UNIVERSITÁ DEGLI STUDI DI PAVIA

DOTTORATO IN SCIENZE CHIMICHE E FARMACEUTICHE XXXI CICLO

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Gold(I)-catalyzed intramolecular enantioselective hydroalkoxylation reaction for the total synthesis of metabolites containing the tetrahydrofuran core

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Tesi di dottorato di
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Alla mia famiglia...

E così ha termine un "aureo" mattino di vita...

SUMMARY

CHAPTER 1: Overview of natural THF-containing metabolites

1.1 Introduction

Several natural products and biologically active compounds present oxygenated five-membered rings as structural motif. In particular, substituted tetrahydrofurans are commonly occurring building blocks found both within terrestrial and marine metabolites. These substances exhibit a wide range of biological activities such as anti-microbial, anti-tumoral, anthelmintic, anti-malarial and anti-protozoal.

For these reasons, over the last decades, considerable efforts have been devoted towards the development of efficient and completely stereoselective strategies for the construction of substituted THF rings.[1]

The most important classes of natural products containing tetrahydrofuran systems are: acetogenins from *Annonaceae*, lignans, marine macrolides and communiols.

1.2 Natural metabolites containing substituted THF moieties

1.2.1 Annonaceous acetogenins[2]

Annonaceous acetogenins (ACGs) represent a group of secondary metabolites isolated from *Annonaceae*, typical plants mainly found in tropical and subtropical areas.

The common framework is generally characterized by an unbranched C_{32} or C_{34} linear chain, with a terminal γ-lactone moiety (Figure 1.1).

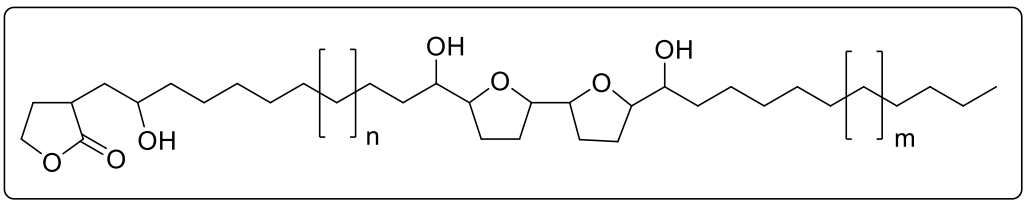


Figure 1.1. General structure of acetogenins

Different types of ACG have been isolated and characterized, and the classification is based on the kind of functional groups present within the chain. In most cases, these substituents

[1] P. Wolfe and M. B. Hay, *Tetrahedron,* **2007**, 63, 261.

[2] A. Bermejo, B. Figadere, M. Polo, I. Barrachina and D. Cortes, *Nat. Prod. Rep*, **2005**, 22, 269.

are oxygenated functions such as hydroxyl groups, ketones, epoxides, tetrahydrofuran rings (THF) and tetrahydropyran rings (THP) but also double and triple bonds were found.

Acetogenins exhibit a wide range of biological activities, in particular some of them possess properties such as anti-cancer, cytotoxic, anti-parasitic, pesticidal, anti-microbial and immunosuppressive agents.

Previous studies revealed that the mechanism of action of acetogenins is based on the ability of these compounds to strongly inhibit the mitochondrial respiratory chain complex I.[3]

The biosynthesis of such metabolites remains still unknown, but a probable biogenetic pathway has been postulated.

At first, the terminal γ-lactone moiety is generated on a long polyunsaturated fatty acid chain, then THF and THP rings are introduced by enzymatic oxidation of specific double bonds, followed by opening and closing reactions.[4]

The extraction and purification of these metabolites were performed by following the common protocol, based on successive solvent extractions with increasingly polar solvents. The separation of all the components of the crude mixture was carried out by preparative HPLC.[5]

On the basis of their general structure and the nature of the substituents, acetogenins are divided into 6 groups:

- Linear acetogenins: these compounds do not show any cyclic system within the chain, except the terminal γ-lactone. They are considered as the biogenetic precursor of epoxy and THF ACGs. Linear acetogenins are divided into 4 subgroups depending on the degr*ee* of unsaturation and hydroxylation of the alkyl chains. These subgroups are: vicinal dihydroxylated and olefinic acetogenins (giganin type), hydroxylated (or ketonic) linear acetogenins (reticulatamol type, Figure 1.2), olefinic and acetylenic acetogenins (muridienin-1 type) and bis-lactonic linear acetogenins (rollicosin type).

[3] R. Tormo, T. Gallardo, M.C. Gonzales and E. Estornell, *Curr. Top. Phytochem.* **1999**, 2, 69.
[4] M. Polo, B. Figadere, T. Gallardo, R. Tormo and D. Cortes, *Phytochemistry*, **1998**, 48, 1087.
[5] L. Zeng, Q. Ye, N.H. Oberlies, G. Shii and J.L. McLaughing, *Nat. Prod. Rep.* **1996**, 13, 275.

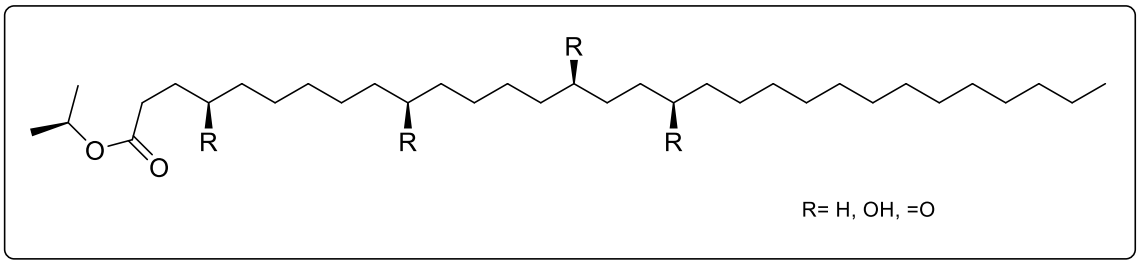


Figure 1.2. Reticulatamol type (linear acetogenins).

- Epoxy acetogenins: they originate from the oxidation of linear and olefinic acetogenins and are characterized by the presence of epoxide rings (Figure 1.3).

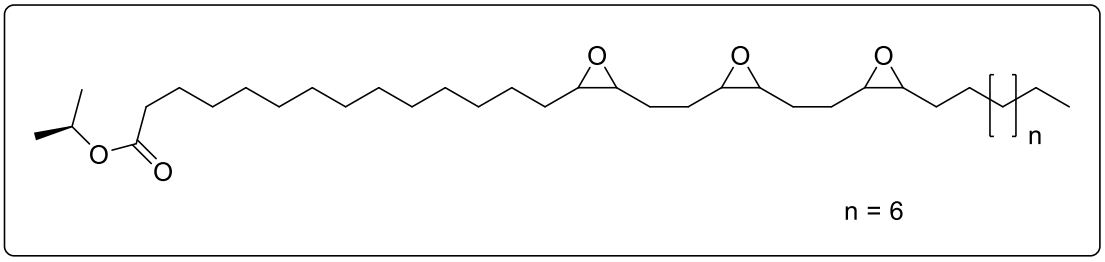


Figure 1.3. Epoxy acetogenins.

- Mono-THF acetogenins: this is the bigger class of acetogenins, all the compounds show a 2,5-disubstituted THF ring, and sometimes a hydroxyl group on the C3 of the THF ring occurs (Figure 1.4).

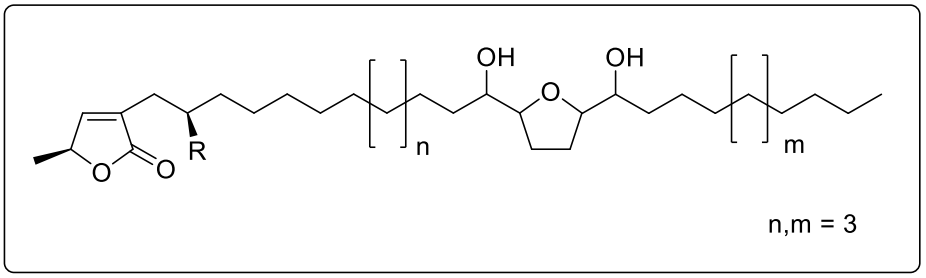


Figure 1.4. Mono-THF acetogenins.

- Bis-THF acetogenins: these compounds possess two THF rings that can be adjacent or not adjacent (Figure 1.5).

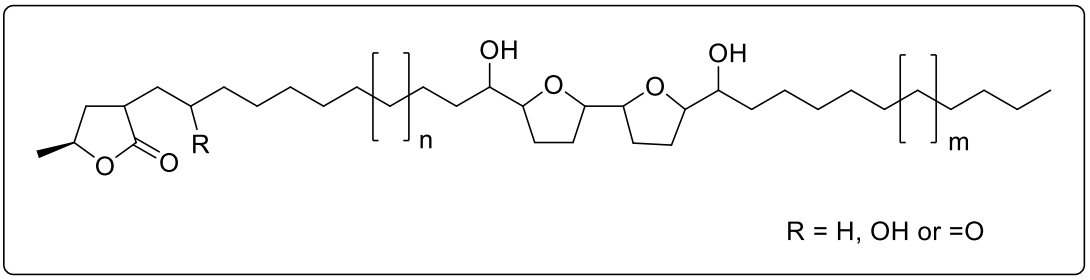


Figure 1.5. Bis-THF acetogenins.

- Tri-THF acetogenins: only one compound, namely Goniocin, is included in this group (Figure 1.6).

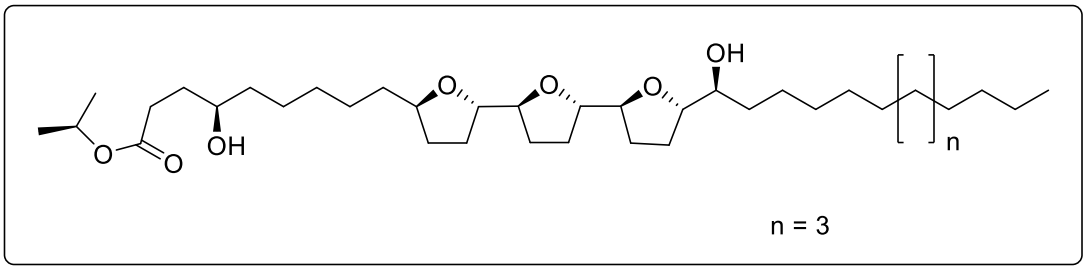


Figure 1.6. Goniocin.

- THP acetogenins: in this class, tetrahydropyran-containing acetogenins are included (Figure 1.7).

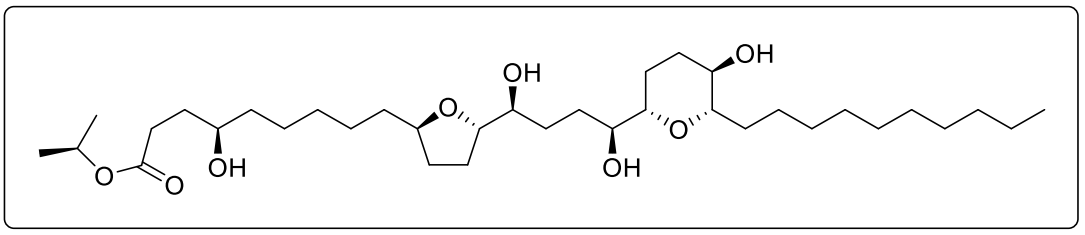


Figure 1.7. THP acetogenins.

1.2.2 Lignans[6]

Lignans represent a large class of secondary metabolites produced by plants. These substances derive from oxidative dimerization of two phenylpropanoid units.

Despite their molecular framework consists only of two simple building blocks (C6-C3), lignans exhibit an enormous structural diversity. Most of them contain at least one

[6] M. Saleem, H. Kim, M. Ali and Y.S. Lee, *Nat. Prod. Rep.* **2005,** 22, 696.

oxygenated five-membered ring, such as substituted tetrahydrofuran moieties [(+)-taxiresinol)][7], γ-butyrolactol [(-)-cubebin][8] and γ-butyrolactone systems [(-)-Pluviatolide][9] (Fig. 1.8).

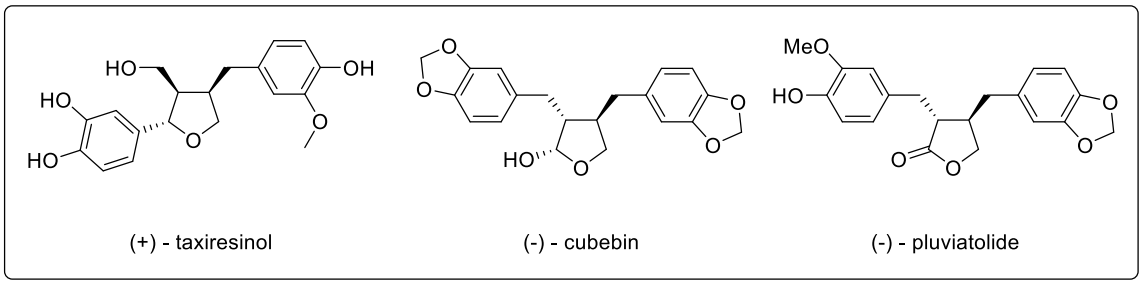


Figure 1.8. Lignans.

Within this class, several compounds showed very important biological activities, in particular anti-cancer, anti-inflammatory, anti-microbial, anti-oxidative and immunosuppressive properties. For this reason, during the last years, several efforts have been taken in order to develop stereoselective total syntheses of such molecules.

1.2.3 Tetrahydrofuran-containing marine macrolides[10]

Marine organisms have produced several structurally diverse secondary metabolites with important biological activities as a defense against various aggressions typical of their environment.

This structural diversity makes marine natural products excellent candidates for the investigation of new bioactive molecules with high pharmacological potential.[11]

A significant number of metabolites have been isolated in the last years from sponges, algae, dinoflagellate and other marine invertebrates, characterized by their structural novelty. Most of them show a very complex chemical structure bearing several oxygenated functionalities.

The determination of biological activity, mechanism of action, and further medical applications of these compounds is few of the main challenges, because their isolation from natural sources often furnishes very small sample amounts.

[7] S.K. Chattopadhyay et al. *Bioorg. Med. Chem.* **2003**, 11, 4945.
[8] K.C.S. Rezende et al. *Revista Brasileira de Farmacognosia*, **2016**, 26, 296.
[9] B. Feringa et al. *J. Org. Chem.* **1994**, 59, 20, 5999.
[10] A. Lorente, J. Merketegi, F. Albericio and M. Alvarez, *Chem. Rev.* **2013**, 113, 4567.
[11] I. Bhatnagar, S.K. Kim, *Mar. Drugs*, **2010**, 8, 2702.

Thus, synthesis is necessary to further development of these molecules not only in terms of their supply, but also in many cases for structural and stereochemical assignments.

Large molecular size tetrahydropyran (THP)-containing polyketide macrolides are a class of marine macrolides with diverse and interesting biological activities, as in the case of Halicondrin B (Figure 1.9), extracted from a rare marine Japanese sponge, *Halicondria okadai*. The anti-cancer agent eribulin[12] (Figure 1.9), a fully synthetic macrocyclic synthetic ketone analogue of Halicondrin B, inhibits cancer cell proliferation by binding tubulin and destabilizing microtubule dynamics.[13] At nanomolar concentrations, eribulin works through an end-poisoning mechanism by inhibiting the growth phase of microtubule dynamic instability in interphase cells. Eribulin was approved by the U.S. Food and Drug Administration on November 15, 2010, to treat patients with metastatic breast cancer who have received at least two prior chemotherapy regimens for late-stage disease.

[12] K.L. Jackson, J.A. Henderson, A.J. Phillips, *Chem. Rev.* **2009**, 109, 3044.
[13] M.A. Jordan, K. Kamath, T. Manna et al. *Mol. Cancer Ther.* **2005**, 4, 1086.

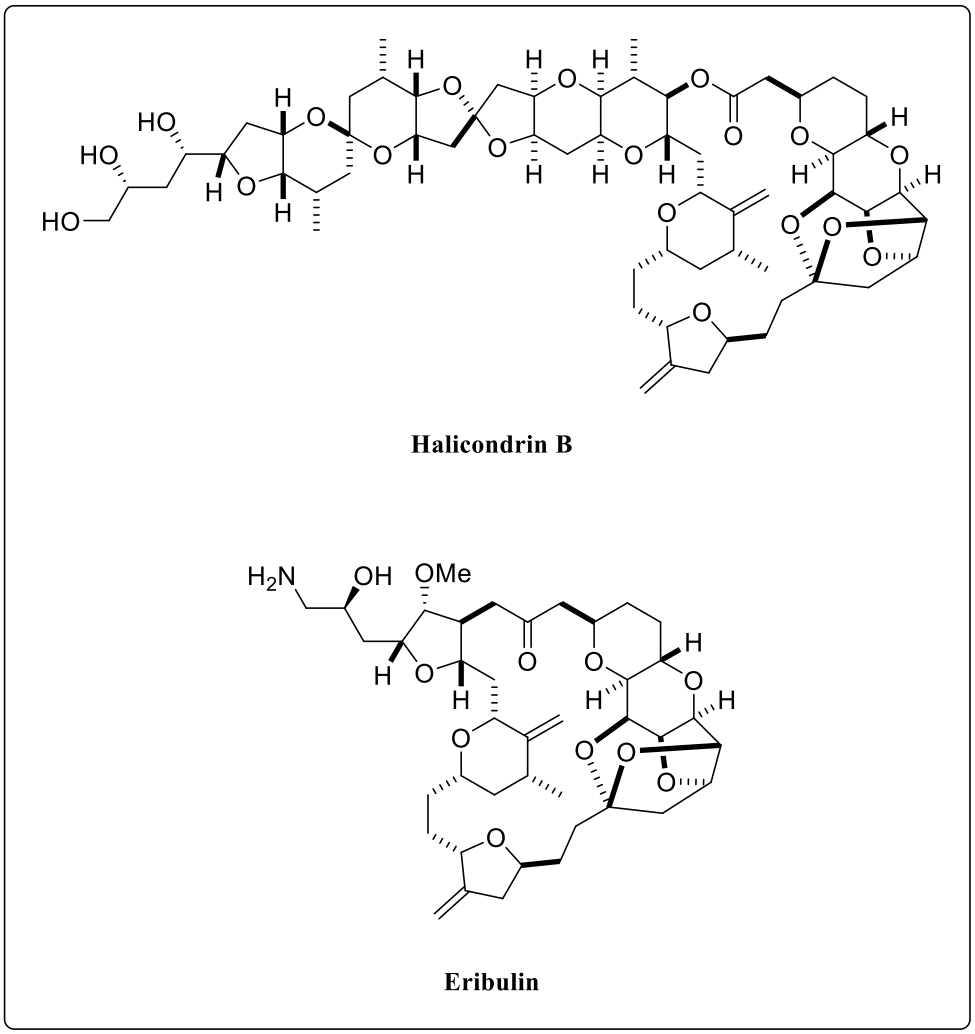


Figure 1.9. Structures of Halicondrin B and Eribulin.

Large molecular size THP-containing macrolides rarely include tetrahydrofuran (THF) rings in their structure.

Nevertheless, some natural compounds are found where both systems are included, such as the pectenotoxins, the family of the halistatins and the above reported eribulin.

More recently, THF rings instead of THP rings, have occurred in structures of new bioactive compounds.

Over the last twenty years more THF containing polyketide macrolides have been described, and their potential as drug candidate has increased exponentially. It is worth mentioning that THF containing macrolides (see Haterumalide NA, Figure 1.10) are often of small molecular weight and less complex than their THP congeners (see Bryostatin, Figure 1.10).

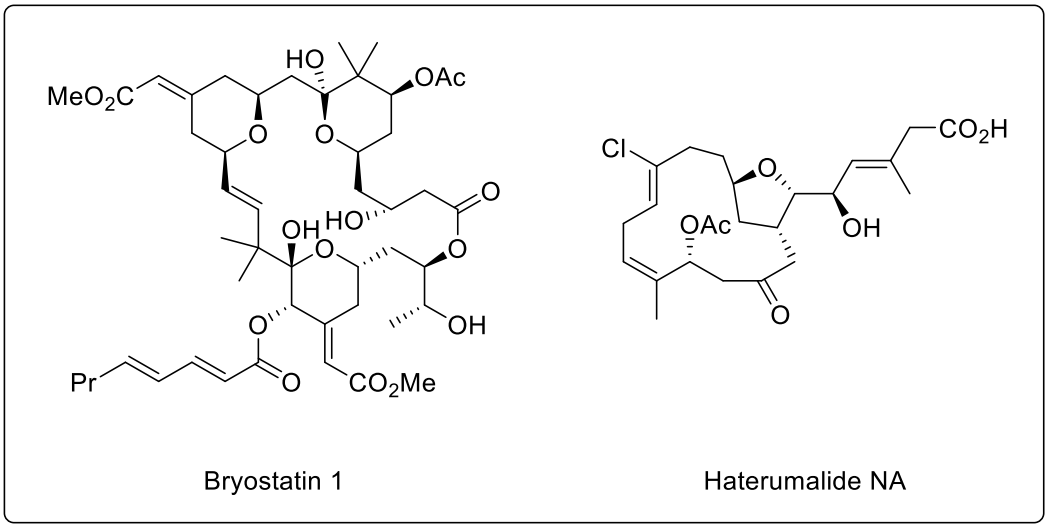


Figure 1.10. Structures of Bryostatin 1 and Haterumalide NA.

1.2.4 Biosynthesis of macrolides

According to their biological origin, metabolites are divided into six classes: ribosomal and non-ribosomal peptides, alkaloids, phenylpropanoids, polyketides, terpenes and steroids, and carbohydrates.

Ribosomal peptides and carbohydrates are primary metabolites: they are fundamental for execution of base activity of the normal life of the organism and they are the simplest structures. The other categories are secondary metabolites, that change from species to species, and they are involved in secondary biological activities. These last categories are characterized by much more complicated biosynthetic pathways that involve many other simpler molecules.[14]

Polyketides are a big class of natural products including fatty acids, polyacetylenes, prostaglandins, macrolides and some aromatic compounds. All these natural products are characterized by their common biosynthetic origin: they are synthetized through the acetate pathway by big proteic complexes called PKS's (polyketide synthase). These proteins catalyze consecutive Claisen condensations in order to build poly-β-ketonic chains that undergo further transformations to give the final products. The simplest method to outline the reaction for the formation of the carbon skeleton is to imagine two identical molecules of acetyl-CoA that condense with a Claisen reaction to give an acetoacetyl-CoA; this reaction is repeated many times, to build a poly-β-ketonic chain (Scheme 1.1). The first

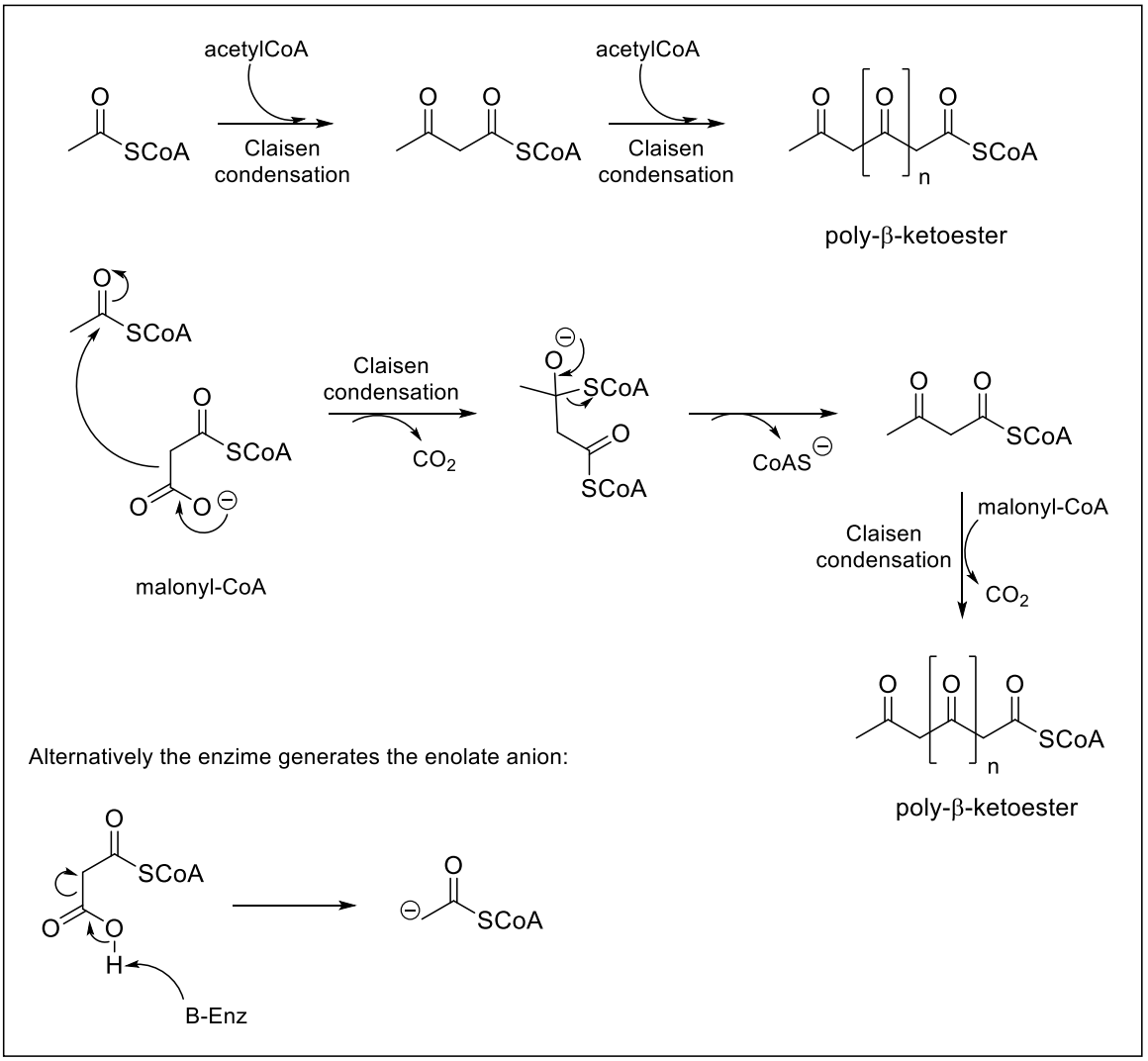
[14] P.M. Dewick, *Medicinal Natural Products: A Biosynthetic Approach*; Wiley: New York, **2001**.

scientist who supposed this mechanism was Arthur Birch in the '50s. He experimentally verified his theory by using ^{14}C marker in a culture of an organism that produces polyketides.[15]

However, the real mechanism of the reaction is a little more complex: initially a carboxylation of acetyl-CoA to malonyl-CoA takes place. In this way, there is an increase of the acidity of the α hydrogen of the carboxylic group, in order to provide a better nucleophile for the Claisen condensation. It is important to underline that in the biosynthesis, the derivate of the acylation of the malonic acid is not observed, nor any atom resulted from the ^{14}C marked bicarbonate is incorporated. Thus, the carboxylic group introduced in the malonyl-CoA is immediately lost by decarboxylation during the condensation. Another hypothesis is that the decarboxylation is essential in order to generate the acetyl enolate anion without using a strong base.

Different families of PKS synthetize various types of polyketides; currently, the knowledge concerning the relation betw*ee*n the structure and the catalytic mechanism of the PKSs, allows to obtain many variants of the original natural products through the genetic manipulation of the synthetic processes.[16] However, the basic mechanism is the same: the chain is built through consecutive Claisen condensations that use malonyl-CoA (or methylmalonyl-CoA) as fundamental unit of extension, and the acetyl-CoA (or propionyl-CoA) as starting unit. Every condensation produces a β-ketoester that can be, or not, reduced before the following step. The PKS's have different domains showing different functions in the synthetic chain: the ketosynthetic domain (KS), the ketoreducting domain (KR), the dehydrating domain (DH), enolreducting domain (ER) and acyltranferasing (AT).

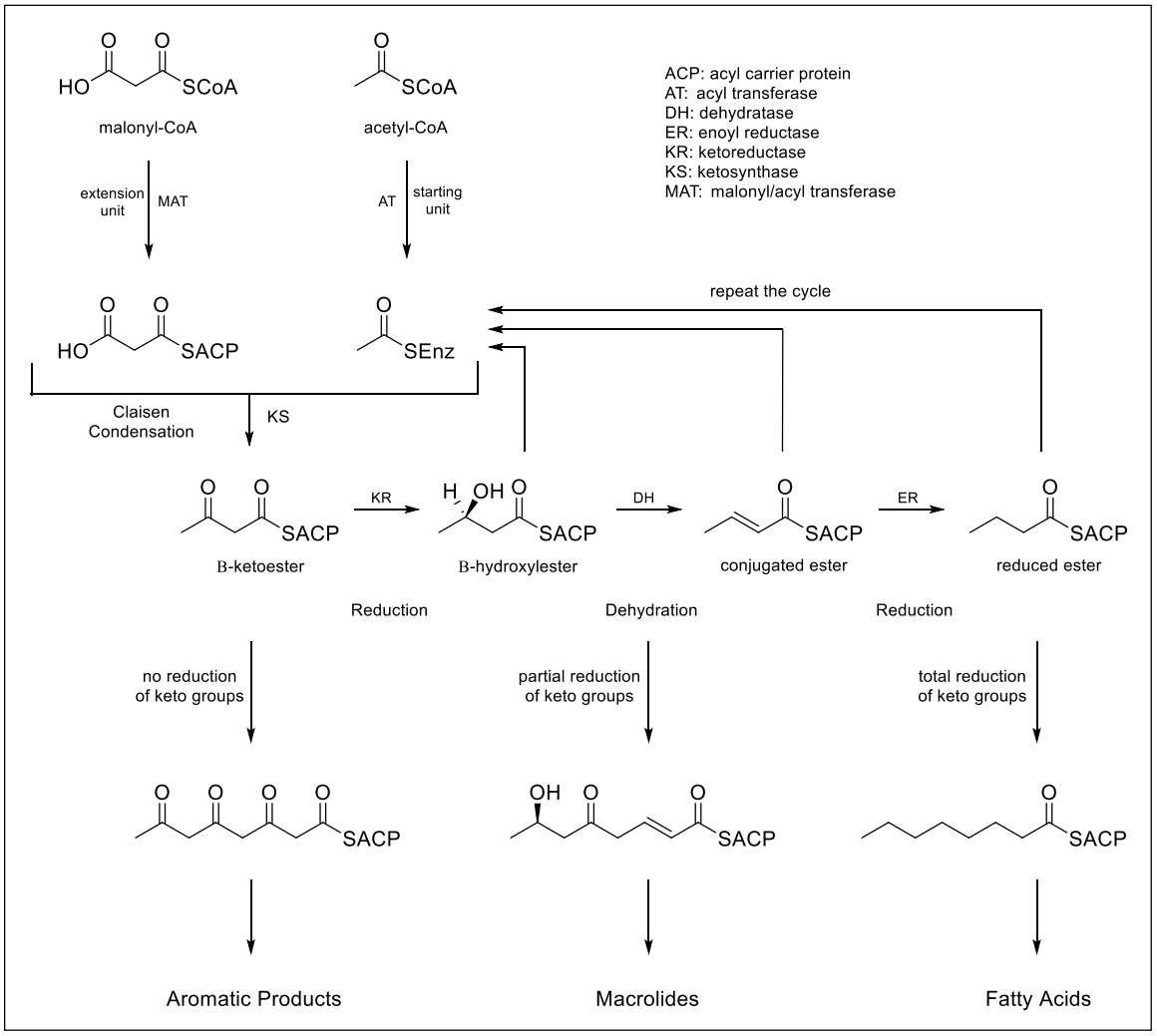
[15] A.J. Birch, P.A. Massy-Westropp, C.J. Moye, *Aust. J. Chem.* **1955**, 8, 539.
[16] C.R. Hutchinson, R. McDaniel*, Curr. Opin. Investig. Drugs*, **2001**, 2, 1681.



Scheme 1.1. Formation of poly-β-ketoester.

If no reduction of carbonyl functions takes place, the product is a poly-β-ketoester with alternated methylene and ketonic functions. As reported in Scheme 1.2, this highly reactive intermediate can undergo enzyme-catalyzed intramolecular cyclizations, which lead to aromatic products. On the contrary, if all the keto groups are reduced, the product is a fatty acid. In this case, the reduction proc*ee*ds through thr*ee*-steps: reduction of the ketone to alcohol, dehydration to a conjugated ester and reduction of the double bond. On the other hand, if the β-polyketo chain undergoes a partial reduction of the carbonylic functions, the result is a carbon skeleton where, hydroxyl, double bond, methylene and carbonyl functions are alternated. This is the case of macrolides.

The reduction degr*ee* of the product and the distributions of the various functions depend on how active the domains of the enzyme are during the process.



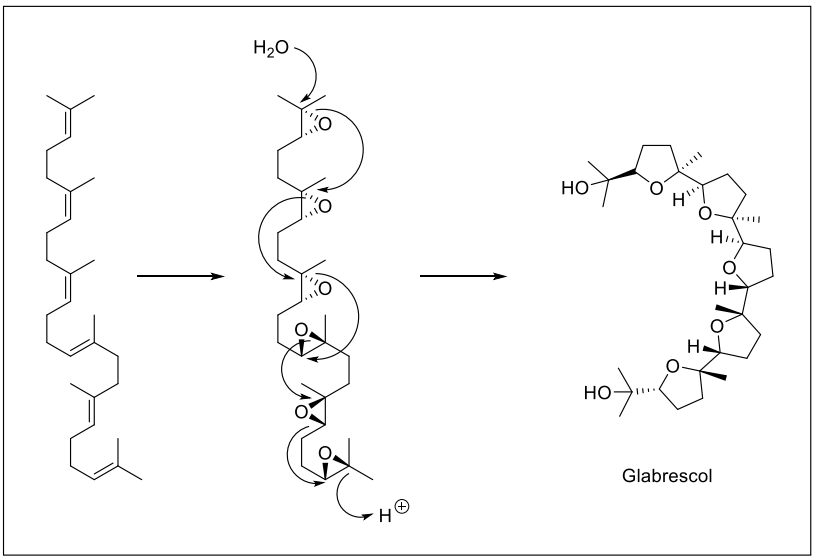
Scheme 1.2. PKS mechanism of action.

It is possible to distinguish thr*ee* different groups of PKS's: the type I are big multifunction proteins with individual functional domains and they are found in bacteria and fungi, the type II are composed of an individual multifunction protein complex and they are found in bacteria, while the type III are homodimeric proteins and they are found in plants, bacteria and fungi. The PKS's type I can be further divided in two more classes, iterative and non-iterative: the first group uses periodically their functional domains to synthetize a polyketide, while the second group has a dedicated active site for each step. The PKS's type II are non- iterative. Both those systems use ACP (acyl carrier protein) as acyl-CoA activating agent. The type I enzymes catalyze the macrolide synthesis, to whom little variation of the single steps bring a high structural diversity. Type II PKS catalyzes the synthesis of aromatics polyketides, while flavonoids and stilbenes are synthetized by type III enzymes. The last one uses esters of the CoA instead of the ACP and only one active site is used for a series of decarboxylations, condensations and cyclizations.

Despite the differences observed in the molecular structure of the PKS's in the kind of extension units employed, the chain synthesis is substantially the same. All the natural products cited are synthetized by the acetate pathway (apart from the flavonoids, that derive as from the acetate pathway as from the shikimate pathway, in fact the starting unit involved is the cumaryl-CoA, a shikimate pathway metabolite).

1.2.5 Biosynthetic pathways toward tetrahydrofuran rings

The cyclic ether ring formation is a normal modification in the post-PKS activity. The synthesis of these rings is not direct, but nature has developed different methods to obtain these structures with high efficiency and, if necessary, with high enantioselectivity and regioselectivity.[17] Some enzymes, like the peroxidase and the alkene monooxydase (AMO), show the property to build epoxides from double bonds. The consecutive opening of these epoxide rings results in the cyclic ethers. In some cases, this process happens with a "cascade" mechanism, and leads to the formation of polycyclic natural products: this is the case of the biosynthesis of Glabrescol[18] (Scheme 1.3).

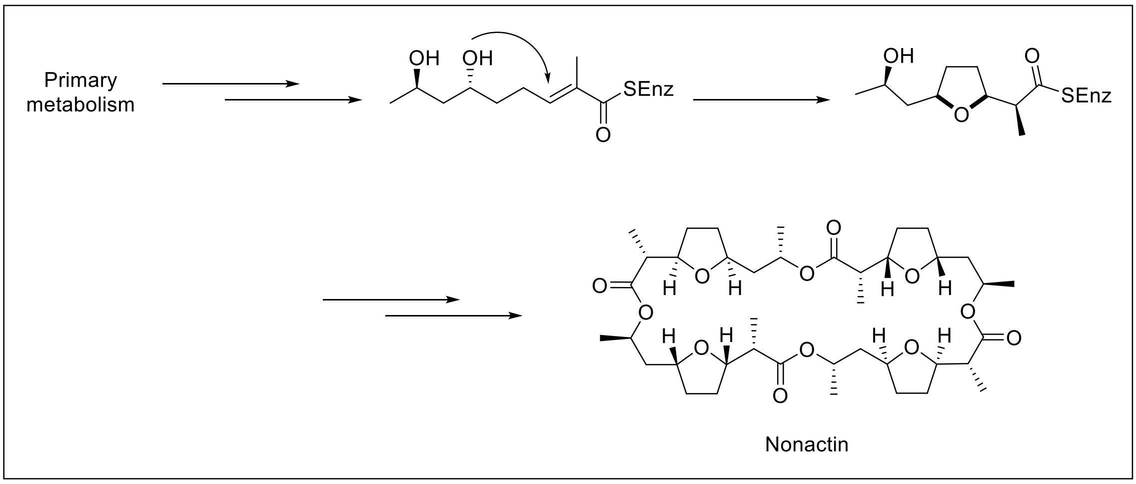


Scheme 1.3. THF rings' biosynthesis by epoxides opening.

Another approach to the synthesis of oxygenated heterocycles is the addition of a hydroxyl group to an activated double bond, a Michael enantioselective intramolecular addition, like

[17] P. Dominguez de Maria, R.W. Van Gemert, A.J. Straathof, U. Hanefeld, *Nat. Prod. Rep.* **2010**, 27, 370.
[18] Y. Morimoto, T. Iway, T. Kinoshita, *J. Am. Chem. Soc.* **2000**, 122, 7124.

in the case of the anti-cancer agent Nonactine[19] (scheme 1.4).



Scheme 1.4. THF rings' biosynthesis by intramolecular Michael addition.

1.2.6 Amphidinolides[20]

Amphidinolides are members of a secondary metabolites class isolated from *Amphidinium sp*.

Despite around forty members of this big class of macrolides have been isolated up to 2010, only 15 of them show an additional fused or bridged THF in the macrolactone framework. Typical features of such molecules are the presence of exomethylene units, polyene side chains and oxygenated five-membered rings.

One of the most interesting members of Amphidinolides is Amphidinolide C that exhibits strong cytotoxicity in the nanomolar range against murine lymphoma L1210 (IC_{50} = 5,8 ng/mL) and human epidermoid carcinoma KB cells in vitro (IC_{50} = 4,6 ng/mL).

Figure 1.11 reports the structures of some of the most important amphidinolides.

[19] A. J. Woo, W.R. Strohl, N.D. Priestley, *Antimicrob. Agents Chemoter.* **1999**, 43, 1662.

[20] J. Kobayashi, *J. Antibiot.* **2008**, 61, 271.

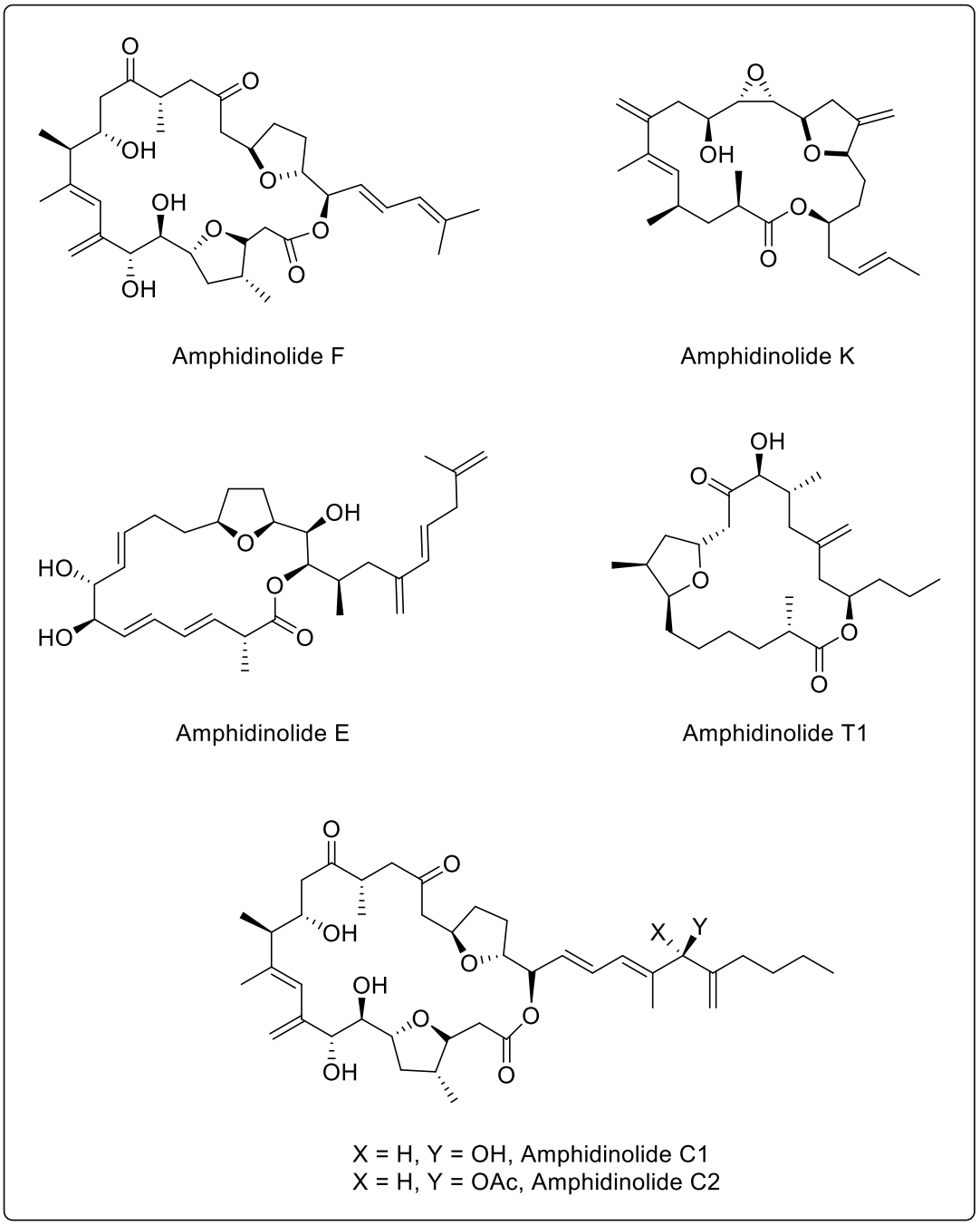


Figure 1.11. Some examples of THF-containing amphidinolides.

1.2.7 Haterumalides, Oocidin A and Biselides[21]

Haterumalides is a group of chlorinated macrolides isolated in 1999 from an Okinawan sea sponge of the species *Ircinia* and Okinawan ascidian *Lissoclinum* sp. The most important member of this class is Haterumalide NA (Figure 1.4), that showed strong cytotoxicity

[21] K. Ueda, Y. Hu, *Tetrahedron Lett.* **1999**, 40, 6305.

against leukemia cell lines.

Oocydin A is a natural diastereomer of Haterumalide NA, which was isolated from the South American epiphyte *Serratia marcescens*, while Biselides are oxygenated analogs of Haterumalides that were extracted from the Okinawan ascidian *Didemnidae sp*.

From a structural point of view, all these compounds possess intriguing moieties in their complex backbone, for example the THF ring bridged with a macrocyclic lactone, a *Z*-chlorovinyl function, two allylic alcohols and several stereogenic centers.

1.2.8 Caribenolide I[22]

Caribenolide I is an interesting marine secondary metabolite obtained from cultured cells of *Amphidinium sp*. From a pharmacological point of view it is considered as a cytotoxic agent against the human colon carcinoma cell line (HCT 116) and it was found to be 100 times more potent than amphidinolide B.

It shows a new type of macrocyclic lactone, which contains one α-methylidene epoxide, one disubstituted THF, one tetrasubstituted THP ring, one keto group, one *E*-double bond, four hydroxyl groups and one butyl lateral chain.

1.2.9 Communiols

Communiols represent a class of metabolites isolated for the first time in 2004 by Y. Che and co-workers[23] while studying the culture broth of Podospora Communis, a dung-colonizing fungus belonging to the class of coprophilous fungi.

Four compounds, called Communiols A-D, managed to be isolated through inverse phase HPLC analysis. Among those, Communiol A-C are of particular interest owing to their biological activities and related chemical structures.[24]

In this context, all of the thr*ee* molecules possess thr*ee* stereocenters, which are respectively *5S*, *7R*, *8S* in the case of Communiols A and B and *3R*, *5R*, *6S* in the case of Communiol C, determined by Kuwahara and Enomoto after a synthetic study, which led to a revision of the chemical assignments proposed by Che.[25]

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[22] I. Bauer, L. Maranda, K.A. Young, Y. Shimizu, C. Fairchild, L. Cornell, J. Macbeth, S. Huang, *J. Org. Chem.* **1995**, 60, 1084.

[23] Y. Che, J.B. Gloer, J.A. Scott, D. Malloch, *Tetrahedron Lett.* **2004**, 45, 6891.

[24] Y. Che, A. Araujo, J.B. Gloer, J.A. Scott, D. Malloch, *J. Nat. Prod.* **2005**, 68, 435.

[25] S. Kuwahara and M. Enomoto, *Tetrahedron Lett.* **2005**, 46, 6297.

More interestingly, the Communiols A-C are characterized by the presence of a 2,4-disubstituted THF system (Figure 1.12), an unusual structural unit for this type of natural metabolites.

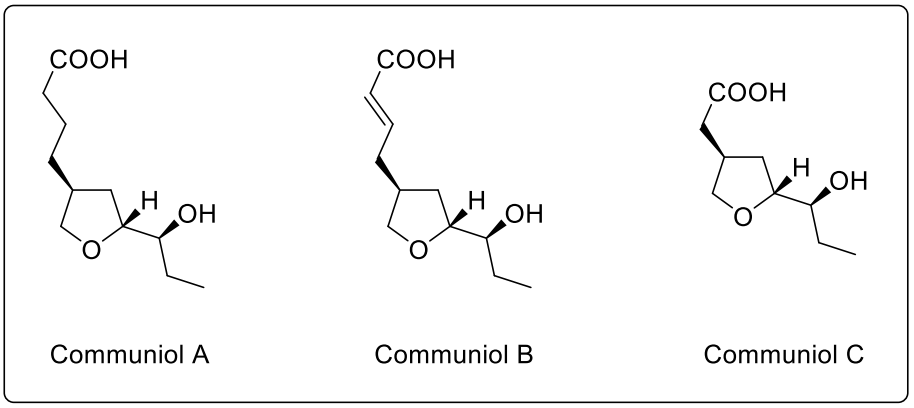


Figure 1.12. Communiols A-C.

In vitro studies established that these compounds possess a remarkable antibacterial activity against *Bacillus subtilis* and *Staphylococcus aureus*.

CHAPTER 2: Stereoselective syntheses of tetrahydrofurans

Due to the importance of biologically active compounds containing oxygenated five-membered rings, over the last decades considerable efforts have been devoted towards the development of stereoselective strategies for the construction of substituted tetrahydrofuran systems.[26]

In this section, the attention will be focused on those methods involving the formation of the C- O bond as key step (except for the nucleophilic capture of oxocarbenium ions that involves a C-C bond formation), since they can be considered inherent in the methodology developed in this PhD thesis, which will be described in the next chapters.

The strategies reported in literature can be summarized in the following list:

- Nucleophilic substitution processes
- Nucleophilic capture of oxocarbenium ions
- Conjugate addition/anion capture
- Oxidation of alkenes, diene and polyenes
- Alkene carboetherification
- Ring closure via allyl transition metal intermediates

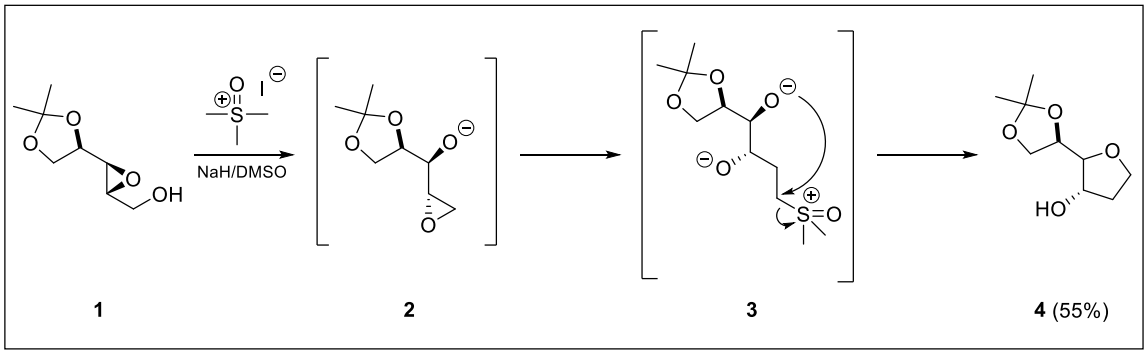
2.1 Nucleophilic substitution processes

Nucleophilic substitution reactions have been employed in several strategies for stereoselective THF ring construction. Most of them involve intramolecular S_N2 processes betw*ee*n a hydroxyl group and a tethered leaving group, for example halides or sulfonates. Scheme 2.1 shows that by treating compound **1** with trimethylsulfoxonium iodide under basic conditions,[27] a Payne rearrangement of epoxide **2** takes place followed by nucleophilic attack of a sulfoxonium ylide to give **3**, which subsequently undergoes S_N2 ring closure to afford hydroxytetrahydrofuran **4**. Excellent results were obtained with

[26] P. Wolfe and M.B. Hay, *Tetrahedron*, **2007**, 63, 261.
[27] J.M. Schomaker, V.R. Pulgam, B. Borhan, *J. Am. Chem. Soc.* **2004**, 126, 13600.

epoxides bearing ether substitution at C4, C5 or C6.

Most of the substrates employed in the nucleophilic substitution approaches come from the natural chiral pool and contain all the stereocenters of the product.

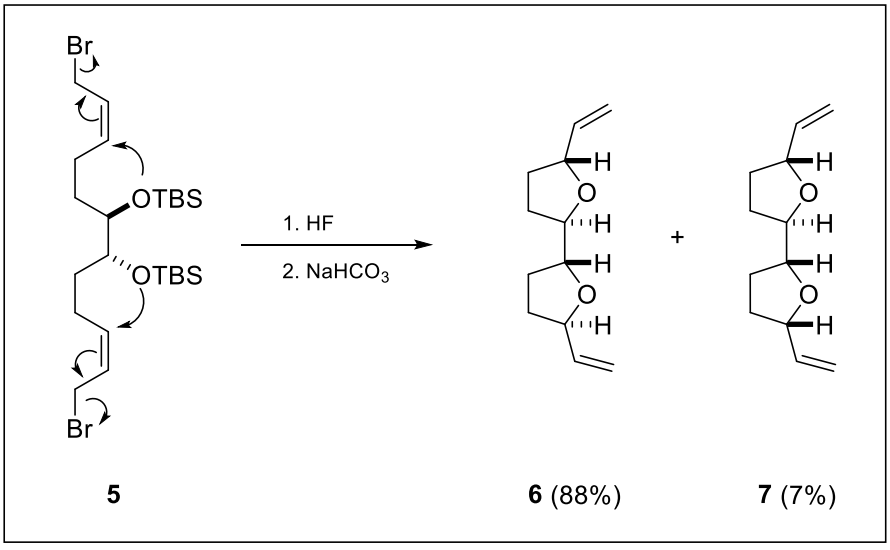


Scheme 2.1. Borhan's work in 2004.

However, some examples of approaches in which stereocenters are generated from achiral substrates have also been reported in literature.

Zhao[28] reported the use of a double S_N2' reaction to generate 2-vinyltetrahydrofurans with installation of a new stereocenter on each newly formed ring (Scheme 2.2).

The double cyclization of **5** proc*ee*ds with 13:1 diastereoselectivity and afforded the major 2,5-*trans*-2,5-*trans* isomer **6** in 88% yield.



Scheme 2.2. Zhao's work in 1999.

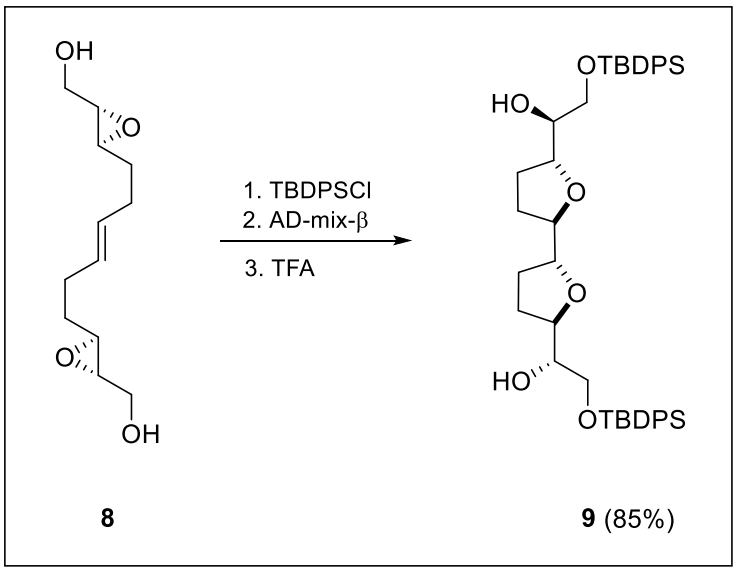
[28] P. Li, J. Yang, K. Zhao, *J. Org. Chem.* **1999**, 64, 2259.

According to the authors, hydrogen bonding betw*ee*n hydroxyl groups may play an important role to determine the diastereoselectivity.

Another way to generate oxygenated rings through substitution processes is represented by intramolecular addition of alcohols to epoxides.

Different methods for *in situ* generation of epoxide rings have been carried out, including biocatalytic epoxidations, transition metal-catalyzed epoxidations and S_N2 epoxide formations from 1,2 diol derivatives. Cascade reactions have also been reported, in which an alkene containing two epoxide rings undergoes dihydroxylation followed by double cyclization.

For example, the bis-tetrahydrofuran core found in several acetogenins (see Chapter 1, Figure 1.1), can be achieved by TBDPS-protection and Sharpless asymmetric dihydroxylation of **8**, followed by addition of trifluoroacetic acid. Compound **9** is obtained as single diastereoisomer in 85% yield[29] (Scheme 2.3).



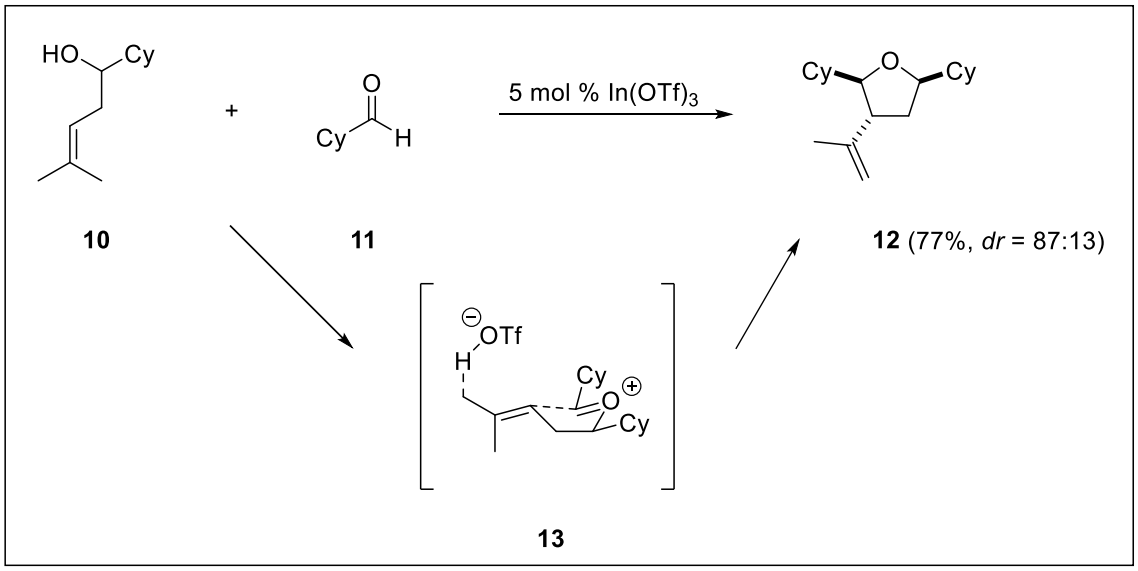
Scheme 2.3. Ye's work in 1996.

2.2 Nucleophilic capture of oxocarbenium ions

Several approaches towards the stereoselective construction of tetrahydrofurans are characterized by generation of reactive oxocarbenium ion intermediates that undergo intramolecular capture by a tethered nucleophilic alkene.

[29] T.R Hoye, Z. Ye, *J. Am. Chem. Soc.* **1996**, 118, 1801.

For example, Scheme 2.4 shows that tetrahydrofuran **12** can be achieved in 77% yield, with 87:13 dr through $In(OTf)_3$-mediated coupling of alcohol **10** and aldehyde **11**, as reported by Loh.[30] Oxocarbenium ion **13** is the intermediate of the reaction. The stereoselectivity observed is the consequence of the pseudoequatorial orientation of the cyclohexyl substituents in the transition state (Scheme 2.4).



Scheme 2.4. Loh's work in 2001.

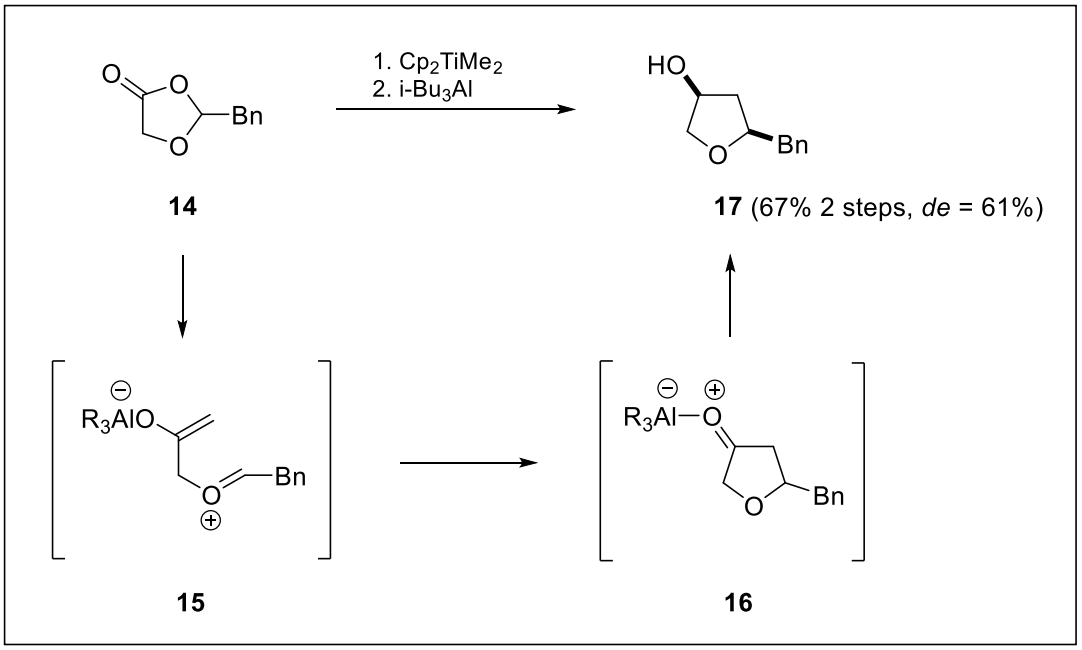
Petasis[31] has described the conversion of substituted 1,3-dioxolan-4-ones to tetrahydrofuran products through methylenation and Lewis-acid mediated rearrangement.

Modest stereoselectivity has been achieved when compound **14** was treated with dimethyltitanocene followed by triisobutylaluminium to give tetrahydrofuran **17** (Scheme 2.5).

The reaction proc*ee*ds via rearrangement of oxocarbenium ion **15** followed by *in situ* reduction of the resulting trialkylaluminium-ketone complex **16**.

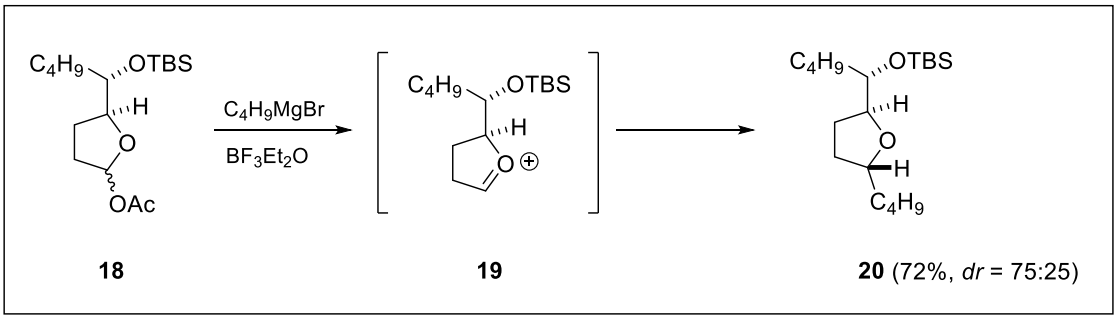
Moreover, oxocarbenium ions derived from γ-lactol derivatives have been widely employed for the stereoselective synthesis of THF rings, because they can undergo addition of nucleophiles like Grignard reagents and organozinc species.

[30] T.P. Loh, Q.Y. Hu, K.T. Tan, H.S. Cheng, *Org. Lett.* **2001**, 3, 2669.
[31] N.A. Petasis, S.P. Lu, *J. Am. Chem. Soc.* **1995**, 117, 6394.



Scheme 2.5. Petasis' work in 1995.

A useful example of such strategy is the one reported in Scheme 2.6,[32] where acetoxytetrahydrofuran **18** was converted to substituted ring **20** in 72% yield and a diastereomeric ratio of 75:25. Reaction conditions involved BF_3•Et_2O and butylmagnesium bromide.



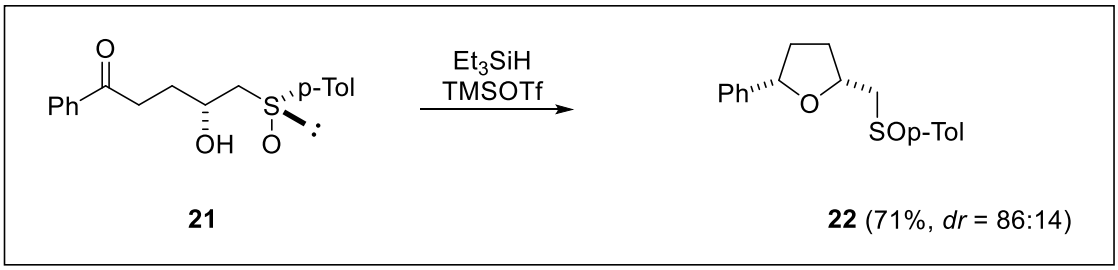
Scheme 2.6. Figadere's work in 2002.

The example illustrated in Scheme 2.7 describes a *cis* selective asymmetric synthesis of a 2,5- disubstituted tetrahydrofuran system, involving the reduction of an oxocarbenium ion generated *in situ* from a γ-hydroxyketone bearing a sulfoxide function.[33]

The enantiopure substrate **21** is obtained by addition of the lithium anion deriving from [*(S)-R*]-methyl-*p*-tolylsulfoxides to succinic anhydride and subsequent conversion of the

[32] X. Franck, R. Hocquemiller, B. Figadere, *Chem. Comm.* **2002**, 160.
[33] M.C. Carreno, R. Des Mazery, A. Urbano, F. Colobert, G. Solladie, *J. Org. Chem.* **2003**, 68, 7779.

resulting carboxylic acid to ketone.

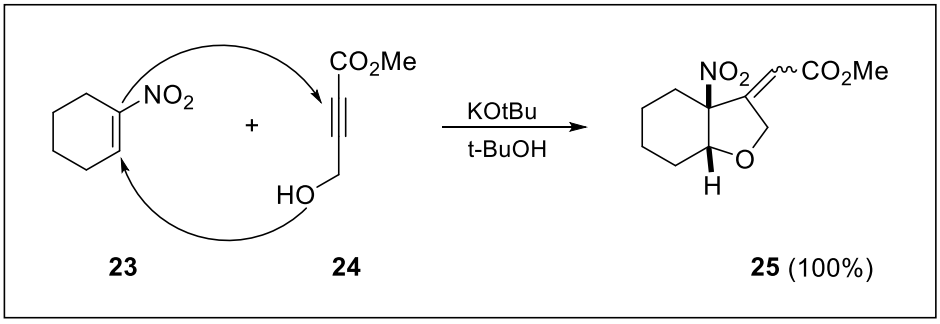


Scheme 2.7. Solladie's work in 2003.

2.3 Conjugate addition /anion capture

Several stereoselective methods for THF ring construction reported in literature showed as key step a tandem conjugate addition of an allylic or propargylic alcohol to a Michael acceptor resulting in the capture of the intermediate stabilized anion. Nitroalkenes were widely used as electrophilic acceptors within this approach, followed by trapping via a second conjugate addition, radical cyclization or dipolar cycloaddition.

Scheme 2.8 reports that treatment of nitroalkene **23** with propargylic alcohol **24** in the presence of tBuOK, affords tetrahydrofuran **25** quantitatively as a mixture of *Z/E* olefin.[34]

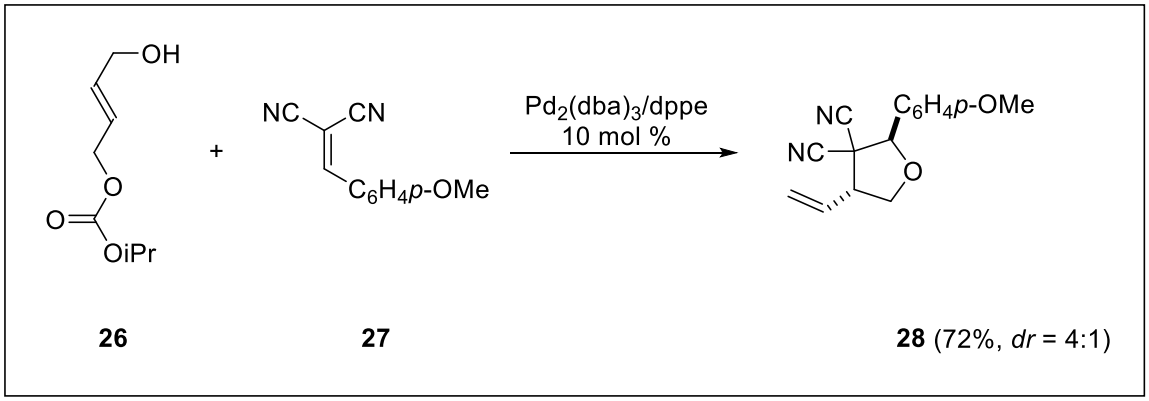


Scheme 2.8. Ikeda's work in 1996.

Yamamoto employed Pd-catalyzed reaction of allylic alcohols containing allylic carbonate functionality at C4 with alkylidene malonate derivatives for the construction of highly substituted 3-vinyl-THF derivatives. The outcomes showed high yields but moderate levels of stereocontrol.

[34] T. Yakura, T. Tsuda, Y. Matsumura, S. Yamada, M. Ikeda, *Synlett*, **1996**, 985.

For example, treatment of allylic alcohol **26** with compound **27** in the presence of a Pd-dppe catalyst provided THF **28** in 72% yield and 4:1 *dr* (Scheme 2.9).[35]



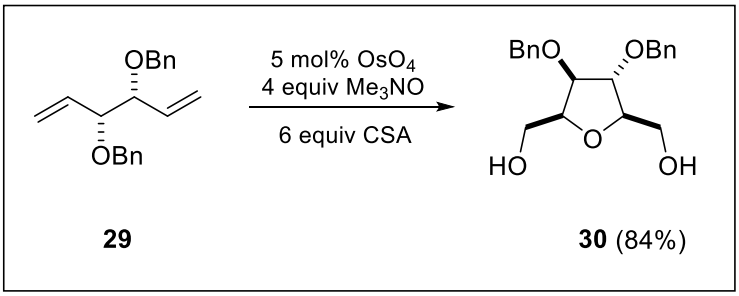
Scheme 2.9. Yamamoto's work in 2001.

2.4 Oxidation of alkenes, dienes and polyenes

The oxidative cyclization of 1,5-dienes to hydroxylated tetrahydrofuran derivatives is another way to achieve polysubstituted tetrahydrofuran systems that are often employed for the synthesis of complex molecules.

An issue concerning this approach is of course the use of stoichiometric amount of highly toxic strong oxidant such as $KMnO_4$ and OsO_4. Anyway, during the last years several efforts have been devoted to the development of catalytic version of these protocols.

For example, Donohoe has reported (Scheme 2.10) the conversion of **29** into **30** in 84% yield as a single diastereoisomer, by involving catalytic OsO_4 and excess trimethylamine N-oxide under acidic conditions.[36]

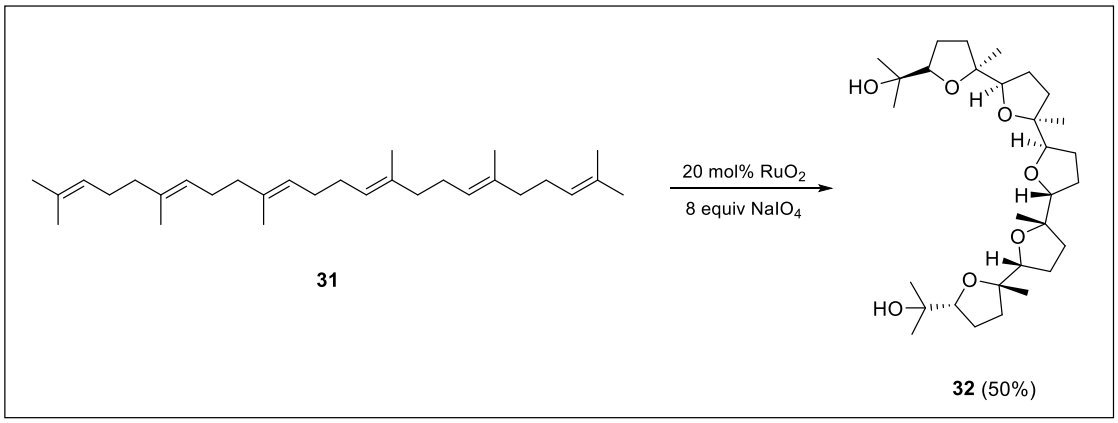


Scheme 2.10. Donohoe's work in 2003.

[35] M. Sekido, K. Aoyagi, H. Nakamura, C. Kabuto, Y. Yamamoto, *J. Org. Chem.* **2001**, 66, 7142.
[36] T.J. Donohoe, S. Butterworth, *Angew. Chem. Int. Ed.* **2003**, 42, 948.

Also the stereoselective construction of bis-, tris- and penta-THF systems has recently been reported.

An impressive example of such strategy (Scheme 2.11) is the RuO_4-catalyzed oxidation of squalene **31**,[37] that leads to penta-THF **32** in 50% yield. It's very intriguing that during the reaction, 12 bonds and 10 stereocenters are generated in a single step.



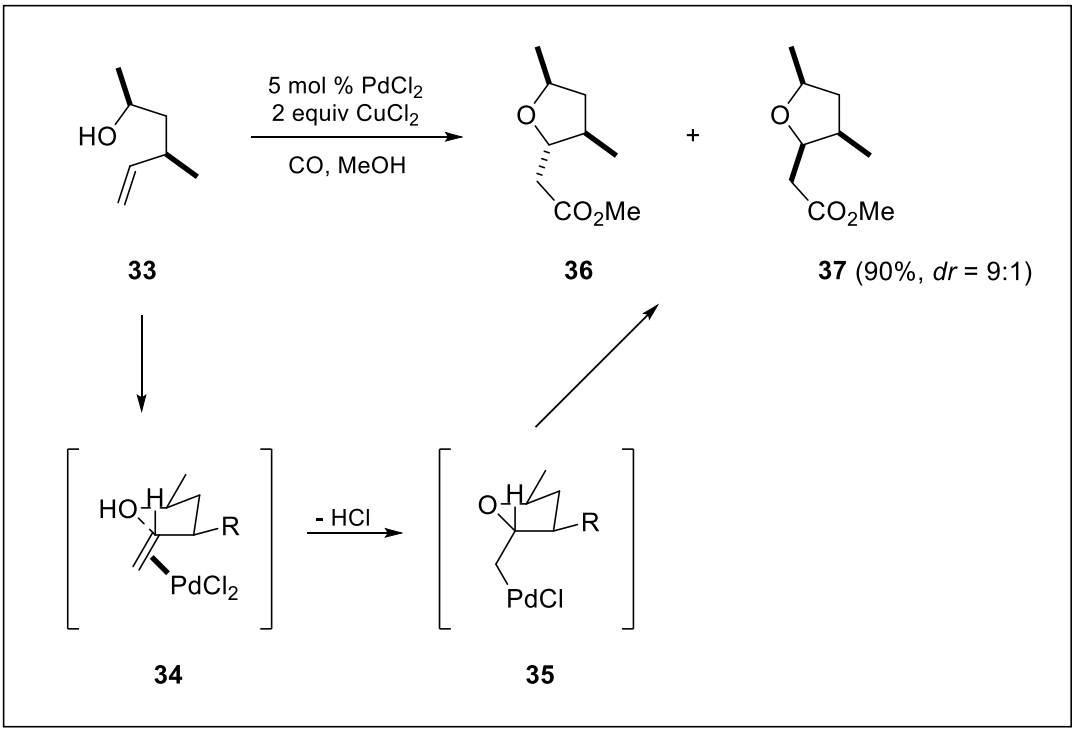
Scheme 2.11. Bifulco's work in 2005.

2.5 Alkene carboetherifications

Reactions that generate both a carbon-oxygen and a carbon-carbon bond are much less common.

A strategy based on a Pd-catalyzed Wacker-type carbonylation reaction of unsaturated alcohols has been developed by Semmelhack[38] and is reported in Scheme 2.12. Treatment of compound **33** with a catalytic amount of $PdCl_2$ in the presence of an excess of $CuCl_2$, under a CO atmosphere in methanol, results in a 9:1 mixture of **36** and **37** in 90% yield.

[37] T. Caserta, V. Piccialli, L. Gomez-Paloma, G. Bifulco, *Tetrahedron*, **2005**, 61, 927.
[38] M.F. Semmelhack, C. Bodurow, *J. Am. Chem. Soc.* **1984**, 106, 1496.



Scheme 2.12. Semmelhack's work in 1984.

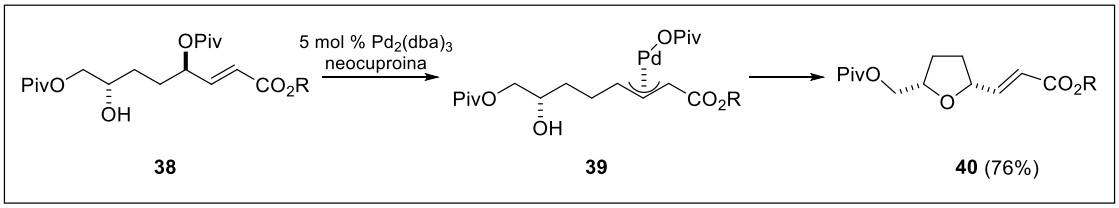
As reported in Scheme 2.12, this reaction leads to ring closure and installation of ester functionality at C1' position in one step through activation of the alkene by the metal to give **34**, followed by nucleophilic attack of the tethered alcohol resulting in **35**. The corresponding alkylpalladium complex then undergoes CO insertion and reductive elimination to give the tetrahydrofuran products **36** and **37**.

2.6 Ring closure via allyl transition metal intermediates

Several stereoselective tetrahydrofuran syntheses are based on a strategy involving nucleophilic capture of intermediate allyl transition metal complexes. Highly diastereoselectivity and enantioselectivity have been achieved when chiral enantiopure catalysts have been used. For example, Rein[39] has reported the construction of THF **40** (Scheme 2.13) in 76% yield as a single diastereoisomer via Pd-catalyzed intramolecular allylic alkylation of compound **38**.

In contrast to S_N2 allylation reactions, the Pd-catalyzed allylation occurs with complete retention of stereochemistry, as both the generation and trapping of the allylpalladium complex proc*ee*d with inversion of configuration (Scheme 2.13).

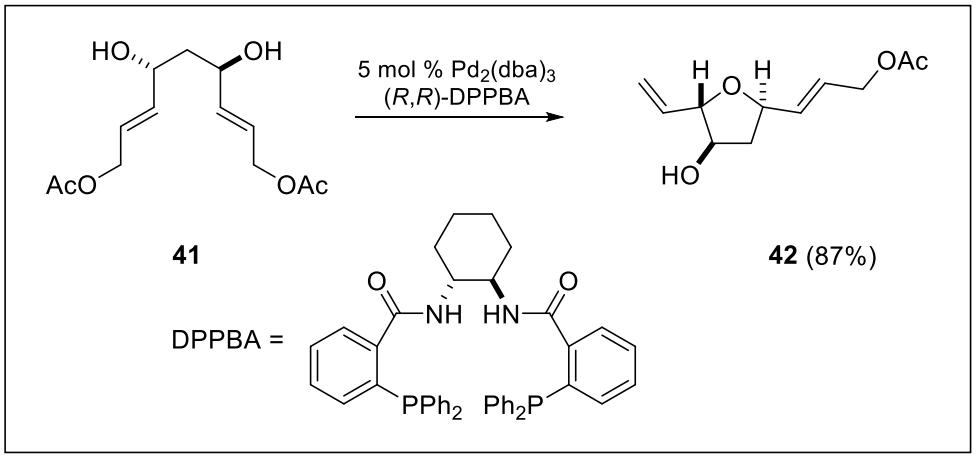
[39] L. Vares, T. Rein, *Org. Lett.* **2000**, 2, 2611.



Scheme 2.13. Rein's work in 2000.

Burke employed a desymmetrization strategy[40] using Pd(0)-catalyzed allylation reaction for the conversion of *meso* or C_2-symmetric diols to highly substituted THF cores (Scheme 2.14).

In a representative example, treatment of **41** with a catalytic amount of $Pd_2(dba)_3$ and the chiral Trost ligand DPPBA, generated trisubstituted THF **42**.

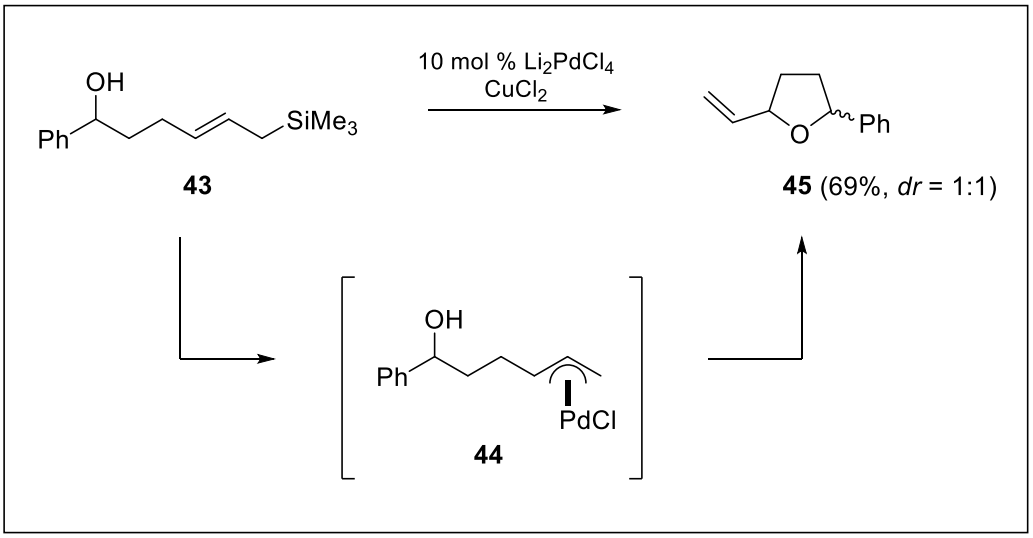


Scheme 2.14. Burke's work in 2002.

Commonly, the allyl-palladium complex intermediate is generated via oxidative addition of an allylic acetate or related compounds. Nevertheless, some examples of allylpalladium species that are generated through formal transmetalation reactions have also been reported. For example, Szabo and coworkers[41] have performed the Pd-catalyzed conversion of hydroxyl-substituted allylsilane **43** to THF **45** in 69% yield but with poor diastereoselectivity (1:1) (Scheme 2.15).

This reaction requires the use of stoichiometric amounts of Cu(II) salts, which are n*ee*ded to reoxidize Pd(0) to Pd(II) after the cyclization and provide an alternative strategy to obtain 2- vinyl-tetrahydrofurans.

[40] L. Jiang, S.D. Burke, *Org. Lett.* **2002**, 4, 3411.
[41] I. Macsari, K.J. Szabo, *Chem. Eur. J.* **2001**, 7, 4097.



Scheme 2.15. Szabo's work in 2001.

CHAPTER 3: Homogeneous Gold catalysis

3.1 Gold electronic and chemical properties

Gold is a transition metal belonging to the XI group of the periodic table presenting some interesting properties. To begin with, it is the most malleable and ductile metal.[42] It also has an electrochemical potential which is the lowest of any metal. This means that gold in cationic form is easily reducible and will accept electrons from virtually any reducing species to form metallic gold.

It is the most electronegative of all metals: on the Pauling scale, the electronegativity of gold, the highest among the metallic elements, is 2.4, which is the same as Se and close to that of S (2.5) and I (2.5).

It shows a very high electronic affinity (2.309 eV) as well.

The outer electronic configuration of gold(0) is $5d^{10}6s^{1}$; for gold(I) it is $5d^{10}6s^{0}$, for gold(III) it is $5d^{8}$ and for the gold(-I) anion it is $5d^{10}6s^{2}$.[43]

The two most common oxidation states for gold complexes are +1 and +3,[44] although some Au^{II} species have been reported.[45]

It is generally observed that gold complexes do not cycle betw*ee*n these states, in other words they do not undergo oxidative addition and reductive elimination processes easily. This points out that Au(I) species are generally tolerant of oxygen, property which allows reactions to be run in the presence of air, without the n*ee*d of inert atmosphere.[46] Such feature must be attributed to the high ionization potential (9.225 eV) recorded for gold's 6s orbital.[47]

The preferential coordination mode for Au(I) ion, a d^{10} species with 14 electrons in the valence shell, is a linear dicoordinated geometry, in which the two ligands are anti-parallel to each other at about 180°, which is thoroughly different from Cu(I) and Ag(I), both belonging to the 11^{th} group of the periodic table, both of which adopt tricoordinate or tetracoordinate geometries. Consequence to this is the necessity to remove one of the two

[42] P. Pyykkö, *Chem. Rev.* **1988**, 88, 563.
[43] M.C. Daniel, D. Astruc, *Chem. Rev.* **2004**, 104, 293.
[44] B.K. Min, C.M. Friend, *Chem. Rev.* **2007**, 107, 2709.
[45] N. Mirzadeh, M.A. Bennett, S.K. Bhargava, *Coord. Chem. Rev.* **2013**, 257 (15-16), 2250.
[46] D.J. Gorin, F.D. Toste, *Nature*, **2007**, 446, 395.
[47] K.S. Pitzer, *Acc. Chem. Res.*, **1979**, 12, 271.

ligands from the neutral or cationic species, in order to activate the "dormant" metal centre to catalytic activity.

The linear structure can be explained by analyzing the lowest unoccupied molecular orbital (LUMO) which is composed only of the 6s and 6p orbitals, the former being more stabilized than the latter. As a result, the sp hybridized molecular orbitals display a more pronounced s character, thus explaining the preferential linear structure.[48] Au(III), on the contrary, is a d^8 ion with 16 electrons in the valence shell and it adopts a square planar structure.

The poor tendency to be oxidized, the peculiar high stability of metallic gold as well as the preference for a linear coordination mode exhibited by Au(I) are all manifestations of the same phenomenon, *i.e.* a general contraction of the s and p orbitals, which is often referred to as 'relativistic effect'.[49] The term was introduced in 1928 by Dirac, who considered relativity to formulate an equation which calculates the energy of atomic orbitals for systems in which electrons move at sp*ee*ds which approach the sp*ee*d of light.

Post-lanthanide elements are characterized by a large number of protons in their atomic nuclei; therefore, the electrons move in a field of very high nuclear charge, which leads to velocities approaching that of light and, consequently, they have to be treated according to Einstein's theories of relativity.

This is particular true for electrons that are in s orbitals, which have wavefunctions that correspond to a finite electron density at the atomic nucleus, but it is less important for electrons in p or d orbitals.

Electrons moving at a sp*ee*d close to the sp*ee*d of light are assigned a relativistic mass that is larger than the mass of the electron at rest.

The effect on the 6s electrons, in the post-lanthanide elements, is that the orbital radius is contracted and the distance of the electrons from the nucleus is reduced.

Figure 3.1 shows a plot where the ratio of the relativistic radius of the valence electrons to their non-relativistic radius is presented as a function of atomic number.

[48] A. Leyva-Perez, A. Corma, *Angew. Chem. Int. Ed.* **2012**, 51, 614.
[49] J. Desclaux, *Atomic Data and Nuclear Data Tables*, **1973**, 12, 311.

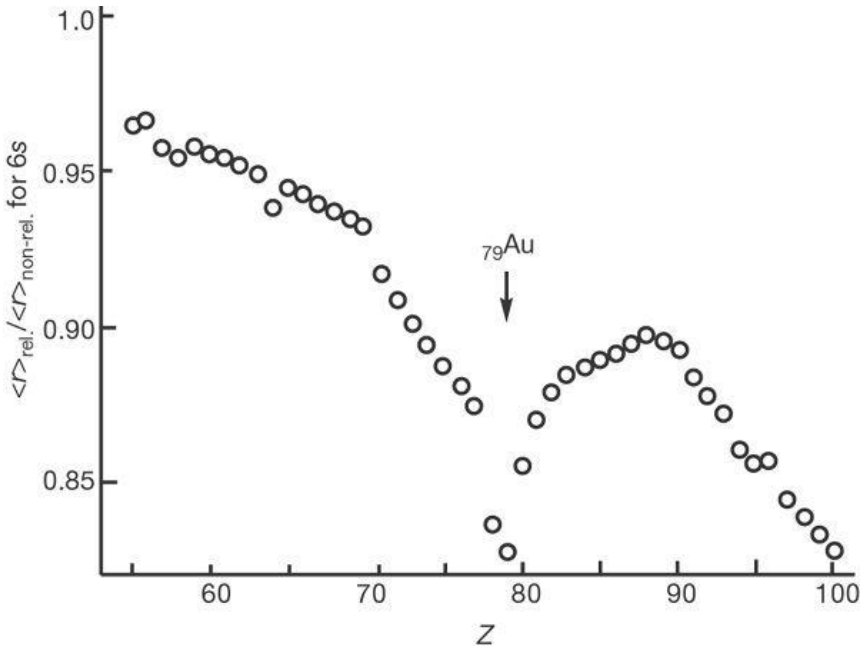


Figure 3.1. The relativistic contraction of the 6s orbital. The relativistic and non-relativistic orbital radii were determined by Desclaux. Gold is highlighted.

It is clear that this ratio strongly deviates from unity as Z increases, and it reaches a pronounced local minimum for gold.

3.1.1 The relativistic contraction

According to the special relativity, the relativistic mass of the electron m_{rel} is defined by equation 3.1:

$$m_{rel} = \frac{m_e}{\sqrt{\left(1 - {}^{v_e}/_{c}\right)^2}}$$

where m_e is the mass of the electron at rest, v_e is the velocity of the electron and c the sp*ee*d of light.

In non-relativistic conditions c is approximated to $c = \infty$ and no mass correction should be applied to the mass of the electron, thus $m_{rel} = m_e$.

In ultimate relativistic conditions, if v_e is equal to c (if the electrons move at the sp*ee*d of light), m_{rel} of the electron is approximated to ∞ ($m_{rel} = \infty$).

So, in general, the higher the value of v_e, the bigger the value of m_{rel} of the electron is.

Since the Bohr radius of an electron orbiting around a nucleus is inversely proportional to m_e, the increase in mass corresponds to a decrease in radius, which will lead to an orbital contraction, in particular for s and p orbitals.

The process is significant for elements with Z > 70, as described in Fig. 3.1: the high positive charge of these nuclei exerts a strong attraction on the electrons, which increments their velocity to a significant fraction of c. Furthermore, the tightly bound s and p orbitals are shielded, leading to a partial deshielding of d and f orbitals.

In the case of gold, whose atomic number is Z = 79, relativistic effects play an important part in the description of the energy of the 5d and 6s frontier orbitals, the HOMO (Highest Occupied Molecular Orbital) and the LUMO, respectively (Fig. 3.2). The former is destabilized, promoting Au-Au bonding, a phenomenon called 'aurophilicity' that would be unexpected in a closed-shell state such as a d^{10}, but which ind*ee*d occurs through London forces.[50] The LUMO, on the other hand, is well stabilized, conferring gold its extreme soft Lewis acidity, thus enabling it to activate multiple bonds (alkynes, allenes and alkenes).

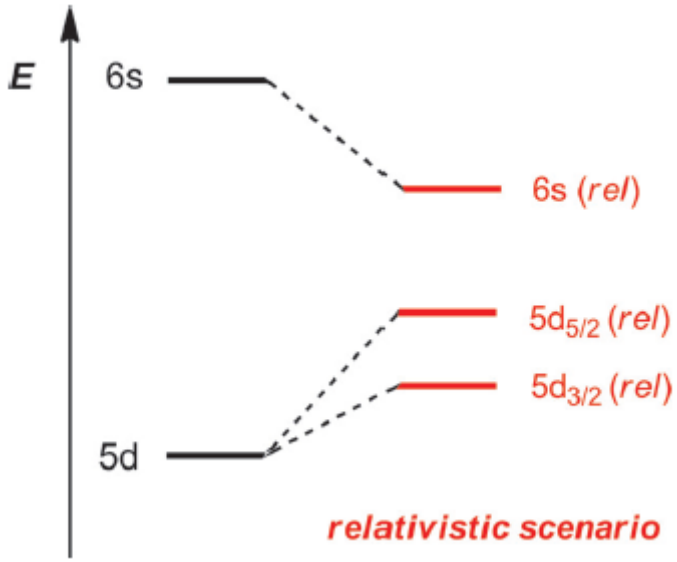


Figure 3.2. The relative energies of the atomic frontier orbitals of gold in the non-relativistic case (on the left) and in the relativistic case (on the right).

Thus, without describing this aspect any further, the relativistic effect on gold has some fundamental consequences:

1. The colour of gold. Gold has and absorption beginning at 2.4 eV, attributed to a

[50] H. Schmidbaur, *Nature*, **2001**, 413, 31.

transition from the filled 5d band to the Fermi level (essentially the 6s band). It therefore reflects red and yellow light and strongly absorbs blue and violet.

2. A marked reduction in the lengths of covalent bonds involving gold atoms.
3. The closed shell $5d^{10}$ is no longer chemically inert and can interact with other elements, that is, with other gold atoms in molecules or clusters. Bonding betw*ee*n two gold(I) centers (equilibrium distance is betw*ee*n 2.7 and 2.2 Å) with equal charge and a closed shell $5d^{10}$ cannot be understood in terms of classical bonding.
4. The small difference in energy betw*ee*n the s, p and d orbitals leads to the efficient formation of linear two-coordinate complexes in gold(I).[51]
5. The destabilization of the 5d orbitals allows the easy formation of the oxidation state III in gold to be explained (this is almost absent in silver), and the stabilization of the 6s orbitals explains the formation of the gold(-I) oxidation state (which is unknown in silver).

For all these reasons gold can be considered as an element with unique chemical features, and gold catalysis can be seen as one of the most important breakthroughs in organic synthesis during the last decades.[52]

3.2 Gold(I)-catalyzed reactions

As mentioned above, the soft carbophilic nature of gold(I) towards functionalities bearing multiple bonds makes this metal extremely useful for activation of allenyl, alkynyl and alkenyl groups.

In particular, Au(I) catalysis has been initially exploited for the functionalization of alkenes and alkynes, forming C-O and C-N bonds by nucleophilic attack of –OH and $-NH_2$ groups.[53] Only after some time this type of reaction was employed on allenic substrates.

The allenic system, as far as reactivity is concerned, may be classified as a strong σ donor and a weak π acceptor. As a consequence, metal-allene complexes are characterized by a strong σ donation from the filled p orbitals of the allene to the empty orbital of the metal, which causes either a weakening of one of the two allenyl double bonds and a marked

[51] L.-S. Wang, *Phys. Chem. Chem. Phys*. **2010**, 12, 8694.
[52] A.S.K. Hashmi, *Chem. Rev.* **2007**, 107, 3180.
[53] J. Barluenga, A. Dieguez, A. Fernandez, F. Rodriguez, F.J. Fanana's, *Angew. Chem. Int. Ed.* **2006**, 45, 2091.

increase of the electrophilicity of the allenyl functionality.

Compared to other metal catalyst belonging to 10^{th}-12^{th} group, Au(I) shows thr*ee* main advantages: firstly, the Au(I) species is much more prone to turn from the η^2 coordination mode to the η^1 one. Secondly, Au(I) catalysts are usually air-stable, affording to run reactions without any particular worrying about inert atmosphere. Finally, Au(I) catalysis affords a remarkable selectivity control of the reaction, since the catalytic cycle does not involve a β-elimination step, unlike many others do.

Thanks to the above mentioned noteworthy advantages, gold(I) catalysis has emerged as a powerful tool in organic synthesis to promote novel transformations to access elaborated structures from simple starting materials.

Several applications of gold(I) chemistry are well known, like (cyclo)isomerization reactions,[54-55-56] catalysis through gold-oxonium intermediates,[57-58-59] carbene transfer reactions,[60-61-62] as well as cyclization reactions of alkynoic/allenoic acids[63-64]/amides[65]/protected amines[66]/alcohols (see next section) through nucleophlic attack of the heteroatom on the activated π-system to obtain differently-substituted heterocycles.

The attention, however, will be drawn towards gold(I)-catalyzed hydroalkoxylation reactions, which represent the main topic of this thesis.

3.2.1 Gold(I)-catalyzed hydroalkoxylation reactions

Gold(I)-catalyzed hydroalkoxylation reactions represent a valuable tool in organic chemistry to make C-O bond in an inter- or intramolecular fashion.

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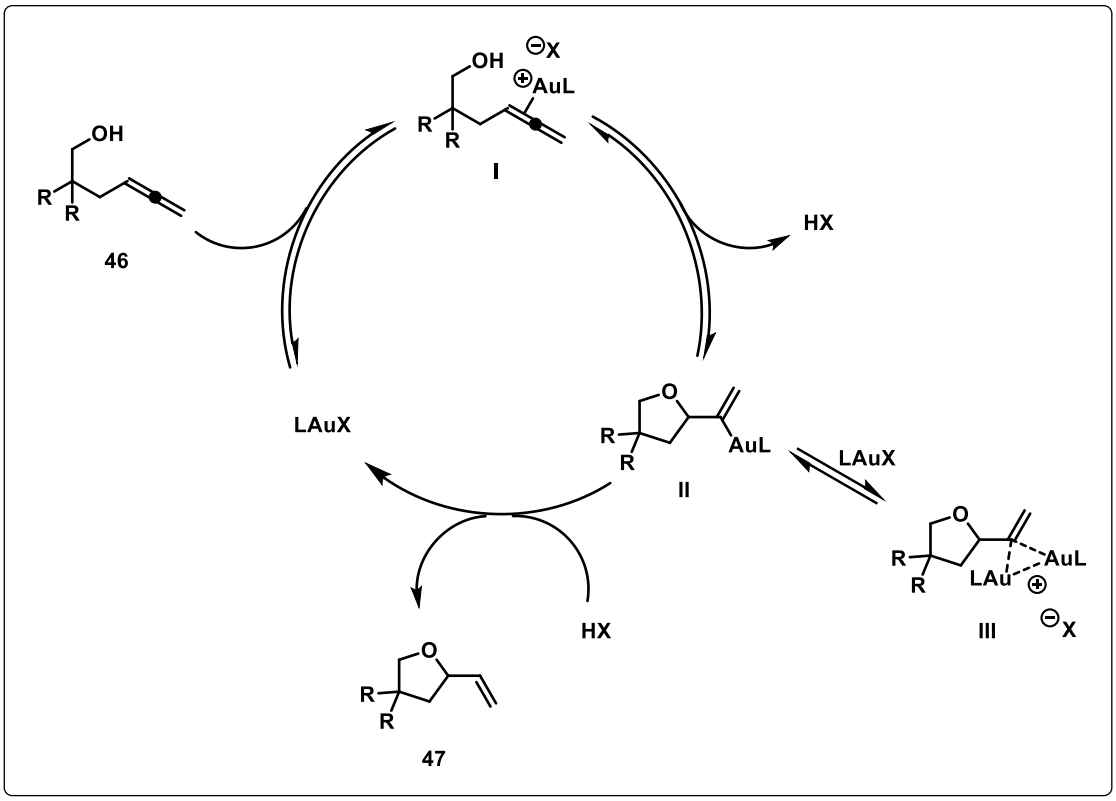
[54] Z. Wang, A. Ying, Z. Fan, C. Hervieu, L. Zhang, *ACS Catal.* **2017**, 7, 3676.
[55] E. Jiménez-Núnes, A.M. Echavarren, *Chem. Rev.* **2008**, 108, 3326.
[56] R.E.M. Brooner, T.J. Brown, R.A. Widenhoefer, *Angew. Chem. Int. Ed.* **2013**, 52, 6259.
[57] L.P. Liu, D. Malhotra, Z. Jin, R.S. Paton, K.N. Houk, G.B. Hammond, *Chem. Eur. J.* **2011**, 17, 10690.
[58] T. Wang, S. Shi, M.H. Vilhelmsen, T. Zhang, M. Rudolph, F. Rominger, A.S.K. Hashmi, *Chem. Eur. J.* **2013**, 19, 12512.
[59] J. Renault, Z. Qian, P. Uriac, N. Gouault, *Tetrahedron Lett.* **2011**, 52, 2476.
[60] A. Wetzel, F. Gagosz, *Angew. Chem. Int. Ed.* **2011**, 50, 7354.
[61] N.D. Shapiro, F.D. Toste, *J. Am. Chem. Soc.* **2007**, 129, 4160.
[62] R.K. Kawade, P.-H. Huang, S.N. Kara, R.-S. Liu, *Org. Biomol. Chem.* **2014**, 12, 737.
[63] D. Gasperini, L. Maggi, S. Dupuy, R.M.P. Veenboer, D.B. Cordes, A.M.Z. Slawin, S.P. Nolan, *Adv. Synth. Catal.* **2016**, 358, 3857.
[64] E. Genin, P.Y. Toullec, P. Marie, S. Antoniotti, C. Brancour, J.-P. Genet, V. Michelet, ARKIVOC 2007, 5, 67.
[65] A. Gimeno, A.B. Cuenca, S. Suarez-Pantiga, C.R. de Arellano, M. Medio-Simon, G. Asensio, *Chem. Eur. J.* **2014**, 20, 683.
[66] X. Zeng, R. Kinjo, B. Donnadieu, G. Bertrand, *Angew. Chem. Int. Ed.* **2010**, 49, 942.

In particular, our attention will be focused on intramolecular hydroalkoxylation reactions regarding allenic substrates.

Firstly, it is worth taking into consideration the mechanism of this type of reaction, considering as a model the catalytic cycle reported in Scheme 3.1 proposed by Widenhoefer in 2012.[67]



Scheme 3.1. Proposed mechanism of gold(I)-catalyzed hydroalkoxylation reactions.

The first step of the catalytic cycle is the activation of the allenic double bond through the η^2 coordination with the Au(I) catalyst, which turns the allenic system from nucleophile to electrophile, thus causing an "umpolung" as far as its reactivity is concerned.

At this stage, the activated electrophilic allenyl system **I** undergoes intramolecular attack by the hydroxyl group, leading to the formation of the mono(gold) vinyl complex **II** with release of HOTs. Complex **II** undergoes turnover-limiting protodeauration with HOTs to form the desired product **47**. Complex **II** is alternatively sequestered by $(L)Au^+$ forming bis(gold) complex **III**, which is considered as an off-cycle reservoir of Au(I) catalyst.

A few important representative cases of this class of reactions are described below, which

[67] T.J. Brown, D. Weber, M.R. Gagné, R.A. Widenhoefer, *J. Am. Chem. Soc.* **2012**, 134, 9134.

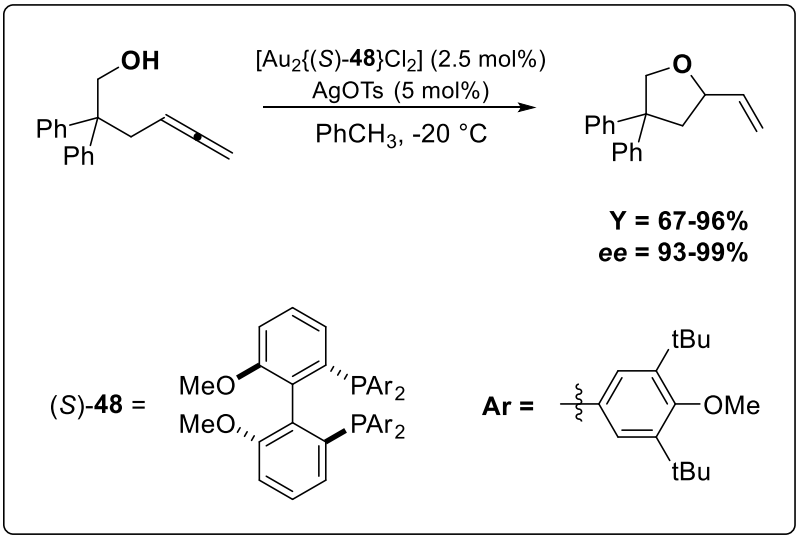
can be considered as fundamental breaktroughs in this type of catalysis.

Generally, in order to establish chiral selectivity in the reaction, three main strategies can be adopted:

1. Use of chiral Au(I) ligands
2. Use of chiral counterions
3. Synergistic effect

Widenhoefer et al. in 2007 developed a new protocol to access substituted tetrahydrofuran and tetrahydropyran rings enantioselectively and in high yields from allenol substrates using the first approach.[68]

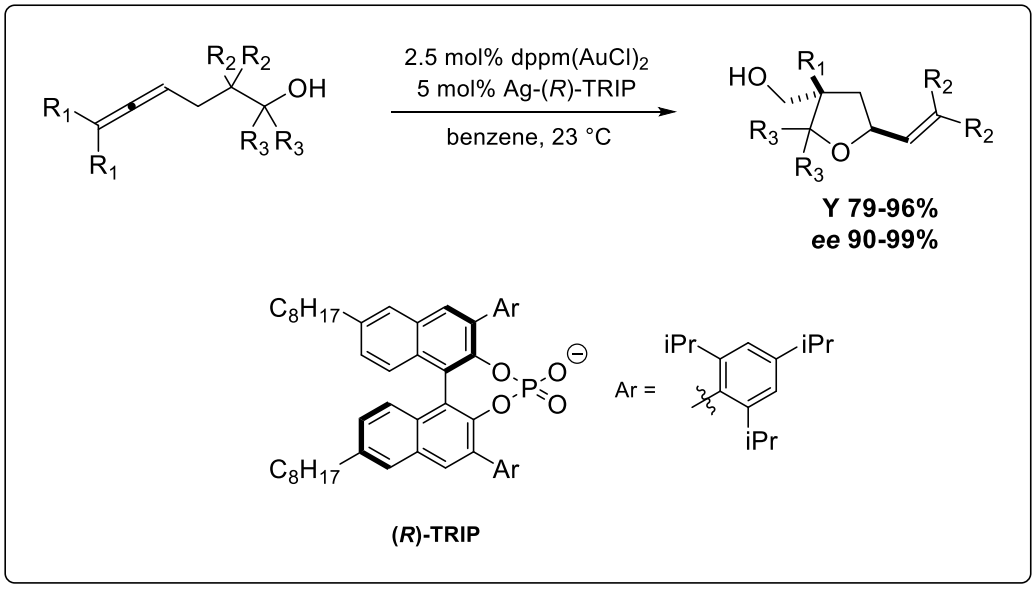
He managed to optimize the reaction conditions employing the chiral Au(I) ligand **48** and AgOTs as achiral counterion in toluene at -20 °C (Scheme 3.2).



Scheme 3.2. Widenhoefer's work in 2007.

Toste et al. in the same year used the second strategy to obtain the same THF and THP products as Widenhoefer (Scheme 3.3), exploiting the chiral counterion Ag-(*R*)-TRIP **49** and the achiral dinuclear gold complex bearing the bis(diphenylphosphinomethane) ligand (dppm).[69]

[68] Z. Zhang, R.A. Widenhoefer, *Angew. Chem. Int. Ed.* **2007**, 46, 283.
[69] G.L. Hamilton, E.J. Kang, M. Mba, F.D. Toste, *Science*, **2007**, 317, 496.



Scheme 3.3. Toste's work in 2007.

The silver phosphate enables facile generation of the cationic gold(I) catalyst from the phosphinegold(I) chloride driven by precipitation of silver chloride from solution.

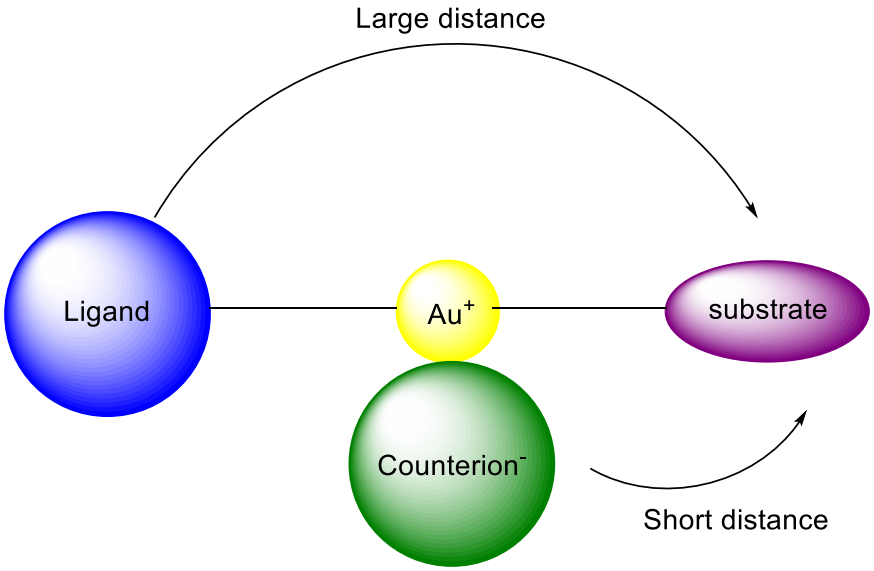
Control experiments demonstrated that the reaction is not catalyzed by the phosphoric acid corresponding to protonated **49**, nor is there an appreciable background reaction from either gold(I) complex or the silver phosphate alone.

Examination of other solvents demonstrated that more-polar solvents, such as nitromethane or acetone, gave significantly lower enantiomeric excess values. However, the less-polar benzene proved to be the optimal medium, providing the desired product in an exceptional 97% *ee*. These findings are consistent with an ion-paired model (see below).

This type of catalysis is often referred to as ACDC (Asymmetric Counterion Directed Catalysis).

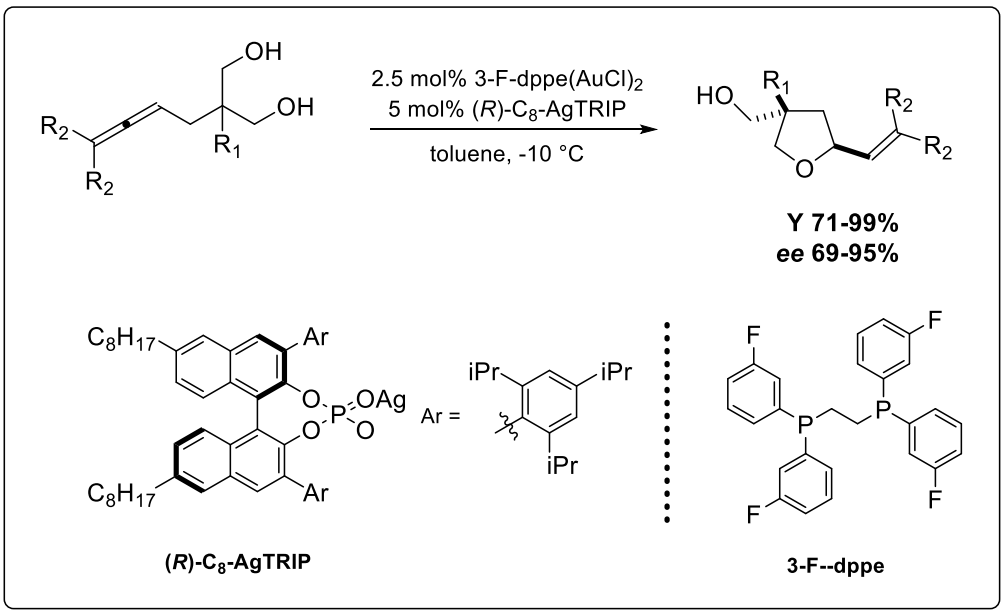
In general, chiral catalysts rely on covalent (dative or nondative) bonds betw*ee*n the reactive site and the chiral moiety. An alternative approach, which takes advantage of the fact that many enantioselective catalysts bear a positive charge, is the induction of asymmetry by interaction of the cationic catalyst with a chiral counteranion associated with the metal in an ion pair. This idea is potentially very powerful because, in principle, the same or a small library of chiral anionic counterions could be used to make a wide range of cationic catalysts enantioselective. The chiral counterion approach is especially appealing for Au(I) catalysis, given the difficulty of transferring chiral information from a ligand disposed 180° from the substrate. Scheme 3.4 gives evidence to the fact that

modification of the counterion can be used to circumvent this problem by introducing an additional source of chirality near the metal center.



Scheme 3.4. ACDC catalysis.

Another case in which Toste and collaborators exploited the chiral counterion strategy is the development of a new protocol which afforded a desymmterization of 1,3-diols to furnish 2,4-disubstituted THF products.[70]

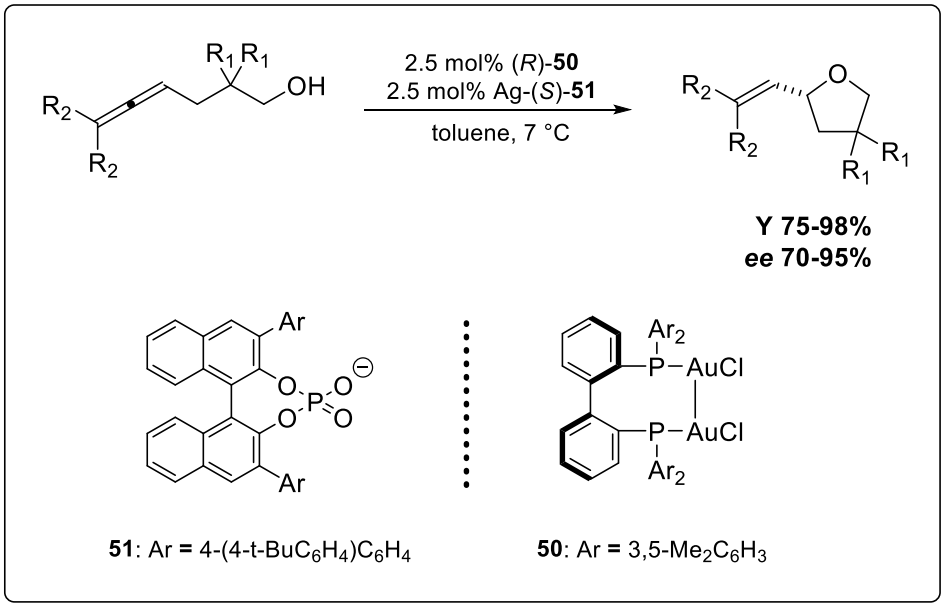


Scheme 3.5. Toste's work in 2015.

[70] W. Zi, F.D. Toste, *Angew. Chem. Int. Ed.* **2015**, 54, 14447.

This represents the first method established to construct heterocycles incorporating more than one stereocenter via these transformations.

Mikami et al. in 2010 developed a protocol exploiting the so-called "synergistic effect", in which both a chiral Au(I) ligand and a chiral counterion are employed.[71]
In this case, the two chiral species can interact either in a "positive" way ("matched" pair), increasing *ee* values, or in a "negative" way ("mismatched" pair), causing a drop in *ee* values.
The authors optimized the reaction conditions using the chiral gold(I) catalyst (*R*)-**50** and the chiral counterion **51** in toluene at 7 °C, leading to high *ee* values and yields.



Scheme 3.6. Mikami's work in 2010.

[71] K. Aikawa, M. Kojima, K. Mikami, *Adv. Synth. Catal.* **2010**, 352, 3131.

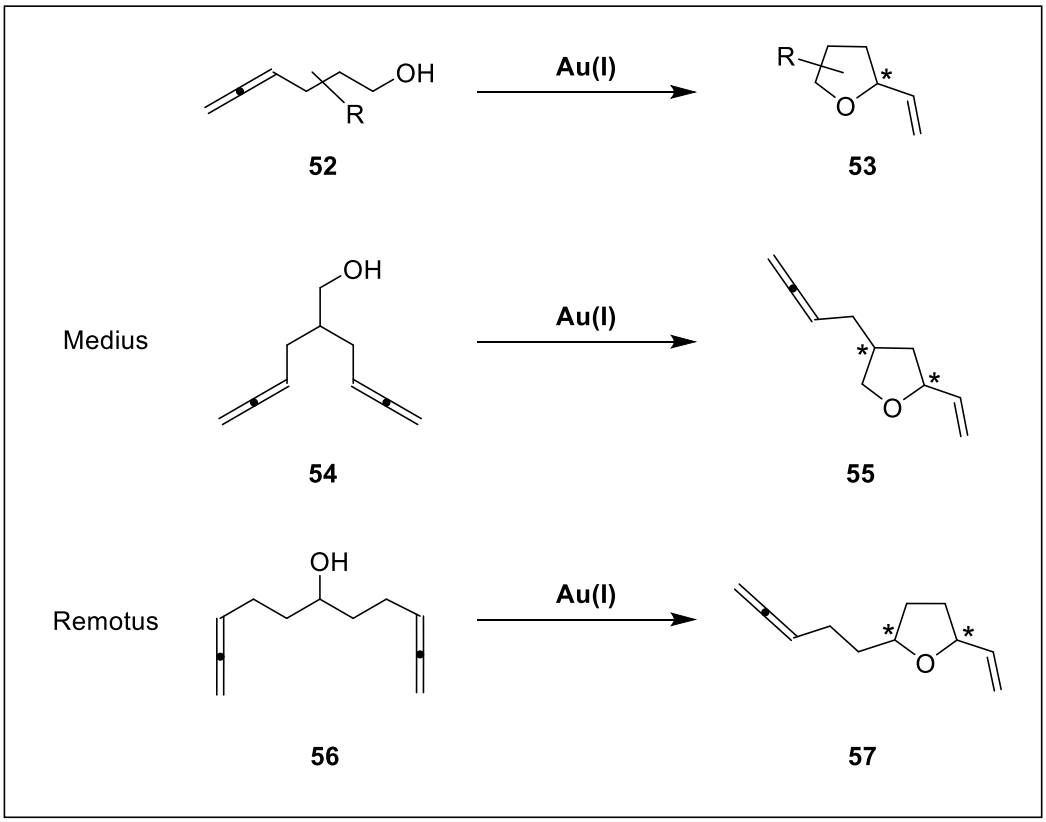
CHAPTER 4: Aim of the Thesis

The studies carried out in this thesis deal with the construction of mono- and polysubstituted THF systems, which, as mentioned before, represent fundamental building blocks in several biologically active molecules.

The syntheses of those targets will be developed exploiting gold(I) catalysis.

In particular, as depicted in Scheme 4.1, the attention will be drawn on the gold(I)-catalyzed intramolecular enantioselective hydroalkoxylation reaction of the 4-allenyl alcohol **52** and the achiral bis-allenyl alcohols **54**, called "**Medius**", and **56**, called "**Remotus**", considering the relative distance of the tertiary carbon atom from the allenic functional groups.

Going further into the detail, a complete methodological study will be performed, whose main goal is that of analyzing the yield, the enantioselectivity and the diastereoselectivity of this reaction through the variation of experimental conditions, i.e. chiral ligands, chiral counter ions, solvents and temperature.



Scheme 4.1. Aim of the Thesis.

Moreover, efforts will be devoted to the development of a protocol in order to functionalize the products of the cyclization reactions, installing a chromophore within the molecular structure without affecting the already present stereogenic centers. This is necessary to make the products detectable for HPLC analysis, since this device possesses a diode array detector.

In addition, the applicability of this reaction will be evaluated: in this context, substrates bearing chemically and spacially different substituents will undergo the cyclization reaction in the optimized conditions.

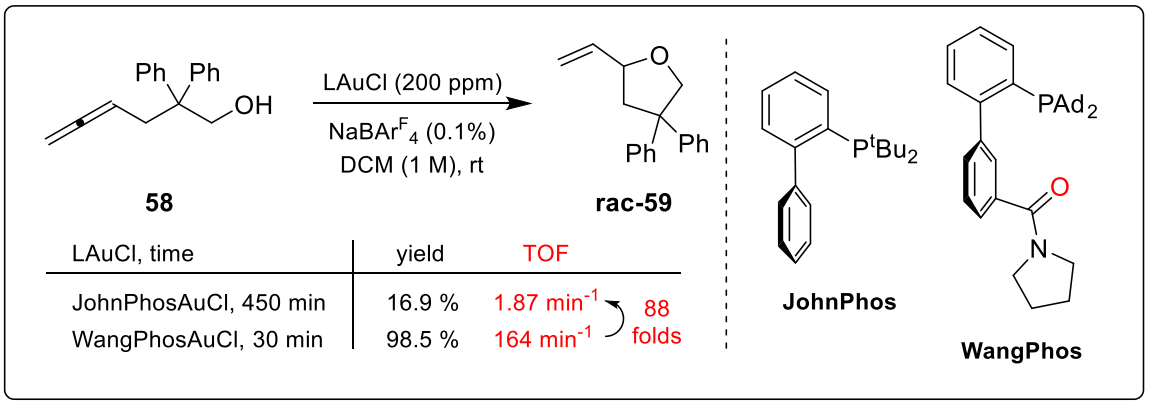
Finally, a method which affords to determine the absolute and the relative configurations of the stereogenic centers present in the products will be developed.

CHAPTER 5: Study on the cyclization of 4-allenyl-alcohols

5.1 Hypothesis

Zhang's research team has recently developed a series of novel biphenyl-2-ylphosphinic ligands[72-73] characterized by the presence of basic functional groups at the bottom half of the pendant phenyl ring.[74] With WangPhos[75] (Scheme 5.1) possessing a 3′-amide group as ligand, the gold-catalyzed intermolecular nucleophilic attack of carboxylic acid to alkynes is accelerated by an estimated 800-fold, comparing to nonfunctionalized JohnPhos, due to the cooperation of the remote amide group in the form of general basic catalysis.[76]

In the context of asymmetric gold catalysis, it has been reckoned that the same cooperative strategy can be exploited in order to access the cyclization of 4-allen-1-ols such as **58** (Scheme 5.1), where a new stereocenter in the newly formed THF system is created.



Scheme 5.1. Preliminary study.

It is noteworthy that cyclizations of allenols have been studied extensively in asymmetric gold and silver catalysis, as described in the previous chapters.

Noteworthy, the decision of considering only simple monosubstituted allenes as substrates has been taken. As such, no terminally disubstitued allenes has been investigated, as they require excessive steps for preparation and do not show any apparent synthetic utility. On

[72] D.S. Surry, S.L. Buchwald, *Angew. Chem. Int. Ed.* **2008**, 47, 6338.
[73] R. Martin, S.L. Buchwald, *Acc. Chem. Res.* **2008**, 41, 1461.
[74] Z. Wang, A. Ying, Z. Fan, C. Hervieu, L. Zhang, *ACS Catal.* **2017**, 7, 3676.
[75] Z. Wang, Y. Wang, L. Zhang, *J. Am. Chem. Soc.* **2014**, 136, 8887.
[76] Y. Wang, Z. Wang, Y. Li, G. Wu, Z. Cao, L. Zhang, Nat. Commun. 2014, DOI: 10.1038/ncomms4470.

the contrary, monosubstituted allenes such as **58** are easily accessible via the Crabbe allene synthesis,[77] and the vinyl group in cyclization product can be promptly derivatized.

To our delight, comparing to JohnPhos, a sterically and electronically comparable ligand but lacking any remote cooperative group, WangPhos promotes the gold-catalyzed cyclization of **58** to racemic 2-vinyltetrahydrofuran **rac-59** at a rate at least 88 times faster.

5.2 Stereochemical features

The above-reported consistent rate acceleration can be promptly explained by invoking ligand metal cooperative catalysis and specifically the general base catalysis by the remote amide group.

Ligand accelerated catalysis[78-79-80] (LAC) represents a versatile tool in metal catalysis for achieving efficient asymmetric catalysis.[81]

An often-practiced approach to achieve enantioselectivity in LAC is that of introducing asymmetric steric hindrance to selectively slow down the formation of one of the enantiomers, albeit it may still be faster than the nonaccelerated scenario (Figure 1C vs 1A). This is a superior strategy to those based only on steric retardation (Figure 1B) due to faster reaction times and lower catalyst loadings. Alternatively but relatively rare in transition metal catalysis, high enantioselectivity could be achieved by means of a selective acceleration of the formation of only one of the enantiomers via asymmetric ligand substrate interactions and/or ligand metal cooperation (Figure 1D).

In comparison to the case in Figure 1C, this latter approach does not accelerate the formation of the minor enantiomer and hence offers enhanced chances of achieving excellent enantioselectivity. In addition, owing to the highly efficient type of catalysis, it often affords to carry out reactions in more feasible conditions.

Asymmetric gold catalysis, despite the challenge stemming from the linear structure of Au(I) complexes and the *anti* attack by incoming nucleophile, has experienced significant progress in recent years.

However, highly enantioselective cases in literature do not rely on ligand accelerated

[77] P. Crabbe, H. Fillion, D. Andre, J.-L. Luche, *J. Chem. Soc., Chem. Commun.* **1979**, 859.
[78] D.J. Berrisford, C. Bolm, K.B. Sharpless, *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 1059.
[79] M. Sawamura, Y. Ito, *Chem. Rev.* **1992**, 92, 857.
[80] H. Grutzmacher, *Angew. Chem. Int. Ed.* **2008**, 47, 1814.
[81] D. Brodbeck, F. Broghammer, J. Meisner, J. Klepp, D. Garnier, W. Frey, J. Kastner, R. Peters, *Angew. Chem. Int. Ed.* **2017**, 56, 4056.

catalysis and mostly base their results on decelerative and hence efficiency-lowering steric hindrance (i.e., Figure 1B) imposed by chiral ligands, counteranions, or their combination. As a consequence, those reactions typically require relatively high catalyst loadings due to decreased reaction rates.

In this thesis the first example of asymmetric ligand-accelerated gold catalysis is reported,[82] where the formation of one enantiomer is selectively accelerated via asymmetric ligand substrate interaction. This interaction enables ligand metal cooperation and is realized in the secondary ligand sphere by a remote and asymmetrically positioned Lewis basic group in new chiral binaphthyl-2-ylphosphinic ligands. The utility of this accelerative strategy is proved and confirmed by the very low catalyst loadings (as low as 100 ppm) and the generally excellent stereoselectivities in the cyclization of 4-allen-1-ols.
Importantly, it representes a new and highly efficient strategy to achieve challenging asymmetric gold catalysis, which to date has mostly been limited to the scenario depicted in Figure 1B.

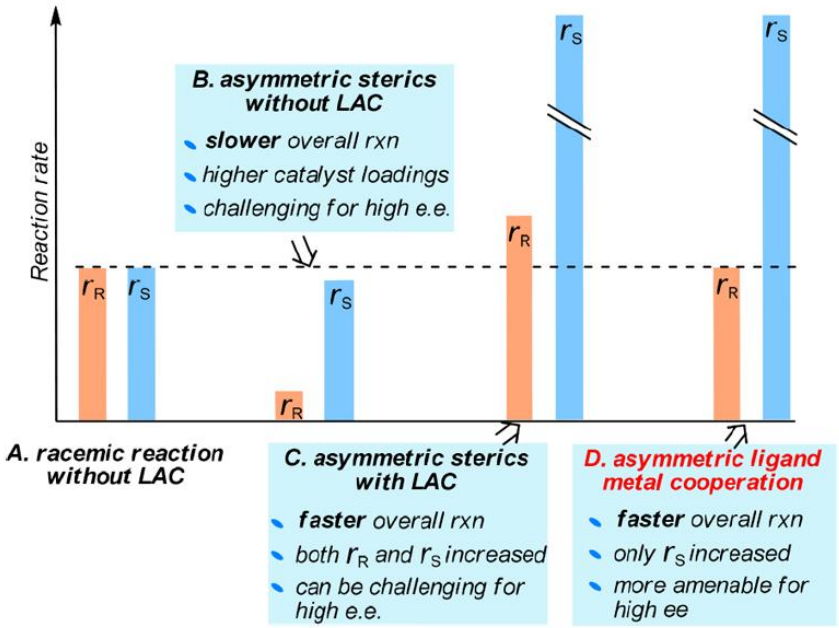
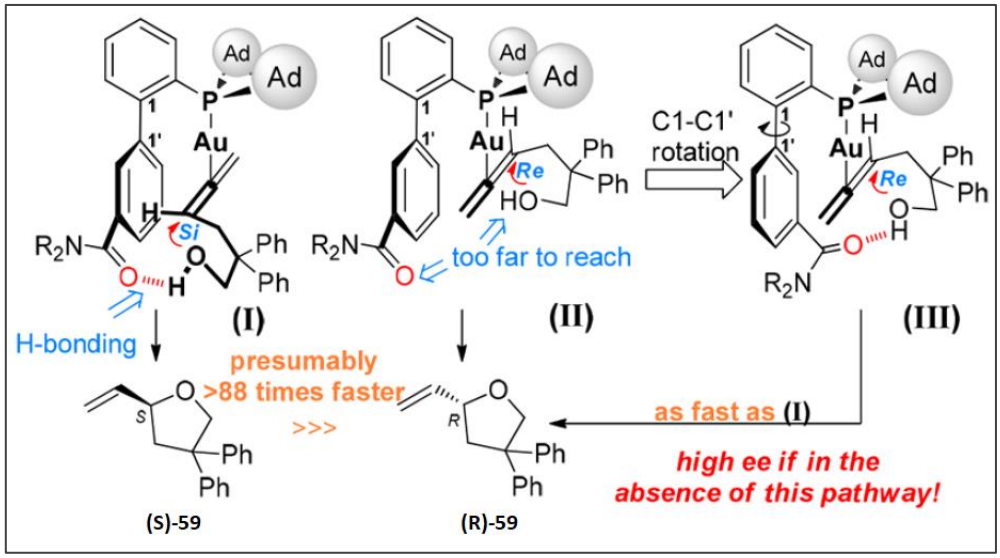


Figure 5.1. Common scenarios of asymmetric catalysis.

As shown in Scheme 5.2, the allene coordination would lead to two diastereomeric complexes **I** and **II**. In contrast to complex **II**, complex **I** places the alcohol adjacent to the

[82] Z. Wang, C. Nicolini, C. Hervieu, Y.-F. Wong, G. Zanoni, L. Zhang, *J. Am. Chem. Soc.* **2017**, 139, 16064.

pendant amide group and hence affords a general base catalysis in the form of H-bonding, which would enhance the nucleophilicity of alcohol via partial deprotonation in transition state.



Scheme 5.2. Stereochemical features of the reaction.

As a result, *Si*-face attack in complex **I** that produces (*S*)-**59** would largely (presumably ≥ 88 times faster) outcompete *Re*-face attack in complex **II**, where the amide group is positioned too far from the alcohol -OH group to allow H-bonding and hence should undergo cyclization in a similar rate to that with JohnPhos as ligand.

However, due to the low barrier of rotating C1−C1′ bond in the ligand and likely its gold complex, WangPhosAu$^+$ would exist in equal amount as the enantiomer or enantiomeric conformer to that in complex **I**. The resulting complex **III** would equally accelerate the *Re*-face attack, which delivers racemic **59** as a net result.

Nevertheless, it is reckonable that by using a chiral version of WangPhos with the rotation of C1−C1′ locked the cyclization of 4-allenols could become asymmetric.

5.3 Synthesis of gold(I) complexes

At the outset, we chose the configurationally much more stable binaphthyl as the ligand framework, and targeted the (1,1′-binaphthyl)-2-yldi(adamantan-1-yl)phosphinic ligands **L1**−**L3** (Figure 5.2).

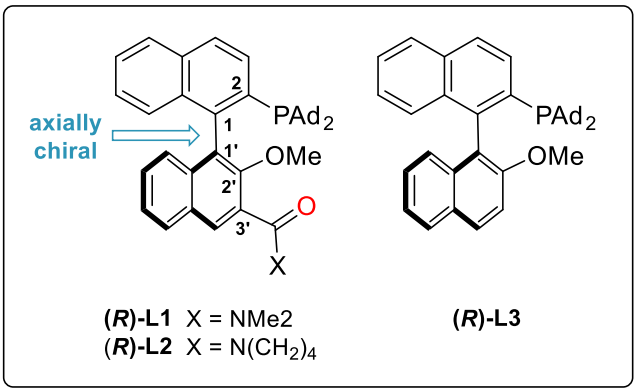
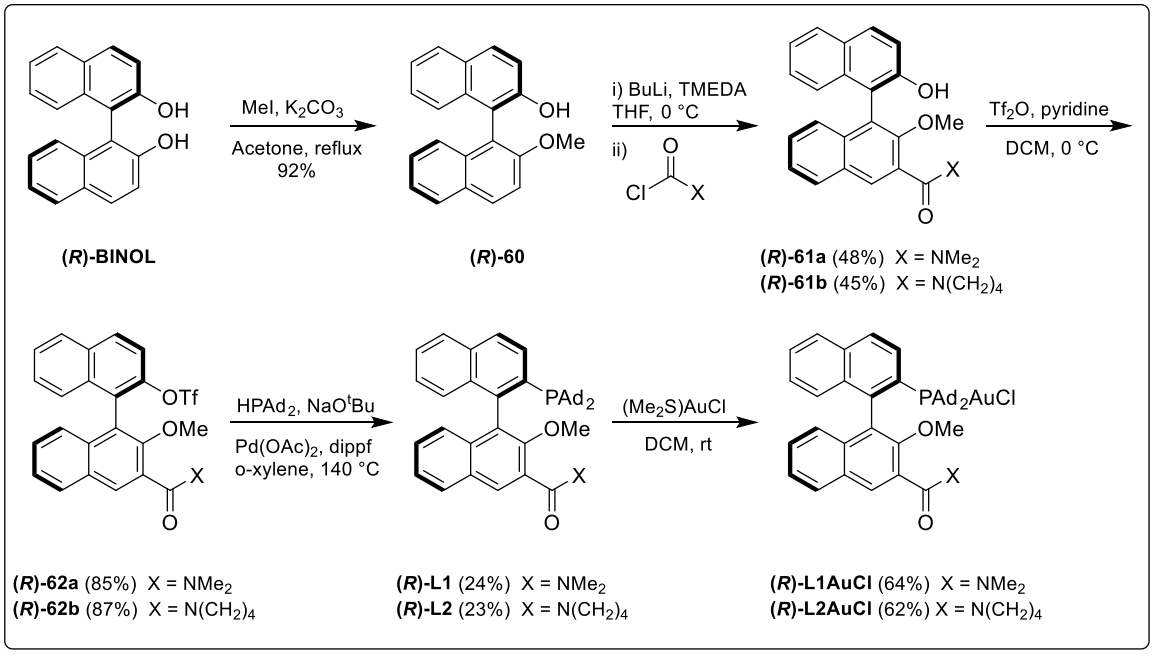


Figure 5.2. Selected ligands for this study.

They can be readily synthesized from commercially available **(*R*)-BINOL** in a short sequence of 3−4 steps.

In Scheme 5.3 the synthetic steps in order to prepare the gold(I) complexes **(*R*)-L1AuCl** and **(*R*)-L2AuCl** are presented.

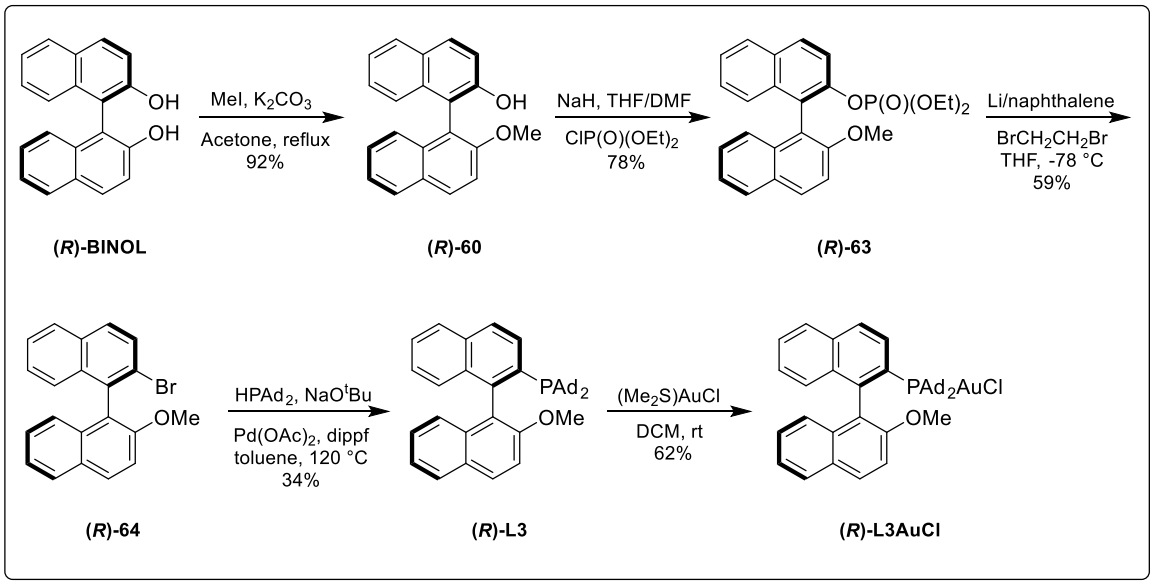


Scheme 5.3. Synthesis of gold(I) complexes **(*R*)-L1AuCl** and **(*R*)-L2AuCl**.

The synthetic process begins with **(*R*)-BINOL**, which undergoes substitution reaction to afford the mono-methylated BINOL derivative **(*R*)-60**. *Orto*-lithiation and subsequent electrophilic attack of the acyl chloride give **(*R*)-61**s, whom hydroxyl group is transformed into a triflate through a substitution reaction to furnish **(*R*)-62**s. Pd-mediated nucleophilic aromatic substitution allows to obtain the ligands **(*R*)-L1** and **(*R*)-L2**; treating them with

(dimethylsulfide)gold(I)chloride in DCM leads to the gold(I) complexes **(*R*)-L1AuCl** and **(*R*)-L2AuCl**.

In Scheme 5.4 the synthetic steps in order to prepare the gold(I) complex **(*R*)-L3AuCl** are described.



Scheme 5.4. Synthesis of gold(I) complex **(*R*)-L3AuCl**.

The synthetic process begins once again with **(*R*)-BINOL**, which undergoes once again substitution reaction to afford the mono-methylated BINOL derivative **(*R*)-60**. The following step is represented by the transformation of the hydroxyl group into a phosphonate through a substitution reaction to furnish **(*R*)-63**. At this point, running the reaction with Li/naphthalene in the presence of dibromoethane in THF at -78 °C leads to **(R)-64**. Pd-mediated nucleophilic aromatic substitution allows to obtain the ligand **(*R*)-L3**; treating it with (dimethylsulfide)gold(I)chloride in DCM affords gold(I) complex **(*R*)-L3AuCl**.

To confirm the identity of the ligand **(*R*)-L2**, we ascertained the structure and stereochemistry of its gold complex by X-ray diffraction studies (Figure 5.3).

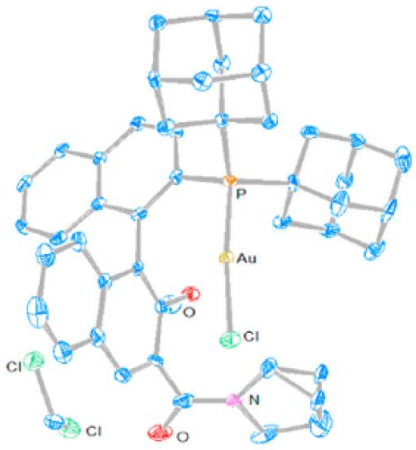


Figure 5.3. ORTEP drawings of **(*R*)-L2AuCl** with 50% ellipsoid probability.

5.4 Optimization of reaction conditions

The initial study using 5 mol % **(*R*)-L1AuCl** as the catalyst precursor gave access to **(*R*)-59** in 98.4% *ee* within 5 min.

The absolute configuration of **59** was assigned as (*R*) based on literature precedent,[83] and is consistent with the rationale/design shown in Scheme 5.2, where the front-orienting amide in **I** leads to the (*S*)-product.

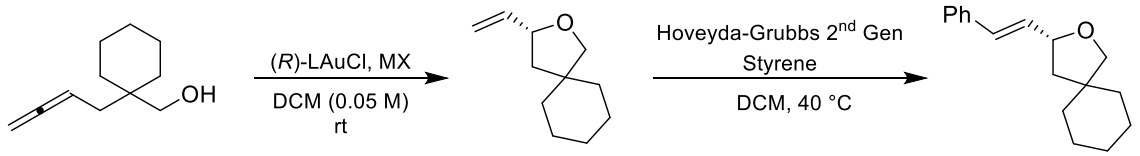
This exceptional initial result validated our ligand design concept and, moreover, was achieved with the very first chiral ligand of this type.

The *ee* value achieved with substrate **59** was so high that it did not afford condition optimization and ligand development. For this reason, reaction optimization was carried out with 4-allenol **65** as the substrate.

Due to lack of desirable UV absorption for chiral HPLC analysis of the product **66**, a subsequent olefin metathesis was carried out to install a styryl group as the chromophore.

The control experiment with **59** confirmed that there is no erosion of stereochemistry in the cross metathesis step.

[83] J.L. Arbour, H.S. Rzepa, J. Contreras-Garcia, L.A. Adrio, E.M. Barreiro, K.K. Hii, *Chem. – Eur. J.* **2012**, 18, 11317.



65 **66** **67**

Entry	Cat. (mol %)	MX (mol %)	Temp./time	Yield (%)	*ee* (%)
1	(*R*)-**L1**AuCl (1)	$NaBAr^F_4$ (5)	rt /15 min	98	95.5
2	(*R*)-**L2**AuCl (1)	$NaBAr^F_4$ (5)	rt /15 min	97	96.6
3	(*R*)-**L3**AuCl (2)	$NaBAr^F_4$ (5)	rt /1 h	11	- 8.8
4	(*R*)-**L2**AuCl (1.2)	$AgNTf_2$ (1)	rt /15 min	96	93.4
5	(*R*)-**L2**AuCl (1.2)	AgOTf (1)	rt /15 min	95	78.9
6	(*R*)-**L2**AuCl (1.2)	$AgSbF_6$ (1)	rt /15 min	92	94.1
7	(*R*)-**L2**AuCl (1)	$NaBAr^F_4$ (5)	rt /15 min	92	97.5
8	(*R*)-**L2**AuCl (1)	$NaBAr^F_4$ (5)	-20°C /30 min	90	95.5
9	(*R*)-**L2**AuCl (1)	$NaBAr^F_4$ (5)	40°C /15 min	89	97.0
10[a]	(*R*)-**L2**AuCl (1)	$NaBAr^F_4$ (5)	60°C /15 min	94	97.1
11	(*R*)-**L2**AuCl (0.1)	$NaBAr^F_4$ (1)	rt /30 min	94	97.1
12	(*R*)-**L2**AuCl (0.01)	$NaBAr^F_4$ (0.5)	rt /2.5 h	92	96.9
13[b]	(*R*)-**L2**AuCl (0.01)	$NaBAr^F_4$ (0.5)	rt /1 h	92	95.7

[a]DCE was used as solvent. [b]0.25M in DCM.

Table 5.1. Optimization of reaction conditions.

Gladly, treating **65** with 1 mol % **L1AuCl** as catalyst and 5% $NaBAr^F_4$ as chloride scavenger furnished **66** in 98% yield and 95.5% *ee* within 15 min (Table 5.1, entry 1). Consistent with the case of **59**, its configuration is assigned as (*R*). Moreover, using **L2** with a pyrrolidin-1-ylcarbonyl group, which is more basic than N,N-dimethylcarbamyl group in **L1**, a better enantioselectivity (96.6% *ee*) was achieved.

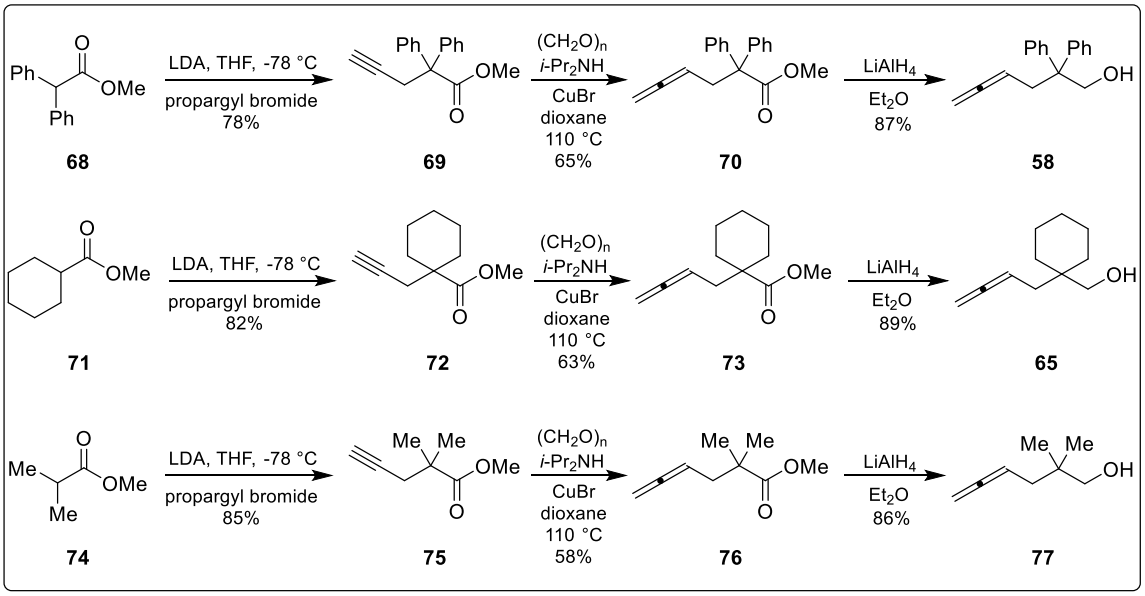
(*R*)-L3, bearing no cooperative amide group, was used in a control experiment, which gave access to an expected dramatic drop of *ee* (-8.8%). Once again the cooperative nature of the amide group in the gold(I) complex is confirmed (Table 5.1, entry 3). Replacing $BAr^F_4{}^-$ with more coordinative counteranions caused decreased enantioselectivities (Table 5.1, entries 4−6).

It has also been observed that the removal water by 3 Å MS improved *ee* to 97.5% (Table 5.1, entry 7), possibly because the residual water, capable of acting as both H-bonding

donor and acceptor, would disrupt the H-bonding between the alcohol and amide group.
Along with this rationale, the key role of the non coordinating anion $NaBAr^{F}_{4}$ in achieving high enantioselectivity, in contrast with more coordinating anions, can be better highlighted.
In contrast to the common temperature profiles in asymmetric catalysis, lowering the reaction temperature led to a decreased *ee*, whereas higher temperatures did not cause much *ee* erosion (Table 5.1, entries 8−10). This uncommon temperature trend witnesses, once again, the high level of efficiency in this type of catalysis, which can be considered as not (or very little) temperature dependent.
Owing to the accelerated nature of the catalysis, the catalyst loadings could be dramatically lowered down to 100 ppm without noticeably affecting *ee* (Table 5.1, entries 11−12).
At last, a higher concentration was proven to be detrimental to *ee* despite a faster reaction rate (Table 5.1, entry 13), which can be attributed to the disruption of ligand-substrate H-bonding by unreacted alcohol.

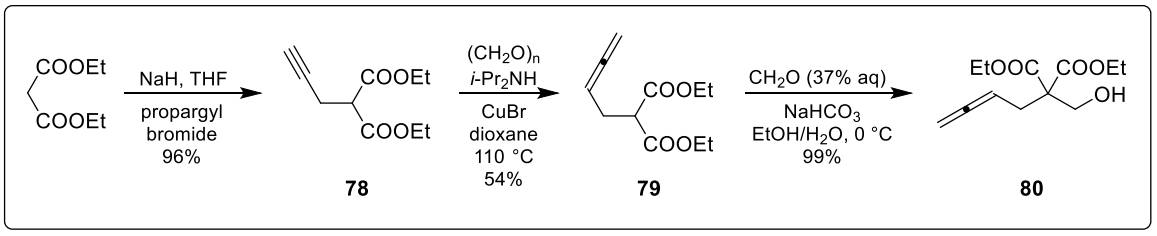
5.5 Substrates synthesis

At this stage, efforts have been devoted to the synthesis of the substrates in order to broad the reaction scope.
In this section only the synthetic ways to prepare the substrates will be discussed, without going into details; for further information see the experimental part.
To begin with, substrates **58**, **65, 77** were prepared in a similar way through a 3-steps protocol, involving an ester α-alkylation, followed by Crabbé reaction and reduction with $LiAlH_4$ (Scheme 5.5).



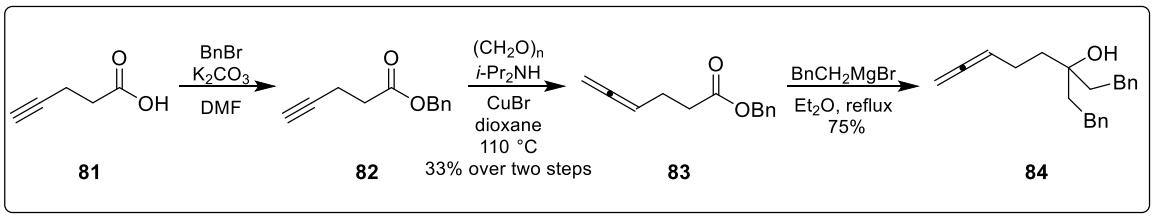
Scheme 5.5. Preparation of allenols **58**, **65**, **77**.

Substrate **80** was prepared from diethyl malonate and propargyl bromide through a malonic reaction, followed by Crabbé reaction and nucleophilic addition of enolate of **79** to formaldehyde (Scheme 5.6).



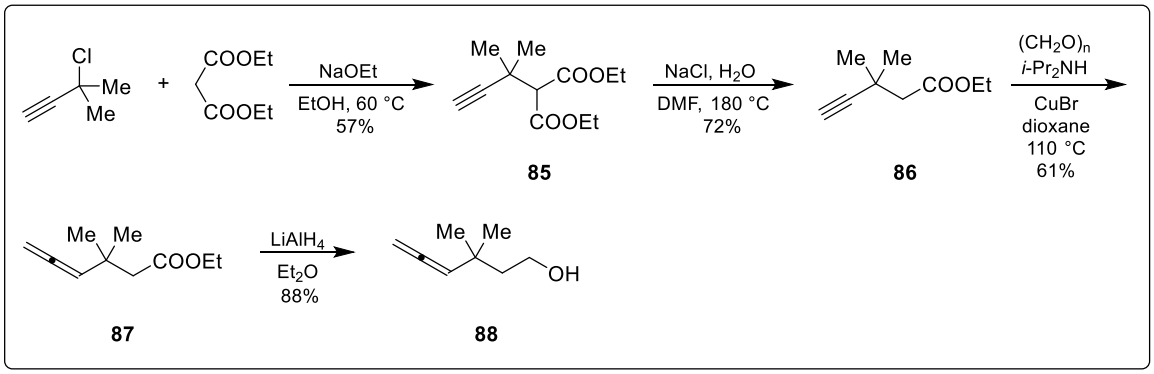
Scheme 5.6. Preparation of allenol **80**.

Tertiary alcohol **84** was prepared from pentynoic acid **81**, which underwent esterification, Crabbé reaction and double Grignard attack (Scheme 5.7).



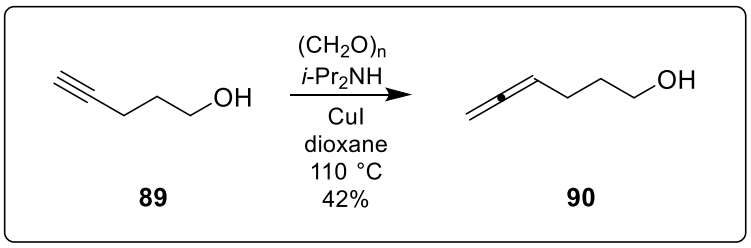
Scheme 5.7. Preparation of allenol **84**.

Substrate **88** was prepared from diethyl malonate through a malonic reaction, followed by Krapcho decarboxylation, Crabbé reaction and ester reduction with $LiAlH_4$ (Scheme 5.8).



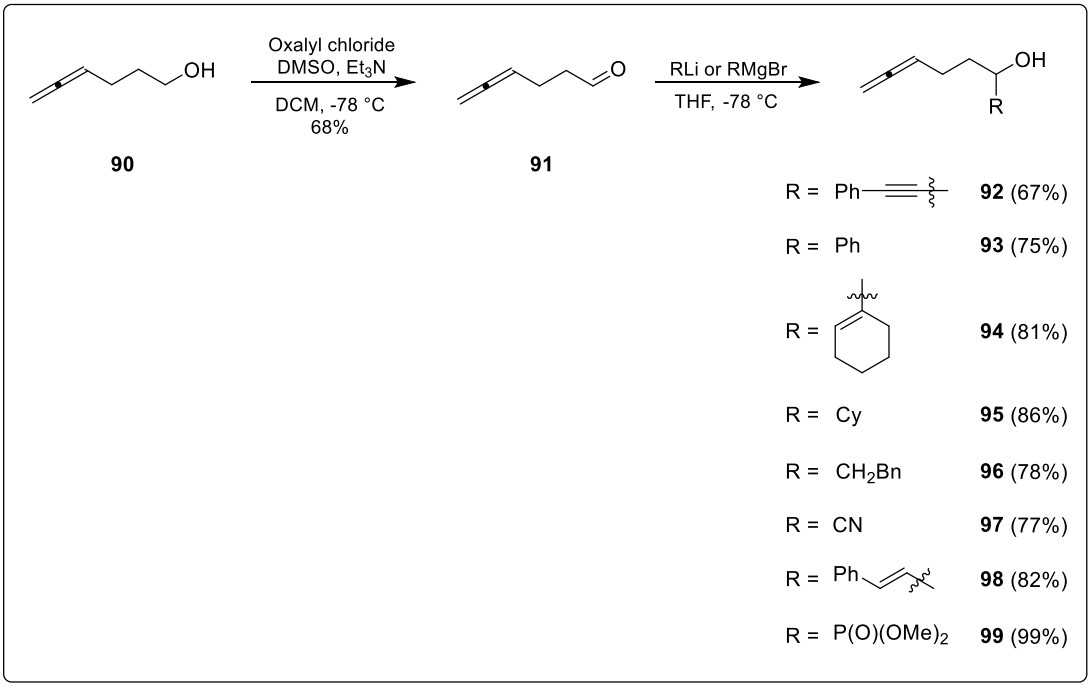
Scheme 5.8. Preparation of allenol **88**.

Substrate **90** was prepared from 4-pentyn-1-ol **89** through a simple Crabbé reaction (Scheme 5.9).



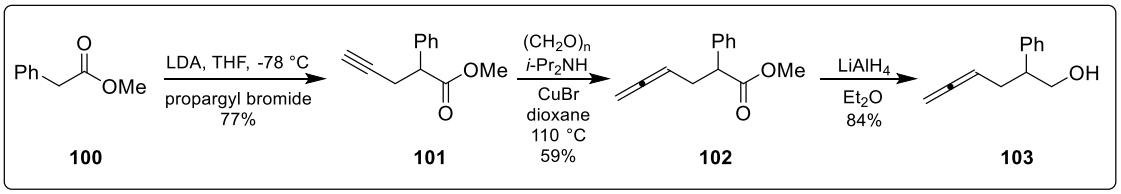
Scheme 5.9. Preparation of allenol **90**.

Substrate **90** underwent Swern oxidation, and the aldehyde **91** was attacked by different Grignard/Organolithium reagents to furnish **92-99** (Scheme 5.10).



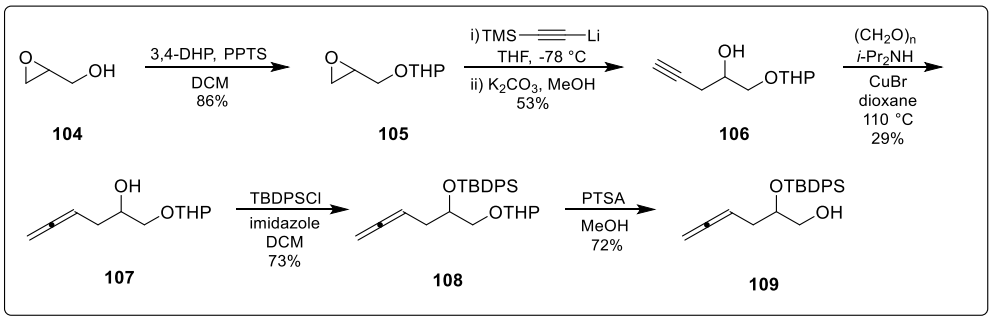
Scheme 5.10. Preparation of allenols **92-99**.

Substrate **103** was prepared from the precursor **100** through an ester α-alkylation with propargyl bromide, followed by Crabbé reaction and reduction with $LiAlH_4$ (Scheme 5.11).



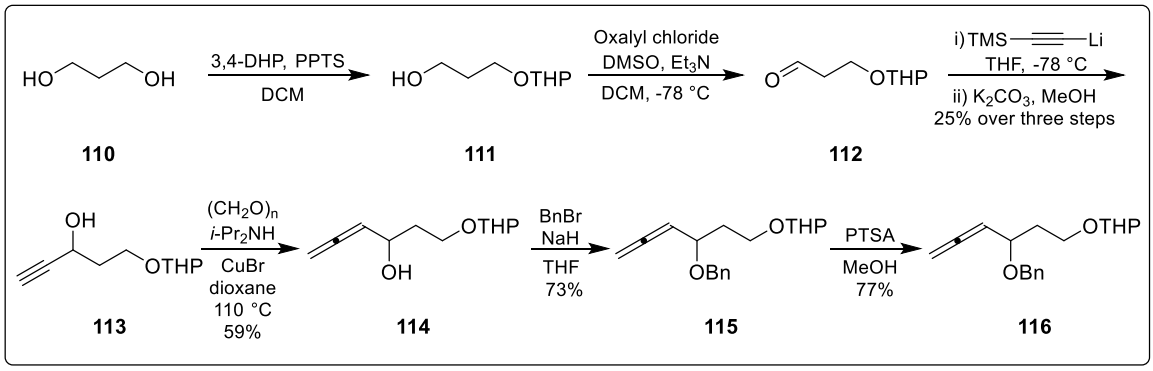
Scheme 5.11. Preparation of allenol **103**.

Substrate **109** was prepared from epoxy alcohol **104**, which underwent protection of the hydroxyl group, epoxyde opening, Crabbé reaction, silylation of the secondary hydroxyl group, and finally deprotection of the primary one (Scheme 5.12).



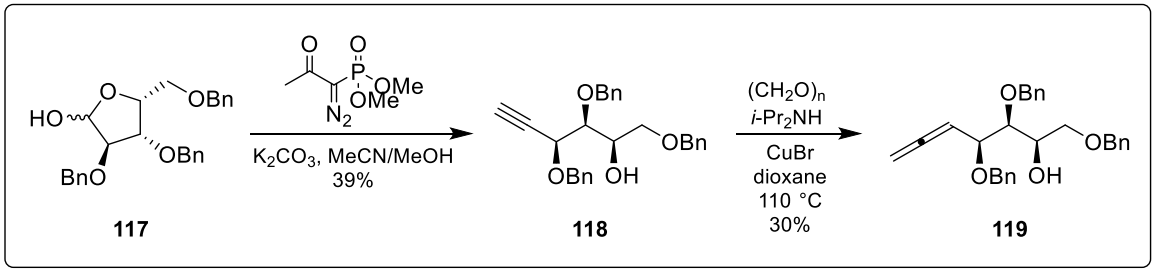
Scheme 5.12. Preparation of allenol **109**.

Substrate **116** was prepared from 1,3-propandiol **110**, which underwent mono-protection of one hydroxyl group and Swern oxidation to give aldehyde **112**, which in turn is attacked by TMS-acetylide to furnish alcohol **113**. At this point, Crabbé reaction, benzylation of the secondary hydroxyl group and deprotection of the primary one led to the desired product (Scheme 5.13).



Scheme 5.13. Preparation of allenol **116**.

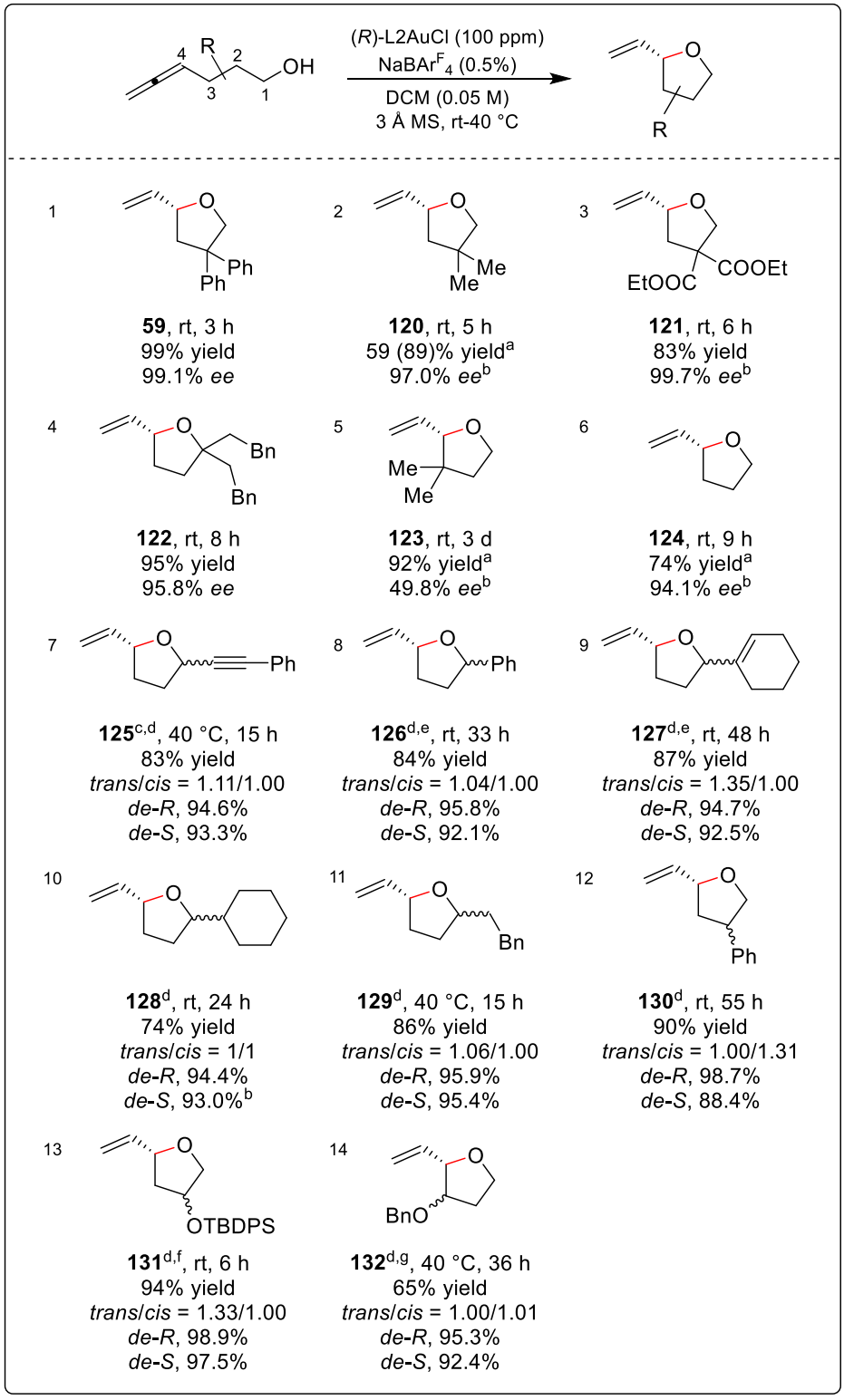
Substrate **119** was prepared from lactol **117**, which was treated with Ohira-Bestmann reagent to obtain **118**, which was transformed into the corresponding allene through the Crabbé reaction (Scheme 5.14).



Scheme 5.14. Preparation of allenol **119**.

5.6 Reaction scope

With the best conditions in hand, we promptly explored the reaction scope (Table 5.2).



[a]Volatile product. [b]The product was converted into its styril derivative via olefin cross metathesis for subsequent chiral HPLC analysis. [c]500 ppm catalyst were used. [d]The *de* value is given for each enantiomeric substrate and designated by its configuration. [e]200 ppm catalyst were used. [f]0.5 mol % catalyst and 1 mol % NaBAr$^F_4$ were used. [g]0.2 mol % catalyst were used.

Table 5.2. Reaction scope.

As shown in Table 5.2, entries 1-4, 4-allenols with germinal disubstitutions at the sp^3-

carbons generally exhibited excellent yield and enantioselectivity (up to 99.7%, entry 3) with 100-ppm catalyst loadings.

This includes the product **122**, which derives from the tertiary alcohol **84** (entry 4), indicating the steric hindrance around the -OH group does not affect in any way the reaction path. On the other hand, sterics next to the allene moiety, as in entry 5, led to a moderate *ee*.

In absence of the Thorpe−Ingold effect, the cyclization of the parent 4-allenol **90** remained highly enatioselective (94.1% *ee*, entry 6).

Besides the achiral 4-allen-1-ols, we also expanded the scope to the racemic substrates with pre-existing stereogenic centers, which are complicated by diastereoselective outcomes but of high synthetic significance due to their frequent occurrence in complex molecule synthesis.

As shown in entries 7−11, 4-allen-1-ols with various substituents at C1 such as phenylethynyl (entry 7), phenyl (entry 8), alkenyl (entry 9), cyclohexyl (entry 10) and phenethyl (entry 11) underwent the cyclization smoothly, affording the cyclized products in good yields (74% - 87%).

Most importantly, these reactions exhibited excellent allene *Re* face selectivities regardless the substrate configurations.

In each entry, the *de-R* and *de-S* values reflect the diastereomeric excesses of the products derived from the (*R*)- and (*S*)-substrates, respectively, and are calculated based on complete separation of the four product stereoisomers by chiral HPLC.

The reaction of a 2-phenyl-substituted 4-allen-1-ol, i.e. **103**, gave access to an exceptional 98.7% *de-R*, and a lower yet still good *de-S* (entry 12).

The reaction of **109**, instead, demanded a higher catalyst loading (0.5 mol %), possibly due to the bulky 2-tertbutyldiphenylsilanoxyl group, but the allene facial selectivities are excellent with both substrate enantiomers (entry 13).

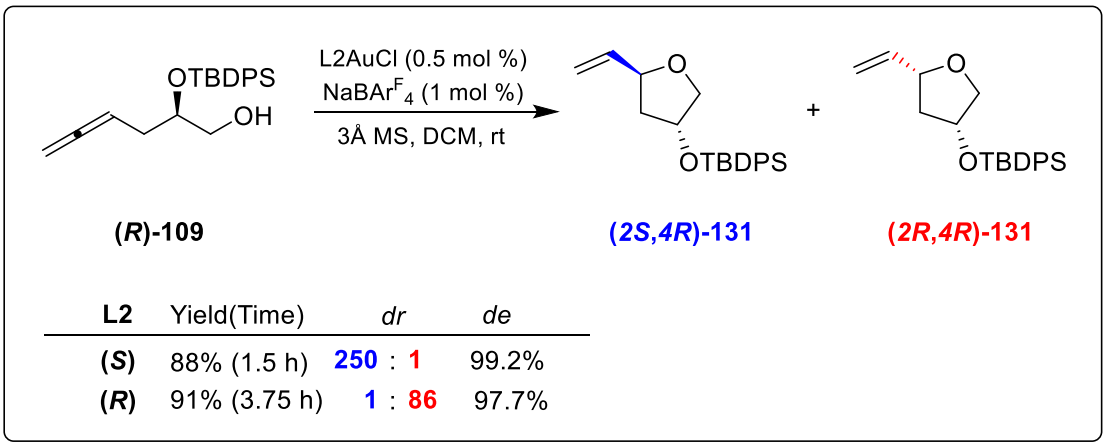
Finally, the reaction of a 3-benzyloxy group in **116** (entry 14) was also highly stereoselective, despite a moderate yield.

Notably, in all these cases (entries 7−14), the reactions exhibited poor *cis*/*trans* selectivities, confirming that the cyclization stereochemical outcomes can be little controlled by the substrate pre-existing chiral centers.

To confirm the exceptional allene facial selectivities with chiral substrates, the

enantiomerically enriched (*R*)-**109** (98.8% *ee*) was prepared from (*S*)-glycidol and subjected to the gold catalysis with **(*S*)-** and **(*R*)-L2AuCl** as catalyst precursor, respectively.

As expected, a complete switch of diastereoselectivity was observed along with excellent yields (Scheme 5.15); moreover, the *de* values are nearly identical to those obtained with racemic **109**.

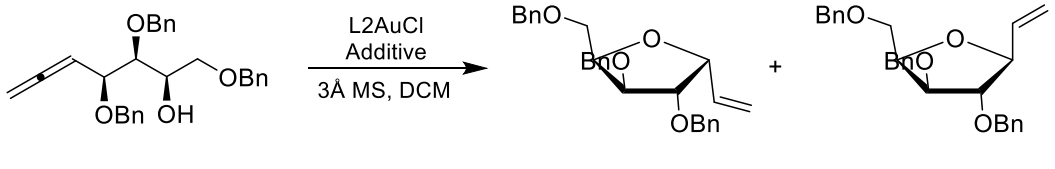


L2	Yield(Time)	*dr*	*de*
(*S*)	88% (1.5 h)	250 : 1	99.2%
(*R*)	91% (3.75 h)	1 : 86	97.7%

Scheme 5.15. Cyclization of (*R*)-**109**.

We attempted to briefly demonstrate the synthetic potential of this chemistry towards the synthesis of C-glycosides.

When the partially protected allene-polyol **119** was subject to the gold catalysis with **(*S*)-L2** as ligand, the vinyl C-xyloside α-**133** was formed exclusively in 82% yield (Scheme 5.16).



Catalyst	Yield(Temp, Time)	α-133 : β-133	*de*
(*S*)-L2 (1%)/NaBAr$^F_4$ (2%)	82% (40 °C,15 h)	Exclusive : -	>99.9%
(*R*)-L2 (5%)/AgSbF$_6$ (5%)	76% (rt, < 0.5 h)	1 : 6.5	73.3%
WangPhosAuCl/NaBAr$^F_4$	clean rxn, >99% conv.	16 : 1	
JohnPhosAuCl/NaBAr$^F_4$	messy reaction, trace product, >99% conv.		

Scheme 5.16. Cyclization of **119**.

With the ligand antipode, β-**133** was obtained in 76% yield and in a 6.5:1 diastereoselectivity.

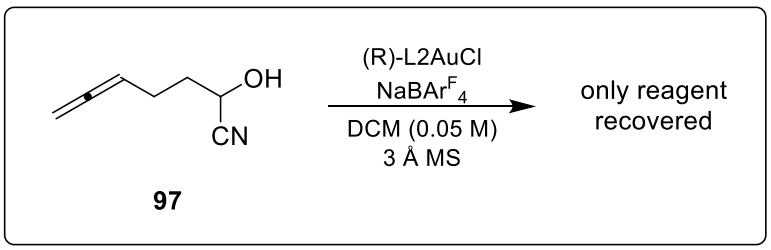
As the intrinsic diastereoselectivity with WangPhos favors α-**133** by a ratio of 16:1, this fair yet serviceable selectivity for the much disfavored β-isomer is noteworthy and can be synthetically useful.

Notably, when JohnPhos was used as gold ligand, the reaction was messy and traces of **133** were formed, which reveals the enabling nature of our designed ligands for cyclizations regardless asymmetric induction.

5.7 Unsuccessful attempts

Besides the successful attempts presented above, it is also important to describe the unsuccessful cases encountered in the reaction scope.

Firstly, cyclization of allenol **97** in the conditions reported in Table 5.2 did not lead to the desired product, but only reagent was recovered (Scheme 5.17).



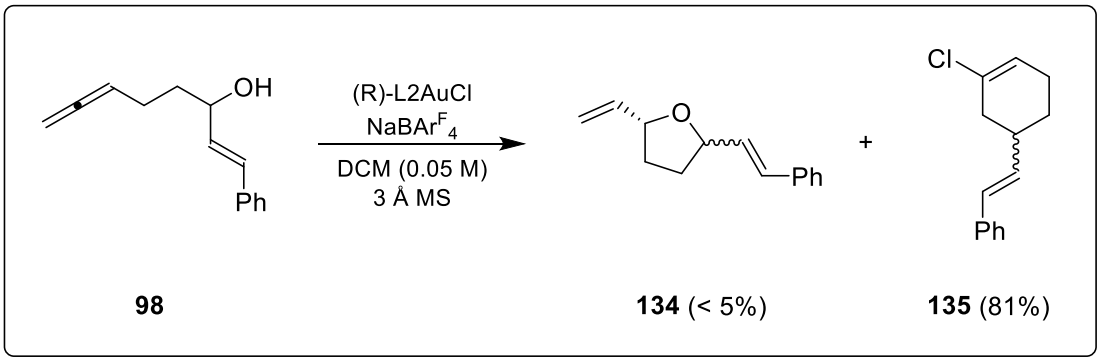
Scheme 5.17. Cyclization of **97**.

It is important to point out that during the reaction a very small amount of the aldehyde **90** was detected, as if the gold(I) catalyst would promote the dissociation of the cyanide functionality from the cyanohydrin **97**, forming a little amount of the corresponding aldehyde.

Better results were not obtained increasing the amount of gold(I) catalyst nor the temperature of the reaction.

The second unsuccessful attempt is represented by the cyclization of allenol **98**.

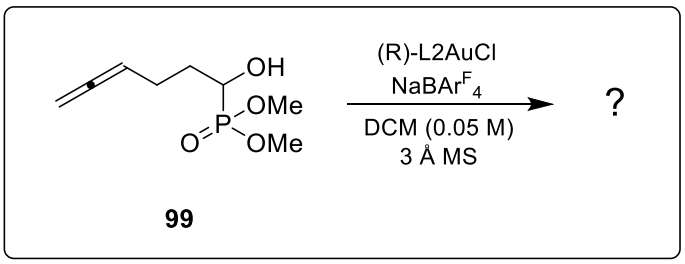
In this case the desired product **134** is obtained only in traces amount, whereas the major product of the reaction is the compound **135** (Scheme 5.18), obtained in 81% yield.



Scheme 5.18. Cyclization of **98**.

The mechanism leading to the undesired product **135** is still unknown, but the reagent is likely to react very fast with the counterion present in the reaction mixture, thus presumably forming a stabilized carbocation, which undergoes intramolecular cyclization reaction with the allene functionality.

The third unsuccessful case to date is that of allenol **99** (Scheme 5.19).
In this case, ths substrate bears a phosphonate group which may interact in an unknown way with the catalyst or the counterion present in the reaction mixture.
Like the previous case, the reaction goes to completion altough the product is not the desired one. However, its chemical structure has not been assigned yet.



Scheme 5.19. Cyclization of **99**.

CHAPTER 6: Study on the cyclization of Medius 54

6.1 Hypothesis

After focusing on the gold(I)-catalyzed hydroalkoxylation of 4-allenols, the attention has been drawn on the challenging gold(I)-catalyzed desymmetrization of the achiral bisallen alcohol **54** called "Medius", affording 2,4-disubstituted THF cores.

6.2 Optimization of reaction conditions

As regards the optimization of reaction conditions "naked" Medius **54** has been used as the substrate. The choice has been driven by the fact that in this case no Thorpe-Ingoldt effect can affect the outcome of the reaction.

Due to lack of desirable UV absorption for chiral HPLC analysis of the product **55**, a subsequent step was carried out to install a phenyl group as the chromophore.

In this context, a gold(I)-catalyzed intermolecular hydroalkoxylation reaction[84] has been exploited, through which a 3-phenyl-1-propanol unit could be added.

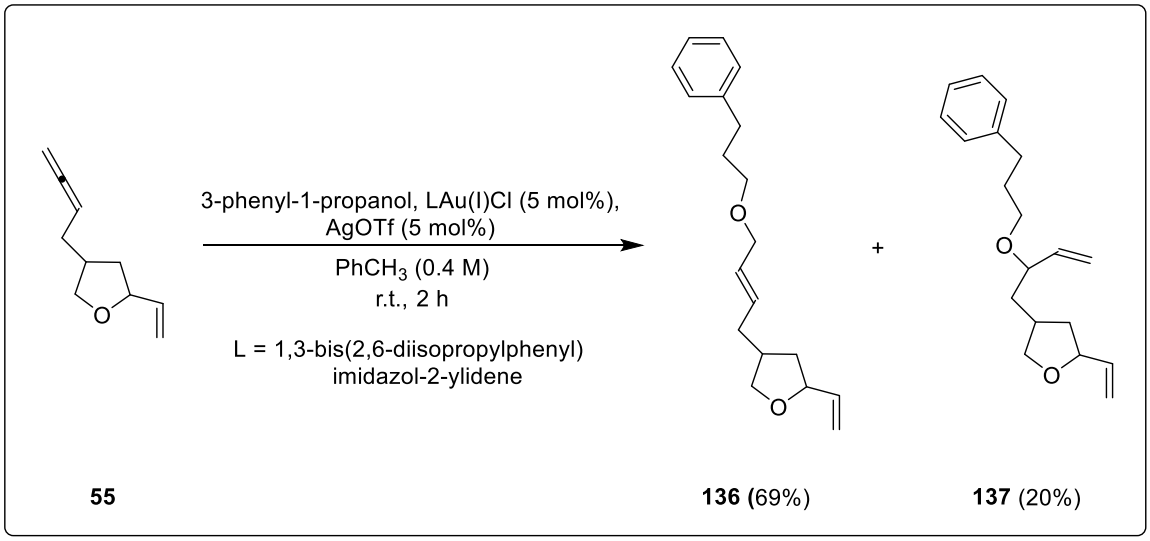
The reaction has been optimized using IPrAuCl as the gold(I) complex, AgOTf as the counterion, toluene as solvent, at room temperature.

Moreover, it can be performed without purification of the cyclized product.

The nucleophilic attack of the –OH group of the 3-phenyl-1-propanol can occur on both outer carbons of the allene system, and for this reason two regioisomers are obtained.

The major regioisomer is compound **136**, obtained in 69% yield, in which the attack of the hydroxyl group is on the terminal carbon of the allene system (Scheme 6.1).

[84] Z. Zhang, R.A. Widenhoefer, *Org. Lett.* **2008**, 10 (10), 2079.



Scheme 6.1. Functionalization of **55**.

For this reason, HPLC analyses were performed on **136**, the major regioisomer of the functionalized product.

Since the cyclization reaction promotes the formation of two new stereogenic centers, four possible stereoisomer of **55** can be obtained: a mixture of diastereoisomer (*cis* and *trans*), each of which is present as a racemate in achiral environmental conditions and as hopefully enantioenriched mixture in chiral environmental conditions (Figure 6.1).
The functionalization reaction, as proved by control experiments, does not affect the stereogenic centers already present in the cyclized product.

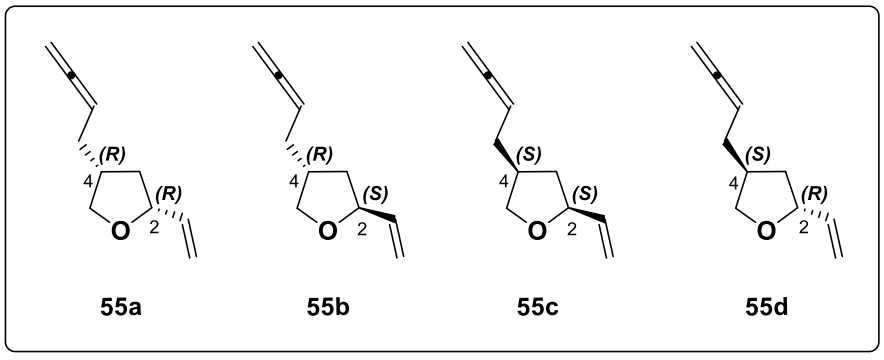


Figure 6.1. Stereoisomeric products of the cyclization reaction.

Unlike the gold(I)-catalyzed cyclization of 4-allenols described in Chapter 5, which was already present throughout the literature with the strategies of Widenhoefer, Toste and Mikami (see Chapter 3), the gold(I) cyclization of bisallen alcohols, and in particular of

Medius **54**, represents a novel issue in the literature scenario.
For this reason the optimization of reaction conditions, in this case, involves the variation of the experimental parameters in accordance with the above-illustrated strategies.

Firstly, the strategy adopted was that of Widenhoefer, relying on the use of chiral phosphinic gold(I) ligands (Figure 6.2) and achiral counterions.

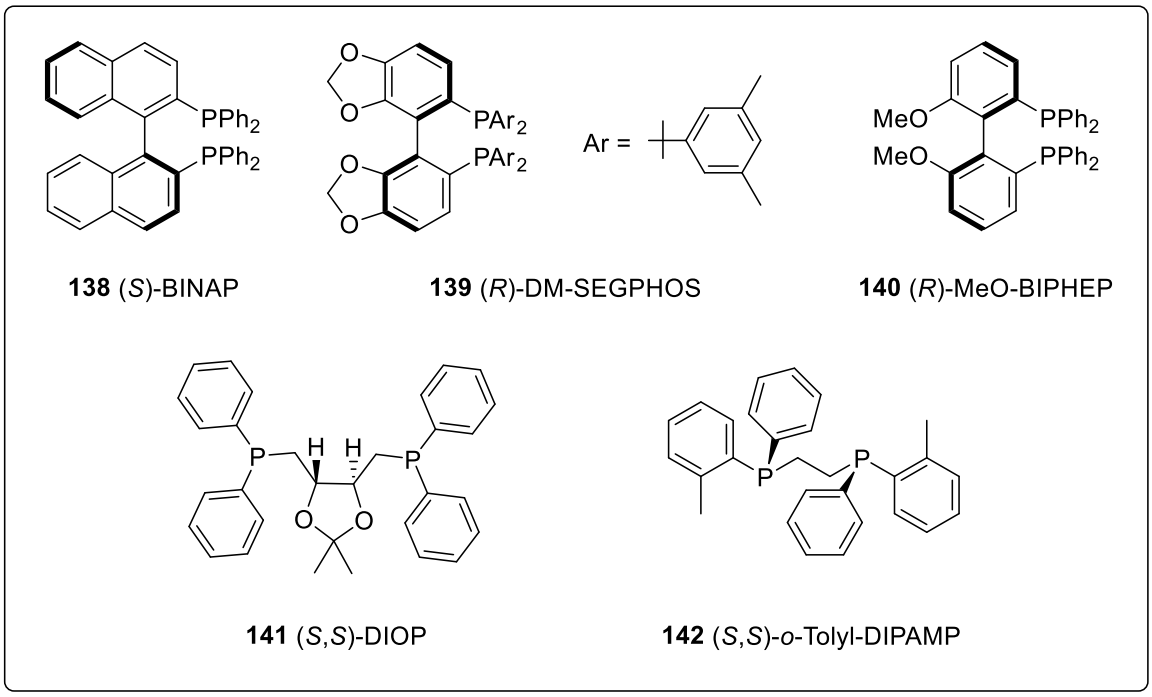


Figure 6.2. Chiral gold(I) ligands.

Reactions were conducted for three hours at room temperature, with toluene as solvent, 2.5 mol % of gold(I) catalyst, 5 mol % of counterion.
In Table 6.1 the results are reported, providing yields, *ee* and *dr* values.
For the determination of the absolute and relative configurations of the products see Chapter 8.
It is important to underline that in each of the following reported cases the major diastereoisomer is the *cis* one; the reported *ee* % values are represented with no sign if, considering **55**, the absolute configuration of C-2 of the major enantiomer is (*R*), whereas with the minus sign if its absolute configuration is (*S*).

Entry	Gold(I) ligand	Counterion	Yield(%)	ee_{cis} (%)	ee_{trans} (%)	$dr_{cis/trans}$
1	**138**	AgOTs	93	- 7	- 17	51/49
2	**139**	AgOTs	97	- 28	- 34	51/49
3	**140**	AgOTs	97	- 45	- 49	53/47
4	**141**	AgOTs	96	- 16	- 19	70/30
5	**142**	AgOTs	98	- 1	- 3	68/32

Table 6.1. Optimization of reaction conditions employing common chiral gold(I) phosphinic ligand.

As represented above, the best result is that reported in entry 3.

It is worth giving evidence to the fact that none of the common gold(I) phosphinic ligands used in Table 6.1 offers a good selectivity as regards either the *ee* and the dr values.

Thus, it can be assessed that the strategy exploited by Widenhoefer for the cyclization of 4-allenols is not suitable for this kind of substrate.

Better results were obtained using the chiral counterion strategy developed by Toste in 2007.

In this case different gold(I) mono- and bisphosphinic achiral ligands (Figure 6.3) as well as NHC carbenes have been used, together with a chiral counterion represented by Ag-(*S*)-TRIP **49**.

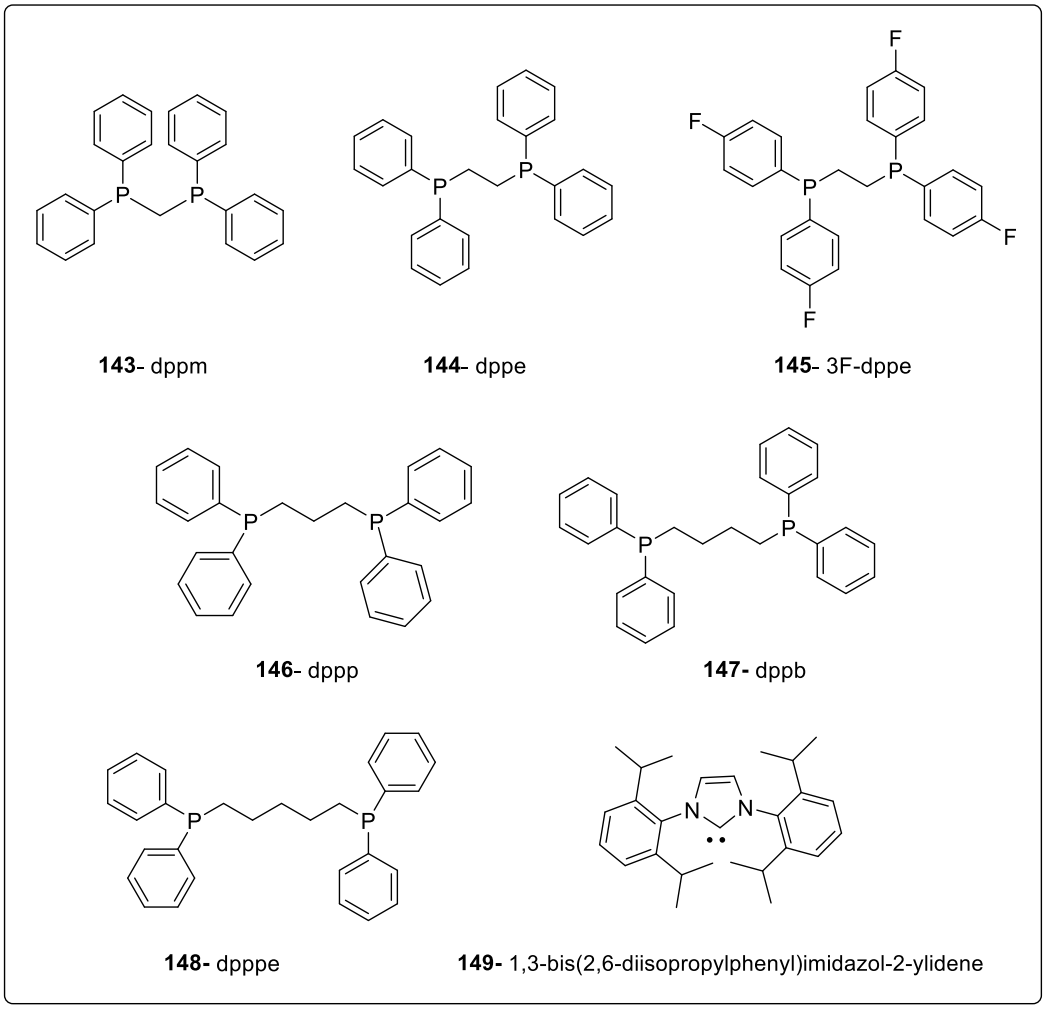


Figure 6.3. Achiral gold(I) ligands.

The reactions have been performed at room temperature, for 4 hours, using toluene as solvent, 2.5-5 mol % of gold(I) catalyst (depending on the type of phosphinic ligand, if respectively bidentate or monodentate), and 5 mol % of chiral counterion.

In Table 6.2 the results are reported, using the same conventions explained for the previous table.

Entry	Gold(I) ligand	Counterion	Yield(%)	ee_{cis} (%)	ee_{trans} (%)	$dr_{cis/trans}$
1	PPh_3	Ag-(*S*)-TRIP	98	60	70	64/36
2	tri-(*p*-OMe)PPh_3	Ag-(*S*)-TRIP	96	67	66	62/38
3	tri-(*p*-F)PPh_3	Ag-(*S*)-TRIP	99	39	43	57/43
4	**143**	Ag-(*S*)-TRIP	93	48	53	55/45
5	**144**	Ag-(*S*)-TRIP	96	62	82	54/46
6	**145**	Ag-(*S*)-TRIP	98	44	64	56/44
7	**146**	Ag-(*S*)-TRIP	98	55	68	56/44
8	**147**	Ag-(*S*)-TRIP	95	50	62	60/40
9	**148**	Ag-(*S*)-TRIP	97	46	42	61/39
10	**149**	Ag-(*S*)-TRIP	95	- 14	- 31	57/43

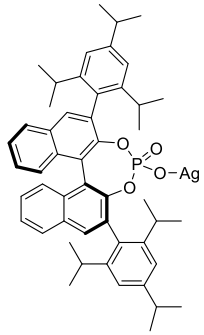
Table 6.2. Optimization of reaction conditions employing Ag-(*S*)-TRIP as chiral counterion.

Entry 5 represents, as can be seen, the best attempt using dppe **144** as gold(I) ligand.

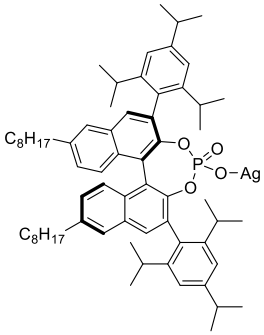
As a consequence, the optimization went on keeping fixed achiral ligand **144**, and changing type of chiral counterions.

In Table 6.3 the results of the chiral counterion screening are listed.

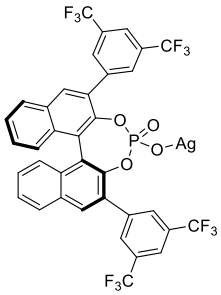
The reaction conditions are identical to those of Table 6.2.



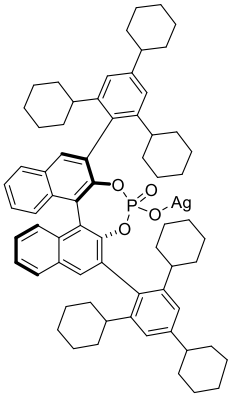
49- Ag-(*S*)-TRIP



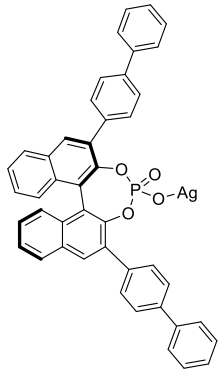
150- Ag-(*R*)-C8-TRIP



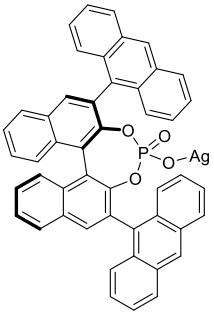
151- Ag-(*S*)-3,3'-bis[3,5-bis(trifluoromethyl)phenyl]-1,1'-binaphthyl-2,2'-diyl phosphate



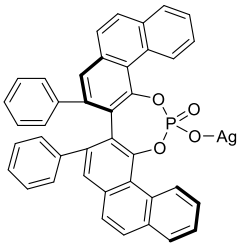
152- Ag-(*R*)-TCYP



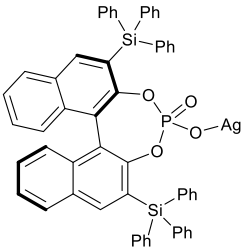
153- Ag-(*R*)-3,3'-bis(bisphenyl)-1,1'-binaphthyl-2,2'-diyl phosphate



154- Ag-(*R*)-3,3'-bis(9-anthracenyl)-1,1'-binaphthyl-2,2'-diyl phosphate



155-Ag-(*S*)-VAPOL phosphate



156- Ag-(*R*)-3,3'-bis(triphenylsilyl)-1,1'-binaphthyl-2,2'-diyl phosphate

Entry	Gold(I) ligand	Counterion	Yield(%)	ee_{cis} (%)	ee_{trans} (%)	$dr_{cis/trans}$
1	**144**	**150**	99	- 59	- 76	58/42
2	**144**	**151**	95	55	41	65/35
3	**144**	**152**	99	- 76	- 83	66/34
4	**144**	**153**	97	- 25	- 37	67/33
5	**144**	**154**	96	- 44	- 61	66/34
6	**144**	**155**	95	12	11	68/32
7	**144**	**156**	98	- 19	- 25	54/46

Table 6.3. Optimization of reaction conditions employing different chiral counterions.

As shown in Table 6.3, the *ee* values increase if the source of chirality is represented by the counterion.

In particular, the best result is reported in entry 3 using Ag-(*R*)-TCYP as chiral counterion,

which can be considered as a structural analogue of TRIP, in which the isopropyl groups are replaced by cyclohexyl ones.
Noteworthy is also the fact that higher *ee* values are accessed whenever a highly steric hindered chiral counterion is used (entries 1 and 3), instead of those characterized by an intrinsic spatial planarity (4-6).

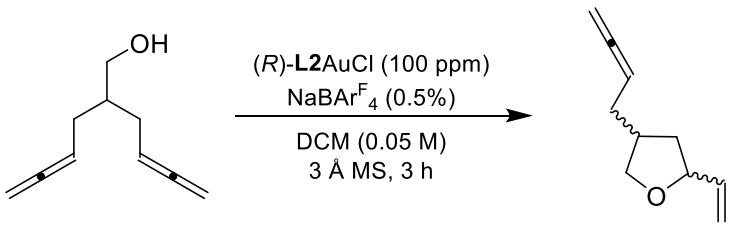
The strategy developed by Mikami in 2010 has also been briefly evaluated, exploiting the double source of chirality, deriving from either the Au(I) ligand and the counterion (Table 6.4).

Entry	Gold(I) ligand	Counterion	Yield(%)	ee_{cis} (%)	ee_{trans} (%)	$dr_{cis/trans}$
1	(*S*)-**140**	Ag-(*S*)-TRIP	45	59	52	53/47
2	(*R*)-**140**	Ag-(*S*)-TRIP	46	- 55	- 25	57/43

Table 6.4. Optimization of reaction conditions employing synergistic effect.

Unfortunately, this strategy does not lead to high selectivities.

Since "classical" methods relying on Au(I) catalysis for achieving enantioslectivity have proven to be not suitable in the cyclization of Medius, attention has been drawn on LAC approach described in the previous chapter.
In particular, the same reaction conditions used for the cyclization of 4-allenyl alcohols (see Table 5.2) has been used for the cyclization of Medius, that is the use of 100 ppm of **(*R*)-L2AuCl** (see Scheme 5.3) as gold(I) chiral complex, 0.5 mol % of $NaBAr^F_4$ as achiral counterion.
Moreover, a scr*ee*ning of the temperature of the reaction and the solvent has been performed (Table 6.5).



54 **55**

Entry	Solvent	Temperature	Yield(%)	ee_{cis} (%)	ee_{trans} (%)	$dr_{cis/trans}$
1	dioxane	rt	/	/	/	/
2	$CHCl_3$	rt	/	/	/	/
3	DCE	rt	96	89	95	67/33
4	toluene	-30 °C	93	80	71	71/29
5	DCM	rt	98	90	88	71/29
6	DCM	0°C	97	91	94	70/30
7	DCM	-10 °C	99	90	95	70/30
8	DCM	-30 °C	99	91	96	74/26
9	DCM	-65 °C	95	89	93	80/20
10	$PhCF_3$	rt	96	85	92	64/36
11	PhF	rt	97	88	94	63/37

Table 6.5. Optimization of reaction conditions employing **(*R*)-L2AuCl** 100 ppm and NaBAr$^F_4$ 0.5 mol %.

As shown in the table above, the best solvent for the selectivity of the reaction is DCM, which, at -30 °C, affords the best *ee* values (entry 8).

At higher or lower temperature *ee* values slightly decrease (entries 6, 7, 9).

One aspect to underline is that lowering the reaction temperature causes an increase in the *dr*. Thus, it can be stated that the temperature of -30 °C is the best compromise between high *ee* and *dr* values.

Trifluorotoluene, fluorobenzene and DCE afford good but not excellent selectivities (entries 3, 10, 11).

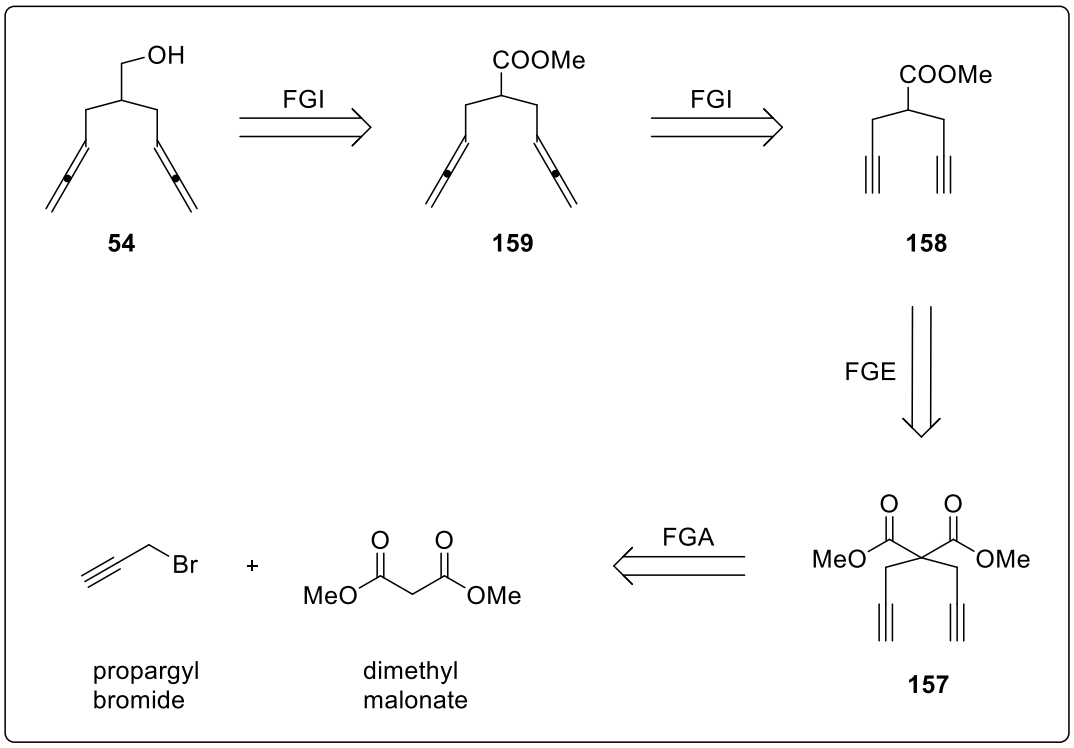
In the case of toluene (the best solvent for the classical strategies) *ee* values show a consistent decrease (entry 4).

With dioxane and chloroform the reaction did not lead to the expected product, but the reagent was entirely recovered (entries 1-2); in the case of dioxane, probably, the too marked polarity of the solvent did not afford the NaCl to precipitate and did make the formation of the active catalyst species inefficient.

6.3 Substrates synthesis

To begin with, analysis of the retrosynthesis of Medius **54** is described.

The first step of the retrosynthesis (Scheme 6.2) is represented by a FGI (functional group interconvertion) of Medius **54**, deriving from bisallenyl ester **159**, which is obtained from the corresponding bisalkynyl ester **158**. The latter, in turn, arise from compound **157** through a FGE (functional group elimination), whom synthons might be the commercially available and cheap methyl malonate and propargyl bromide.

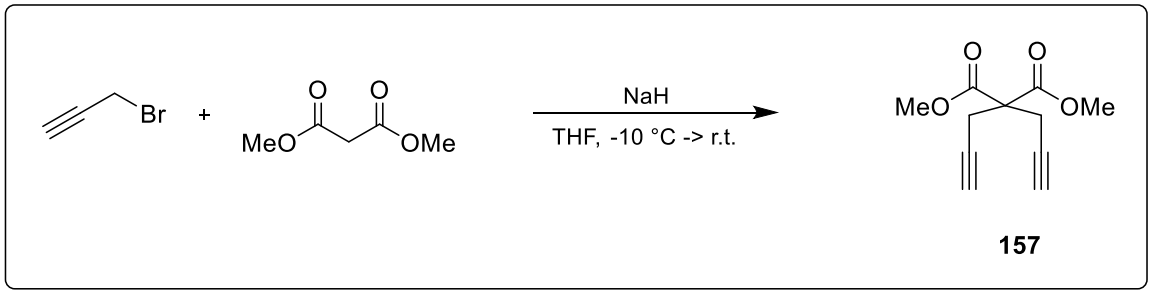


Scheme 6.2. Retrosynthesis of Medius.

The first steps of the synthesis of Medius, until bisalkynyl ester **158**, exploit the known synthesis proposed by Helquist.[85]

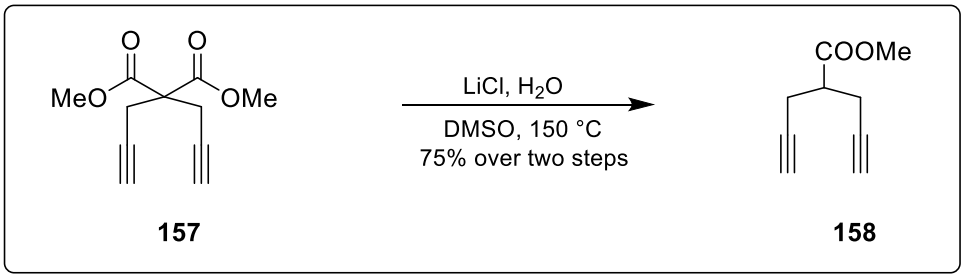
The first reaction is represented by a malonic protocol deprotonating dimethyl malonate with sodium hydride and making it react with two equivalents of propargyl bromide (Scheme 6.3).

[85] J.M. Carney, P.J. Donoghue, W.M. Wuest, O. Wlest, P. Helquist, *Org. Lett.* **2008**, 10, 3903.



Scheme 6.3. Malonic reaction.

As regards the subsequent decarboxylation reaction, an optimized variant of the classical protocol by Krapcho has been exploited, using lithium chloride and water (Scheme 6.4).

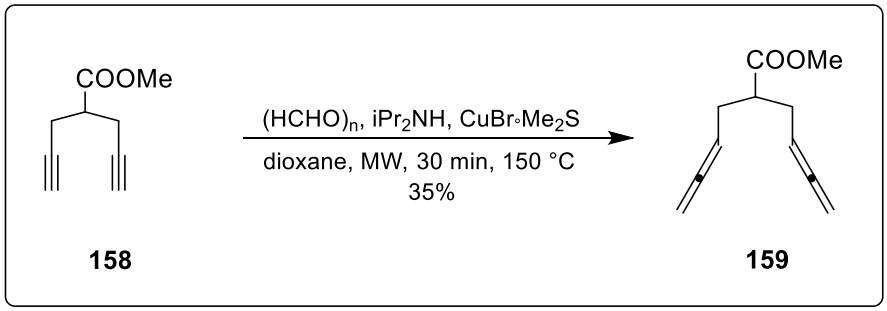


Scheme 6.4. Krapcho's decarboxylation reaction.

At standard temperature conditions, i.e. 180 °C, the product **158** undergoes degradation through formation of aromatic derivatives. For this reason, the temperature has been decreased at 150 °C, affording the desired product in 75% yield.

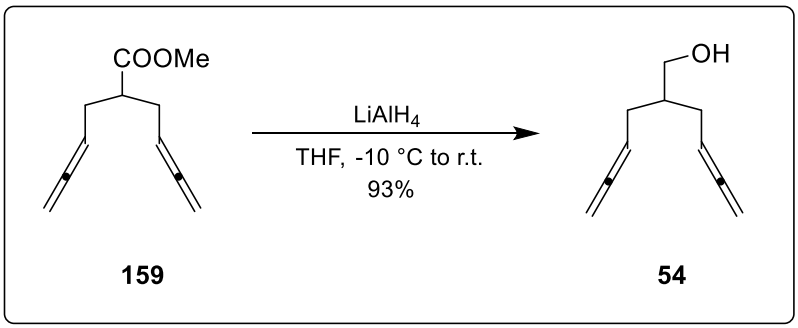
The preparation of the allene **159** is the most challenging step of the synthesis, since there are very few methods known in literature for this purpose, and all of them are characterized by low yields.

Optimization studies have proven for the Crabbé reaction to be the best solution to solve out this problem (Scheme 6.5).



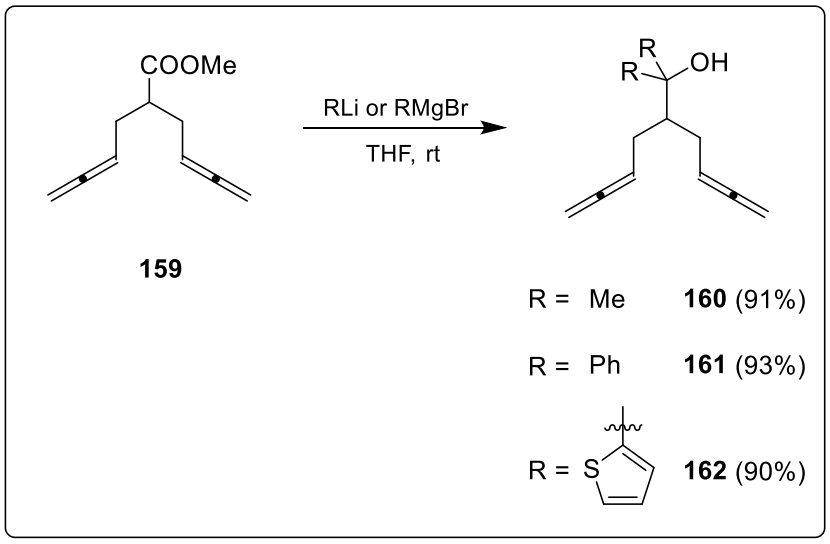
Scheme 6.5. Crabbé reaction.

The last step of the synthesis is the reduction of the bisallenyl ester **159** with $LiAlH_4$ to afford Medius **54** (Scheme 6.6).



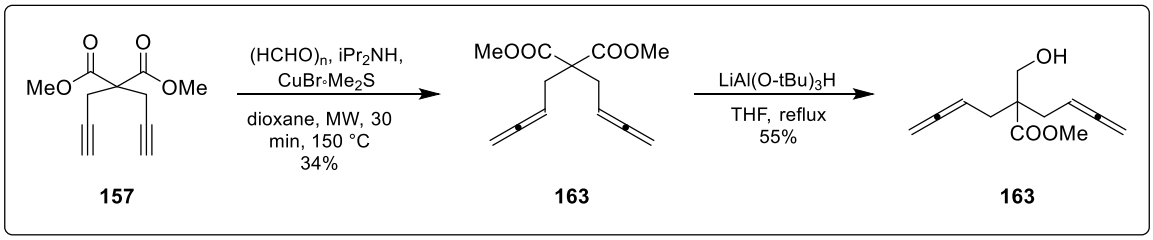
Scheme 6.6. Reduction of the ester **159**.

The synthesis of bisallenyl alcohols **160**-**162** is presented below.
Once obtained compound **159** through the above described synthetic pathway, treating it with two equivalents of the desired Grignard or organolithium reagent affords α-disubstituted bisallenyl alcohols (Scheme 6.7).



Scheme 6.7. Preparation of substrates **160**-**162**.

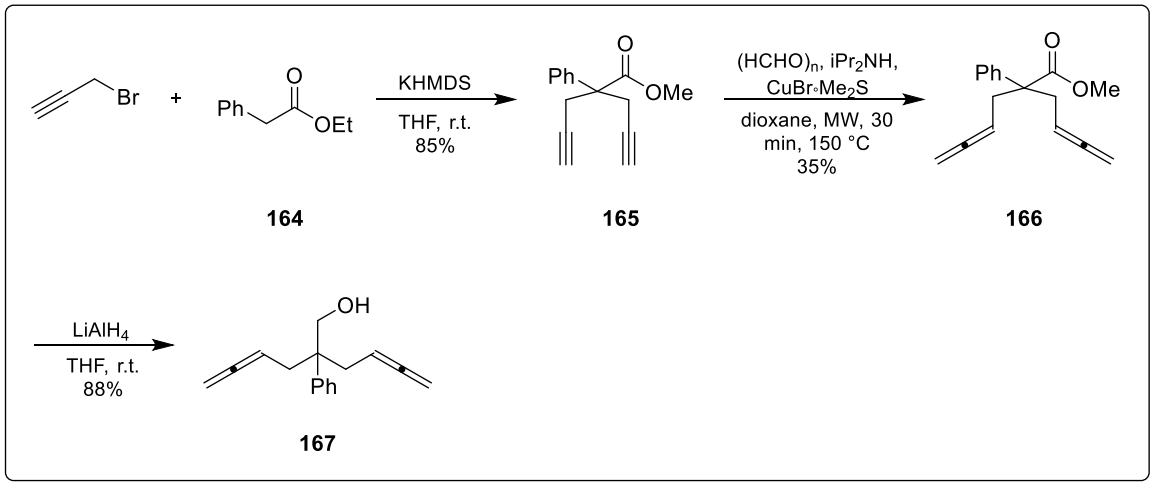
The synthesis of substrate **163** starts exploiting once again the above mentioned malonic reaction, compound **157** is obtained, which undergoes Crabbé reaction and subsequent mono-reduction of one of the two ester groups in 55% yield (Scheme 6.8).



Scheme 6.8. Preparation of substrate **163**.

The first step of the synthesis of substrate **167** can be considered a variant of the classical malonic reaction, in which two equivalents of propargyl bromide attack the commercially available ester **164**.

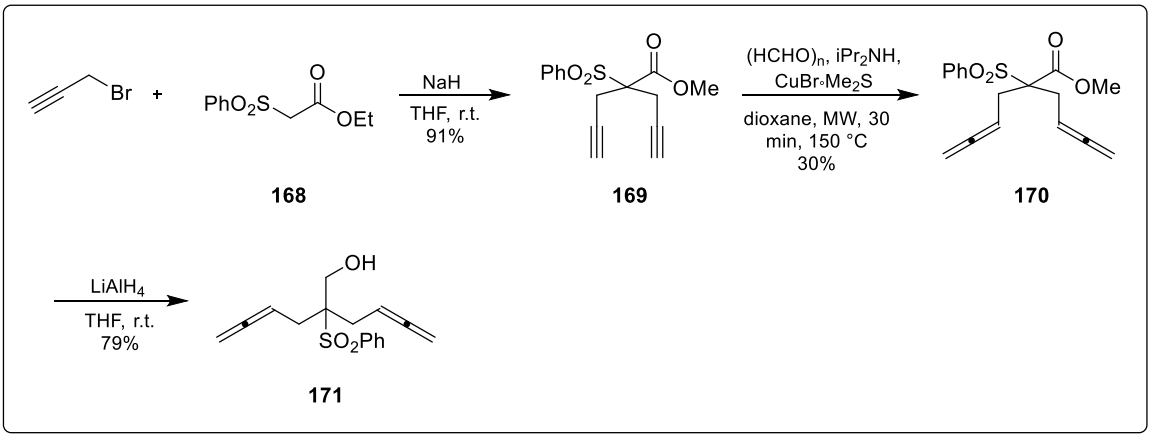
Subsequent Crabbé reaction and reduction of the ester group lead to the desired product (Scheme 6.9).



Scheme 6.9. Preparation of substrate **167**.

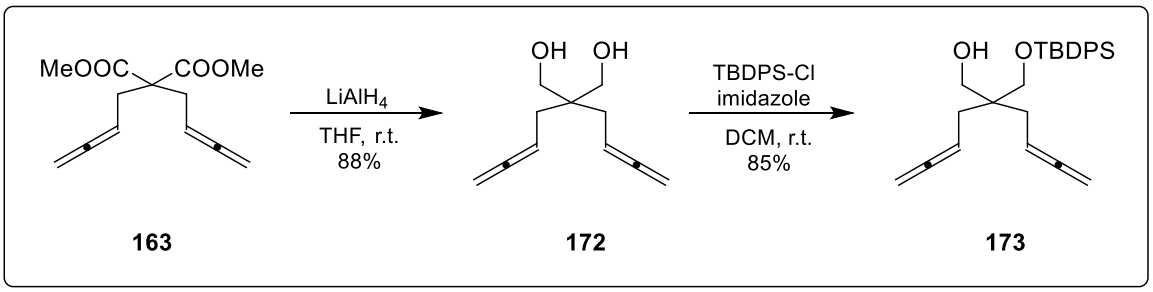
This synthetic route providing access to substrate **171** is similar to the previous one: the first step is a variant of the classical malonic reaction, in which two equivalents of propargyl bromide attack the commercially available compound **168**.

Subsequent Crabbé reaction and reduction of the ester group lead to the desired product (Scheme 6.10).



Scheme 6.10. Preparation of substrate **171**.

To prepare substrate **173**, the previously prepared compound **163** undergoes double reduction of the ester groups and subsequent monoprotection of diol **172** with TBDPS-Cl to obtain the desired product (Scheme 6.11).



Scheme 6.11. Preparation of substrate **173**.

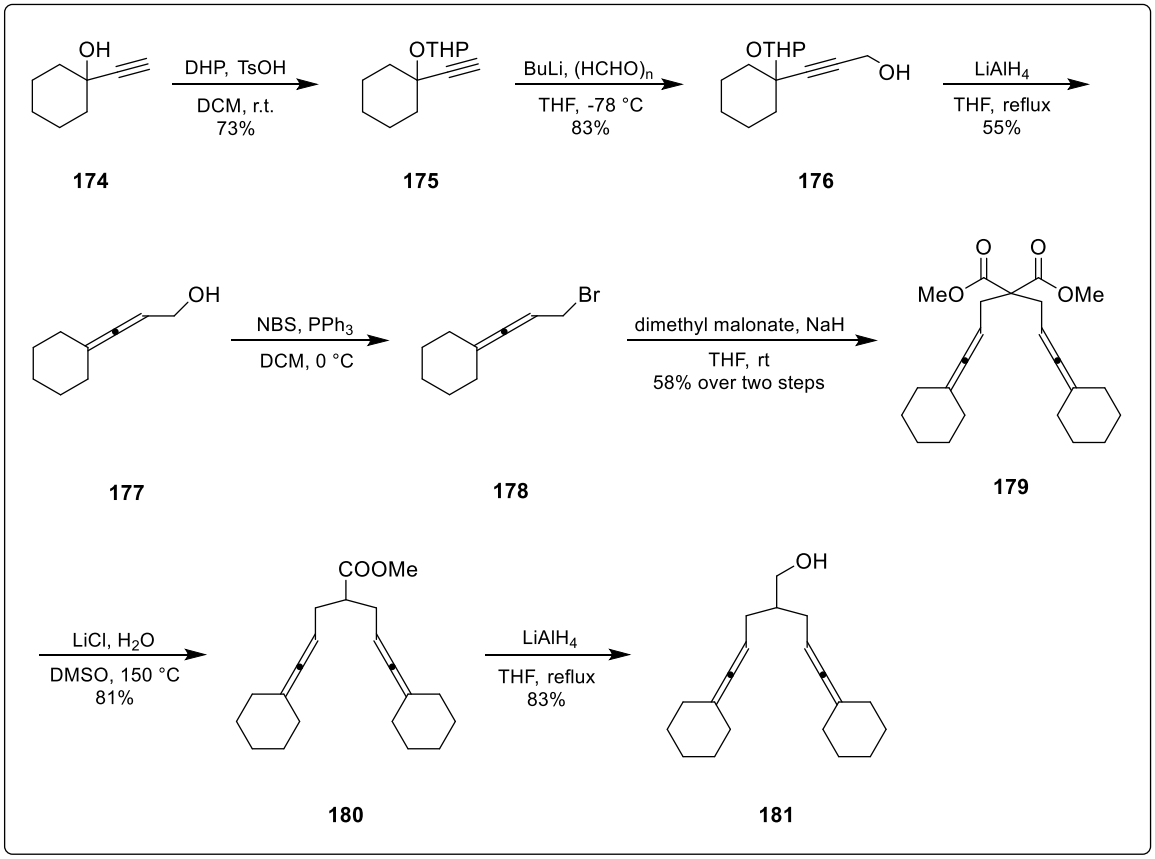
In order to prepare substrate **181**, as regards the first thr*ee* synthetic steps the protocol described by Tsuji[86] has been followed (Scheme 6.12).

The protection of the hydroxyl group of commercially available alcohol **174** affords the subsequent nucleophilic attack of the acetylide over formaldehyde to give **176**, which undergoes allenation reaction through a S_N2' mechanism.

At this point, primary alcohol **177** is transformed into the corresponding bromide **178**, which is submitted to the malonic reaction with dimethyl malonate.

Subsequent Krapcho's decarboxylation and reduction of the ester group afford the desired product.

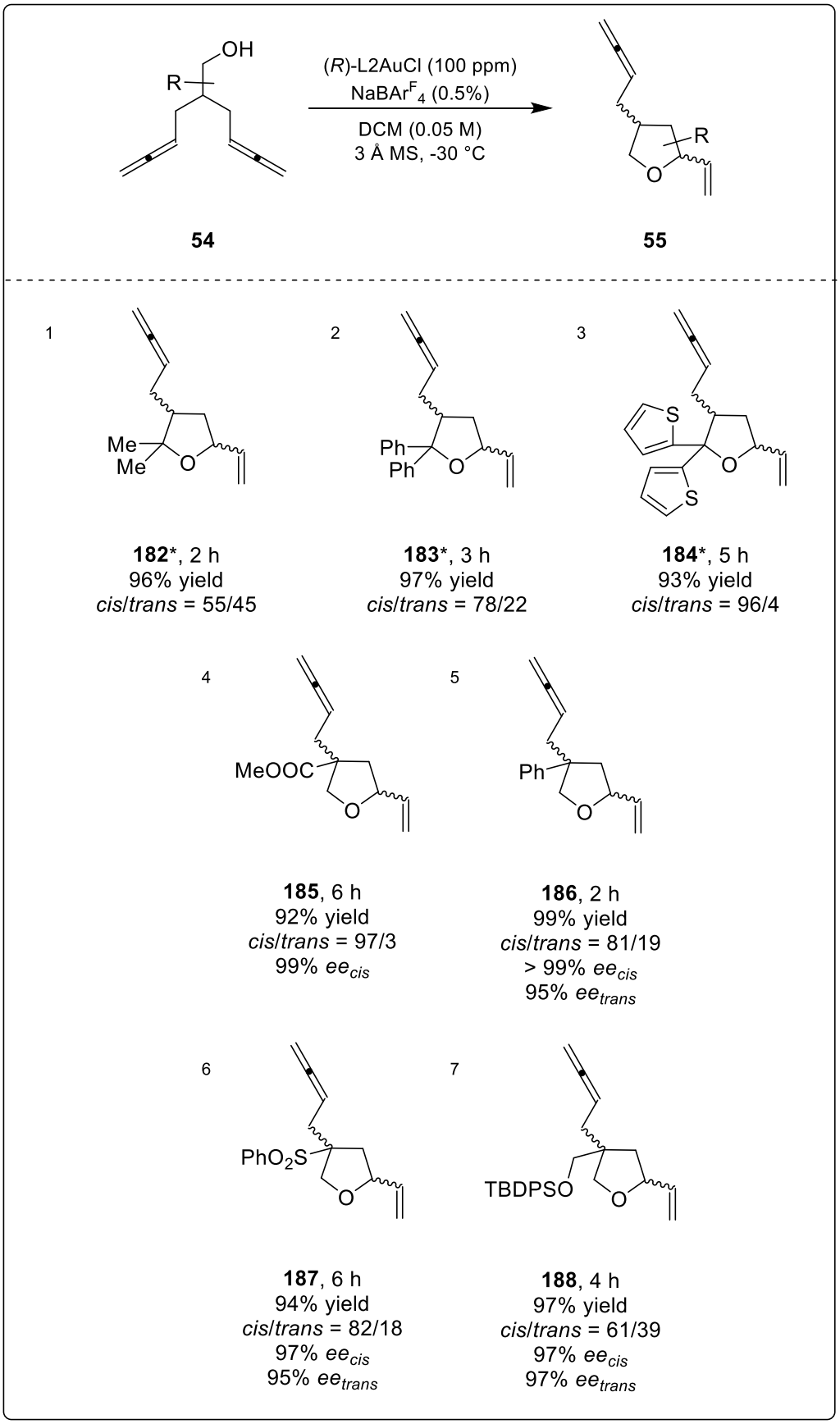
[86] K. Semba, T. Fujihara, J. Terao, Y. Tsuji, *Angew. Chem. Int. Ed.* **2013**, 52, 12400.



Scheme 6.12. Preparation of substrate **181**.

6.4 Reaction scope

With the best conditions in hand, we promptly explored the reaction scope (Table 6.6).



* *ee* values not determined yet.

Table 6.6. Reaction scope.

As shown in Table 6.6, entries 1-3, bisallen alcohols bearing a double substitution at the α position with respect to the –OH group generally exhibited excellent yield and moderate to high diastereoselectivity (*dr* 96/4 in favour of the *cis* diastereoisomer, entry 3) with 100-ppm catalyst loadings.

This includes the products **182** and **183**, which derive respectively from the tertiary alcohols **160** (entry 1) and **161** (entry 2), indicating the steric hindrance around the -OH does not limit the outcome of the reaction. In addition, thienyl groups present in product **184** are well tolerated (entry 3).

In absence of the Thorpe−Ingold effect, the cyclization of the parent bisallen alcohols possessing a substitution at the β position with respect to the –OH group remained as good as the previous cases.

In particular, product **185** possessing an ester group is obtained in 92% yield as a single *cis* diastereoisomer (*dr*: 97/3) in 99% *ee* (entry 4).

The same exceptional trend as regards yields and enantioselectivities is maintained in entries 5-6, in which products **186** and **187** present respectively a phenyl and a sulphonyl substituent, although the diastereomeric ratio exhibits a slight decrease compared to entry 4.

Also a tert butyl diphenyl silyloxy group as substituent in product **188** is well tolerated as represented in entry 7.

On the whole, all these reactions exhibited excellent yields accompanied by moderate to excellent *dr* values in favour of the *cis* isomer and exceptional enantiomeric excesses, in the cases they could have been determined.

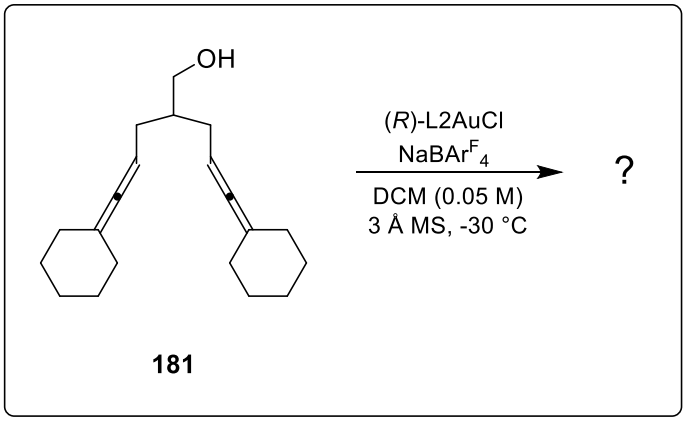
Unfortunately, owing to problems related to the HPLC analyses caused by the particular features of the products obtained, some of the *ee* values could not be determined. In the next future, these *ee* values will hopefully be obtained.

6.5 Unsuccessful attempts

Besides the successful attempts presented above, it is also important to describe the unsuccessful cases encountered in the reaction scope.

Notably, cyclization of bisallen alcohol **181** (bearing two cyclohexyl groups on the allene moieties) in the conditions reported in Table 6.6 did not lead to the desired product, which was found only in traces amount (Scheme 6.13).

The reaction proc*ee*ded to completion, forming several by-products, whose chemical structure has not been assigned.



Scheme 6.13. Cyclization of **181**.

CHAPTER 7: Study on the cyclization of Remotus 56

7.1 Hypothesis

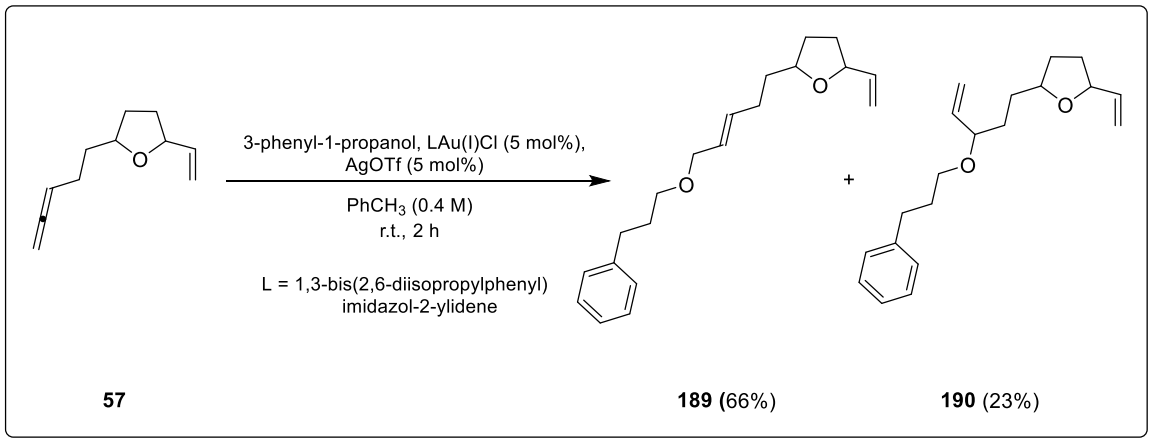
After focusing on the gold(I)-catalyzed hydroalkoxylation of Medius **54**, the attention has been drawn on the gold(I)-catalyzed desymmetrization of the achiral bisallen alcohol **56** called "Remotus", providing access to 2,5-disubstituted THF cores.

7.2 Optimization of reaction conditions

As regards the optimization of reaction conditions "naked" Remotus **56** has been used as the substrate.

Like in the case of Medius, due to lack of desirable UV absorption for chiral HPLC analysis of the product **57**, a subsequent step was carried out to install a phenyl group as the chromophore.

In this context, the same strategy used for Medius has been exploited, affording compound **189** in 66% yield as the major regioisomer and compound **190** as the minor one (Scheme 7.1).



Scheme 7.1. Functionalization of **57**.

For this reason, HPLC analyses were performed on **189**, the major regioisomer of the functionalized product.

The stereochemical features of the reaction resemble those described in the case of Medius.

As the cyclization reaction promotes the formation of two new stereogenic centers, four possible stereoisomer of **57** can be obtained: a mixture of diastereoisomer (*cis* and *trans*), each of which is present as a racemate in achiral environmental conditions and as hopefully enantioenriched mixture in chiral environmental conditions (Figure 7.1).

The functionalization reaction, as proved by control experiments, does not affect the stereogenic centers already present in the cyclized product.

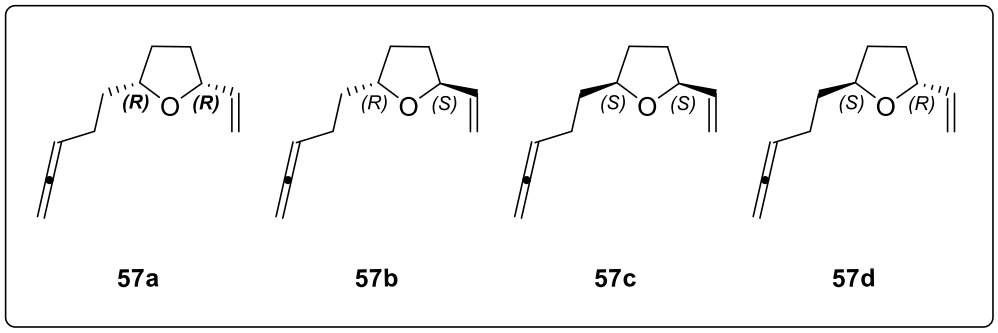


Figure 7.1. Stereoisomeric products of the cyclization reaction.

Considering the results obtained in the case of Medius, the decision not to test classical chiral gold(I) phosphinic complexes as source of selectivity has been taken.

Accordingly, the attention has been focused directly on the screening of chiral counterions, keeping fixed dppe **144** as achiral gold(I) ligand.

Reactions were conducted for four hours at room temperature, with toluene as solvent, 2.5 mol % of gold(I) catalyst, 5 mol % of counterion.

In Table 7.1 the results are reported, providing yields, *ee* and *dr* values.

For the determination of the absolute and relative configurations of the products see Chapter 8.

It is important to underline that, like in the case of Medius, in each of the following reported cases the major diastereoisomer is the *cis* one; the reported *ee* % values are represented with no sign if, considering **57**, the absolute configuration of C-2 of the major enantiomer is (*R*), whereas with the minus sign if its absolute configuration is (*S*).

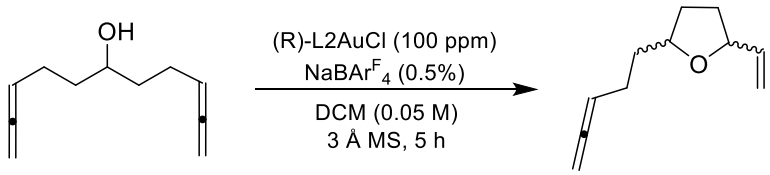
Entry	Gold(I) ligand	Counterion	Yield(%)	ee_{cis} (%)	ee_{trans} (%)	$dr_{cis/trans}$
1	**144**	**49**	96	82	65	71/29
2	**144**	**150**	98	- 86	- 74	71/29
3	**144**	**151**	93	39	56	61/39
4	**144**	**152**	95	- 87	- 81	68/32
5	**144**	**153**	95	- 34	- 35	61/39
6	**144**	**154**	97	- 71	- 72	68/32
7	**144**	**155**	98	19	27	56/44

Table 7.1. Optimization of reaction conditions employing different chiral counterions.

As already described for the cyclization of Medius, the best results as regards enantioselectivity have been achieved using Ag-(*R*)-TCYP **152** as chiral counterion (entry 4), although good *ee* values can be obtained also employing Ag-(*R*)-C8-TRIP **152** (entry 2).

Since the method relying on chiral counterions for achieving enantioslectivity has proven to be not excellent in the cyclization of Remotus, attention has been drawn on LAC approach described in the previous chapters.

In particular, the same reaction conditions used for the cyclization of Medius (see Table 6.5) has been used for the cyclization of Remotus, that is the use of 100 ppm of **(*R*)-L2AuCl** (see Scheme 5.3) as gold(I) chiral complex, 0.5 mol % of $NaBAr^F_4$ as achiral counterion. Moreover, a brief screening of the temperature of the reaction has been carried out (Table 7.2).



56 **57**

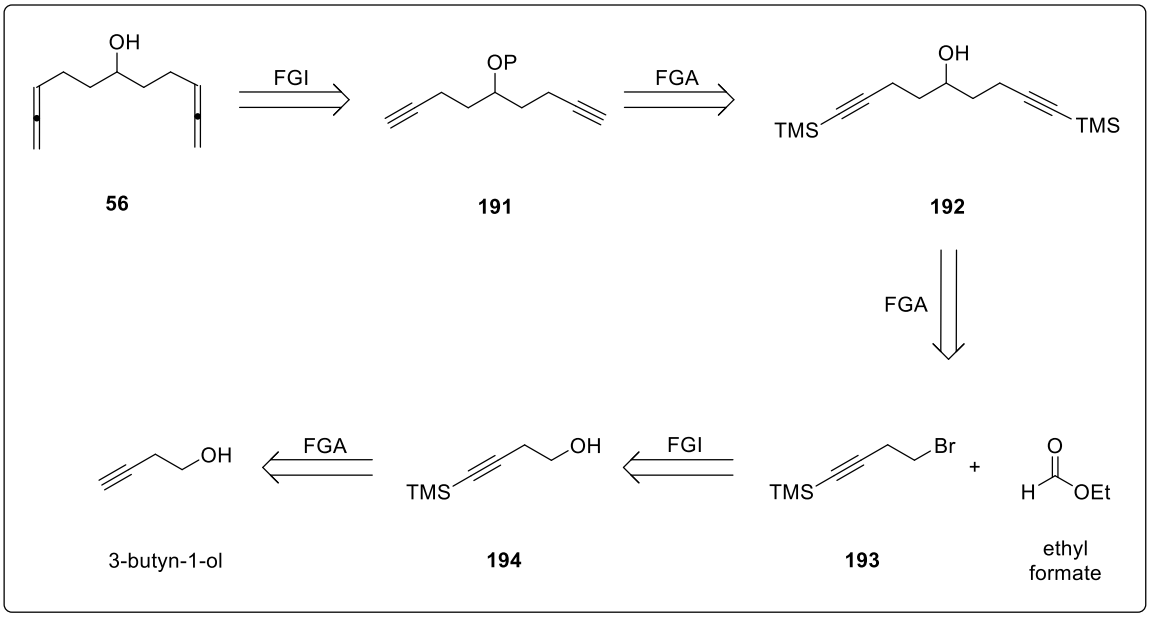
Entry	Solvent	Temperature	Yield(%)	ee_{cis} (%)	ee_{trans} (%)	$dr_{cis/trans}$
1	DCM	rt	98	93	94	50/50
2	DCM	-10 °C	97	91	89	54/46
3	DCM	-30 °C	/	/	/	/

Table 7.2. Optimization of reaction conditions employing (R)-L2AuCl 100 ppm and $NaBAr^F_4$ 0.5 mol %.

As shown in the table above, the best temperature for the enantioselectivity of the reaction is room temperature, affording the best *ee* values (entry 1).
At lower temperatures *ee* values, like in the case of Medius and 4-allenols, slightly decrease and dr values slightly increase (entry 2).
At a temperature of -30 °C the reaction does not proc*ee*d at all (entry 3), recovering the substrate.

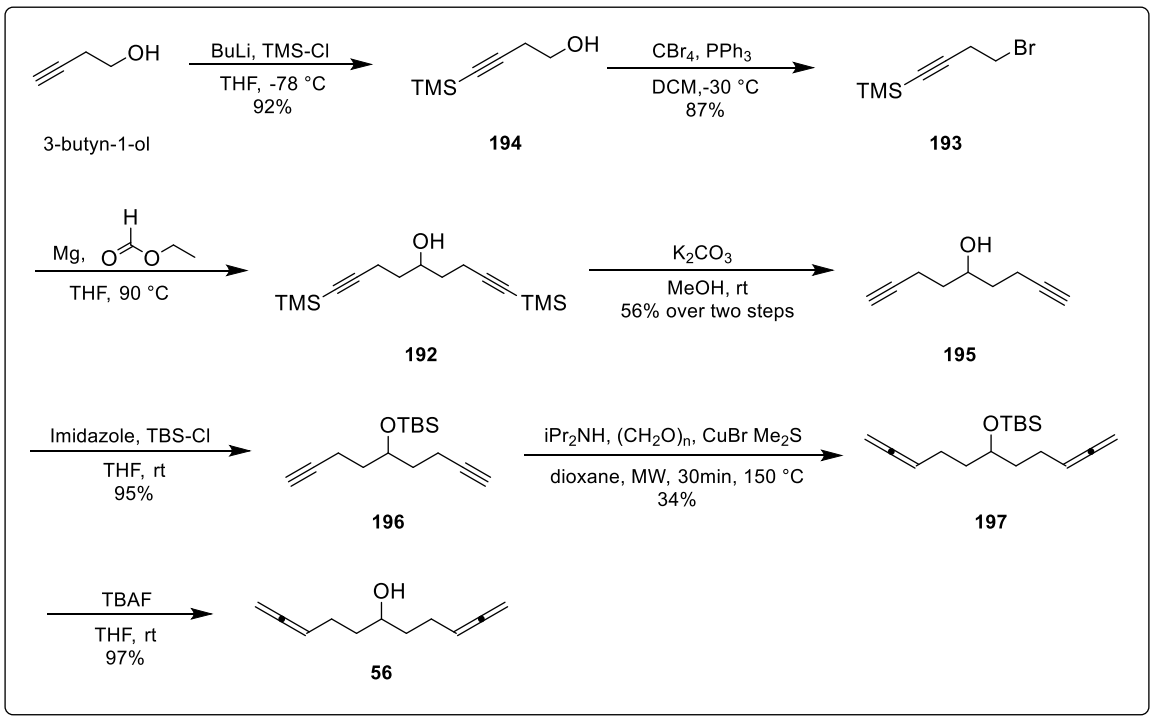
7.3 Substrates synthesis

To start, the retrosynthesis of Remotus is described (Scheme 7.2).
The first step is represented by a FGI of Remotus **56**, deriving from bisalkynyl protected alcohol **191**, which is obtained from **192** and again from bromide **193** and commercially available ethyl formate through a FGA (functional group addition). The former arise from the commercially available 3-butyn-1-ol.



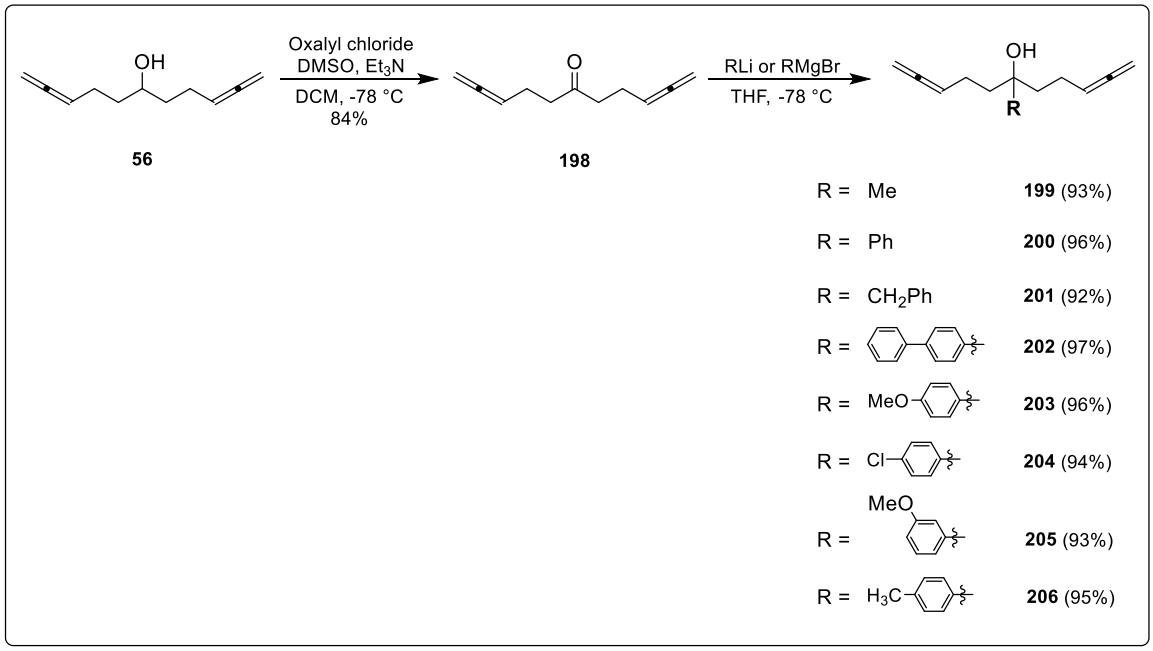
Scheme 7.2. Retrosynthesis of Remotus **56**.

From a synthetic point of view (Scheme 7.3), the process starts with the sylilation of the 3-butyn-1-ol, followed by bromination of the hydroxyl group to afford bromide **193**.
Subsequent double Grignard addition over ethyl formate and deprotection of –TMS groups leads to alcohol **195**, which undergoes protection, allenation reaction and deprotection to obtain the desired product.



Scheme 7.3. Synthesis of Remotus **56**.

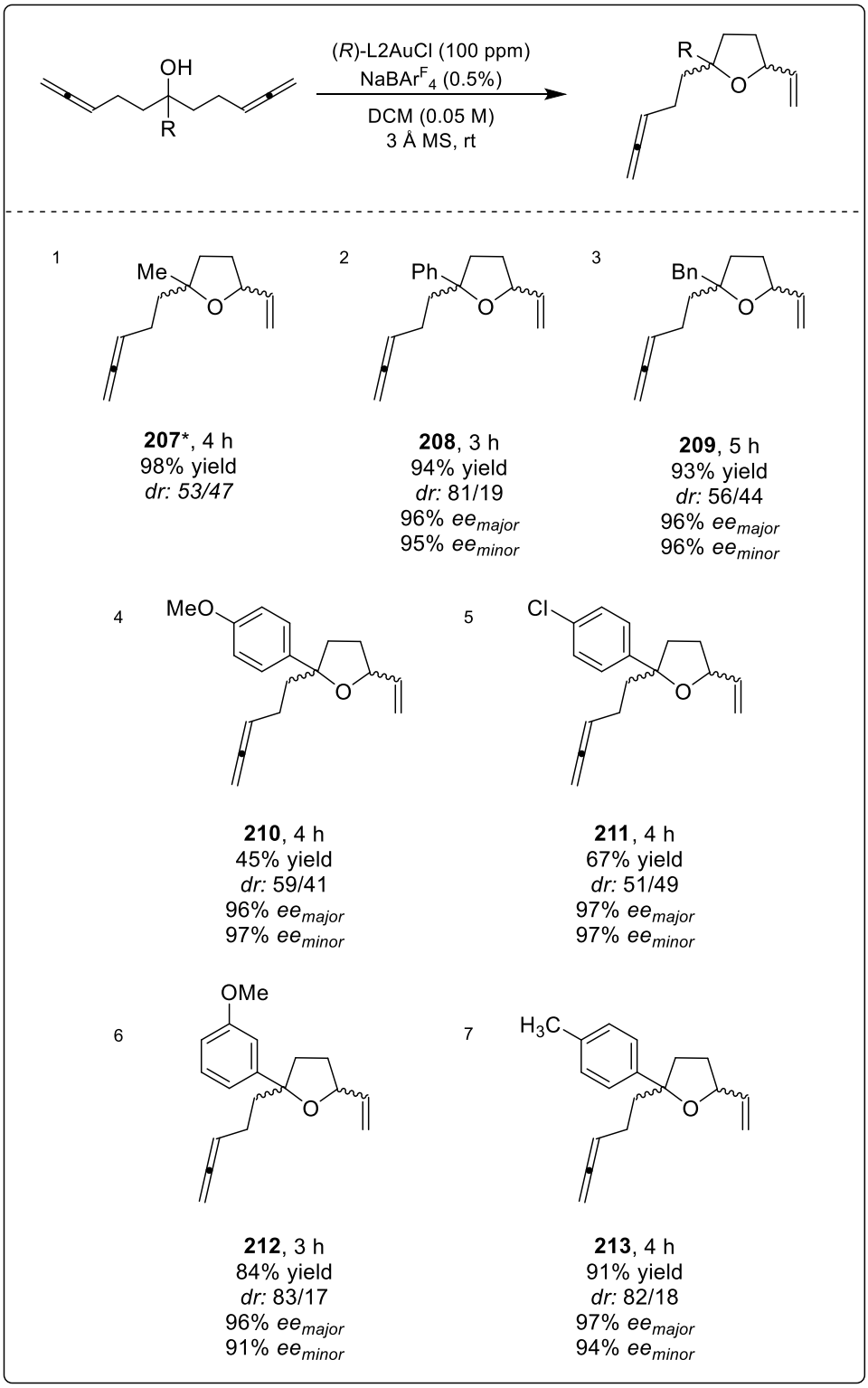
Remotus **56** underwent Swern oxidation, and the ketone **198** was attacked by different Grignard/Organolithium reagents to furnish **199-206** (Scheme 7.4).



Scheme 7.4. Preparation of substrates **199-206**.

7.4 Reaction scope

With the best conditions in hand, we promptly explored the reaction scope (Table 7.3).



* *ee* value not determined yet.

Table 7.3. Reaction scope.

As shown in Table 7.3 bisallen alcohols bearing a single substitution at the α position with respect to the –OH group have only been taken into account, owing to the long and complicate synthetic processes necessary to obtain different substitution patterns. Generally these substrate exhibited modest to exceptional yields and moderate to good diastereoselectivities (*dr* 81/19, entry 2) with 100 ppm catalyst loadings.

Enantiomeric excesses, with values steadily higher than 90%, show the same exceptional values as in the case of Medius.

The highest yields, in accordance with those obtained in the previous chapters, are obtained in entry 1-3, in which the products **207**, **208** and **209** bear respectively a methyl, a phenyl and a benzyl group as substituent.

In entry 4-7, on the contrary, a decrease in yield is observed, as a consequence of a collateral reaction which gives origin to a different product compared to what expected.

Notably, the collateral reaction seems to assume more importance by increasing the stability of the carbocation that can be formed in the substrate if the hydroxyl group is lost as OH^-. In fact, the more the carbocation is stabilized, the higher is the yield of the by-product and, of course, the lower is the yield of the right product. In this context, the methoxy group present in the *para* position of the phenyl ring of substrate **203** promptly exerts a strong mesomeric stabilization of the carbocation, which causes a dramatic decreasing of the reaction yield of the product **210** (entry 4). Also in the case of substrate **204** the same situation occurs (entry 5), but of slight lesser extent due to the weaker donation power of the chloride group with respect to the methoxy one.

The last two entries of the table show a significant improvement in the reaction yields, since the weak electron-donating nature of the 3-methoxy and the 4-methyl groups in the phenyl rings of substrate **205** and **206**.

Finally, the cyclization of substrate **202**, possessing an extremely strong biphenyl group as substituent, did not lead to the desired product **214**, but only the formation of the byproduct is observed.

The exact structure of the byproducts has not been investigated in detail, but it is reckonable that an analogue situation/plausible mechanism compared to that described in Scheme 5.18 can occur even in this case.

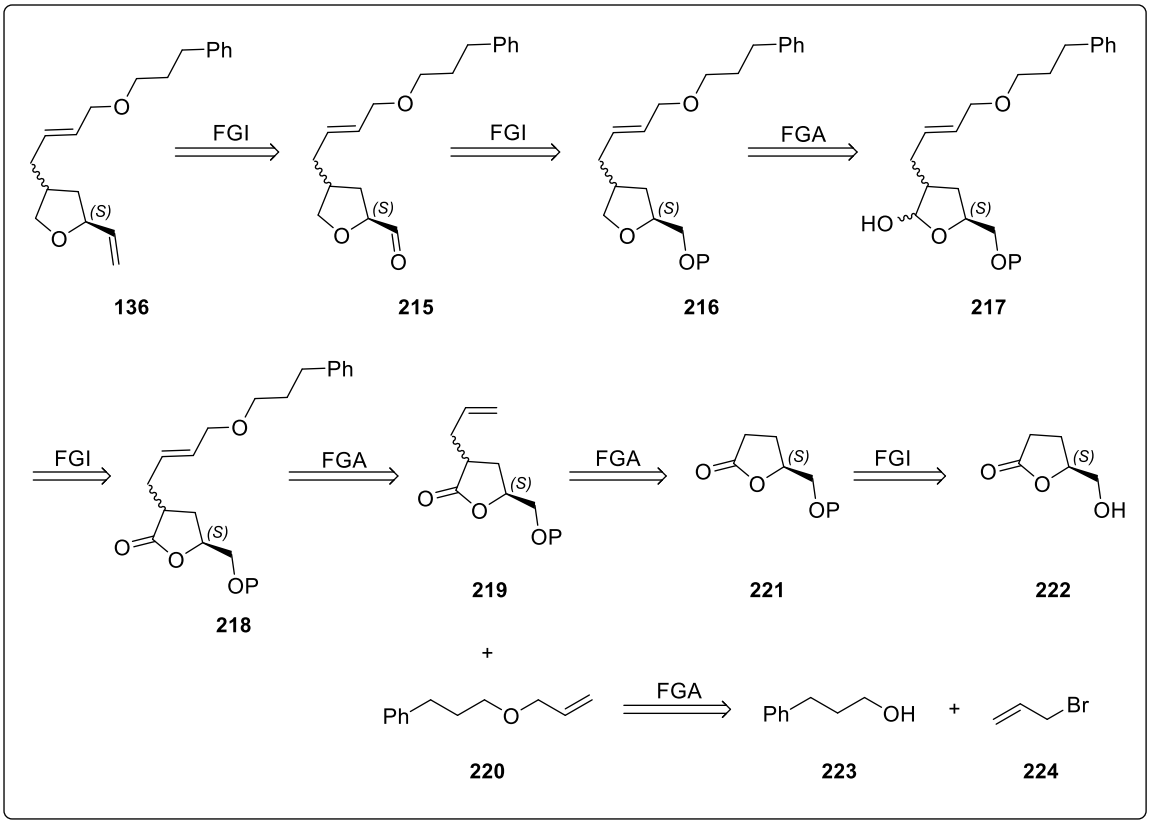
Unfortunately, owing to the same problems related to the HPLC analyses previously described, the *ee* value for the compound in entry 1 could not be determined.

CHAPTER 8: Determination of the absolute and relative configuration of the cyclization products of Medius 54

After having carried out a complete methodological work for the gold(I)-catalyzed cyclization reaction of Medius and Remotus, the attention has been drawn towards the determination of the absolute and relative configuration of the stereogenic centers present in the cyclized products of Medius, in order to verify the selectivity of the reaction.

In this context, the strategy adopted for the purpose is that of synthesizing the functionalized product **136**, starting from commercially available enantiopure lactone **218**, proceeding through reaction pathways which could afford a complete control over the formation of the second stereogenic center.

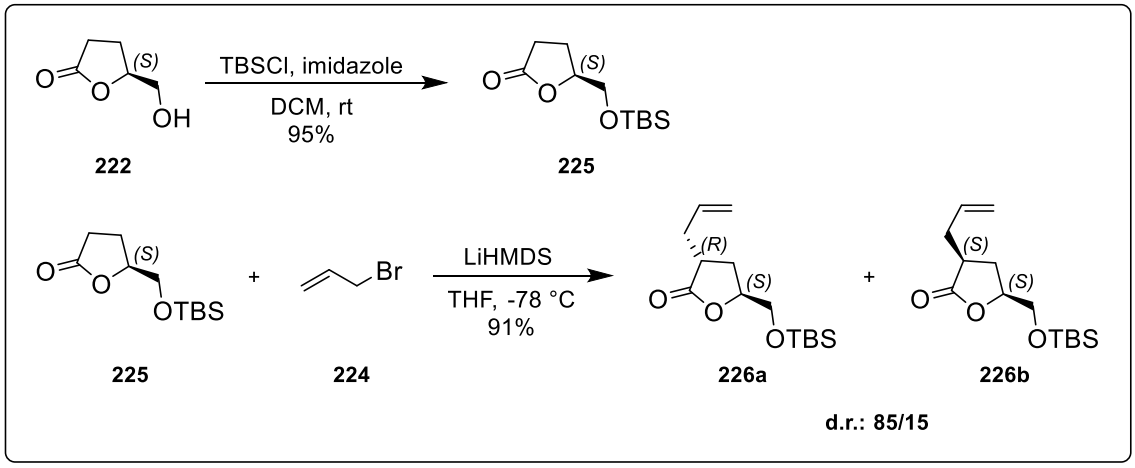
The retrosynthetic analysis is reported in Scheme 8.1: compound **136** derives trough a series of FGAs and FGIs from **219** and **220**, which can be obtained respectively from lactone **222** and allyl bromide **224**, both of them commercially available.



Scheme 8.1. Retrosynthesis of **136**.

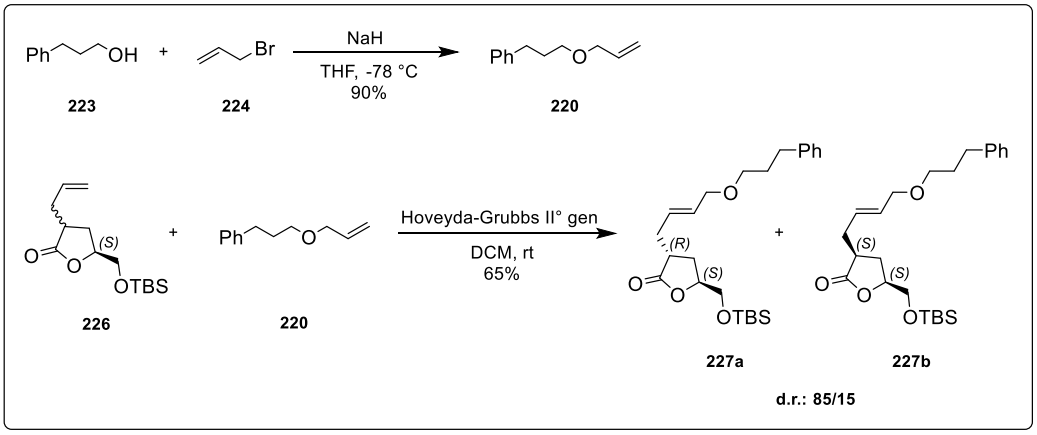
In the first two steps of the synthesis (Scheme 8.2) the hydroxyl group of enantiopure

lactone **222** is protected as -TBS derivative, and subsequent allylation reaction with allyl bromide **224** leads to the diastereomeric mixture **226a**-**226b**.



Scheme 8.2. Synthesis of **226**.

The two diastereomeric products have been separated through flash column cromatography, and the major one was subjected to ^{1}H-NMR analysis: the spectroscopic data were in accordance with those known in literature[87] for the *trans* diastereoisomer.
The two of them have been put together again and a GC-MS analysis has been carried out in order to evaluate the diastereomeric ratio, which turned out to be 85/15 = *trans*/*cis*.
Compound **220** has been prepared treating 3-phenyl-1-propanol with sodium hydride and subsequently allyl bromide **224** in a classical substitution reaction (Scheme 8.3).
The following step is a metathesis reaction betwe*e*n compounds **226** and **220** to provide access to the diastereomeric mixture **227a**-**227b**.



Scheme 8.3. Synthesis of **227**.

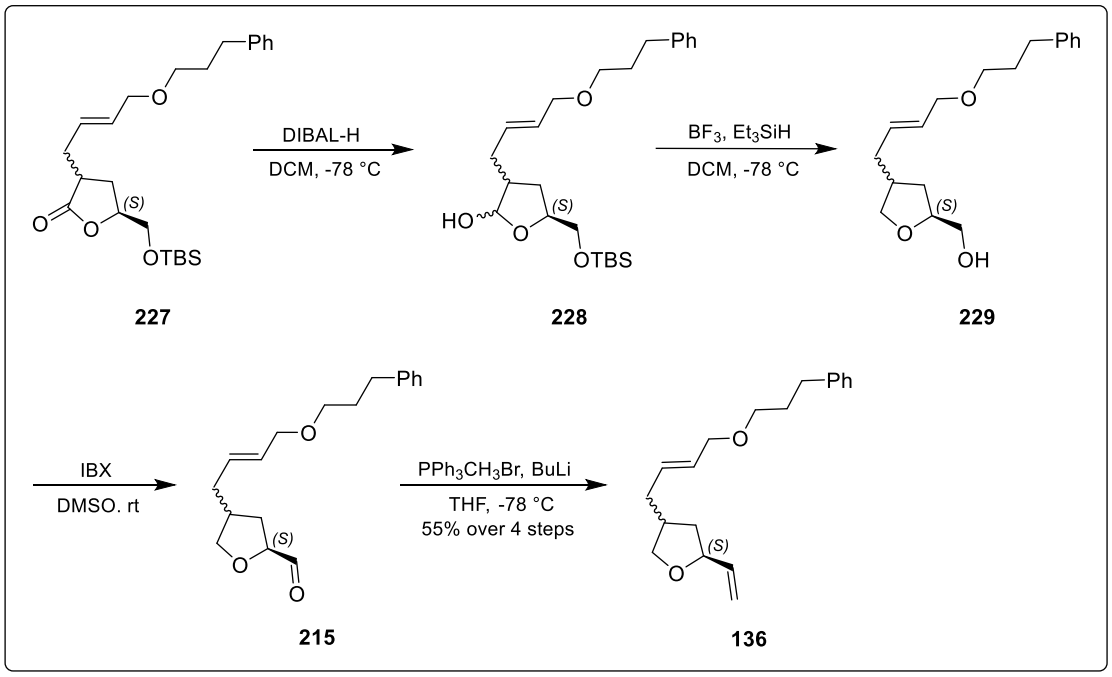
[87] T.B. Sells, V. Nair, *Tetrahedron*, **1994**, 50 (1), 117.

The diastereomeric ratio has been evaluated again thanks to GC-MS analysis, which confirmed that it has not changed during the reaction, remaining 85/15 in favour of the *trans* diastereoisomer.

From now on, each of the following steps have been performed without purification (Scheme 8.4).

The carboxylic group of lactone **227** is reduced with DIBAL-H, and lactol **228** is treated with BF_3•Et_2O and Et_3SiH to remove simultaneously hydroxyl and silyl groups affording compound **229**.

It then undergoes oxidation reaction with IBX to aldehyde **215**, which is turned into compound **136** through a Wittig reaction.



Scheme 8.4. Synthesis of **136**.

The diastereomeric ratio of **136** has been determined thorugh GC-MS analysis, and is equal to 88.3/11.7 in favour of the *trans* diastereoisomer, as shown in Figure 8.1.

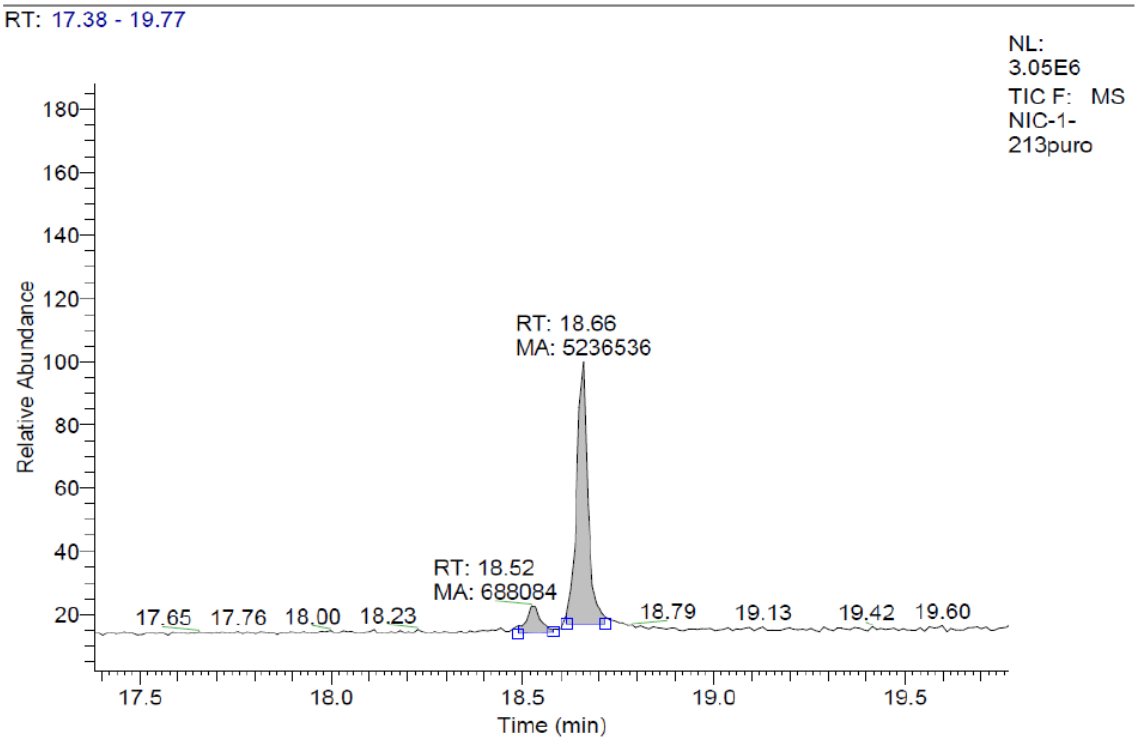
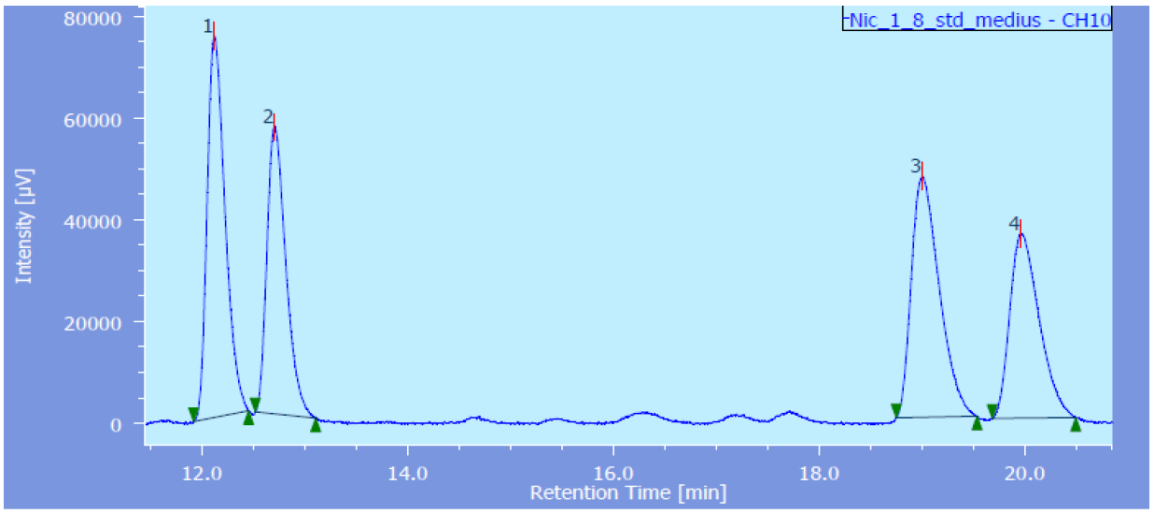
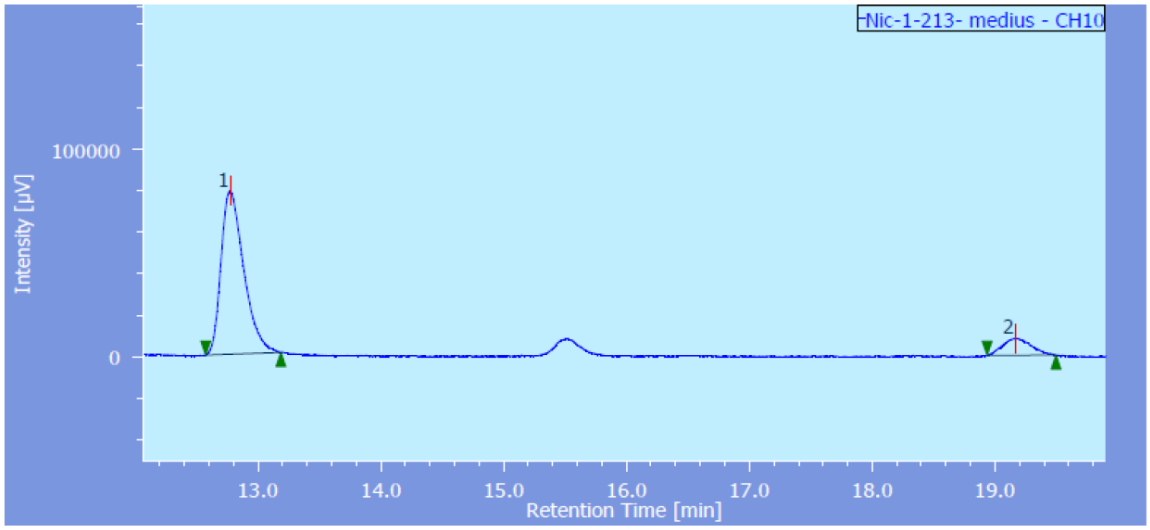


Figure 8.1. GC-MS analysis of **136**.

The diastereomeric mixture **136a-136b** has been subjected to HPLC analysis (Figure 8.2 below). Comparing it with the HPLC analysis of racemic **136** (Figure 8.2 above), and since the dr of the products is known, it can be possible to assign the absolute configuration to each of the peaks in the chromatogram, as reported in Figure 8.2.



Entry	Retention time (min)	Area (µV•sec)	Height (µV)	Area (%)
1	12.120	902542	74882	**27.878**
2	12.707	721396	56366	**22.283**
3	19.000	892609	47331	**27.571**
4	19.960	720925	36147	**22.268**



Entry	Retention time (min)	Area (µV•sec)	Height (µV)	Area (%)
1	12.773	1008130	78702	**88.363**
2	19.160	132760	8144	**11.637**

Figure 8.2. Chromatogram of racemic **136** (above) and enantioenriched **136** (below).

Relying on retention times, it can be seen that the major peak in the chromatogram below corresponds to the second peak in the chromatogram above, whereas the minor peak corresponds to the third peak in the chromatogram of racemic **136**.

Moreover, from the areas % of the peaks of the chromatogram above enantiomers can be recognized, and thus they are peaks 1-3 and 2-4.

For what stated above, the assignment for each of the peaks comes as a consequence (Figure 8.3).

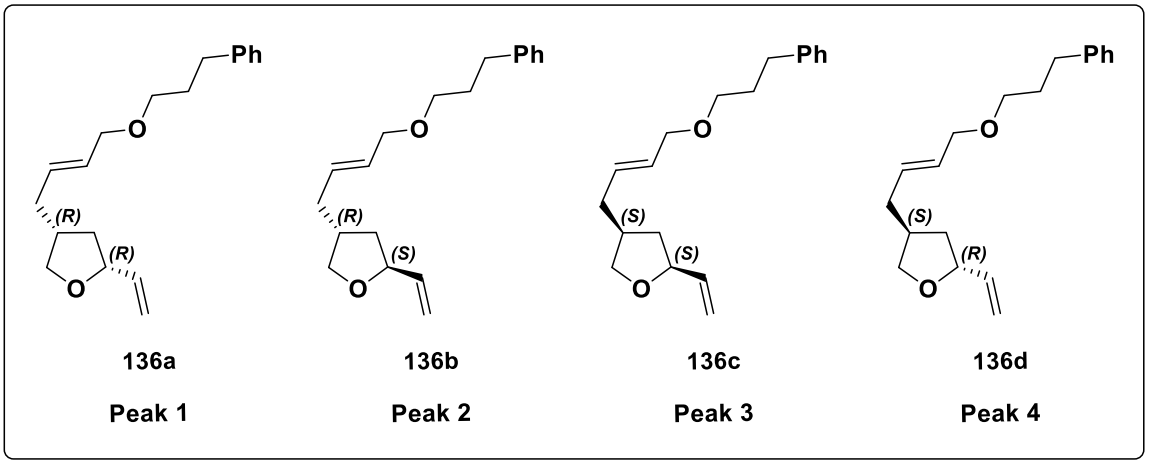


Figure 8.3. Determination of the absolute configuration of stereoisomeric **136**.

Since the major product in the optimized reaction conditions of Medius (Table 6.5, entry 8) is Peak 1 (*2R*,*4R*), we can state that this method exploiting gold(I) catalysis affords the construction of *cis*-2,4-disubstituted THF systems enantioselectively.

This represents a novel way to access this type of products.

In addition, noteworthy is the fact that the *cis* 2,4-substitution is, in general, much more difficult to achieve in comparison with the *trans* one, as proved by the synthesis for the assignment of the absolute and relative configuration of the products.

We reserve for the future to investigate a reliable synthetic method in order to determine the absolute and the relative configuration of the cyclized products of Remotus.

CHAPTER 9: Conclusions

In conclusion, this thesis reports the first example of accelerative asymmetric gold(I) catalysis via chiral ligand metal cooperation.

An asymmetrically positioned remote amide group in the 3' position of the designed gold(I) chiral binaphthyl ligand enables a selective acceleration of the cyclization reaction of allenyl substrates into one prochiral allene face through general base catalysis, achieved by H-bonding with the incoming nucleophilic hydroxyl group.

Owing to the accelerative nature of the catalysis, a high level of efficiency and selectivity can be accessed, which is proved thanks to exceptional *ee* values and extremely low catalyst loading, as low as 100 ppm.

This type of catalytic scenario demonstrates to be of wide applicability.

Firstly, attention has been drawn towards 4-allen-1-ols, which can undergo the gold(I) cyclization reaction smoothly in feasible conditions with almost quantitative yields and very high *ee* values, both with achiral and chiral substrates; in the latter case the reaction remains highly efficient and most importantly maintains excellent allene facial selectivities regardless of the substrate stereochemistry. Moreover, many functional groups are well tolerated.

Secondly, the attention has been driven towards Medius, which undergoes cyclization reaction affording disubstituted THF systems in high yields and exceptionally high *ee* values exploiting the same type of approach above described. The employment of classical approaches such as Toste's or Widenhoefer's or Mikami's does not afford high *ee* or *dr* values, despite excellent yields.

On the other hand, moderate *dr* values are obtained as a consequence of poor control of the catalyst over the prochiral center present in the substrate, as can be expected. Nevertheless, extremely high *ee* values are ensured by the great allene facial selectivity attack by the nucleophile.

Moreover, the absolute as well as the relative configurations of the stereogenic centers present in the product of the cyclization of Medius have been determined, proving that the *cis* product is preferred over the *trans* one. This type of catalysis on this type of substrate, therefore, can be considered as a new tool in organic synthesis to build enantioselective *cis*-

2,4-disubstituted THF rings. Notably, the *cis*-2,4 configuration is quite rare in THF systems and, ind*ee*d, only few valuable methods to obtain this structural motif are available in literature.

In the third place, a complete methodological work on the gold(I) cyclization reaction of Remotus has been also carried out. Even in this case, like in Medius' one, quantitative yields and very high *ee* values can be obtained through Zhang's catalyst.

However, as expected, very poor *dr* values can be accessed as a consequence of the nature of the substrate.

To sum up, this thesis proves that gold(I) catalysis, in particular in the case of gold(I) ligand accelerative catalysis, represents a powerful tool in organic synthesis to enantioselectively build variably substituted THF systems in almost quantitative yields, exceptionally high *ee* values, and good *dr* values, using an extremely low catalyst loading thanks to the efficiency of the catalysis.

CHAPTER 10: Experimental part

10.1 General remarks

During the execution of the experimental part of this thesis the below-listed materials and devices have been used.

For compounds characterization:

- NMR spectrometer: Bruker 300, 200 MHz or Varian 600, 500, 400 MHz

For chromatographic tecniques:

- Kieselgel 60 Merck (230-400 mesh) for standard silica gel purifications
- Silica gel GF-254 Merck (0.25 mm) for TLCs
- Fluorescent lamp (254 and 366 nm), vanilline solution 0.5% H_2SO_4/EtOH, solution of $KMnO_4$ in acetone for revelation of compounds in TLCs
- Gas cromatograph Helwett-Packard mod. 5890 II with capillary column HP-5 (crosslinked 5% Ph-Me silicon) 25 m, 0,25 mm i.d., 0,33 µm f.t
- Mass spectrometer ESI-MS thermo LTQ-XL
- MPLC Isolera One Biotage Flash Cromatography for automated preparative chromatographic purifications
- HUPLC-MS: mass Thermo LTQ-XL; UHPLC JASCO XLC SERIES 31, pumps XLC 3080DG, column oven 3067 CO, autosampler 3159AS, column Agilent Poroshell 120 EC-18, particle size 2.7 micron, eluents H_2O-MeCN with 0.2% of HCOOH
- Infrared spectra were recorded with a Perkin Elmer FT-IR spectrum 2000 spectrometer and are reported in reciprocal centimeter (cm^{-1})
- Analytical HPLC: pumps JASCO PU-2080 Plus, detector diode array MD-2010 Plus, autosampler AS-2055 Plus, column LiChroCART Hypersil 5 micron

All preparations requiring oxygen and water-fr*ee* conditions have been conducted under static Argon atmosphere.
Unstable substances have been handled in a glovebox under inert atmosphere.

Most of the solvents have been dried through distillation over suitable drying agents under Argon atmosphere.
In particular: THF, diethyl ether, and toluene from sodium/benzophenon, dichloromethane from calcium hydride. Other commercially available solvents have been employed as received, without further purification.
Syringes, n*ee*dles and the other glassware were dried at 140 °C for at least one night and allowed to cool in a desiccator over calcium chloride before use.

Mass spectra of **L1AuCl**, **62b**, **L2AuCl**, **L3**, **L3AuCl**, **119** and **133** were determined with Xevo G2-XS QTof Quadrupole Time-of-Flight Mass Spectrometry using electron spray ionization.

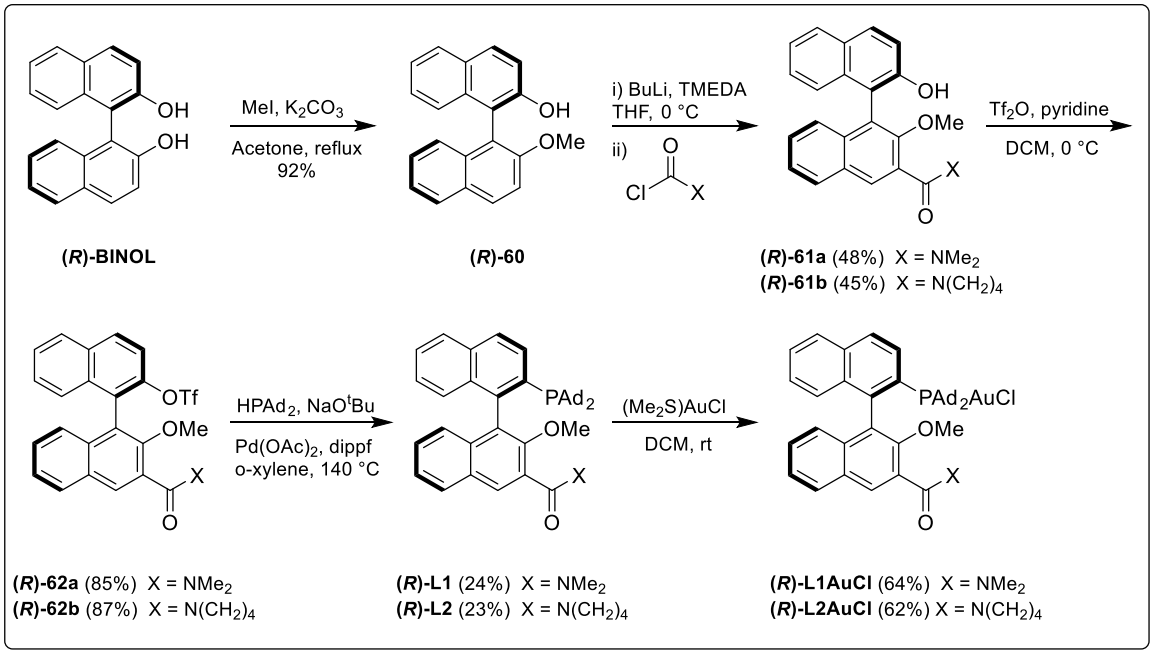
NMR spectra have been reported with chemical shift (δ, ppm) and the coupling constants (*J*, Hz). Signals multiplicities have been reported as: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet).

Common abbreviations used:
Brine: saturated acqueous solution of sodium chloride
DCM: dichloromethane
DMSO: dimethylsulfoxide
THF: tetrahydrofuran
DME: dimethoxyethane
Et_2O: diethyl ether
EtOAc: ethyl acetate

10.2 Cyclization of 4-allenyl-alcohols

Synthesis of Ligands and Catalysts

Synthesis of gold complex (*R*)-L1AuCl



(*R*)-60 was synthesized from (*R*)-BINOL according to the literature procedure.[88] Its spectroscopic data were in accordance with the literature data.

(*R*)-61a was prepared in a similar way as the literature procedure.[89] In a flame-dried schlenk flask under nitrogen atmosphere, **(*R*)-60** (3 mmol, 900 mg) and TMEDA (7.5 mmol, 1.12 mL) were dissolved in 15 mL anhydrous THF at room temperature. The solution was cooled to 0 °C before *n*-BuLi (7.5 mmol, 2.5 M, 3 mL) was added slowly via syringe. The dark brown reaction solution was stirred for 3 h at 0 °C. After being cooled to -78 °C, dimethylcarbamyl chloride (4.75 mmol, 0.29 mL) was added slowly to the reaction mixture. The reaction solution was stirred at -78 °C for 15 min and allowed to warm up to room temperature slowly during 2 h. The reaction was quenched by addition of saturated NH_4Cl solution. The mixture was extracted with ca. 50 mL THF three times. The combined

[88] Y. Zhou, D. Zhang, L. Zhu, Z. Shuai, D. Zhu, *J. Org. Chem.* **2006**, 71, 2123.
[89] F. Kaiser, L. Schwink, J. Velder, H.-G. Schmalz, *Tetrahedron*, **2003**, 59, 3201.

organic layers were washed with ca. 30 mL HCl (1 M) twice and brine and dried over Na_2SO_4. After evaporation of solvent under reduced pressure to ca. 10 mL, the product was precipitated out as yellow solids by adding ca. 50 mL DCM slowly. The precipitate was grinded and vacuumed overnight to give 530 mg **(*R*)-61a** as solids in 48% yield. The product was used in next step without further purification.

(*R*)-62a was prepared according the literature procedure.[90] To a suspension of **(*R*)-61a** (1.08 mmol, 402 mg) and pyridine (1.62 mmol, 0.131 mL) in 5 mL DCM at 0 °C was added triflic anhydride (1.30 mmol, 0.218 mL) dropwise. The mixture was stirred at 0 °C for 10 min, then warmed up to room temperature and stirred for 2 h. The mixture was quenched with water and washed with HCl (1 M) and brine. After dried over $MgSO_4$, the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (ethyl acetate : hexanes = 1 : 1) to give 460 mg **(*R*)-62a** as solids in 85% yield.

(*R*)-L1 was prepared in a similar way as the literature procedure[74]. Under nitrogen atmosphere **(*R*)-62a** (0.35 mmol, 178 mg), $Pd(OAc)_2$ (8 mol%), dippf (1,1'-bis(diisopropylphosphino)ferrocene, 10 mol%), di(1-adamantyl)phosphine (1.2 equiv.), NaOtBu (1.05 equiv.) and 1 mL dry o-xylene were added to a flamed dried Schlenk flask and the resulting suspension was stirred until apparently homogeneous (around 15 min). The flask was heated at 140 °C in oil bath overnight, which then was cooled to room temperature. The residue was filtered through celite and the celite pad was washed with DCM. The solution was evaporated under reduced pressure and purified by flash column chromatography (ethyl acetate : hexanes = 1 : 1) to give 55 mg **(*R*)-L1** as solids in 24% yield. The product contains ca. 10 % impurity which was removed in the next step.

(*R*)-L1AuCl was prepared according to the literature procedure[75]. To a solution of ligand **(*R*)-L1** (107 mg) in 3 mL anhydrous DCM was added chloro(dimethylsulfide)gold(I) (0.9 equiv., 45.0 mg). The mixture was stirred for 30 min at room temperature and the solvent was evaporated off under reduced pressure. The crude gold complex was recrystallized

[90] X. Shen, S.L. Buchwald, *Angew. Chem. Int. Ed.* **2010**, 49, 564.

thr*ee* times with DCM and hexanes to give 78 mg pure **(*R*)-L1AuCl** as clear crystals (m.p. > 260 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1H), 8.03 (d, J = 3.7 Hz, 2H), 7.98 (d, J = 8.2 Hz, 1H), 7.93 (d, J = 8.1 Hz, 1H), 7.53 (t, J = 7.5 Hz, 1H), 7.41 (t, J = 7.5 Hz, 1H), 7.21 (q, J = 8.1 Hz, 2H), 7.02 (d, J = 8.6 Hz, 1H), 6.94 (d, J = 8.5 Hz, 1H), 3.24 (s, 3H), 3.17 (s, 3H), 3.15 (s, 3H), 2.34 – 2.12 (m, 12H), 2.05 – 1.91 (m, 6H), 1.77 – 1.59 (m, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.60, 151.76, 144.77, 144.68, 134.61, 134.53, 134.44, 134.05, 134.03, 131.21, 131.02, 130.41, 130.08, 130.06, 129.20, 128.26, 128.13, 127.70, 127.65, 127.62, 126.83, 126.82, 126.81, 126.78, 126.61, 125.98, 125.60, 125.57, 125.25, 60.52, 43.58, 43.40, 42.83, 42.80, 42.78, 42.64, 42.43, 42.40, 39.39, 36.48, 36.47, 36.30, 36.28, 35.24, 28.80, 28.76, 28.72, 28.69. ^{31}P NMR (162 MHz, $CDCl_3$) δ 65.23. IR (neat): 2905, 2850, 1634, 1452, 1393, 1344, 1042, 748. HRMS ESI (m/z): $[2M\text{-}Cl]^+$ calcd. For $C_{88}H_{100}Au_2ClN_2O_4P_2$, 1739.6178; found, 1739.5914.

Gold complex (*R*)-L2AuCl

(*R*)-61b was prepared similar to **(*R*)-61a**. In a flame-dried schlenk flask under nitrogen atmosphere, **(*R*)-60** (20 mmol, 6.00g) and TMEDA (46 mmol, 6.84 mL) were dissolved in 100 mL anhydrous THF at room temperature. The solution was cooled to 0 °C before *n*-BuLi (46 mmol, 2.5 M, 18.4 mL) was added slowly via syringe. The dark brown reaction solution was stirred for 3 h at 0 °C. After being cooled to -78 °C, 1-pyrrolidinecarbonyl chloride (23 mmol, 1.78 mL) was added slowly to the reaction mixture. The reaction solution was stirred at -78 °C for 15 min and allowed to warm up to room temperature slowly during 2 h. The reaction was quenched by addition of saturated NH_4Cl solution. The mixture was extracted with ca. 200 mL THF thr*ee* times. The combined organic layers were washed with ca. 100 mL HCl (1 M) twice and brine and dried over Na_2SO_4. After evaporation of solvent under reduced pressure to ca. 30 mL, the product was precipitated out as pale-yellow solids by adding ca. 200 mL ethyl acetate slowly. The precipitate was grinded and vacuumed overnight to give 4.14 g **(*R*)-61b** as solids in 53% yield. The product was used in next step without further purification.

(*R*)-62b was prepared similar to **(*R*)-62a**. To a suspension of **(*R*)-61b** (8.56 mmol, 3.4 g)

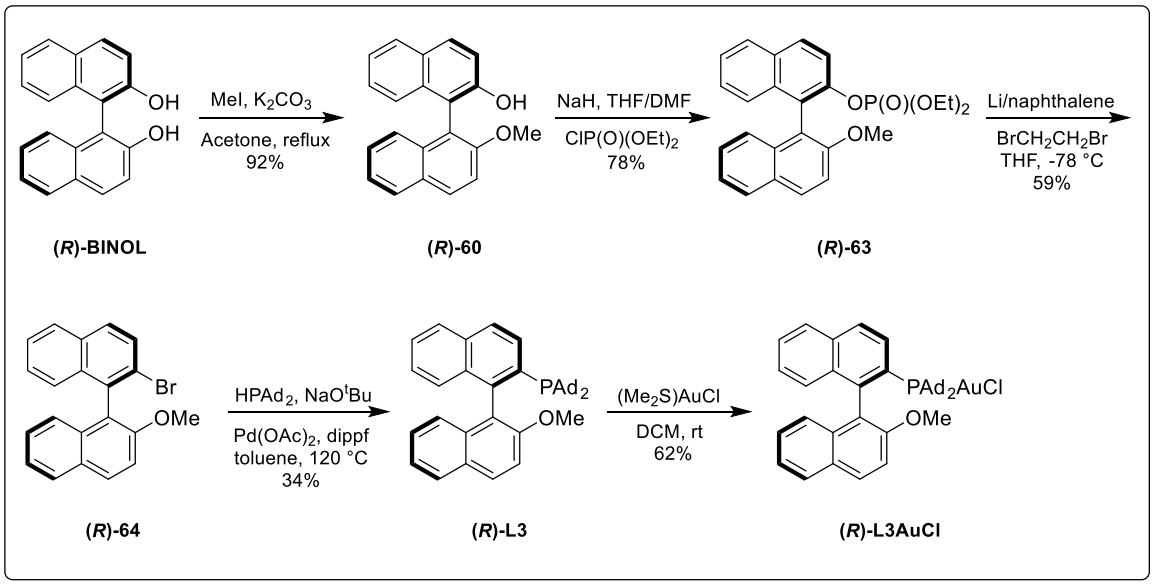
and pyridine (17.1 mmol, 1.38 mL) in 5 mL DCM at 0 °C was added triflic anhydride (12.0 mmol, 2.01 mL) dropwise. The mixture was stirred at 0 °C for 30 min, then warmed up to room temperature and stirred for 2 h. The mixture was quenched with water and washed with HCl (1 M) and brine. After dried over $MgSO_4$, the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (ethyl acetate : hexanes = 1 : 1) to give 3.82 g **(*R*)-62b** as solids (m.p. 130-137 °C) in 84% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, J = 11.4 Hz, 2H), 7.97 (d, J = 8.3 Hz, 1H), 7.90 (d, J = 8.2 Hz, 1H), 7.58 (d, J = 9.1 Hz, 1H), 7.53 (t, J = 7.4 Hz, 1H), 7.42 (t, J = 7.5 Hz, 1H), 7.36 (t, J = 7.6 Hz, 1H), 7.31 (d, J = 8.5 Hz, 1H), 7.29 – 7.24 (m, 1H), 7.09 (d, J = 8.5 Hz, 1H), 3.71 (h, J = 5.6 Hz, 2H), 3.51 (dt, J = 12.5, 6.9 Hz, 1H), 3.41 (s, 3H), 3.27 (dt, J = 11.8, 6.6 Hz, 1H), 2.02 – 1.81 (m, 4H). ^{13}C NMR (126 MHz, CDCl3) δ 167.35, 152.34, 145.58, 133.55, 133.43, 132.30, 131.92, 130.70, 130.12, 129.32, 128.27, 128.23, 127.69, 127.23, 126.95, 126.63, 126.32, 125.57, 125.47, 121.91, 119.28, 118.14 (q, J = 320.2 Hz), 61.76, 47.82, 45.76, 25.76, 24.56. ^{19}F NMR (376 MHz, CDCl3) δ 79.62. IR (neat): 3059, 2976, 2880, 1631, 1456, 1421, 1217, 1140, 949, 836, 753, 614, 500. HRMS ESI (m/z): $[M+H]^+$ calcd. for $C_{27}H_{23}F_3NO_5S$, 530.1249; found, 530.1265.

(*R*)-L2 was prepared in the same way as **(*R*)-L1** from **(*R*)-62b** (6.84 mmol, 3.62 g), $Pd(OAc)_2$ (10 mol%), dippf (12 mol%), di(1-adamantyl)phosphine (1.5 equiv.), NaOtBu (1.1 equiv.) and 10 mL dry o-xylene, giving 1.25 g **(*R*)-L2** as solids in 27% yield. The product contains ca. 10 % impurity which was removed in the next step.

(*R*)-L2AuCl was prepared in the same way as **(*R*)-L1AuCl** from **(*R*)-L2** (1.04 mmol, 710 mg), chloro(dimethylsulfide)gold(I) (0.9 equiv., 275 mg) and 10 mL DCM, giving 625 mg pure **(*R*)-L2AuCl** as clear crystals (m.p. > 260 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (s, 1H), 8.03 (d, J = 3.7 Hz, 2H), 7.98 (d, J = 8.1 Hz, 1H), 7.93 (d, J = 7.9 Hz, 1H), 7.53 (ddd, J = 8.0, 6.8, 1.1 Hz, 1H), 7.40 (ddd, J = 8.0, 6.7, 1.1 Hz, 1H), 7.20 (dddd, J = 10.7, 8.3, 6.8, 1.3 Hz, 2H), 7.01 (d, J = 8.5 Hz, 1H), 6.93 (d, J = 8.3 Hz, 1H), 3.95 (dt, J = 11.6, 6.2 Hz, 1H), 3.74 (dt, J = 12.3, 7.0 Hz, 1H), 3.66 – 3.55 (m, 2H), 3.22 (s, 3H), 2.32 – 2.11 (m, 12H), 2.04 – 1.82 (m, 8H), 1.81 – 1.74 (m, 1H), 1.74 – 1.58 (m, 13H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.86, 151.74, 144.89, 144.80, 134.55, 134.48, 134.41, 134.06, 134.04, 131.27,

131.12, 130.91, 130.05, 130.03, 129.23, 128.21, 128.20, 128.11, 127.74, 127.68, 127.61, 126.81, 126.78, 126.76, 126.75, 126.57, 125.95, 125.56, 125.50, 125.21, 60.70, 48.80, 46.00, 43.54, 43.35, 42.82, 42.78, 42.76, 42.63, 42.44, 42.42, 36.45, 36.44, 36.27, 36.26, 28.80, 28.75, 28.72, 28.67, 26.00, 24.53. ^{31}P NMR (162 MHz, $CDCl_3$) δ 65.00. IR (neat): 2905, 2851, 1626, 1453, 1302, 1246, 1006, 733. HRMS ESI (m/z): $[2M\text{-}Cl]^+$ calcd. for $C_{92}H_{104}Au_2ClN_2O_4P_2$, 1791.6491; found, 1791.6351.

Synthesis of gold complex (*R*)-L3AuCl



(*R*)-64 was prepared in 3 steps according to the literature procedure.[91] The spectroscopic data were in accordance with the literature data.[92]

(*R*)-L3 was prepared according to the literature procedure,[75] giving 300mg solid (m.p. > 160 °C) in 34% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 8.6 Hz, 1H), 8.00 (d, J = 9.0 Hz, 1H), 7.91 (t, J = 8.6 Hz, 2H), 7.84 (d, J = 8.2 Hz, 1H), 7.45 (t, J = 7.4 Hz, 1H), 7.40 (d, J = 9.1 Hz, 1H), 7.28 – 7.07 (m, 4H), 6.92 (d, J = 8.5 Hz, 1H), 3.75 (s, 3H), 2.05 – 1.86 (m, 9H), 1.86 – 1.72 (m, 9H), 1.72 – 1.64 (m, 6H), 1.64 – 1.52 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.91, 153.89, 144.87, 144.53, 134.42, 134.24, 134.22, 134.15, 133.61,

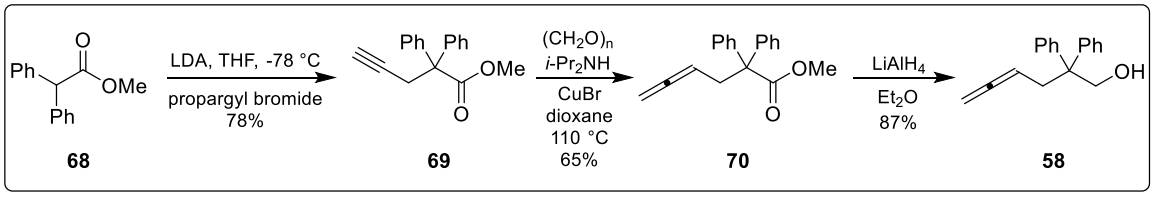
[91] Y. Nishioka, T. Uchida, T. Katsuki, *Angew. Chem. Int. Ed.* **2013**, 52, 1739.
[92] F. Ma, X. Xie, L. Zhang, Z. Peng, L. Ding, L. Fu, Z. Zhang, *J. Org. Chem.* **2012**, 77, 5279.

133.53, 133.41, 133.39, 133.34, 129.35, 128.46, 127.62, 127.30, 127.28, 127.01, 126.20, 125.69, 125.18, 125.04, 122.94, 122.85, 122.76, 112.10, 55.10, 42.07, 41.94, 41.81, 37.28, 37.17, 37.07, 37.03, 36.93, 29.10, 29.01, 28.86, 28.77. 31P NMR (162 MHz, $CDCl_3$) δ 28.18. IR (neat): 3054, 2902, 2847, 1622, 1594, 1510, 1481, 1269, 1081, 805, 742. HRMS ESI (m/z): $[M+K]^+$ calcd. for $C_{41}H_{45}OKP$, 623.2845; found, 623.2905.

(*R*)-L3AuCl (m.p. decompose gradually >130 °C) was prepared according to the literature Procedure.[75] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, J = 9.1 Hz, 1H), 8.07 – 7.98 (m, 2H), 7.94 (d, J = 8.1 Hz, 2H), 7.53 (ddd, J = 8.1, 6.8, 1.1 Hz, 1H), 7.40 (d, J = 9.1 Hz, 1H), 7.29 (ddd, J = 8.1, 6.8, 1.1 Hz, 1H), 7.22 (ddd, J = 8.4, 6.8, 1.3 Hz, 1H), 7.10 (ddd, J = 8.3, 6.8, 1.3 Hz, 1H), 6.96 (d, J = 8.6 Hz, 1H), 6.73 (d, J = 8.5 Hz, 1H), 3.72 (s, 3H), 2.31 – 2.09 (m, 12H), 2.03 – 1.90 (m, 6H), 1.65 (dd, J = 17.1, 3.0 Hz, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.59, 145.60, 145.48, 134.31, 134.22, 134.18, 134.16, 134.14, 131.30, 130.15, 130.12, 129.29, 128.67, 127.91, 127.74, 127.72, 127.64, 126.84, 126.43, 126.36, 125.77, 125.32, 125.09, 124.64, 123.58, 120.46, 120.38, 112.41, 55.21, 43.07, 42.83, 42.70, 42.67, 42.59, 42.19, 42.16, 36.39, 36.38, 36.27, 36.26, 28.81, 28.71, 28.61. ^{31}P NMR (162 MHz, $CDCl_3$) δ 65.16. IR (neat): 3051, 2905, 2850, 1622, 1593, 1510, 1269, 1080, 806, 735, 528. HRMS ESI (m/z): $[2M-Cl]^+$ calcd. for $C_{82}H_{90}Au_2ClO_2P_2$, 1597.5436; found, 1597.5509.

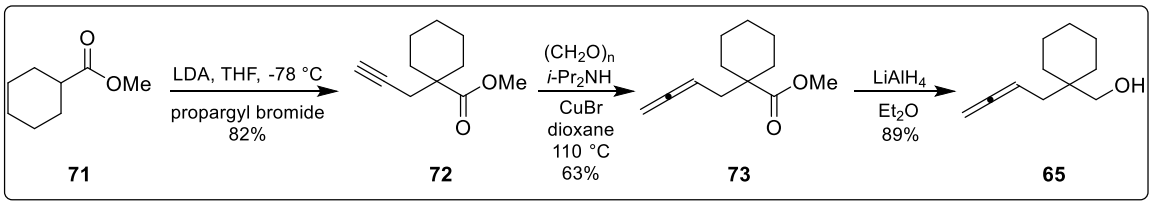
Preparation of 4-Allenyl Alcohols

2,2-diphenylhexa-4,5-dien-1-ol (58)



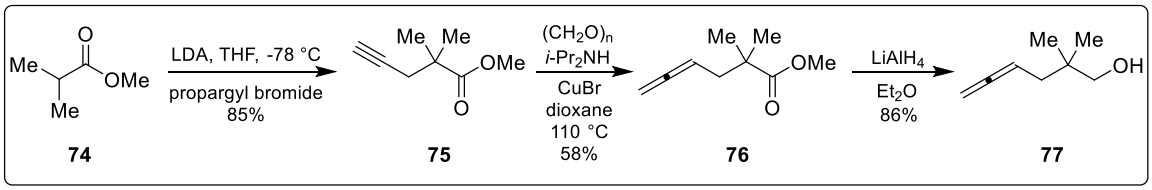
58 was synthesized according to the literature procedure.[93] The spectroscopic data were in accordance with the literature data.[93]

(1-(buta-2,3-dienyl)cyclohexyl)methanol (65)



65 was synthesized according to the literature procedure.[93] The spectroscopic data were in accordance with the literature data.[93]

2,2-dimethylhexa-4,5-dien-1-ol (77)

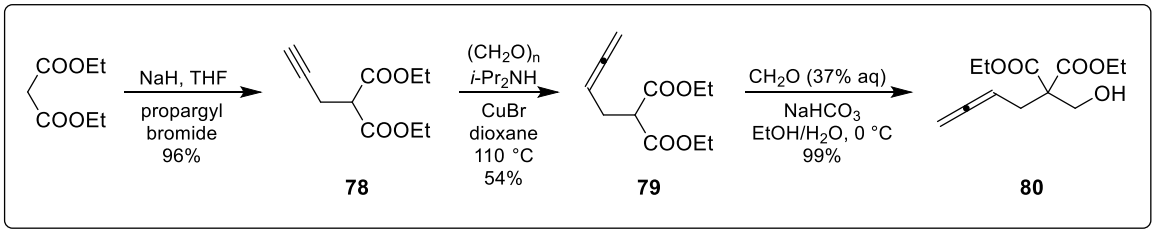


77 (liquid) was prepared was synthesized similar to the literature procedure.[93] ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.12 – 5.01 (m, 2H), 4.64 (dt, J = 6.7, 2.4 Hz, 2H), 3.35 (s, 2H), 1.97

[93] J.L. Arbour, H.S. Rzepa, A.J.P. White, K.K. Hii, *Chem. Commun.* (Cambridge, U.K.) **2009**, 7125.

(dt, J = 8.3, 2.4 Hz, 2H), 1.69 – 1.50 (m, 1H), 0.89 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.50, 86.01, 73.66, 71.29, 37.94, 35.96, 23.66. IR (neat): 3363, 2959, 1956, 1437, 1365, 1046, 841. HRMS CI(m/z): $[M+H]^+$ calcd. for $C_8H_{15}O$, 127.1123; found, 127.1124.

diethyl 2-(buta-2,3-dienyl)-2-(hydroxymethyl)malonate (80)



78 was prepared according to the literature procedure.[94] The spectroscopic data were in accordance with the literature data.[94]

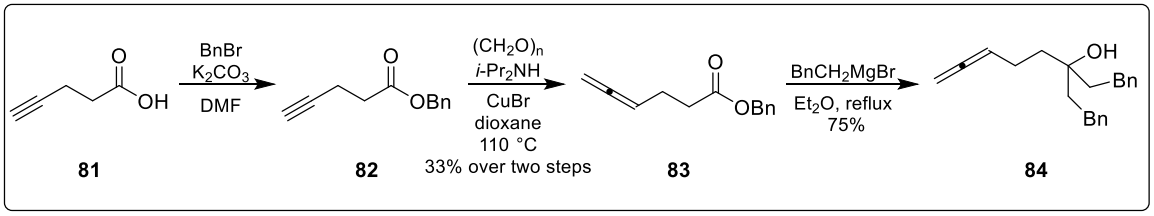
79 was prepared in a similar way as the literature report.[93] A solution of **78** (14.3 mmol, 2.85 g), CuBr (30 mmol%), paraformaldehyde (3 equiv, 1.29 g), diisopropylamine (3 equiv., 2 mL) in 5 mL dioxane was refluxed at 110 °C for 4 h. The crude reaction mixture was diluted with Et_2O and washed with HCl (aq.) 3 times. The organic phase was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by flash column chromatography with ethyl acetate and hexanes (1:10) to give 430 mg **79** (liquid) 54% yield. The spectroscopic data were in accordance with the literature data.[95]

80 was prepared according to the literature report.[96] To **79** (2 mmol, 424 mg) and $NaHCO_3$ (0.4 mmol, 33.6 mg) in EtOH (2 mL) and water (1 mL) at 0 °C, 37% formaldehyde (2.2 mmol, 164 μL) in water was added slowly. The reaction mixture was slowly warmed up to room temperature and stirred overnight. After completion comfirmed by TLC, reaction mixture was extracted with DCM. The organic layer was washed with water and brine,

[94] J. Mandal, S. Krishna Prasad, D.S.S. Rao, S. Ramakrishnan, *J. Am. Chem. Soc.* **2014**, 136, 2538.
[95] R. Kumareswaran, S. Shin, I. Gallou, T.V. Rajanbabu, *J. Org. Chem.* **2004**, 69, 7157.
[96] S. Boyd, C.D. Davies, *Tetrahedron Lett.* **2014**, 55, 4117.

dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography with ethyl acetate and hexanes (1:4) to give quantitative amount of **80** (liquid). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.04 (tt, J = 7.9, 6.7 Hz, 1H), 4.68 (dt, J = 6.6, 2.5 Hz, 2H), 4.23 (q, J = 7.1 Hz, 4H), 3.98 (d, J = 6.7 Hz, 2H), 2.64 (dt, J = 7.9, 2.5 Hz, 2H), 2.61 (t, J = 7.1 Hz, 1H), 1.27 (t, J = 7.1 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.94, 170.43, 84.37, 74.83, 64.60, 61.58, 59.59, 31.05, 14.01. IR (neat): 3522, 2984, 1957, 1732, 1446, 1369, 1195, 1044, 856. HRMS CI(m/z): $[M+H]^+$ calcd. For $C_{12}H_{19}O_5$, 243.1232; found, 243.1227.

3-phenethyl-1-phenylocta-6,7-dien-3-ol (84)



82 was prepared according to the literature procedure.[97] After work-up, the product was subjected to next step without further purification. The spectroscopic data were in accordance with the literature data.[97]

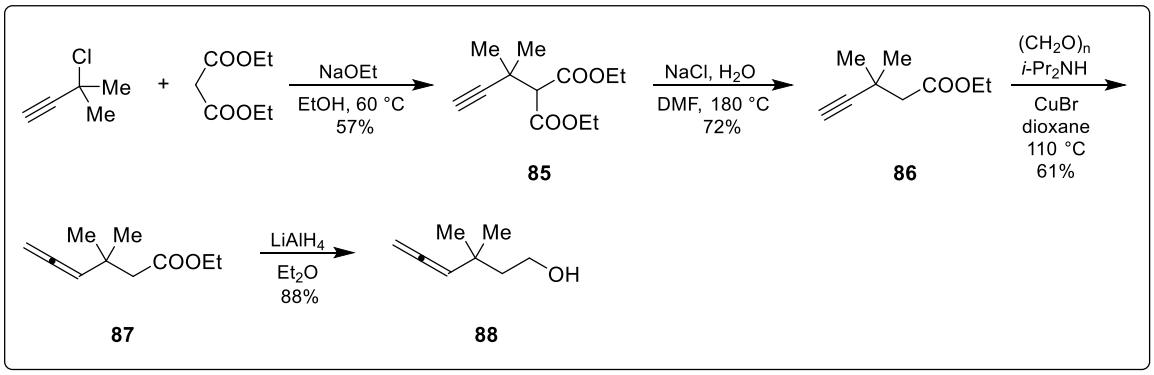
83 (liquid) was prepared in a similar way as the literature report[93] in 33% yield for two steps.

In a flamed dried flask equipped with condenser and septum was added magnesium turnings (120 mg, 5 mmol), 15 mL anhydrous Et_2O and a small piece of iodine under nitrogen. A small portion of 2-bromoethylbenzene (5 mmol, 683 μL) was added to initiate the reaction. After brown color faded away and the solution started a gentle reflux, the rest of 2-bromoethylbenzene was added slowly. The reaction mixture was refluxed for 30 min. After cooled down to room temperature, **83** (2 mmol, 400 mg) was added dropwise. The reaction mixture was further refluxed for 1 h. After cooled down to room temperature, the

[97] M.M. Lorion, F.J.S. Duarte, M.J. Calhorda, J. Oble, G. Poli, *Org. Lett.* **2016**, 18, 1020.

reaction mixture was quenched by NH_4Cl (aq.) and extracted thr*ee* times with Et_2O. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography with ethyl acetate and hexanes (1:10) to give 461 mg **84** (liquid) in 75% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (t, J = 7.6 Hz, 4H), 7.27 – 7.21 (m, 6H), 5.22 (p, J = 6.7 Hz, 1H), 4.75 (dq, J = 6.5, 2.9 Hz, 2H), 2.77 – 2.66 (m, 4H), 2.21 – 2.11 (m, 2H), 1.94 – 1.84 (m, 4H), 1.80 – 1.71 (m, 2H), 1.39 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.40, 142.34, 128.51, 128.35, 125.91, 90.04, 75.53, 74.30, 74.20, 41.23, 38.26, 30.08, 22.49. IR (neat): 3564, 3425, 3027, 2938, 1955, 1804, 1603, 1496, 1063, 847, 699. HRMS CI(m/z): $[M+H]^+$ calcd. for $C_{22}H_{27}O$, 307.2062; found, 307.2060.

3,3-dimethylhexa-4,5-dien-1-ol (88)

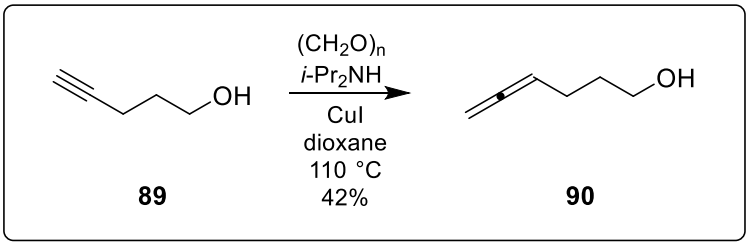


86 was prepared in two steps according to the literature procedure.[98] The spectroscopic data were in accordance with the literature data.[98]

88 (liquid) was prepared according to the literature procedure.[93] ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.10 (t, J = 6.7 Hz, 1H), 4.74 (d, J = 6.7 Hz, 2H), 3.71 (t, J = 7.2 Hz, 2H), 1.68 – 1.61 (m, 2H), 1.33 (s, 1H), 1.05 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.35, 100.37, 76.68, 60.19, 45.49, 33.22, 28.22. IR (neat): 3337, 2963, 1956, 1470, 1365, 1569, 1026, 843. HRMS CI(m/z): $[M+H]^+$ calcd. for $C_8H_{15}O$, 127.1123; found, 127.1125.

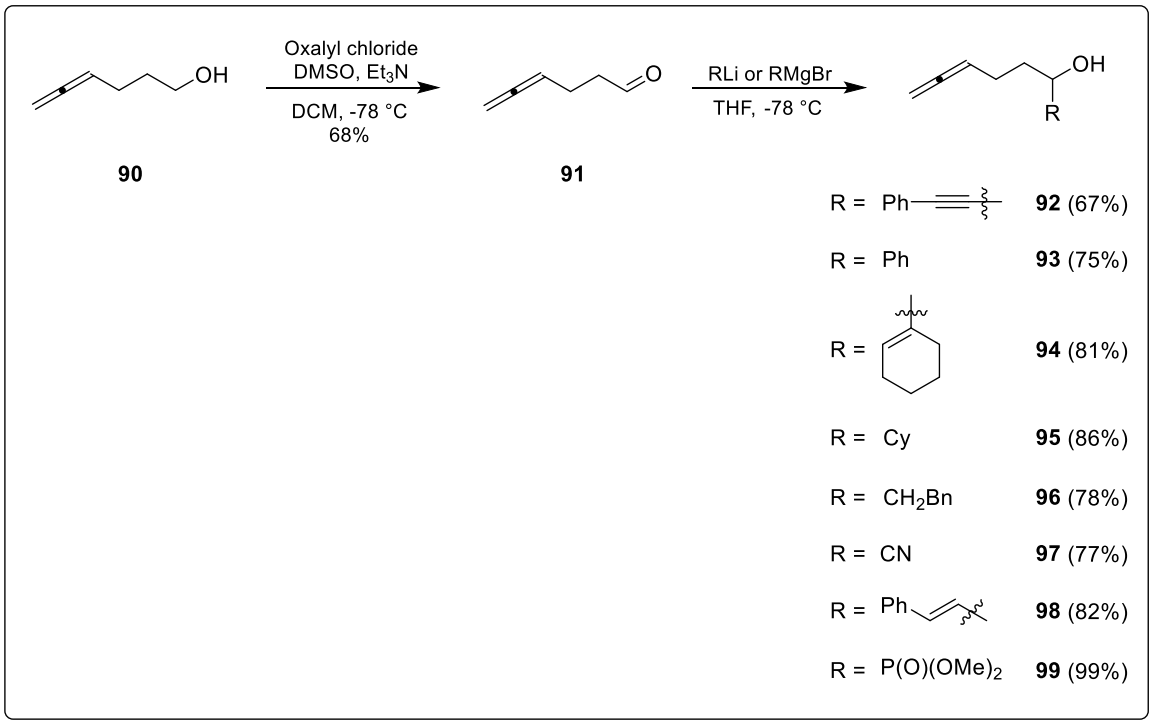
[98] E. Rank, R. Bruckner, *Eur. J. Org. Chem.* **1998**, 1045.

hexa-4,5-dien-1-ol (90)



90 (liquid) was prepared according to the literature procedure.[99] The spectroscopic data were in accordance with the literature data.[99]

4-allenyl-alcohols 92-99



91 (liquid) was prepared according to the literature procedure.[100] The resulting aldehyde was used in next step without purification.

[99] H. Tsukamoto, T. Matsumoto, Y. Kondo, *J. Am. Chem. Soc.* **2008**, 130, 388.
[100] G. Ma, S. Afewerki, L. Deiana, C. Palo-Nieto, L. Liu, J. Sun, I. Ibrahem, A. Cordova, *Angew. Chem. Int. Ed.* **2013**, 52, 6050.

Preparation of **92**. To a solution of phenylacetylene (3.5 mmol, 0.384 mL) in 10 mL anhydrous THF in a flame-dried flask was added nBuLi (3.5 mmol, 2.5 M, 1.4 mL) at -78 °C under nitrogen. After stirred at -78 °C for 30 min, **91** (3 mmol, 308 mg) was added. The reaction was slowly warmed up to room temperature and further stirred for 1 h. The reaction was quenched with water and extracted with ethyl acetate thr*ee* times. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography with ethyl acetate and hexanes (1:10) to give **92** (liquid) 400 mg in 67% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 – 7.40 (m, 2H), 7.35 – 7.28 (m, 3H), 5.18 (p, J = 6.6 Hz, 1H), 4.72 (dt, J = 6.7, 3.3 Hz, 2H), 4.70 – 4.64 (m, 1H), 2.30 – 2.21 (m, 2H), 2.08 (d, J = 3.6 Hz, 1H), 2.00 – 1.88 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.51, 131.64, 128.37, 128.24, 122.53, 89.75, 89.09, 85.11, 75.40, 62.29, 36.88, 23.84. IR (neat): 3345, 3057, 2925, 2230, 1956, 1599, 1490, 1443, 1068, 847, 691. HRMS CI(m/z): $[M+H]^+$ calcd. for $C_{14}H_{15}O$, 199.1123; found, 199.1127.

93 (liquid) was prepared in a similar way as **84** with phenylmagnesium bromide. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.34 (m, 4H), 7.31 – 7.26 (m, 1H), 5.15 (p, J = 6.6 Hz, 1H), 4.74 (ddd, J = 7.8, 5.4, 2.3 Hz, 1H), 4.70 (dt, J = 6.7, 3.4 Hz, 2H), 2.17 – 2.01 (m, 2H), 1.97 (t, J = 3.0 Hz, 1H), 1.95 – 1.88 (m, 1H), 1.88 – 1.79 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.49, 144.55, 128.43, 127.53, 125.83, 75.27, 73.82, 38.05, 24.34. IR (neat): 3367, 3030, 2921, 1956, 1685, 1453, 1062, 846, 701, 545. HRMS CI(m/z): $[M+H]^+$ calcd. for $C_{12}H_{15}O$, 175.1123; found, 175.1122.

94 (liquid) was prepared in a similar way as **93**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.68 (s, 1H), 5.18 – 5.13 (m, 1H), 4.69 (dt, J = 6.6, 3.3 Hz, 2H), 4.03 (t, J = 6.7 Hz, 1H), 2.26 – 1.35 (m, 13H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.37, 139.60, 123.15, 89.56, 75.91, 74.96, 33.89, 24.86, 24.36, 23.32, 22.52, 22.52. IR (neat): 3356, 2928, 2857, 1956, 1437, 1056, 842. HRMS ESI(m/z): $[M+Na]^+$ calcd. for $C_{12}H_{18}NaO$, 201.1255; found, 201.1254.

95 (liquid) was prepared in a similar way as **93**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.19 – 5.12 (m, 1H), 4.70 (dt, J = 6.7, 3.3 Hz, 2H), 3.43 (ddd, J = 8.9, 5.4, 3.4 Hz, 1H), 2.34 – 1.93 (m, 2H), 1.92 – 0.86 (m, 14H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.33, 89.75, 75.44, 74.99,

43.62, 33.15, 29.09, 27.69, 26.42, 26.23, 26.07, 24.55. IR (neat): 3358, 2925, 2852, 1956, 1449, 1045, 841. HRMS ESI(m/z): $[M+Na]^+$ calcd. for $C_{12}H_{20}NaO$, 203.1412; found, 203.1413.

96 (liquid) was prepared in a similar way as **93**. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30 (t, J = 7.5 Hz, 2H), 7.25 – 7.17 (m, 3H), 5.19 – 5.08 (m, 1H), 4.74 – 4.62 (m, 2H), 3.70 (tt, J = 8.2, 4.3 Hz, 1H), 2.81 (ddd, J = 15.0, 9.5, 5.9 Hz, 1H), 2.74 – 2.63 (m, 1H), 2.22 – 2.05 (m, 2H), 1.87 – 1.72 (m, 2H), 1.61 (dtt, J = 16.0, 8.0, 4.7 Hz, 2H), 1.57 – 1.41 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 208.41, 142.03, 128.36, 125.78, 89.58, 75.15, 70.65, 39.04, 36.53, 32.00, 24.31. IR (neat): 3348, 3027, 2920, 1955, 1603, 1496, 1084, 847, 699. HRMS CI(m/z): $[M+H]^+$ calcd. for $C_{14}H_{19}O$, 203.1436; found, 203.1435.

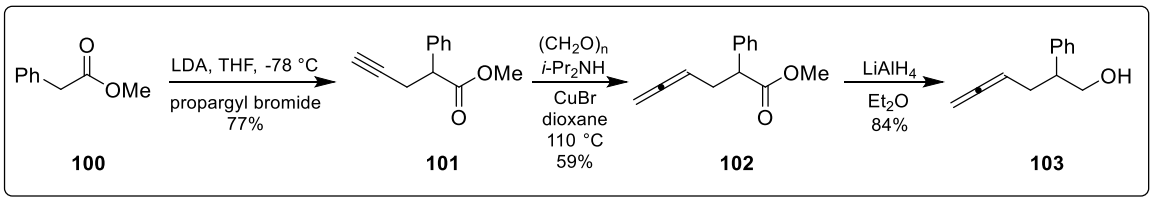
97 (liquid) was prepared in a similar way as the literature procedure.[101] To a solution of **91** (100 mg, 1 mmol) in 10 mL ethyl acetate was added a solution of sodium cyanide (3 mmol, 147 mg) in 10 mL water and the resulting mixture was vigorously stirred at room temperature for 24 h. The layers were separated and the aqueous layer was extracted 2 times with ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography with diethyl ether and hexanes (3:7) to give **97** (liquid) 95 mg in 77% yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.19 – 5.12 (m, 1H), 4.72 – 4.65 (m, 2H), 4.52 (t, J = 3.3 Hz, 1H) 3.18 (s, 1H), 2.17 – 2.09 (m, 2H), 2.02 – 1.93 (m, 2H).

98 (liquid) was prepared in a similar way as **93**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 – 7.25 (m, 5H), 6.61 (d, J = 15.9 Hz, 1H), 6.25 (dd, J = 15.9, 6.77 Hz, 1H), 5.23 – 5.14 (m, 1H), 4.75 – 4.70 (m, 2H), 4.41 – 4.34 (m, 1H), 2.20 – 2.13 (m, 2H), 1.83 – 1.70 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.43, 136.53, 132.05, 130.36, 128.49, 127.59, 126.36, 89.39, 75.19, 72.31, 36.21, 23.99. HRMS CI(m/z): $[M+H]^+$ calcd. for $C_{14}H_{17}O$, 201.1279; found, 201.1278.

[101] A.J. Fatiadi, in *Preparation and synthetic applications of cyano compounds* (Eds.: S. Patai, Z. Rappaport), Wiley-Interscience, New York, **1983**.

99 (liquid) was prepared in a similar way as the literature procedure.[102] A 5.0 mL Schlenk tube was charged with *n*BuLi (1 mol %, 1.6 M, 26 μL), 3 mL THF and dimethyl phosphite (0.5 mmol, 46 μL) under dry Argon. The mixture was stirred for 5 min before **91** (40 mg, 0.42 mmol) was added. The resulting mixture was allowed to stir at room temperature for 5 min. The reaction was quenched by adding ethyl acetate and water. The layers were separated and the aqueous layer was extracted 2 times with ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography with ethyl acetate 99% to give **99** (liquid) 56 mg in 65% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.20 – 5.11 (m, 1H), 4.75 – 4.70 (m, 2H), 4.04 – 3.97 (m, 2H), 3.86 (s, 3H), 3.82 (s, 3H), 2.34 – 2.29 (m, 1H), 2.22 – 2.18 (m, 1H), 1.95 – 1.81 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.52, 88.72, 77.09, 75.36, 67.94, 65.81, 53.22, 30.45, 24.02. HRMS CI(m/z): $[M+H]^+$ calcd. for $C_8H_{16}O_4P$, 207.0786; found, 207.0788.

2-phenylhexa-4,5-dien-1-ol (103)

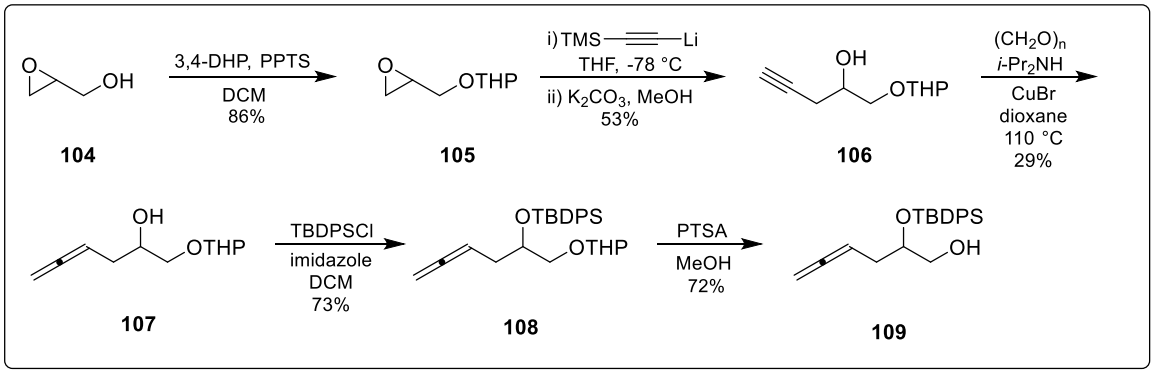


100 **101** **102** **103**

103 (liquid) as prepared in a similar way as **58**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.31 (m, 2H), 7.27 – 7.21 (m, 3H), 5.05 – 4.97 (m, 1H), 4.62 (tt, J = 6.6, 3.3 Hz, 2H), 3.84 (dd, J = 10.9, 5.7 Hz, 1H), 3.77 (dd, J = 10.9, 7.4 Hz, 1H), 2.93 (dt, J = 13.7, 7.3 Hz, 1H), 2.45 (dddt, J = 14.5, 7.6, 6.9, 2.7 Hz, 1H), 2.35 (dddt, J = 14.5, 8.0, 6.6, 3.2 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.00, 141.70, 128.62, 128.06, 126.85, 87.69, 74.84, 66.78, 48.20, 31.12. IR (neat): 3364, 3029, 2928, 1955, 1602, 1494, 1453, 1067, 1027, 845, 759, 457. HRMS CI(m/z): $[M+H]^+$ calcd. for $C_{12}H_{15}O$, 175.1123; found, 175.1131.

[102] C. Liu, Y. Zhang, Q. Qian, D. Yuan, Y. Yao, *Org. Lett.* **2014**, 16 (23), 6172.

2-(*tert*-butyldiphenylsilyloxy)hexa-4,5-dien-1-ol (109)



106 was prepared according to the literature procedure.[103] The spectroscopic data were in accordance with the literature data.[103]

107 (liquid) was prepared according to the literature procedure[93] in 28-30% yield.

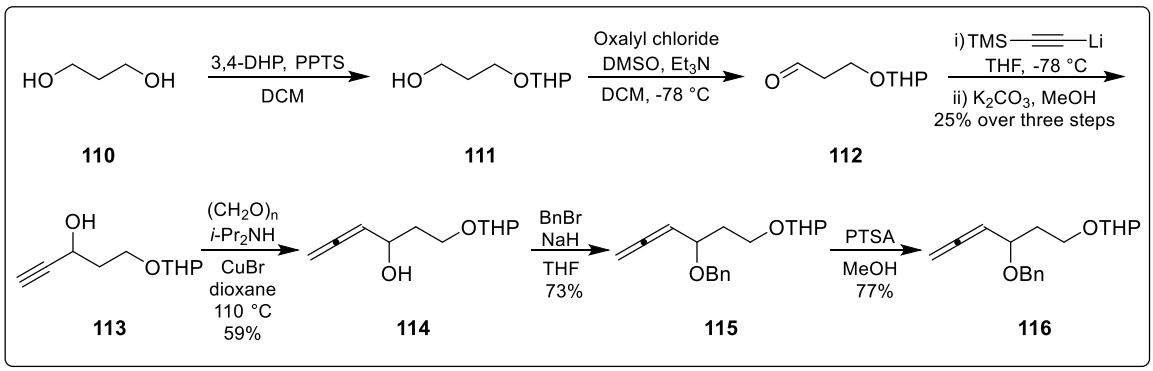
Preparation of **108**. A solution of **107** (2.63 mmol, 522 mg), TBDPSCl (1.1 equiv., 0.75 mL) and imidazole (1.1 equiv., 200 mg) in 20 mL DCM. The reaction was stirred overnight before the reaction was quenched with water. The mixture was extracted with DCM. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography with ethyl acetate and hexanes (1:10) to give 844 mg **108** (liquid) in 73% yield.

Preparation of **109**. A solution of **108** (1.93 mmol, 844 mg), PTSA·H_2O (0.3 equiv., 110 mg) in 20 mL MeOH. Upon completion confirmed by TLC the reaction was quenched with $NaHCO_3$ (aq.). The mixture was extracted with ethyl acetate. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography with ethyl acetate and hexanes (1:10) to give 491 mg **109** (liquid) in 72% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 – 7.66 (m, 4H), 7.45 (td, J = 7.4, 1.4 Hz, 2H), 7.39 (t, J = 7.1 Hz, 4H), 4.94 (p, J = 7.1 Hz, 1H), 4.57 (dt, J = 5.6, 2.7 Hz, 2H), 3.86 (dq, J = 8.8, 4.6 Hz, 1H), 3.56 (qdd, J = 11.4, 6.4, 4.5 Hz, 2H), 2.32 – 2.21 (m, 1H),

[103] H.M. Ko, C.W. Lee, H.K. Kwon, H.S. Chung, S.Y. Choi, Y.K. Chung, E. Lee, *Angew. Chem. Int. Ed.* **2009**, 48, 2364.

2.21 – 2.11 (m, 1H), 1.80 – 1.73 (m, 1H), 1.09 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.30, 135.83, 135.66, 133.68, 133.58, 129.84, 129.80, 127.75, 127.65, 85.57, 74.51, 73.47, 65.53, 32.73, 26.98, 19.31. IR (neat): 3582, 3432, 3072, 2859, 1957, 1590, 1472, 1428, 1111, 999, 844, 740, 611. HRMS CI(m/z): $[M+H]^+$ calcd. for $C_{22}H_{29}O_2Si$, 353.1937; found, 353.1949.

3-(benzyloxy)hexa-4,5-dien-1-ol (116)



111 was prepared according to the literature procedure.[104] The spectroscopic data were in accordance with the literature data.[104]

112 (liquid) was prepared according to the literature procedure.[100] The resulting aldehyde was used in next step without purification.

113 (liquid) was prepared in a similar way as **106** giving 860 mg in 25% total yield for three steps.

114 (liquid) was prepared according to the literature procedure[93] giving 550 mg in 59% yield.

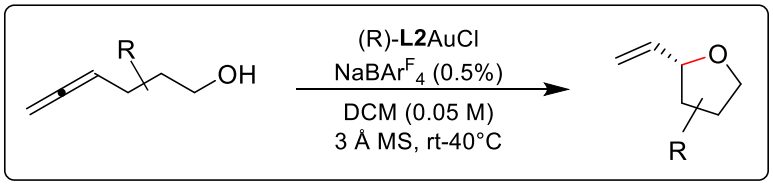
Preparation of **115**. To a solution of **114** (1.14 mmol, 225 mg) in 5 mL THF at 0 °C was added NaH (1.3 mmol, 60 wt%, 52 mg) slowly. After bubbles ceased, benzyl bromide (1.3

[104] Y. Uetake, T. Niwa, M. Nakada, *Tetrahedron Lett.* **2014**, 55, 6847.

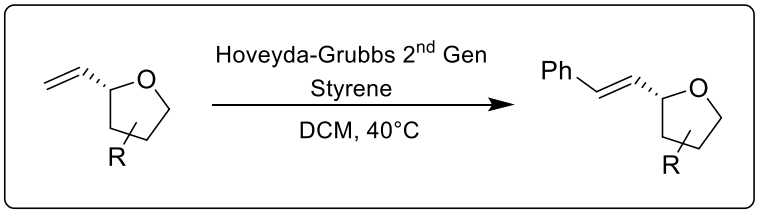
mmol, 0.155 mL) was added at the resulting solution was stirred at room temperature for 5 h. The reaction was quenched with water and extracted with ethyl acetate thr*ee* times. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography with ethyl acetate and hexanes (1:10) to give 241 mg **115** (liquid) in 73% yield.

116 (liquid) was prepared in a similar way as **109**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 5H), 5.14 (dt, J = 8.1, 6.6 Hz, 1H), 4.90 – 4.77 (m, 2H), 4.70 (d, J = 11.7 Hz, 1H), 4.43 (d, J = 11.7 Hz, 1H), 4.14 (dddt, J = 8.2, 7.0, 4.5, 1.3 Hz, 1H), 3.86 – 3.67 (m, 2H), 2.33 (s, 1H), 1.99 – 1.83 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.65, 138.00, 128.45, 127.92, 127.73, 90.97, 76.07, 70.35, 60.61, 38.23. IR (neat): 3386, 3032, 2936, 1955, 1722, 1454, 1066, 851, 458. HRMS CI(m/z): $[M+H]^+$ calcd. for $C_{13}H_{17}O_2$, 205.1228; found, 205.1236.

Asymmetric intramolecular cyclization of 4-allenyl alcohols

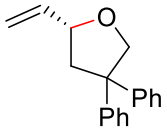


General procedure A: To a 3-dram vial were added sequentially 0.2 mmol 4-allenyl alcohol, indicated volume (18.3 µL for 100 ppm) of **(*R*)-L2AuCl** solution (1 mg/mL in DCM), 3 Å molecular sieves and 4 mL anhydrous DCM as solvent. The mixture was stirred at room temperature for 15 min before 0.001 mmol $NaBAr^F_4$ (0.5 mol%) was added. The reaction was then stirred at the indicated temperature monitored by TLC. Upon completion, the reaction was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography to obtain pure product.



General procedure B: To a N_2 flushed schlenk tube were added sequentially ca. 20 mg vinyl tetrahydrofuran product (1 equiv), styrene (2 equiv.), 1 mL anhydrous DCM as solvent and ca. 1 mg Hoveyda-Grubbs 2nd Generation catalyst. The mixture was stirred at 40 °C overnight. Upon completion indicated by TLC, the reaction was concentrated under reduced pressure. The residue was purified through silica gel flash column chromatography to obtain pure product.

(*R*)-4,4-diphenyl-2-vinyltetrahydrofuran (59)

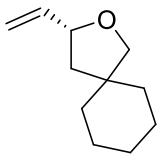


59

The compound **59** (liquid) was prepared in 99% yield from **58** with **(*R*)-L2AuCl** (100 ppm) at room temperature for 3 h according to General procedure A. Purification was performed by silica gel flash column chromatography with ethyl acetate and hexanes (1 : 10). The spectroscopic data were in accordance with the literature data.[93] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.27 (m, 6H), 7.25 – 7.18 (m, 4H), 5.90 (ddd, J = 17.1, 10.2, 6.9 Hz, 1H), 5.25 (dt, J = 17.1, 1.4 Hz, 1H), 5.11 (dt, J = 10.3, 1.3 Hz, 1H), 4.68 (dd, J = 8.7, 1.2 Hz, 1H), 4.44 (dddd, J = 9.7, 7.0, 6.0, 1.2 Hz, 1H), 4.16 (d, J = 8.7 Hz, 1H), 2.67 (ddd, J = 12.1, 6.0, 1.3 Hz, 1H), 2.45 (dd, J = 12.2, 9.7 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.96, 145.54, 138.78, 128.41, 128.34, 127.14, 127.10, 126.48, 126.29, 115.84, 79.68, 77.00, 56.17, 45.12.

99.1% *ee* [determined by HPLC: Chiralcel OJ-H column, iPrOH/Hexane = 5/95, 0.8 mL/min, λ = 210 nm; t_R(minor) = 15.77 min, t_R(major) = 19.85 min]. Absolute stereochemistry is determined by the literature report.[83]

(*R*)-3-vinyl-2-oxaspiro[4.5]decane (66)

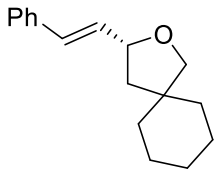


66

The compound **66** (liquid) was prepared in 93% yield from **65** with **(*R*)-L2AuCl** (100 ppm) at room temperature for 4 h according to General procedure A. Purification was performed by silica gel flash column chromatography with ethyl acetate and hexanes (1 : 20). The

spectroscopic data were in accordance with the literature data.[93] ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 (ddd, J = 17.0, 10.3, 6.5 Hz, 1H), 5.21 (dt, J = 17.1, 1.5 Hz, 1H), 5.06 (dt, J = 10.3, 1.5 Hz, 1H), 4.41 – 4.30 (m, 1H), 3.63 (d, J = 8.4 Hz, 1H), 3.56 (d, J = 8.4 Hz, 1H), 1.93 (dd, J = 12.4, 6.8 Hz, 1H), 1.52 – 1.35 (m, 11H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.49, 114.99, 114.98, 79.64, 78.55, 44.80, 44.07, 36.78, 35.53, 26.00, 24.03, 23.56.

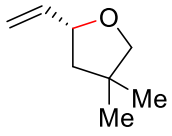
(*R*,*E*)-3-styryl-2-oxaspiro[4.5]decane (67)



67

The compound **67** (liquid) was prepared according to General procedure B. Purification was performed by silica gel flash column chromatography with ethyl acetate and hexanes (1 : 20). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.36 (m, 2H), 7.33 – 7.28 (m, 2H), 7.25 – 7.19 (m, 1H), 6.57 (dd, J = 15.9, 1.0 Hz, 1H), 6.23 (dd, J = 15.8, 6.9 Hz, 1H), 4.55 (dtd, J = 9.0, 6.8, 1.1 Hz, 1H), 3.70 (d, J = 8.4 Hz, 1H), 3.63 (d, J = 8.4 Hz, 1H), 2.01 (dd, J = 12.5, 6.8 Hz, 1H), 1.55 – 1.37 (m, 11H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.87, 130.86, 130.35, 128.47, 127.46, 126.45, 79.35, 78.65, 45.23, 44.19, 36.86, 35.55, 26.01, 24.07, 23.59. IR (neat): 3027, 3059, 2924, 1945, 1800, 1600, 1494, 1449, 1372, 1049, 963, 746, 693. HRMS CI(m/z): $[M+H]^+$ calcd. for $C_{17}H_{23}O$, 243.1749; found, 243.1760.
97.1% *ee* [determined by HPLC: Chiralpak IB column, iPrOH/Hexane = 1/200, 1 mL/min, λ = 210 nm; t_R(major) = 8.61 min, t_R(minor) = 19.97 min].

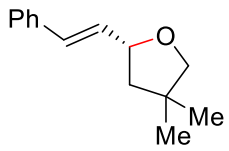
(*R*)-4,4-dimethyl-2-vinyltetrahydrofuran (120)



120

The compound **120** (liquid) was prepared in 59% yield (89% NMR yield using 1,3,5-triisopropylbenzene as internal reference) from **77** with **(*R*)-L2AuCl** (100 ppm) at room temperature for 5 h according to General procedure A. Purification was performed by silica gel flash column chromatography with dichloromethane and pentane (2 : 1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87 (ddd, J = 17.0, 10.3, 6.6 Hz, 1H), 5.22 (dt, J = 17.1, 1.4 Hz, 1H), 5.07 (ddd, J = 10.3, 1.6, 1.1 Hz, 1H), 4.44 (dtt, J = 8.9, 6.8, 1.1 Hz, 1H), 3.56 (d, J = 8.0 Hz, 1H), 3.49 (d, J = 8.1 Hz, 1H), 1.85 (dd, J = 12.3, 6.9 Hz, 1H), 1.48 (dd, J = 12.3, 8.8 Hz, 1H), 1.11 (s, 3H), 1.10 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.59, 114.89, 80.27, 80.18, 47.13, 39.93, 26.54, 26.39. IR (neat): 2955, 2870, 1467, 1368, 1049, 840. HRMS CI(m/z): $[M+H]^+$ calcd. for $C_8H_{15}O$, 127.1123; found, 127.1125.

(*R*,*E*)-4,4-dimethyl-2-styryltetrahydrofuran (120a)

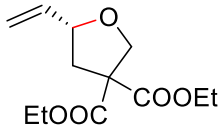


120a

The compound **120a** (liquid) was prepared according to General procedure B. Purification was performed by silica gel flash column chromatography with ethyl acetate and hexanes (1 : 20). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.36 (m, 2H), 7.33 – 7.28 (m, 2H), 7.25 – 7.20 (m, 1H), 6.57 (d, J = 15.9 Hz, 1H), 6.23 (dd, J = 15.8, 6.9 Hz, 1H), 4.63 (dtd, J = 8.9, 6.9, 1.2 Hz, 1H), 3.63 (d, J = 8.1 Hz, 1H), 3.55 (d, J = 8.1 Hz, 1H), 1.97 – 1.89 (m, 1H), 1.59 (dd, J = 12.4, 8.9 Hz, 1H), 1.15 (s, 3H), 1.14 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.87, 130.97, 130.27, 128.49, 127.47, 126.46, 80.37, 79.89, 47.53, 40.04, 26.60, 26.40. IR (neat): 3072, 2958, 2869, 1450, 1368, 1051, 964, 747, 693. HRMS CI(m/z): $[M+H]^+$ calcd. for $C_{14}H_{19}O$, 203.1436; found, 203.1429.

97.0% *ee* [determined by HPLC: Chiralpak IB column, iPrOH/Hexane = 1/200, 1 mL/min, λ = 210 nm; t_R(major) = 7.98 min, t_R(minor) = 15.32 min].

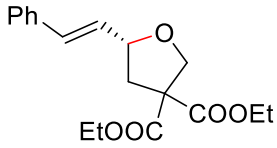
(*R*)-diethyl 5-vinyldihydrofuran-3,3(2H)-dicarboxylate (121)



121

The compound **121** (liquid) was prepared in 83% yield from **80** with **(*R*)-L2AuCl** (100 ppm) at room temperature for 6 h according to General procedure A. Purification was performed by silica gel flash column chromatography with ethyl acetate and hexanes (1 : 10). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84 (ddd, J = 17.1, 10.4, 6.6 Hz, 1H), 5.27 (dt, J = 17.2, 1.3 Hz, 1H), 5.14 (dt, J = 10.3, 1.3 Hz, 1H), 4.44 – 4.35 (m, 2H), 4.25 – 4.16 (m, 4H), 4.12 (d, J = 9.3 Hz, 1H), 2.68 (dd, J = 13.1, 6.5 Hz, 1H), 2.19 (dd, J = 13.1, 8.7 Hz, 1H), 1.25 (td, J = 7.1, 3.6 Hz, 7H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.21, 169.96, 136.97, 116.83, 80.52, 72.98, 61.87, 61.84, 61.15, 39.90, 13.94, 13.94. IR (neat): 3085, 2985, 2877, 1735, 1467, 1369, 1254, 1197, 1098, 1053, 932, 863, 693. HRMS CI(m/z): $[M+H]^+$ calcd. for $C_{12}H_{19}O_5$, 243.1232; found, 243.1227.

(*R*,*E*)-diethyl 5-styryldihydrofuran-3,3(2H)-dicarboxylate (121a)



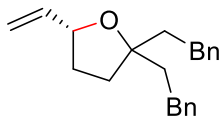
121a

The compound **121a** (liquid) was prepared according to General procedure B. Purification was performed by silica gel flash column chromatography with ethyl acetate and hexanes (1 : 10). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.35 (m, 2H), 7.34 – 7.28 (m, 2H), 7.26 – 7.22 (m, 1H), 6.62 (d, J = 15.9 Hz, 1H), 6.20 (dd, J = 15.9, 7.0 Hz, 1H), 4.58 (dtd, J = 8.7, 6.7, 1.1 Hz, 1H), 4.48 (d, J = 9.3 Hz, 1H), 4.27 – 4.20 (m, 4H), 4.19 (d, J = 9.3 Hz, 1H), 2.77 (dd, J = 13.1, 6.5 Hz, 1H), 2.31 (dd, J = 13.1, 8.7 Hz, 1H), 1.29 (t, J = 7.1 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.28, 170.05, 136.38, 132.20,

128.54, 128.12, 127.85, 126.59, 80.44, 73.12, 61.97, 61.95, 61.29, 40.37, 14.01. IR (neat): 2983, 1731, 1449, 1264, 1185, 1050, 969, 861, 749, 694. HRMS CI(m/z): $[M+H]^+$ calcd. for $C_{18}H_{23}O_5$, 319.1545; found, 319.1532.

99.7% *ee* [determined by HPLC: Chiralpak IB column, iPrOH/Hexane = 1/200, 1 mL/min, λ = 210 nm; t_R(major) = 19.23 min, t_R(minor) = 25.08 min].

(*R*)-2,2-diphenethyl-5-vinyltetrahydrofuran (122)

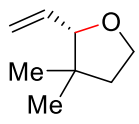


122

The compound **122** (liquid) was prepared in 95% yield from **84** with **(*R*)-L2AuCl** (100 ppm) at room temperature for 8 h according to General procedure A. Purification was performed by silica gel flash column chromatography with ethyl acetate and hexanes (1 : 20). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (t, J = 7.2 Hz, 4H), 7.25 – 7.17 (m, 6H), 5.92 (dddd, J = 17.0, 10.3, 6.6, 1.6 Hz, 1H), 5.32 (d, J = 17.1 Hz, 1H), 5.14 (d, J = 10.3 Hz, 1H), 4.46 (q, J = 6.6 Hz, 1H), 2.82 – 2.63 (m, 4H), 2.15 (dq, J = 11.5, 7.3, 6.7 Hz, 1H), 2.01 – 1.85 (m, 6H), 1.83 – 1.72 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.63, 142.58, 139.61, 128.37, 128.30, 128.29, 125.71, 115.30, 85.06, 80.16, 41.53, 41.09, 35.40, 32.86, 30.85, 30.72. IR (neat): 3063, 3026, 2944, 2865, 1603, 1497, 1454, 1304, 1052, 920, 747, 699. HRMS CI(m/z): $[M+H]^+$ calcd. for $C_{22}H_{27}O$, 307.2062; found, 307.2070.

95.8% *ee* [determined by HPLC: Chiralpak IB column, iPrOH/Hexane = 1/400, 1 mL/min, λ = 210 nm; t_R(minor) = 8.67 min, t_R(major) = 10.53 min].

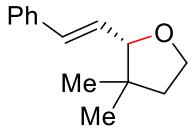
(*S*)-3,3-dimethyl-2-vinyltetrahydrofuran (123)



123

The compound **123** (liquid) was prepared in 92% yield from **88** with **(*R*)-L2AuCl** (100 ppm) at room temperature for 3 d according to General procedure A. Purification was performed by silica gel flash column chromatography with dichloromethane and pentane (2 : 1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.76 (ddd, J = 17.3, 10.5, 6.9 Hz, 1H), 5.23 (ddd, J = 17.2, 1.9, 1.2 Hz, 1H), 5.16 (ddd, J = 10.5, 2.0, 1.0 Hz, 1H), 3.96 – 3.89 (m, 1H), 3.85 (td, J = 8.5, 4.9 Hz, 1H), 3.78 (dt, J = 6.9, 1.1 Hz, 1H), 1.83 – 1.71 (m, 2H), 1.04 (s, 3H), 0.89 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.56, 116.73, 88.53, 65.91, 41.45, 40.91, 25.20, 21.99. IR (neat): 3082, 2959, 2874, 1644, 1466, 1368, 1209, 1131, 1064, 1031, 922, 841. HRMS CI(m/z): $[M+H]^+$ calcd. for $C_8H_{15}O$, 127.1123; found, 127.1119.

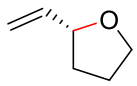
(*S*,*E*)-3,3-dimethyl-2-styryltetrahydrofuran (123)



123a

The compound **123** (liquid) was prepared according to General procedure B. Purification was performed by silica gel flash column chromatography with ethyl acetate and hexanes (1 : 20). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.37 (m, 3H), 7.35 – 7.29 (m, 2H), 7.25 – 7.21 (m, 1H), 6.59 (d, J = 15.9 Hz, 1H), 6.16 (dd, J = 15.9, 7.1 Hz, 1H), 4.04 – 3.96 (m, 2H), 3.92 (td, J = 8.5, 4.7 Hz, 1H), 1.90 – 1.77 (m, 2H), 1.10 (s, 3H), 0.97 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.00, 131.79, 128.49, 127.45, 127.06, 126.47, 88.21, 66.04, 42.16, 41.10, 25.33, 22.20. IR (neat): 3060, 3027, 2959, 2872, 1600, 1495, 1465, 1368, 1129, 968, 905, 743, 694. HRMS CI(m/z): $[M+H]^+$ calcd. for $C_{14}H_{19}O$, 203.1436; found, 203.1440. 49.8% *ee* [determined by HPLC: Chiralcel OJ-H column, iPrOH/Hexane = 1/400, 0.8 mL/min, λ = 210 nm; t_R(minor) = 17.86 min, t_R(major) = 23.73 min].

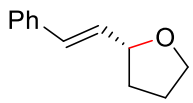
(*R*)-2-vinyltetrahydrofuran (124)



124

The compound **124** (liquid) was prepared in 74% yield from **90** with **(*R*)-L2AuCl** (100 ppm) at room temperature for 9 h according to General procedure A. Purification was performed by silica gel flash column chromatography with dichloromethane and pentane (2 : 1). The spectroscopic data were in accordance with the literature data.[105] ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84 (ddd, J = 17.1, 10.3, 6.2 Hz, 1H), 5.23 (ddd, J = 17.2, 1.8, 1.3 Hz, 1H), 5.08 (ddd, J = 10.4, 1.7, 1.1 Hz, 1H), 4.34 – 4.23 (m, 1H), 3.90 (ddd, J = 8.3, 7.4, 6.2 Hz, 1H), 3.78 (td, J = 8.0, 6.3 Hz, 1H), 2.04 (dddd, J = 12.1, 8.1, 6.7, 5.3 Hz, 1H), 1.97 – 1.83 (m, 2H), 1.61 (ddt, J = 12.0, 8.5, 7.3 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.13, 115.00, 79.87, 68.02, 31.89, 25.70. IR (neat): 2940, 1714, 1356, 1279, 1129, 1036, 801. GC-MS (m/z): 98 $[M]^+$.

(*R,E*)-2-styryltetrahydrofuran (124a)



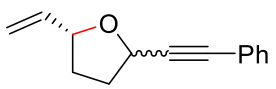
124a

The compound **124a** (liquid) was prepared according to General Procedure B. The spectroscopic data were in accordance with the literature data.[106] Purification was performed by silica gel flash column chromatography with ethyl acetate and hexanes (1 : 20). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.35 (m, 2H), 7.34 – 7.28 (m, 2H), 7.25 – 7.20 (m, 1H), 6.58 (d, J = 15.8 Hz, 0H), 6.21 (dd, J = 15.9, 6.6 Hz, 1H), 4.50 – 4.44 (m, 1H), 3.97 (ddd, J = 8.3, 7.4, 6.2 Hz, 1H), 3.84 (td, J = 7.9, 6.1 Hz, 1H), 2.13 (dddd, J = 12.0, 8.1,

[105] Y. Xie, P.E. Floreancig, *Angew. Chem. Int. Ed.* **2014**, 53, 4926.
[106] M. Wan, Z. Meng, H. Lou, L. Liu, *Angew. Chem. Int. Ed.* **2014**, 53, 13845.

6.7, 5.1 Hz, 1H), 2.03 – 1.91 (m, 2H), 1.72 (ddt, J = 12.2, 8.5, 7.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.88, 130.54, 130.41, 128.49, 127.47, 126.45, 79.65, 68.17, 32.40, 25.92. 94.1% *ee* [determined by HPLC: Chiralpak IB column, iPrOH/Hexane = 1/200, 1 mL/min, λ = 210 nm; t_R(major) = 12.46 min, t_R(minor) = 17.15 min].

(*R*)-2-(phenylethynyl)-5-vinyltetrahydrofuran (125)



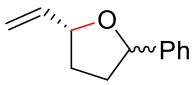
125

The compound **125** (liquid) was prepared in 83% yield (*trans*/*cis* = 1.01/1) from **92** with **(*R*)-L2AuCl** (500 ppm) at 40 °C for 15 h according to General procedure A. Purification was performed by silica gel flash column chromatography with ethyl acetate and hexanes (1 : 10). [Major diastereomer] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (dq, J = 5.2, 1.7 Hz, 2H), 7.33 – 7.27 (m, 3H), 5.86 (ddd, J = 16.9, 10.4, 6.3 Hz, 1H), 5.29 (dt, J = 16.2, 1.4 Hz, 1H), 5.13 (dt, J = 10.4, 1.4 Hz, 1H), 4.99 – 4.92 (m, 1H), 4.61 (q, J = 6.4 Hz, 1H), 2.37 – 2.08 (m, 3H), 1.76 – 1.67 (m, 1H); [Minor diastereomer] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 – 7.40 (m, 2H), 7.32 – 7.27 (m, 3H), 5.97 (ddd, J = 17.0, 10.3, 6.6 Hz, 1H), 5.33 (dt, J = 16.0, 1.4 Hz, 1H), 5.14 (dt, J = 10.3, 1.3 Hz, 1H), 4.83 (dd, J = 7.4, 5.5 Hz, 1H), 4.45 – 4.36 (m, 1H), 2.37 – 2.08 (m, 3H), 1.97 – 1.85 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.06, 138.30, 131.70, 131.66, 128.24, 128.22, 128.19, 122.88, 122.81, 115.88, 115.68, 89.23, 89.18, 84.56, 84.55, 81.02, 79.78, 68.93, 68.66, 33.51, 33.48, 31.89, 31.77. IR (neat): 3063, 2983, 1599, 1491, 1443, 1337, 1040, 924, 757, 692. HRMS CI(m/z): $[M+H]^+$ calcd. for $C_{14}H_{15}O$, 199.1123; found, 199.1115.

[Match] 94.6% *de* [determined by HPLC: Chiralpak IB column, iPrOH/Hexane = 1/200, 1 mL/min, λ = 210 nm; t_R(minor) = 7.81 min, t_R(major) = 11.82 min].

[Mismatch] 93.3% *de* [determined by HPLC: Chiralpak IB column, iPrOH/Hexane = 1/200, 1 mL/min, λ = 210 nm; t_R(minor) = 24.52 min, t_R(major) = 67.10 min].

(*R*)-2-phenyl-5-vinyltetrahydrofuran (126)



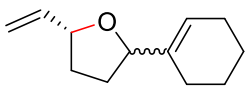
126

The compound **126** (liquid) was prepared in 84% yield (*trans*/*cis* = 1.04/1) from **93** with **(*R*)-L2AuCl** (200 ppm) at room temperature for 33 h according to General procedure A. Purification was performed by silica gel flash column chromatography with ethyl acetate and hexanes (1 : 20). This compound was previously reported.[107] [Major diastereomer] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.31 (m, 4H), 7.30 – 7.23 (m, 1H), 5.96 (ddd, J = 17.0, 10.3, 6.2 Hz, 1H), 5.33 (d, J = 15.6 Hz, 1H), 5.15 (d, J = 10.9 Hz, 1H), 5.09 (t, J = 7.1 Hz, 1H), 4.69 (q, J = 6.6 Hz, 1H), 2.44 – 2.13 (m, 2H), 1.96 – 1.76 (m, 2H); [Minor diastereomer] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.31 (m, 4H), 7.30 – 7.23 (m, 1H), 6.03 (ddd, J = 17.0, 10.4, 6.5 Hz, 1H), 5.36 (d, J = 15.9 Hz, 1H), 5.18 (d, J = 11.0 Hz, 1H), 4.97 (t, J = 7.1 Hz, 1H), 4.51 (q, J = 6.8 Hz, 1H), 2.44 – 2.13 (m, 2H), 1.96 – 1.76 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.49, 143.12, 139.29, 139.06, 128.24, 128.19, 127.13, 127.07, 125.80, 125.54, 115.51, 114.98, 81.06, 80.69, 80.61, 80.55, 35.09, 34.26, 32.66, 31.87. IR (neat): 3064, 3030, 2975, 2944, 1716, 1494, 1450, 1317, 1049, 926, 758, 700. HRMS CI(m/z): $[M+H]^+$ calcd. for $C_{12}H_{15}O$, 175.1123; found, 175.1125.

[Match] 95.8% *de* [determined by HPLC: Chiralcel OJ-H column, iPrOH/Hexane = 5/95, 0.8 mL/min, λ = 210 nm; t_R(major) = 30.78 min, t_R(minor) = 44.07 min].

[Mismatch] 92.1% *de* [determined by HPLC: Chiralcel OJ-H column, iPrOH/Hexane = 5/95, 0.8 mL/min, λ = 210 nm; t_R(minor) = 26.05 min, t_R(major) = 48.89 min].

(*R*)-2-cyclohexenyl-5-vinyltetrahydrofuran (127)

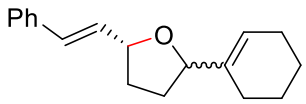


127

[107] I. Macsari, K.J. Szabo, *Chem. Eur. J.* **2001**, 7, 4097.

The compound **127** (liquid) was prepared in 87% yield (*trans*/*cis* = 1.35/1) from **94** with **(*R*)-L2AuCl** (200 ppm) at room temperature for 48 h according to General procedure A. Purification was performed by silica gel flash column chromatography with diethyl ether and hexanes (1 : 4). [Major diastereomer] ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.89 (ddd, J = 17.4, 10.5, 6.6 Hz, 1H), 5.75 – 5.72 (m, 1H), 5.30 – 5.23 (m, 1H), 5.13 – 5.08 (m, 1H), 4.30 (q, J = 6.9 Hz, 1H), 2.23 – 1.43 (m, 13H). [Minor diastereomer] ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91 (ddd, J = 17.4, 10.5, 6.6 Hz, 1H), 5.75 – 5.72 (m, 1H), 5.30 – 5.23 (m, 1H), 5.13 – 5.08 (m, 1H), 4.43 (q, J = 6.7 Hz, 1H), 2.23 – 1.43 (m, 13H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.47, 139.14, 137.87, 137.67, 122.85, 122.44, 115.12, 114.68, 83.36, 82.98, 80.23, 80.04, 32.74, 32.02, 30.58, 29.88, 24.87, 24.85, 23.77, 23.64, 22.51. The number of carbons is less than what expected owing to overlapping of the signals. IR (neat): 2932, 2859, 1438, 1188, 1054, 920. HRMS ESI(m/z): $[M+H]^+$ calcd. for $C_{12}H_{19}O$, 179.1436; found, 179.1434.

(*R*,*E*)-2-cyclohexenyl-5-styryltetrahydrofuran (127a)



127a

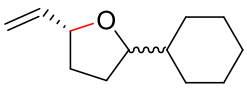
The compound **127a** (liquid) was prepared according to General Procedure B. Purification was performed by silica gel flash column chromatography with diethyl ether and hexanes (5 : 95). [Major diastereomer] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 – 7.15 (m, 5H), 6.62 (d, J = 15.8 Hz, 1H), 6.27 (dd, J = 15.9, 6.8 Hz, 1H), 5.84 – 5.70 (m, 1H), 4.63 – 4.41 (m, 1H), 4.39 – 4.20 (m, 1H), 2.26 – 1.42 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.68, 136.88, 130.53, 130.48, 128.36, 127.33, 126.37, 122.99, 83.41, 79.77, 32.43, 29.99, 24.90, 23.85, 22.52, 22.52. [Minor diastereomer] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 – 7.07 (m, 5H), 6.61 (d, J = 15.9 Hz, 1H), 6.24 (dd, J = 15.9, 6.6 Hz, 1H), 5.75 (s, 1H), 4.66 (dd, J = 15.1, 8.0 Hz, 1H), 4.44 (t, J = 7.1 Hz, 1H), 2.36 – 1.00 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.02, 137.84, 130.91, 130.03, 128.35, 127.27, 126.33, 122.56, 83.12, 79.91, 34.53, 30.74, 24.87, 23.68, 22.52, 22.52. IR (neat): 2928, 2856, 1448, 1056, 964, 913, 747, 692. HRMS

ESI(m/z): $[M+H]^+$ calcd. for $C_{18}H_{23}O$, 255.1749; found, 255.1746.

[Match] 94.7% *de* [determined by HPLC: Chiralpak IB column, iPrOH/Hexane = 1/200, 1 mL/min, λ = 210 nm; t_R(major) = 8.06 min, t_R(minor) = 19.11 min].

[Mismatch] 92.5% *de* [determined by HPLC: Chiralpak IB column, iPrOH/Hexane = 1/200, 1 mL/min, λ = 210 nm; t_R(major) = 6.22 min, t_R(minor) = 7.43 min].

(5*R*)-2-cyclohexyl-5-vinyltetrahydrofuran (128)

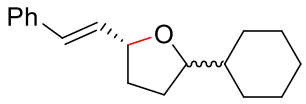


128

The compound **128** (trans/cis = 1/1, liquid) was prepared in 74% yield from **95** with **(*R*)-L2AuCl** (100 ppm) at room temperature for 24 h according to General procedure A. Purification was performed by silica gel flash column chromatography with diethyl ether and hexanes (1 : 4). This compound was previously reported.[108] [Major diastereomer] ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83 (ddd, J = 17.4, 10.5, 6.6 Hz, 1H), 5.20 (dt, J = 17.4, 1.5 Hz, 1H), 5.05 (dt, J = 10.5, 1.5 Hz, 1H), 4.29 (q, J = 7.0 Hz, 1H), 3.60 (q, J = 7.2 Hz, 1H), 2.09 – 0.90 (m, 15H). [Minor diastereomer] ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83 (ddd, J = 17.4, 10.5, 6.6 Hz, 1H), 5.20 (dt, J = 17.4, 1.5 Hz, 1H), 5.05 (dt, J = 10.5, 1.5 Hz, 1H), 4.36 (q, J = 7.0 Hz, 1H), 3.71 (q, J = 7.2 Hz, 1H), 2.09 – 0.90 (m, 15H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.60, 139.51, 114.91, 114.67, 84.25, 83.70, 79.68, 79.56, 43.14, 43.06, 32.63, 31.73, 29.80, 29.53, 28.97, 28.74, 28.55, 26.47, 26.01, 25.86. The number of carbons is less than what expected owing to overlapping of the signals. IR (neat): 3080, 2924, 2853, 1449, 1055, 950. HRMS ESI(m/z): $[M+H]^+$ calcd. for $C_{12}H_{21}O$, 181.1592; found, 181.1593.

[108] A. Aponick, C.-Y. Li, B. Biannic, *Org. Lett.* **2008**, 10, 669.

(5*R*)-2-cyclohexyl-5-((*E*)-styryl)tetrahydrofuran (128a)



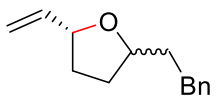
128a

The compound **128a** was prepared according to General Procedure B. Purification was performed by silica gel flash column chromatography with diethyl ether and hexanes (5 : 95). [Major diastereomer] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 – 7.10 (m, 5H), 6.58 (d, J = 15.8 Hz, 1H), 6.22 (dd, J = 15.8, 6.8 Hz, 1H), 4.60 – 4.45 (m, 1H), 3.86 – 3.70 (m, 1H), 2.25 – 1.86 (m, 4H), 1.81 – 0.86 (m, 11H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.83, 131.01, 130.12, 128.34, 127.27, 126.35, 83.86, 79.34, 43.22, 33.14, 29.83, 29.69, 28.77, 26.47, 26.03, 25.87. [Minor diastereomer] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 – 7.13 (m, 5H), 6.60 (d, J = 15.9 Hz, 1H), 6.23 (dd, J = 15.8, 6.8 Hz, 1H), 4.56 – 4.34 (m, 1H), 3.74 – 3.51 (m, 1H), 2.24 – 1.85 (m, 4H), 1.85 – 0.75 (m, 11H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.86, 130.89, 130.36, 128.34, 127.30, 126.38, 84.32, 79.48, 43.10, 32.15, 29.83, 29.00, 28.72, 26.47, 26.00, 25.87. IR (neat): 2924, 2852, 1449, 1054, 962, 920, 746, 693. HRMS ESI(m/z): $[M+H]^+$ calcd. for $C_{18}H_{25}O$, 257.1905; found, 257.1904.

[Match] 94.4% *de* [determined by HPLC: Chiralpak IB column, iPrOH/Hexane = 1/200, 1 mL/min, λ = 210 nm; t_R(major) = 5.00 min, t_R(minor) = 5.26 min].

[Mismatch] 93.0% *de* [determined by HPLC: Chiralpak IB column, iPrOH/Hexane = 1/200, 1 mL/min, λ = 210 nm; t_R(major) = 5.69 min, t_R(minor) = 6.68 min].

(*R*)-2-phenethyl-5-vinyltetrahydrofuran (129)

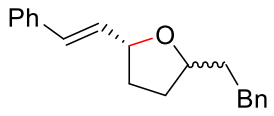


129

The compound **129** (liquid) was prepared in 86% yield (*trans*/*cis* = 1.06/1) from **96** with

(*R*)-L2AuCl (100 ppm) at 40 °C for 15 h according to General procedure A. Purification was performed by silica gel flash column chromatography with ethyl acetate and hexanes (1 : 20). The spectroscopic data were in accordance with the literature data.[105] [Major diastereomer] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.17 (m, 5H), 5.96 – 5.81 (m, 1H), 5.26 (dt, J = 12.5, 1.8 Hz, 1H), 5.10 (dt, J = 4.9, 1.4 Hz, 1H), 4.45 (q, J = 6.5 Hz, 1H), 4.04 (ddd, J = 13.2, 7.5, 5.7 Hz, 1H), 2.86 – 2.62 (m, 2H), 2.18 – 1.51 (m, 6H); [Minor diastereomer] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.17 (m, 5H), 5.96 – 5.81 (m, 1H), 5.30 (dt, J = 12.5, 1.6 Hz, 1H), 5.13 (dt, J = 5.2, 1.4 Hz, 1H), 4.33 (q, J = 6.7 Hz, 1H), 3.93 (qd, J = 7.0, 5.7 Hz, 1H), 2.86 – 2.62 (m, 2H), 2.18 – 1.51 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.13, 139.56, 139.45, 128.35, 128.34, 128.25, 125.66, 115.16, 114.89, 80.06, 79.53, 79.01, 78.51, 37.75, 37.71, 32.52, 32.50, 32.49, 31.96, 31.76, 31.00. IR (neat): 3027, 2936, 2863, 1604, 1497, 1454, 1051, 921, 700. HRMS CI(m/z): $[M+H]^+$ calcd. for $C_{14}H_{19}O$, 203.1436; found, 203.1431.

(*R,E*)-2-phenethyl-5-styryltetrahydrofuran (129a)



129a

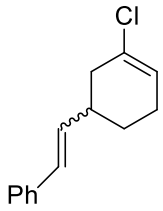
The compound **129a** (liquid) was prepared according to General procedure B. Purification was performed by silica gel flash column chromatography with ethyl acetate and hexanes (1 : 20). [Major diastereomer] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.13 (m, 10H), 6.61 (d, J = 15.9 Hz, 1H), 6.30 – 6.16 (m, 1H), 4.48 (q, J = 6.9 Hz, 1H), 3.96 (p, J = 6.7 Hz, 1H), 2.89 – 2.63 (m, 2H), 2.25 – 1.91 (m, 3H), 1.91 – 1.59 (m, 3H); [Minor diastereomer] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.13 (m, 10H), 6.59 (d, J = 15.9 Hz, 1H), 6.30 – 6.16 (m, 1H), 4.62 (q, J = 7.0 Hz, 1H), 4.16 – 4.04 (m, 1H), 2.89 – 2.63 (m, 2H), 2.25 – 1.91 (m, 3H), 1.91 – 1.59 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.14, 136.82, 130.91, 130.86, 130.59, 130.31, 128.46, 128.40, 128.31, 127.47, 127.44, 126.48, 126.45, 125.72, 79.89, 79.32, 79.13, 78.71, 77.20, 37.79, 33.03, 32.57, 32.22, 32.16, 31.19. IR (neat): 3026, 2927, 1601, 1496, 1452, 1331, 1047, 965, 746, 693. HRMS CI(m/z): $[M+H]^+$ calcd. for $C_{20}H_{23}O$,

279.1749; found, 279.1758.

[Match] 95.9% *de* [determined by HPLC: Chiralpak IB column, iPrOH/Hexane = 1/200, 1 mL/min, λ = 210 nm; t_R(major) = 10.77 min, t_R(minor) = 16.12 min].

[Mismatch] 95.4% *de* [determined by HPLC: Chiralpak IB column, iPrOH/Hexane = 1/200, 1 mL/min, λ = 210 nm; t_R(minor) = 13.69 min, t_R(major) = 23.14 min].

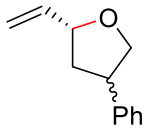
(2-(3-chlorocyclohex-3-en-1-yl)vinyl)benzene (135)



135

The compound **135** (liquid) was prepared in 81% yield from **98** with **(*R*)-L2AuCl** (100 ppm) at room temperature for 30 min according to General procedure A. Purification was performed by silica gel flash column chromatography with hexanes (100%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.22 (m, 5H), 6.46 (d, J = 16 Hz, 1H), 6.21 (dd, J = 16, 7.1 Hz, 1H), 5.87 (s, 1H), 2.64 – 2.22 (m, 5H), 1.90 – 1.84 (m, 1H), 1.54 – 1.47 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.29, 133.41, 130.53, 128.91, 128.43, 127.08, 125.98, 124.14, 38.47, 38.18, 27.48, 25.28. HRMS CI(m/z): $[M+H]^+$ calcd. for $C_{14}H_{16}Cl$, 219.0941; found, 219.0938.

(*R*)-4-phenyl-2-vinyltetrahydrofuran (130)



130

The compound **130** (liquid) as prepared in 90% yield (*trans*/*cis* = 1/1.31) from **103** with

(*R*)-L2AuCl (100 ppm) at room temperature for 55 h according to General procedure A. Purification was performed by silica gel flash column chromatography with ethyl acetate and hexanes (1 : 20). This compound has been reported by previous literature.[109] [Major diastereomer] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.28 (m, 2H), 7.30 – 7.20 (m, 3H), 5.98 (ddd, J = 17.0, 10.3, 6.6 Hz, 1H), 5.33 (dt, J = 17.2, 1.4 Hz, 1H), 5.17 (dt, J = 8.6, 1.2 Hz, 1H), 4.53 – 4.43 (m, 1H), 4.21 (t, J = 8.2 Hz, 1H), 3.85 (t, J = 8.4 Hz, 1H), 3.49 (dt, J = 15.5, 7.9 Hz, 1H), 2.52 (ddd, J = 12.4, 7.5, 5.9 Hz, 1H), 1.83 (dt, J = 12.3, 10.0 Hz, 1H); [Minor diastereomer] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.29 (m, 2H), 7.29 – 7.21 (m, 3H), 5.93 (ddd, J = 17.1, 10.4, 6.0 Hz, 2H), 5.30 (dt, J = 17.1, 1.5 Hz, 1H), 5.17 – 5.12 (m, 1H), 4.67 – 4.61 (m, 1H), 4.30 (dd, J = 8.5, 7.4 Hz, 1H), 3.80 (t, J = 8.2 Hz, 1H), 3.57 – 3.46 (m, 1H), 2.27 – 2.11 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.10, 141.84, 139.09, 138.64, 128.56, 128.55, 127.25, 127.20, 126.57, 126.53, 115.71, 115.06, 81.09, 79.85, 74.59, 74.42, 45.76, 44.30, 41.18, 40.03. IR (neat): 3063, 3029, 2938, 2864, 1645, 1604, 1494, 1455, 1052, 990, 924, 758, 700. HRMS CI(m/z): $[M+H]^+$ calcd. for $C_{12}H_{15}O$, 175.1123; found, 175.1128.

[Match] 98.7% *de* [determined by HPLC: Chiralcel OJ-H column, Hexane, 0.8 mL/min, λ = 210 nm; t_R(minor) = 33.74 min, t_R(major) = 40.34 min].

[Mismatch] 88.4% *de* [determined by HPLC: Chiralcel OJ-H column, Hexane, 0.8 mL/min, λ = 210 nm; t_R(minor) = 28.61 min, t_R(major) = 28.61 min].

Calculations for **130**:

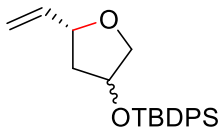
$$\begin{cases} dr = \dfrac{[Match](major) + [Mismatch](minor)}{[Match](minor) + [Mismatch](major)} = \dfrac{1.31}{1} \\ [Mismatch](major) + [Mismatch](minor) = 45.602 \\ [Match](major) = 54.055 \\ [Match](minor) = 0.343 \end{cases}$$

Solving the system, we obtain:

[109] P. Li, T. Wang, T. Emge, K. Zhao, *J. Am. Chem. Soc.* **1998**, 120, 7391.

$$\begin{cases} [Match](major) = 54.055 \\ [Match](minor) = 0.343 \\ [Mismatch](major) = 42.947 \\ [Mismatch](minor) = 2.655 \end{cases}$$

(*R*)-*tert*-butyldiphenyl(5-vinyltetrahydrofuran-3-yloxy)silane (131)



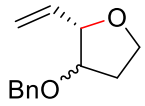
131

The compound **131** (liquid) was prepared in 94% yield (*trans*/*cis* = 1.33/1) from **109** with **(*R*)-L2AuCl** (0.5 mol%) and $NaBAr^F{}_4$ (1 mol%) at room temperature for 6 h according to General procedure A. Purification was performed by silica gel flash column chromatography with ethyl acetate and hexanes (1 : 20). [Major diastereomer] ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 – 7.62 (m, 4H), 7.45 (tt, J = 7.2, 1.7 Hz, 2H), 7.42 – 7.35 (m, 4H), 5.81 (ddd, J = 15.2, 10.4, 6.7 Hz, 1H), 5.28 (dt, J = 17.1, 1.4 Hz, 1H), 5.11 (d, J = 9.7 Hz, 1H), 4.67 – 4.59 (m, 1H), 4.52 – 4.43 (m, 1H), 3.92 – 3.86 (m, 1H), 3.76 (dd, J = 9.4, 2.4 Hz, 1H), 2.05 (ddd, J = 12.9, 5.6, 2.0 Hz, 1H), 1.60 (ddd, J = 13.0, 9.8, 5.3 Hz, 1H), 1.09 (s, 9H); [Minor diastereomer] ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 – 7.61 (m, 4H), 7.45 (tt, J = 7.2, 1.7 Hz, 2H), 7.42 – 7.36 (m, 4H), 6.11 – 6.01 (m, 1H), 5.23 (d, J = 17.2 Hz, 1H), 5.12 (d, J = 9.1 Hz, 1H), 4.53 – 4.42 (m, 1H), 4.26 (q, J = 7.2 Hz, 1H), 3.84 (dd, J = 9.2, 3.2 Hz, 1H), 3.69 – 3.64 (m, 1H), 2.17 (dt, J = 13.6, 7.0 Hz, 1H), 1.81 (ddd, J = 12.9, 6.7, 3.9 Hz, 1H), 1.07 (d, J = 2.8 Hz, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 139.28, 138.35, 135.70, 135.66, 135.64, 133.82, 133.79, 133.75, 133.73, 129.72, 129.71, 127.68, 127.66, 115.91, 115.49, 79.87, 79.23, 75.82, 75.04, 73.88, 73.75, 42.15, 41.64, 26.86, 26.81, 19.07, 19.03. IR (neat): 3072, 2932, 2859, 1961, 1891, 1826, 1590, 1428, 1390, 1112, 1042, 998, 741, 613, 505. HRMS CI(m/z): $[M+H]^+$ calcd. for $C_{22}H_{29}O_2Si$, 353.1937; found, 353.1950. [Match] 98.9% *de* [determined by HPLC: Chiralpak IA column, Hexane, 1 mL/min, λ =

210 nm; t_R(major) = 18.73 min, t_R(minor) = 25.15 min].

[Mismatch] 97.5% *de* [determined by HPLC: Chiralpak IA column, Hexane, 1 mL/min, λ = 210 nm; t_R(minor) = 10.16 min, t_R(major) = 11.17 min].

(*S*)-3-(benzyloxy)-2-vinyltetrahydrofuran (132)



132

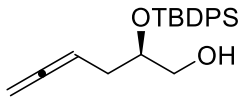
The compound **132** (liquid) was prepared in 65% yield (*trans*/*cis* = 1/1.01) from **116** with **(*R*)-L2AuCl** (0.2 mol%) and $NaBAr^F_4$ (0.5 mol%) at 40 °C for 36 h according to General procedure A. Purification was performed by silica gel flash column chromatography with ethyl acetate and hexanes (1 : 10). [Major diastereomer] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.31 (m, 4H), 7.31 – 7.27 (m, 1H), 6.09 (ddd, J = 17.3, 10.4, 7.0 Hz, 1H), 5.37 (dt, J = 17.3, 1.5 Hz, 1H), 5.29 (ddd, J = 10.4, 1.9, 1.0 Hz, 1H), 4.63 – 4.48 (m, 2H), 4.27 – 4.21 (m, 1H), 4.15 – 4.04 (m, 2H), 3.84 (td, J = 8.0, 6.2 Hz, 1H), 2.17 – 2.07 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.27, 134.47, 128.31, 127.52, 127.38, 117.62, 82.98, 80.22, 71.43, 66.22, 32.32. IR (neat): 3165, 3032, 2886, 1725, 1454, 1205, 1065, 740. GC-MS (m/z): 186 $[M]^+$. [Minor diastereomer] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.27 (m, 5H), 5.83 (ddd, J = 16.7, 10.4, 5.9 Hz, 1H), 5.33 (dt, J = 17.1, 1.6 Hz, 1H), 5.15 (dt, J = 10.4, 1.5 Hz, 1H), 4.55 (s, 2H), 4.41 – 4.34 (m, 1H), 4.06 – 3.93 (m, 2H), 3.90 (dt, J = 5.9, 3.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.01, 136.96, 128.41, 127.68, 127.60, 115.99, 84.36, 83.40, 71.28, 67.11, 31.77. IR (neat): 3089, 3031, 2944, 2871, 1644, 1454, 1109, 1064, 926, 737, 698. HRMS CI(m/z): $[M+H]^+$ calcd. for $C_{13}H_{17}O_2$, 205.1228; found, 205.1229.

[Match] 95.3% *de* [determined by HPLC: Chiralcel OJ-H column, iPrOH/Hexane = 2/98, 0.8 mL/min, λ = 210 nm; t_R(major) = 16.47 min, t_R(minor) = 18.53 min].

[Mismatch] 92.4% *de* [determined by HPLC: Chiralcel OJ-H column, iPrOH/Hexane = 2/98, 0.8 mL/min, λ = 210 nm; t_R(minor) = 16.62 min, t_R(major) = 20.35 min].

Ligand Controlled Stereoselective Cyclization from (*R*)-109

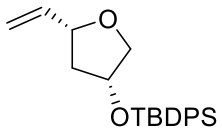
(*R*)-2-(*tert*-butyldiphenylsilyloxy)hexa-4,5-dien-1-ol ((*R*)-109)



(R)-109

Enantiomeric pure **(*R*)-109** (liquid) was prepared from (*S*)-glycidol (purchased from Combi-Blocks, Inc. without any purification) in the same way as **109**. The spectroscopic data were in accordance with **109**.

***tert*-butyldiphenyl((*3R*,*5R*)-5-vinyltetrahydrofuran-3-yloxy)silane ((5*R*)-131)**

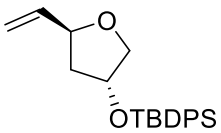


(5R)-131

The compound **(*5R*)-131** (liquid) was synthesized in 91% yield (*dr* = 86/1) from **(*R*)-109** with **(*R*)-L2AuCl** (0.5 mol%) and $NaBAr^{F}_{4}$ (1 mol%) at room temperature for 3.75 h according to General procedure A. Purification was performed by silica gel flash column chromatography with ethyl acetate and hexanes (1 : 20). The spectroscopic data were in accordance with minor diastereomer of **131**.

97.7% *de* [determined by HPLC: Chiralpak IA column, Hexane, 1 mL/min, λ = 210 nm; t_R(minor) = 10.90 min, t_R(major) = 11.86 min].

***tert*-butyldiphenyl((*3R,5S*)-5-vinyltetrahydrofuran-3-yloxy)silane ((5*S*)-131)**



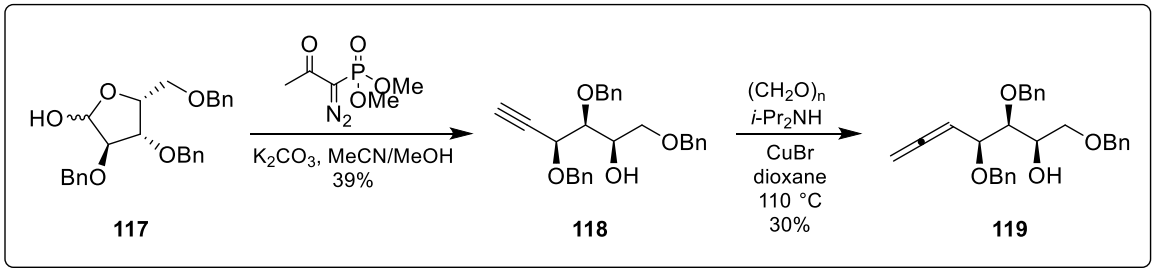
(5S)-131

The compound **(*5S*)-131** (liquid) was synthesized in 88% yield (*dr* = 250/1) from **(*R*)-109** with **(*S*)-L2AuCl** (0.5 mol%) and $NaBAr^F_4$ (1 mol%) at room temperature for 1.5 h according to General procedure A. Purification was performed by silica gel flash column chromatography with ethyl acetate and hexanes (1 : 20). The spectroscopic data were in accordance with major diastereomer of **131**.

99.2% *de* [determined by ^{1}H NMR].

Ligand Controlled Stereoselective Cyclization of 119

(*2R,3S,4R*)-1,3,4-tris(benzyloxy)hepta-5,6-dien-2-ol (119)



117 (liquid) was prepared according to the literature procedure[110] in two steps. The spectroscopic data were in accordance with the literature data.[110]

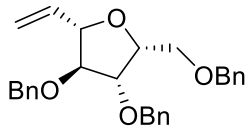
118 was prepared according to the literature report.[111] In a solution of TsN_3 (3 mmol, 0.46 mL) and dimethyl 2-oxopropylphosphonate (3mmol, 0.415 mL) in 10 mL acetonitrile was added K_2CO_3 (12 mmol, 1.66 g). After the resulting mixture was stirred at room temperature for 2 h, a solution of **117** (2 mmol, 840 mg) in 10 mL MeOH was added and further stirred overnight. The solution was evaporated under reduced pressure and resulting mixture was purified by flash column chromatography with ethyl acetate and hexanes (1 : 4) to give **118** (liquid) 330 mg in 39% yield.

119 (liquid) was prepared according to the literature report[93] in 30% yield. Purification was performed by silica gel flash column chromatography with ethyl acetate and hexanes (1 : 4). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.26 (m, 15H), 5.21 (dt, J = 8.5, 6.6 Hz, 1H), 4.90 – 4.80 (m, 3H), 4.72 (d, J = 11.8 Hz, 1H), 4.58 (d, J = 11.3 Hz, 1H), 4.49 – 4.41 (m, 3H), 4.20 (ddt, J = 8.7, 6.5, 1.2 Hz, 1H), 4.01 (dtd, J = 6.9, 6.1, 2.7 Hz, 1H), 3.64 (dd, J = 6.4, 2.7 Hz, 1H), 3.49 – 3.40 (m, 2H), 2.47 (d, J = 6.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.50, 138.29, 138.08, 138.00, 128.37, 128.32, 128.30, 128.20, 128.01, 127.84, 127.72,

[110] E.R. van Rijssel, P. Van Delft, G. Lodder, H.S. Overkleeft, G.A. van der Marel, D.V. Filippov, J.D.C. Codéè, *Angew. Chem. Int. Ed.* **2014**, 53, 10381.
[111] I. Arora, A.K. Shaw, *Tetrahedron*, **2016**, 72, 5479.

127.69, 127.59, 88.46, 80.40, 79.15, 79.13, 75.90, 75.04, 75.02, 74.99, 73.29, 71.19, 70.77, 70.76, 70.75, 70.11. IR (neat): 3456, 3030, 2864, 1954, 1454, 1070, 846, 733. HRMS ESI (m/z): $[M+K]^+$ calcd. for $C_{28}H_{30}KO_4$, 469.1781; found, 469.1768.

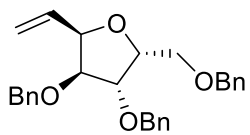
(*2R,3S,4S,5S*)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-5-vinyltetrahydrofuran (β-133)



β-133

The compound **β-133** (liquid) was synthesized in 76% yield (dr = 6.5/1) from **119** with **(*R*)-L2AuCl** (5 mol%) and $AgSbF_6$ (5 mol%) at room temperature for 30 min according to General procedure A. Purification was performed by silica gel flash column chromatography with ethyl acetate and hexanes (1 : 10). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.24 (m, 15H), 5.95 (ddd, J = 17.2, 10.3, 7.5 Hz, 1H), 5.33 (dt, J = 17.2, 1.4 Hz, 1H), 5.16 (ddd, J = 10.3, 1.6, 1.0 Hz, 1H), 4.65 – 4.43 (m, 6H), 4.30 (dd, J = 7.5, 3.8 Hz, 1H), 4.26 (ddd, J = 6.2, 5.5, 4.2 Hz, 1H), 4.02 (dd, J = 4.2, 1.6 Hz, 1H), 3.85 (dd, J = 3.8, 1.6 Hz, 1H), 3.81 (dd, J = 9.9, 5.5 Hz, 1H), 3.75 (dd, J = 9.9, 6.3 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 138.21, 137.93, 137.67, 137.06, 128.45, 128.38, 128.31, 127.83, 127.78, 127.71, 127.57, 127.54, 127.53, 116.99, 87.32, 85.09, 82.98, 80.02, 73.46, 71.76, 71.66, 68.41. IR (neat): 3030, 2920, 1953, 1871, 1605, 1497, 1206, 1069, 734. HRMS ESI (m/z): $[M+K]^+$ calcd. for $C_{28}H_{30}KO_4$, 469.1781; found, 469.1768.

(*2R,3S,4S,5R*)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-5-vinyltetrahydrofuran (α-133)



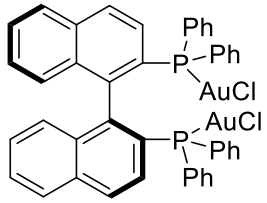
α-133

The compound **α-133** (liquid) was synthesized in 82% yield (dr = 100/0) from **119** with

(*S*)-L2AuCl (1 mol%) and $NaBAr^F_4$ (2 mol%) at 40 °C for 15 h according to General procedure A. Purification was performed by silica gel flash column chromatography with ethyl acetate and hexanes (1 : 10). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.23 (m, 15H), 6.04 (ddd, J = 17.4, 10.0, 7.9 Hz, 1H), 5.37 (d, J = 17.3 Hz, 1H), 5.27 (d, J = 10.3 Hz, 1H), 4.68 – 4.46 (m, 7H), 4.46 – 4.41 (m, 1H), 4.08 (d, J = 3.9 Hz, 1H), 3.95 (d, J = 3.8 Hz, 1H), 3.74 (ddd, J = 27.3, 9.7, 6.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.27, 137.89, 137.87, 134.12, 128.40, 128.36, 128.28, 127.76, 127.71, 127.55, 127.51, 127.47, 118.05, 83.21, 81.90, 81.68, 78.87, 73.42, 72.30, 72.06, 68.42. IR (neat): 3064, 3030, 2919, 1953, 1873, 1812, 1606, 1454, 1351, 1072, 930, 734, 697, 604. MS ESI (m/z): $[M+K]^+$ calcd. for $C_{28}H_{30}KO_4$, 469.1781; found, 469.1768.

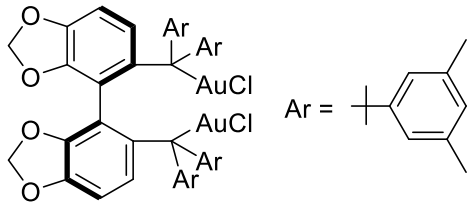
10.3 Cyclization of Medius 54

Synthesis of gold(I) Complexes



138-$(AuCl)_2$

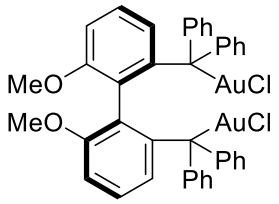
In a flamed dried flask under Argon atmosphere was dissolved $Au(Me_2S)Cl$ (2 eq) in dry DCM. The reaction mixture is cooled at 0 °C, and the phosphinic ligand **138** dissolved in DCM is added dropwise via cannula. The mixture is stirred at room temperature for 3 h. The solvent is removed under reduced pressure and the resultant residue was washed three times with Et_2O and dried in vacuo to give white solid **138-$(AuCl)_2$** quantitavely.
The spectroscopic data were in accordance with the literature.[68]



139-$(AuCl)_2$

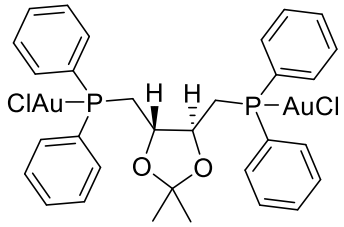
139-$(AuCl)_2$ (white solid) was prepared in a similar way as **138-$(AuCl)_2$**.
The spectroscopic data were in accordance with the literature data.[112]

[112] L. Huang, H.-B. Yang, D.-H. Zhang, Z. Zhang, X.-Y. Tang, Q. Xu, M. Shi, *Angew. Chem. Int. Ed.* **2013**, 52 (26), 6767.



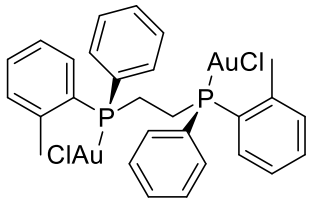
140-(AuCl)$_2$

140-(AuCl)$_2$ (white solid) was prepared in a similar way as **138-(AuCl)$_2$**. The spectroscopic data were in accordance with the literature data.[68]



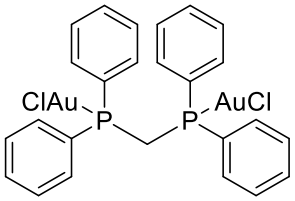
141-(AuCl)$_2$

141-(AuCl)$_2$ (white solid) was prepared in a similar way as **138-(AuCl)$_2$**. The spectroscopic data were in accordance with the literature data.[112]



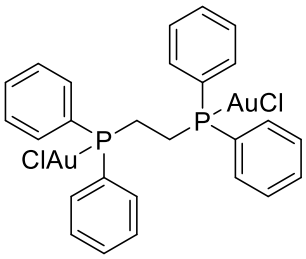
142-(AuCl)$_2$

142-(AuCl)$_2$ (white solid) was prepared in a similar way as **138-(AuCl)$_2$**. The spectroscopic data were in accordance with the literature data.[112]



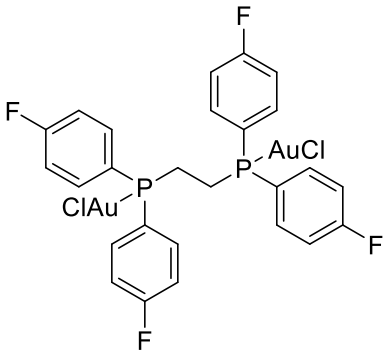
143-(AuCl)$_2$

143-(AuCl)$_2$ (white solid) was prepared in a similar way as **138-(AuCl)$_2$**. The spectroscopic data were in accordance with the literature data.[70]



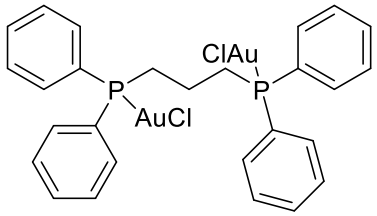
144-(AuCl)$_2$

144-(AuCl)$_2$ (white solid) was prepared in a similar way as **138-(AuCl)$_2$**. The spectroscopic data were in accordance with the literature data.[70]



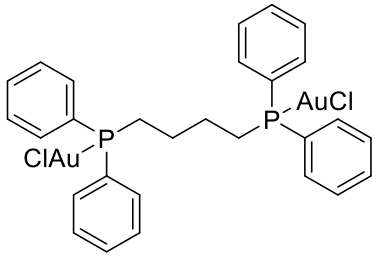
145-(AuCl)$_2$

145-(AuCl)$_2$ (white solid) was prepared in a similar way as **138-(AuCl)$_2$**. The spectroscopic data were in accordance with the literature data.[70]



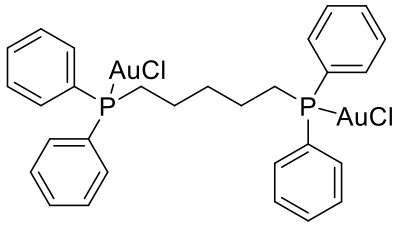
146-(AuCl)$_2$

146-(AuCl)$_2$ (white solid) was prepared in a similar way as **138-(AuCl)$_2$**. The spectroscopic data were in accordance with the literature data.[70]



147-(AuCl)$_2$

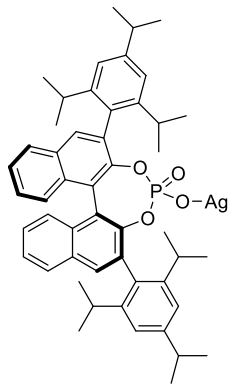
147-(AuCl)$_2$ (white solid) was prepared in a similar way as **138-(AuCl)$_2$**. The spectroscopic data were in accordance with the literature data.[70]



148-(AuCl)$_2$

148-(AuCl)$_2$ (white solid) was prepared in a similar way as **138-(AuCl)$_2$**. The spectroscopic data were in accordance with the literature data.[70]

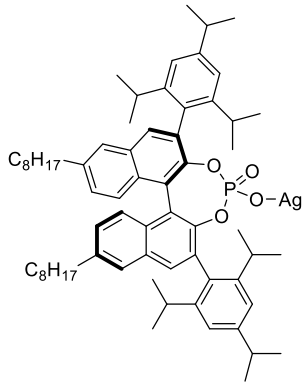
Synthesis of chiral counterions



49

To a solution of the corresponding commercially available phosphoric acid (0.2 mmol) in DCM (2.0 mL) in the dark were added in one portion Ag_2O (0.1 mmol), followed by distilled H_2O (2.0 mL). The resulting mixture was stirred vigorously for 1 h at room temperature. Then, the reaction mixture was diluted with DCM (4.0 mL) and H_2O (4.0 mL). The layer of biphasic suspension were separated, and aqueous layer was extracted with DCM (2 x 5.0 mL). The combined organic layer was filtered through celite and concentrated to afford **49** as a white solid (quantitatively).

The spectroscopic data were in accordance with the literature data.[113-114]



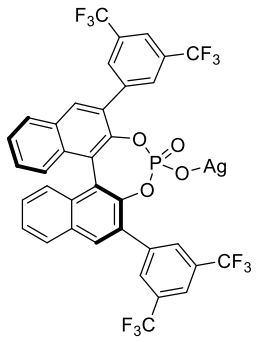
150

[113] S. Mayer, B. List, *Angew. Chem.* **2006**, 118, 4299.

[114] M. Klussmann, L. Ratjen, S. Hoffmann, V. Wakchaure, R. Goddard, B. List, *Synlett*, **2010**, 14, 2189.

150 (white solid) was prepared in a similar way as **49**.

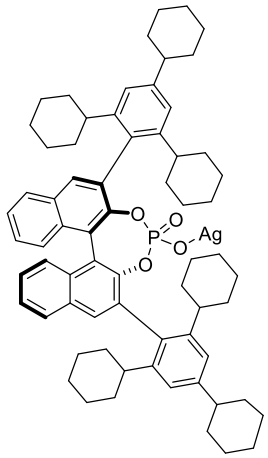
The spectroscopic data were in accordance with the literature data.[70]



151

151 (white solid) was prepared in a similar way as **49**.

The spectroscopic data were in accordance with the literature data.[115]

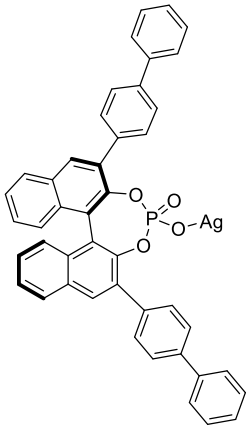


152

152 (white solid) was prepared in a similar way as **49**.

The spectroscopic data were in accordance with the literature data.[70]

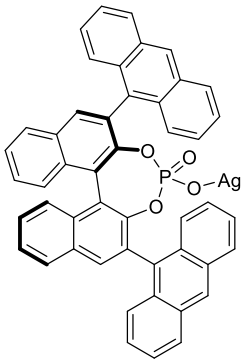
[115] K. Aikawa, M. Kojima, K. Mikami, *Angew. Chem. Int. Ed.* **2009**, 48, 6073.



153

153 (white solid) was prepared in a similar way as **49**.

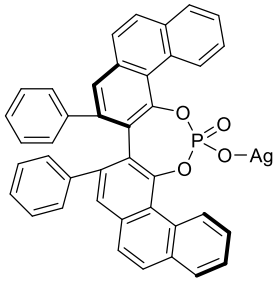
The spectroscopic data were in accordance with the literature data.[114]



154

154 (white solid) was prepared in a similar way as **49**.

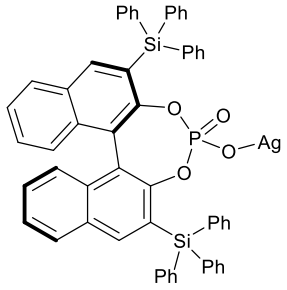
The spectroscopic data were in accordance with the literature data.[114]



155

155 (white solid) was prepared in a similar way as **49**.

The spectroscopic data were in accordance with the literature data.[114]



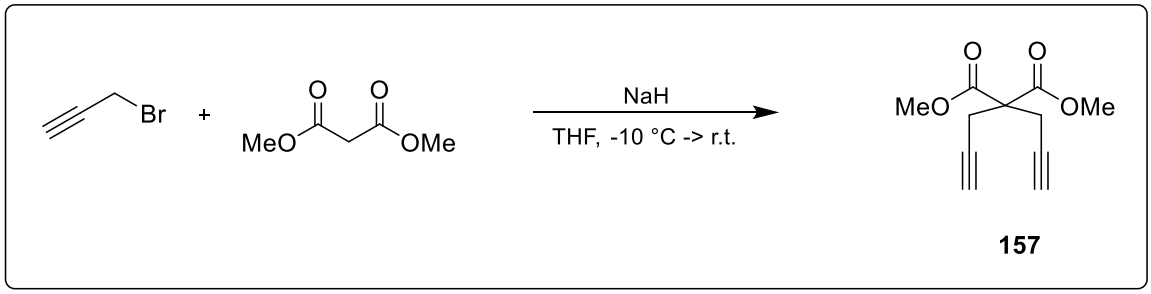
156

156 (white solid) was prepared in a similar way as **49**.

The spectroscopic data were in accordance with the literature data.[114]

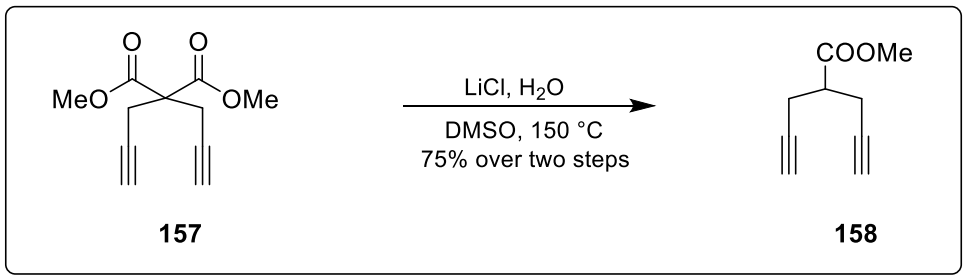
Preparation of the substrates

Dimethyl 2,2-di(prop-2-yn-1-yl)malonate (157)



In a flamed dried flask under Argon atmosphere NaH (2.1 equiv) was suspended in dry THF (0.5M). The mixture was cooled to -10 °C before adding dimethyl malonate dropwise. The mixture was allowed to stir at -10 °C for 5 min, and then propargyl bromide (2.1 equiv) was added. The reaction mixture was allowed to stir at room temperature for 20 h. The reaction was quenched with water and extracted with Et_2O thr*ee* times. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was used in the next step without further purification.

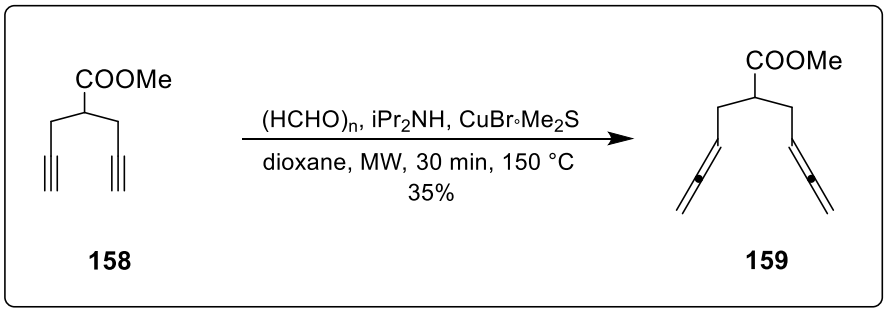
Methyl 2-(prop-2-yn-1-yl)pent-4-ynoate (158)



In a round-bottomed flask **157** (1 equiv) and LiCl (3.1 equiv) were dissolved in DMSO (0.5 M) and water (2.5 equiv). The mixture was heated at 150 °C for 1 h and then cooled to room temperature. The reaction was quenched with water and extracted with DCM thr*ee* times. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting mixture was purified by flash column chromatography with diethyl

ether and hexanes (1 : 9) to give **158** (liquid) in 75% yield over two steps.
The spectroscopic data were in accordance with the literature data.[116]

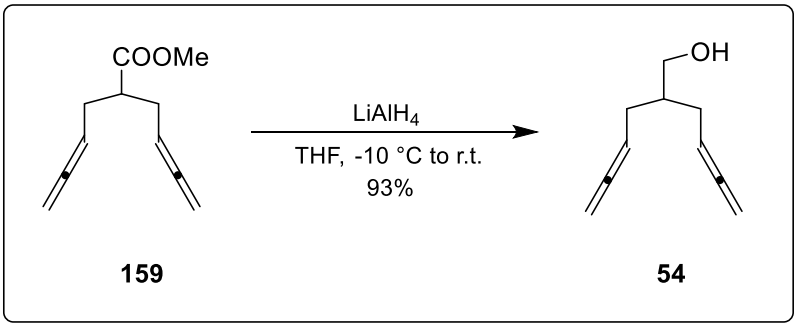
Molecule 159



159 was prepared in a similar way as **79**. A solution of **158**, CuBr (30 mol%), paraformaldehyde (6 equiv), diisopropylamine (6 equiv) in 5 mL dioxane was refluxed at 150 °C for 30 min in Microwave equipment. The crude reaction mixture was diluted with Et_2O and washed with HCl (aq.) 3 times. The organic phase was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by flash column chromatography with diethyl ether and hexanes (5 : 95) to give **159** (liquid) 35% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.07 (q, J = 6.9 Hz, 2H), 4.70 – 4.67 (m, 4H), 3.69 (s, 3H), 2.63 – 2.60 (m, 1H), 2.34 – 2.31 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.93, 174.98, 86.85, 75.05, 51.45, 44.77, 30.08. IR (neat): 3458, 3297, 2988, 2952, 1956, 1736, 1438, 1168, 847.

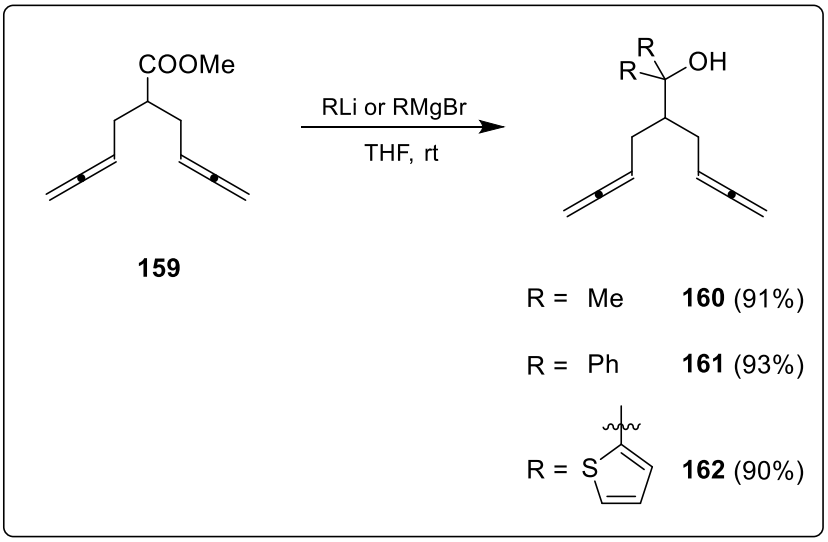
[116] M. Wilking, C.G. Daniliuc, U. Hennecke, *Chem. Eur. J.* **2016**, 22, 18601.

Molecule 54



54 (liquid) was prepared in a similar way as **88**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.13 – 5.10 (m, 2H), 4.71 – 4.68 (m, 4H), 3.67 – 3.64 (m, 3H), 2.17 – 2.14 (m, 4H), 1.80 – 1.78 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.96, 87.52, 74.51, 64.80, 40.51, 29.60. IR (neat): 3339, 2919, 1955, 1438, 1031, 842.

Molecules 160-162

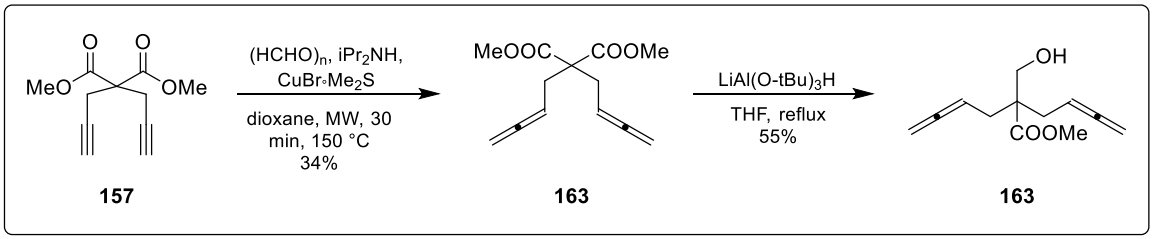


160 (liquid) was prepared in a similar way as **93**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.19 – 5.16 (m, 2H), 4.71 – 4.69 (m, 4H), 2.31 – 2.28 (m, 2H), 2.09 – 2.07 (m, 2H), 1.66 – 1.63 (m, 1H), 1.54 (s, 1H), 1.24 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.77, 89.25, 74.66, 73.56, 48.47, 28.84, 27.60. IR (neat): 3339, 2919, 1955, 1438, 1031, 842.

161 (liquid) was prepared in a similar way as **93**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, J = 7.3 Hz, 4H), 7.31 (t, J = 7.8 Hz, 4H), 7.22 (dd, J = 7.1, 2.1 Hz, 2H), 5.15 – 5.12 (m, 2H), 4.70 – 4.67 (m, 4H), 2.93 – 2.89 (m, 1H), 2.61 (s, 1H), 2.34 – 2.31 (m, 2H), 2.18 – 2.15 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.83, 146.40, 128.17, 126.44, 125.41, 88.37, 81.52, 74.72, 45.08, 28.05. IR (neat): 3539, 3058, 1953, 1725, 1492, 1447, 1160, 843, 703.

162 (liquid) was prepared in a similar way as **93**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 – 7.27 (m, 2H), 7.01 – 6.95 (m, 4H), 5.22 – 5.17 (m, 2H), 4.79 – 4.74 (m, 4H), 3.05 – 3.01 (m, 5H), 1.58 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.27, 143.86, 140.02, 126.71, 126.48, 125.44, 88.12, 75.32, 32.37, 28.52. IR (neat): 3528, 3014, 2923, 1953, 1435, 1229, 846, 699.

Molecule 163

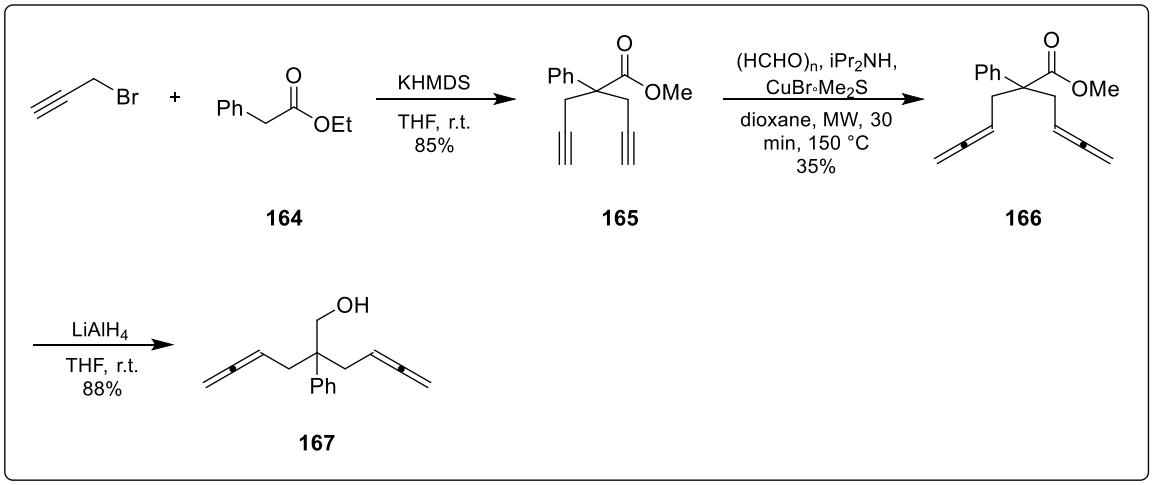


163a (liquid) was prepared in a similar way as **159**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.97 – 4.93 (m, 2H), 4.69 – 4.67 (m, 4H), 3.74 (s, 6H), 2.68 – 2.65 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.97, 170.79, 83.93, 74.52, 57.75, 52.34, 31.79. IR (neat): 2843, 1956, 1736, 1438, 1207, 846.

Preparation of **163**. To a solution of **163a** (1 equiv) in dry THF (0.5M) under argon atmosphere was added $LiAl(O\text{-}tBu)_3H$ (2,5eqv) dropwise. The mixture is stirred at reflux for 12 h. Upon completion confirmed by TLC the reaction was quenched with water and solution of NaOH (10% aq.), until the mixture became white. The mixture was extracted thr*ee* times with Et_2O. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography with diethyl ether and hexanes (3:7) to give **163** (liquid) in 55% yield. ^{1}H NMR (300 MHz,

$CDCl_3$) δ 5.05 – 5.02 (m, 2H), 4.70 – 4.68 (m, 4H), 3.77 (s, 2H), 3.73 (s, 3H), 2.39 – 2.36 (m, 4H), 2.18 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.72, 175.51, 84.60, 74.36, 64.86, 51.77, 51.64, 32.26. IR (neat): 3468, 2951, 1955, 1728, 1439, 1203, 1042, 844.

Molecule 167



164 **165** **166** **167**

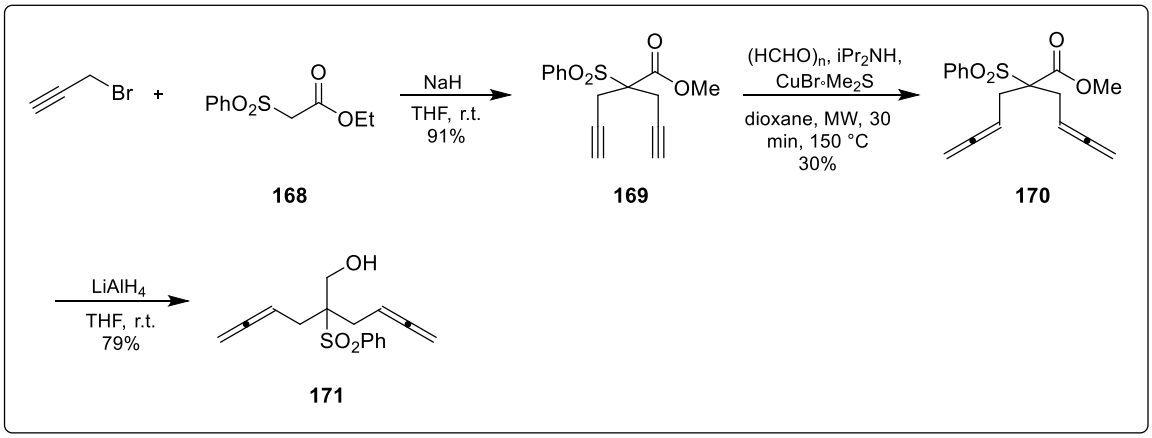
Preparation of **165**. To a solution of KHMDS (2.2 equiv) in dry THF (0.1 M) under argon atmosphere was added at -78 °C ethyl 2-phenylacetate (1 equiv) dropwise. The mixture is stirred at the same temperature for 1 h before adding propargyl bromide (2.4 equiv). The reaction was stirred at room temperature overnight. Upon completion confirmed by TLC the reaction was quenched with saturated NH_4Cl solution. The aqueous phase was extracted thr*ee* times with Et_2O. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography with diethyl ether and hexanes (2:8) to give **165** (liquid) in 85% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.36 – 7.34 (m, 5H), 4.20 (q, J = 7.1 Hz, 2H), 3.19 – 3.11 (m, 4H), 2.02 – 1.98 (m, 2H), 1.23 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.81, 139.30, 128.38, 127.49, 125.95, 79.94, 71.17, 61.45, 52.80, 25.33, 13.84. IR (neat): 3292, 3029, 1730, 1448, 1209, 1062, 698, 645.

166 (liquid) was prepared in a similar way as **159**. ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 – 7.29 (m, 5H), 4.86 – 4.82 (m, 2H), 4.63 – 4.60 (m, 4H), 4.16 (q, J = 7.1 Hz, 2H), 2.83 – 2.80 (m, 4H), 1.21 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.91, 174.48, 141.16,

128.22, 126.81, 126.37, 84.78, 74.02, 60.81, 53.77, 34.13, 13.96. IR (neat): 3029, 1955, 1732, 1449, 1208, 1059, 697, 643.

167 (liquid) was prepared in a similar way as **88**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.34 (m, 5H), 4.94 – 4.90 (m, 2H), 4.65 – 4.61 (m, 4H), 3.86 (d, J = 6.45 Hz, 2H), 2.55 – 2.52 (m, 4H), 1.39 – 1.37 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.54, 142.69, 128.40, 126.79, 126.38, 85.20, 73.95, 67.60, 46.48, 34.34. IR (neat): 3406, 2985, 1954, 1444, 1038, 841, 700.

Molecule 171



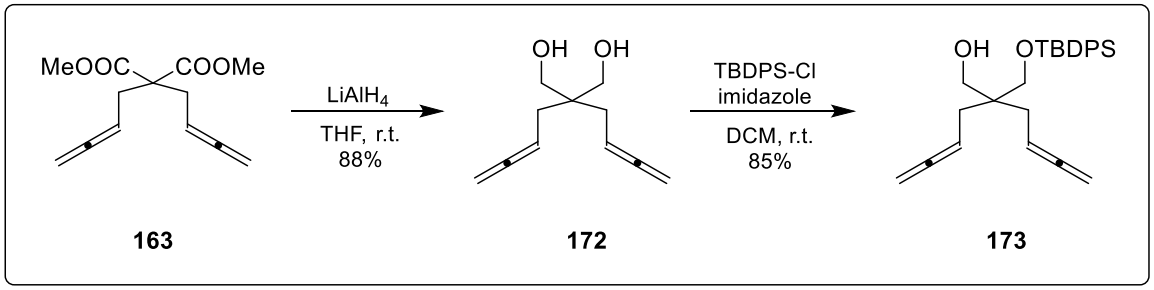
169 (liquid) was prepared in a similar way as **157**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 – 7.90 (m, 2H), 7.74 – 7.72 (m, 1H), 7.63 – 7.58 (m, 2H), 3.75 (s, 3H), 3.19 (s, 4H), 2.11 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.32, 134.69, 130.31, 130.23, 129.14, 77.02, 73.09, 72.27, 53.45, 21.28. IR (neat): 3285, 1739, 1437, 1272, 1151, 1083, 688, 544.

170 (liquid) was prepared in a similar way as **159**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 – 7.84 (m, 2H), 7.71 – 7.68 (m, 1H), 7.61 – 7.56 (m, 2H), 5.24 – 5.20 (m, 2H), 4.74 – 4.71 (m, 4H), 3.66 (s, 3H), 2.99 – 2.86 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.13, 167.49, 134.19, 130.29, 130.24, 128.68, 83.70, 77.09, 75.03, 52.69, 29.73. IR (neat): 1958, 1735, 1447, 1309, 1147, 988, 851, 690.

171 (liquid) was prepared in a similar way as **88**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 – 7.92

(m, 2H), 7.75 – 7.70 (m, 1H), 7.64 – 7.59 (m, 2H), 5.22 – 5.14 (m, 2H), 4.73 – 4.70 (m, 4H), 3.83 (s, 2H), 3.00 (s, 1H), 2.60 – 2.40 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.05, 135.43, 134.20, 130.09, 129.02, 83.34, 74.97, 68.47, 63.02, 29.17. IR (neat): 3516, 1956, 1446, 1289, 1140, 848, 729, 691.

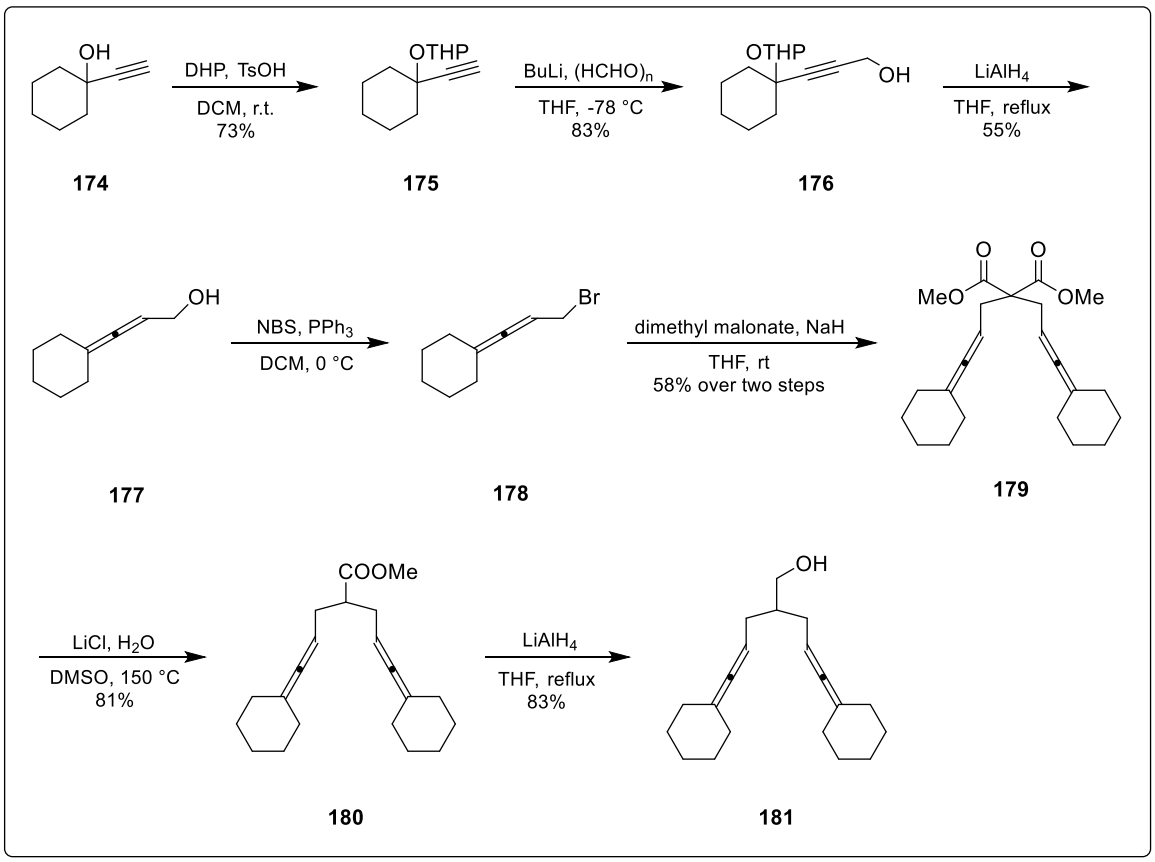
Molecule 173



172 (liquid) was prepared in a similar way as **88**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.13 – 5.08 (m, 2H), 4.71 – 4.68 (m, 4H), 3.65 (s, 4H), 2.11 – 2.07 (m, 4H), 2.02 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.58, 84.74, 74.08, 67.77, 42.85, 30.60. IR (neat): 3356, 2985, 1954, 1439, 1036, 842.

173 (liquid) was prepared in a similar way as **108**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 – 7.67 (m, 4H), 7.48 – 7.40 (m, 6H), 5.04 – 4.99 (m, 2H), 4.63 – 4.60 (m, 4H), 3.60 (s, 2H), 3.57 (s, 2H), 2.09 – 2.06 (m, 4H), 1.59 (s, 1H), 1.10 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.61, 135.54, 132.84, 129.77, 127.69, 84.80, 73.86, 67.66, 66.76, 43.36, 30.41, 26.81. IR (neat): 3354, 2930, 2857, 1954, 1428, 1112, 823, 702.

Molecule 181



175 (liquid) was prepared in a similar way as **105**.

The spectroscopic data were in accordance with the literature data.[86]

Preparation of **176**. To a solution of **175** (1 equiv) in dry THF (0.5 M) under argon atmosphere was added at -78 °C *n*BuLi (1.1 equiv) dropwise. The mixture was stirred at the same temperature for 30 min before adding paraformaldehyde (1.1 equiv). The reaction was stirred at room temperature overnight. Upon completion confirmed by TLC the reaction was quenched with saturated NH_4Cl solution. The aqueous phase was extracted thr*ee* times with Et_2O. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography with diethyl ether and hexanes (3:7) to give **176** (liquid) in 83% yield.

The spectroscopic data were in accordance with the literature data.[86]

Preparation of **177**. To a suspension of $LiAlH_4$ (2 equiv) in dry THF (0.2 M) under argon atmosphere was added at 0 °C **176** (1 equiv) dropwise. The mixture was stirred at room temperature for 30 min and then heated at reflux for 45 min. Upon completion confirmed by TLC the reaction was quenched with adding water and NaOH 10% aq. solution until complete whitening of the suspension. The aqueous phase was extracted thr*ee* times with Et_2O. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography with diethyl ether and hexanes (3:7) to give **177** (liquid) in 55% yield.
The spectroscopic data were in accordance with the literature data.[86]

Preparation of **178**. To a solution of **177** (1 equiv) and PPh_3 in dry DCM (0.2 M) under argon atmosphere was added at -40 °C NBS (1.1 equiv). The mixture was stirred at room temperature for 30 min. Upon completion confirmed by TLC the mixture was diluted with hexanes and the solid residue was filtered off through a celite pad. The resulting solution was concentrated under reduced pressure. The crude residue was used in the next step without further purification.

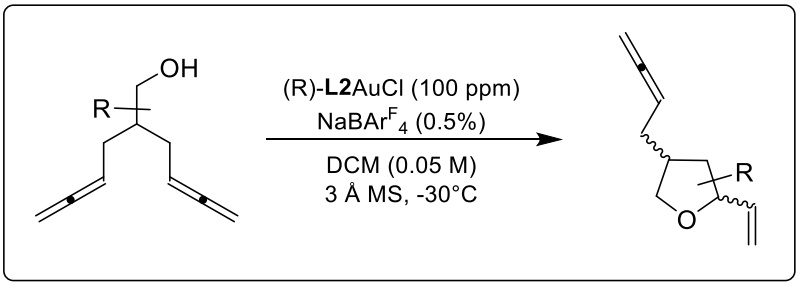
179 (liquid) was prepared in a similar way as **157**, using **178** in place of propargyl bromide. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.83 (t, J = 7.6 Hz, 2H), 3.76 (s, 6H), 2.67 (d, J = 7.6 Hz, 4H), 2.13 – 2.09 (m, 8H), 1.65 – 1.54 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.32, 171.10, 102.09, 82.37, 58.16, 52.20, 32.42, 31.36, 27.09, 25.94. IR (neat): 2841, 1953, 1735, 1438, 1206, 846.

180 (liquid) was prepared in a similar way as **158**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.96 – 4.93 (m, 2H), 3.89 (s, 3H), 2.60 – 2.57 (m, 1H), 2.28 – 2.24 (m, 4H), 2.12 – 2.06 (m, 8H), 1.60 – 1.51 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.72, 175.57, 103.02, 85.76, 51.30, 44.75, 31.52, 31.17, 27.23, 26.00. IR (neat): 2841, 1953, 1737, 1438, 1207, 846.

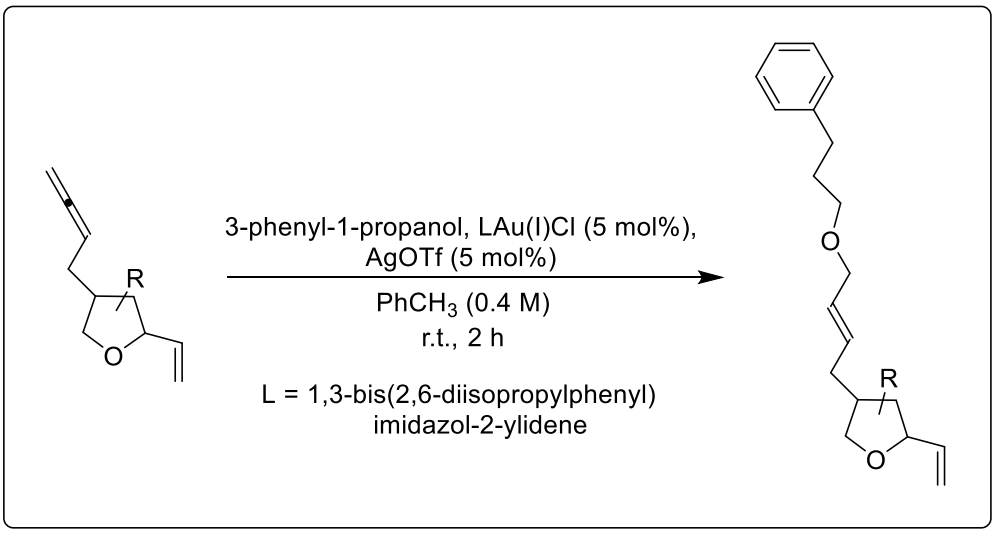
181 (liquid) was prepared in a similar way as **88**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.98 – 4.94 (m, 2H), 3.65 (t, J = 5.5 Hz, 2H), 2.12 – 2.10 (m, 8H), 2.08 – 2.06 (m, 4H), 1.78 – 1.75 (m, 1H), 1.60 – 1.54 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.86, 102.21, 86.31, 65.29,

40.34, 31.56, 30.81, 27.33, 26.03. IR (neat): 3512, 2841, 1953, 1438, 1207, 846.

Asymmetric intramolecular cyclization of Medius and its derivatives



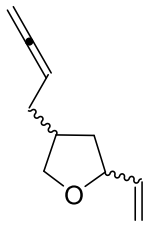
General procedure C: To a 3-dram vial were added sequentially 0.2 mmol of bisallenyl alcohol, indicated volume (18.3 μL for 100 ppm) of **(*R*)-L2AuCl** solution (1 mg/mL in DCM), 3 Å molecular sieves and 4 mL anhydrous DCM as solvent. The mixture was stirred at -30 °C for 15 min before 0.001 mmol $NaBAr^F_4$ (0.5 mol %) was added. The reaction was then stirred at the same temperature monitored by TLC. Upon completion, the reaction was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography to obtain pure product.



General procedure D: A mixture of LAu(I)Cl (5 mol %) and AgOTf (5 mol %) in toluene (0.2 M) was stirred at room temperature for 5 min, treated with a solution of substrate (cyclized product, 1 equiv) and 3-phenyl-1-propanol (1.1 equiv) in toluene (0.2 M). The resulting suspension was stirred at room temperature for 2 h. Upon completion indicated by TLC, the reaction was concentrated under reduced pressure. The residue was purified

through silica gel flash column chromatography to obtain pure product.

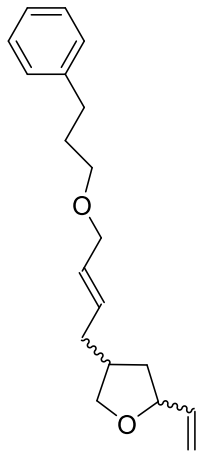
Molecule 55



55

The compound **55** (liquid) was prepared in 99% yield (trans/cis = 26/74) from **54** with **(*R*)-L2AuCl** (100 ppm) at room temperature for 3 h according to General procedure C. Purification was performed by silica gel flash column chromatography with diethyl ether and hexanes (5 : 95). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87 – 5.73 (m, 1H), 5.26 – 5.04 (m, 2H), 5.10 – 5.02 (m, 1H), 4.72 – 4.68 (m, 2H), 4.36 – 4.21 (m, 1H), 4.08 – 3.93 (m, 1H), 3.59 – 3.47 (m, 1H), 2.48 – 2.22 (m, 2H), 2.16 – 2.08 (m, 1H), 1.46 – 1.29 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.77, 139.07, 138.97, 115.30, 114.83, 88.26, 88.19, 80.51, 79.21, 74.94, 74.93, 72.99, 72.78, 39.63, 38.82, 38.48, 37.72, 32.25, 31.95. The number of carbons in less than expected due to partial overlapping of signals. IR (neat): 2837, 1964, 1438, 1426, 1207, 843, 636.

Molecule 136

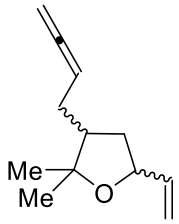


136

The compound **136** (liquid) was prepared in 69% yield (trans/cis = 26/74) from **55** according to General procedure D. Purification was performed by silica gel flash column chromatography with diethyl ether and hexanes (1 : 9). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 – 7.18 (m, 5H), 5.90 – 5.84 (m, 1H), 5.68 – 5.63 (m, 2H), 5.30 – 5.24 (m, 1H), 5.14 – 5.09 (m, 1H), 4.47 – 4.29 (m, 1H), 4.06 – 3.91 (m, 3H), 3.57 – 3.42 (m, 3H), 2.72 (t, J = 7.4 Hz, 2H), 2.38 – 2.16 (m, 3H), 1.98 – 1.81 (m, 3H), 1.35 – 1.29 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.86, 139.13, 138.99, 131.72, 131.68, 128.35, 128.19, 128.07, 127.98, 125.65, 115.28, 114.79, 80.54, 79.20, 73.01, 72.80, 71.20, 69.23, 69.20, 39.59, 38.80, 38.31, 37.64, 36.10, 35.79, 32.27, 31.18. The number of carbons in less than expected due to partial overlapping of signals. IR (neat): 2995, 2942, 1435, 1429, 1204, 842, 633.

ee_{cis} % = 91%; ee_{trans} % = 96% [determined by HPLC: Chiralcel IB-3 column, iPrOH/Heptane = 0.5/99.5, 1.0 mL/min].

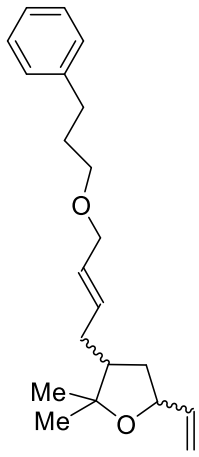
Molecule 182



182

The compound **182** (liquid) was prepared in 96% yield (trans/cis = 45/55) from **160** with **(*R*)-L2AuCl** (100 ppm) at room temperature for 2 h according to General procedure C. Purification was performed by silica gel flash column chromatography with diethyl ether and hexanes (5 : 95). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.85 – 5.71 (m, 1H), 5.26 – 5.21 (m, 1H), 5.13 – 5.06 (m, 2H), 4.71 – 4.59 (m, 2H), 4.37 – 4.32 (m, 1H), 2.28 – 2.17 (m, 1H), 2.13 – 1.95 (m, 2H), 1.48 – 1.36 (m, 2H), 1.31 (s, 3H), 1.09 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.64, 140.20, 127.75, 114.94, 114.11, 88.68, 82.00, 77.99, 77.54, 77.02, 76.89, 74.86, 49.09, 47.06, 38.90, 37.58, 29.25, 29.15, 28.22, 24.15. The number of carbons in less than expected due to partial overlapping of signals. IR (neat): 2839, 1964, 1437, 1424, 1207, 843, 636.

Molecule 182a

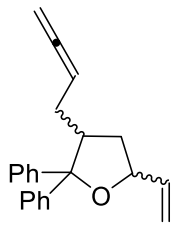


182a

The compound **182a** (liquid) was prepared in 67% yield (trans/cis = 45/55) from **182** according to General procedure D. Purification was performed by silica gel flash column chromatography with diethyl ether and hexanes (1 : 9). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 – 7.21 (m, 5H), 5.89 – 5.82 (m, 1H), 5.67 – 5.63 (m, 2H), 5.26 – 5.20 (m, 1H), 5.10 – 5.06 (m, 1H), 4.38 – 4.31 (m, 1H), 3.94 (d, J = 4.6 Hz, 2H), 3.44 (t, J = 6.5 Hz, 2H), 2.72 (t, J = 7.4 Hz, 2H), 2.21 – 2.18 (m, 2H), 2.02 – 1.91 (m, 5H), 1.29 (s, 3H), 1.09 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.85, 140.21, 132.32, 128.34, 128.19, 127.75, 125.66, 114.93, 82.01, 78.02, 71.21, 69.21, 49.11, 38.83, 32.98, 32.26, 31.16, 28.17, 24.11. The number of carbons in less than expected due to partial overlapping of signals. IR (neat): 2997, 2940, 1435, 1429, 1205, 841, 633.

ee% values not determined yet.

Molecule 183

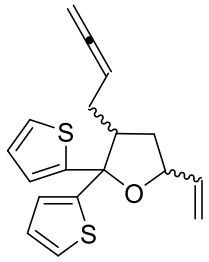


183

The compound **183** (liquid) was prepared in 97% yield (trans/cis = 22/78) from **161** with **(*R*)-L2AuCl** (100 ppm) at room temperature for 3 h according to General procedure C. Purification was performed by silica gel flash column chromatography with diethyl ether and hexanes (4 : 96). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 – 7.16 (m, 10H), 6.20 – 6.03 (m, 1H), 5.42 – 4.97 (m, 3H), 4.70 – 4.64 (m, 2H), 4.40 – 4.29 (m, 1H), 3.16 – 3.04 (m, 1H), 2.32 – 2.25 (m, 1H), 2.03 – 1.97 (m, 1H), 1.79 – 1.71 (m, 1H), 1.59 – 1.53 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.55, 208.87, 143.89, 140.22, 139.01, 136.63, 128.09, 127.92, 127.74, 127.57, 126.86, 126.74, 126.64, 126.49, 126.36, 126.31, 115.43, 115.06, 89.79, 88.48, 79.35, 74.84, 46.68, 45.25, 37.34, 36.55, 31.53, 29.80. IR (neat): 2926, 2854, 1954, 1495, 1446, 1070, 1043, 924, 843, 701.

ee% values not determined yet.

Molecule 184

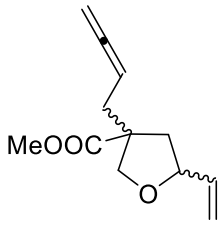


184

The compound **184** (liquid) was prepared in 93% yield (trans/cis = 4/96) from **162** with **(*R*)-L2AuCl** (100 ppm) at room temperature for 5 h according to General procedure C. Purification was performed by silica gel flash column chromatography with diethyl ether and hexanes (4 : 96). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 – 6.79 (m, 6H), 6.16 – 6.08 (m, 1H), 5.44 – 5.38 (m, 1H), 5.26 – 5.22 (m, 1H), 5.09 – 5.01 (m, 1H), 4.72 – 4.68 (m, 2H), 4.59 – 4.55 (m, 1H), 3.02 – 2.98 (m, 1H), 2.44 – 2.23 (m, 2H), 1.85 – 1.60 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.68, 151.15, 148.42, 137.78, 126.51, 126.33, 124.94, 124.71, 124.45, 123.77, 116.55, 88.26, 86.77, 79.44, 75.17, 51.13, 38.06, 30.52. IR (neat): 2960, 2925, 1955, 1434, 1229, 1038, 849, 699.

ee% values not determined yet.

Molecule 185



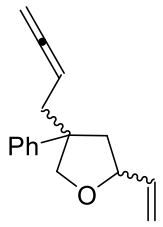
185

The compound **185** (liquid) was prepared in 92% yield (trans/cis = 3/97) from **163** with **(*R*)-L2AuCl** (100 ppm) at room temperature for 6 h according to General procedure C. Purification was performed by silica gel flash column chromatography with diethyl ether

and hexanes (7 : 93). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.92 – 5.83 (m, 1H), 5.33 – 5.26 (m, 1H), 5.18 – 5.14 (m, 1H), 5.07 – 4.99 (m, 1H), 4.72 – 4.68 (m, 2H), 4.46 – 4.41 (m, 1H), 4.11 (d, J = 9.0 Hz, 1H), 3.83 (d, J = 9.0 Hz, 1H), 3.75 (s, 3H), 2.67 – 2.61 (m, 1H), 2.54 – 2.51 (m, 1H), 2.44 – 2.39 (m, 1H), 1.67 – 1.59 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.66, 175.04, 137.90, 116.09, 85.53, 80.44, 77.09, 74.88, 74.83, 55.01, 52.09, 41.28, 36.20. IR (neat): 2951, 2862, 1955, 1734, 1437, 1202, 1050, 848.

ee_{cis} % = 99% [determined by HPLC: Chiralcel IB-3 column, iPrOH/Heptane = 0.5/99.5, 1.0 mL/min].

Molecule 186

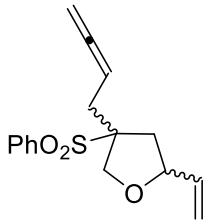


186

The compound **186** (liquid) was prepared in 99% yield (trans/cis = 19/81) from **167** with **(*R*)-L2AuCl** (100 ppm) at room temperature for 2 h according to General procedure C. Purification was performed by silica gel flash column chromatography with diethyl ether and hexanes (5 : 95). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.15 (m, 5H), 6.02 – 5.91 (m, 1H), 5.31 – 5.26 (m, 1H), 5.17 – 5.13 (m, 1H), 4.79 – 4.73 (m, 1H), 4.61 – 4.55 (m, 2H), 4.44 – 4.38 (m, 1H), 4.17 – 3.99 (m, 2H), 2.57 – 2.44 (m, 3H), 2.05 – 1.99 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.74, 144.51, 139.10, 139.03, 128.20, 128.13, 126.75, 126.30, 126.23, 115.53, 115.13, 85.81, 85.59, 79.83, 79.47, 77.10, 76.47, 76.25, 73.89, 51.89, 43.43, 42.40, 40.52, 39.37, 29.58. The number of carbons in less than expected due to partial overlapping of signals. IR (neat): 2924, 2856, 1955, 1495, 1446, 1071, 1043, 922, 844, 702.

ee_{cis} % = 100%; ee_{trans} % = 95% [determined by HPLC: Chiralcel IB-3 column, iPrOH/Heptane = 0.5/99.5, 1.0 mL/min].

Molecule 187

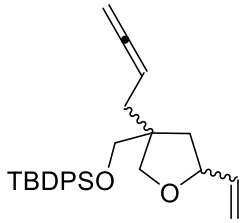


187

The compound **187** (liquid) was prepared in 94% yield (trans/cis = 18/82) from **171** with **(*R*)-L2AuCl** (100 ppm) at room temperature for 6 h according to General procedure C. Purification was performed by silica gel flash column chromatography with diethyl ether and hexanes (3 : 7). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 – 7.93 (m, 2H), 7.74 – 7.70 (m, 1H), 7.65 – 7.60 (m, 2H), 5.87 – 5.80 (m, 1H), 5.34 – 5.13 (m, 3H), 4.76 – 4.72 (m, 2H), 4.41 – 4.38 (m, 2H), 3.89 – 3.86 (m, 1H), 2.83 – 2.76 (m, 1H), 2.54 – 2.51 (m, 2H), 1.88 – 1.80 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.53, 136.38, 136.29, 134.05, 133.95, 130.03, 129.87, 129.15, 129.04, 117.24, 117.12, 83.77, 81.15, 80.88, 77.10, 75.23, 75.15, 72.66, 71.43, 71.35, 38.13, 37.96, 34.14, 32.51. The number of carbons in less than expected due to partial overlapping of signals. IR (neat): 2928, 2873, 1955, 1446, 1303, 1147, 1074, 852, 691.

ee_{cis} % = 97%; ee_{trans} % = 95% [determined by HPLC: Chiralcel IA-3 column, iPrOH/Heptane = 1/99, 1.0 mL/min].

Molecule 188



188

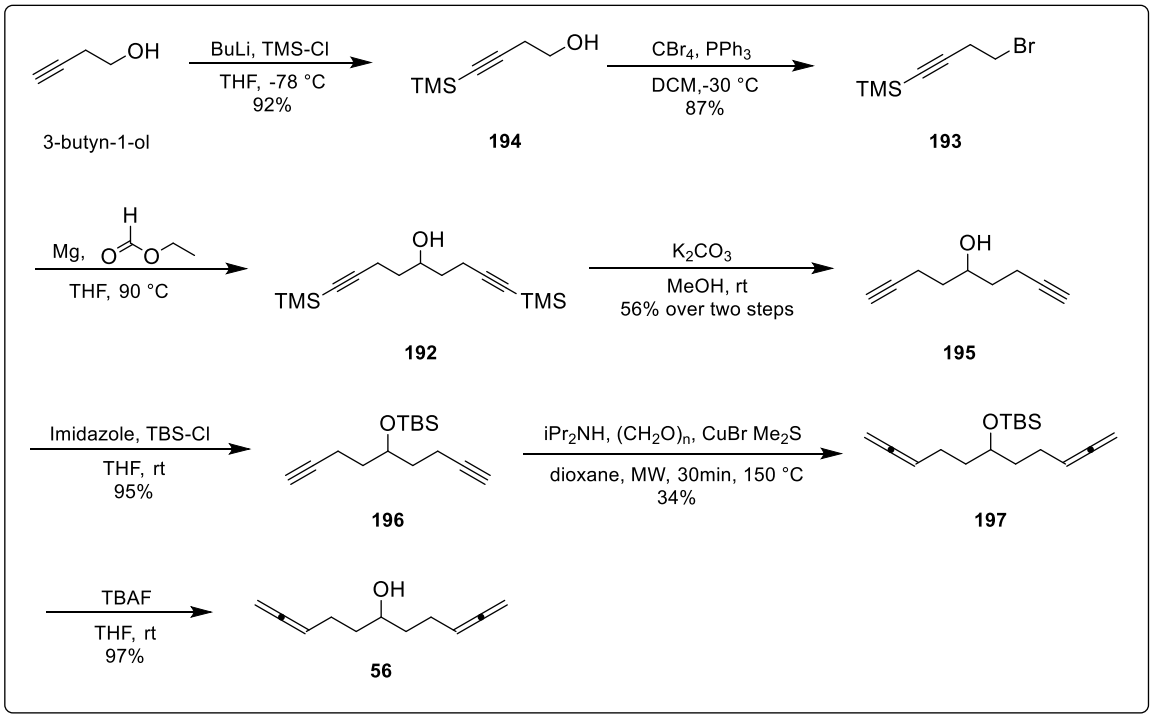
The compound **188** (liquid) was prepared in 97% yield (trans/cis = 39/61) from **173** with **(*R*)-L2AuCl** (100 ppm) at room temperature for 4 h according to General procedure C. Purification was performed by silica gel flash column chromatography with diethyl ether and hexanes (1 : 99). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 – 7.66 (m, 4H), 7.47 – 7.42 (m, 6H), 5.87 – 5.78 (m, 1H), 5.25 – 4.98 (m, 3H), 4.67 – 4.62 (m, 2H), 4.41 – 4.22 (m, 1H), 3.91 – 3.88 (m, 1H), 3.76 – 3.68 (m, 1H), 3.61 – 3.52 (m, 2H), 2.39 – 2.32 (m, 2H), 2.03 – 1.91 (m, 1H), 1.54 – 1.43 (m, 1H), 1.09 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.78, 138.82, 138.79, 135.55, 133.34, 133.30, 133.25, 129.63, 129.59, 127.61, 127.58, 115.36, 115.29, 85.95, 85.90, 79.98, 79.83, 77.12, 74.72, 74.61, 74.10, 67.16, 66.35, 49.66, 49.59, 40.09, 39.83, 34.47, 33.54, 26.78, 19.26. The number of carbons in less than expected due to partial overlapping of signals. IR (neat): 3013, 2857, 1955, 1472, 1427, 1112, 1053, 840, 824, 702, 613.

ee_{cis} % = 97%; ee_{trans} % = 97% [determined by HPLC: Chiralcel IA-3 column, iPrOH/Heptane = 0.2/99.8, 1.0 mL/min].

10.4 Cyclization of Remotus 56

Preparation of the substrates

Molecule 56



Preparation of **194**. In a flamed dried flask under Argon atmosphere 3-butyn-1-ol (1 equiv) was dissolved in dry THF (0.5M). The mixture was cooled to -78 °C before adding *n*BuLi (2.1 equiv) dropwise. The mixture was allowed to stir at the same temperature for 1 h, and then TMS-Cl (2.2 equiv) was added. Afterwards, 50 mL water were added and the solvent was removed under reduced pressure. The residue was then treated with 30 mL acetonitrile, 30 mL water and 10 mL saturated $NaHSO_4$ aqueous solution. The mixture was allowed to stir at room temperature for 12 h. The organic solvent was removed under reduced pressure and the aqueous phase was extracted with Et_2O thr*ee* times. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography with diethyl ether and hexanes (1:9) to give **194** (liquid) in 92% yield.

The spectroscopic data were in accordance with the literature data.[117]

Preparation of **193**. To a solution of **194** (1 equiv) in dry DCM (0.2 M) under argon atmosphere was added at -30 °C CBr_4 (1.4 equiv). The mixture was stirred at the same temperature for 10 min before adding a solution of PPh_3 (1.2 equiv) in DCM (0.2 M). The mixture was allowed to stir at -30 °C for 2 h and then at room temperature for 2 h. Upon completion confirmed by TLC the mixture was diluted with hexanes and the solid residue was filtered off through a silica gel pad. The resulting solution was concentrated under reduced pressure. The residue was purified by flash column chromatography with hexanes (100%) to give **193** (liquid) in 87% yield.
The spectroscopic data were in accordance with the literature data.[118]

Preparation of **192**. In a flamed dried flask equipped with condenser and septum was added magnesium turnings (1.5 equiv) in anhydrous THF (0.1 M). A small portion of 1,2-dibromoethane (0.2 equiv) was added and heated at reflux for 2 min to initiate the reaction. Afterwards a solution of **193** (1 equiv) in THF was added slowly and the mixture was heated in a gentle reflux for 1 h. The reaction mixture was cooled to 0 °C, ethyl formate (0.55 equiv) was added dropwise and the mixture was allowed to stir at room temperature for 1 h. The reaction mixture was quenched by NH_4Cl (aq.) and extracted thr*ee* times with Et_2O. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was used in the next step without further purification.

Preparation of **195**. To a solution of **192** (1 equiv) in MeOH (0.5 M) under argon atmosphere was added K_2CO_3 (3 equiv). The mixture was stirred at room temperature for 12 h. Upon completion confirmed by TLC the mixture was diluted with diethyl ether and the solid residue was filtered off through a silica gel pad. The resulting solution was concentrated under reduced pressure. The residue was purified by flash column chromatography with diethyl ether and hexanes (2 : 8) to give **195** (liquid) in 56% yield over two steps. ^1H NMR (300 MHz, $CDCl_3$) δ 3.85 (p, J = 7.1 Hz, 1H), 2.38 (t, J = 3.2 Hz,

[117] G. Pileio, J.T. Hill-Cousins, S. Mitchell, I. Kuprov, L.J. Brown, C.D. Richard, M.H. Levitt, *J. Am. Chem. Soc.* **2012**, 134 (42), 17494.
[118] C. Leitner, T. Gaich, *Chem. Commun.* **2017**, 53 (54), 7451.

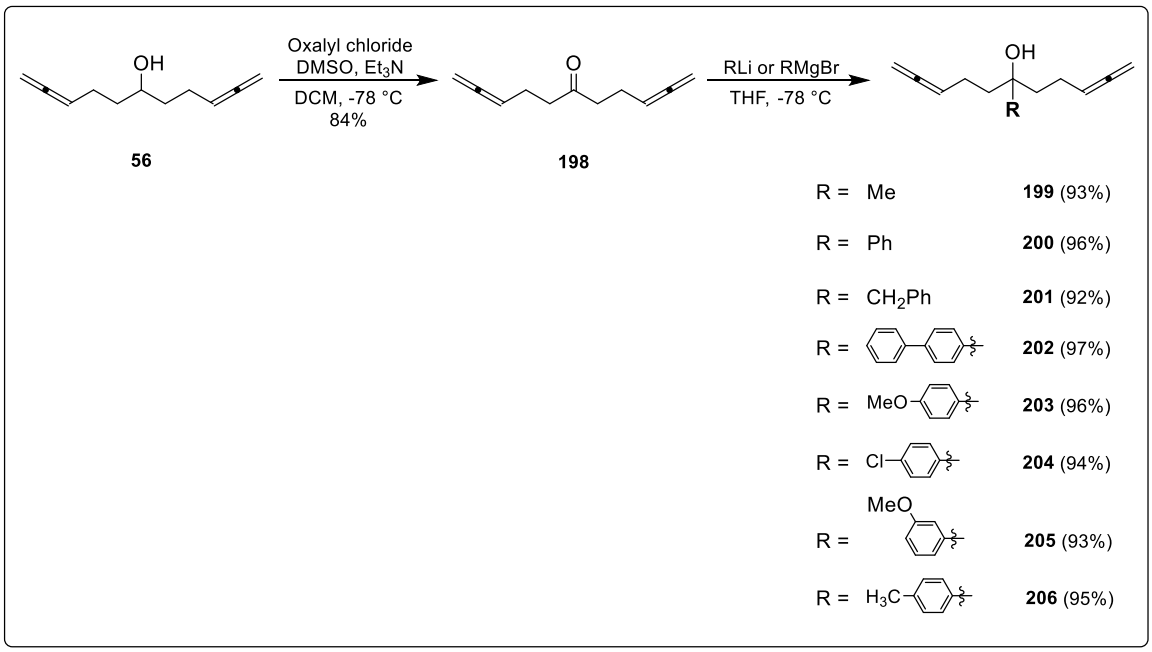
4H), 2.01 (s, 1H), 1.96 (s, 2H), 1.72 (q, J = 6.7 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 84.19, 69.29, 68.27, 35.34, 25.74. IR (neat): 3314, 3296, 2943, 2867, 1456, 1433, 1094, 983, 634.

196 (liquid) was prepared in a similar way as **173**, using TBS-Cl in place of TBDPS-Cl. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.74 (p, J = 7.1 Hz, 1H), 2.24 (t, J = 3.2 Hz, 4H), 1.96 (s, 2H), 1.71 (q, J = 6.7 Hz, 4H), 0.91 (s, 9H), 0.11 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 84.18, 69.29, 68.27, 35.34, 25.74, 17.92, 14.21, - 4.65. IR (neat): 3310, 2953, 2931, 2898, 1472, 1327, 1098, 1029, 836, 775, 631.

197 (liquid) was prepared in a similar way as **159**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.18 – 5.09 (m, 2H), 4.71 – 4.67 (m, 4H), 3.94 (p, J = 7.1 Hz, 1H), 2.10 – 2.01 (m, 4H), 1.58 (q, J = 6.7 Hz, 4H), 0.89 (s, 9H), 0.07 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.24, 89.88, 74.91, 70.74, 36.08, 25.81, 23.73, 17.99, - 4.53. IR (neat): 2953, 2932, 2899, 1956, 1472, 1328, 1097, 1029, 835, 775, 630.

Preparation of **56**. In a flamed dried flask under Argon atmosphere **197** (1 equiv) was dissolved in dry THF (0.2M). The mixture was cooled to 0 °C before adding TBAF (2 equiv) dropwise. The mixture was allowed to stir at room temperature for 12 h. The reaction mixture was quenched with phosphate buffer and the aqueous phase was extracted with Et_2O thr*ee* times. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography with diethyl ether and hexanes (2:8) to give **56** (liquid) in 97% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.18 – 5.13 (m, 2H), 4.73 – 4.66 (m, 4H), 3.74 (s, 1H), 2.19 – 2.10 (m, 4H), 1.65 – 1.56 (m, 4H), 1.44 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.37, 89.53, 75.04, 70.59, 36.38, 24.25. IR (neat): 3338, 2917, 1956, 1437, 1031, 841.

Molecules 199-206



198 (liquid) was prepared in a similar way as **91**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.23 – 5.17 (m, 2H), 4.74 – 4.69 (m, 4H), 2.57 (t, J = 7.2 Hz, 4H), 2.33 – 2.25 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.01, 208.19, 88.97, 75.84, 41.37, 21.74. IR (neat): 2921, 1956, 1715, 1434, 1410, 1369, 1091, 847.

199 (liquid) was prepared in a similar way as **93**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.19 – 5.15 (m, 2H), 4.73 – 4.69 (m, 4H), 2.13 – 2.04 (m, 4H), 1.60 (t, J = 4.2 Hz, 4H), 1.28 (s, 1H), 1.21 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.22, 90.00, 75.20, 72.34, 40.76, 26.63, 25.57. IR (neat): 2920, 1955, 1716, 1434, 1410, 1368, 1091, 845.

200 (liquid) was prepared in a similar way as **93**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.23 (m, 5H), 5.12 – 5.06 (m, 2H), 4.69 – 4.65 (m, 4H), 2.06 – 1.99 (m, 4H), 1.86 (s, 1H), 1.85 – 1.77 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.14, 145.25, 128.07, 126.38, 125.09, 89.87, 77.34, 75.26, 41.96, 22.15. IR (neat): 2921, 1955, 1716, 1457, 1434, 1410, 1368, 1091, 845, 658.

201 (liquid) was prepared in a similar way as **93**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 – 7.22

(m, 5H), 5.20 – 5.12 (m, 2H), 4.72 – 4.68 (m, 4H), 2.80 (s, 2H), 2.17 – 2.09 (m, 4H), 1.62 – 1.56 (m, 4H), 1.44 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.24, 136.80, 130.48, 128.19, 126.47, 89.93, 75.24, 73.74, 45.44, 37.58, 22.43. IR (neat): 2922, 1955, 1714, 1457, 1431, 1410, 1364, 1091, 847, 655.

202 (liquid) was prepared in a similar way as **93**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 – 7.35 (m, 9H), 5.16 – 5.09 (m, 2H), 4.71 – 4.68 (m, 4H), 2.11 – 1.83 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.22, 144.41, 140.67, 139.20, 128.64, 127.08, 126.89, 126.76, 125.60, 89.89, 76.76, 75.27, 41.98, 22.21. IR (neat): 2921, 1955, 1715, 1457, 1448, 1425, 1410, 1368, 1093, 844, 658.

203 (liquid) was prepared in a similar way as **93**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 – 7.26 (m, 2H), 6.90 – 6.85 (m, 2H), 5.21 – 5.07 (m, 2H), 4.76 – 4.64 (m, 4H), 3.82 (s, 3H), 2.03 – 1.78 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.05, 141.06, 136.45, 128.72, 114.88, 90.72, 90.35, 76.74, 76.58, 43.36, 23.59. IR (neat): 2923, 1956, 1715, 1457, 1448, 1425, 1410, 1369, 1093, 847, 658.

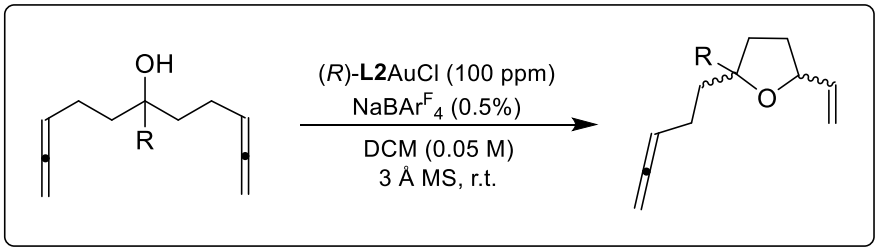
204 (liquid) was prepared in a similar way as **93**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 – 7.33 (m, 4H), 5.11 – 5.05 (m, 2H), 4.69 – 4.66 (m, 4H), 2.00 – 1.82 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.58, 145.23, 133.63, 129.61, 128.11, 91.11, 78.02, 76.80, 43.39, 23.50. IR (neat): 2922, 1955, 1714, 1457, 1431, 1410, 1364, 1091, 847, 655.

205 (liquid) was prepared in a similar way as **93**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 – 7.25 (m, 1H), 6.99 – 6.93 (m, 2H), 6.81 – 6.78 (m, 1H), 5.12 – 5.06 (m, 2H), 4.69 – 4.65 (m, 4H), 3.84 (s, 3H), 2.04 – 1.77 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.16, 159.50, 147.15, 129.07, 117.52, 111.46, 111.27, 89.86, 76.79, 75.24, 55.09, 41.94, 22.14. IR (neat): 2923, 1955, 1719, 1457, 1410, 1364, 1091, 847, 656.

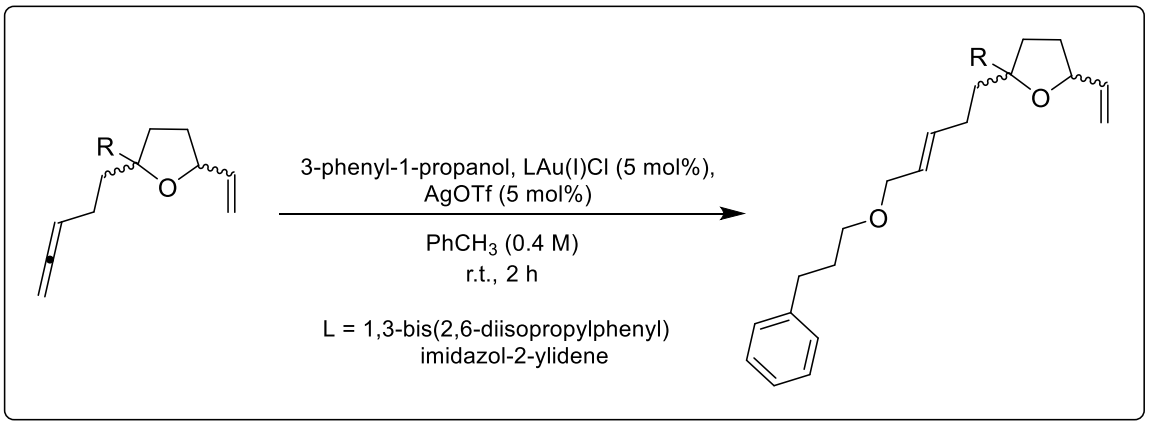
206 (liquid) was prepared in a similar way as **93**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, J = 8.1 Hz, 2H), 7.17 (d, J = 8.1 Hz, 2H), 5.12 – 5.06 (m, 2H), 4.68 – 4.65 (m, 4H), 2.36 (s, 3H), 2.03 – 1.75 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.15, 142.26, 135.87, 128.77,

125.00, 89.90, 76.69, 75.20, 41.92, 22.17, 20.84. IR (neat): 2922, 1953, 1714, 1457, 1431, 1415, 1364, 1090, 845, 655.

Asymmetric intramolecular cyclization of Remotus and its derivatives

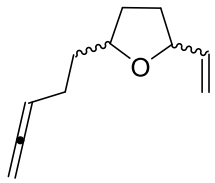


General procedure E: To a 3-dram vial were added sequentially 0.2 mmol of bisallenyl alcohol, indicated volume (18.3 μL for 100 ppm) of **(*R*)-L2AuCl** solution (1 mg/mL in DCM), 3 Å molecular sieves and 4 mL anhydrous DCM as solvent. The mixture was stirred at room temperature for 15 min before 0.001 mmol NaBAr$^F_4$ (0.5 mol %) was added. The reaction was then stirred at the same temperature monitored by TLC. Upon completion, the reaction was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography to obtain pure product.



General procedure D: A mixture of LAu(I)Cl (5 mol %) and AgOTf (5 mol %) in toluene (0.2 M) was stirred at room temperature for 5 min, treated with a solution of substrate (cyclized product, 1 equiv) and 3-phenyl-1-propanol (1.1 equiv) in toluene (0.2 M). The resulting suspension was stirred at room temperature for 2 h. Upon completion indicated by TLC, the reaction was concentrated under reduced pressure. The residue was purified through silica gel flash column chromatography to obtain pure product.

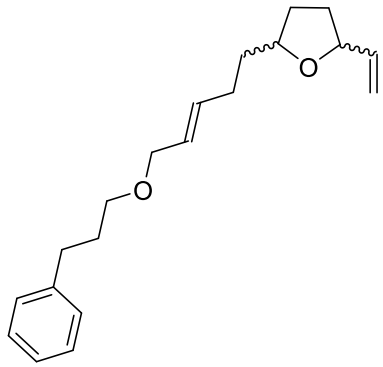
Molecule 57



57

The compound **57** (liquid) was prepared in 98% yield (*trans*/*cis* = 1/1) from **56** with **(*R*)-L2AuCl** (100 ppm) at room temperature for 5 h according to General procedure E. Purification was performed by silica gel flash column chromatography with diethyl ether and hexanes (5 : 95). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.05 – 5.93 (m, 1H), 5.32 – 5.29 (m, 1H), 5.20 – 5.15 (m, 2H), 4.73 – 4.58 (m, 2H), 4.34 – 4.22 (m, 1H), 4.02 – 3.95 (m, 1H), 2.13 – 2.09 (m, 4H), 1.53 – 1.50 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.38, 139.52, 139.43, 115.16, 114.83, 89.72, 89.70, 80.04, 79.45, 79.09, 78.56, 77.15, 75.04, 75.02, 35.20, 35.15, 32.46, 31.89, 31.73, 30.94, 24.79. The number of carbons in less than expected due to partial overlapping of signals. IR (neat): 2839, 1961, 1437, 1424, 1206, 843, 635.

Molecule 189



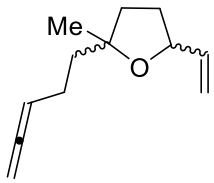
189

The compound **189** (liquid) was prepared in 66% yield (*trans*/*cis* = 1/1) from **57** according

to General procedure D. Purification was performed by silica gel flash column chromatography with diethyl ether and hexanes (1 : 9). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 – 7.21 (m, 5H), 5.89 – 5.78 (m, 1H), 5.75 – 5.68 (m, 2H), 5.29 – 5.14 (m, 1H), 5.14 – 5.03 (m, 1H), 4.40 – 4.31 (m, 1H), 4.10 – 4.02 (m, 1H), 3.94 – 3.91 (m, 2H), 3.48 – 3.42 (m, 2H), 2.75 – 2.70 (m, 2H), 2.30 – 1.93 (m, 6H), 1.77 – 1.49 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.92, 139.49, 139.40, 133.77, 133.74, 128.36, 128.18, 126.56, 125.61, 115.05, 114.76, 79.96, 79.39, 79.10, 78.57, 76.47, 71.43, 69.14, 35.33, 35.27, 32.39, 32.28, 31.84, 31.68, 31.21, 30.90, 28.89. The number of carbons in less than expected due to partial overlapping of signals. IR (neat): 2996, 2941, 1435, 1428, 1205, 842, 636.

ee_{major} % = 93%; ee_{minor} % = 94% [determined by HPLC: Chiralcel IB-3 column, iPrOH/Heptane = 0.2/99.8, 1.0 mL/min].

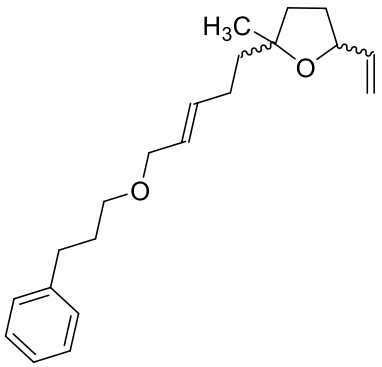
Molecule 207



207

The compound **207** (liquid) was prepared in 98% yield (*d.r.* = 53/47) from **199** with **(*R*)-L2AuCl** (100 ppm) at room temperature for 4 h according to General procedure E. Purification was performed by silica gel flash column chromatography with diethyl ether and hexanes (5 : 95). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.94 – 5.77 (m, 1H), 5.30 – 5.05 (m, 3H), 4.71 – 4.66 (m, 2H), 4.41 – 4.36 (m, 1H), 2.10 – 2.03 (m, 4H), 1.92 – 1.61 (m, 4H), 1.24 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.22, 139.97, 139.57, 115.01, 114.90, 90.17, 82.90, 82.84, 80.06, 79.31, 75.00, 74.97, 40.98, 40.38, 36.99, 36.77, 32.57, 32.49, 26.83, 26.16, 23.34, 23.26. The number of carbons in less than expected due to partial overlapping of signals. IR (neat): 2837, 1960, 1438, 1422, 1205, 843, 633.

Molecule 207a

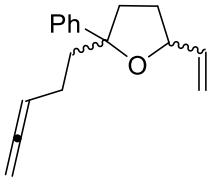


207a

The compound **207a** (liquid) was prepared in 63% yield (*d.r.* = 53/47) from **207** according to General procedure D. Purification was performed by silica gel flash column chromatography with diethyl ether and hexanes (1 : 9). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 – 7.18 (m, 5H), 5.87 – 5.58 (m, 3H), 5.28 – 5.22 (m, 1H), 5.11 – 5.08 (m, 1H), 4.37 – 4.33 (m, 1H), 3.93 (s, 2H), 3.44 (t, J = 6.4 Hz, 2H), 2.72 (t, J = 7.4 Hz, 2H), 2.17 – 2.11 (m, 3H), 1.93 – 1.58 (m, 7H), 1.24 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.94, 139.97, 139.60, 134.39, 128.37, 128.19, 126.16, 125.63, 115.07, 114.89, 82.95, 80.07, 79.33, 77.12, 71.50, 69.16, 41.19, 40.58, 37.00, 36.79, 32.57, 32.50, 32.29, 31.22, 29.60, 27.49, 27.41, 26.82, 26.14. The number of carbons in less than expected due to partial overlapping of signals. IR (neat): 2996, 2940, 1435, 1427, 1205, 843, 636.

ee% not determined yet.

Molecule 208

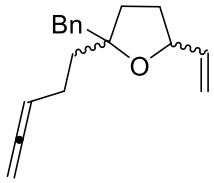


208

The compound **208** (liquid) was prepared in 94% yield (*d.r.* = 81/19) from **200** with **(*R*)-L2AuCl** (100 ppm) at room temperature for 3 h according to General procedure E. Purification was performed by silica gel flash column chromatography with diethyl ether and hexanes (3 : 97). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 – 7.21 (m, 5H), 5.99 – 5.87 (m, 1H), 5.33 – 5.29 (m, 1H), 5.15 – 5.05 (m, 2H), 4.67 – 4.53 (m, 3H), 2.27 – 1.46 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.15, 146.97, 139.54, 139.36, 127.96, 127.74, 126.26, 126.18, 125.32, 125.08, 115.64, 114.94, 90.03, 86.85, 80.80, 79.49, 77.58, 74.98, 42.21, 41.50, 38.96, 37.88, 31.96, 31.88, 30.23, 22.97. The number of carbons in less than expected due to partial overlapping of signals. IR (neat): 2925, 2854, 1955, 1495, 1447, 1070, 1043, 925, 843, 700.

ee_{major} % = 96%; ee_{minor} % = 95% [determined by HPLC: Chiralcel IA-3 column, iPrOH/Heptane = 0.5/99.5, 1.0 mL/min].

Molecule 209



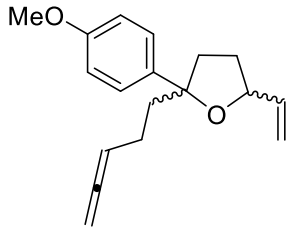
209

The compound **209** (liquid) was prepared in 93% yield (*d.r.* = 56/44) from **201** with **(*R*)-L2AuCl** (100 ppm) at room temperature for 5 h according to General procedure E. Purification was performed by silica gel flash column chromatography with diethyl ether and hexanes (3 : 97). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 – 7.24 (m, 5H), 5.94 – 5.73 (m, 1H), 5.26 – 5.07 (m, 3H), 4.70 – 4.67 (m, 2H), 4.34 – 4.16 (m, 1H), 2.90 – 2.75 (m, 2H), 2.20 – 2.13 (m, 2H), 1.92 – 1.63 (m, 5H), 1.28 – 1.15 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.23, 139.44, 139.17, 138.05, 137.90, 130.62, 130.50, 127.85, 127.69, 126.08, 126.03, 115.58, 115.13, 90.08, 90.02, 85.30, 85.27, 80.68, 80.19, 77.10, 75.08, 75.02, 45.63, 45.16, 39.47, 39.22, 34.17, 33.95, 32.65, 23.07, 22.99. The number of carbons in less than expected due to partial overlapping of signals. IR (neat): 2928, 2856, 1955, 1497, 1447,

1071, 1043, 924, 843, 702.

ee_{major} % = 96%; ee_{minor} % = 96% [determined by HPLC: Chiralcel IA-3 column, iPrOH/Heptane = 0.4/99.6, 1.0 mL/min].

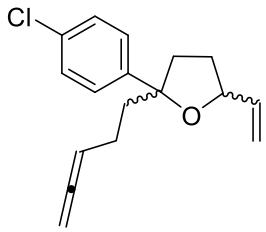
Molecule 210



210

The compound **210** (liquid) was prepared in 45% yield (*d.r.* = 59/41) from **203** with **(*R*)-L2AuCl** (100 ppm) at room temperature for 4 h according to General procedure E. Purification was performed by silica gel flash column chromatography with diethyl ether and hexanes (3 : 97). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 – 7.28 (m, 2H), 6.90 – 6.86 (m, 2H), 5.99 – 5.86 (m, 1H), 5.34 – 5.26 (m, 1H), 5.16 – 5.05 (m, 2H), 4.67 – 4.62 (m, 2H), 4.53 – 4.42 (m, 1H), 3.82 (s, 3H), 2.21 – 1.58 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.13, 158.02, 157.93, 139.60, 139.44, 139.08, 138.63, 126.39, 126.21, 115.59, 114.88, 113.28, 113.05, 90.05, 86.71, 86.62, 80.77, 79.35, 77.10, 74.95, 55.11, 42.28, 41.60, 38.89, 37.72, 31.91, 23.03. The number of carbons in less than expected due to partial overlapping of signals. IR (neat): 2929, 2854, 1955, 1495, 1447, 1256, 1070, 1045, 928, 843, 700, 658. ee_{major} % = 96%; ee_{minor} % = 97% [determined by HPLC: Chiralcel IA-3 column, iPrOH/Heptane = 0.2/99.8, 1.0 mL/min].

Molecule 211

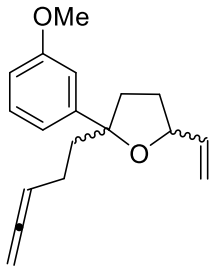


211

The compound **211** (liquid) was prepared in 67% yield (*d.r.* = 51/49) from **204** with **(*R*)-L2AuCl** (100 ppm) at room temperature for 4 h according to General procedure E. Purification was performed by silica gel flash column chromatography with diethyl ether and hexanes (3 : 97). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.28 (m, 4H), 5.97 – 5.84 (m, 1H), 5.35 – 5.26 (m, 1H), 5.17 – 5.05 (m, 2H), 4.67 – 4.62 (m, 2H), 4.56 – 4.41 (m, 1H), 2.21 – 1.58 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.12, 145.55, 145.25, 139.27, 139.06, 132.03, 131.96, 128.09, 127.86, 126.80, 126.58, 115.84, 115.09, 89.85, 89.83, 86.57, 86.46, 80.85, 79.59, 75.10, 65.74, 42.07, 41.36, 38.96, 37.93, 31.89, 31.78, 22.86, 15.16. The number of carbons in less than expected due to partial overlapping of signals. IR (neat): 2925, 2855, 1955, 1495, 1447, 1072, 1043, 921, 843, 698.

ee_{major} % = 97%; ee_{minor} % = 97% [determined by HPLC: Chiralcel IA-3 column, iPrOH/Heptane = 0.1/99.9, 1.0 mL/min].

Molecule 212

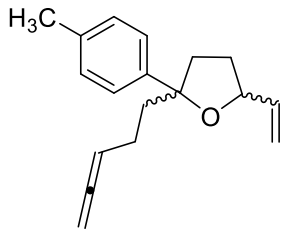


212

The compound **212** (liquid) was prepared in 84% yield (*d.r.* = 83/17) from **205** with **(*R*)-L2AuCl** (100 ppm) at room temperature for 3 h according to General procedure E. Purification was performed by silica gel flash column chromatography with diethyl ether and hexanes (4 : 96). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 – 7.23 (m, 1H), 7.06 – 6.97 (m, 2H), 6.79 – 6.76 (m, 1H), 6.00 – 5.89 (m, 1H), 5.34 – 5.28 (m, 1H), 5.15 – 5.03 (m, 2H), 4.67 – 4.62 (m, 2H), 4.58 – 4.48 (m, 1H), 3.84 (s, 3H), 2.27 – 1.62 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.14, 159.17, 148.86, 139.50, 139.33, 128.97, 128.73, 117.71, 117.54, 115.62, 114.93, 111.49, 111.33, 111.16, 90.01, 86.82, 80.83, 79.50, 74.97, 55.07, 42.09, 41.44, 39.01, 37.86, 31.90, 31.84, 29.58, 22.96. The number of carbons in less than expected due to partial overlapping of signals. IR (neat): 2925, 2855, 1956, 1495, 1445, 1072, 1041, 921, 843, 699.

ee_{major} % = 96%; ee_{minor} % = 91% [determined by HPLC: Chiralcel IA-3 column, iPrOH/Heptane = 0.2/99.8, 1.0 mL/min].

Molecule 213



213

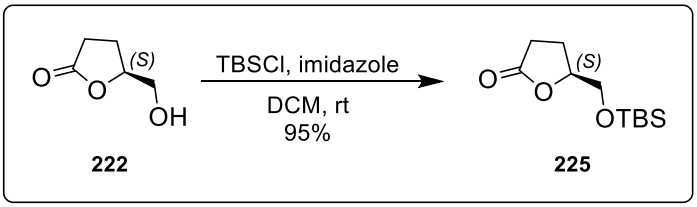
The compound **213** (liquid) was prepared in 91% yield (*d.r.* = 82/18) from **206** with **(*R*)-L2AuCl** (100 ppm) at room temperature for 4 h according to General procedure E. Purification was performed by silica gel flash column chromatography with diethyl ether and hexanes (3 : 97). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 – 7.28 (m, 2H), 7.16 – 7.13 (m, 2H), 5.96 – 5.87 (m, 1H), 5.33 – 5.27 (m, 1H), 5.14 – 5.05 (m, 2H), 4.66 – 4.62 (m, 2H), 4.56 – 4.41 (m, 1H), 2.36 (s, 3H), 2.25 – 1.58 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.16, 144.02, 139.46, 135.62, 128.63, 128.41, 125.24, 125.02, 115.50, 114.81, 90.05, 86.79, 80.74, 74.89, 42.24, 41.55, 38.89, 37.77, 31.90, 22.99, 20.83. The number of carbons in less than expected due to partial overlapping of signals. IR (neat): 2930, 2853, 1955,

1495, 1449, 1254, 1069, 1045, 927, 843, 700, 655.

ee_{major} % = 97%; ee_{minor} % = 94% [determined by HPLC: Chiralcel IA-3 column, iPrOH/Heptane = 0.1/99.9, 1.0 mL/min].

10.5 Determination of the absolute and relative configuration of the cyclization products of Medius 54

(*S*)-5-(((tert-butyldimethylsilyl)oxy)methyl)dihydrofuran-2(3H)-one (225)

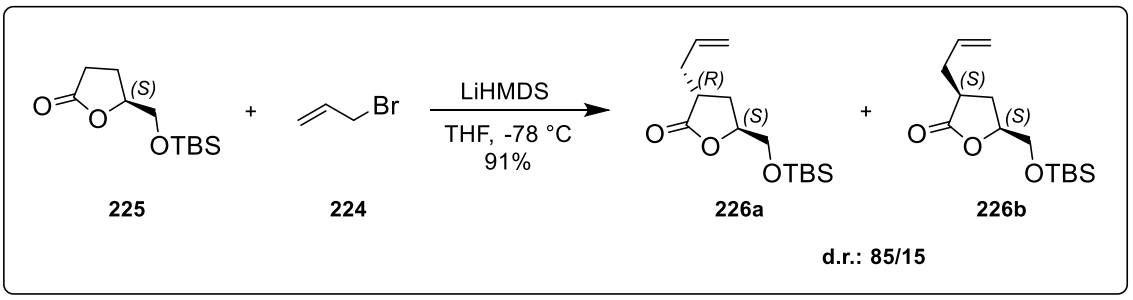


222 **225**

Preparation of **225**. In a flamed dried flask under Argon atmosphere **222** (1 equiv) was dissolved in dry DCM (0.2M). The mixture was cooled to 0 °C before adding imidazole (4 equiv) and TBS-Cl (1.1 equiv). The mixture was allowed to stir at room temperature for 12 h. The reaction mixture was quenched with water and the aqueous phase was extracted with DCM thr*ee* times. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography with diethyl ether and hexanes (1:1) to give **225** (liquid) in 95% yield.

The spectroscopic data were in accordance with the literature data.[87]

(*5S*)-3-allyl-5-(((tert-butyldimethylsilyl)oxy)methyl)dihydrofuran-2(3H)-one (226)



225 **224** **226a** **226b**

d.r.: 85/15

Preparation of **226**. In a flamed dried flask under Argon atmosphere **225** (1 equiv) was dissolved in dry THF (0.2M). The mixture was cooled to -78 °C before adding LiHMDS (1.1 equiv). The mixture was stirred at the same temperature for 40 min and then allyl bromide (1.5 equiv) was added. The reaction mixture was stirred for further 30 min. Upon

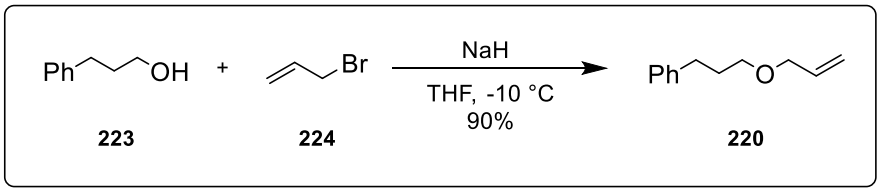
completion confirmed by TLC analysis, the reaction was quenched with saturated NH_4Cl solution and the aqueous phase was extracted with Et_2O thr*ee* times. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography with diethyl ether and hexanes (25:75) to give **226** (liquid) in 91% yield.

The diastereomeric mixture was subjected to GC-MS analysis to determine the diastereomeric ratio, which turned out to be 85/15 = *trans*/*cis*, m/z : 213 $[M - tBu]^+$.

The diastereomeric mixture was then further purified obtaining the pure diastereoisomers, whose spectroscopic data were in accordance with the literature data.[87]

Finally, the diastereomeric compounds were put together again for the next synthetic steps.

(3-(allyloxy)propyl)benzene (220)

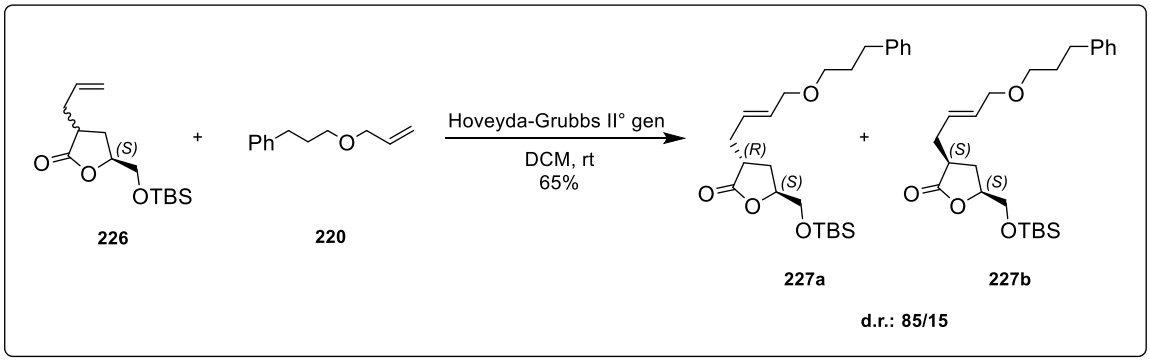


Preparation of **220**. In a flamed dried flask under Argon atmosphere NaH (1.5 equiv) was suspended in dry THF (0.2M). The mixture was cooled to -10 °C before adding **223** (1 equiv). The mixture was allowed to stir at the same temperature for 15 min and then allyl bromide (1.1 equiv) was added dropwise. The reaction mixture was stirred at room temperature for 3 h. Upon completion confirmed by TLC analysis, the reaction mixture was quenched with water and the aqueous phase was extracted with Et_2O thr*ee* times. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography with diethyl ether and hexanes (1:9) to give **220** (liquid) in 90% yield.

The spectroscopic data were in accordance with the literature data.[119]

[119] N. Sakai, Y. Usui, T. Moriya, R. Ikeda, T. Konakahara, *Eur. J. Org. Chem.* **2012**, 24, 4603.

(*5S*)-5-(((tert-butyldimethylsilyl)oxy)methyl)-3-((*E*)-4-(3-phenylpropoxy)but-2-en-1-yl)dihydrofuran-2(3H)-one (227)

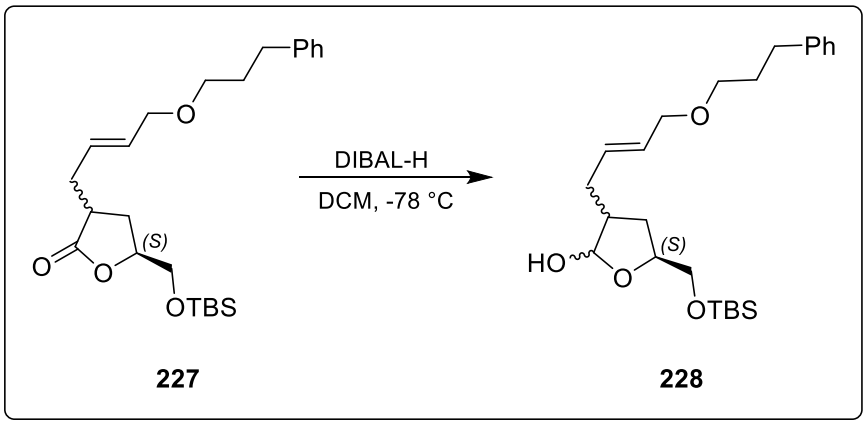


Preparation of **227**. In a flamed dried flask under Argon atmosphere **226** (1 equiv) was dissolved in dry DCM (0.2M) together with **220** (2 equiv) and the catalyst (5 mol %). The mixture was allowed to stir at room temperature for 12 h. Upon completion confirmed by TLC analysis, the reaction mixture was directly purified by flash column chromatography with diethyl ether and hexanes (3:7) to give **227** (liquid) in 65% yield.

The diastereomeric mixture was subjected to GC-MS analysis to determine the diastereomeric ratio, which turned out to be 85/15 = *trans*/*cis*, m/z : 361 $[M - tBu]^+$.

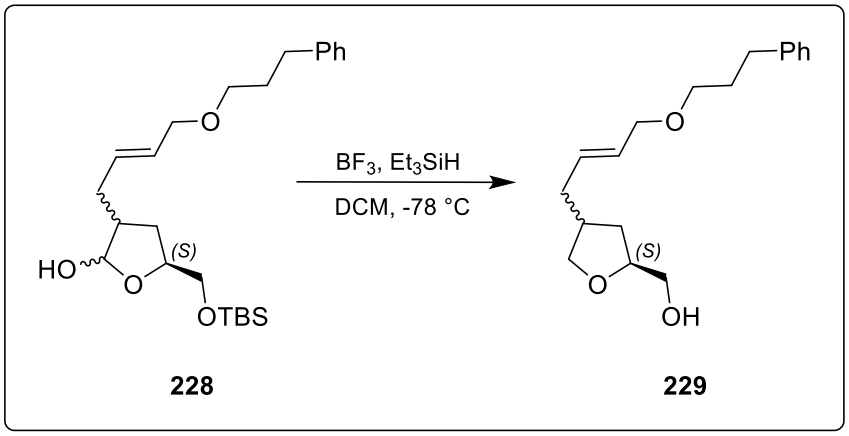
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 – 7.19 (m, 5H), 5.70 – 5.66 (m, 2H), 4.54 – 4.50 (m, 1H), 3.96 – 3.84 (m, 3H), 3.69 – 3.65 (m, 1H), 3.46 – 3.42 (m, 2H), 2.86 – 2.69 (m, 4H), 2.33 – 2.27 (m, 4H), 2.05 – 1.90 (m, 3H), 0.90 (s, 9H), 0.09 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.83, 141.82, 129.79, 129.49, 129.30, 128.34, 128.19, 125.65, 77.93, 77.09, 70.98, 69.32, 69.27, 64.94, 39.12, 33.74, 32.23, 31.20, 31.14, 29.24, 25.69, 18.13, -5.60, 5.70. The number of carbons in less than expected due to partial overlapping of signals. IR (neat): 2932, 2858, 1768, 1454, 1366, 1178, 1103, 701.

(*5S*)-5-(((tert-butyldimethylsilyl)oxy)methyl)-3-((*E*)-4-(3-phenylpropoxy)but-2-en-1-yl)dihydrofuran-2-ol (228)



Preparation of **228**. In a flamed dried flask under Argon atmosphere **227** (1 equiv) was dissolved in dry DCM (0.2M). The mixture was cooled to -78 °C before DIBAL-H (1.2 equiv) was added. The reaction mixture was allowed to stir at the same temperature for 30 min. Upon completion confirmed by TLC analysis, the reaction mixture was quenched with water and the aqueous phase was extracted with DCM thr*ee* times. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was used in the next step without further purification.

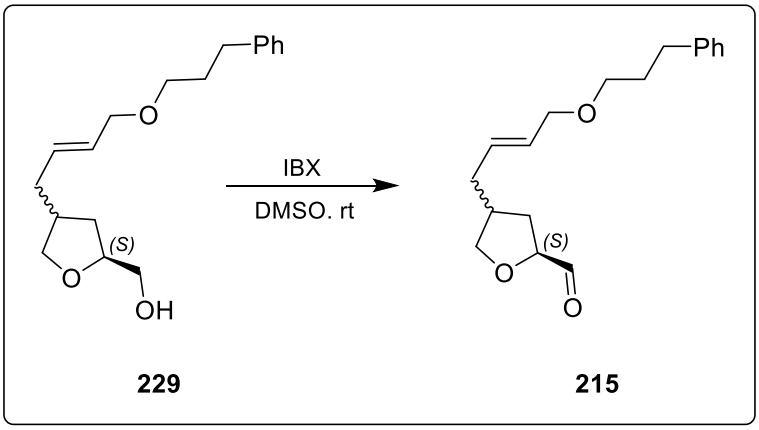
((*2S*)-4-((*E*)-4-(3-phenylpropoxy)but-2-en-1-yl)tetrahydrofuran-2-yl)methanol (229)



Preparation of **229**. In a flamed dried flask under Argon atmosphere **228** (1 equiv) was

dissolved in dry DCM (0.2M) together with Et_3SiH (1.7 equiv). The mixture was cooled to -78 °C before BF_3 (1.2 equiv) was added dropwise. The reaction mixture was allowed to stir at 0 °C for 1 h. Upon completion confirmed by TLC analysis, the reaction mixture was quenched with saturated $NaHCO_3$ aq. solution. The aqueous phase was extracted with DCM thr*ee* times. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was used in the next step without further purification.

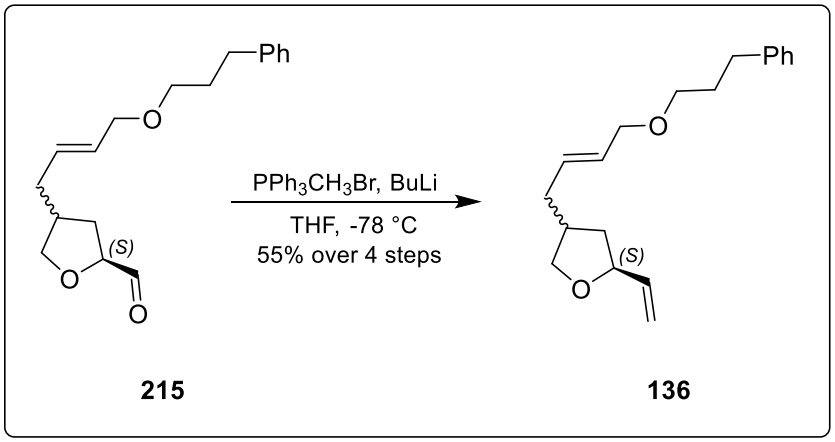
((*2S*)-4-((*E*)-4-(3-phenylpropoxy)but-2-en-1-yl)tetrahydrofuran-2-carbaldehyde (215)



229 **215**

Preparation of **215**. In a flamed dried flask under Argon atmosphere **229** (1 equiv) was dissolved in dry DMSO (0.2M) together with IBX (1.2 equiv). The mixture was allowed to stir at 50 °C for 3 h. Upon completion confirmed by TLC analysis, the reaction mixture was quenched with saturated and $Na_2S_2O_3$ and $NaHCO_3$ aq. solutions. The aqueous phase was extracted with Et_2O thr*ee* times. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was used in the next step without further purification.

(*2S*)-4-((*E*)-4-(3-phenylpropoxy)but-2-en-1-yl)-2-vinyltetrahydrofuran (136)



Preparation of **136**. In a flamed dried flask under Argon atmosphere triphenylphosphonium bromide (1.2 equiv) was suspended in dry THF (0.2 M). The mixture was cooled to -78 °C before adding *n*BuLi (1.2 equiv) and then was allowed to stir at 0°C for 30 min. The reaction was cooled to -78 °C again and a solution of **215** (1 equiv) in dry THF (0.2 M) was added dropwise via cannula. The reaction mixture was allowed to stir at room temperature for 3 h. Upon completion confirmed by TLC analysis, the reaction mixture was quenched with saturated NH_4Cl and $NaHCO_3$ aq. solutions. The aqueous phase was extracted with Et_2O thr*ee* times. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography with diethyl ether and hexanes (1:9) to give **136** (liquid) in 55% yield over 4 steps.

The diastereomeric mixture was subjected to GC-MS analysis to determine the diastereomeric ratio, which turned out to be 88.3/11.7 = *trans*/*cis*, m/z : 135 $[M - 151]^+$.

The spectroscopic data were in accordance with **136** prepared through gold(I)-catalyzed functionalization reaction of **55**.

Acknowledgements

Finally, I would like to say thanks to every special person met in this fantastic adventure. To make everybody understand, I am going to write the following words in italian.

Desidero ringraziare tutte le persone che mi hanno aiutato direttamente e/o indirettamente ad intraprendere, vivere e portare a temine questa mia nuova avventura, senza il contributo delle quali tutto ciò non sarebbe stato realizzabile.
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