cation of the catalyst. Again, as the previously reported five catalysts, the oxa-Michael attack occurs on the *β-Re* face of the electrophile to afford an intermediate with the correct (*R*) configuration at the chiral center to provide, by the further Michael ring closure, (2*R*,3*S*,4*S*)-**471** (Scheme 363).

Scheme 363. Chirality Transfer in the [Oxa-Michael/Michael] Reaction Between 100 and 469b, with Thiourea (*S*)-CIVas Organocatalyst.[215]



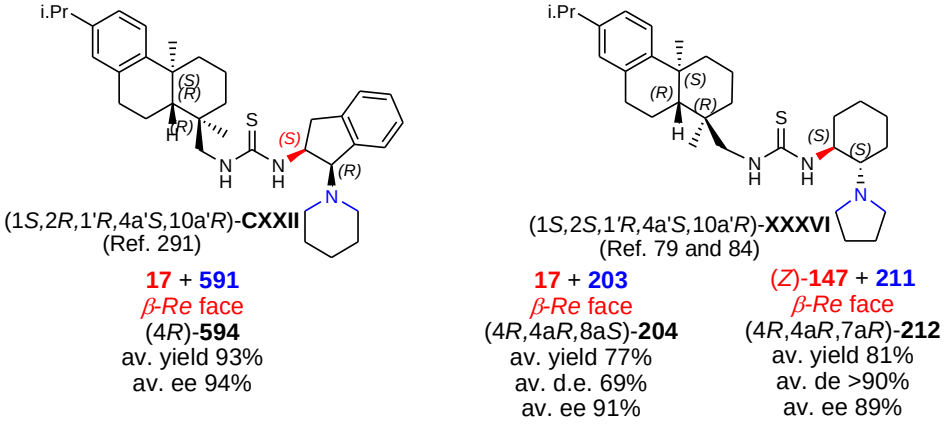
The next cluster of thiourea-based organocatalysts deals with molecules with more than one chiral center; for facility of discussion, this cluster is divided into different groups depending on their complexity. Scheme 364 reports three reactions with three different thiourea-based organocatalysts with more than one chiral center, the first near nitrogen with the (*S*) configuration.

Scheme 364. Different Thiourea-based Organocatalysts with More Than One Chiral Center, the First Near Nitrogen with the (*S*) Configuration, and the Transmission of Chirality.



Scheme 365 describes three reactions with two different thiourea-based organocatalysts with two optically active substituents. The first substituent is always a (1*R*,4a*S*,10a*R*)-octahydro-7-isopropyl-1,4a-dimethylphenanthrenyl-1-methylene group, the second has two chiral centers, the first of them near the nitrogen with the (*S*) configuration.

Scheme 365. Different Thiourea-based Organocatalysts with More Than One Chiral Substituents, the First One Near Nitrogen with the (*S*) Configuration, and the Transmission of Chirality.

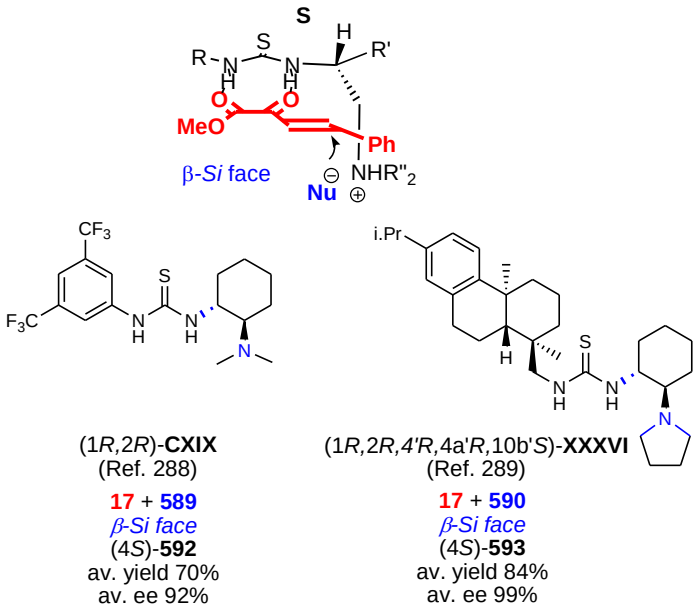


All the reactions reported in Schemes 364 and 365 occur through a reacting intermediate **831** that promotes the attack of the nucleophile to the *β-Re* face of the coordinated electrophile: For the reaction catalysed by (1*S*,2*S*,1'*R*,4a'*S*,10a'*R*)-**XXXVI** (Scheme 69)[84] the absolute configuration (4*R*,4a*R*,7a*R*)-**212** can be rationalized through an attack to the *β-Re* face of 1,4-diphenyl-4-aryliden-5-pyrazolone **147** only because it has a (*Z*) configuration.[405]

In conclusion, everybody may evaluate the importance that the (*S*) configuration of the chiral center near the thiourea function has on the stereochemical outcome, and the limited influence that more complex structures, as well as the introduction of multiple chiral centers, have on the transmission of chirality from the organocatalyst to the product.

Complementary to the above results, two thiourea organocatalysts with the first chiral center adjacent to nitrogen with the (*R*) configuration (Scheme 366) catalysed two reactions through type **832** reacting intermediates that induce the attack to the *β-Si* face (Table 24, entries 2 and 3).

Scheme 366. Different Thiourea-based Organocatalysts with More Than One Chiral Substituents, the First One Near Nitrogen with the (*R*) Configuration, and the Transmission of Chirality

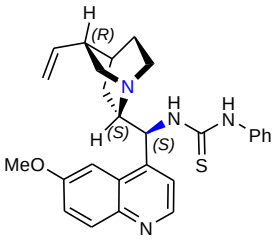


A further cluster of thiourea-based organocatalysts is that in which at least one substituent is a *Cinchona* alkaloid. This contains several sub-clusters depending on the structure modifications and

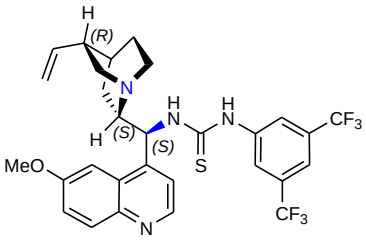
on further substituents. An important group is that of *9-amino Cinchona* alkaloids, in which the hydroxy function in position 9 is substituted by an amino group.

This specific substituent is important because it allows to insert in this position the thiourea fragment that is completed by an aryl group as the second substituent. Six organocatalysts with this framework have been used (Scheme 367).

Scheme 367. The Transmission of Chirality in Reactions Organocatalyzed by Thioureas with 9-*Amino-Cinchona* Alkaloid and an Aryl Group as Substituents.

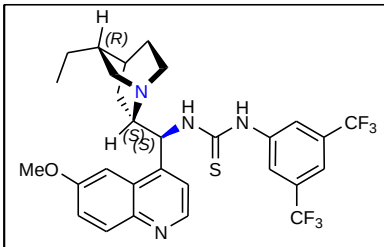


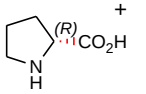
9-amino-*epi*quinine-thiourea
(3*R*,8*S*,9*S*)-**CLXXII** (Ref. 380)
786 + **792**
β-Si face
(9b*S*)-**793,794**.
av. yield 92%
av. ee 78%



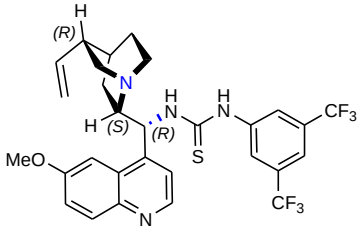
9-amino-*epi*quinine-thiourea
(3*R*,8*S*,9*S*)-**XXXIV** (Ref. 77, 310)
626 + **627**
β-Si face
(2*S*,3*S*,4*R*)-**628**
av. yield: 80%
av. de 79%
av. ee 98.5%

17 + **199**
β-Si face
(2*S*,3*S*,4*R*)-**200**
av. yield 87%
av. de 93%
av. ee 94%

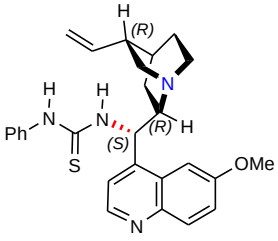


9-amino-dihydro*epi*quinine-thiourea
(3*R*,8*S*,9*S*)-**XXXIV** (Ref. 230)
+

(*R*)-**XXXVIII**

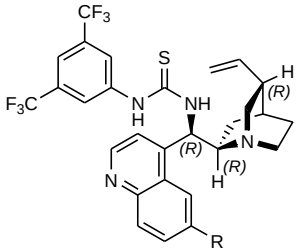
475 + **120**
β-Si face
(4a*S*,10*R*,10a*S*)-**500**
av. yield 78%
av. de 94%
av. ee 97%

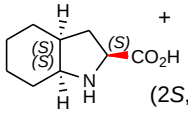


9-amino-quinine-thiourea
(3*R*,8*S*,9*R*)-**CXL** (Ref. 303)
17 + **554b**
β-Si face
(S)-**614** [(*S*)-**615**]
av. yield 70%
av. ee 81%



9-amino-quinidine-thiourea
(3*R*,8*R*,9*S*)-**CLXXI** (Ref. 379)
786 + **789**
β-Re face
(6*S*,6a*R*,10a*R*)-**790**
av. yield 74%
av. ee 84%



9-amino-*epi*quinidine-thiourea
(3*R*,8*R*,9*R*)-**XXXIX** (Ref. 85)
+

(2*S*,3a*S*,7a*S*)-**XL**

8 + **126**
β-Re face
(3*R*,4*S*)-**132**
av. yield 93%
av. de 29%
av. ee 91%

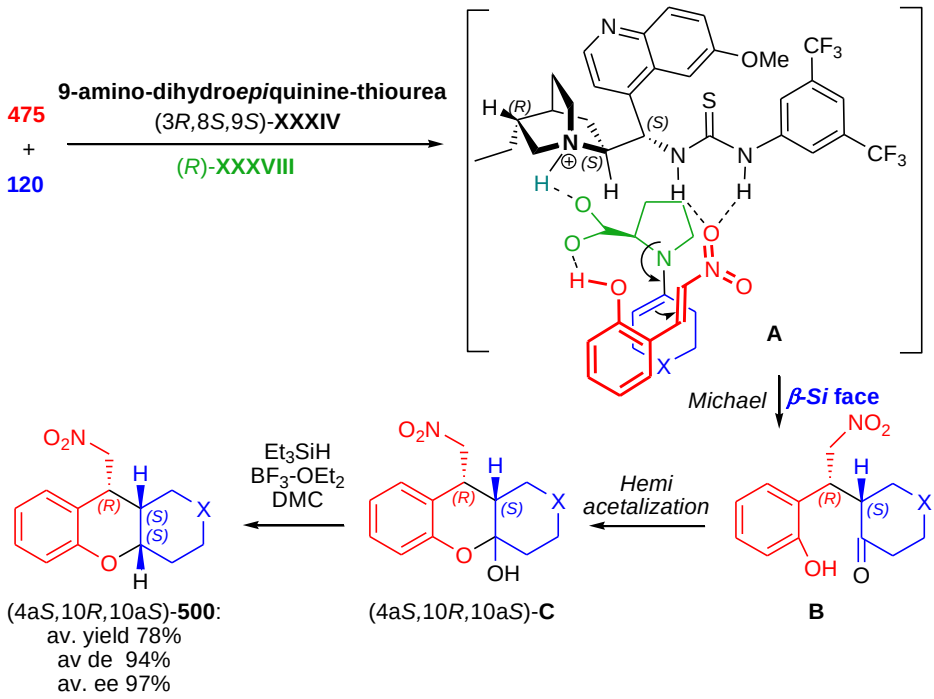
17 + **126**
***β-Re* face**
(3*R*,4*S*)-**127**
av. yield 90%
av. d.e. 71%
av. ee 94%

Three organocatalysts belong to the family of *9-amino-epiquinine*. (3*R*,8*S*,9*S*)-**CLXXII** is the catalyst of the 1,3-cyclization reaction between **786** and 3-isothiocyanatoindolin-2-one **792** (Scheme 319).[380] (3*R*,8*S*,9*S*)-**XXXIV**, which has a 3-(3,5-trifluoromethyl)phenyl substituent instead of a phenyl group, catalyzes two Michael reactions: the first is that between nitromethane and **627** (Scheme 261),[310] the second one involves ethyl 4,4,4-trifluoro-3-oxobutanoate **199** with **17** (Scheme 64).[77] (3*R*,8*S*,9*S*)-**XXXIV**, which is a *9-amino-3-dihydroepiquinine* derivative, in the presence of (*R*)-proline, is the catalyst the domino [Michael/hemiacetalyzation] reactions between **475** and **120** (Scheme 213).[230]

Despite the intrinsic differences in the reactions, and specifically in the electrophile structure, all reactions occur through the attack of the nucleophile to the *β-Si* face of the electrophile.

About the reacting intermediate, we begin to discuss the most intrigued one because the Authors elucidate the mechanism of the reaction between *ortho*-nitrovinylphenols **475** and cyclic ketones **120**, catalyzed by (3*R*,8*S*,9*S*)-**XXXIV** in admixture with (*R*)-proline (**XXXVIII)**, through the correct cyclic 19-membered assembly of reagents and catalysts **A** (Scheme 368).[230]

Scheme 368. Enantioselective Domino [Michael/Hemiacetalyzation] Reaction Between *ortho*-Nitrovinylphenols 475 and Cyclic Ketones 120, with a Self-assembly of (3*R*,8*S*,9*S*)-XXXIV with (*R*)-Proline XXXVIII as Organocatalyst.[230]

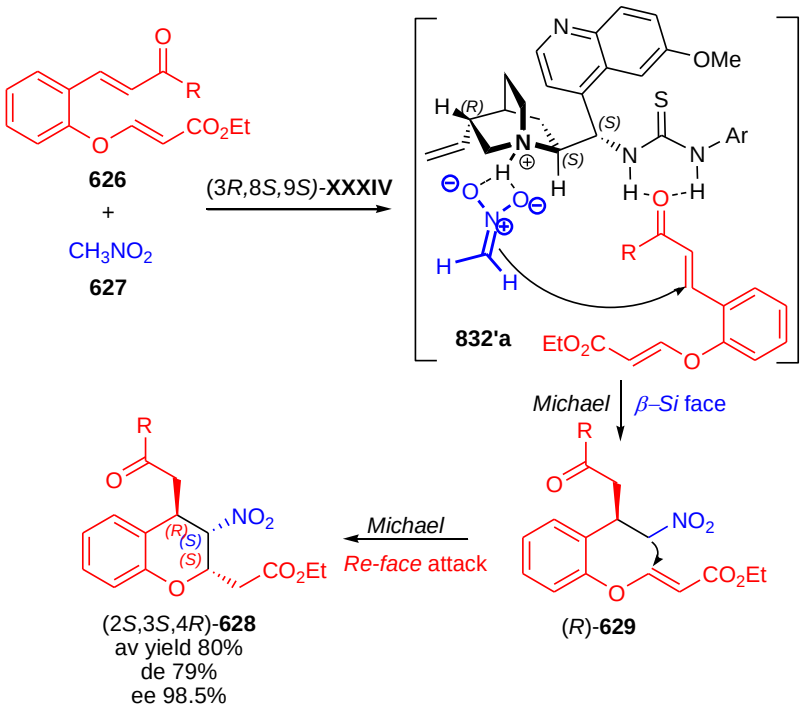


After the formation of the (*R*) enamino-acid between **120** and proline, the organocatalyst (3*R*,8*S*,9*S*)-**XXXIV** activates **475** through the double hydrogen bonding between two NH and the nitro group, while the protonated tertiary amine of *dihydroepiquinine* activates the nucleophilic anion. The intramolecular Michael attack occurs to the *β-Re* face of *ortho*-nitrovinylphenol (for priority reasons this corresponds to the *β-Si* face of the conventional electrophile) and this gives **B** with two of the three chiral centers of (4a*S*,10*R*,10a*S*)-**500**.

Which reacting intermediate could be proposed for the other reactions catalysed by *9-amino-epiquinine*-based (3*R*,8*S*,9*S*)-**CLXXII** and (3*R*,8*S*,9*S*)-**XXXIV** (with the same configuration, in the absence of proline)?

The [Michael/Michael] cascade reaction between **626** and nitromethane **627**, catalysed by (3*R*,8*S*,9*S*)-**XXXIV**, gives poly-substituted chromans **628** (Scheme 369).[270] This catalyst allows to coordinate the ketonic group of **626** by hydrogen bonding and to activate nitromethane through the nitrogen quaternary ion affording the reacting intermediate **832′a**.

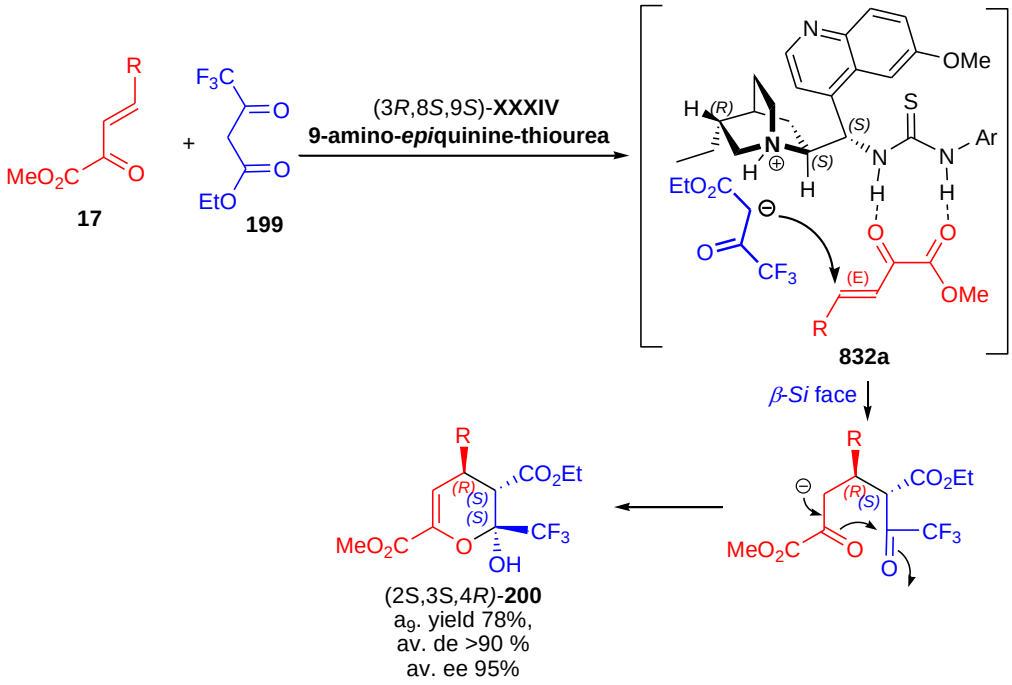
Scheme 369. Enantioselective Domino [Michael/Michael] Reaction Between 626 and Nitromethane with (3*R*,8*S*,9*S*)-XXXIV as Organocatalyst.[270]



This promotes an "intramolecular" *Michael* attack of the nitromethane enolate to the *β-Si* face of the enone fragment and the adduct (*R*)-**629** gives a second *Michael* attach of the new nitromethane anion to the *β-Re* face of the acrylate with formation of the chromans (2*S*,3*S*,4*R*)-**628**.

The cascade [Michael addition/hemiketalization] reactions between α-keto butenoate **17** and trifluoromethyl β-keto esters **199**, again catalyzed by (3*R*,8*S*,9*S*)-**XXXIV**, involves the reacting intermediate **832a** derived from the coordination of the carbonyls of **17** by double hydrogen bonding, and the activation of the ketoester anion (Scheme 370).[77] The Michael attack occurs to the *β-Si* face of the α-keto butenoate giving the stable (4*R*) chiral center of the intermediate whose ring closure affords 2,3-dihydro-pyrans (2*S*,3*S*,4*R*)-**200** in excellent yields, diastereo-, and enantioselectivities.[77]

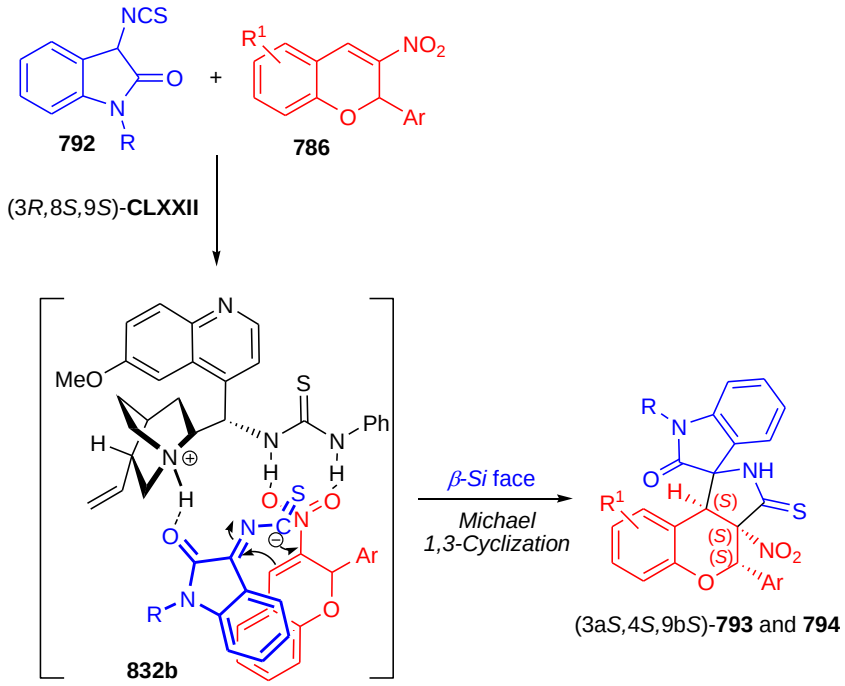
Scheme 370. Enantioselective Domino [Michael/Hemiacetalization] Reaction Between α-Keto Butenoates 17 and Trifluoromethyl β-Keto Ester 199, with (3*R*,8*S*,9*S*)-XXXIV as Organocatalyst.[77]



The third *9-amino-epiquinine*-thiourea (3*R*,8*S*,9*S*)-**CLXXII** is the catalyst of the 1,3-cyclization reaction between **786** and **792** (Scheme 319).[380] The **832b**-type reacting intermediate has the thiourea fragment of the catalyst that coordinates the nitro group of nitroarylchromenes **786**, and the tertiary aminic center of the organocatalyst that deprotonates and coordinates **792**. The 1,3-cycloaddition begins with the Michael attack of the nucleophilic anion to the *β-Si* face of the nitroalkene, followed by the cyclization to the proximate cyano group and the ring closure to (1*S*,3a*S*,4*S*,9b*S*)-**793** (Scheme 371). This product nearly represents the half part of the reaction mixture. The second half is its diastereoisomer (1*R*,3a*S*,4*S*,9b*S*)-**794**.

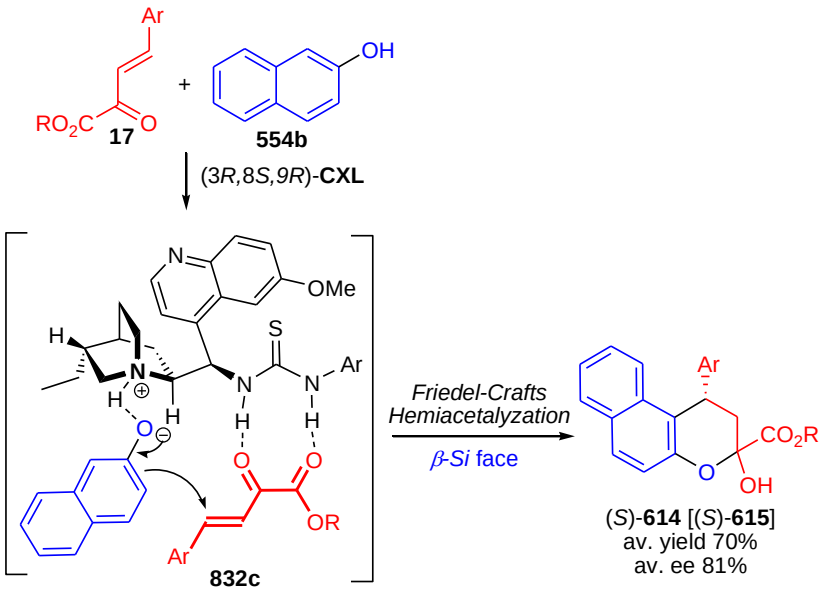
What about organocatalysts in which the thiourea has a substituent belonging to other families of *9-amino Cinchona* alkaloids?

Scheme 371. 1,3-Cycloaddition Between 792 and Nitroarylchromenes 786 with (3*R*,8*S*,9*S*)-CLXXII as Organocatalyst.[380]



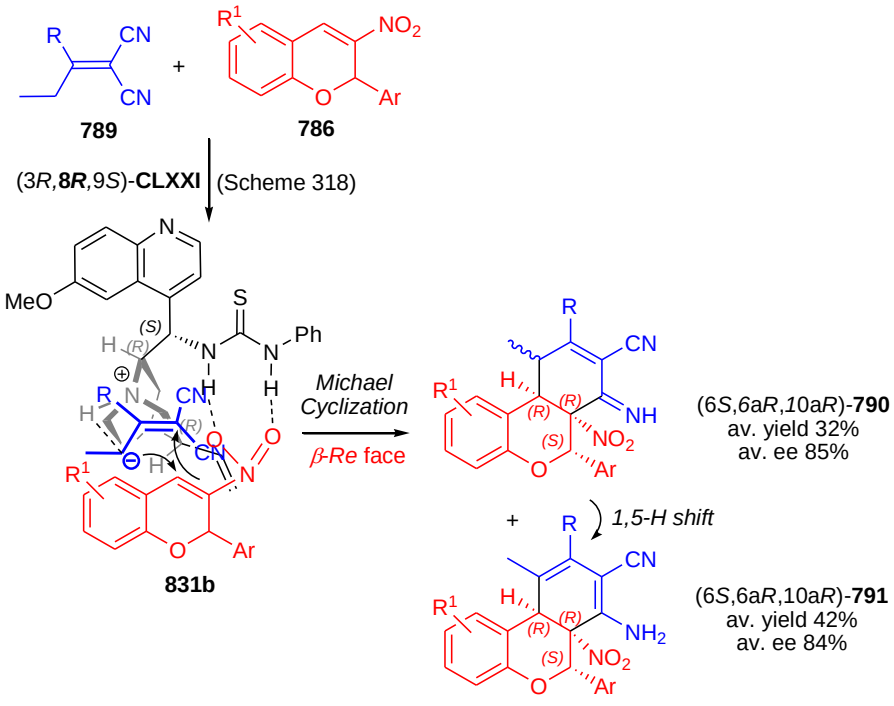
The Friedel-Crafts reaction between α-keto butenoates **17** and 2-naphthol **554b** can be catalysed by *quinine*-based thiourea organocatalyst (3*R*,8*S*,**9*R***)-**CXL** (Scheme 255).[303] The reacting intermediate **832c**, as above, has the α-keto butenoate bicoordinated by hydrogen bonding, and the naphtholate bound to protonated quinine. The Friedel-Crafts step occurs by attack to the *β-Si* face of **17** to afford (*S*)-**614** that is acetalyzed and dehydrated to (*S*)-**615** (Scheme 372). The change of configuration of the chiral center in position (9) from (*S*) *to* (*R*) does not change the *β-Si* face of attack to the electrophile **17** (compare Scheme 372 with 370).

Scheme 372. Organocatalyzed [Fiedel-Crafts/Hemiacetalization] Cascade Reaction Between 2-Naphtol 554b and 17.[303]



The asymmetric domino reaction of nitroarylchromenes **786** with different dicyano olefins **789** is catalyzed by the *9-aminoquinidine*-derived thiourea (3*R*,8***R***,9*S*)-**CLXXI** in which the chiral center in position (8) is changed from *S to R* (Scheme 373).[379]

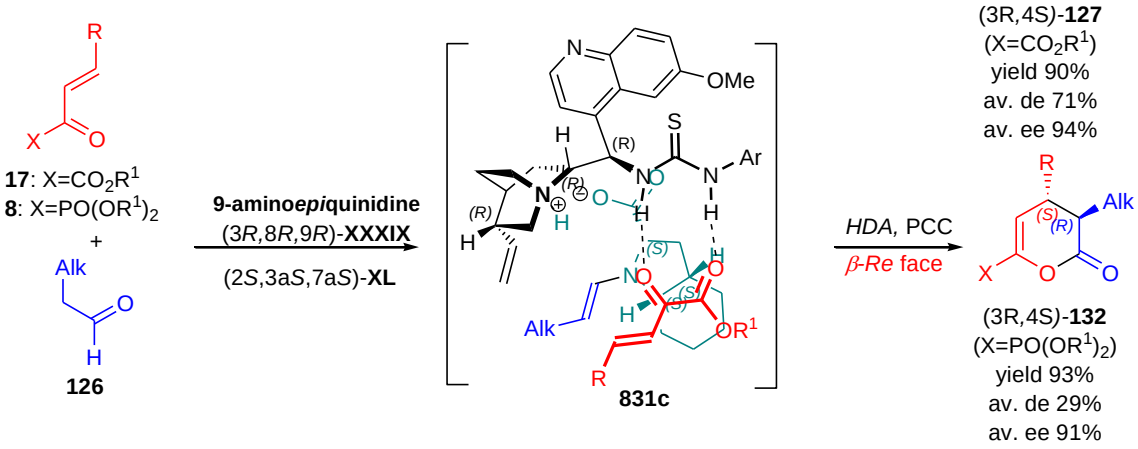
Scheme 373. Domino [Michael/Cyclization/Tautomerization] Reaction Between α,α-Dicyano Olefins 792 and Nitroarylchromenes 789 Catalyzed by (3*R*,8*R*,9*S*)-CLXXI.[379]



The Authors propose the reacting intermediate **831b** in which the tertiary amine of the organocatalyst deprotonates **789** affording the anion suitable for the *Michael* reaction on **786**, activated by the thiourea moiety through double hydrogen bonding**.** Hence, the *Michael* step occurs with the attack of the nucleophile to the *β-Re* face of the specific nitroalkene, followed by the attack to the proximate cyano group and the ring closure to (6*S*,6a*R*,10a*R*)-**790**, which was partly isomerized to (6*S*,6a*R*,10a*R*)-**791**.

The last organocatalyst derived from thiourea substituted with a *9-amino Cinchona* alkaloid is the *epiquinidine* derivative (2*R*,8*R*,9*R*)-**XXXIX** that catalyzes the HDA reaction between **17** or **8** and aldehydes **126**, with (2*S*,3a*S*,7a*S*)-octahydro-1*H*-indole-2-carboxylic acid [(2*S*,3a*S*,7a*S*)-**XL**; (OHIC)] as co-catalyst (Scheme 70).[85] The aldehyde and OHIC give an enamine whose carboxylic acid protonates the tertiary amine of **XXXIX** and coordinates the dienophile, whereas the thiourea fragment binds **17** by double hydrogen bonding. The resulting reacting intermediate **831c** has enone and enamine suitably placed to give a HDA reaction in which the dienophile attacks the *β-Re* face of the heterodiene to afford, after oxidation with PCC, (3*R*,4*S*)-**127** from **17**, and (3*R*,4*S*)-**132** from **8** (Scheme 374).[85] The importance of the synergistic effect of the assembly is given by the failure of both **XXXIX** and OHIC alone to catalyze the reaction.

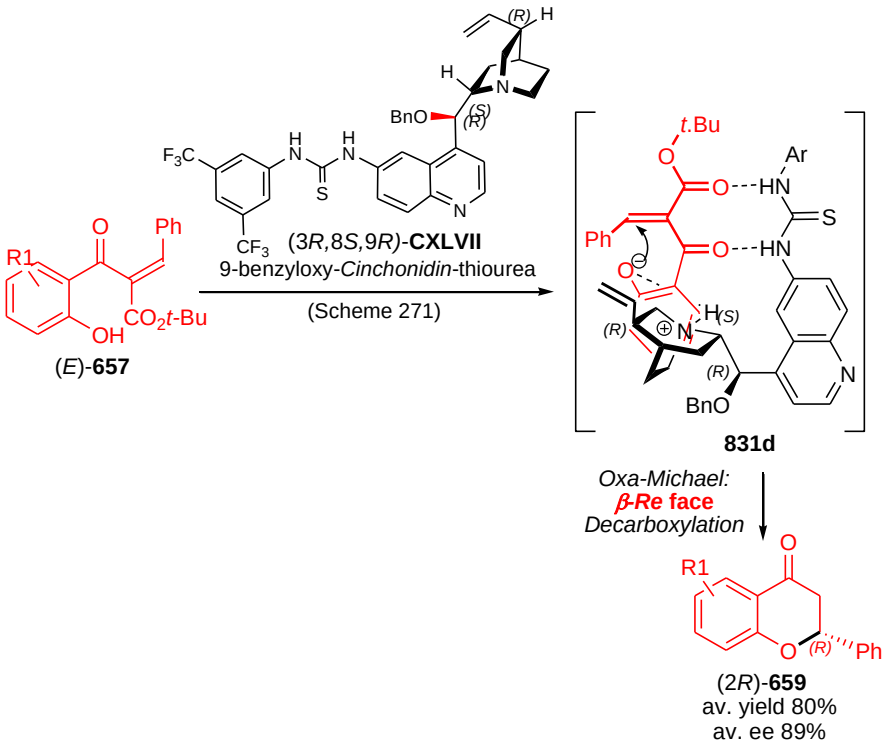
Scheme 374. The Transmission of Chirality in the Reaction Between 17 and Aldehydes 126 Catalyzed by the Self-assembly of 9-*Amino-epiquinine* (3*R*,8*R*,9*R*)-XXXIX and OHIC.[85]



The *Cinchona alkaloids* may be functionalized with a thiourea group which substitutes the 6′-OMe group with the sequence [OH/OTf/NH_2/thiourea].[406] Following this protocol, starting from *Quinine* and *Quinidine* whose 9-OH groups were benzylated, the 9-benzyloxy-*Cinchonidin*-thiourea (3*R*,**8*S*,9*R***)-**CXLVII** and the 9-benzyloxy-*Cinchonin*-thiourea (3*R*,**8*R*,9*S***)-**CXLIX** were respectively obtained. These organocatalysts were tested on two intramolecular ring closures with formation of the O(1)-C(2) bond, the former of which specifically consists in the reaction of (*E*)-**657** that gives (2*R*,2*S*)-**659** (Scheme 271).[320]

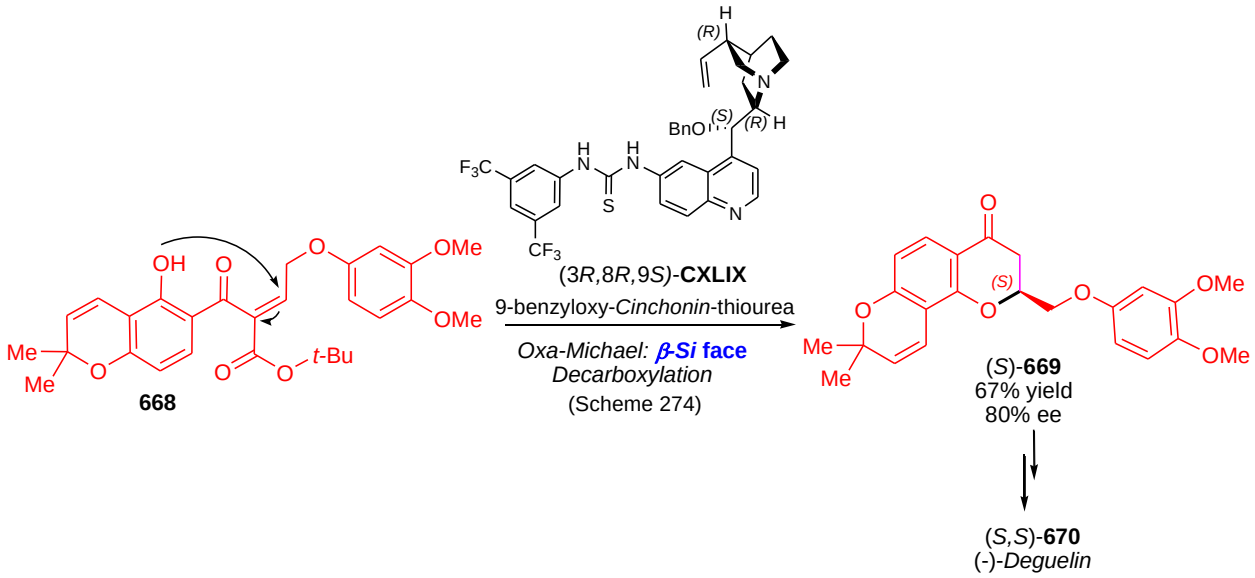
To rationalize the attack of the hydroxy group onto the *β-Re* face of the specific α,β-unsaturated carbonyl fragment, the reacting intermediate **831d** can be proposed in which the enedione is activated by thiourea moiety through double hydrogen bonding, while the hydroxy protonates the tertiary amine and the benzyloxy group favours the conformation suitable for the attack (Scheme 375).

Scheme 375. The Transmission of Chirality in the Intramolecular Oxa-Michael Cyclization of (*E*)-657 with 9-Benzyloxy *Cinchonidin*-derived Thiourea (3*R*,8*S*,9*R*)-CXLVII as Organocatalyst.[320]



The 9-benzyloxy-*Cinchonin*-thiourea (3*R*,**8*R*,9*S***)-**CXLIX** is the organocatalyst of the the intramolecular oxa-Michael cyclization that involves the attack of the hydroxy group to the *β-Si* face of the α,β-enone of **668** to afford (*S*)-**669** (Scheme 274), an intermediate in the synthesis of (-)-*Deguelin*, a rotenoid natural product with specific potential as chemopreventive agent (Scheme 376).[328]

Scheme 376. The Transmission of Chirality in the Intramolecular Oxa-Michael Cyclization of (*E*)-668 with 9-Benzyloxy *Cinchonin*-derived Thiourea (3*R*,8*S*,9*R*)-CXLIX as Organocatalyst.[328]



The effect of the configuration of the chiral centers in position (3), (8) and (9) on the transmission of the chirality from the *Cinchona alkaloids*-substituted thioureas to the products can be evaluated by the above reactions in which two organocatalysts that have the common (3*R*) configuration, but an enantiomerically opposite configuration of (**8*S*,9*R***) *versus* (**8*R*,9*S***), give products with enantiomerically opposite configuration of their respective chiral centers.

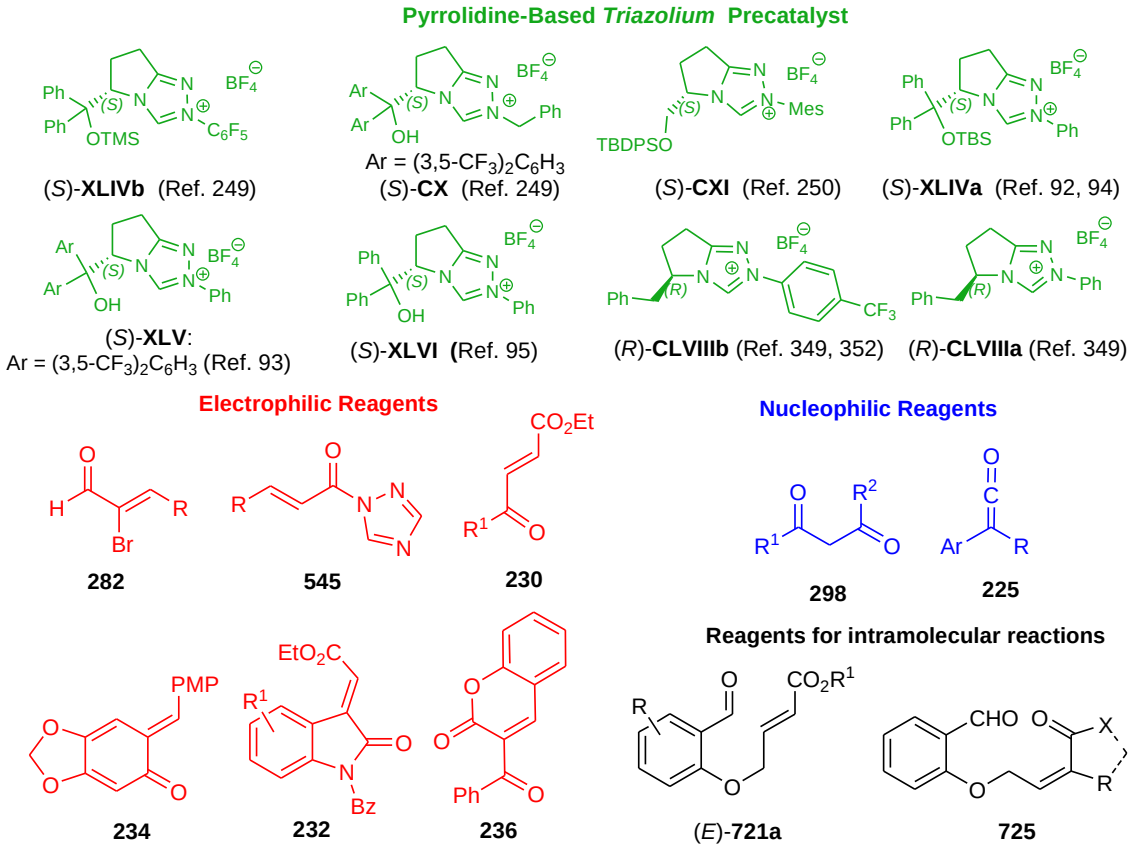
8.4. *N*-Heterocyclic Carbenes

In section 2.1.2.5. we have discussed in detail the application of *N*-heterocyclic carbenes, mainly the most applied amidoindane-based triazolium *N*HCs, as organocatalysts for HDA cycloadditions, and the correlation between their configuration and that of the related product. But,

the topic of this review covers the enantioselective syntheses of 3,4-dihydropyran derivatives through so many different reactions that it seemed interesting to compare structure and configuration of different clusters of heterocyclic homogeneous *N*HC organocatalysts with the transfer of the chirality to the products through different reaction pathways. This argument will be discussed below.

The family of pyrrolidine-based triazolium *N*HCs consists of eight different precatalysts that, after base treatment, give *N*HCs characterized by a 3,5,6,7-tetrahydro-2*H*-pyrrolo[2,1-*c*] [1,2,4]triazolium framework with a chiral centre in the 5-position. The precatalysts and the reagents are listed in Chart 24.

Chart 24. Pyrrolidine-based Triazolium Precatalysts and Reagents Involved in Their *N*HC-Catalyzed Reactions.



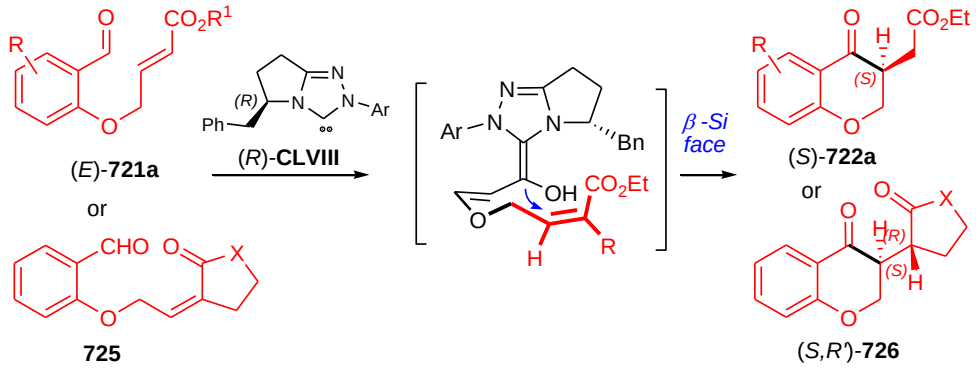
As observed in the above sections, the first step of the mechanism is the reaction of *N*HC with a reagent to give the Breslow intermediate, but the reagent involved may be either that will act as the electrophile or as the nucleophile. The reactions were either intermolecular, in which the

electrophile was an α,β-unsaturated enone and the nucleophile a β-dicarbonyl derivative,[249,250] or intramolecular reactions that consist in the formation of benzopyran derivatives through ring closure of the C(3)-C(4) bond.[349,352]

The intermolecular reactions were catalysed by two different types of *N*-HC: The first group collects the organocatalysts whose –OH group is protected as a silyl ether [(*S*)-**XLIVa,b** and (*S*)-**CXI]**, while the second group assembles the derivatives presenting the unprotected –OH function [(*S*)-**CX**, (*S*)-**XLV**, and (*S*)-**XLVI]**. As previously discussed in Schemes 84 and 229, the first group of catalyst gives a stereochemical outcome that is determined by steric interactions, since the reacting intermediate is attached from its less hindered *β-Re* face.[92,94,249,250] When the *N*-HC have a free OH group, the adduct stereochemistry is determined by the ability to form a hydrogen bond that drive the approach of the H-bound reagent to the *β-Si* face of the substrate activated by the organocatalyst.[93,95,249]

The intramolecular reactions were catalysed by (*R*)-**CLVIIIa**,**b** that have the (*R*)-benzyl as chiral group. The reacting intermediate generated with **721a** or with **725** has the electrophilic fragment suitably placed to undergo the intramolecular attack of the nucleophilic center to its *β-Si* face (Scheme 377; Table 27, entries 7, 11, and 12).[349,353]

Scheme 377. Chirality Transfer in Intramolecular Reactions Catalyzed by Pyrrolidine-based Triazolium *N*HCs.[349,353]

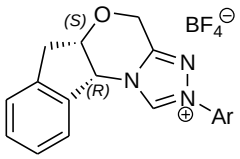


What can be concluded from the all these data is that an overall rationale of the chirality transfer in reactions catalyzed by pyrrolidine-based triazolium *N*HCs can be proposed for either

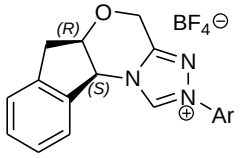
inter- or intra-molecular reactions. The steric control governs the reactions in which the chiral center has a group unsuitable to act through H-bonding, otherwise the opposite attack is preferred.

Chiral amidoindane-based triazolium *N*HCs, which were first prepared by Rovis in 2002,[347] for the easy availability of the starting product aminoindanol and for the optimal selectivity, rapidly became the widest used carbene organocatalyst. The basic structure is constant with either the (5a*S*,10b*R*) or the (5a*R*,10b*S*) configuration, but several catalysts differing for the different aryl group in position 2 were prepared (Chart 25).

Chart 25. Amidoindane-based Triazolium *N*HC Precatalysts.



(5a*S*,10b*R*)-**XLVIIa**: Ar = 2,4,6-$Me_3C_6H_2$
(5a*S*,10b*R*)-**XLVIIb**: Ar = 4-$OMeC_6H_4$
(5a*S*,10b*R*)-**XLVIIc**: Ar = Ph
(5a*S*,10b*R*)-**XLVIId**: Ar = 3,5-$(CF_3)_2C_6H_3$
(5a*S*,10b*R*)-**XLVIIe**: Ar = C_6F_5.



(5a*R*,10b*S*)-**XLVIIa**: Ar = 2,4,6-$Me_3C_6H_2$
(5a*R*,10b*S*)-**XLVIIb**: Ar = 4-$OMeC_6H_4$
(5a*R*,10b*S*)-**XLVIIc**: Ar = Ph
(5a*R*,10b*S*)-**XLVIId**: Ar = 3,5-$(CF_3)_2C_6H_3$
(5a*R*,10b*S*)-**XLVIIf**: Ar = 2,6-$Et_2C_6H_3$

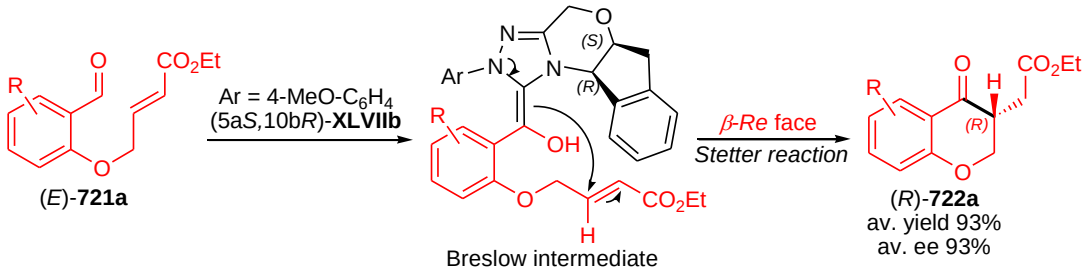
Among the different reactions catalyzed by amidoindane-based triazolium carbenes we begin to discuss the intramolecular processes because the Breslow intermediate, developed from reagent and *N*HC, contains both the nucleophilic and the electrophilic reagent. This makes easy to perceive the sterically preferred process that builds enantioselectively the C-C bond, object of the reaction.

The Stetter reaction on (*E*)-**721a** was catalysed with the *N*HC derived from (5a*S*,10b*R*)-**XLVIIb** (Scheme 378).[347] In the Breslow intermediate the addition of the nucleophile to the electrophilic carbon of the double bond occurs from the rear, hence to the less hindered conventional *β-Re* face of the unsaturated ester to give (*R*)-**722a**.

Following this first protocol, the Stetter reaction was performed on (*E*)-**721a-c,** (*E*)-**723**, and (*E*)-**729** with *N*-HC derived from either (5a*S*,10b*R*)-**XLVII** or (5a*R*,10b*S*)-**XLVII** and the stereochemical results of nine examples are reported in Table 30. Seven examples run with *N*HC derived from (5a*S*,10b*R*)-**XLVIIb-d** gave results that can be all rationalized with the rear attack to the conventional *β-Re* face of the electrophile (Table 30, entries 1-7). Two examples run with *N*-HC

derived from the enantiomeric (5a*R*,10b*S*)-**XLVIId** gave products whose absolute configuration derives from a front attack to the conventional *β-Si* face of the electrophile (Table 30, entries 8 and 9).

Scheme 378. Chirality Transfer in the Intramolecular *Stetter* Reactions Catalyzed by Amidoindane-based Triazolium *N*HC Derived from (5a*S*,10b*R*)-XLVIIb.[347]



Other intramolecular enantioselective cyclizations to 3,4-dihydro-2*H*-chromenes via the formation of a C-C bond have been catalysed with amidoindane-based triazolium *N*HC. The *benzoin reaction*, in its intramolecular version with 2-(2-oxopropoxy)benzaldehyde derivatives **731**, is catalysed with the *N*HC derived from (5a*R*,10b*S*)-**XLVIIc** (Scheme 297). The Breslow intermediate undergoes an *aldol* reaction with the front attack to the less hindered *Si*-face of the carbonyl group that affords 3-substituted-2,3-dihydro-3-hydroxychroman-4-one (*R*)-**732**. (Scheme 379).[355,356] The same reaction performed with **733** (R^1 = OMe, R = 3,4-$(MeO)_2C_6H_3$), catalyzed with the *N*HC derived from (5a*R*,10b*S*)-**XLVIId** (Scheme 298), occurs through the same front attack to the *Si*-face of the carbonyl group and (*R*)-**734** has the correct absolute configuration to be the starting product for the synthesis of (+)-*Sappanone B*.[356]

Scheme 379. Chirality Transfer in the Intramolecular *Benzoin* Reactions Catalyzed by Amidoindane-based Triazolium *N*HC.[355,356]

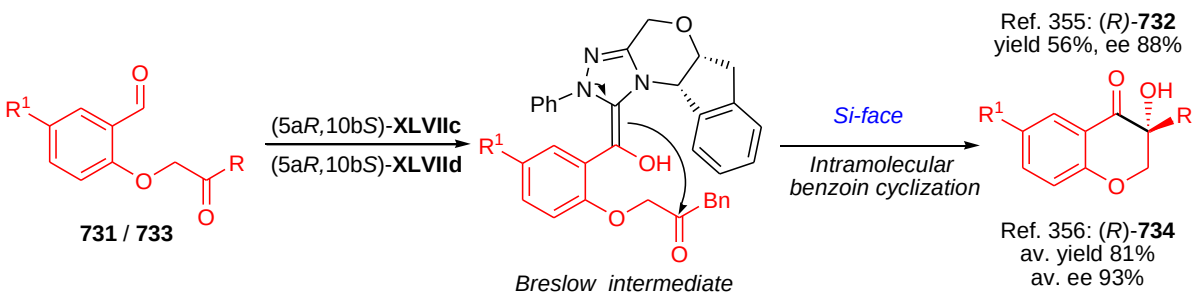
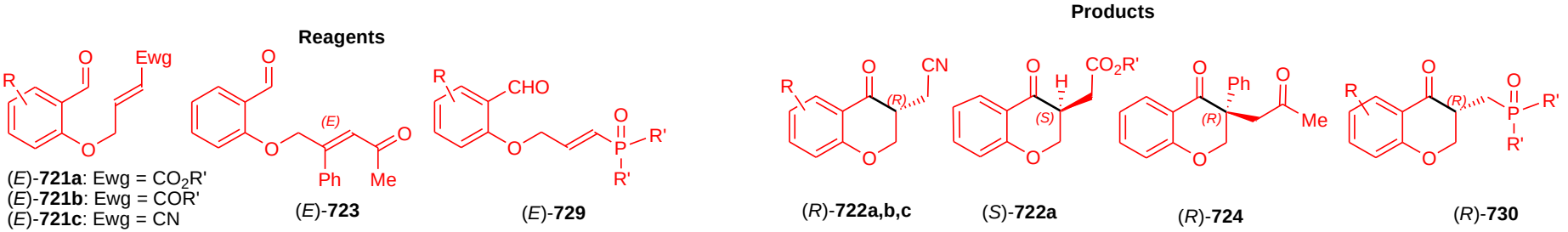


Table 30. Asymmetric Intramolecular *Stetter* Reactions with Reagents, and Products, Catalyzed with Amidoindane-based Triazolium *N*HC Derived from (5a*S*,10b*R*)- and (5a*R*,10b*S*)-**XLVII**.

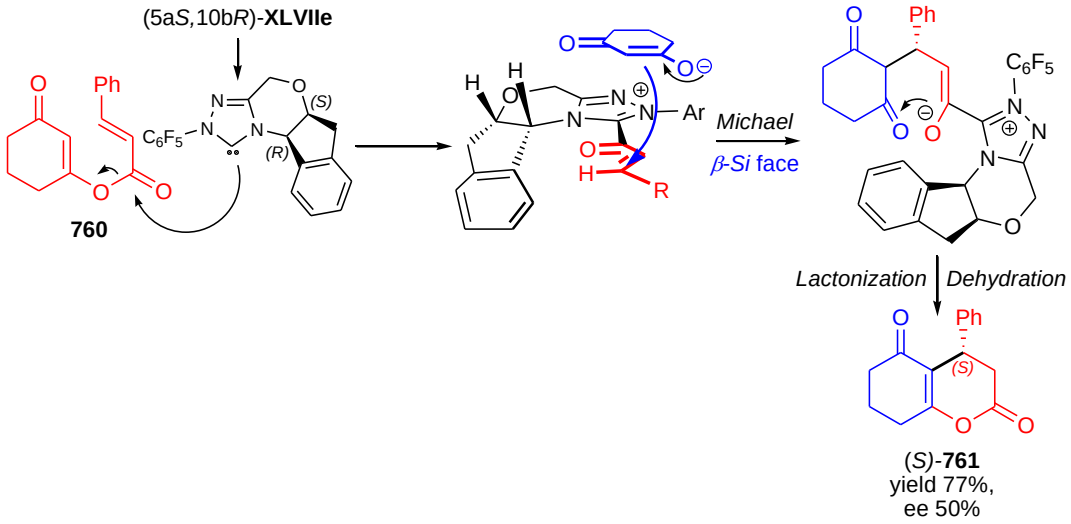


Entry	Reagents	Pre-Catalyst of *N*-CH	n. Exp.	*Product config.*	av. Yield % (s.d.)	av. ee % (s.d.)	Attached face	Ref.
1	(*E*)-**721a**	(5a*S*,10b*R*)-**XLVIIb**	4	(*R*)-**722a**	93 (6)	93 (5)	*β-Re*	347
2	(*E*)-**721a**	(5a*S*,10b*R*)-**XLVIIc**	1	(*R*)-**722a**	58	95	*β-Re*	348
3	(*E*)-**721b**	(5a*S*,10b*R*)-**XLVIIc**	1	(*R*)-**722b**	90	92	*β-Re*	348
4	(*E*)-**721c**	(5a*S*,10b*R*)-**XLVIIc**	1	(*R*)-**722c**	78	75	*β-Re*	348
5	(*E*)-**723**	(5a*S*,10b*R*)-**XLVIId**	1	(*R*)-**724**	55	99	*β-Re*	351
6	(*E*)-**721a**	(5a*S*,10b*R*)-**XLVIIb**	5	(*R*)-**722a**	87 (13)	84 (16)	*β-Re*	349
7	(*E*)-**729**	(5a*S*,10b*R*)-**XLVIId**	6	(*R*)-**730**	85 (6)	91.5 (4)	*β-Re*	353
8	(*E*)-**721a**	(5a*R*,10b*S*)-**XLVIId**	8	(*S*)-**722a**	87 (15)	81 (23)	*β-Si*	349
9	(*Z*)-**721a**	(5a*R*,10b*S*)-**XLVIId**	1	(*S*)-**7252a**	85	22	*β-Si*	349

In conclusion, in all the above reactions, the chirality transfer from the *N*HC to the product occurs during the attack of the nucleophile to the less hindered face of the electrophilic fragment in the Breslow intermediate.

An interesting reaction can be considered a bridge between the intramolecular reactions discussed above and the intermolecular variants. 3-Oxocyclohex-1-enyl cinnamate (**760**), in the presence of (5a*S*,10b*R*)-**XLVIIe** undergoes a ring closure to afford 3,4,7,8-tetrahydro-4-phenyl-6*H*-chromene-2,5-dione (**761**) (Scheme 308).[369] The first step of the reaction is the nucleophilic attach of the *N*-HC to the ester group with formation of the electrophilic Breslow intermediate and the anion of 1,3-cyclohexandione. The next step is the Michael addition of this nucleophile to the less hindered *β-Si* face of the enone-acyltriazolium. The lactonization-dehydration and the elimination of the catalyst affords (S)-**761** (Scheme 380).

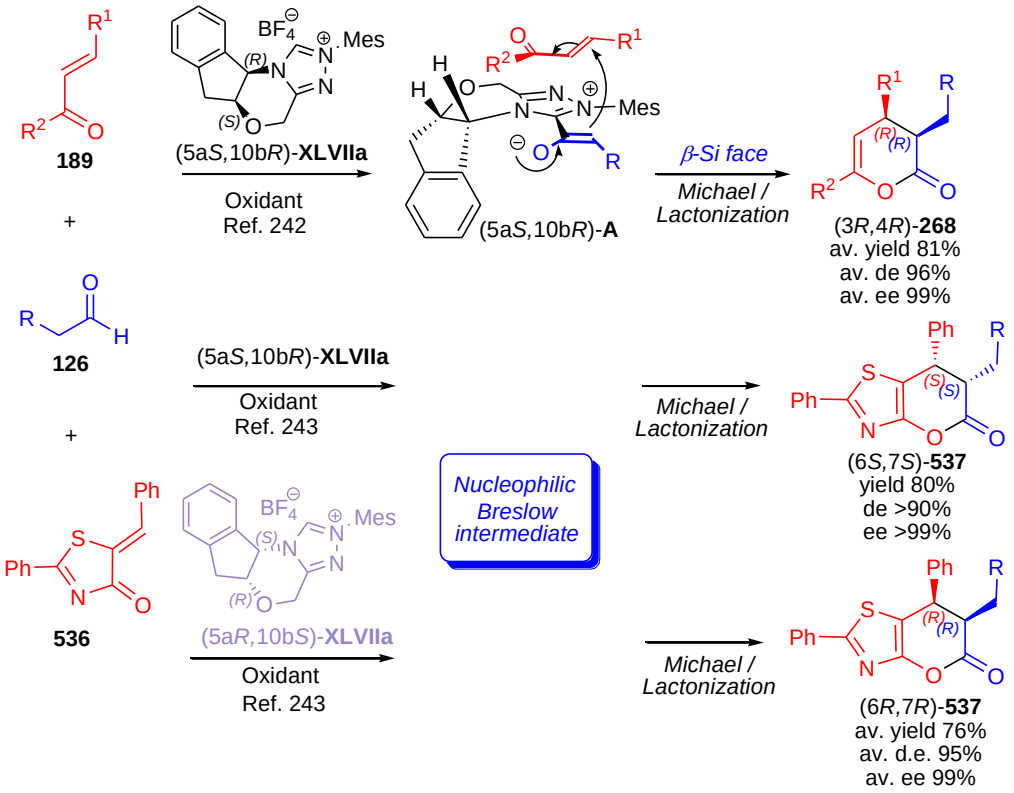
Scheme 380. Chirality Transfer from 760 to 761 Through a Reactions Catalyzed by Amidoindane-based Triazolium *N*HC from (5a*S*,10b*R*)-XLVIIe.[369]



Amidoindane-based triazolium *N*HCs catalyze several intermolecular reactions and, as observed in the above sections, the first step of the mechanism is the reaction of *N*-HC with a reagent to give the Breslow intermediate. The molecule involved may be either the reagent that will become the nucleophile, or that will become the electrophile.

Let us consider first the reactions in which the nucleophile reacts with *N*-HC to give the Breslow intermediate that, depending on the conditions, reacts as it is, or in its oxidized form with the electrophilic reagent.

Scheme 381. Chirality Transfer in Reactions Catalyzed by *N*-HC derived by Amidoindane-based Triazolium Precatalysts (5a*S*,10b*R*)- and (5a*R*,10b*S*)-XLVIIa, in Which the Breslow Intermediate Derives from *N*-HC and the Nucleophilic Reagent.[242,243]



Two reactions catalyzed by (5a*S*,10b*R*)-**XLVIIa** and (5a*R*,10b*S*)-**XLVIIa**, one between α,β-unsaturated ketones **189** and aldehydes **126**,[242] and the other between 5-alkenyl thiazolones **536** and aldehydes **126**,[243] both under oxidative conditions, are reported in Scheme 381.

The former reaction, between α,β-unsaturated ketones **189** and aldehydes **126** is catalyzed by (5a*S*,10b*R*)-**XLVIIa** and, after lactonization, gives (3*R*,4*R*)-**268**. The aldehyde **126** undergoes the attack of the *N*-HC to give the Breslow intermediate, which is oxidized to afford the nucleophilic reagents (5a*S*,10b*R*)-**A** in the conformation suggested by the Authors and reported in Scheme 381.

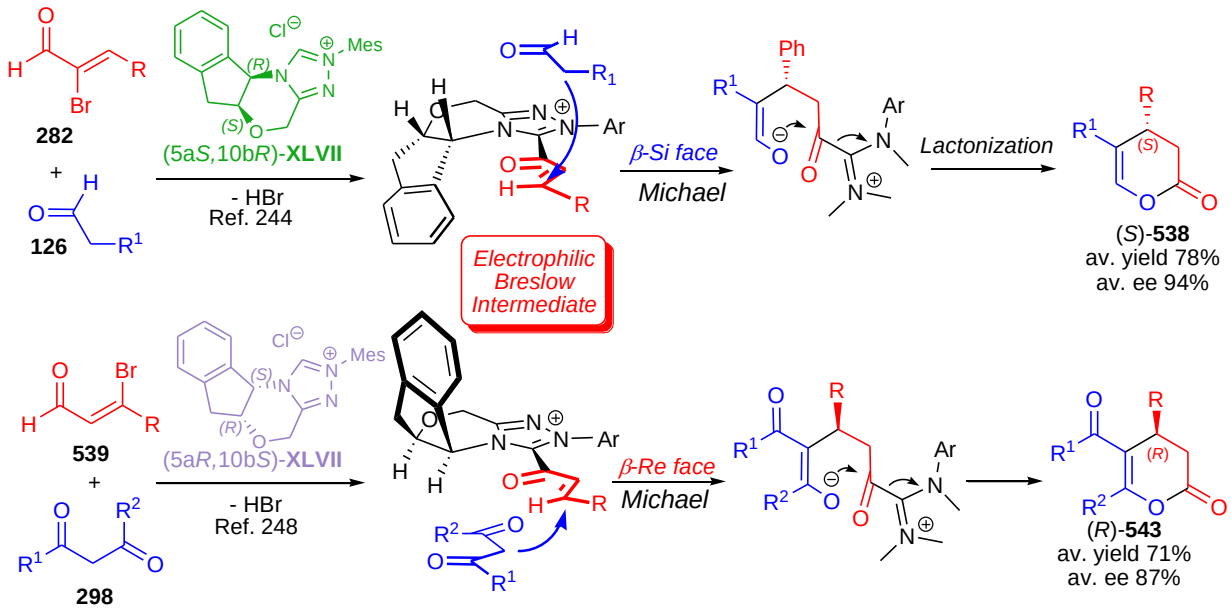
This has the configuration suitable for the Michael attack to the *β-Si* face of **189** to afford (3*R*,4*R*)-**268**.[242]

The latter reaction between 5-alkenyl thiazolones **536** and aldehydes **126** is catalysed by both (5a*S*,10b*R*)-**XLVIIa** and (5a*R*,10b*S*)-**XLVIIa** and, after lactonization, gives (6*R*,7*R*)-**537** and (6*S*,7*S*)-**537** respectively (Scheme 381).[243]

There is a discrepancy between the above sterochemical results which can be rationalized by different reacting species, different conformations of the reagents, different stereochemical approach. It will be interesting to compare the results of other reactions catalyzed by the same *N*-HC.

If the α,β-unsaturated carbonyl compound is an α-haloenal, the reaction takes a different pathway. In the presence of **282** and aldehydes **126**, the *N*-HC from (5a*S*,10b*R*)-**XLVII** reacts with the electrophilic reagent **282** to give, after loss of HBr, the electrophilic Breslow intermediate.[244] This undergoes a Michael addition to the *β-Si* face of **126** affording the reaction intermediate that gives (*S*)-**538** by lactonization (Scheme 382).

Scheme 382. Chirality Transfer in Reactions Catalyzed by *N*HC Derived by Amidoindane-Based Triazolium Precatalysts (5a*S*,10b*R*)- and (5a*R*,10b*S*)-XLVII, in Which the Breslow Intermediate Derives from *N*HC and the Electrophilic Reagent.[244,248]



This rationale is not unusual. This is the model of chirality transfer described in Scheme 380 from **760** to **761**, through an intermolecular reaction catalyzed by an amidoindane-based triazolium *N*-HC, this again with a (5a*S*,10b*R*) absolute configuration. Moreover, it induces the attack to the *β-Si* face of the electrophilic Breslow intermediate.

In a similar way, in the reaction between β-haloenals **539** and β-diketones **298**, the *N*-HC from (5a*R*,10b*S*)-**XLVIIa** reacts with **239** to afford, after loss of HBr, the electrophilic Breslow intermediate.[248] The Michael attack of the nucleophile **298** to the *β-Re* face, followed by lactonization, provides (*R*)-**543** (Scheme 382).

Now, we have two reacting models that rationalize the chirality transfer from the amidoindane-based triazolium *N*-HC. Since several *N*-HC, in which the chiral block is the same and differ the 2-aryl group, have been used as catalysts in many reaction, are the above model suitable to be applied to other reactions?

We begin to discuss the chirality transfer in reactions in which the Breslow Intermediate derives from amidoindane-based triazolium *N*-HC and the nucleophilic reagent, hence reactions that involve as intermediate a *nucleophilic Breslow intermediate* (Scheme 381). Nucleophilic and electrophilic reagents involved in *22 reactions* with these characteristics are listed in Chart 26, while Table 31 collects and compares all the obtained results.

It can be observed that *7 different nucleophiles react with 16 different electrophiles*, all of which have the structure of α,β-unsaturated carbonyl derivative. Table 31 conveys the chirality transfer of the reactions.

If the model reaction of Scheme 381 is suitable to be generalized, we should observe the reactions catalysed by (5a*S*,10b*R*)-***N*-CH** to occur through a step in which the nucleophilic Breslow intermediate attacks "*bottom/up"* the β-*Si* face of the electrophile, whereas (5a*R*,10b*S*)-***N*-CH** should promote the attack "*top/down"* to the *β-Re* face of the electrophilic unsaturated enone. The results can be evaluated from the above data and, apart from the results in Table 31 entries 2 and 3, the concordance with the model is good.

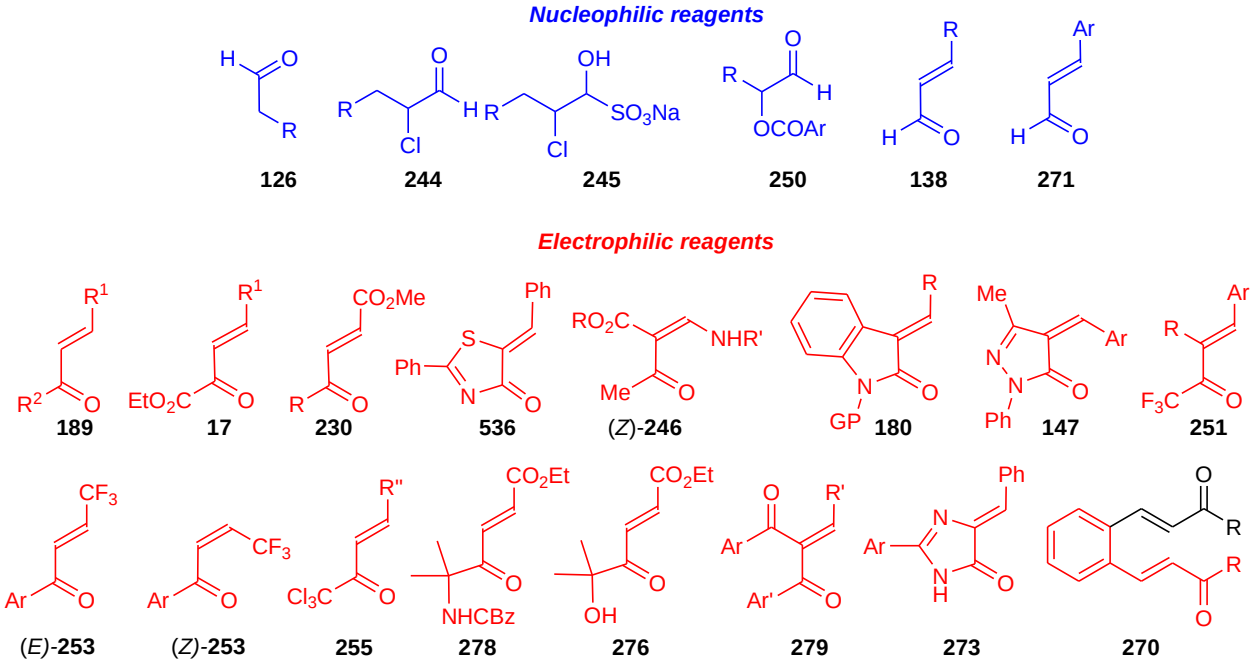
Table 31. Chirality Transfer in Reactions in which the Breslow Intermediate Derives from Amidoindane-based Triazolium *N*HC and the Nucleophilic Reagent.

Entry	Electroph. reagent	Nucleoph. reagent	*N*-HC Catalyst	N. exp.	Product	av. yield % (s.d.)	av. d.e. % (s.d.)	av. ee % (s.d.)	Attached face	Ref.
1	**189**	**126**	(5a*S*,10b*R*)-**XLVIIa**	9	(3*R*,4*R*)-**268**	81 (16)	96 (2)	99 (0.5)	β-*Si*	242
2	**536**	**126**	(5a*R*,10b*S*)-**XLVIIa**	17	(6*R*,7*R*)-**537**	76 (5)	95 (2)	99 (0.5)	-	243
3	**536**	**126**	(5a*S*,10b*R*)-**XLVIIa**	1	(6*S*,7*S*)-**537**	80	>95	>99	-	243
4	**17**	**244**	(5a*R*,10b*S*)-**XLVIIa**	5	(3*S*,4*S*)-**243**	79 (7)	>95	97 (2)	*β-Re*	97
5	**230**	**244**	(5a*R*,10b*S*)-**XLVIIa**	8	(3*S*,4*S*)-**127**	84 (8)	90 (7)	97 (5)	*β-Re*	97
6	**17** or **230**	**245**	(5a*R*,10b*S*)-**XLVIIa**	15	(3*S*,4*S*)-**127** or **243**	74 (13)	*a*	96 (7)	*β-Re*	99
7	(*Z*)-**246**	**244**	(5a*R*,10b*S*)-**XLVIIa**	6	(3*S*,4*R*)-**247**	64 (13)	72 (9)	98 (1)	*β-Si*[a]	100
8	**180**	**244**	(5a*R*,10b*S*)-**XLVIIa**	16	(3*S*,4*S*)-**248**	82 (11)	>99	97 (4)	*β-Si*	101
9	**147**	**244**	(5a*R*,10b*S*)-**XLVIIa**	14	(4*S*,5*S*)-**249**	89 (5)	82 (1)[c]	98 (2)	*β-Re*	102
10	**251**	**250**	(5a*R*,10b*S*)-**XLVIIa**	22	(3*S*,4*S*)-**252**	69 (12)	>90	99 (0.5)	*β-Re*	103
11	(*E*)-**253**	**250**	(5a*R*,10b*S*)-**XLVIIa**	12	(3*S*,4*R*)-**254**	66 (8)	87 (5)	≥90	*β-Re*	104
12	(*Z*)-**253**	**250**	(5a*R*,10b*S*)-**XLVIIa**	5	(3*S*,4*S*)-**254**	70 (6)	85 (5)	97 (2)	*β-Si*[b]	104
13	**255**	**250**	(5a*R*,10b*S*)-**XLVIIa**	6	(3*S*,4*S*)-**256**	77 (12)	89 (4)	99	*β-Re*	105

14	**189**	(±)-**265**	(5a*R*,10b*S*)-**XLVIIa**	30	(3*S*,4*S*)-**266**	75 (20)	88 (4)	≥99	*β-Re*	106
15	**276**	**138**	(5a*S*,10b*R*)-**XLVIIa**	6	(3*R*,4*R*)-**277**	91 (4)	≥90	99	*β-Si*	110
16	**278**	**138**	(5a*S*,10b*R*)-**XLVII**	5	(3*R*,4*R*)-**279**	91 (10)	≥90	99	*β-Si*	110
17	**230**	**138**	(5a*S*,10b*R*)-**XLVII**	10	(3*R*,4*R*)-**243**	71 (16)	≥90	98.5 (0.5)	*β-Si*	110
18	**17**	**138**	(5a*S*,10b*R*)-**XLVII**	5	(3*R*,4*R*)-**127**	71 (20)	≥90	98 (1)	*β-Si*	110
19	**189a**	**271**	(5a*S*,10b*R*)-**XLVII**	21	(3*R*,4*R*)-**280**	75 (10)	89 (2)	99	*β-Si*	111
20	**273**	**138** or **271**	(5a*R*,10b*S*)-**XLVII**	24	(6*S*,7*S*)-**274**	65 (13)	95 (4)	64 (23)	*β-Re*	109
21	**189**	**138**	(5a*R*,10b*S*)-**XLVIIa**	21	(3*S*,4*S*)-**268**	74 (10)	88 (4)	>98	*β-Re*	107
22	**270**	**271**	(5a*R*,10b*S*)-**XLVII**	23	(4a*S*,10b*S*)-**272**[c]	72 (10)	87 (3)	98 (2)	*β-Re*	108

[(a)] From (*Z*)-**246** through *exo* t.s. [(b)] From (*Z*)-**253** through *endo* t.s. [(c)] The full name of the product is (4a*S*,5*R*,6*S*,10b*S*)-**272**, the first step gives 4a*S* and 10b*S* chiral centers.

Chart 26. Nucleophilic Reagents and Electrophiles of Reactions Catalysed from Amidoindane-based Triazolium *N*HC in Which the Breslow Intermediate Derives from the Nucleophilic Reagent.



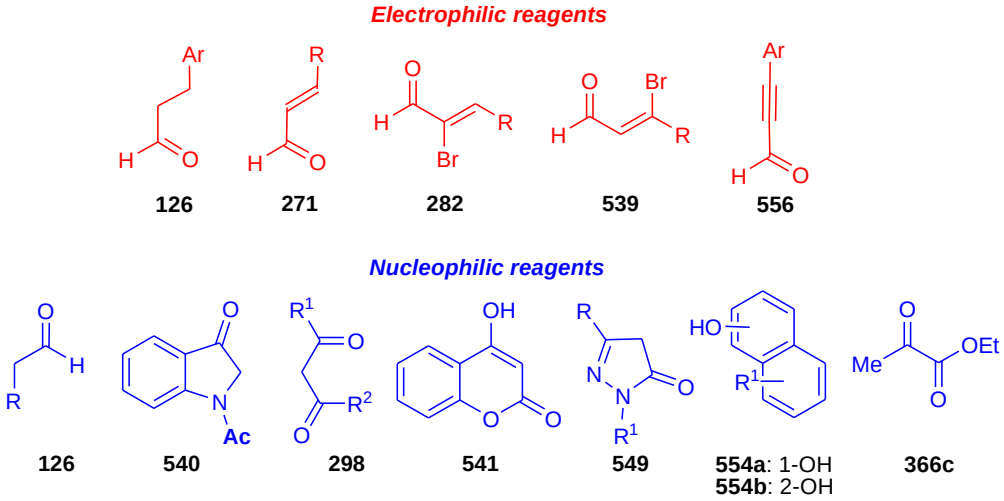
When the Breslow intermediate derives from amidoindane-based triazolium *N*HC and the electrophilic reagent, the reactions involves an *electrophilic Breslow intermediate* analogous to that applied in Scheme 382. Reagents and products of *eleven reactions* that satisfy this requirement are listed in Chart 27. The reactions catalysed by (5a*S*,10b*R*)-**XLVII** should occur through a step in which the electrophilic Breslow intermediate undergoes the attack "*top/down"* to its β-*Si* face, whereas (5a*R*,10b*S*)-**XLVII** should suffer the attack "*bottom/up"* to the *β-Re* face of the enone. The results are reported in Table 32 and all the four reactions catalysed by (5a*R*,10b*S*)-**XLVII** show the attack to the β-*Re* face of the electrophile and six of the seven reactions catalysed by (5a*S*,10b*R*)-**XLVII** transfer the chirality from organocatalyst to the product through attack to the β-*Si* face of the electrophile. Again, the concordance with the model is good. The only exception is the reaction between **282** and **541** (Table 32, entry 8).[247]

Table 32. Chirality Transfer in Reactions in which the Breslow Intermediate Derives from Amidoindane-based Triazolium *N*HC and the Electrophilic Reagent.

Entry	Electroph. reagent	Nucleoph. reagent	*N*-HC Catalyst	n. Exp.	Product	av. yield % (s.d.)	av. ee % (s.d.)	Attached face	Ref.
1	**282**	**126**	(5a*S*,10b*R*)-**XLVIIa**	18	(*S*)-**538**	78 (15)	94 (4)	*β-Si*	244
2	**271**	**126**	(5a*S*,10b*R*)-**XLVIIa**	1	(*S*)-**538**	33	98	*β-Si*	244
3	**556**	**126**	(5a*S*,10b*R*)-**XLVIIa**	1	(*S*)-**538**	40	95	*β-Si*	244
4	**282**	**540**	(5a*S*,10b*R*)-**XLVIIa**	12	(*S*)-**542**	66 (4)	91 (8)	*β-Si*	245
5	**282**	**298**	(5a*S*,10b*R*)-**XLVIIa**	16	(*S*)-**543**	86 (6)	93 (6)	*β-Si*	246
6	**271**	**549**	(5a*S*,10b*R*)-**XLVIIa**	22	(*S*)-**550**	66 (12)	87.5 (6)	*β-Si*	252
7	**556**	**366c**	(5a*R*,10b*S*)-**XLVIIa**	1	(*R*)-**559**	74	99	*β-Re*	257
8	**282**	**541**	(5a*S*,10b*R*)-**XLVIIa**	4	(*R*)-**544**	79 (11)	81 (6)	*β-Re*	247
9	**539**	**298**	(5a*R*,10b*S*)-**XLVIIa**	12	(*R*)-**543**	71 (14)	87 (8.6)	*β-Re*	248
10	**271**	**554** [a,b]	(5a*R*,10b*S*)-**XLVII**	6	(*R*)-**555**	66 (21)	68 (8)	*β-Re*	256
11	**126**	**298**	(5a*R*,10b*S*)-**XLVII**	17	(*R*)-**543**	80 (13)	85 (7)	*β-Re*	258

[(a)] Cs_2CO_3 in addition to oxidant. [(b)] The nucleophiles are α- and β-naphthols.

Chart 27. Electrophilic Reagents and Nucleophiles of Reactions Catalysed by Amidoindane-based Triazolium *N*HC in Which the Breslow Intermediate Derives from the Electrophilic Reagent.

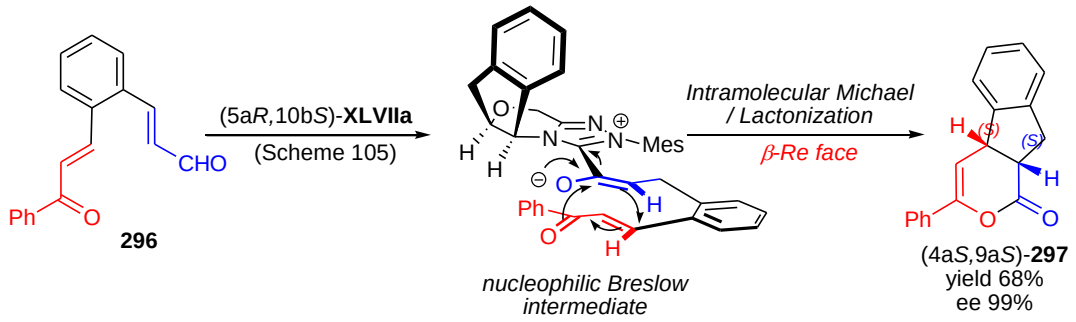


The above discussion concerned intermolecular reactions, but amidoindane-based triazolium *N*-HC has been used as organocatalyst in intramolecular reactions in which the first step is a Michael addition, followed by further steps that makes these reactions interesting. Some of them will be now considered.

The first intramolecular [Michael/lactonization] reaction catalysed by (5a*R*,10b*S*)-**XLVIIa** involves (2*E*)-3-(2-[(*E*)-3-oxo-3-phenylprop-1-enyl)phenyl]acrylaldehyde (**296**) which gives the Breslow intermediate reported in Scheme 383. As expected, due to the structure of the catalyst, the intramolecular nucleophilic attack occurs to the *β-Re* face of the enone fragment and gives (4a*S*,9b*S*)-**297** (Scheme 383).[114]

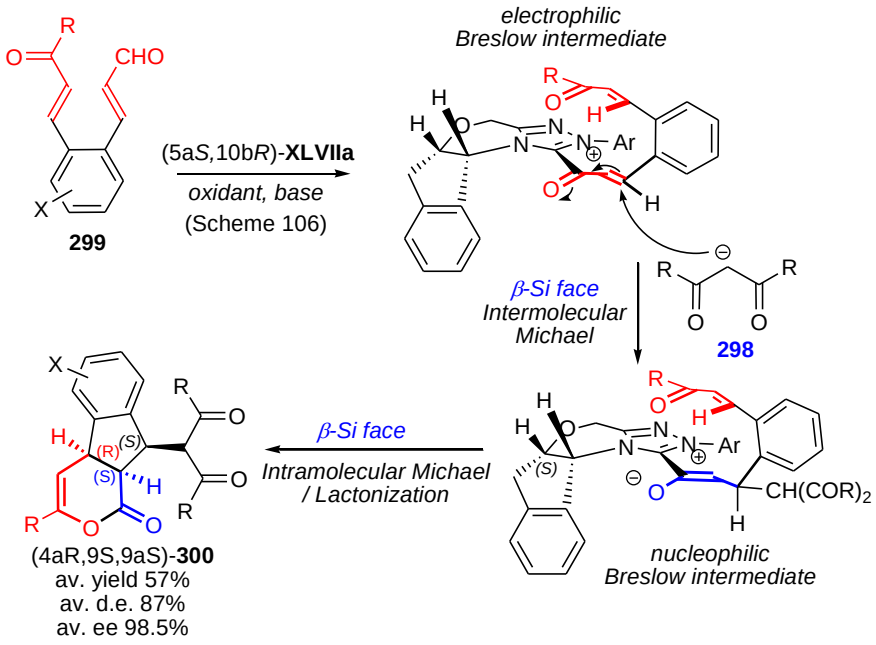
Often, the above process is complicated by the addition of either an electrophile or a nucleophile to the stage of the reaction in which the Breslow intermediate is formed from *N*-HC and 3-(2-(3-oxo-3-arylprop-1-enyl)aryl)acrylaldehydes. After this step, the reaction follows the intramolecular protocol, and the overall process is a carbene-catalyzed cascade reaction to give indane derivatives with three or more stereocenters in which the Breslow intermediate may play part either as an electrophilic or a nucleophilic intermediate.

Scheme 383. Chirality Transfer in the [Intramolecular Michael/Lactonization] Reaction of 296, Catalyzed by (5a*R*,10b*S*)-XLVIIa to Give (4a*S*,9a*S*)-297.[114]



An example is the reaction between **299** and various β-diketones **298**, with quinone as oxidant, catalyzed by (5a*S*,10b*R*)-**XLVIIa** (Scheme 384).[115]

Scheme 384. Chirality Transfer in the Oxidative [Intermolecular/Intramolecular Michael/Lactonization] Reaction of 299 with 298, Catalyzed by (5a*S*,10b*R*)-XLVIIa to Give (4a*R*,9*S*,9a*S*)-300.[115]



The reaction of the enal fragment of **299** with the carbene derived by (5a*S*,10b*R*)-**XLVIIa**, in the presence of the oxidant, generates the *electrophilic Breslow intermediate* suitable to undergo the nucleophilic addition of **298** to the *β-Si* face. The product, a *nucleophilic Breslow intermediate enolate*, undergoes the intramolecular 1,4-addition that consists of an intramolecular Michael

addition to the *β-Si* face of the electrophilic fragment, followed by lactonization. The product is (4a*R*,9*S*,9a*S*)-**300** and its absolute configuration, determined by X-ray analysis, supports the above stereochemical considerations.

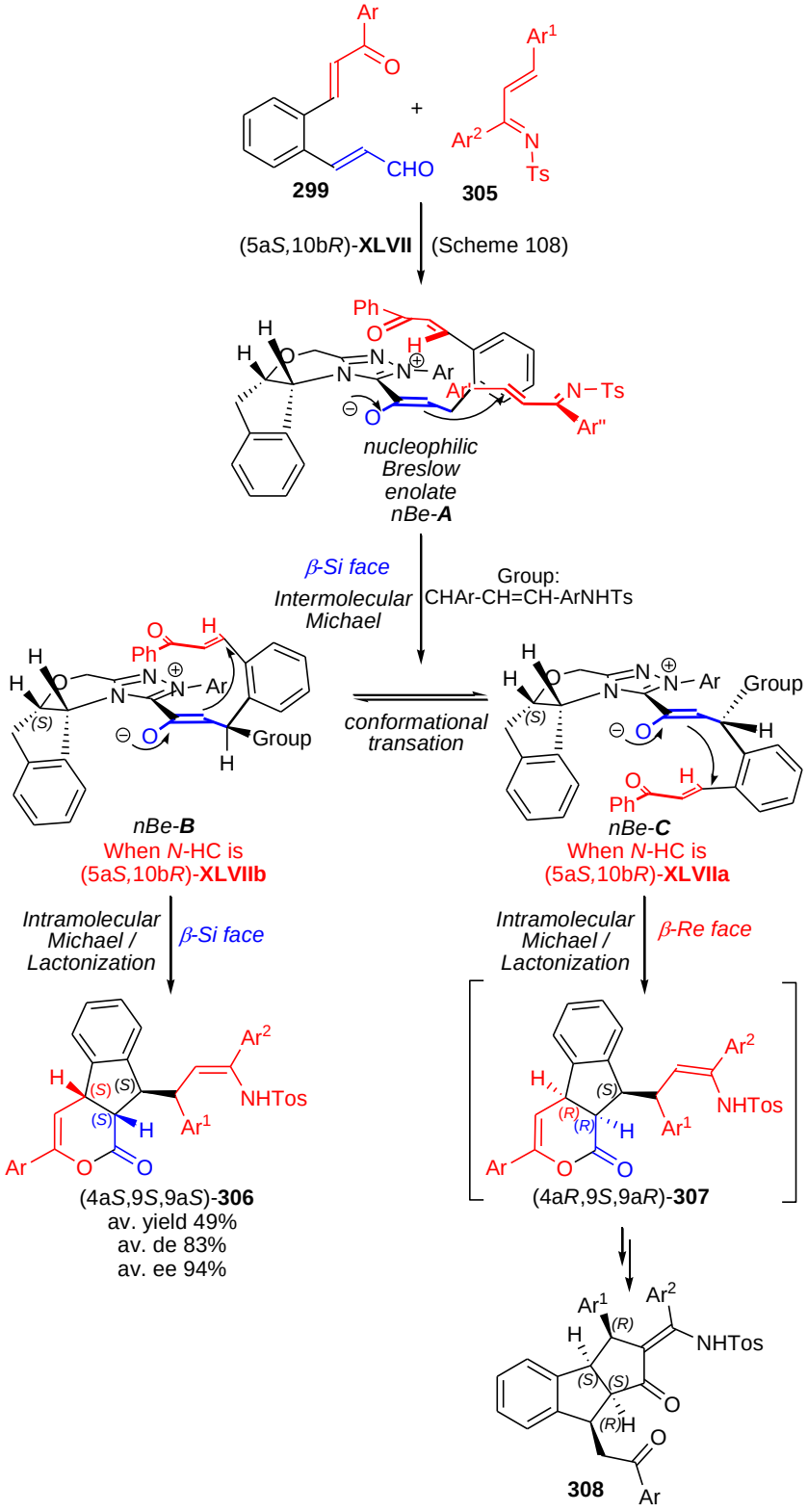
Another version of [intermolecular/intramolecular Michael/lactonization] cascade is the reaction between 2-aroylvinylcinnamaldehydes **299** and α,β-unsaturated imines **305**, catalysed by the *N*-HC derived from (5a*S*,10b*R*)-**XLVII** (Scheme 385).[116]

In the absence of the oxidant, which in the previous reaction affords to an electrophilic Breslow intermediate, now the reaction of **299** with (5a*S*,10b*R*)-**XLVIIb** (Ar= 4-MeO-C_6H_4) gives the *nucleophilic Breslow enolate* **A** [*nBe*-**A**]. This provides an intermolecular Michael addition to the *β-Si* face of the α,β-unsaturated imine **305**. The [*nBe*-**B**] affords the intramolecular 1,4-addition to the *β-Re* face of the electrophilic enone and the product is (4a*S*,9*S*,9a*S*)-**306**, whose absolute configuration was determined by X-ray diffraction analysis

When the same reaction is performed with (5a*S*,10b*R*)-**XLVIIa** (Ar= Mes) as catalyst, the first part of the reaction follows the same pathway with the attack of [*nBe*-**A**] to **305**, but the resulting Breslow enolate assumes the most stable conformation [*nBe*-**C**] in which the repulsion between the interaction between the mesityl and the 2-aroylvinyl group are minimized. Under these circumstances the intramolecular 1,4-addition to the *β-Re* face of the electrophilic enone is preferred and the unstable (4a*R*,9*S*,9a*R*)-**307** is obtained that converts to the stable **308**.[116]

These reactions show how difficult is to rationalize the results in a field in which so many variants can change the stereochemical outcome. This is a limit for planning "*a priori which is the best for what*" but it increases the appeal of an area in which a serendipitous discover is not unexpected.

Scheme 385. Chirality Transfer in the [Intermolecula/Intramolecular Michael/Lactonization] Reaction of 299 with 305, Catalyzed by (5a*S*,10b*R*)-XLVII to Give (4a*S*,9*S*,9a*S*)-306.[116]



This discussion about the various stereochemical results of the reactions catalysed by *N*-HC points out how important is the geometry of the intermediate enolate for the absolute configuration

of the reaction products, and the adequate emphasis put on this argument is our personal homage to the genius of Ronald Breslow.

9. Conclusions

Forty years after a review on "*Heterodiene Syntheses with α,β-Unsaturated Carbonyl Compounds*" (in which the single example known of acid-catalyzed hetero-Diels-Alder cycloaddition was the last argument discussed, and the catalysis with chiral Lewis acids was not consider, simply because, at that time, no examples of enantioselective catalysed Diels-Alder cycloadditions were known) the argument is now re-examined. But forty years of research are more than a geological era, and to write a review on a such extended topic as the synthesis of optically active 3,4-dihydropyran derivatives requires finding definite borders to confine the discussion.

A simple heterocyclic ring with five carbons and one oxygen and no more than three chiral centers was taken by the community of the Organic Chemists and placed on a surgical table to be dissected. The number of modes to dissect the body were several: one single cut, two or more cuts, all were experienced, and on the table remained one, two, or even more than two pieces. This is the retrosynthetic step of the process.

Now, the organic chemists, forgotten the dead body, take the pieces of the former 3,4-dihydropyran derivative and, with art and fantasy, put them together to rebuild the molecule, but with the purpose to create it more beautiful, more sophisticated, more functionalized, more useful for future purposes. And they tried different single surgical seams, the [5+1], the [4+2], the [3+3] assembly modes, and even the transplants were attempted and successfully performed, all in different modes, but each time trying to build a special molecule, different from that of its mirror image. The construction of molecules enantiomerically enriched is not a miracle, it is the pure expression of the extraordinary power of asymmetric synthesis, and an example of enantioselective synthesis of a 3,4-dihydropyran derivative is shown in the abstract.

This is what has been done in these forty years, with an incredible number of devices, the catalysts, and this is what we reviewed in previous pages. We had the best Scientists that gave us the accurate descriptions of the protocols for the success, we tried to read accurately what they did, and we have reported and divulged it.

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The authors declare no competing financial interest

Biographies

Giovanni Desimoni was born in 1936. He received his laurea degree from the University of Pavia. After a research and teaching period at the same university and one year with Alan Katritzky at UEA, in 1975 he joined the Science Faculty at the University of Pavia as a full professor. He was Dean of the Faculty and Director of the Department of Organic Chemistry. His recent research interests concern the development of new catalysts for enantioselective reactions, especially those derived from optically active heterocycles used as chiral ligands, and the understanding of their mechanisms in inducing selectivity. Since 2010 he is Professor emeritus of the University of Pavia.

Giuseppe Faita received his degree in Chemistry in 1986 at the University of Pavia. In 1990 he obtained his Ph.D. at the same university under the supervision of G. Desimoni and he became a researcher in the Desimoni group in the Department of Organic Chemistry. In 2000 he became

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DEDICATION

Dedicated to our friend and colleague Gianfranco TACCONI, author of the original review that was the beginning of this contribution.

Supporting Information.

List catalysts and organocatalysts discussed in the review are reported. This material is available free of charge via the Internet at http://pubs.acs.org

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