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Silver-Based Radical Reactions: Development and Insights

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Abstract: Silver-mediated reactions have been emerging as a frontier area in organic chemistry. Particularly, recognition of silver as a single-electron-transfer (SET) oxidant has led to a deployment into the field of radical chemistry. The good reactivity and high selectivity of silver salts make them as one of the most prominent reagents in the contemporary free radical chemistry, which have provided accomplishing extensive applications in organic synthesis. However, so far, there has been no discrete book or review available systematically on silver-mediated radical reactions. This review aims to give a critical overview of silver-based radical reactions, especially emphasizing the reactivity, selectivity and the detailed mechanistic description, which provided an intrinsic understanding the role and catalytic cycle of silver compounds for triggering and promoting the radical reactions. It described in accordance to the type of radicals generated *in situ* such as carbon centered radicals and heteroatom such as nitrogen, oxygen, phosphorus, sulfur centered radicals. These sections emphasized the generation of these radicals from chemicals and their versatility in organic synthesis through oxidation, addition, coupling, and radical cascades, *etc*.

Keywords: silver catalysis; radical reactions; mechanistic insights, SET process

Xihe Bi was born in Jilin (P. R. of China) in 1977. He obtained his BSc in 2000 and PhD in 2006 under the guidance of Prof. Qun Liu at Northeast Normal University (P. R. of China). He spent two years (2006–2008) as an Alexander von Humboldt post-doctoral fellow with Prof. Michael Famulok at Kekulé-Institut für Organische Chemie und Biochemie, University of Bonn (Germany). At the end of 2008, he returned to Northeast Normal University and started his independent research as an Associate Professor. In 2013, he was promoted to full Professor. His research interests mainly focused on silver catalysis in organic chemistry. He has received honors and awards, including Winner of NSFC Foundation for Excellent Young Scientist (2015), Thieme Chemistry Journal Award 2014, New Century Excellent Talents in University of Ministry of Education of China (2013), and Alexander von Humboldt research fellowship (2006).

1. Introduction

The radical reactions are one of the fundamental entries for approaching target organic synthesis.[1] The preceding four decades have witnessed a major expansion in the field of radical reactions and they have become a key tool in the synthesis of fine chemicals,[2] polymers,[3] pharmaceuticals,[4] and natural products.[5] At the same time, silver-mediated reactions have been attracted much attention and have been emerging as one of frontier areas in organic chemistry.[6] Particularly, recognition of silver as a single-electron-transfer (SET) oxidant has led to a deployment into radical chemistry.[7] The good reactivity and high selectivity proved silver salts as one of the most prominent reagents in the field of contemporary free radical chemistry, providing accomplishing extensive applications in organic synthesis which are difficult to achieve by the established synthetic processes. However, in comparison with the flourishing carbon centered radicals,[8] the investigations of heteroatom centered radicals are indeed underdeveloped. This was witnessed by myriad of carbon centered radical reactions described in the literatures.

The previous books and reviews available are all limited to describe the need and significance of either silver catalysis or radical chemistry in organic synthesis. From 2008, six excellent review articles from other groups and one review from our group on silver-catalyzed/mediated organic synthesis describing coupling and heterocyclization reactions,[9] synthesis of heterocycles,[10] asymmetric silver-catalyzed reactions,[11] C(sp)–H and C(sp)–Si bond transformations,[12] atom transfer reactions,[13] C–H/C–C bond functionalization,[14] alkyne chemistry,[15] carboxylation,[16] and aryne reactions.[17] Although silver-based radical reactions have been partly presented from different aspects in above review articles, to the best of our knowledge, no discrete book or review article is available systematically describing the potential of silver compounds for radical reactions. Consequently, it highly appeals and also is the appropriate time to deliver an individual review as common platform to survey and summarize these silver-based radical reactions.

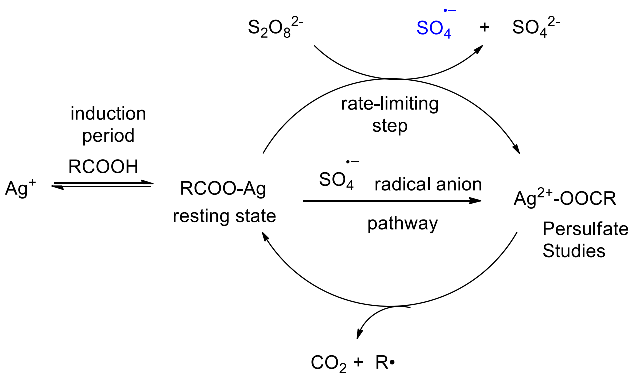
Scope and Limitations of the Review

This review aims to give a critical overview of silver-based radical reaction, especially emphasizing the reactivity, selectivity and the detailed mechanistic description. This will provide an intrinsic understanding the role and catalytic cycle of silver compounds for triggering and promoting the radical reactions. These reports will be described in accordance to the type of radicals generated *in situ* such as carbon centered radicals and heteroatom such as nitrogen, oxygen, phosphorus, sulfur centered radicals. These sections emphasize the generation of these radicals and their versatility in organic synthesis through oxidation, addition, coupling, and radical cascades, *etc*.

Ag(I)-Ag(II) catalysis

Ag(I) performs an extensive redox chemistry based on reduction to Ag(0) and oxidation to Ag(II) and/or Ag(III) through a SET process.[18] Ag(II) is a strong oxidant, with $E°(Ag^{2+}/Ag^{+})$ = 1.98 V.[19] Although invoked less commonly, there is precedence for involvement of more highly oxidizing Ag(III).[20] Ag(III) is very unstable, and usually stablized with electron-donating and/or sterically demanding ligands ($E°$ = 1.8 V, Ag^{3+}/Ag^{2+}).[21]

Ag(I)-persulfate catalysis has a long-established history in the literature, in which Ag(II) is generated upon oxidation of Ag(I). Work performed by Kochi and co-workers in the early 1970s on the Ag(I)-persulfate catalyzed oxidation of aliphatic carboxylic acids revealed that Ag(II) was the active oxidant.[22] Now, it is generally accepted that Ag(I) is oxidized to Ag(II) intermediate by persulfate, which then undergoes single electron transfer with a carboxylate to produce the carboxyl radical. Fast decarboxylation of the carboxyl radical gives the corresponding alkyl radical (Scheme 1). $K_2S_2O_8$ generates the $SO_4^{-\bullet}$ anion radical at ambient temperature.[23] _ENREF_43 The strong oxidation capacity of Ag^{2+} can further transform the generated alkyl radical to alkyl cation that forms byproduct subsequently. α-Oxocarboxylic acids also undergo an analogous pathway to provide the corresponding acyl radicals.[22, 24] One of the most widely applicable reactions via the combination of silver(I) salts and persulfate is the Minisci reaction, as exemplified as radical alkylation, acylation, (hetero)arylation. Due to the simple raw materials and the simple reaction conditions the Minisci reactions become a versatile and practical strategy for the C–H functionalization of heterocyclic compounds.[4, 25]



Scheme 1. Mechanistic insights into silver(I)-persulfate catalysis.

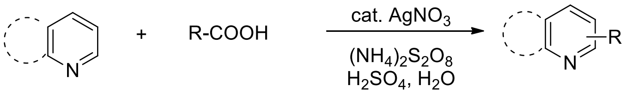
2. Carbon Radical

2.1 Carboxylic Acids

2.1.1 Alkyl radicals

Decarboxylation reactions of low cost, ease to operate, and commercially available aliphatic carboxylic acids have been one of the important strategies to introduce the alkyl group. At this point, Hunsdiecker decarboxylation and Minisci reaction are important decarboxylation interacted with silver salts.[22, 24a, 26] However, the Hunsdiecker decarboxylation reaction was required anhydrous silver salt as material, delivered moderate yields and narrow reaction scopes. Hence, developments have been accomplished to solve the issues to make simple, versatile and practicle conditions, such as Cristol reaction and Kochi reaction.[27]

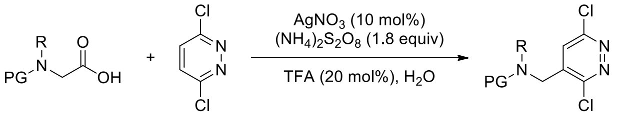
The Minisci radical alkylation reaction offers a unique and complementary means of functionalizing electron-deficient aromatic heterocycles,[28] providing a powerful method for the formation of $C(sp^2)–C(sp^3)$ bonds.[4, 24g, 29] Generally limited to moderate to low yields due to the harsh oxidizing conditions required, this transformation has been relatively overlooked compared to more intensely studied metal-catalyzed cross-coupling reactions. In the 1970s, Minisci *et al.* described a decarboxylative alkylation process, which started to become a useful synthetic method due to it allows the introduction of a wide range of primary, secondary and tertiary alkyl groups with good yield under very simple and mild conditions. The acidic conditions were useful and promoted the efficiency and selectivity of this radical process. The oxidative decarboxylation of aliphatic carboxylic acids **2** under silver(I)/peroxydisulphate conditions offered a general way to provide alkyl radicals to form the 2-alkylated products **3**.[22, 24a, 24e] Heterocyclic compounds **1**, like quinoline scaffolds, isoquinoline, and pyridine scaffolds were compatible (Scheme 2).[30] Later, other *N*-containing heterocycles, involving five-membered ring 1*H*-imidazole[31] and *N*-alkyl 1,2,4-triazoles[32] also furnished the 2-alkylated products.



1 **2** **3**

Scheme 2. Silver-catalyzed Minisci alkylation reactions.

Cowden and co-workers further extended the substrate scope of the Minisci reaction to *N*-protected glycine derivatives **4** with pyridazines **5**, thus furnished a range of the expected alkylation products **6** in good to high yields. Notably, secondary amides are shown to be compatible with this reaction, which overcame the obstacle that the 1-amidoalkyl radicals have tendency to undergo oxidation to give imine, and the corresponding (secondary amide) products are unstable under the strongly oxidizing reaction conditions. In this reaction, trifluoroacetic acid (TFA) was used to provide a milder reaction whereas the typical sulfuric acid also gave a similar yield. When other amino acids, particularly with *N*-alkyl groups were applized, phthalimide protecting group was required to make the reaction perform (Scheme 3).[33]



4 **5** **6**

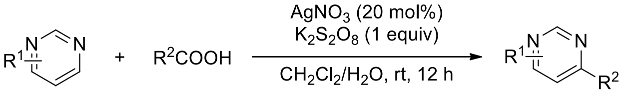
PG = Bz, Cbz, Ts, Boc, Ac, phthaloyl
R = H, Me

19 examples
up to 88% yields

Scheme 3. Radical alkylation of *N*-alkyl 1,2,4-triazoles.

The Minisci reactions have been widely explored and utilized extensively in the preparation of bioactive molecules.[4] For instance, Minisci reactions have been used to prepare functional organoreceptors *via* a tridirectional coupling of *cis*-1,3,5-cyclohexane-tri-carboxylic acid and a heteroaromatic building block with silver(I)/peroxydisulphate/sulfuric acid system. The resulting tripodal adducts functioned as carbohydrate receptors, with particular sensitivy for α-octyl-glucopyranoside._ENREF_18[34]

Although alkylated pyrimidines are very simple, for years, only a few methods are available for preparing 4-alkylated pyrimidines which are commonly obtained *via* metal catalyzed cross-coupling reactions of polyhalogenated pyrimidines with Grignard reagents or organolithium reagents. However, these methods only produced aryl and primary alkyl substituted products. Therefore, a general and practical method with simple substrates for the synthesis of 4-alkylsubstituted pyrimidine is highly desirable. Recently, Mai, Mao and Qu *et al.* reported a decarboxylative alkylation and acylation of pyrimidines **7** to afford 4-substituted pyrimidine derivatives **9** *via* C(sp^2)–H functionalization. Starting from simple pyrimidines and readily available carboxylic acids **8**, the coupling proceeded at room temperature. The α-heteroatom-substituted primary alkyl acids were also acceptable and received good yields (Scheme 4).[35] Estrada and co-workers also reported that pyrimidines in the presence of stoichiometric amounts of $AgNO_3$ and $(NH_4)_2S_2O_8$, furnished the corresponding alkylated products in high yields with carboxylic acid.[36]



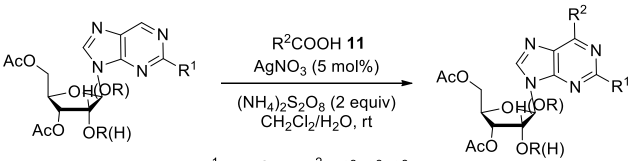
7 **8** **9**

R^1 = Cl, Br, F, CN, Me, CF_3, *etc.*
R^2 = 1°, 2°, 3° alkyl and acyl

29 examples
up to 79% yields

Scheme 4. Silver-catalyzed decarboxylative alkylation and acylation of pyrimidines.

In 2014, Qu and Guo *et al.* developed a practical and highly regioselective Minisci reaction for the synthesis of bioactive C6-alkylated purine nucleosides **12** using the easily available carboxylic acids **11** under mild conditions. With 5 mol % $AgNO_3$ as a catalyst and $(NH_4)_2S_2O_8$ as an oxidant, a series of purine nucleosides including ribosyl, deoxyribosyl, arabinosyl purine nucleosides **10** worked well with primary/secondary/tertiary aliphatic carboxylic acids **11**. The machanistic experiment disclosed that a radical substitution process may be involved in this system. The C6-H was activated through the coordination between Ag(I) cation with N7 on the purine derivative, which resulted in the high regioselectivity. Furthermore, the carboxylic acid bearing O or N atom, such as phenoxyacetic acid and phthalimidoacetic acid also performed the reaction smoothly (Scheme 5).[37]



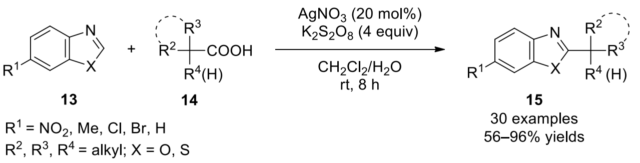
R^1 = H, Cl, F; R^2 = 1°, 2°, 3° alkyl
R = Ac, Bz

10
ribosyl, deoxyribosyl,
arabinosyl

12
21 examples
67–99%

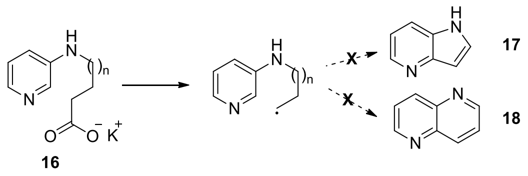
Scheme 5. Synthesis of C6-alkylated purine nucleosides.

In 2014, Chen and Zhao *et al.* reported the first example of C2-alkylation of benzothiazoles **13** through direct decarboxylative cross-coupling reaction with carboxylic acids **14** under silver(I) catalysis (Scheme 6).[38] In comparison with the metal free di-*tert*-butyl peroxide (DTBP)-promoted transformation of cyclic alkane acids,[39] a wide range of carboxylic acids **14** was employed in the reaction, including secondary or tertiary α-substituted, cyclic and acyclic carboxylic acids. Note that halogen-containing saturated aliphatic carboxylic acids were not suitable because of forming an immediate AgBr precipitate. The electronic effect had an obvious impact that benzothiazoles with electron-rich groups were more efficient. A radical pathway was suggested and resulted in the 2-alkylated products **15** in 56–96% yields.



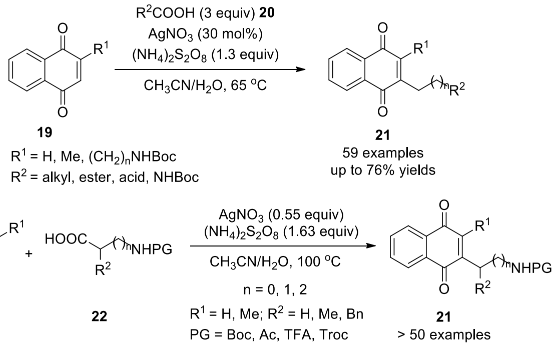
Scheme 6. Silver-catalyzed C2-alkylation of benzothiazoles.

Jones and co-workers uncovered that the route based on the Minisci reaction was inappropriate for the formation of anticipative products, containing azaindoles **17**, 1,5-naphthyridines **18**, and the homologue towards a 6,7-fused system. Competing β-scission, hydrolytic cleavage and lactonisation reactions of carboxylate precursor **16** were found as major obstacles for the transformation (Scheme 7).[40]



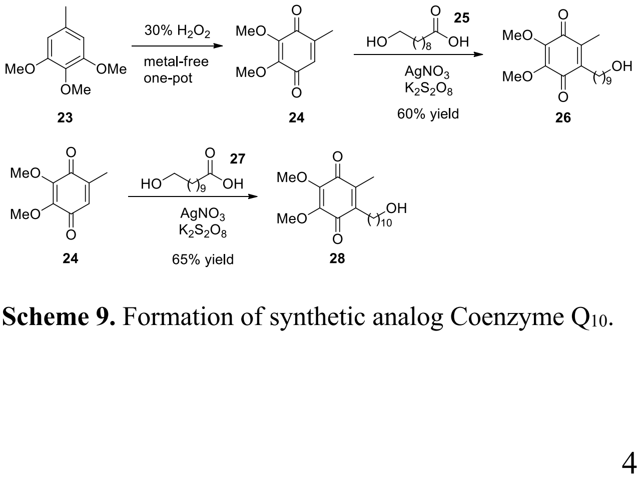
Scheme 7. Scope and limitations of the Minisci reaction for the synthesis of aza-heterocycles.

Functionalized naphthoquinones **21** are known to be obtained by a systematic study of the Kochi–Anderson process for the alkylation of quinones **19**.[22, 41] The silver-catalyzed decarboxylative alkylation process proved to be very efficient to access naphthoquinones **21**, as it is compatible with wide substrate scope including *N*-protected amino acids and linear or branched carboxylic acids **20**. A double alkylation with 1,4-naphthoquinone could be done, even with different reactants.[42] Afterwards, the group extended the reaction scope to diverse α, β and γ *N*-protected amino acids **22**.[43] Note that the chiral amino acids with different alkyl chain lengths were well applicable under the conditions. This radical alkylation reaction was strongly affected by the the steric hindrance, electronic effect, and stability issue. Importantly, this decarboxylative alkylation process has been used to synthesize versatile antiparasitic drug (Scheme 8).[44]



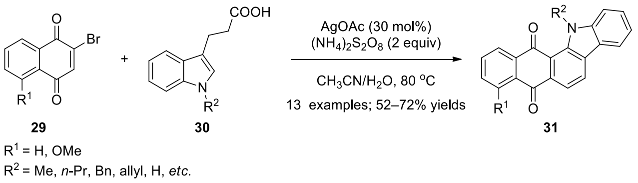
Scheme 8. Silver-catalyzed alkylation of quinones.

The decarboxylative alkylation has been used for the formation of synthetic analog coenzyme Q_{10} **24**, which can function as a free radical scavenger for reactive oxygen species (ROS) as well as facilitate electron transfer along the mitochondrial respiratory chain. A synthetic analog that 2-(9-hydroxynonyl)-5,6-dimethoxy-3-methyl-1,4-benzoquinone **26** was readily synthesized from commercially available 3,4,5-trimethoxytoluene **23** in two steps. First, 2,3-dimethoxy-5-methyl-1,4-benzoquinone (coenzyme Q_0) was obtained in one step by treatment of 3,4,5-trimethoxytoluene **23** with hydrogen peroxide (H_2O_2) under metal-free conditions, followed by radical alkylation with 10-hydroxydecanoic acid **25** under Minisci oxidative conditions to afford the target **26** in good yields (60%, based on coenzyme Q_0). This radical alkylation was the first example for a hydroxy acid as coupling partner to perform the direct C5-alkylation of coenzyme Q_0 to form coenzyme Q analogues.[45] By mean of decarboxylative alkylation process, idebenone **28** was also produced from coenzyme Q_0 with 11-hydroxyundecanoic acid **27**.[46] The natural product primin and its isomer can be formed by this radical alkylation process as well (Scheme 9).[47]



Scheme 9. Formation of synthetic analog Coenzyme Q_{10}.

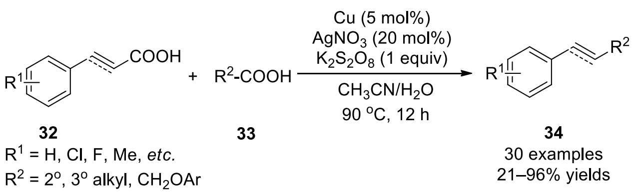
In 2010, Yao, Hu and Zhang *et al.* developed a three-step, one-pot tandem radical nucleophilic alkylation/cyclization/aromatization approach to assemble pentacyclic complex carbazoles **31**, which were previously synthesized by multi-step organic synthesis.[48] Using AgOAc/$(NH_4)_2SO_8$ oxidant conditions, a series of naphtho[2,3-*a*]carbazole-5,13-diones **31** were synthesized in 52–72% overall yields from aryl-fused bromobenzoquinones **29** and indol-3-ylpropanoic acids **30**. This new approach provided a significant improvement over the previously reported methods (Diels–Alder reaction or Suzuki–Miyaura coupling) and would greatly facilitate analog library construction of pentacyclic complex carbazoles and benefit further biological evaluation of these compounds (Scheme 10).[49] In term of this process, an efficient three-step approach was developed to assemble indole- or benzofuran-fused benzocarbazole-1,4-diones in moderate overall yields.[50]



Scheme 10. Tandem radical reactions to access pentacyclic complex carbazoles.

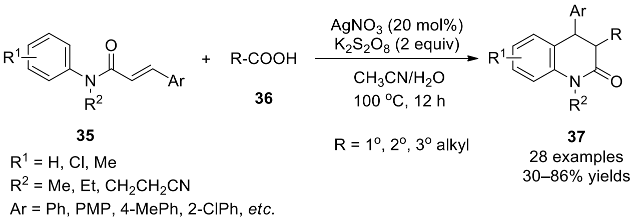
Moreover, an intramolecular radical addition of a quinone core was reported through a silver(I)-catalyzed oxidative decarboxylation process, which offered a key step to access the biologically active natural product Bauhinoxepin J in a simple way.[51]

A novel double decarboxylative cross-coupling catalyzed by copper and silver(I) salt was reported by Mai, Sun and co-workers, which provided a practical approach for the flexible synthesis of alkenes and alkynes **34** from the readily available cinnamic acids or phenylpropiolic acid **32** and aliphatic acids **33**. The reaction was proposed to initially start by alkyl radical generated from aliphatic acids **33** inserted to carbon-carbon multiple bonds catalyzed by Ag(I) (Scheme 11).[52]



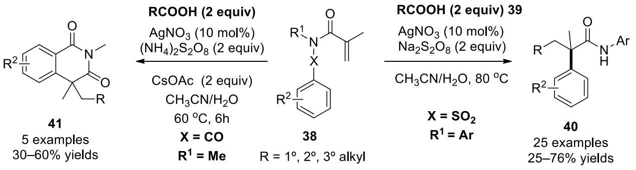
Scheme 11. Cu/Ag-catalyzed double decarboxylative cross-coupling of cinnamic acids or phenylpropiolic acid.

In 2014, Mai and Xiao *et al.* developed a novel tandem *trans*-selective 6-*endo* radical cyclization of *N*-arylcinnamamides **35**, affording various 3-alkyl substituted 3,4-disubstituted dihydroquinolin-2(1*H*)-ones **37** in moderate yields. Various primary, secondary, and tertiary aliphatic carboxylic acids **36** furnished alkyl radicals under the silver(I)/$S_2O_8^{2-}$ conditions. The stabilization effect of the aryl group at the β-position of the acrylamides **35**, plausibly resulted in the formation of a six-membered ring (Scheme 12).[53]



Scheme 12. Tandem radical cyclization of *N*-arylcinnamamides with aliphatic carboxylic acids.

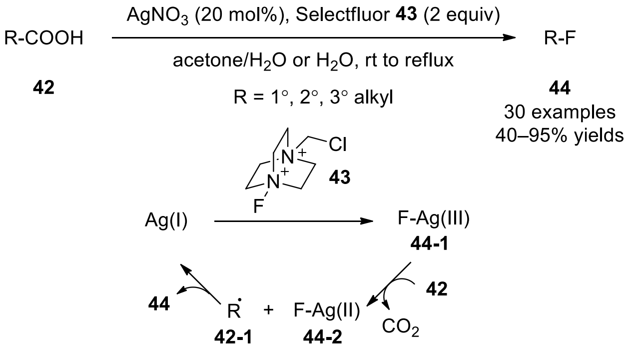
The methodology that silver-catalyzed decarboxylative addition/aryl migration/desulfonylation of *N*-aryl-*N*-(phenylsulfonyl)-methacrylamides established by Nevado group could be accomplished with simple aliphatic carboxylic acids **39**, which furnished α-all-carbon quaternary stereocenters amides **40** in 25–76% yields. While studying the substituent groups of amide substrates, the Liang group found 2-(*p*-tolyloxy)acetic acids (X = CO) delivered the alkylated isoquinolinediones **41** under the oxidative conditions. Diverse primary, secondary, and tertiary carboxylic acids were compatible for the two processes (Scheme 13).[54]



Scheme 13. Decarboxylative addition/cyclization of activated alkenes with aliphatic carboxylic acids.

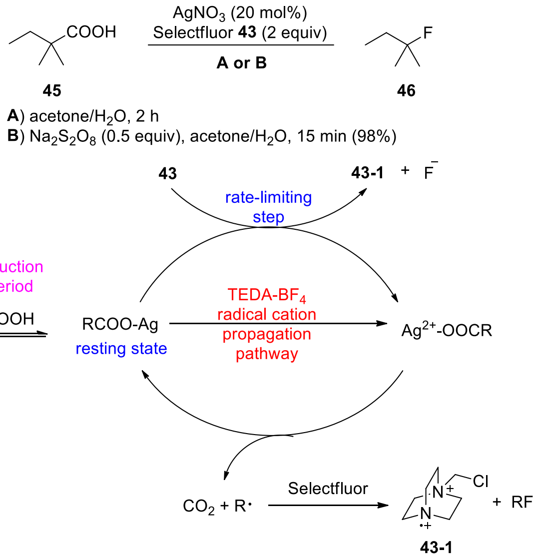
Although fluorinated compounds have found widespread applications in the chemical and materials industries, general and site-specific $C(sp^3)$–F bond formations are still a challenging task.[55] In comparison with nucleophilic or electrophilic fluorination, radical fluorination[55-56] is rarely explored in which the synthetic potential as well as the detailed mechanisms remain unclear. In 2012, Li *et al.* developed a novel, general, and chemoselective decarboxylative fluorination of aliphatic carboxylic acids **42** that used Selectfluor reagent (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)

43 as the fluorine source/oxidant and $AgNO_3$ as the catalyst in aqueous solution, providing the corresponding alkyl fluorides in moderate to excellent yields. From the experiment results, the reactivity of carboxylic acids **42** decreases in the order of tertiary > secondary > primary >> aromatic. Unfortunately, aromatic acids were observed ineffective in the reaction. Silver(I) salts, involving $AgNO_3$, AgOAc, and AgOTf exhibited almost the same catalytic behavior. Water also proved to be essential. Moreover, substrates could be performed in pure water owing to better solubility in water. A presumable mechanism was proposed involving a Ag(III)-mediated single electron transfer and a subsequent fluorine atom transfer. As shown in Scheme 14, a trivalent silver species Ag(III)−F intermediate **44-1** was generated by oxidation insertion of Ag(I) with Selectfluor reagent **43**. The Ag(III)−F **44-1** then underwent SET with a carboxylate anion to give the divalent silver intermediate Ag(II)−F **44-2** and a carboxyl radical. The fast decarboxylation of the carboxyl radical provided the corresponding alkyl radical **42-1** which then abstracted the fluorine atom of the adjacent Ag(II)−F **44-2** to afford the alkyl fluoride product **44** and regenerate the Ag(I) catalyst.[24i]



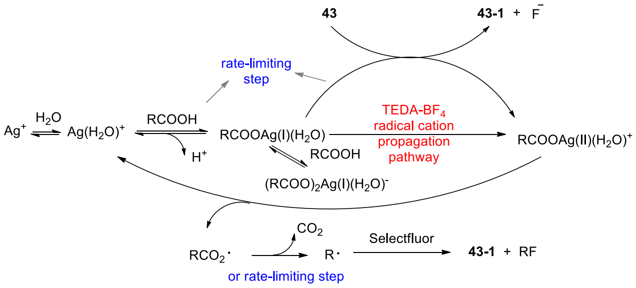
Scheme 14. Decarboxylative fluorination of aliphatic carboxylic acids.

By spectroscopic and kinetic studies, the role of the individual reaction components in decarboxylative fluorination was revealed by Flowers, II *et al.* Since Ag(III) complexes are unstable and typically generated under a specific conditions, requiring ligands, or under basic conditions, it is unlikely that Ag(III) is presented under this current oxidative conditions. A plausible pathway that Ag(I) is oxidized to Ag(II) by Selectfluor **43** generating the key TEDA-BF_4 radical cation **43-1** was proposed in the rate-limiting step of the reaction. Selectfluor oxidizes the Ag(I)-carboxylate forming Ag(II) intermediate that oxidizes the carboxylate ligand to produce an alkyl radical. Then, the alkyl radical performs fluorine abstraction from Selectfluor leading to the expected product **46**. Water is critical for solubilizing Selectfluor and ligates to Ag(I) to solvate the metal center. Furthermore, an extra $Na_2S_2O_8$ speeds up the reaction, and the use of $AgNO_3$/$Na_2S_2O_8$/NFSI instead of $AgNO_3$/Selectfluor also allowed an efficient process, which was in line with a Ag(II) intermediate pathway (Scheme 15).[24k]



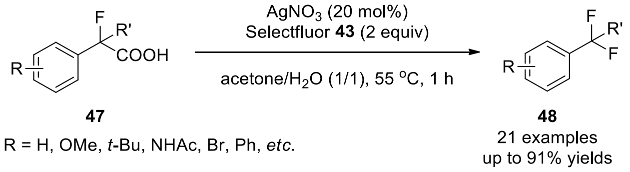
Scheme 15. Mechanism of the decarboxylative fluorination.

Recently, with density functional theory (DFT), Zhang reported a systematic mechanistic study for the Ag(I)-catalyzed decarboxylative fluorination reaction. It was proposed that the transformation involved five steps, namely the formation of the H_2O-ligated Ag-carboxylate, oxidation, homolytic cleavage of the O–Ag(II) bond, decarboxylation (loss of CO_2) and fluorine abstraction. At this point, the formation of the H_2O-ligated Ag-carboxylate rather than Ag(II)–F or Ag(III)–F intermediate that initiates the decarboxylative fluorination, which might be reasoned the role of H_2O. Two possibilities were suggested as the rate-determining step: (i) the formation of the H_2O-ligated Ag-carboxylate and its oxidation by Selectfluor **43**; (ii) decarboxylation (loss of CO_2). The structure of the carboxylic acid substrate highly influenced the efficiency of the decarboxylation procedure (Scheme 16).[57]



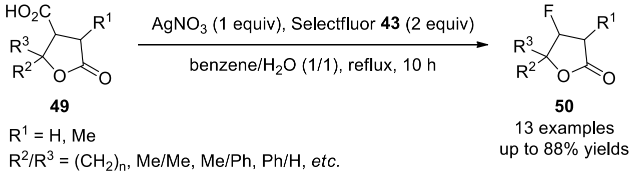
Scheme 16. Mechanistic insights of the decarboxylative fluorination.

More commonly, halogen exchanges of ArCF$_2$X (X = bromide, chloride, and fluoride) with [^{18}F]fluoride offered an entry to generate ArCF$_2$[^{18}F], whereas these reactions were limited with harsh reaction conditions, narrow substrate scope and low specific activity, *etc.* In 2013, Gouverneur *et al.* employed the silver(I)-catalyzed decarboxylative fluorination of α,α-difluoro and α-fluoroarylacetic acids **47**, providing tri- and difluoromethylarenes **48** that were often generated relying on trifluoromethylating reagents *via* classical methods. This novel protocol tolerated various functional groups and succeccfully furnished [^{18}F]labeled tri- and difluoromethylarenes by using [^{18}F]Selectfluor bis-(triflate). Remarkably, [^{18}F]Selectfluor bis-(triflate) displayed better performance than [^{18}F]F$_2$, even yielding those could not be obtained with [^{18}F]F$_2$ (Scheme 17)._ENREF_96[58]



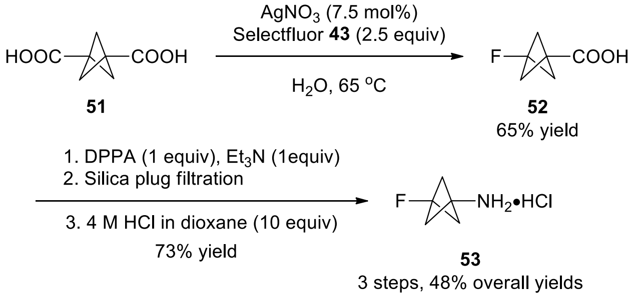
Scheme 17. Decarboxylative fluorination to α,α-difluoro and α-fluoroarylacetic acids.

Soorukram and co-workers developed a silver(I)-mediated decarboxylative fluorination of paraconic acids **49** using Selectfluor as a fluorine source, leading to the corresponding β-fluorinated γ-butyrolactones **50** in moderate to good yields. This approach served as a direct and site-selective strategy for introducting a fluorine atom at the β-position of γ-butyrolactone cores that are basic structural motifs in natural products as well as used as building blocks in organic synthesis. Unsymmetrical γ-substituted paraconic acids and α-methylated paraconic acid also allowed the corresponding β-fluorinated γ-butyrolactones in a mixture of diastereomers in which the fluorine atom was located on the opposite side to the larger substituent on the γ position (Scheme 18).[59] This general and practical decarboxylative fluorination was used for the synthesis of fluticasone propionate. The key decarboxylative fluorination was advocated rather than the usage of toxic, extremely costly, and pollutive BrCH$_2$F.[60]



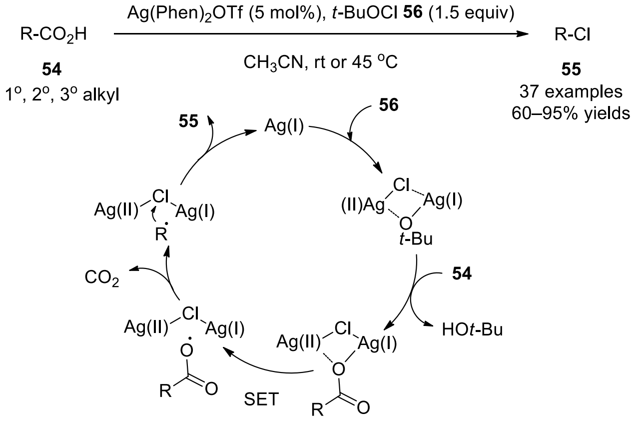
Scheme 18. Formation of β-fluorinated γ-butyrolactones.

Recently, Adsool *et al.* employed the decarboxylative fluorination for the synthesis of bioactive compound 3-fluorobicyclo[1.1.1]pentan-1-amine **53**, in which the formation of fluoro analogue of bicyclo[1.1.1]pentane (BCP) was never reported. Starting from available material bis acid **51**, intermediate **52** was delivered and furnished 3-fluorobicyclo[1.1.1]pentan-1-amine **53** in three steps (Scheme 19).[61]



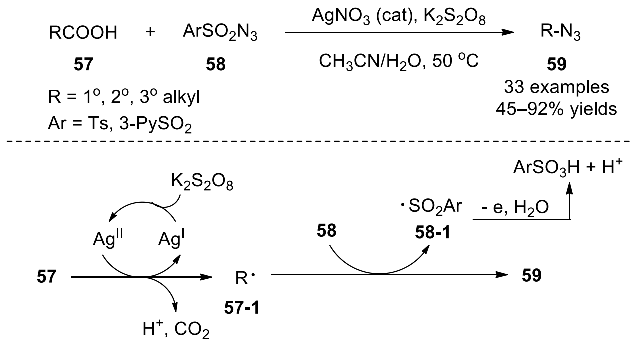
Scheme 19. Three-step synthesis of 3-fluorobicyclo[1.1.1]pentan-1-amin.

Hunsdiecker reaction (decarboxylative halogenation) of carboxylic acids is one of the fundamental functional group transformations in organic chemistry. However, the conventional methods of Hunsdiecker reaction suffer from the use of highly toxic reagents, harsh reaction conditions, or limited scope of application. In addition, none is catalytic for aliphatic carboxylic acids. In 2012, Li *et al.* reported the first catalytic Hunsdiecker reaction of aliphatic carboxylic acids **54** which performed with silver triflate−bis(1,10-phenanthroline) complex [Ag(Phen)$_2$OTf] as the catalyst and *tert*-butyl hypochlorite (*t*-BuOCl) **56** as the chlorine source. Various carboxylic acids **54** with wide range of substrate scope and excellent functional-group compatibility were acceptable and furnished the corresponding chlorodecarboxylated products **55** in excellent yields under mild conditions. It was revealed that the reactivities of carboxylic acids decrease in the order of benzyl ≈ tertiary > secondary > primary >> aromatic. As a result, aromatic acids were unreacted under the optimal conditions. In comparision with I$_2$, Br$_2$, or *N*-iodo-, *N*-bromo-, or *N*-chlorosuccinimide, only the stable and easily available *t*-BuOCl **56** could function as the chlorine source. Learning from the silver-catalyzed decarboxylative fluorination, a mechanism that single electron transfer followed by chlorine atom transfer was plausibly involved (Scheme 20).[62]



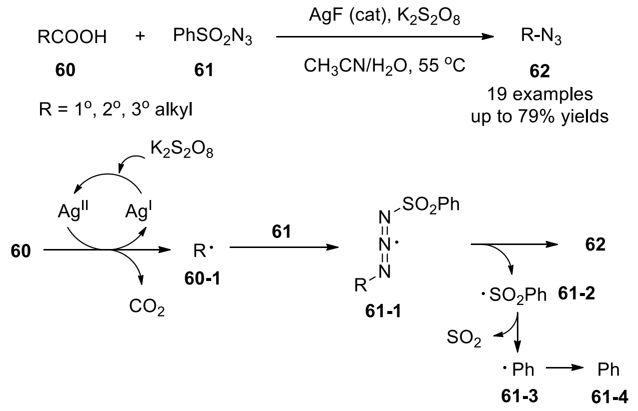
Scheme 20. Silver-catalyzed Hunsdiecker reaction of aliphatic carboxylic acids.

Li group recommended a convenient and efficient approach for the assembly of wide range of organic azides **59** by silver-catalyzed decarboxylative azidation of aliphatic carboxylic acids **57**. With $AgNO_3/K_2S_2O_8$ system, the reactions of carboxylic acids **57** with tosyl azide or pyridine-3-sulfonyl azide **58** afforded the corresponding alkyl azides **59** efficiently. Among various azide reagents screened, pyridine-3-sulfonyl azide was proved to be the most efficent in most cases, and tosyl azide also received an excellent yield. In the case of primary acids, an increased temperature (80°C) was suggested. Mechanistic studies were supported a radical process. Initially, the alkyl radical **57-1** formed by decarboxylation of carboxylic acids **57** subsequently attacked to a sulfonyl azide **58**, affording the alkyl azide **59** along with the generation of a sulfonyl radical **58-1**. Further oxidation of the sulfonyl radical **58-1** led to the formation of arenesulfonic acid. With azidodecarboxylation as the key step, the asymmetric synthesis of natural molecules (−)-indolizidine 209D and 167B were carried out and delivered in good yields (Scheme 21).[63]



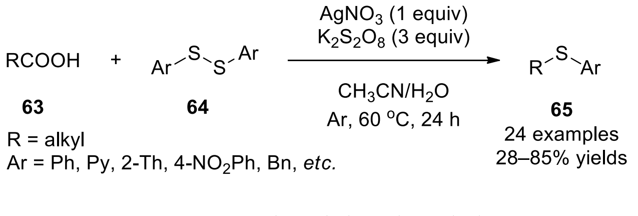
Scheme 21. $AgNO_3$-catalyzed decarboxylative azidation of aliphatic carboxylic acids.

A similar report was developed by Jiao and co-workers individually. Aliphatic carboxylic acids **60** furnished diverse tertiary, secondary, and primary organic azides **62** with benzenesulfonyl azide ($PhSO_2N_3$) **61**, in the presence of AgF as catalyst and $K_2S_2O_8$ as oxidant. Although $AgNO_3$ exhibits similar catalytic behavior, AgF was selected because of the higher stability under light. Through the EPR experiment and DFT calculations, a mechanism involving a generation of alkyl radical **60-1**, a SET process (in decarboxylation) and a stepwise SH2 (two homolytic substitution) process were revealed, showing the intermediacy of *N*-radical species **61-1** to afford the azide product **62**. The sulfonyl radical **61-2** furnished aryl radical **61-3** with releasing a molecular of SO_2. The aryl radical **61-3** was quenched by either *H*-abstraction or a reduction−protonation sequence delivering the corresponding aromatic compound **61-4** (confirmed by GC-MS analysis) (Scheme 22).[64]



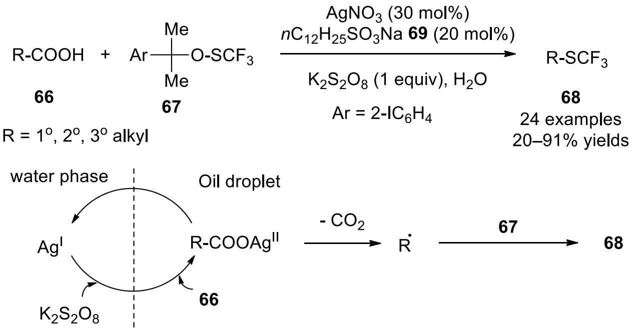
Scheme 22. AgF-catalyzed decarboxylative azidation of aliphatic carboxylic acids.

Recent progress has been made in C−S cross-couplings catalyzed by Pd, Cu, and Ni, but many of these approaches suffer from harsh reaction conditions, limited substrate scope, and catalyst poisoning by the sulfide. In 2014, Feng and Xu *et al.* developed a silver-promoted decarboxylative C−S cross-coupling reaction to access alkyl aryl sulfides **65** in moderate to good yields with aliphatic carboxylic acids **63**. It offered an efficient route to construct C−S bonds, using $K_2S_2O_8$ as the oxidant and diaryl disulfides **64** as the sulfur source. Electron-rich/poor aryl disulfides and heteroaryl groups (*i.e.* thienyl, pyridyl) were tolerated, and the reaction could run in a gram-scale procedure (Scheme 23).[65]



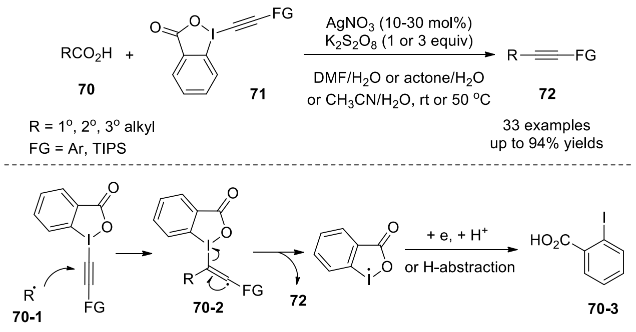
Scheme 23. $AgNO_3$-catalyzed decarboxylative C−S cross-coupling reaction.

Electrophilic Trifluoromethylthiolating Reagent. In 2014, Shen and co-workers successfully developed a silver-catalyzed decarboxylative trifluoromethylthiolation of secondary and tertiary alkyl carboxylic acids **66** under mild conditions, which provided a general, site-specific, and efficient route to construct C(sp^3)–SCF_3 bonds. A wide range of alkyl carboxylic acids **66** with different functional groups, such as chloride, bromide, esters, and electron-rich arenes, underwent the efficient cross-coupling reaction with the electrophilic trifluoromethylthiolating reagent **67** affording the corresponding products **68** in moderate to excellent yields. A biphasic system could physically separate the alkyltrifluoromethylthioether **68** from the oxidant. The aqueous emulsion, which was formed by the addition of sodium dodecyl sulfate (SDS) **69** to water, was crucial to accelerate the transformation. The employment of water as the solvent has extraordinary solvent, environmental, economic effects. Mechanistic experiments suggested a free alkyl radical process, which was generated from the silver-catalyzed decarboxylation in the "oil-in-water" droplets (Scheme 24)._ENREF_57[66]



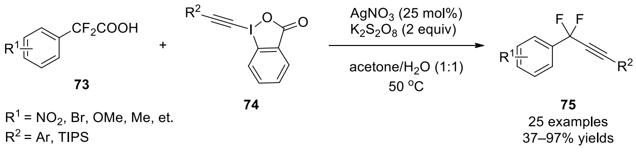
Scheme 24. Decarboxylative trifluoromethylthiolation of aliphatic carboxylic acids.

Compared with nucleophilic and electrophilic alkynylations, the radical version of alkynylations has received substantially less attention. Furthermore, the reported radical methods rely heavily on the use of alkynylsulfones as alkynylating agents. In 2012, Li and co-workers realized the chemo- and stereoselective radical decarboxylative alkynylation of aliphatic carboxylic acids **70** with commercially available ethynyl benziodoxolones (TIPS- and aryl-EBXs)[67] **71** under silver(I)/persulfate conditions in an aqueous solution. This C(sp^3)–C(sp) cross-coupling tolerated a broad spectrum of aliphatic carboxylic acids **70**, including primary/secondary/tertiary with good functional-group compatibility. Mechanistically, the corresponding alkyl radical **70-1** generated from carboxylate by oxidative decarboxylation added to the triple bond of EBXs **71** to form the adduct radical **70-2**, which then converted to the final product **72** along with the release of 2-iodobenzoic acid **70-3** (Scheme 25).[24h]



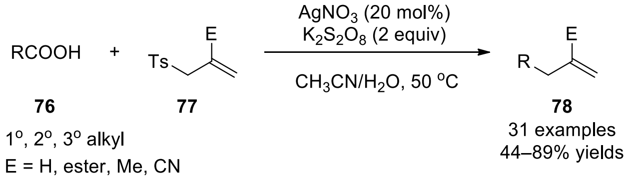
Scheme 25. Decarboxylative alkynylation of aliphatic carboxylic acids.

Further, this silver(I)-catalyzed decarboxylative alkynylation was extended to a variety of α,α-difluoroarylacetic acids **73** with ethynyl benziodoxolones **74**, affording the corresponding alkynes **75** with good functional- group tolerance, and in moderate to good yields. This method offered a simple entry to synthesize difluorinated compounds (Scheme 26).[68]



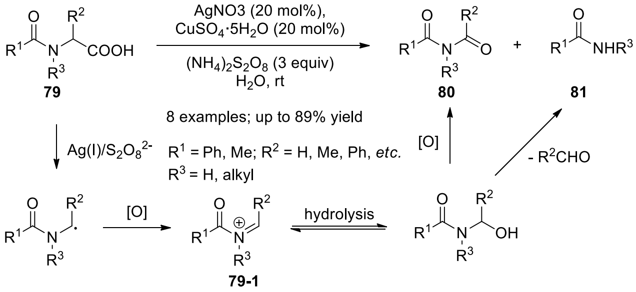
Scheme 26. Decarboxylative alkynylation of α,α-difluoroarylacetic acids.

Very recently, Li and colleagues developed the operational simple decarboxylative allylation of aliphatic carboxylic acids **76** with alkenes **77** under silver(I) catalysis in aqueous solution. An array of allyl compounds **78** with a broad substrate scope and good functional-group compatibility were obtained in 44–89% yields. The initially formed carbon radical underwent substitution step to release the Ts• species which subsequently evolved a 4-methylbenzenesulfonic acid (Scheme 27).[69]



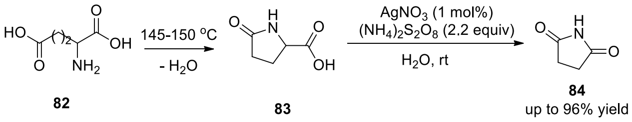
Scheme 27. Decarboxylative allylation of aliphatic carboxylic acids.

The transformation of *N*-acyl amino acids **79** into imides **80** was discussed by Huang *et al.*, participating in oxidative decarboxylation under $Ag^+/Cu^{2+}/S_2O_8^{2-}$ conditions at room temperature in water. *N*-benzoylvaline and *N*-benzoylleucine were compatible, which presumably involved oxidative cleavage of an enamide intermediate **79-1**. Although *N*-aroylglycine ($R^2 = R^3 = H$) delivered imide **80** in the presence of $Ag^+/S_2O_8^{2-}$ at 60°C, other amino acids, *i.e., N*-benzoylalanine gave benzamide **81** instead under the reaction conditions (Scheme 28).[70]



Scheme 28. Oxidative decarboxylation of *N*-acyl amino acids.

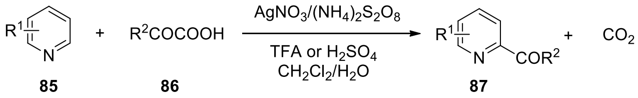
Conventionally, succinic acid and nitrogen sources, including ammonia and urea, are required for succinimide synthesis. Fu *et al.* reported a sustainable succinimide preparation method without the use of external nitrogen. Using silver as the catalyst, they achieved the conversion from a biobased chemical (glumatic acid) **82** to succinimide **84** in excellent yields under mild conditions. The reaction took place in a two-step procedure involving a dehydration step to pyroglutamic acid **83** followed by an oxidative decarboxylation in water. (Scheme 29).[71]



Scheme 29. Formation of succinimide *via* two-step procedure.

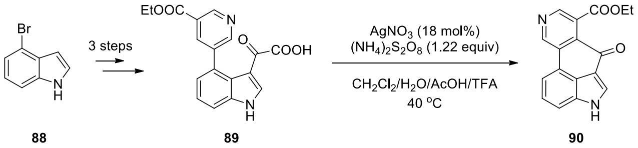
2.1.2 Acyl Radicals

Acyl radicals generated by silver-catalyzed decarboxylation of α-keto acids **86** underwent the selective homolytic acylation to access 2-acylted products **87** with pyridine and pyrazine derivatives **85** (Scheme 30).[2f, 72]_ENREF_66 _ENREF_66Compared with the previously developed source of acyl radicals by hydrogen abstraction from aldehydes, this procedure is more effective in monoacylation despite multiple positions of high nucleophilic reactivity are available in the heterocyclic ring. The monoacylation can be achieved owing to benefit from difference in basicity and lipophilicity between the starting base and the monoacylation products in a two-phase system.[73] Besides alkyl and aryl carbonyl radicals, methoxy- and ethoxycarbonyl radicals were also explored and compatible.[74] In addition, 2-indolylacyl radicals, generated from the corresponding α-keto acids under silver(I)/persulfate conditions, opened new synthetic possibilities for the preparation of 2-indolyl ketones, which are usually formed by electrophilic acylation of the indole ring.[75] An implementation of trialkylpyrazines bearing alkyl groups at C-2 and C-5, occurred the Minisci radical process with alkyl α-keto acids, thus achieved the expected acylated products in moderate to excellent yields. Several compounds obtained from trialkylpyrazines prove to be active as components of pheromones in ants.[76]



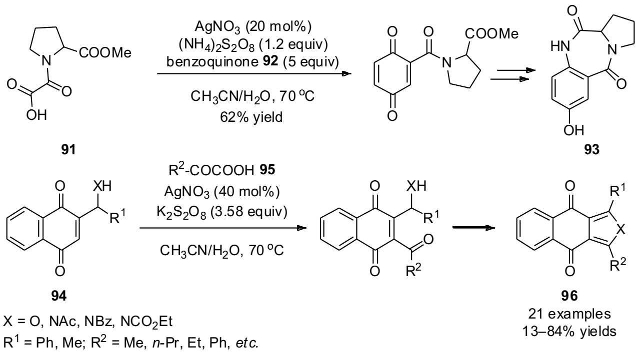
Scheme 30. Silver-catalyzed decarboxylative acylation with α-oxocarboxylic acids.

The Minisci reaction was used for the construction of polyaromatic heterocyles. Starting from commercially available precursors **88**, tetracycle (8-azaergoline) **90** was obtained in only four steps. The straightforward intramolecular tandem decarboxylation-cyclization reaction of precursor **89** was demonstrated (Scheme 31).[77]



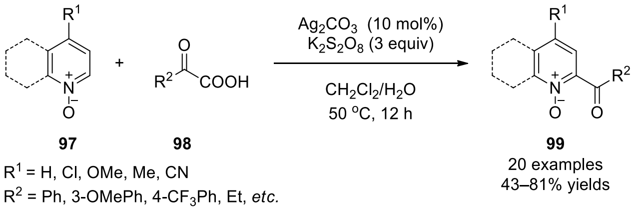
Scheme 31. Formation of tetracycle *via* four steps.

The acylation of 1,4-quinones with α-keto acids has been developed and utilized for the formation of polyaromatic heterocyles. The preparation of tricyclic compound **93** was initially started from the oxidative decarboxylation of the amide acid **91** with benzoquinone **92**. This method to access acylhydroquinones was efficient and environmentally benign.[78] Moreover, 2-(1-hydroxyalkyl)-1,4-naphthoquinones and 2-(1-amidoalkyl)-1,4-naphthoquinones **94** underwent radical addition with α-keto acids **95** in the presence of silver(I) nitrate and persulfate in CH_3CN/H_2O at 70°C, thus led to the formation of naphtho[2,3-*c*]furan-4,9-diones and benzo[f]isoindole-4,9-diones **96** in one-pot process, respectively (Scheme 32).[79]



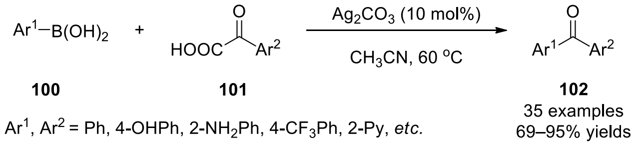
Scheme 32. Silver-mediated acylation of 1,4-quinones with α-keto acids.

Unsymmetrical heteroaryl aryl ketone is an important structural unit found in biologically active and medicinally relevant compounds. The conventional procedure to synthesize C2-acylated pyridine *N*-oxide[80] starting from *ortho*-acylated pyridine suffers from the competitive Baeyer–Villiger oxidation involving the acyl group. In 2014, Muthusubramanian group solved the issue and offered an applicable acylation reaction of pyridine *N*-oxides **97** with α-oxocarboxylic acids **98** in presence of silver catalyst and persulphate. As a result, acylated heteroarene *N*-oxides **99**, which are difficult to access by the conventional methods, can be synthesized successfully in high yields under mild conditions (Scheme 33).[81]



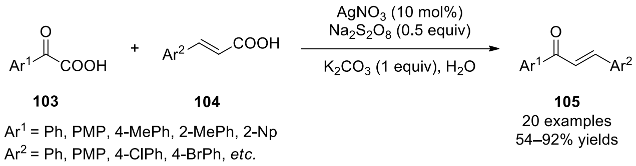
Scheme 33. Silver-catalyzed decarboxylative acylation of pyridine *N*-oxides.

Recently, Qi *et al.* provided a direct and scalable route for the synthesis of unsymmetrical diaryl ketones **102** under silver(I) catalysis. Various arylboronic acid **100** with good functional-group compatibility, even free amine or free hydroxyl groups were applicable for this cross-coupling. A free acyl radical was proposed to be generated from α-oxocarboxylic acid **101** during the course (Scheme 34).[82]



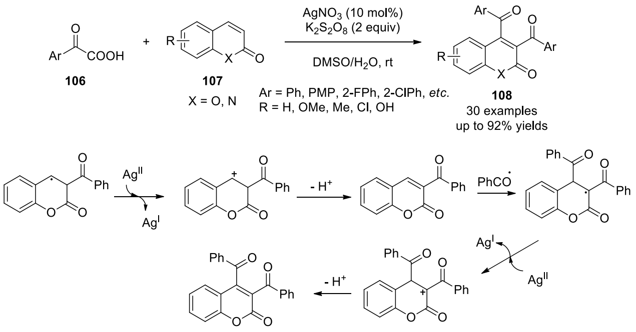
Scheme 34. Decarboxylative acylation of arylglyoxylic acids with arylboronic acids.

Recently, Yang and Wang *et al.* developed the first example of silver-catalyzed doubled carboxylative reaction of α-keto acids **103** and cinnamic acids **104**. A series of chalcones **105** with good functional-group tolerance could be efficiently obtained in 54–92% yields under the mild aqueous conditions. This facile and environment friendly approach offered a complement to the conventional synthetic methods for the production of chalcones. The reaction began as the generation of acyl radical, which subsequently added to the double bond of cinnamate anion (Scheme 35).[83]



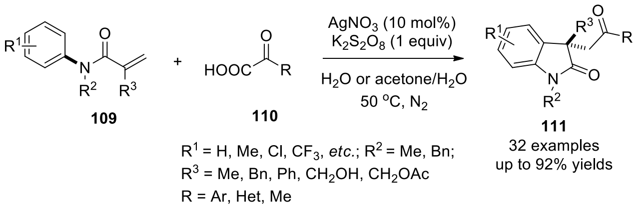
Scheme 35. Doubled carboxylative reaction of α-keto acids and cinnamic acids.

In comparison with the approach for synthesizing monosubstituted coumarins, the corresponding polysubstituted coumarins are less explored, especially using environmentally friendly and inexpensive reagents. A direct acylation of coumarins **107** for the synthesis of high functionalized 3,4-diacylcoumarins or 3-acylcoumarins **108** was reported by Duan *et al.*, through the silver-catalyzed decarboxylation cross-coupling reaction. The use of α-oxocarboxylic acids **106** with *o*-substituted at aryl group was contributed to access 3,4-diacylcoumarins with high levels of selectivity (Scheme 36).[84]_ENREF_127



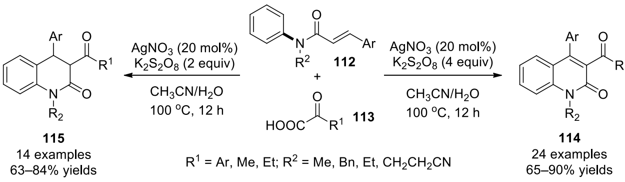
Scheme 36. Silver-catalyzed diacylation of coumarins.

Although remarkable results have been achieved, the metal-catalyzed intramolecular oxidative difunctionalization of alkenes *via* C–H bond cleavage remains underdeveloped. In 2013, Guo and Duan *et al.* described an efficient silver-catalyzed tandem radical cyclization reaction to furnish a large variety of functionalized oxindoles **111**. This method involved the first decarboxylative acylarylation of acrylamides **109** with readily available α-oxocarboxylic acids **110**. Acrylamides bearing different functional groups at the α-position, such as methyl, benzyl, phenyl, CH_2OH worked well, affording the products **111** in high yields. By radical-scavenging, intramolecular and intermolecular KIE experiments, a free-radical mechanism was proposed (Scheme 37).[85]



Scheme 37. Silver-catalyzed acylarylation to access oxindoles.

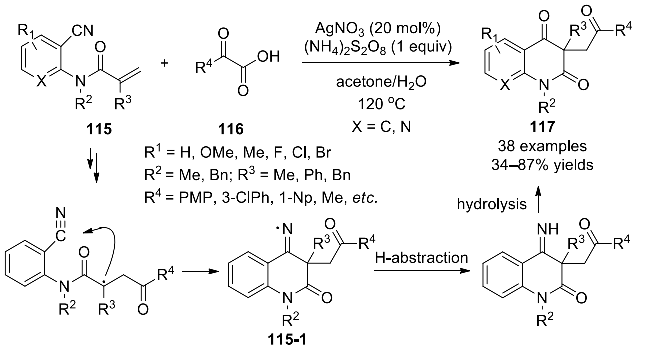
When cinnamamides **112** were used in lieu of acrylamides, Mai, Sun and Xiao *et al.* described a new tandem radical reaction of cinnamamides **112** with α-keto acids **113** under silver catalysis in aqueous solution at 100 °C. Two types of products could be controlled and obtained only by adjusting the amount of oxidant. This method provided a novel and straightforward route to substituted quinolin-2-ones **114** or 4-aryldihydroquinolin-2(1*H*)-ones **115** with good functional-group tolerance (Scheme 38).[86]



Scheme 38. Silver-catalyzed acylarylation of cinnamamides.

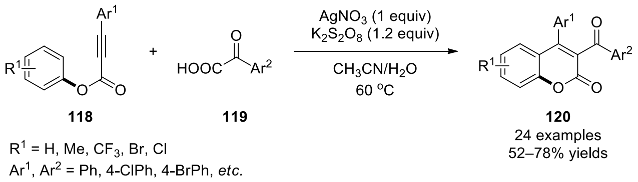
Simultaneously, the Duan research group reported a similar acylarylation approach to 3-acyl-4-aryldihydroquinolin-2(1*H*)-ones **115** at room temperature. This acylarylation reaction, by contrast, proceeded with lower catalyst loading (2 mol% Ag_2CO_3), milder reaction conditions (1 equiv. oxidant and at room temperature), whereas within longer reaction time.[87]

Very recently, the silver(I)-catalyzed oxidative radical tandem reaction was applized to *o*-cyanoarylacrylamides **115**. A set of carbonyl-containing quinoline-2,4(1*H*,3*H*)-diones **117** with wide substrate scope and good functional-group compatibility were obtained. The *in situ* generated acyl radical from α-keto acids **116** was reasoned to undergo addition to C=C double bond moiety and an intramolecular addition to the C=N functional group thus forming the imine radical **115-1**. The imine radical **115-1** underwent *H*-abstraction and hydrolysis process to produce the final product **117**. Additionally, a similar oxidative radical cascade of aldehydes with *o*-cyanoarylacrylamides was also developed in which acyl radical was obtained with $K_2S_2O_8$ as oxidant under silver-free conditions (Scheme 39).[88]



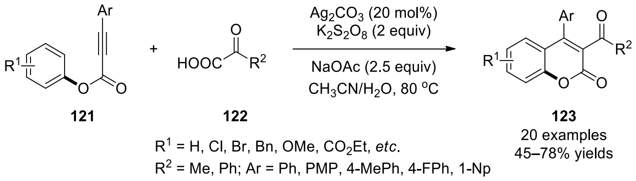
Scheme 39. Oxidative radical addition/cyclization cascade of *o*-cyanoarylacrylamides with α-keto acids.

Similarly, alkynoates **118** were able to allow a silver-mediated tandem radical cyclization with α-keto acids **119**, affording diverse potentially biological coumarin frameworks **120** in moderate to good yields. This practical and convenient strategy for the synthesis of coumarin derivatives **120** showed potential applications in synthetic and pharmaceutical chemistry. The transformation conducted *via* a radical acylation and 6-*endo* cyclization step in sequence (Scheme 40).[89]



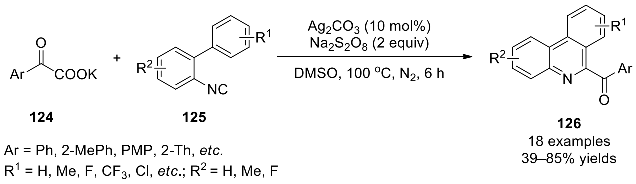
Scheme 40. $AgNO_3$-mediated radical cyclization of alkynoates and α-keto acids.

In comparison, a different report for the generation of 3-acylcoumarins **123** were developed by Ding and Qiu *et al.*, which featured in the involvement of a 5-*exo* cyclization and an ester migration. This protocol represented the first example for the preparation of coumarin derivatives from alkynoates **121** with α-keto acids **122** *via* radical 5-*exo* annulation and ester migration (Scheme 41).[90]



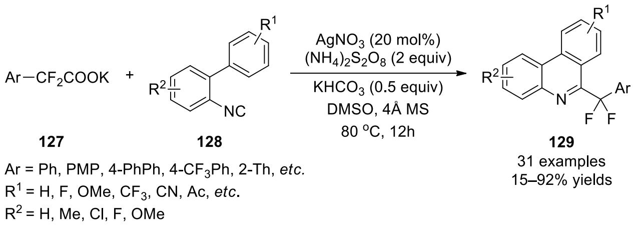
Scheme 41. Formation of 3-acylcoumarins from alkynoates.

Isocyanides can also act as radical acceptors, forming imidoyl radicals. Lei *et al.* demonstrated a novel approach for the synthesis of 6-acyl phenanthridines **126** by the silver-catalyzed oxidative radical decarboxylation–cyclization with isocyanides **125**. This reaction provided a complementary method to realize C1 insertion *via* a radical process, which displayed potential application in pharmaceutical synthesis and materials science. A variety of biarylisonitriles **125** and α-oxocarboxylates **124** with good functional-group tolerance was compatible, whereas the use of $CH_3C(O)CO_2Na$ furnished 6-formyl phenanthridine with low yield (37% yield). The electron paramagnetic resonance (EPR) experiments revealed that the mechanism involved a Ag(I)–Ag(II) catalytic circle *via* a SET process. The oxidative radical decarboxylation of isocyanide insertion was realized for the first time (Scheme 42).[91]



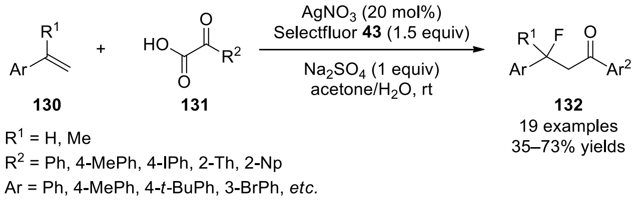
Scheme 42. Oxidative radical decarboxylation-cyclization of α-oxocarboxylates and isocyanides.

Though the development of decarboxylative trifluoromethylation has caught great attention during the past decades, decarboxylative *gem*-difluoromethylenation protocol for direct introduction of a difluoromethyl moiety into molecule has been scarcely explored, owing to the insufficiency of the difluoromethyl source and the instability of the difluoromethylating reagents. Recently, Wan and Hao *et el.* demonstrated the simple and practical protocol for the generation of aryl difluoroemthylene radicals through the Ag(I)-catalyzed oxidative decarboxylation–cyclization of (hetero)aryl difluoroacetates **127**. This oxidative decarboxylative *gem*-difluoromethylenation offered a novel and convenient synthetic strategy for constructing *gem*-difluoromethylenated phenanthridine **129** from biarylisonitriles **128**, which highlighted in the stability, easy availability of difluoroacteates and catalyst, the mild conditions and the wide functional-group compatibility. However, the aryl difluoroacetates bearing electron-withdrawing substituents, such as trifluoromethyl, cyano, afforded the *gem*-difluoroalkylenated phenanthridines with much lower yields (Scheme 43).[92]



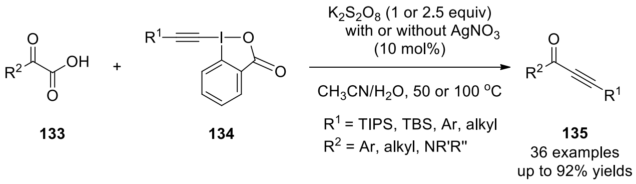
Scheme 43. Silver-catalyzed decarboxylation-cyclization of difluoroacetates with biarylisonitriles.

Learning from the decarboxylative fluorination reactions of carboxylic acids and anhydrides to construct $C(sp^3)$–F bonds, an intermolecular tandem decarboxylative fluorination was first developed by Duan *et al.* A novel, facile and selective decarboxylative acylfluorination between activated aryl-substituted olefins **130** and α-oxocarboxylic acids **131** was unravelled, delivering β-fluorinated 3-aryl ketones **132** under silver(I)/Selectfluor conditions. However, the studies of aliphatic terminal alkenes displayed poor results under the reaction conditions. A set of α-oxocarboxylic acids **131** with electron-rich/poor functional group afforded the corresponding products in moderate to high yields, whereas steric hindrance should be considered as *ortho*-methyl phenylglyoxylic acid and α-naphthyloxoacetic acid gave trace products. Na_2SO_4 as an additive improved the yields enormously. Learning from Li's report, a plausible mechanism involving a generation of acyl radical by Ag(III)-F intermediate oxidation and fluorine transfer was proposed (Scheme 44).[93]



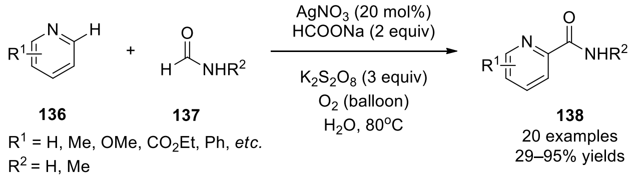
Scheme 44. Silver-catalyzed decarboxylative acylfluorination of styrenes.

On the basis of the Li's report for radical alkynylation,[24h] Duan *et al.* further extended the reaction scope to a series of α-keto acids **133**, providing a facile and efficient approach for the generation of functionalized ynones **135** in moderate to excellent yields, which serve as important building blocks in organic chemistry. Both acid components **133** and alkynyliodonium reagents **134** demonstrated wide substrate scopes and high functional-group tolerance. Moreover, the extension to oxamic acids and DMF as the radical source, allowed propiolamides in moderate yields in the presence of 10 mol% $AgNO_3$ as a catalyst at an increasing temperature (Scheme 45).[94]



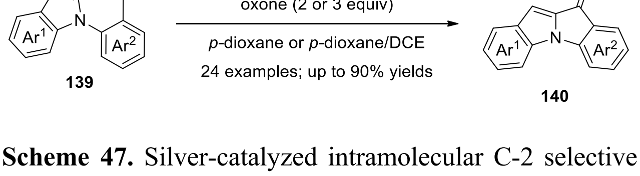
Scheme 45. Decarboxylative alkynylation of α-keto acids and oxamic acids.

Besides the α-keto acids, amides and aldehydes can provide acyl radicals as well. The carbamoyl radicals generated *in situ* by oxidation of monoamides of oxalic acids were applized for the synthesis of isocyanates, and the intermolecular and intramolecular substitution of (hetero)arenes.[95] Obviously, formamides offer a direct route to provide carbamoyl radicals. A simple and ligand-free CDC reaction of pyridines **136** with unprotected formamide **137** was reported for the first time, affording primary pyridylcarboxamides **138** under silver catalysis in water as solvent. Although excess formamides are required, they can be readily recycled for the next reaction (Scheme 46).[96]



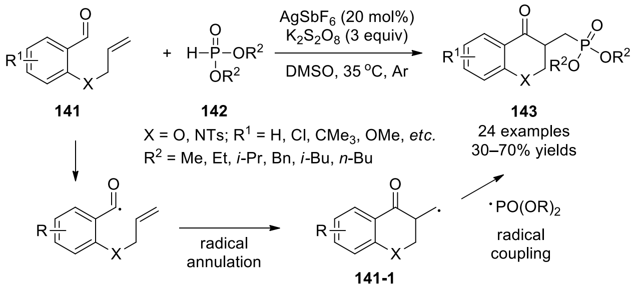
Scheme 46. Cross dehydrogenative carbamoylation of pyridines with formamides.

Very recently, Rao and co-workers developed the direct silver mesylate (AgOMs)-catalyzed direct intramolecular acylation of *N*-(2-formylaryl)indoles **139** for the assembly of indole-indolone framworks **140** of biologically and medicinally importance. This reaction provided an efficient route in delivering new drug-like compounds with indole-indolone cores (Scheme 47). A mechanism involving an acyl radical was proposed. [97]



Scheme 47. Silver-catalyzed intramolecular C-2 selective acylation of indoles with aldehydes.

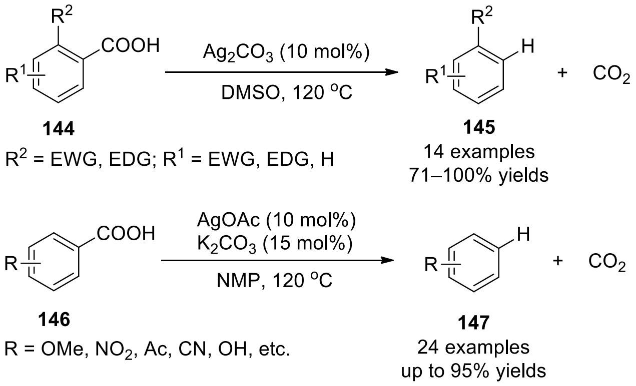
A novel and straightforward approach to synthesize phosphonate chroman-4-ones **143** was developed by the Li group, starting from 2-(allyloxy)arylaldehydes **141** with phosphites **142** under silver(I)/persulfate oxidative conditions. Preliminary mechanical investigations suggested a mechanism involving an acyl radical addition to the alkene moeity forming radical **141-1**, followed by a selective coupling with a phosphonyl radical, rather than the initiation of phosphonyl radical. Moreover, this strategy initiated by acyl radical could be also extended to azido and hydroxyl radicals, and furnished the corresponding functionalized chroman-4-ones successfully (Scheme 48).[98]



Scheme 48. Synthesis of functionalized chroman-4-ones.

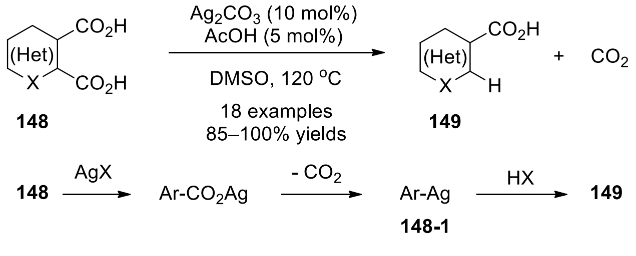
2.1.3 Aromatic Acids

Earlier reports on the photodecarboxylation of aromatic acids had limited practical applicability, involving harsh conditions and the use of stoichiometric amounts of copper or silver salts.[99] In 2009, the Larrosa group established a mild and simple strategy for the silver-catalyzed photodecarboxylation of *ortho*-substituted benzoic acids **144** that was compatible with a range of functionalities, such as halogens, NO_2, alkoxides, and even unprotected hydroxy and amino group.[100] The nature of the ortho substituents was revealed extremely important, and both strongly electron-donating and -withdrawing groups could be activated the acids. Furthermore, on the basis of these results, those Pd/Ag-based decarboxylative cross-coupling reactions may actually proceed *via* a silver-promoted decarboxylation, instead of the commonly-invoked palladium-catalyzed pathway. Meanwhile, Gooßen *et al.* also presented a similar, ligand-free photodecarboxylation reaction of aromatic acids **146** with 10 mol% AgOAc as the catalyst and 15 mol% K_2CO_3 as the base in NMP at 120 °C. Both of the procedures furnished the photodecarboxylated products **145** and **147** in excellent yields. The temperature used was much lower than the corresponding Cu-based methods (Scheme 49).[101].



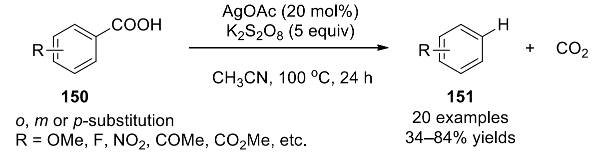
Scheme 49. Silver-catalyzed photodecarboxylation of benzoic acids.

A photodecarboxylation of various heteroaromatic carboxylic acids **148** was reported by the Larrosa research group in the presence of Ag_2CO_3 and acetic acid as catalysts in DMSO at 120°C. A range of heterocycles such as benzofurans, benzothiophenes, quinolones, isoquinolines, pyridines, furans, thiophenes, and thiazoles, afforded the corresponding decarboxylated heteroarenes **149** in excellent yields. The presence of a heteroatom α to the carboxylate was found to be essential for the decarboxylation, as exemplified by β-carboxylated benzofuran which was inefficient under the optimal conditions. The silver arene intermediate **148-1** was proposed to be generated and subsequently be protonated (Scheme 50).[102] What's more, a series of substituted coumarin-3-carboxylic acids was extended for the photodecarboxylation under similar conditions.[103]



Scheme 50. Photodecarboxylation of heteroaromatic carboxylic acids.

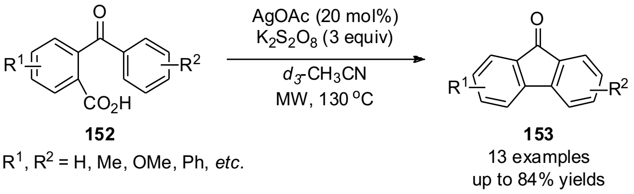
The requirement of an *ortho*-substituent, frequently a heteroatom, for benzoic acid photodecarboxylation is a significant restriction. To expand the scope beyond *ortho*-substituted benzoic acids, Greaney *et al.* developed an oxidative radical protocol for the photodecarboxylation of *ortho*-, *meta*-, and *para*-substituted benzoic acids **150** under $Ag(I)/S_2O_8^{2-}$ catalytic conditions. Arenes **151** were obtained in 34–84% yields. In comparison, electron-rich benzoic acids were less efficient (Scheme 51).[104] Based on these silver(I)-catalyzed photodecarboxylations, a range of *ipso*-deuterated arenes were obtained from *ortho*-substituted arenes as well as heteroaromatic α-carboxylic acids in good to excellent yields with good deuteration grades.[105] Moreover, a silver supported on alumina and silica (about 40 nm size) was developed as an active catalyst for the photodecarboxylation of *ortho*-substituted benzoic acid and heteroaromatic carboxylic acids. XPS revealed that the silver catalyst was covered by a surface layer of silver oxide. The silver oxide layer, polar aprotic solvents such as DMSO, DMA or NMP, and a base were all required for the high efficiency.[106]



Scheme 51. Silver(I)-catalyzed photodecarboxylation of benzoic acids.

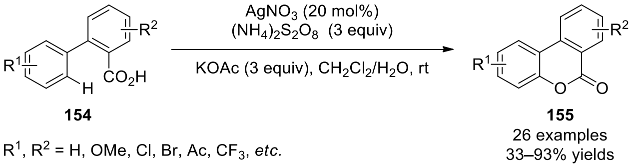
Although Cu/ligand-catalyzed systems have broad substrate scope and good functional-group tolerance, high temperatures are required to assist decarboxylation. The Ag-system served as the complement that was particularly highly effective for many *ortho*-substituted benzoic and heteroaromatic α-carboxylic acids, which was supported by the DFT and experimental studies.[107] Larrosa and Campanera *et al.* revealed that ortho substituents allowed a much lower activation energy barrier for decarboxylation compared to their *meta*- and *para*-position counterparts, owing to a combination of steric and electronic effects. The discovery was in contrast to previous studies by Lin and Su who suggested only a steric effect on the rate of decarboxylation.[108]

A decarboxylative cyclization reaction has been developed by Greaney group for the synthesis of fluorenones **153**. Arylbenzoic acids **152** underwent an oxidative decarboxylation and a subsequent intramolecular cyclization under silver(I) catalysis, affording fluorenone products **153** in good yields. This reaction represented the first practical and general instance of aroic acids functioned as aryl radicals *via* decarboxylation process. Acetonitrile was proved vital as other solvent resulted in little yields. Interestingly, the use of d_3-CH_3CN allowed the desired fluorenone with photodecarboxylated product (9:1), whereas CH_3CN produced a mixture in a 1:1.2 ratio. The stronger C–D bond likely hindered hydrogen atom abstraction from the solvent (d_3-CH_3CN), which promoted the intramolecular C–C bond formation in a selective manner (Scheme 52).[109]



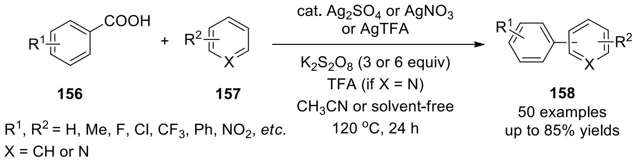
Scheme 52. Decarboxylative C–H arylation of benzoic acids.

In 2014, Xu *et al.* successfully provided a operationally simple entry for the formation of various lactones **155** from 2-aryl acid derivatives **154** by employing $AgNO_3/(NH_4)_2S_2O_8$ oxidative system. This chemoselective C−H functionalization/C−O cyclization reaction tolerated a broad range of functional groups and allowed moderate to excellent yields. Importantly, an unprotected hydroxyl group at aryl moiety was compatible for this lactonization. A radical mechanism was proposed *via* the kinetic isotope effect (KIE) study (Scheme 53).[110] Seven compounds with DNA-intercalating property were synthesized *via* this Minisci acyloxylation process as key step.[111]



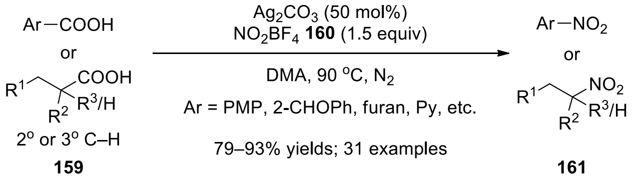
Scheme 53. Synthesis of lactones from 2-aryl acid derivatives.

A long-standing challenge in Minisci reactions is achieving the arylation of heteroarenes by oxidative decarboxylation of aromatic carboxylic acids, probably because it was either difficult for aromatic carboxylic acids generating aryl radicals *via* oxidative decarboxylation, or the aryl radicals generated were too reactive to be captured by electron-deficient (hetero)arenes.[112] To address the challenge, a silver(I)-catalyzed intermolecular Minisci reaction of aromatic carboxylic acids **156** was developed by the Su group. An array of *ortho*-, *meta*-, and *para*-substituted aromatic carboxylic acids **156** was appropriate for the decarboxylative coupling with electron-deficient arenes or heteroarenes **157**, significantly breaking through the limitation of *ortho*-substituted aromatic carboxylic acids. In comparison to the Minisci reaction of boronic acids reported by Baran and co-workers, the reaction system in the absence of water largely made contribution to facilitate the reaction progress smoothly. The arylation occurred preferentially at the C2-position of pyridines over the C3- and C4-positions, whereas electron-withdrawing groups obviously reduced the reaction selectivity. Moreover, in the case of pyridines coupling with aromatic carboxylic acids, TFA was essential for the decarboxylative arylation, presumably because the introduction of TFA enhances the reactivity of the pyridines towards capturing nucleophilic aryl radical intermediates (Scheme 54).[113]



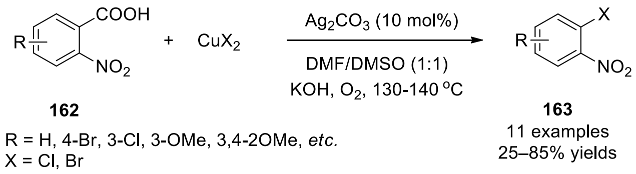
Scheme 54. Silver-catalyzed oxidative decarboxylation of aromatic carboxylic acids.

Considering the drawback of deborylative nitration of arylboronic acids, such as the use of highly toxic and explosive reagents and many unstable/expensive boronic acids, Natarajan *et al.* recently described an efficient approach for the *ipso*-nitration of various aliphatic and aromatic carboxylic acids **159**, providing the corresponding nitro compounds **161** in 79–93% yields. The approach was highlighted by mild reaction conditions, good functional-group compatibilities, and excellent selectivities in comparison to previous methods for synthesis of nitroalkyls and nitroarenes. The reaction progressed with Ag_2CO_3 (0.5 equiv.) and nitronium tetrafluoroborate (NO_2BF_4) **160** as nitration reagent in dimethylacetamide (DMA) without strong acids as additive. An alkyl-silver or aryl-silver intermediate was presumably involved, which subsequently reacted with the nitronium ion to form nitro products **161**. Furthermore, the *ipso*-nitration reaction was employed to synthesize nitro drugs fexinidazole and nitazoxanide from the corresponding carboxylic acids (Scheme 55).[114]



Scheme 55. Silver(I)-promoted *ipso*-nitration of carboxylic acids.

Among the previous reports, the boron–halogen exchange was efficient for aryl halides formation, which suffered from the use of stoichiometric amounts of costly organometallic reagent. A decarboxylative halogenation of the commercially available carboxylic acids **162** was demonstrated by the Wu group in 2010. *ortho*-Nitrobenzoic acids **162** proceeded with CuX_2 under Ag_2CO_3 catalysis in DMF/DMSO at 130–140°C, leading to the corresponding aryl halides **163** in 25–85% yields. The strong electron-withdrawing nitro group in the *ortho*-position played a vital role in this reaction (Scheme 56).[115]

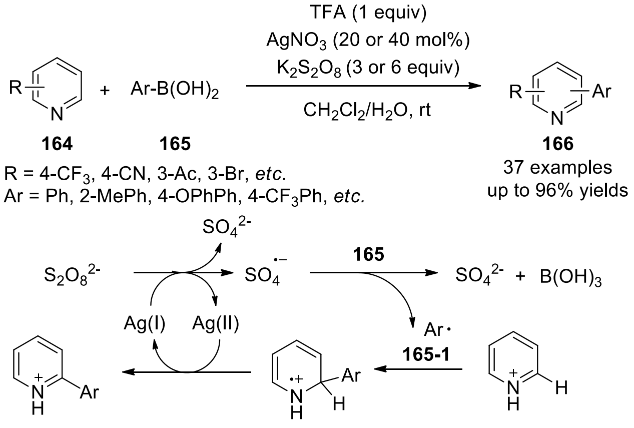


Scheme 56. Decarboxylative halogenation of carboxylic acids.

2.3 Boronic Acids and Esters

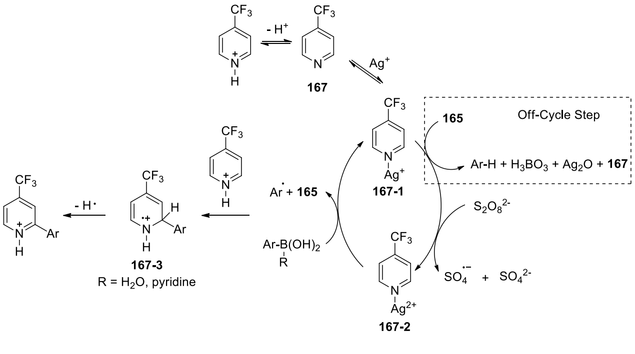
Among various nucleophiles, organoboronic acids and their derivatives are particularly attractive substrates due to their ease of handling, broad availability and good functional-group compatibility. It is well-known that silver complexes can serve as effective catalysts for the reactions with allenyl- and arylboronic acids or esters as nucleophiles. In these reactions, transmetalation from boron to silver can easily proceed in the presence of a suitable base, in which highly reactive species bearing sp^2-hybridized carbon–silver bonds are thought to be formed.[116]

The limited access towards nucleophilic radicals, especially of the aryl variety results in a restriction of the Minisci reaction. The Baran group in 2010 developed the first example of silver(I)-catalyzed coupling reaction of arylboronic acids **165** with various electron-deficient heteroarenes **164**. By comparison, arylcarboxylates failed to produce the coupling products **166** *via* oxidative decarboxylation reaction. The C–H arylation displayed a wide range of substrate scope and excellent functional-group compatibility, which proceeded under operationally simple silver(I)/$S_2O_8^{2-}$ system at room temperature. This generality and practicality made it advanced and available for the arylation reaction of heterocycles. The experiment results revealed the reaction regioselectivity was governed by the inherent reactivity of substrates rather than the reagents. In most cases, the *ortho*-position products were primarily obtained, and bis-addition proved to be minimal. A possible mechanism involving a generation of highly reactive species (tentatively assumed to be aryl radicals **165-1**) from arylboronic acids **165** was suggested. Moreover, a second addition of $K_2S_2O_8$ and $AgNO_3$ is required if large amounts of heterocycles still remain after 3 hours (Scheme 57).[117]



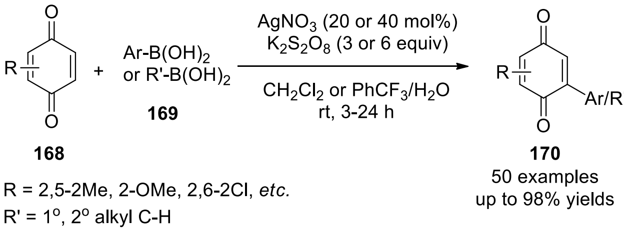
Scheme 57. Arylation of electron-deficient heterocycles with arylboronic acids.

On the basis of the observed kinetic and spectroscopic data, Flower and co-workers proposed a mechanism in detail. Under the reaction conditions, the coordination of pyridine **167** with Ag(I) can yield complex **167-1**. And then, complex **167-1** can be oxidized by $S_2O_8^{2-}$ to give Ag(II)–pyridine complex **167-2**, which is the rate-determining step. Finally, the resulting Ag(II)–pyridine complex **167-2** instead of $SO_4^{\bullet-}$, can oxidize arylboronic acid **165**, producing an aryl radical that can react with the pyridinium ion forming the coupling product **167-3**. An off-cycle step is also involved outside of the desired pathway, in which the arylboronic acid **165** is protodeboronated giving the side products (toluene and boric acid). The capability control of the off-cycle process provided higher efficiency and yields (Scheme 58).[118]



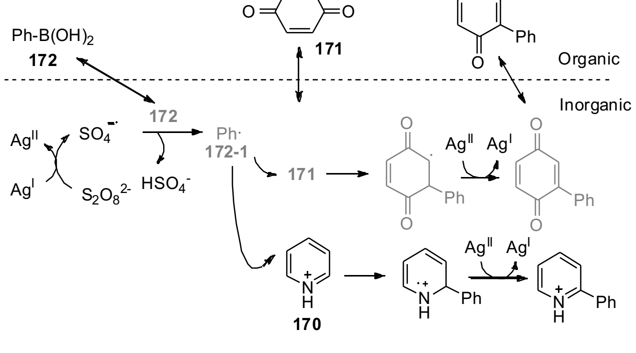
Scheme 58. Mechanism of cross-coupling reaction of arylboronic acids and heteroarenes.

Further, a silver(I)-catalyzed C–H arylation and alkylation of quinones **168** with boronic acids **169** was developed by the Baran group, which proceeded readily at room temperature in air conditions, even in the absence of organic solvents. It was scalable, practical and highly chemoselective, in which a broad range of electron-rich/withdrawing arylboronic acids as well as alkyl boronic acids were applicable. Phenylboronic acids bearing nitro, cyano, trifluoromethyl, ketone, and silane groups were compatible for the arylation. It was found that the use of trifluorotoluene ($PhCF_3$) (an environmentally benign substitute for dichloromethane) as a cosolvent was essential to achieve a broad scope of quinones. The mechanism was presumed through a nucleophilic radical addition to the quinone **168** with *in situ* reoxidation of the resulting dihydroquinone. The complex substrates, including a steroid derivative and a farnesyl natural product were explored and led to the arylated products efficiently (Scheme 59).[119]



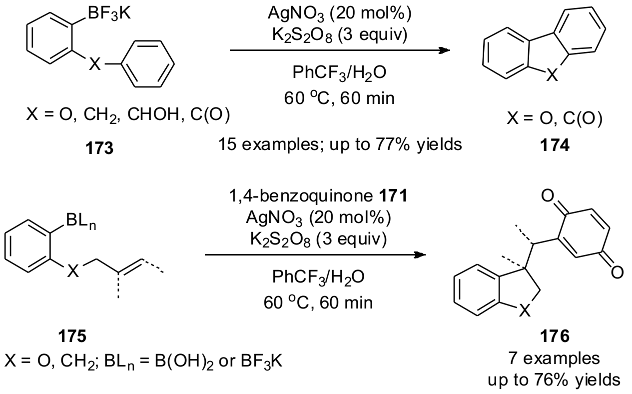
Scheme 59. Silver(I)-catalyzed coupling of quinones with boronic acids.

Afterwards, kinetic, spectroscopic, and computational studies were conducted to explain the two radical C−H arylation reactions, which emphasized the interaction between chemical and physical rate processes in the multi-phase reactions. The efficiency of the arylation of pyridines is depended on the concentration of protonated pyridine **170**, as the rate-determining step is the addition of phenyl radical **172-1** from boronic acid **172** in the aqueous phase. Whereas, the intrinsic kinetics of the quinone system are highly controlled by the mass transfer processes which have an impact on the distribution and concentration of benzoquinone **171** between phases. The Ag^I−Ag^{II} redox mechanism for both pyridine and benzoquinone substrates **170** and **171** was suggested without the need to invoke the formation of organometallic catalysts (Scheme 60).[120]



Scheme 60. Mechanism of two-phase radical C–H arylations.

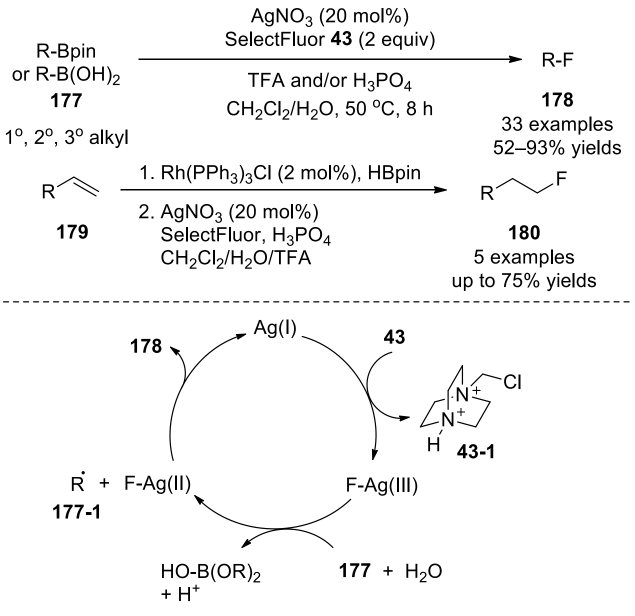
Baran and co-workers further discussed the chemistry of aryl radicals derived from boronic acids and trifluoroborates **173** and **175** in an intramolecular mode. This radical transformation occurred under mild conditions without the use of toxic and/or expensive metals and hazardous arenediazonium salts. Therefore, it could be safely conducted on gram scale.[121] Starting from substrates **173** and **175**, both Pschorr-type cyclizations and tandem radical cyclization/trap cascades were described, providing mild entries for the formation of polycyclic scaffolds **174** and **176** in high yields. Concomitant benzylic oxidation into 9*H*-fluoren-9-one scaffolds demonstrated step economy of the strategy. Importantly, the vicinal olefin difunctionalization for the assembly of polycyclics **176** acted as a complement to the conventional tributyltin hydride-based radical cyclization and the palladium-catalyzed Heck-type process, both of which were failing with benzoquinone **171** as a radical capture. It was showed that the efficiency of this tandem radical cascades was diminished with higher degrees of olefin substitution (Scheme 61).[122]



Scheme 61. Silver(I)-catalyzed cyclizations with arylboronic acids and trifluoroborates.

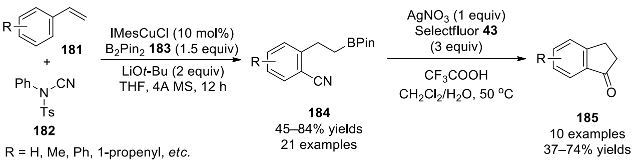
Other heterocycle compounds, such as pyridine *N*-oxides, *N*-iminoquinolinium ylides, histidines were also used for the arylation with arylboronic acids under silver(I) catalysis.[123]

Following the Ag(I)-catalyzed decarboxylative fluorination of aliphatic carboxylic acids with Selectfluor, Li *et al.* reported a general and site-specific method for $C(sp^3)$–F bond formation by radical deboronofluorination of alkylboronic acids or their pinacol esters **177**. A variety of alkyl fluorides **178** were generated upon the corresponding primary/secondary/tertiary alkylboronic acids and alkylboronates **177** with Selectfluor reagent **43** in acidic aqueous solution under silver catalysis. Compared to the additive acetic acid, trifluoroacetic acid (TFA) or H_3PO_4 provided better results, which likely benefits from the increasing solubility of boronates in the aqueous phase. In addition, the synthesis of the *gem*-difluorides was achieved from the corresponding geminal bis(boronates). With this radical fluorination, unactivated alkenes **179** furnished hydrofluorination products **180** *via* a two-step and one-pot procedure, whereas the previous pathway resulted in Markovnikov hydrofluorination products. Firstly, an interaction of Ag(I) with Selectfluor generates the Ag(III)-F intermediate presumably *via* oxidative addition. Then, a single electron oxidation of alkylboronates **177** by Ag(III)-F gives alkyl radicals **177-1** and Ag(II)-F. The subsequent fluorine atom transfer between alkyl radicals **177-1** and Ag(II)-F affords alkyl fluorides **178** as the final products and regenerates Ag(I) as the catalyst. In view of the convenient and divergent access of alkylboronates, the deboronofluorination potentially displayed important application in organic synthesis (Scheme 62).[124]



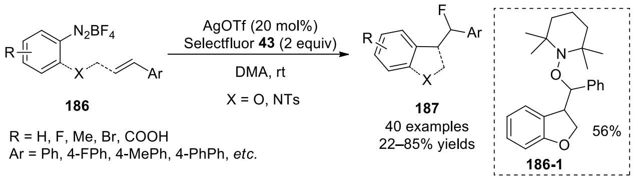
Scheme 62. Silver(I)-catalyzed radical fluorination of alkylboronates.

A facile and practical two-step protocol to access indanone derivatives **185** has been developed by the Montgomery group starting from a simple vinyl arene **181**. First, an IMesCuCl-catalyzed borylation/*ortho*-cyanation of styrenes **181** with bis(pinacolato)diboron (B_2pin_2) **183** and *N*-cyano-*N*-phenyl-pmethylbenzenesulfonamide (NCTS) **182** resulted in the *ortho*-cyanated products **184** in a regioselective manner; a subsequent $AgNO_3$/Selectfluor-mediated cyclization of products **184** furnished indanones **185** bearing a new five-membered ring. A broad range of vinyl arenes **181** with highly functionalized (hetero)aromatic groups were well applicable for the transformation. On the basis of Li's reports, mechanism involving Ag(I)/Ag(III)/Ag(II) catalytic cycle was proposed, generating homobenzylic radical and nitrogen-centered radical. This combined two-step sequence offered a versatile and novel pathway for the functionalization of vinyl arenes (Scheme 63).[125]



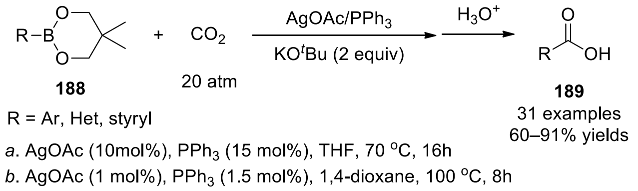
Scheme 63. Synthesis of indanone derivatives.

Aryl diazonium salts have attracted chemists as an important source of aryl radicals, which are easily prepared from aniline derivatives in large quantities. Tang's group reported the first example of a silver-catalyzed intermolecular and intramolecular Meerwein fluoroarylation of styrenes with aryl diazonium salts under mild conditions. The new reaction offers a complementary method for difunctionalization of alkenes **186** to form fluorinated dihydrobenzofurans and indolines **187** and extends the scope of the Meerwein arylation. Aryl diazonium salts or styrenes bearing electron-withdrawing, -neutral, and -donating substituents performed smoothly and afforded the corresponding fluorinated products **187** in moderate to good yields. *trans*-Fluorinated dihydrobenzofurans were formed as the major product with high diastereoselectivity while indolines had low diastereoselectivity. Mechanistic studies suggested that the reaction proceeded through a free-radical process which was confirmed by the synthesis of dihydrobenzofuran **186-1** in a 56% yield (Scheme 64).[126]



Scheme 64. Silver-catalyzed Meerwein arylation.

Given that CO_2 could insert into the sp^2-hybridized carbon–silver bond forming silver carboxylate, silver would be another metal candidate which shows expectant activity towards the carboxylation of arylboronic reagents with CO_2. Zhang and Lu reported the realization of this hypothesis, in which an array of arylboronic esters **188** was efficiently carboxylated with CO_2 using a simple silver(I)/PPh_3 catalytic conditions. This catalytic system showed wide substrate scope and resulted in various functionalized carboxylic acids **189** in good yields. Besides AgOAc, other silver sources such as AgF, $AgBF_4$, and $AgNO_3$ also gave effective performence. P-ligands, such as PPh_3, PCy_3, IPr, SIPr provided high yields. The silver catalytic system proved to be sensitive to the CO_2 pressure, whereas the optimal, relatively high CO_2 pressure (20 atm) caused disadvantage in synthetic application (Scheme 65).[127]



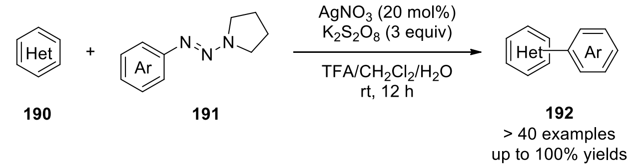
R = Ar, Het, styryl

a. AgOAc (10mol%), PPh_3 (15 mol%), THF, 70 °C, 16h

b. AgOAc (1 mol%), PPh_3 (1.5 mol%), 1,4-dioxane, 100 °C, 8h

Scheme 65. Carboxylation of arylboronic esters with CO_2.

Aromatic triazenes as a kind of activated aryl sources are easily and rapidly prepared from bench-available anilines, which are comparatively stable and can be synthesized in a large scale. Recently, Wang *et al.* reported the facile and scalable coupling reaction of pyridine derivatives **190** with triazenes **191**, providing an entry for the formation of highly functionalized heterobiaryls **192** with excellent yields. In comparision, best results were obtained with electron-deficient heteroarenes. Notably, heteroaryl triazenes failed to provide arylated heterobiaryls, whether at ambient temperature or elevated temperature. The advantage of triazenes **191** made the strategy an efficient and practical tool to synthsize heterobiaryls. A radical pathway was proposed involving aryl radicals generated *in situ* from the TFA-activated triazenes (Scheme 66).[128]



Ar = 4-ClPh, 4-OCF_3Ph, 3-OMePh, *etc.*

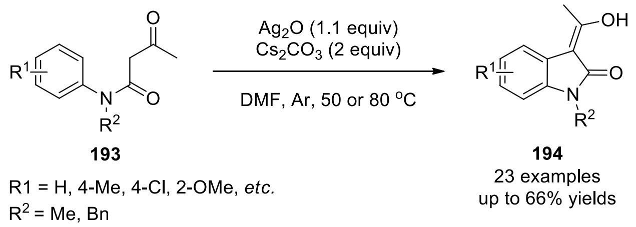
Het = pyridine, isoquinoline, phthalazine, pyrazine, pyridazine, *etc.*

Scheme 66. Synthesis of heterobiaryls from pyridine derivatives with triazenes.

2.4 Active Methylene Compounds

Over the past few years, the direct coupling of the methylenic sp^3 C–H bond in 1,3-dicarbonyl compounds with other partners catalyzed or promoted by transition metal catalysts has been developed as a powerful tool for the synthesis of useful and structurally diverse organic molecules. Generally, α-keto ridical is plausibly generated in the presence of oxidants and/or bases. For instance, the reaction of 1,3-dicarbonyl dipoles with alkenes in the presence of silver salts is known to afford dihydrofuran derivatives. The 1,3-dicarbonyl compound is first oxidized by silver(I) salts to generate the α-oxoalkyl radical, which then attacks the C=C double bond of olefin to give a new carbon-centered radical. The radical subsequently undergoes fast oxidation by silver(I) to give a carbonium ion and deprotonation step, finally yields the desired dihydrofuran.[129]

The direct and intramolecular oxidative C(sp^2)–C(sp^3) coupling of *N*-substituted acetoacetanilides **193** was conducted with Ag_2O as oxidant and Cs_2CO_3 as base, which provided a convenient approach toward 3-acetyloxindoles **194** in moderate to high yields. However, the reaction of benzoyl acetanilide could not be acceptable (Scheme 67).[130]

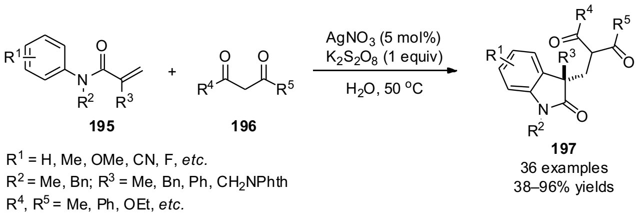


R1 = H, 4-Me, 4-Cl, 2-OMe, *etc.*

R^2 = Me, Bn

Scheme 67. Ag_2O-mediated intramolecular oxidative coupling of acetoacetanilides.

In 2013, Guo and Duan *et al.* reported the first silver-catalyzed oxidative cyclization for the synthesis of oxindoles **197** starting from acrylamides **195** with carbonyl compounds **196** through a tandem radical addition/cyclization process, in which two new C–C bonds were formed.[131] β-Diketones and β-keto esters, even simple ketones **196** were appropriate to provide α-keto ridicals initiated by silver(I)/persulfate system in water.[132] Whereas low yields were still observed only with $K_2S_2O_8$. The reaction was characterized by its significant functional group tolerance and mild reaction conditions, thus providing an environmentally friendly and operationally simple protocol for functionalized oxindoles (Scheme 68).



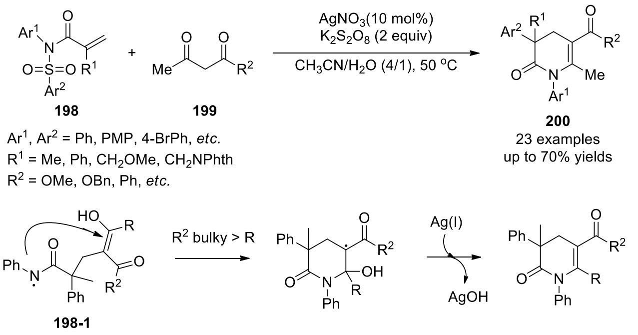
R^1 = H, Me, OMe, CN, F, *etc.*

R^2 = Me, Bn; R^3 = Me, Bn, Ph, CH_2NPhth

R^4, R^5 = Me, Ph, OEt, *etc.*

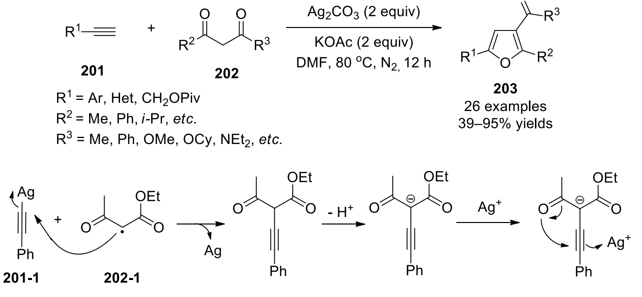
Scheme 68. Silver-catalyzed oxidative cyclization for the synthesis of oxindoles.

Nevado and co-workers reported that 3,3-disubstituted-2-dihydropyridinones **200** were generated in a regioselective and straightforward manner, starting from *N*-(arylsulfonyl)acrylamides **198** and 1,3-dicarbonyl compounds **199** with the combination of $AgNO_3$ and $K_2S_2O_8$ in aqueous solution at 50°C. A radical cascade process was demonstrated through a sequence of α-keto radical insert, a formal 1,4-aryl migration, and desulfonylation of the starting material, providing the key *N*-centered radical **198-1**. Finally, radical **198-1** was evolved into the product **200** by an intramolecular annulation and an elimination of the OH group (Scheme 69).[133]



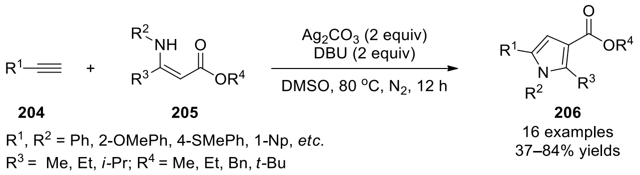
Scheme 69. Synthesis of 3,3-disubstituted-2-dihydropyridinones from *N*-(arylsulfonyl)acrylamides.

Alkynes have been explored and utilized as radical acceptor. The Lei group in 2012, developed a silver(I)-promoted oxidative C–H/C–H functionalization protocol for the assembly of a spectrum of trisubstituted furan derivatives **203** from 1,3-dicarbonyl compounds **202** and terminal alkynes **201** (Scheme 70).[134] An array of aromatic acetylenes and heteroaromatic acetylenes **201** delivered good yields whereas low yields were obtained for the most of aliphatic terminal alkynes under Ag_2CO_3/KOAc conditions. A presumable mechanism was proposed that silver acetylide **201-1** as the key intermediate and a direct intermolecular oxidative C(sp)–C(sp^3) coupling were involved. It should be known that the use of Ag_2CO_3 avoided forming the buta-1,3-diynes that generally presented by using copper salts. Further, Novák and Stirling *et al.* employed DFT analysis and experimental investigations to elucidate the mechanism as successive radical and ionic processes *via* silver acetylide **201-1** as key intermediate.[135] On the basis of the calculations, silver(I) was revealed as an oxidant for the generation of α-keto ridicals **202-1**, and as a catalyst for cyclization step, which was consistent with Lei's proposal. The generated *in situ* silver acetylide **201-1** converted the radical process into an ionic process. Besides, alkynoates could work as radical acceptor and produced an array of polysubstituted furans with dicarbonyl compounds with the aid of stoichiometric amount of AgOAc.[136]



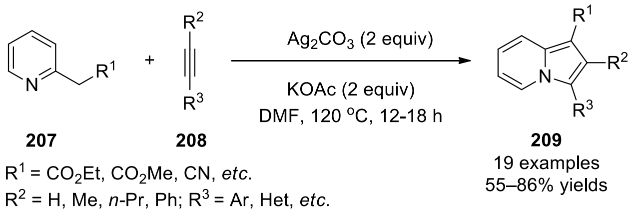
Scheme 70. Silver(I)-promoted oxidative C–H/C–H functionalization to access furans.

Further, Lei and co-workers extended this [3 + 2] cycloaddition for the synthesis of pyrroles **206** from terminal alkynes **204** with β-enamino esters **205**, which was compatible with wide substrate scope and good functional-group tolerance. By IR spectroscopy and the Raman spectrum, silver acetylide was unraveled as the intermediate (Scheme 71).[137]



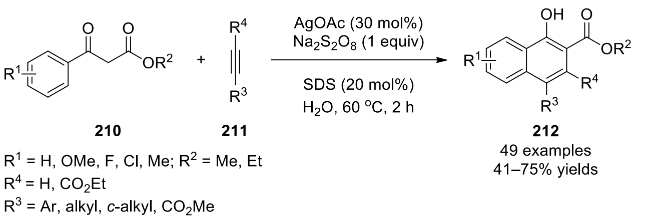
Scheme 71. Synthesis of pyrroles from terminal alkynes and β-enamino esters.

Based on Lei's strategy, a silver-mediated sequential oxidative C–H functionalization and 5-*endo-dig* cyclization of 2-alkylazaarenes **207** with terminal and internal alkynes **208** was developed by Liang and Pan *et al.* This reaction provides a straightforward route to access biologically important indolizines **209** in 55–86% yields. Similarly, the internal alkynes involved a successive radical and ionic pathway, whereas mechanism containing deprotonation with 2-alkylazaarenes and nucleophilic attack on a silver acetylide intermediate was proposed with terminal alkynes (Scheme 72).[138]



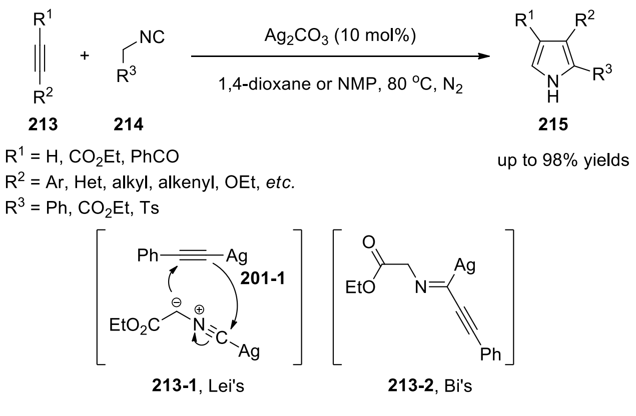
Scheme 72. Synthesis of indolizines from 2-alkylazaarenes with alkynes.

Moreover, a [4+2] cycloaddition of β-ketoesters **210** and terminal/internal alkynes **209** was demonstrated under silver(I)/persulfate conditions in water as solvent. As a result, a series of highly substituted 1-naphthol skeletons **212** were delivered in high yields with high regioselectivity and good functional-group tolerance. This mild and environmentally benign approach was also applied for the assembly of bioactive lignan natural products, such as diphyllin, taiwanin E, and justicidin A with excellent selectivity (Scheme 73).[139]



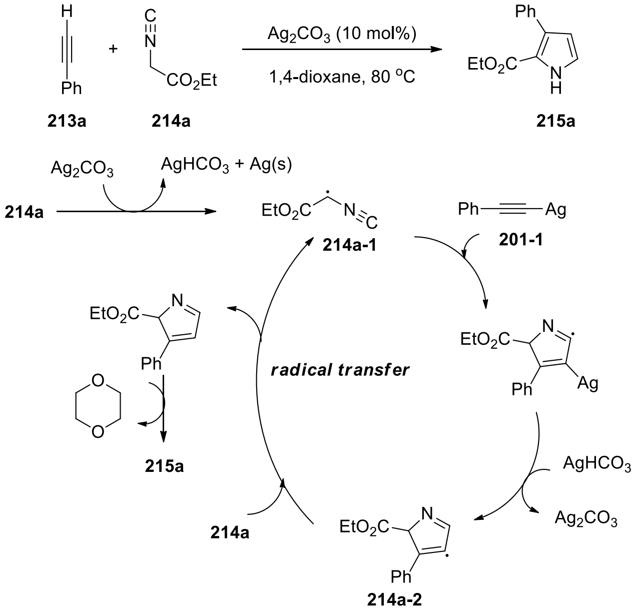
Scheme 73. Synthesis of 1-naphthols from β-ketoesters and terminal/internal alkynes.

Isocyanides and alkynes are two important classes of fundamental chemicals, and their [3 + 2] cycloaddition is an ideal route to pyrrole syntheses. In 2013, Lei's and our groups simultaneously developed the Ag_2CO_3-catalyzed [3 + 2] cycloaddition reaction of isocyanides **214** and a wide range of internal/terminal alkynes **213**. Excellent yields were obtained even with the terminal alkynes that were easily formed homocoupling products. The process provided a direct route to synthesize 2,3-disubstiotuted pyrroles **215** that complemented the click reaction for the rapid construction of heterocyclic compounds. On the basis of the preliminary mechanistic studies, a possible pathway involving the cycloaddition between two activated silver species **201-1** and **213-1** was proposed by Lei *et al.* Whereas, our group suggested a mechanism involving two key steps: (1) catalytic cycling between Ag_2CO_3 and $AgHCO_3$, and (2) 1,1-insertion of isocyanides **214** to silver acetylide forming intermediate **213-2** that was subsequently evolved into the 5-membered ring core (Scheme 74).[140]



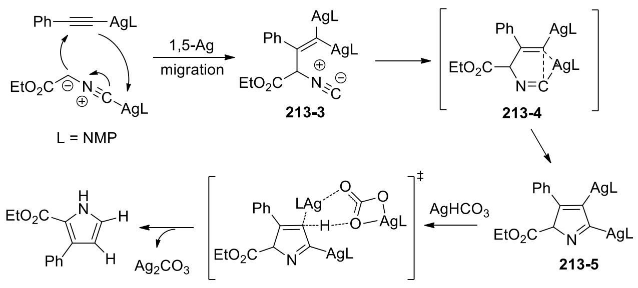
Scheme 74. [3 + 2] cycloaddition for the synthesis of pyrroles.

Further, by mean of a combined DFT and experimental study, a mechanism involving a multicatalyzed radical process was revealed by our group. Ag_2CO_3 acted as both base and oxidant for the generation of isocyanide radical **214a-1**. It was found that isocyanide and 1,4-dioxane work as radical shuttle to regenerate radical **214-1** after forming **214a-2** between **214a-1** and silver-acetylide **201-1**. The employment of 1,4-dioxane significantly decreased the activation barriers during the reaction course, which was as solvent and catalyst (Scheme 75).[141]



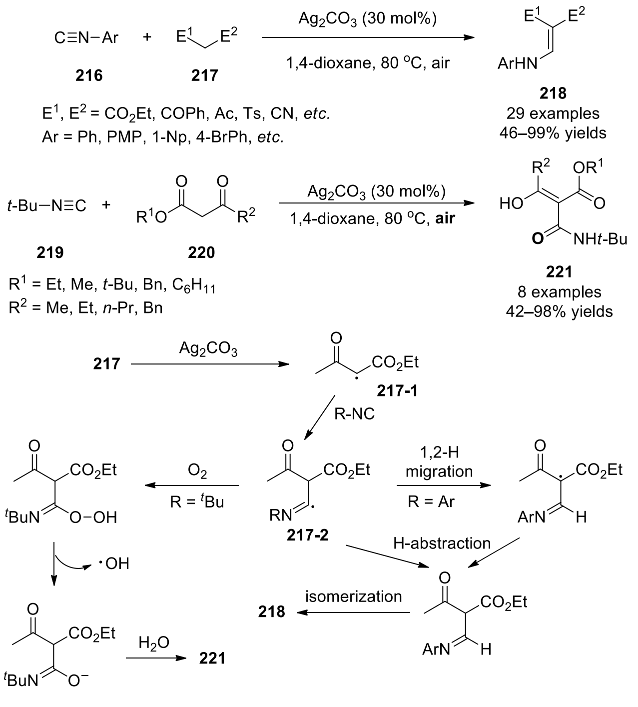
Scheme 75. Mechanism of isocyanide-alkyne cycloaddition.

Simultaneously, the Lan group disclosed the mechanism of isocyanide-alkyne [3 + 2] cycloaddition contains two successive 1,5-silver migration. As shown in Scheme 76, the silver migrates between carbon atoms and finally returns to the first one (**213-3** to **213-5**). Supported by NPA analysis, the important silver-migration was revealed to facilitate the whole reaction by instructing the shift of negative charge into a rational way. Additionally, the mechanism of cycloaddition of isocyanide with internal alkynes was proposed involving a silver migration process as well.[142]



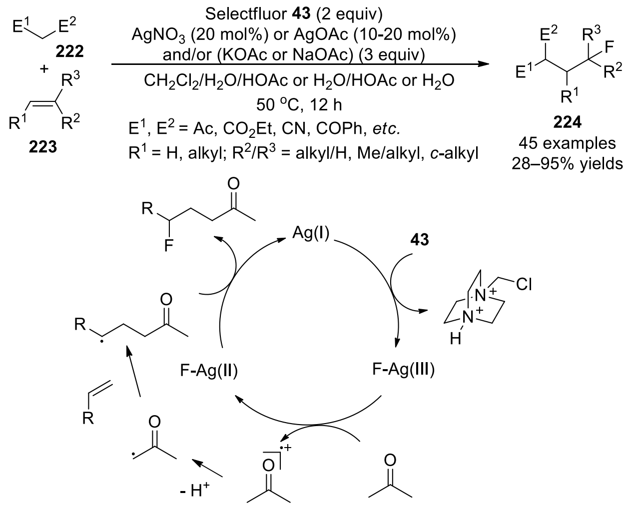
Scheme 76. Mechanism of isocyanide-alkyne cycloaddition *via* 1,5-silver migration.

Isocyanide-involved C–H functionalizations suffered from uncontrollable overinsertion of isocyanides thus allowed tandem cyclization reactions.[143] Therefore, the exploration of effective approaches for isocyanide-involved C–H functionalization, particularly for C(sp^3)–H bonds, remains an urgent task. Recently, our group reported a novel radical coupling/isomerization reaction of isocyanides and dicarbonyl compounds. A wide array of methylene compounds **217** and aryl isonitriles **216** furnished the corresponding β-aminoenones **218** in good to excellent yields. Notably, substrates with different EWGs ($EWG^1 \neq EWG^2$) furnished single stereoisomers that was identified by NOE experiments. The extension scope to *tert*-butyl isocyanide **219** with β-ketoesters **220** allowed an unprecedented C(sp^3)–H carbamoylation transformation providing tricarbonylmethanes **221** in 42–98% yields. However, other aliphatic isocyanides, which have similar structure to *tert*-butyl isocyanide resulted in an unidentified mixture. In terms of the preliminary mechanistic studies, a mechanism containing a radical coupling and a subquential isomerization was proposed. Mechanically, the radical intermediate **217-1** derived from active methylene, inserted to isocyanide forming imidoyl radical intermediate **217-2**. Subsequently, radical **217-2** performed a 1,2-*H* migration (aryl isonitrile **216**) or oxidation by oxygen (*t*-butyl isocyanide **219**) to convert to the desired products. It was disclosed that oxygen was essential for the protocol. Furthermore, theoretical calculations on the oxidation potentials (V) and HOMO energies revealed that intermediate **217-2(*t*Bu)** more easily underwent one-electron oxidation than **217-2(**PMP) (Scheme 77).[144]



Scheme 77. Silver-catalyzed cross-coupling of isocyanides and active methylene compounds.

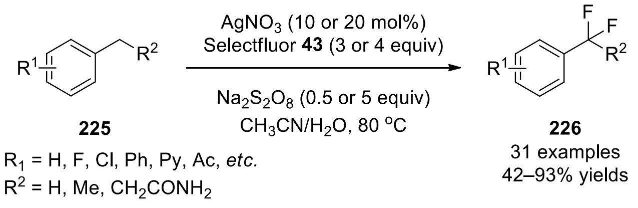
Atom transfer radical addition (ATRA) reactions, discovered by Kharasch and significantly promoted by Curran and others, have been demonstrated to be a versatile tool in organic synthesis. In 2014, Li and co-workers reported the first example of carbofluorination of unactivated alkenes **223**. A three-component reactions of unactivated alkenes **223** with Selectfluor reagent **43** and active methylene compounds **222**, such as ethyl acetoacetate and 1,3-dicarbonyls furnished the corresponding condensation products **224** in moderate to excellent yields. This mild and simple carbofluorination generally performed in the presence of $AgNO_3$ in CH_2Cl_2-H_2O-HOAc at 50°C. It should be noted that $K_2S_2O_8$ was added if the reactions proceeded sluggishly under the above conditions. Further, the extension to acetone or other ordinary ketones (*i.e.* cycloalkanones and 3-pentanone) was accomplished that underwent smoothly with AgOAc as catalysis and acetate as additive. The carbofluorination was efficient and highly regioselective, and enjoyed a broad substrate scope and wide functional-group compatibility. Complex molecules, like steroid were compatiable and afforded the products with highly regioselecties (Scheme 78).[145]



Scheme 78. Silver-catalyzed carbofluorination of unactivated alkenes with ketones.

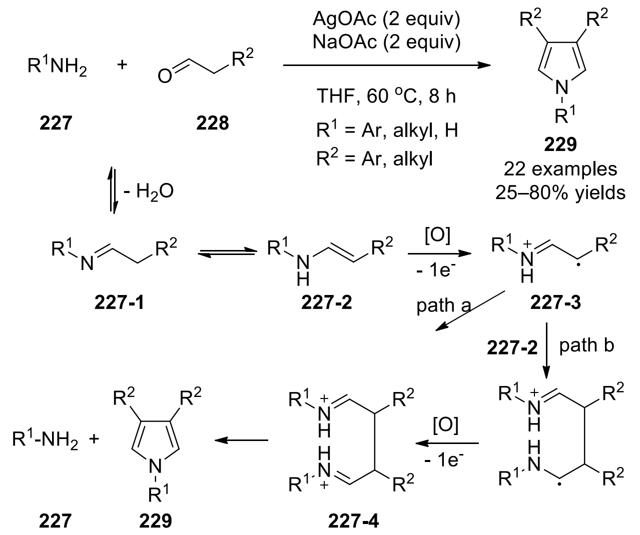
The difluoromethyl group (CF_2) is of interest in medicinal chemistry, and is found in various biologically active compounds.[146] However, methods for the synthesis of difluoromethylated arenes are limited. In light of the Groves's finding that the manganese-catalyzed monofluorination of benzylic C–H bonds,[147] Tang *et al.* presented the first example of a silver-catalyzed oxidative activation of a benzylic C–H bond **225** with the commercially available Selectfluor reagent **43** for the preparation of difluoromethylated arenes **226**. The reaction proceeds under mild conditions, tolerates various functionalities, and is amenable to the gram-scale synthesis of functionalized difluoromethylated arenes **226**. In general, methylated arenes without *ortho*-substituents reacted more slowly, and required high catalyst loadings and a higher amount of

Selectfluor, which might cause by a weak coordination between the carbonyl group and the silver(II) species, which might facilitate the benzylic radical formation. Furthermore, methylated heteroarenes, such as thiophene, furan, and indole migtht be incompatiable. The primary mechanism studies revealed a radical process and the C–H bond cleavage step as the rate-limiting step of this transformation. Note that water proved to be essential for the reaction whereas the role of water has not yet been established (Scheme 79).[148]



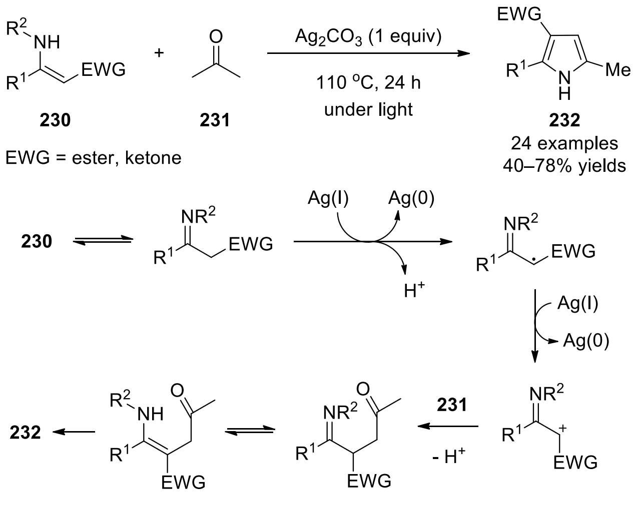
Scheme 79. Formation of difluoromethylated arenes.

The previous oxidative homodimerization of enamino ketones or esters for the synthesis of pyrrole suffered from limited substrate scopes and required pre-synthesis. In 2010, the Jia research group developed the first example of oxidative homodimerization of aldehyde enamine, allowing the direct approach to polysubstituted pyrroles **229** in high yields. A range of simple and readily available amines **227** and functionalized acetaldehydes **228** were well tolerated and progressed in one-pot by using AgOAc as the oxidant and NaOAc as the base. Mechanically, the imine **227-1** generated from amine and aldehyde equilibrated to enamine **227-2**, which occured a one-electron oxidation with AgOAc to form an α-imine radical cation **227-3**. Subsequently, the radical **227-3** underwent self-coupling (path a) or reacted with enamine **227-2** (path b) to produce the diimine **227-4**. Finally, aromatization of diimine **227-4** furnished pyrrole **229** with leaving an amine **227**. The application of the process were illustrated for the formation of natural product purpurone (Scheme 80).[149]



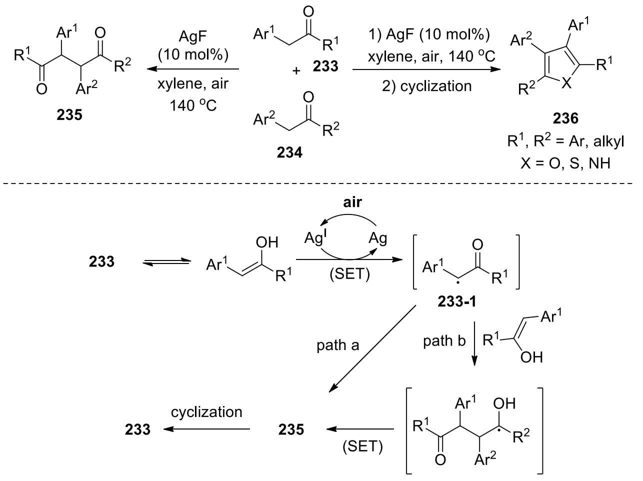
Scheme 80. AgOAc-mediated synthesis of pyrroles from primary amines and aldehydes.

The cross-dehydrogenative coupling (CDC) reactions of β-enaminoesters remain less developed likely owing to the competitive intramolecular oxidative cyclization. A silver(I)-promoted CDC reaction of enamino esters **230** with simple and commercial available acetone **231** was reported by Li *et al.*, which offered an efficient and direct synthesis of tetrasubstituted pyrroles **232**. The reaction was tolerated with a wide range of functional group and constructed a C–C and a C–N bond in one-pot synthesis. Notably, this reaction was not sensitive to laboratory light, and lower yield and lower selectivity were obtained in the dark reaction conditions. On the basis of the mechanism experiments, such as radical inhibitor and acetone-d_6 studies, a radical process was proposed involving the rate-determining step as the cleavage of C–H bond in acetone (Scheme 81).[150]



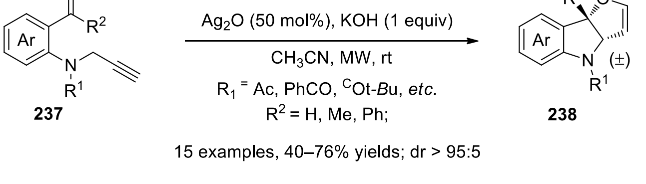
Scheme 81. Formation of tetrasubstituted pyrroles from enamino esters and ketones.

Recently, Wang and colleagues developed the first example of silver-catalyzed coupling of two C(sp^3)–H groups (α-aryl ketones) **233** and **234**, providing a variety of 1,4-diketone derivatives **235** with a broad substrate scope and high functional-group compatibility. Learning from the previous oxidative couplings and radical-trapping experiments, a radical process involving the generation and coupling of α-carbonyl radical **233-1** and two SET steps were discovered, in which air worked as the terminal oxidant. The coupling products **235** were readily to perform cyclization reactions, allowing tetrasubstituted furans, thiophenes, and pyrroles **236** in one-pot procedure, by mean of suitable nucleophilic reagents under optimal reaction conditions (Scheme 82).[151]



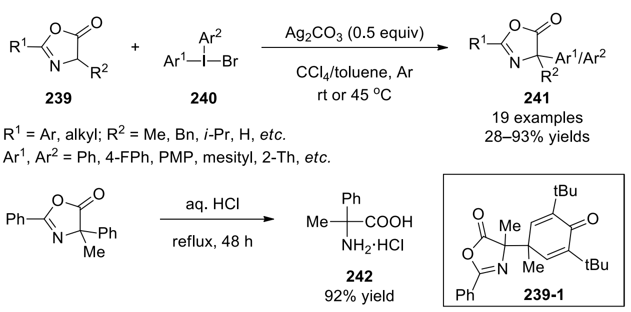
Scheme 82. Synthesis of tetrasubstituted furans, thiophenes, and pyrroles.

In 2012, the Zhang group developed an intramolecular [3+2] cycloaddition for the assembly of functionalized dihydrofuro[3,2-*b*]indoles **238** in a regiospecific and diastereoselective manner. *o*-Propargylamino-acetophenones/-benzaldehydes **237** underwent the cycloaddition reaction promoted by Ag$_2$O under microwave heating. Mechanistic studies were revealed that the precipitate collected was elemental silver rather than Ag$_2$O. Therefore, Ag$_2$O played dual roles as a base and an oxidant. A SET mechanism was plausibly reasoned the formation of heterocyclic frameworks (Scheme 83).[152]



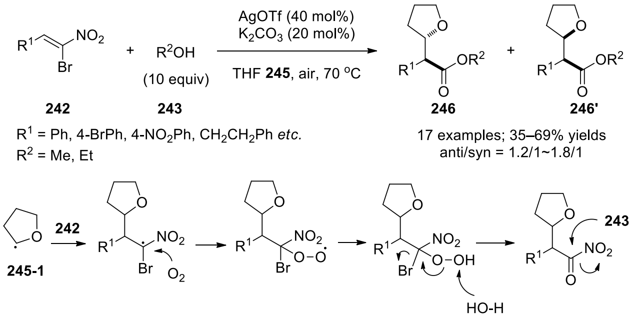
Scheme 83. [3+2] cycloaddition to access dihydrofuro[3,2-b]indoles.

In contrast to the exploration of reactive diaryliodonium salts with weakly coordinating, such as OTf, BF$_4$, diaryliodonium salts bearing coordinating anions like halides have been rarely disscussed which are generally less reactive. Although they are easily accessible and stable towards heat, oxygen and humidity, these diaryliodonium salts were less applized in arylation reactions. In 2014, Chai *et al.* developed a silver(I)-based arylation of azlactones **239** by using diaryliodonium bromides **240** as efficient arylating reagents. The expected products were easily evolved to α-tetrasubstituted amino acid derivatives **242** in good yields under acidic conditions. Although the exact reaction mechanism remains unclear at this stage, they presumed a radical process due to the adduct **239-1** was achieved in a 47% yield by addition of radical inhibitor BHT (Scheme 84).[153]



Scheme 84. Arylation of azlactones using diaryliodonium bromides.

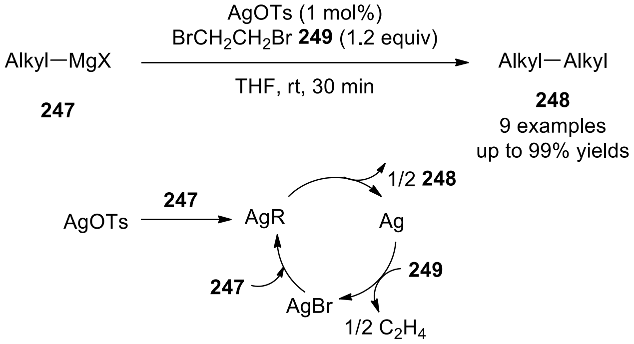
Tetrahydrofuran (THF) molecule can function as carbon radical as well. Liu and co-workers reported that a set of cyclic ethers **246** and **246’** with synthetic biological activity were produced through THF radical **245-1** incorporated into β-bromonitrostyrenes **242** under mild and aerobiotical conditions. To understand the mechanism, isotope labelling experiment $^{18}O_2$ was conducted and showed that molecular oxygen was associated with the formation of carbonyl group. The THF radical **245-1** was plausibly derived from THF **245** in the presence of silver(I) and oxygen. The alcohols **243** were used for the transesterification step. It should be mentioned that the rich electron-density β-bromonitrostyrenes, such as 4-methoxy benzene or furan ring were unreacted (Scheme 85).[154]



Scheme 85. Radical addition of tetrahydrofuran into β-bromonitrostyrenes.

2.5 Alkyl Halides

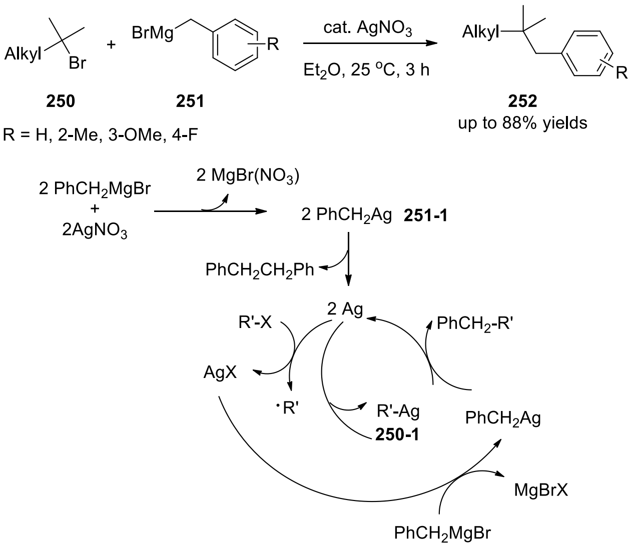
Silver(I) salts as a stoichiometric oxidant for the homo-coupling of alkyl Grignard reagents have been known for a long time, but their application as a catalyst remain unsolved and challenging. The earliest coupling reactions involving silver salts could be traced back to the studies of Wurtz-type coupling of Grignard reagents in the presence of various metal salts.[9] Two plausible mechanistic pathways have been proposed for the coupling of alkylsilver compounds, either a radically-mediated cleavage of the carbon–silver bond or a concerted process for the breaking of the silver–carbon bond and formation of the carbon–carbon bond. However, in light of studies of Whitesides and co-workers, a concerted process is more encouraged, although this has not proved to be general.[155] Encoung by these, Hayashi *et al.* in 2015 developed a practical silver tosylate (AgOTs)-catalyzed oxidative homo-coupling of alkyl Grignard reagents bearing β-hydrogens **247**. In the reaction, 1,2-dibromoethane **249** functioned as a stoichiometric oxidant for the Ag(0)/Ag(I) cycle (Scheme 86).[156]



Scheme 86. AgOTs-catalyzed oxidative homo-coupling of alkyl Grignard reagents.

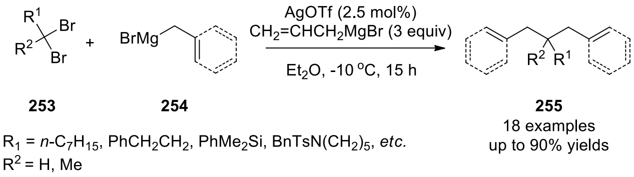
The silver-based cross-coupling reactions of alkyl halides with alkyl Grignard reagents was first learned by Tamura and Kochi. From the reports, a mixture of the cross-coupling and both homocoupling products was acieved by the coupling of primary alkyl halides with primary Grignard reagents, when both were of different chain length. It was noted that during the reaction of Grignard reagents with silver(I) compounds a soluble form of zerovalent silver was originated, which was an active catalyst for the generation of alkyl radicals from alkyl halides.[157]_ENREF_166

A significant development was made by Oshima and colleagues, who reported the selective and efficient silver-catalyzed cross-coupling reactions of secondary and tertiary alkyl chlorides, bromides, or iodides with benzylic or allylic Grignard reagents **251**. By contrast, alkyl bromides **250** displayed best results and tertiary alkyl halides were efficient that required less catalyst loadings. The coupling reactions of tertiary alkyl halides provided efficient access to quaternary carbon centers that are relatively rare because β-elimination usually competes. On the basis of the mechanistic studies on silver-catalyzed reactions by Tamura and Kochi, the circular transform of zerovalent silver and reductive coupling between benzylsilver **251-1** and the alkylsilver **250-1** were pivotal (Scheme 87).[158]



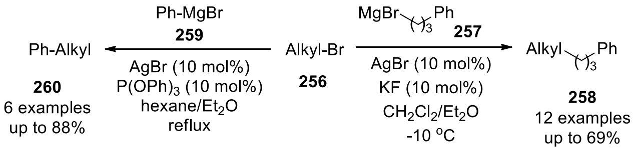
Scheme 87. Coupling of tertiary and secondary alkyl halides with Grignard reagents.

Afterwards, the same group developed an accessible diallylation reaction of *gem*-dibromoalkanes **253** using allylmagnesium bromide **254** catalyzed by AgOTf at -10 °C, affording various useful synthetic compound 1,6-heptadienes **255**. Alkyl moieties with diverse functional groups such as *t*-butyldimethylsiloxy, chloro, and tosylamide were compatible under the reaction conditions. The diallylation plausibly occurred by consist of two sequential silver-catalyzed allylation reactions, rather than the well-known halogen–metal exchange/migration mechanism, even so the exact mechanism of each allylation reaction was still not clear. Controlled sequential treatment of *gem*-dibromoalkane with two different Grignard reagents resulted in selective displacement of the two bromine atoms. Moreover, dibenzylation has also been extended (Scheme 88).[159]



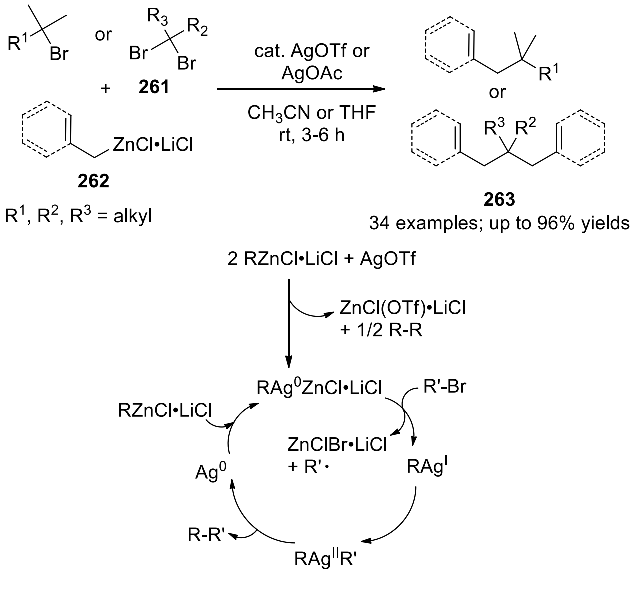
Scheme 88. Diallylation and dibenzylation of *gem*-dibromoalkanes with Grignard Reagents.

Other alkyl- or aryl-substituted Grignard reagents were studied. Under AgBr/KF system, long-chain alkyl Grignard reagents **257** with secondary or tertiary alkyl bromides **256** resulted in the corresponding cross-coupling products **258** in reasonable yields. KF was suggested to dissociate the aggregation of AgBr or stabilize alkylsilver intermediates by coordination to the silver metal. Furthermore, silver showed catalytic activity for the cross-coupling reactions of aryl Grignard reagents **259** with alkyl bromides **256** which occurred under AgBr/P(OPh)$_3$ catalysis in refluxing hexane (Scheme 89).[160]



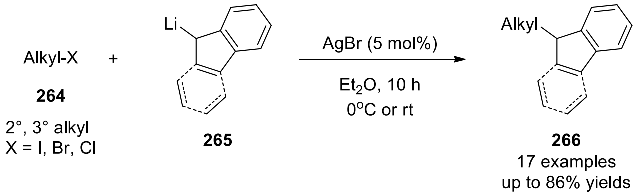
Scheme 89. Cross-coupling reactions of alkyl bromides with alkyl or aryl Grignard reagents.

As is shown above, silver salts have been proven to catalyze the benzylation and allylation of tertiary alkyl halides with benzylic and allylic Grignard reagents, allowing a highly efficient route for the formation of quaternary carbon centers. However, the use of Grignard reagents suffers from poor functional-group compatibility. In 2010, Yorimitsu and Oshima demonstrated that benzylic and allylic zinc reagents **262** were also effective for the silver-catalyzed coupling reaction of *gem*-dibromoalkanes **261**, leading to the corresponding products **263** in good yields with good functional-group tolerance. Although the exact mechanism was unclear, the mechanism of dibenzylation involved double nucleophilic benzylation steps was revealed, which was in accordance to the corresponding monobenzylated tertiary alkyl bromides observed as intermediates (Scheme 90).[161]



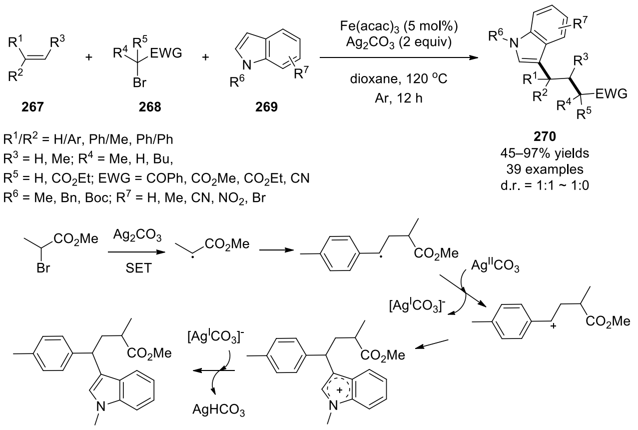
Scheme 90. Benzylation and allylation of tertiary alkyl bromides with organozinc reagents.

In comparison with the rapid development of application with Mg, Zn, Sn, B, or Si as the metal of organometallic reagent, organolithium remains less explored. A silver-catalyzed coupling reaction of secondary/tertiary alkyl halides **264** with indenyllithiums **265** was developed and furnished alkyl-substituted indenes and fluorenes **266** in moderate to good yields. The reaction took place in the presence of 5 mol% AgBr in Et$_2$O at 0 °C or reflux. The mechanism involving monoindenylsilver(0)/ate complex radical was analogous to the coupling with Grignard reagents (Scheme 91).[162]



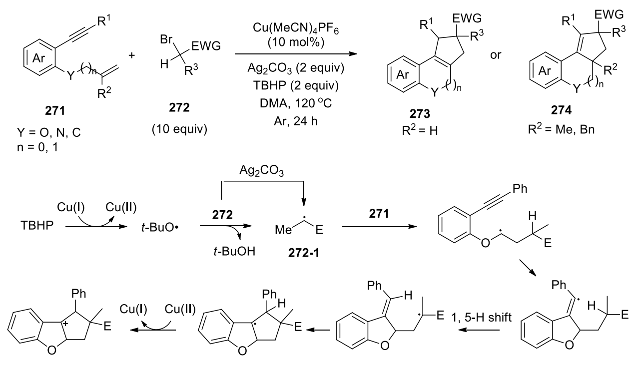
Scheme 91. Coupling reactions of alkyl halides with indenyllithiums.

Despite significant progress in difunctionalization of alkenes, the search for alternatives especially an intermolecular C(sp^2)–H functionalization strategy, beyond oxindole/heterocycles synthesis, for generating two C–C bonds in one step is highly desirable. Recently, Li *et al.* developed the first report of silver-mediated 1,2-alkylarylation of styrenes **267** with α-carbonyl alkyl bromides **268** and indoles **269**. The reaction selectively furnished two C–C bonds in a single step through a sequence of intermolecular C(sp^3)–Br functionalization and C(sp^2)–H functionalization across the alkenes, providing a simple and practical route to synthesize 2- or 3-alkylated indoles **270**. Various primary, secondary, and tertiary α-carbonyl alkyl bromides **268**, including α-bromoalkyl esters, ketones, and nitrile were applicable for the reaction. The strongly electron-deficient aromatic alkenes and aliphatic alkenes were failed to deliver the products. Learning from the mechanistic experiments designed, a probable mechanism involving a generation of C-centered radical and an electrophilic alkylation process was proposed. Fe(acac)$_3$ was observed to improve the yields which might function as a Lewis acid to stabilize the radicals (Scheme 92).[163]



Scheme 92. Intermolecular 1,2-alkylarylation of styrenes with α-carbonyl alkyl bromides and indoles.

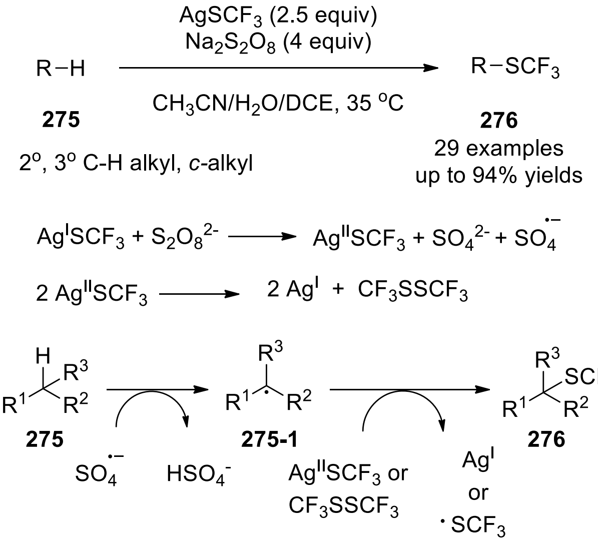
Further, the same group developed the copper(I)-catalyzed oxidative [2+2+1] annulation of 1,*n*-enynes (n = 6, 7) **271** with α-carbonyl alkyl bromides **272**, leading to the formation of a series of substituted heterocycles **273** and **274** in moderate to good yields. Mechanically, alkyl radical **272-1** was generated from α-carbonyl alkyl bromide **272** with Cu(I)/TBHP or Ag_2CO_3. Then, the radical **272-1** inserted into C=C moeity of 1,*n*-enynes followed by radical intramolecular cyclization, 1,5–H shift and annulation in tandem manner, delivering three new C–C bonds and two rings in a single mode. The reaction performed with Ag_2CO_3 and TBHP as oxidant through sequential C(sp^3)–Br cleavage and C(sp^3)–H functionalization. The process represented the first report for the one-step oxidative couplings of the α-C–Br bonds and the α-C–H bonds in α-carbonyl alkyl bromides *via* the 1,5-H shift. Moreover, internal alkene-containing 1,*n*-enynes were incompatible for the transformation (Scheme 93).[164]



Scheme 93. [2+2+1] Annulation of 1,n-enynes with α-carbonyl alkyl bromides.

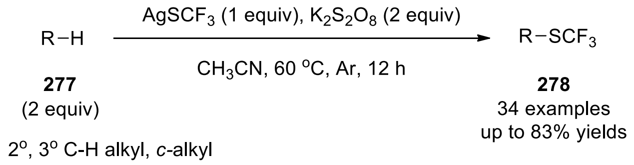
2.6 Unactivated C(sp^3)–H bonds

The development of reagent systems that can efficiently trifluoromethylthiolate the unactivated C(sp^3)–H bonds under mild conditions is highly desirable. Although progress has recently been made in the trifluoromethylthiolation of C(sp)–H and C(sp^2)–H bonds, methods for the transformation of unactivated C(sp^3)–H bonds into C(sp^3)–SCF_3 bonds have hardly been reported and remains a significant challenge.[165] Recently, Tang and co-workers reported the first report of a practical and direct C(sp^3)–H trifluoromethylthiolation method employing $AgSCF_3$ and $Na_2S_2O_8$ under mild conditions. This new and scable approach allowed the functionalization of diverse substrates with secondary and tertiary C(sp^3)–H bonds **275**, affording the corresponding products **276** with high selectivity and in moderate-to-excellent yields, which is potentially used in the pharmaceutics and agricultural production. They reasoned that a biphasic system could physically separate the starting materials and products from the oxidant by adding nonpolar solvents. A significant KIE displayed that that C–H bond cleavage probably involved in the rate-limiting step of this transformation. A mechanism involving a radial chain mechanism or SET process was suggested by the group. The *in situ* generated carbon radical **275-1** by oxidation of C(sp^3)–H bond **275** was plausibly reacting with the Ag^{II}SCF$_3$ or CF_3SSCF_3 to provide the desired trifluoromethylthiolated product (Scheme 94).[166]



Scheme 94. Silver-mediated oxidative aliphatic C–H trifluoromethylthiolation.

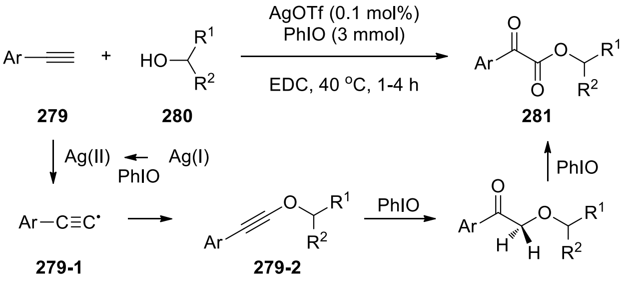
Simultaneously, Liu and Chen *et al.* recommended an analogous trifluoromethylthiolation reaction of unactivated C(sp^3)–H bonds **277** with broad substrate scope and functional-group tolerance by $AgSCF_3/K_2S_2O_8$ at 60°C under argon atmosphere. A similar mechanism was disclosed that $K_2S_2O_8$ played key roles in both the activation of the C(sp^3)–H bond and the oxidation of $AgSCF_3$ to access the trifluoromethylthiolated products **278** in high yields (Scheme 95).[167]



Scheme 95. C(sp^3)–H trifluoromethylthiolation with $AgSCF_3$.

2.7 Alkynes

A highly simple and practical coupling reaction of aryl alkynes **279** and alcohols **280** was reported by the Maiti group, leading to a range of valuable α-ketoesters and their chiral analogues **281** with the aid of silver catalyst as low catalyst loading as 0.1 mol%. Supported by controlled experiments and UV−vis study, a preliminary mechanism was proposed involving a formation of alkynyl radicals **279-1**. Ag(II) species was delivered by iodosylbenzene (PhIO) oxidation, which then converted alkynes **279** into the Ar−C≡C• species **279-1**, followed by C−O coupling with alcohol. The new formed intermediate **279-2** subsequently underwent twice oxidation by PhIO and yielded the final products **281**. With this multiple O−C coupling strategy chiral α-ketoesters could be synthesized with the corresponding chiral alcohol compounds (Scheme 96).[168]

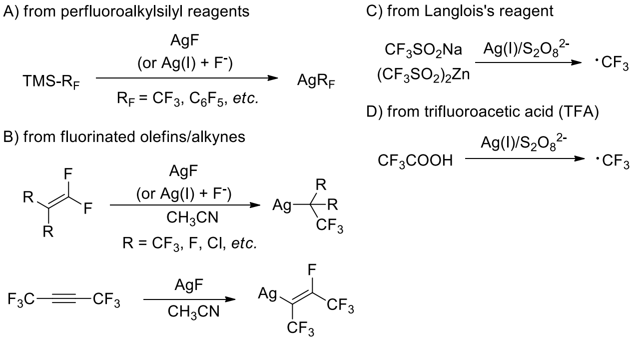


Scheme 96. AgOTf-catalyzed oxo-esterification of alkynes.

2.8 Perfluoroalkyl Radicals

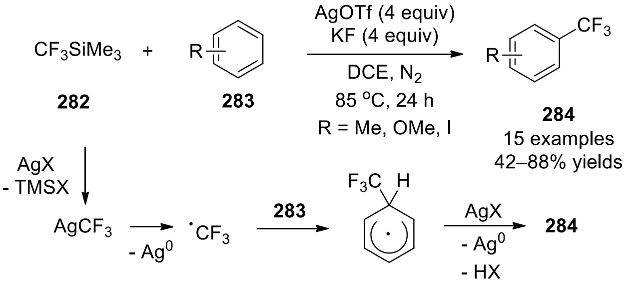
Trifluoromethylated aromatic compounds are widely prevalent in pharmaceuticals, agrochemicals, and organic materials.[169] As a result, the development of transition metal-mediated/catalyzed methods for introducing CF_3 group into organic molecules has been the subject of intense research. Despite the extensive progress, current trifluoromethylation methods have significant limitations, such as expensive trifluoromethylating reagents, high temperature, amd narrow substrate scope. In constrast with electrophilic/nucleophilic reaction, radical-based trifluoromethylation has received increasing attention. By mean of active CF_3 radical species, direct C–H trifluoromethylation could be realized under mild conditions.[170] The original research on CF_3 radical can be traced back in 1968.[171]

As we know, perfluoroorganosilver(I) compounds[172] can be prepared *via* transmetalation step of perfluoroalkylated metal organyls such as (perfluoroalkyl)cadmium compounds with silver(I) salts. Further, they are easily accessible in one step using commercially available AgF with either (perfluoroalkyl)silyl sources or perfluorinated olefins or alkynes (path A and B). However, both of them are limited with the simultaneous generation of a silver(III) species by the *in situ* oxidation of the previously formed perfluoroorganosilver(I) species. More advocated routes to access CF_3 radical are the decomposition of Langlois's reagent (path C) or trifluoroacetic acid (TFA) (path D) under silver(I)/persulfate conditions (Scheme 97).[173]



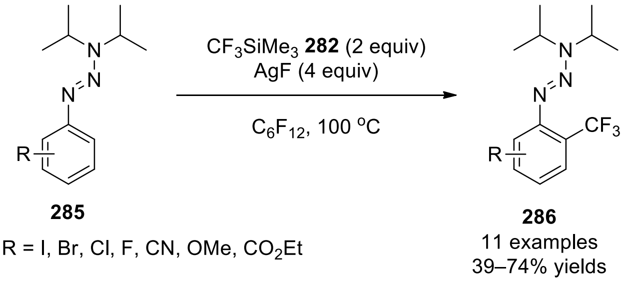
Scheme 97. Generation of CF_3 radical from various precursors.

(Perfluoroalkyl)silyl compounds. The outstanding development for the silver-based CF_3 radical reaction was accomplished by Sanford *et al.* In 2011, Sanford and co-workers reported the silver-mediated direct C−H trifluoromethylation of arenes **283**, affording the trifluoromethylated products **284** in good to excellent yields. An array of electron-rich arenes were well reacted, whereas electron-withdrawing groups, such as chlorine, ester, cyano, sulfone, and nitro group, were not compatible. In comparison with $CuCF_3$ towards $PhCF_3$, the reaction of iodobenzene (PhI) with $AgCF_3$ surprisely afforded low yields of C−H trifluoromethylated product. Among several silver salts tested, AgOTf was the most efficient. The authors proposed that the mechanism involved a [$AgCF_3$] species. $AgCF_3$ was generated *in situ* from the reaction of AgF (AgOTf / KF) with $TMSCF_3$ **282** in CH_3CN, which was the first report for using $TMSCF_3$ **282** as a free CF_3 radical precursor. However, the observed selectivity in the reaction with anisole differs from that obtained by other known radical trifluoromethylation protocols, which suggested against a purely free radical pathway. The requirement of excess aromatic compound, moderate functional-group tolerance and regioselectivities of the products caused limitations of its synthetic application (Scheme 98).[174]



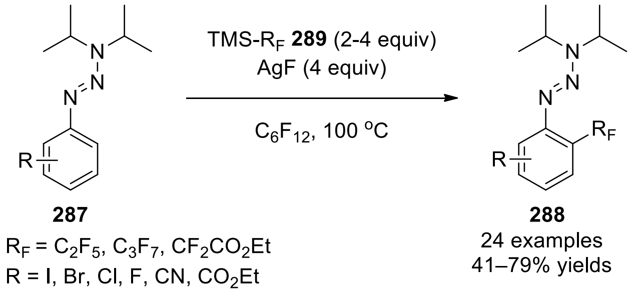
Scheme 98. Silver-mediated trifluoromethylation of arenes with TMSCF$_3$.

Afterwards, Bräse *et al.* demonstrated a silver-mediated *ortho*-selective aromatic C–H trifluoromethylation of substituted aromatic triazenes **285**, furnishing the trifluoromethylated products **286** in high yields and with good functional-group tolerance, such as iodides, bromides. Particularly the application of *para*-substituted triazenes **285** resulted in excellent *ortho*-selectivity. Aromatic triazenes were chosed as particular suitable substrates, which are easily derived from commercially available aniline derivatives. In addition, the triazene group is flexible for further transformations into other functional groups, like iodide and azido group. In contrast to previously reported solvent DCE, CH$_3$CN, perfluorohexane (C$_6$F$_{12}$) was recommended as a nonpolar and inert solvent, thus allowed satisfactory yields. In line with the Sanford's report, the authors proposed a CF$_3$ radical was involved. Nevertheless, the explanation for the remarkable high ortho selectivity of triazenes was still unclear (Scheme 99).[175]



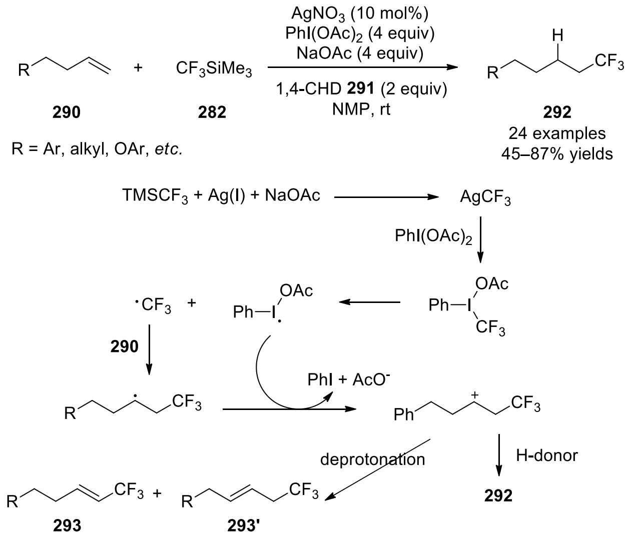
Scheme 99. C–H trifluoromethylation of aromatic triazenes.

Based on the observation, the same group extended this protocol to other silylated perfluoroalkyl sources **289**, containing trimethyl(pentafluoroethyl)silane, (heptafluoropropyl)trimethylsilane, and [(ethoxycarbonyl)difluoromethyl]trimethylsilane, leading to the corresponding fluorinated products **288** in 41–79% yields with high *ortho*-selectivity. Initial reactions under solvent-free conditions indicated a stabilizing interaction between AgR$_F$ species and the triazene moiety, which might be responsible for the good yields and regioselectivity. Moreover, the first quantum chemical calculations suggested that the stabilization of the radical intermediate in the *ortho*-position was distinctly more favored for aromatic triazenes **287** than for other aromatic substrates, which primarily resulted in high reactivity and selectivity. However, in most cases difluorinated products were obtained simultaneously, particularly for the introduction of CF$_2$CO$_2$Et moeity (Scheme 100).[176]



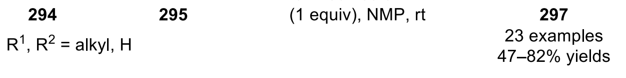
Scheme 100. C–H functionalization of aromatic triazenes with silylated perfluoroalkyl sources.

Despite the pioneering work of Sanford and Bräse, current silver-mediated trifluoromethylation reactions are limited to the construction of C–aryl CF$_3$ bonds, the trifluoromethylation of alkenes, especially unactivated alkenes, is still underdeveloped. Furthermore, these transformations require stoichiometric amounts of silver salts to generate the reactive intermediate AgCF$_3$. To address these limitations, Qing's group developed the first example of the silver-catalyzed hydrotrifluoromethylation of simple unactivated alkenes **290** with TMSCF$_3$ **282** as the trifluoromethyl source and PhI(OAc)$_2$ as the oxidant. The mild reaction conditions allowed an efficient access to a series of trifluoromethylated alkanes **291** bearing a wide range of functional groups which are usually produced by either a two-step reaction of olefins or hydrogenation of trifluoromethylated alkenes. The success of this reaction relied on the use of a silver(I) salt and a hydrogen donor to inhibit the competitive deprotonative trifluoromethylation reaction that allowed by-products **293** and **293'**. The preliminary mechanistic investigations suggested the involvement of CF$_3$ radical species and H-abstraction process. Upon addition of hydrogen donors such as 1,4-cyclohexadiene (1,4-CHD), Bu$_3$SnH, Et$_3$SiH, and 1,3-dioxolane, 1,4-CHD **291** was optimal. Electron-poor alkenes, like benzyl acrylate was uncompatible under the standard reaction conditions (Scheme 101).[177]



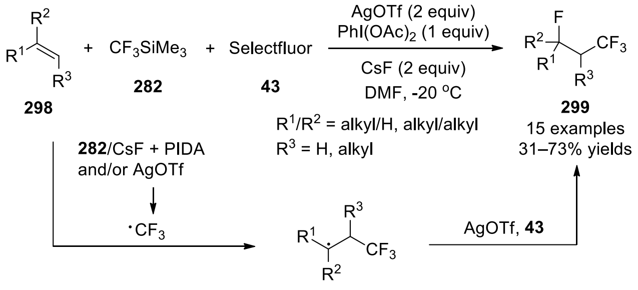
Scheme 101. Hydrotrifluoromethylation of unactivated alkenes.

In contrast to the significant achievements of trifluoromethylation transformations, the transition metal-mediated hydrodifluoroalkylation to construct C(sp^3)–CF$_2$ bonds is still underdeveloped because of the instability of difluoroalkyl intermediates. Despite significant advances in the construction of C(sp^3)–CF$_2$COOEt, the difluoromethylation process still remains challenging, and only several examples have been developed so far. In 2014, Wan and Hao *et al.* described the silver-mediated hydrodifluoromethylation of unactivated alkenes **294**, providing a convenient approach for the assembly of a variety of vicinal α-difluoroacetate alkanes **297** in high yields. Similarly, a CF$_2$COOEt radical species plausibly generated from α-silyldifluoroacetates (TMSCF$_2$COOEt) **295** inserted into double bond of alkene, followed by a single-electron oxidation to afford an alkyl cation intermediate. Hanztsch ester (diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate) **296** worked as a useful hydrogen donor in the reductive intermolecular hydrodifluoromethylation. This practical hydrodifluoromethylation protocol allowed the introduction of a terminal CF$_2$COOEt group into a broad range of simple and complex alkenes, like biologically active compounds (*i.e.*, quinine or estrone derivative) (Scheme 102).[178]



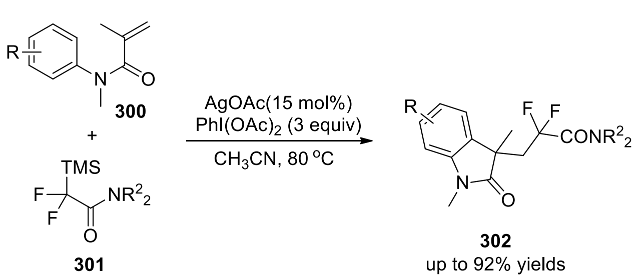
Scheme 102. Hydrodifluoromethylation of unactivated alkenes with α-silyldifluoroacetates.

Recently, the Qing group realized fluorotrifluoromethylation of unactivated alkenes **298** by employing TMSCF$_3$ **282** as trifluoromethylating source, and Selectfluor **43** as fluorine source under oxidative conditions. A series of fluorotrifluoromethylated alkanes **299** with good functional-group compatibility were obtained in 31–73% yields. The silver salt was demonstrated crucial for this transformation. A mechanism involving a CF$_3$ radical insertion, as well as fluorine atom migration by the combination of silver(I) and Selectfluor was proposed (Scheme 103).[179]



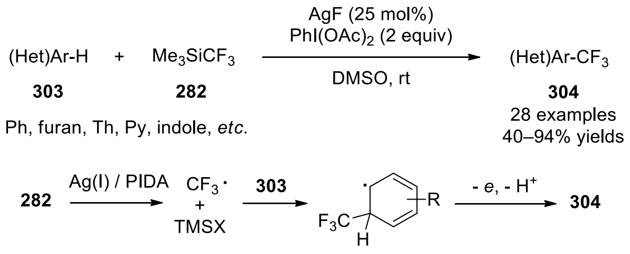
Scheme 103. Silver-mediated oxidative fluorotrifluoromethylation of unactivated alkenes.

A spectrum of functionalized difluoroamidated 3,3-disubstituted oxindoles **302** were delivered under AgOAc catalysis. In this process, a difluoroamidic radical was generated from α,α-difluoro-α-(TMS)-acetamide **301** and added to acrylamide **300** performing a radical substitution procedure to produce the expected product **302**. Moreover, the corresponding oxindoles **302** could be converted to the difluorofunctionalized alcohol, ketone, and ester with high yields under suitable conditions (Scheme 104).[180]



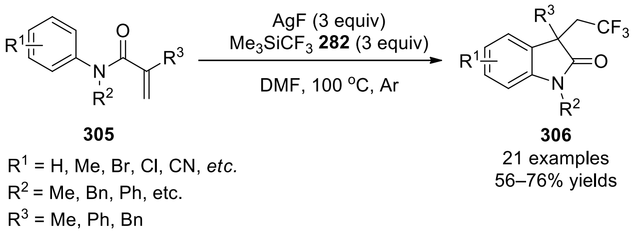
Scheme 104. Synthesis of difluorinated 3,3-disubstituted oxindoles.

With the employment of silver(I)/TMSCF$_3$/PhI(OAc)$_2$ system, an operationally simple trifluoromethylation approach for electron-rich aromatic and heteroaromatic substrates **303** was developed by Greaney *et al.* in 2013, without excessive stoichiometries of substrate or reagent. Arenes with multiple methyl/methoxy group, *N*-protected aniline, heteroarenes (*i.e.*, pyrroles, furan, thiophenes and indoles), and even unactivated arenes benzene **303** were acceptable, leading to the formation of trifluoromethylated products **304** in 40–94% yields. It was unveiled that the AgF/PhI(OAc)$_2$ system was crucial for the effective generation of CF$_3$ radicals. The yields of reactive CF$_3$ radicals were decreased in the presence of TEMPO as a radical scavenger (Scheme 105).[181]



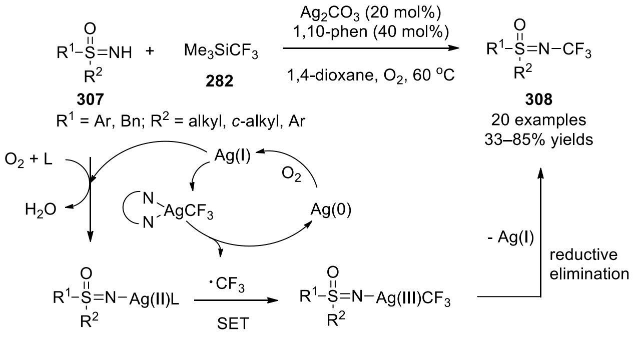
Scheme 105. AgF-catalyzed trifluoromethylation of arenes.

In 2014, the Chen group reported a radical tandem reaction of *N*-arylacrylamides **305** with [AgCF$_3$] species generated *in situ* from TMSCF$_3$ **282** and AgF. This trifluoromethylarylation provided a very concise access to a library of functionalized trifluoromethylated oxindole derivatives **306** in high yields within four hours (Scheme 106).[182]



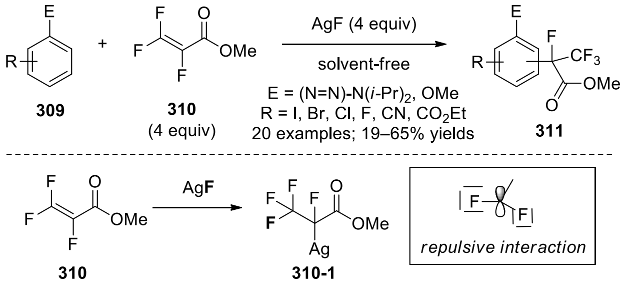
Scheme 106. Formation of trifluoromethylated oxindole.

In sharp contrast to the well-developed C-trifluoromethylations, the formation of *N*−CF$_3$ bonds is still challenging, commonly involving a critical use of toxic reagents under harsh reaction conditions. For direct electrophilic *N*-trifluoromethylations (with the nitrogen atom being a hard nucleophile), only a few methods are known. Recently, a significant development of *N*-trifluoromethylation formation with sulfoximines **307** and TMSCF$_3$ **282** was done by Cheng and Bolm *et al.*, resulting in a range of sulfoximine derivatives **308** with good functional-group tolerance in 33–85% yields. The reaction progressed with the combination of Ag$_2$CO$_3$ and 1,10-phen as cocatalysts under dioxygen condition. Learning from the primary mechanism studies, a radical process was proposed and both Ag$_2$CO$_3$ and 1,10-phenanthroline were essential to generate the CF$_3$ radical. Remarkably, the C−N bond length at the *N*−CF$_3$ moiety was comparable with a C=N double bond, rather than a traditional C−N single bond. In the extension of substrate scope, diphenylmethanimine also furnished the *N*-trifluoromethylated product under standard conditions, albeit gave a low yield (Scheme 107).[183]



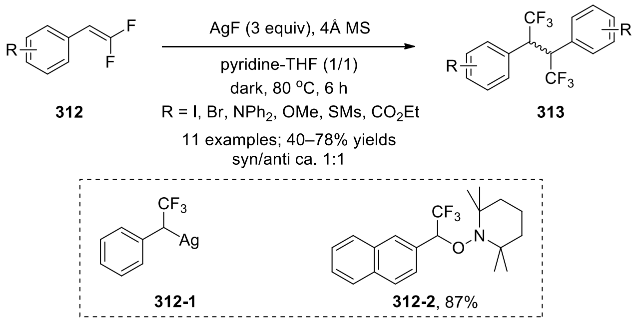
Scheme 107. Ag$_2$CO$_3$-catalyzed *N*-trifluoromethylation of sulfoximines.

Fluorinated Olefins. Learning from [AgCF$_3$] species that can be easily generated *in situ* and decomposed to CF$_3$• radicals, the synthesis and application of other fluorinated silver species have been discussed. The highly fluorinated olefins were used as a perfluoroalkyl source. Due to the repulsive interactions between the lone electron pairs of the fluorine substituent and the π-orbital of the sp^2-carbon, fluoride ions were regioselectively merged into fluorinated olefins **310** in a donor solvent like acetonitrile (**310** → **310-1**). In the light of this concept, the Bräse group used the methoxycarbonyltetrafluoroethyl silver generated *in situ* from AgF and methyl 2,3,3-trifluoroacrylate (MTA) **310** to accomplish the C–H functionalition of substituted arenes **309**. Various aromatic triazenes and anisole derivatives **309** with good functional-group tolerance were acceptable and resulted in the methoxycarbonyltetrafluoroethylated products **311** in moderate yields. The use of solvent-free conditions was contributed to suppress the dimerization/oligomerization of the olefin. When *para*-substituted aromatic triazenes were used, the *ortho*-fluorinated products were synthesized availably, whereas the *para*-fluorinated products were preferred by using *ortho*-substituted triazenes. The highly fluorinated olefins were employed in the perfluoroalkylation reaction with aromatic substrates for the first time (Scheme 108).[184]



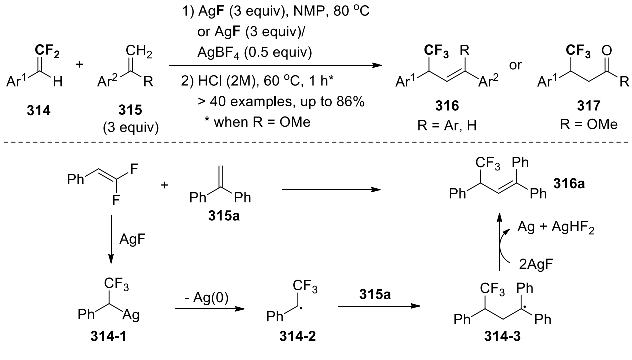
Scheme 108. AgF-mediated methoxycarbonyltetrafluoroethylation of arenes.

Hu *et al.* also envisioned that the *gem*-difluorovinyl group would be an attractive alternative CF_3 precursor, which resulted in a novel AgF-mediated homocoupling reaction of β,β-difluorostyrenes **312**. The dimers **313** possessed unique chemical structure, which might have potential application in biology and materials science. The precursors with electron-donating/poor substituents **312** furnished the products in 40–78% yields, and the syn/anti ratios of the majority of products were nearly 1:1. The transformation was plausibly initiated *via* a nucleophilic addition of β,β-difluorostyrenes **312** with AgF to form (α-trifluoromethyl)benzylsilver species [$CF_3CH(Ar)–Ag^I$] **312-1** which subsequently underwent the dimerization step. A free radical process was confirmed as an adduct with TEMPO **312-2** was detected. AgF acted as both an oxidant and a base throughout the transformation. The chemistry and employment of [$CF_3CH(Ar)–Ag^I$] **312-1** was demonstrated for the first time (Scheme 109).[185]



Scheme 109. AgF-mediated fluorinative homocoupling of β,β-difluorostyrenes.

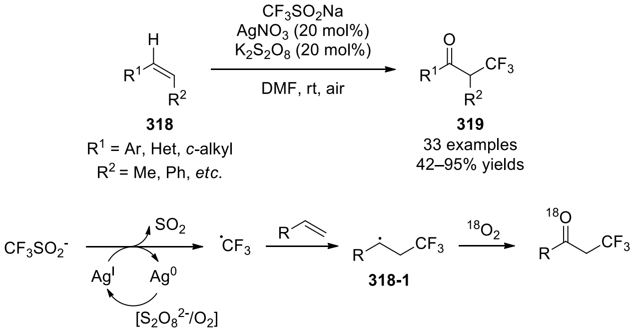
Further, Hu's group incorporated a AgF-mediated fluorination and a concomitant cross-coupling step between a *gem*-difluoroolefin **314** and a non-fluorinated olefin **315**, providing a novel and simple entry for the generation of α-CF_3 alkenes **316** and β-CF_3 ketones **317**. This practical approach represented a conceptually novel route to trifluoromethylated compounds that combines the *in situ* generation of the CF_3 moiety and a C–H functionalization in a single reaction system. A series of β,β-difluorostyrene derivatives **314** were tolerated with a broad range of functional groups; Notably, difluoroolefins with electron-withdrawing groups on the aromatic rings were generally more reactive towards AgF, and therefore, the reaction proceeded more efficiently. Meanwhile, the addition of $AgBF_4$ was beneficial to suppress the hydrofluorination of *gem*-difluoroolefins and accelerate the reaction efficiency. Mechanically, a α-CF_3-benzylsilver intermediate **314-1** generated upon *gem*-difluoroolefin **314**, underwent rapid C–Ag(I) bond homolysis to afford the α-CF_3 benzyl radical **314-2** and silver(0); the nonfluorinated alkene **315a** then reacted with the radical **314-2** forming a new carbon-centered radical **314-3**. The resulting carbon radical **314-3** underwent a SET process and rapid deprotonation to give the α-CF_3 alkene **316a**, thus completing a net fluorination/intermolecular alkenyl C–H functionalization reaction. A subsequent hydrolysis was performed when α-methoxystyrenes was used as a component. Compared with the direct trifluoromethylation or alkylation using CF_3-containing reagents, this procedure shows specific applications, such as for the synthesis of ^{18}F-labelled CF_3 compounds. (Scheme 110).[186]



Scheme 110. Formation of α-CF_3 alkenes and β-CF_3 ketones.

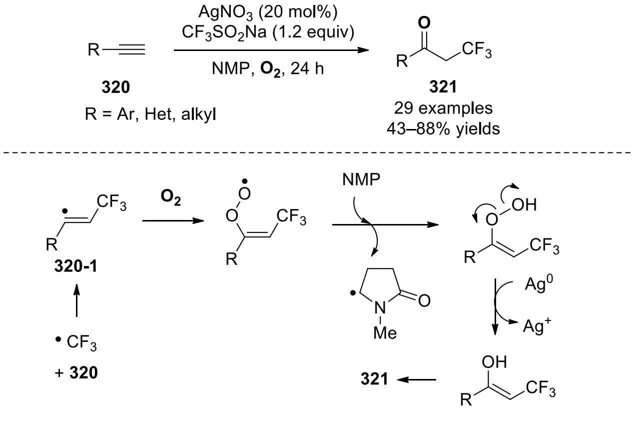
Langlois Reagents. Langlois reagent is an attractive CF_3 source. It has been known since 1989 that alkali metal trifluoromethanesulfinates can transfer the CF_3 group into CF_3• species that, in turn, initiate trifluoromethylation of arenes and electron-rich double bonds. Since the original publication, a considerable number of papers have appeared about the employment of CF_3SO_2Na and also zinc difluoromethanesulfinate [$(CF_2HSO_2)_2Zn$, also known as Baran reagent].[187]

The synthesis of α-CF_3-substituted carbonyl compounds has recently drawn significant attention, owing to their importance for both pharmaceutical and synthetic research. Although simple styrenes successfully functioned as substrate, low yields and usage of costly $[Ph_2SCF_3]^+OTf^-$ as trifluoromethylating agent remained limitations. By using an inexpensive trifluoromethylating reagent (CF_3SO_2Na) and silver(I)/persulfate system, Maiti *et al.* in 2013 disclosed a direct, efficient, and general method for the formation of α-CF_3-substituted ketones **319** from simple unactivated olefins **318** under mild and open-flask conditions. A wide range of olefins with diverse substituents/functional groups, including styrene derivatives, heteroaromatic olefins (*i.e.* pyrazole and indazole) as well as vinyl cycloalkanes were compatible for the transformation and delivered moderate to excellent yields. The preliminary investigations suggested the involvment of CF_3• species. The mechantic experiments, such as ^{18}O-labeling experiment and X-ray photoelectron spectroscopy (XPS) experiment, were revealed that the strategy underwent *via* a benzylic radical intermediate **318-1** followed by oxidation step with O_2 and/or $K_2S_2O_8$ (Scheme 111).[188]



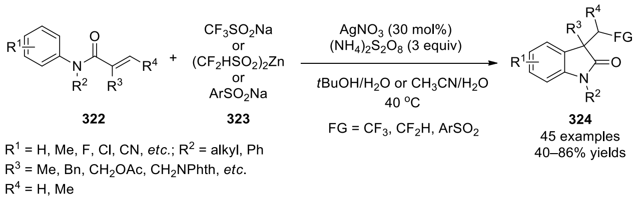
Scheme 111. Synthesis of α-CF_3-substituted ketones from unactivated olefins.

Further, the same group extended the scope of silver-catalyzed oxidative trifluoromethylation reaction to heteroaromatics, such as thiophene, pyrimidine, indole, benothiazole, and thiazolone by using terminal alkynes **320** as the material. A wide range of α-trifluoromethyl ketones bearing aryl, heteroaryl, and alkyl groups **321** could be allowed in 43–88% yields. Mechanistic investigations, such as isotope labeling, kinetic studies, and radical capture experiment with $P(OEt)_3$ were conducted and indicated a generation of α-styrenyl radical intermediate **320-1**. The solvent 1-methyl-2-pyrrolidinone (NMP) was crucial to provide a hydrogen atom (Scheme 112).[189]



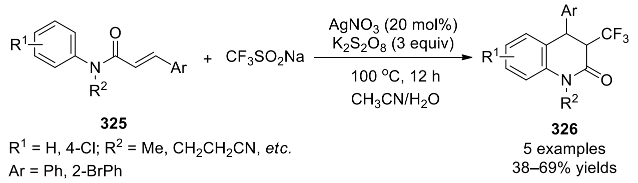
Scheme 112. Synthesis of α-CF_3-substituted ketones from alkynes.

By using Langlois reagent as the CF_3 source and $(NH_4)_2S_2O_8$ as the oxidant, Tan *et al.* developed a silver-catalyzed trifluoromethylation-cyclization reaction of *N*-arylacrylamides **322**, allowing a mild and available strategy for the assembly of trifluoromethyl-substituted oxindoles **324** in moderate to high yields. Various *N*-alkyl or *N*-aryl protected acrylamides **322**, bearing methyl, benzyl, acetoxymethyl, and phthalimidylmethyl at the α-position, reacted smoothly and furnished the corresponding oxindoles **324**. In addition, difluoromethylation and sulfonylation reactions could be also achieved through a similar radical cascade procedure when Langlois reagent was replaced by zinc difluoromethanesulfinate $[Zn(SO_2CF_2H)_2]$ and arylsulfinic acid sodium salt **323** (Scheme 113).[190]



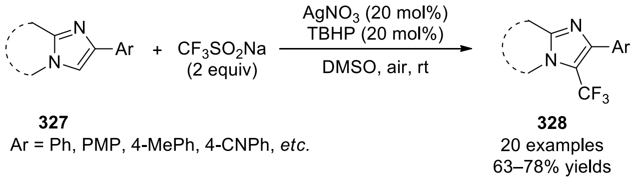
Scheme 113. Silver-catalyzed trifluoromethylation-cyclization reaction of *N*-arylacrylamides.

A contrastive radical cyclization of *N*-arylcinnamamides **325** affording various 3-CF_3 substituted 3,4-disubstituted dihydroquinolin-2(1*H*)-ones **326** was reported, which led to the formation of a six-membered ring *via* a 6-*endo*-type annulation owing to the stabilization effect of the aryl group at the β-position of the acrylamides (Scheme 114).[191]



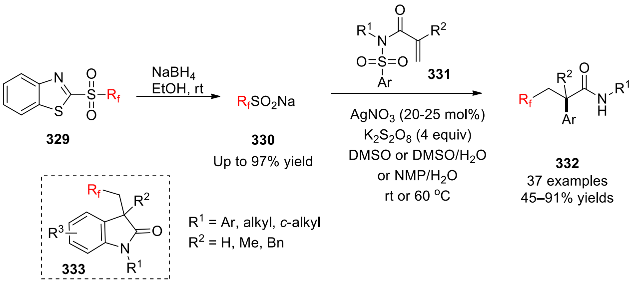
Scheme 114. Synthesis of 3-CF_3 substituted 3,4-disubstituted dihydroquinolin-2(1*H*)-ones.

Despite the significant progress, the direct and catalytic trifluoromethylation of biologically active nonprefunctionalized heterocyles is still remained challenging. In 2015, Hajra and co-workers developed the first report for the direct trifluoromethylation of imidazopyridines **327**, leading to an array of 3-(trifluoromethyl)imidazo[1,2-*a*]pyridine derivatives **328** with broad functionalities and high regioselectives. The facile reaction preformed with Langlois reagent in the presence of $AgNO_3$ and TBHP under air conditions, in which a CF_3 radical was plausibly formed. In addition, imidazo[2,1-*b*]thiazole and benzo[d]imidazo[2,1-*b*]thiazole were compatiable under the standard conditions (Scheme 115).[192]



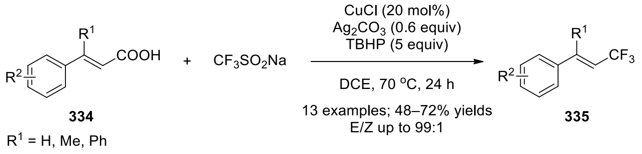
Scheme 115. Direct trifluoromethylation of imidazopyridines.

Compared with the flourishing development of introduction of CF_3 group to molecules, methods for the straightforward introduction of CF_2H and CH_2F groups *via* a radical process are limited. Although zinc sulfonates and sodium difluoromethanesulfinate have been used for di- and monofluoromethylation, complex procedures for the preparation and purification of the zinc sulfonates, and low yield for sodium difluoromethanesulfinate from difluoromethyl halides hindered their wide application. Recently, Hu *et al.* developed a novel, practical and large-scalable method to synthesize sodium fluoroalkanesulfinates R_fSO_2Na (R_f = CF_2H, CF_2Ph, and CH_2F) **330** *via* $NaBH_4$-mediated reduction of the corresponding benzo[*d*]thiazol-2-yl (BT) sulfones **329**. Furthermore, on the basis of Nevado group's work, these sodium fluoroalkylsulfinates R_fSO_2Na **330** were proven to be good radical fluoroalkylation reagents that readily react with tosyl acrylamides **331** under $AgNO_3/K_2S_2O_8$ system. Generally, α-aryl-β-fluoroalkyl amides **332** were achieved selectively, rather than cyclized products (oxindoles) **333**, in the cases of both *N*-alkyl and *N*-alkyl substituted acrylamides **331**. A mechanism containing cascade fluoroalkylation, intramolecular 1,4-aryl migration, desulfonylation, and H atom abstraction step was proposed. The reactivity of these sodium sulfinates in their reactions decreases in the following order: $PhCF_2SO_2Na$ > HCF_2SO_2Na > H_2CFSO_2Na, which resulted in the reaction of H_2CFSO_2Na occurred at a slight elevated temperature and very low yields were obtained with substrates bearing *N*-alkyl substituted moeties (Scheme 116).[193]



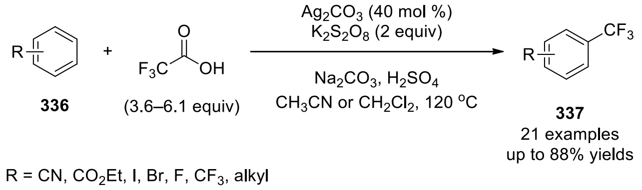
Scheme 116. Fluoroalkylative aryl migration of conjugated sulfonylated amides with R_fSO_2Na.

In 2013, the Liu and Maiti groups independently reported the decarboxylative trifluoromethylation of cinnamic acids with Langlois reagent CF_3SO_2Na under the copper(II)/TBHP[194] or iron(III)/ persulfate catalysis system.[195] However neither Liu's nor Maiti's work apply to halogenated compounds[195] or α,β-unsaturated carboxylic acid compounds that are substituted at the β-position. Inspired by the process mentioned above, the Duan group developed a protocol for the construction of $C(sp^2)-CF_3$ bonds through a Cu/Ag-catalyzed decarboxylative trifluoromethylation of α,β-unsaturated carboxylic acid derivatives **334** with CF_3SO_2Na. This reaction proceeded well for a wide range of α,β-unsaturated carboxylic acids (R^1 = H, Me, Ph) and received the trifluoromethyl-substituted olefins **335** in 48–72% yields with excellent E/Z selectivity. The inclusion of Ag_2CO_3 additives was crucial for promoting the decarboxylation of cinnamic acids **334** (Scheme 117).[196]



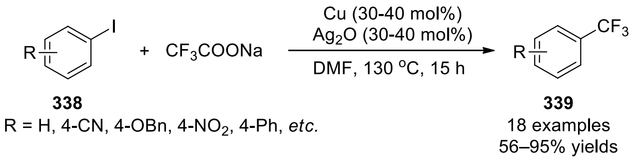
Scheme 117. Decarboxylative trifluoromethylation of cinnamic acids.

Trifluoroacetic Acid. Many of the CF_3 reagents are expensive, toxic, or operationally inconvenient, and some are not commercially available or generate large quantities of chemical waste. In this view, the stable and commercially available trifluoroacetic acid (TFA) was employed as the trifluoromethylating reagent by the Zhang group, who successfully developed a silver-catalyzed C−H trifluoromethylation reaction of arenes **336**. This reaction provides the first example for the generation of CF_3• from TFA, and it is reasoned that can be used for other trifluoromethylation reactions. The reaction tolerated a range of different functional groups, such as F, Br, I, CF_3, and CO_2Me. Regioselectivity varied depending on the substrate. In most cases, products **337** bearing *ortho*-CF_3 group to the cyano group were produced preferentially (Scheme 118).[197]



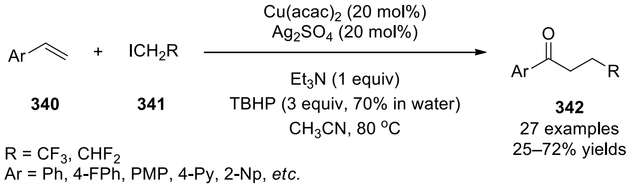
Scheme 118. C−H trifluoromethylation reaction of arenes with TFA.

CF_3CO_2Na can be used as CF_3 source as well. A practical and ligand-free Cu-catalyzed decarboxylative trifluoromethylation of aryl iodides **338** with CF_3CO_2Na was reported by Li and Duan *et al.* in 2012. A variety of trifluoromethyl-substituted aromatics **339** were delivered in moderate to excellent yields and with wide functional-group tolerance. The catalytic amount of Ag_2O was used as a promoter. The experimental results indicated that Ag_2O was crucial for the success of Ar–CF_3 bond forming, which might be because the decarboxylation of CF_3CO_2Na into $AgCF_3$ *in situ* has lower activation energy in comparison with $CuCF_3$, and the formation of silver iodide precipitation accelerated the reductive elimination step (Scheme 119).[198]



Scheme 119. Decarboxylative trifluoromethylation of aryl iodides with CF_3CO_2Na.

Recently, Deng and Xiang *et al.* developed a simple oxidative coupling reaction for the synthesis of β-CF_3/CHF_2-substituted ketones **342** from vinylarenes **340** with ICH_2CF_3 or ICH_2CHF_2 **341** under copper/silver cocatalysis. A radical pathway was proposed. The CF_3CH_2• radical was derived from ICH_2CF_3 **341** by mean of the combination of $Cu(acac)_2$ and Ag_2SO_4. According to the Hard-Soft-Acid-Base (HSAB) theory, Ag(I) was important to facilitate the generation of CF_3CH_2• radical, which resulted in the requirement of Ag_2SO_4 as cocatalyst for the oxidative coupling (Scheme 120).[199]



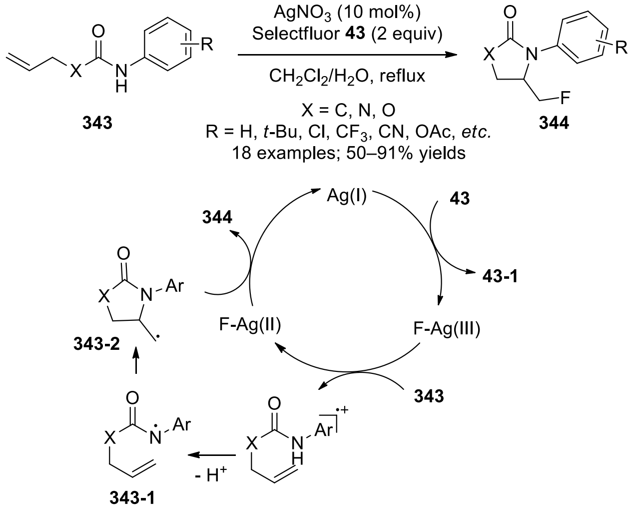
Scheme 120. Synthesis of β-CF_3/CHF_2-substituted ketones.

3. Nitrogen Radicals

3.1 Amino, Imino, and Amidyl radicals

In comparison to the corresponding carbon radicals, nitrogen radicals have not been paid much attention owing to their instability and challenging synthesis. Over the last ten years, nitrogen radical[200] cyclization reactions have been employed to synthesize many useful molecules such as lactams, pyrrolidines and alkaloids. Among nitrogen radicals such as amino radicals, imino radicals, and amidyl radicals have been developed for nitrogen-centered radical cyclizations, which suffer from regioselective control and ease to *H*-abstraction or be oxidized.

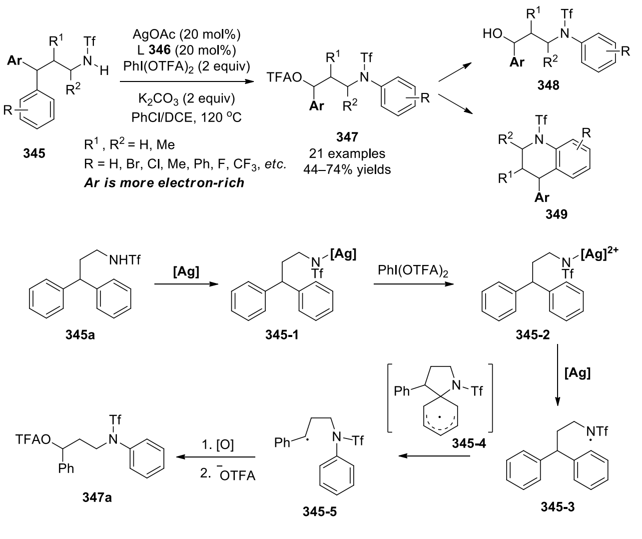
Free radical fluorination is emerging as a powerful tool for C(sp^3)−F bond formation, especially under the catalysis of transition metals. Encouraged by the decarboxylation fluorination, in 2013 the Li group developed a mild silver(I)-catalyzed intramolecular aminofluorination of unactivated alkenes **343** in aqueous media. An array of *N*-arylpent-4-enamides **343** bearing an electron-donating group on the aryl ring (*i.e.*, *t*-Bu, OAc, OCF_3), or a strong electron-withdrawing substituent were compatible, thus leading to the expected 5-fluoromethyl-substituted γ-lactams **344** under the silver(I)/Selectfluor oxidative conditions. Selectfluor **43** serves as both the fluorine source and the oxidant. The biphasic system (such as CH_2Cl_2/H_2O) makes the product from further oxidation, which facilitates the reaction outcomes. A mechanism was proposed, which involves silver(I)-catalyzed oxidative generation of amidyl radicals **343-1** followed by 5-*exo*-mode cyclization to give a new carbon radical **343-2** and a sequent silver-assisted fluorine atom transfer. This current radical difunctionalization procedure provides a convenient and practical entry for the synthesis of fluorinated compounds (Scheme 121).[201]



Scheme 121. Intramolecular aminofluorination of *N*-arylpent-4-enamides.

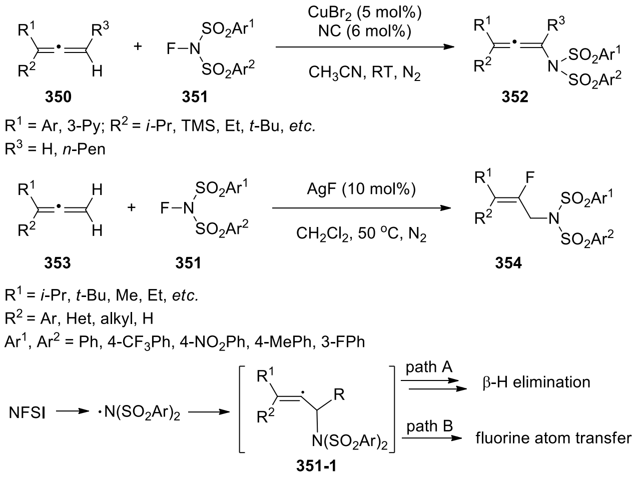
The strategy that radical initiated an aryl migration/desulfonylation sequence of tosyl acrylamides under copper or silver catalysis have been set up by the Nevado group. The generated *in siut* amidyl radicals subsequently undergo various different processes, such as H–abstraction and C–H functionalization to form the new N–H or N–C bonds.[202]

Among different approaches towards selective C−C bond activation/cleavage, the migration of carbon-based groups is common and important to facilitate the C−C cleavage and new C−C formation. In general, group migration takes place only at carbon adjacent to the center carbon of carbon cations, radicals, or carbenes. Recently, the Shi group developed a novel long-distance aryl migration of γ,γ-disubstituted triflic amides **345** through C−C bond cleavage with the combination of AgOAc and *N*-ligand (4,4'-di-tert-butyl-2,2'-bipyridine) **346**, in which aryl migration from a carbon to a nitrogen center took place. More electron-rich aryl groups showed better performance than electron-deficient aryl motifs during the migration. Mechanistic studies indicated a silver-promoted radical pathway. Firstly, substrate **345a** underwent deprotonation and coordination with the activated Ag(I) species forming complex **345-1** which was easily oxidized to Ag(II) complex **345-2** by [bis(trifluoroacetoxy)iodo]benzene (PhI(OTFA)$_2$). Subsequently, homolytic cleavage of the N−Ag bond resulted in the electron-deficient *N*-centered radical **345-3** and regenerated Ag(I) species. Afterwards, radical **345-3** converted into the stable benzylic radical **345-5** through the key intermediate σ-complex **345-4** initiated aryl migration. This benzylic radical **345-5** underwent oxidation and reacted with trifluoroacetoxy anion to achieve the final product **347a**. The migration products were easily converted into γ-hydroxy amines **348** and tetrahydroquinoline derivatives **349** under mild conditions (Scheme 122).[203]



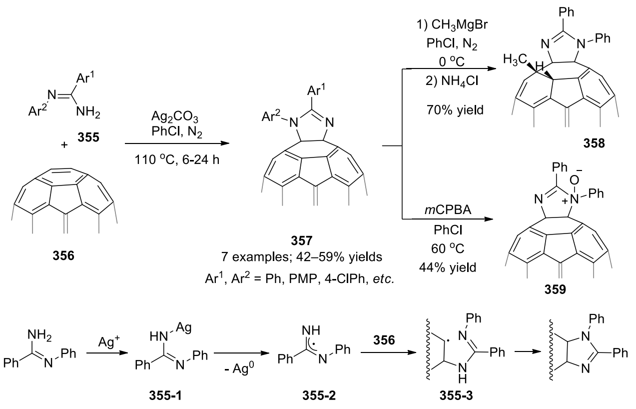
Scheme 122. Long-distance aryl migration of γ,γ-disubstituted triflic amides.

In 2015, the Zhang group developed the first report of the regioselective oxidative C–H amination reaction for the synthesis of various allenamides **352** under copper catalysis, starting from functionalized terminal/internal allenes **350** with *N*-fluoroarylsulfonimides (NFSI) **351**. Whereas, with AgF as catalyst, aminofluorination products (fluorinated tetrasubstituted alkenes) **354** with good functional-group tolerance were allowed directly, in which the terminal allenes **353** should be used. Sterical hindered metal-stabilized nitrogen radical species could be generated upon *N*-fluorobenzenesulfonimide under mild conditions, and then added to allene moiety to form vinyl radical intermediate **351-1**. The vinyl radical **351-1** subsequently underwent β-hyride elimination or fluorine atom transfer to deliver the allenamide **352** or product **354**, respectively (Scheme 123).[204]



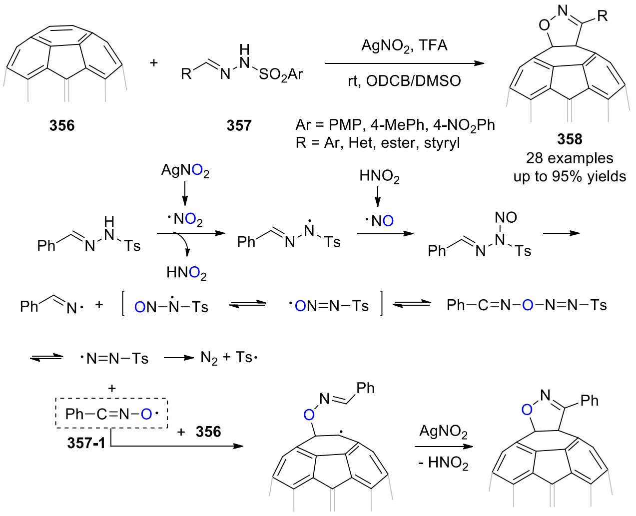
Scheme 123. Reaction of terminal and internal allenes with *N*-fluoroarylsulfonimides.

Although various reactions of [60]fullerene (C$_{60}$) mediated by Mn(OAc)$_3$ and Fe(ClO$_4$)$_3$ have been reported, the utilization of other transition metal salts including silver salts in radical modes is underdeveloped. In 2013, Wang and co-workers applied Ag$_2$CO$_3$ for the radical reaction of [60]fullerene **356** with (Z)-*N'*-arylbenzimidamides **355** affording unprecedented C$_{60}$-fused imidazolines **357** with medium yields.[205] Substrates **355** with both electron-donating and electron-withdrawing groups on aromatic rings were well tolerated. The molar ratio of C$_{60}$/amidine/Ag$_2$CO$_3$ = 1:3:2 was used to achieve higher conversions and product yields. The reaction between *N'*-arylbenzimidamide **355** and Ag$_2$CO$_3$ initially generates N–Ag bond **355-1**, followed by a homolytic cleavage to provide radical species **355-2**. Alternatively, the intermediate **355-3** may also be formed by the homolytic addition of species **355-1** to C$_{60}$. However, the concerted [3+2] annulation process of amidines **355** to C$_{60}$ *via* a nitrene intermediate could not be excluded.[206] Additionally, further selective functionalization of the obtained C$_{60}$-fused imidazolines by a Grignard reagent and 3-chloroperbenzoic acid (*m*CPBA) was demonstrated, leading to regioisomeric products with a 1,2,3,4-configuration or nitroxide products **358** and **359**, which would be difficult to synthesize *via* the existing methods (Scheme 124).



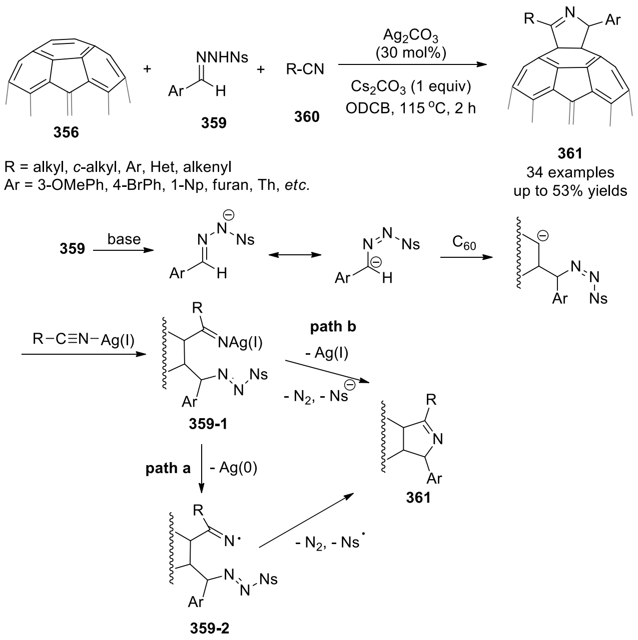
Scheme 124. Formation of C_{60}-fused imidazolines from C_{60} with (Z)-*N'*-arylbenzimidamides.

Further, Zhang *et al.* developed a $AgNO_2$-promoted radical [3+2] annulation to access fulleroisoxazoline derivatives **358** from sulfonylhydrazones **357** with C_{60} **356**. The annulation possessed a wide range of substrate scope and good functional-group compatibility. The coupling (C_{60}/benzenesulfonyl/$AgNO_2$/TFA = 1/2/2/2) occurred in a mixture of anhydrous ODCB (*ortho*-dichlorobenzene) and DMSO at room temperature. A plausible mechanism involving the cleavage of N–N bond and the generation of NO radical to deliver the key radical intermediate **357-1** was suggested. Remarkably, the oxygen atom in isoxazoline framwork was revealed to be originated from $AgNO_2$ (Scheme 125).[207]



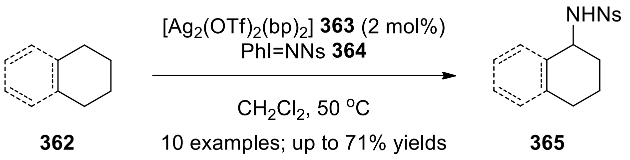
Scheme 125. Radical [3 + 2] annulation of sulfonylhydrazones with C_{60}.

Recently, a novel silver(I)-catalyzed three-component annulation reaction of C_{60} **356** with sulfonylhydrazones **359** and nitriles **360** was reported by Liu and Zhang *et al.*, offering a simple and consice route for the assembly of diverse disubstituted C_{60}-fused dihydropyrroles **361** with excellent functional-group tolerance. Based on the preliminary mechanistic studies, two possible mechanisms were proposed to occurr simultaneously that complex **359-1** underwent one-electron oxidation to give imine radical species **359-2**, followed by a radical cyclization (path a), or underwent an intramolecular nucleophilic addition to give the final product **361** (path b). Moreover, fullerene was likely oxidized by Ag(I) forming a fulleryl radical cation for the initiation of the transformation, which was not ruled out (Scheme 126).[208]



Scheme 126. Formation of [60]fullerene-fused dihydropyrroles.

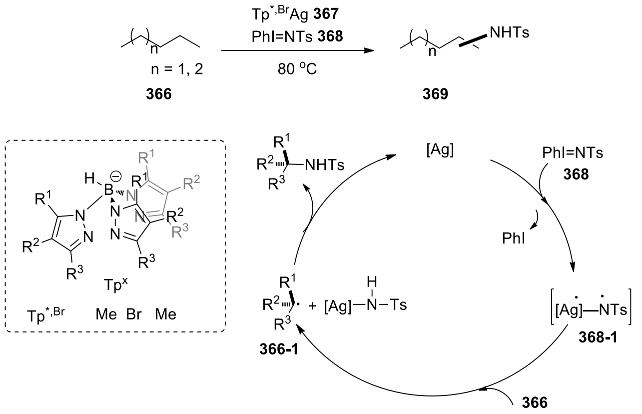
In 2007, He and co-workers reported an intermolecular amination of C(sp^3)–H bonds using a disilver complex **363** as catalyst, PhI=NNs (Ns = *p*-nitrosulfonyl) **364** as the nitrene source. Both benzylic C–H bonds and inert cycloalkanes **362** were applicable, leading to the desired aminated products **365** in high yields under the standard conditions. The application of disilver catalyst **363** offered a facile and efficient strategy for the C–H amination transformation (Scheme 127).[209]



bp = diphenyl-1,10-phenanthroline

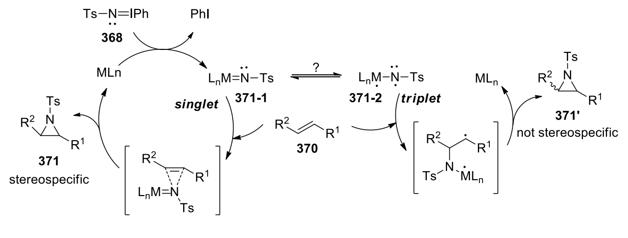
Scheme 127. C(sp^3)–H amination with PhI=NNs.

Complexes Tp^xAg (Tp^x = hydrotris(pyrazolyl)borate ligand) was applized to promote the intermolecular aminations of simple alkanes **366** with PhI=NTs **368** (Scheme 128). The best results have been observed with Tp^{*,Br}Ag **367**. The radical inhibition experiment with BHT indicated an involvement of active radical species in the process. A stepwise nitrene insertion mechanism was also proposed by the authors. Mechanically, the nitrene precursor PhI=NTs **368** reacted with silver(I) to form an silver(I)-nitrene intermediate **368-1**, which abstracted a hydrogen atom from alkane **366** to form carbon radical **366-1** that would be evolved to the expected amine product **369** finally.[210]



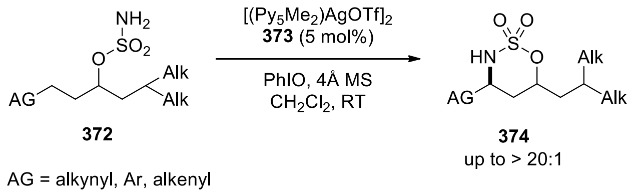
Scheme 128. C(sp^3)–H amination with PhI=NNs by complexes Tp^{x}Ag.

The complexes Tp^{x}Ag have also been used for olefin aziridination reactions.[211] A mechanism involving metal−nitrene complexes **371-1** and **371-2** was proposed, which might involved both the singlet and the triplet pathways. It is generally assumed that singlet species reacts stereospecifically, with retention of the alkene's stereochemistry; whereas triplet species do not react stereospecifically. Learning from experimental and theoretical studies, the silver-based systems were reasoned to hold a minimum energy crossing point (MECP) between the triplet and closed-shell singlet surfaces, which induce the direct formation of the aziridine **371**. Additionally, stereochemistry of the olefin **370** is retained. As a result, a singlet pathway was more suggested, whereas the triplet pathway was preferred and furnished aziridines **371'** under copper catalysis. However, the mechanism is still controversial and experiments on the stereospecificity of the reaction are sometimes contradictory and substrate dependent (Scheme 129).[212]



Scheme 129. Mechanistic insights for metal−nitrene complexes.

A recent report of silver-catalyzed, selective amination of challenging and tough propargylic, benzylic, and allylic C−H bonds **372** was developed by the Schomaker research group. A novel silver complex [(Py$_5$Me$_2$)AgOTf]$_2$ **373**, coordinated with steric bulk *N*-ligands, was key for this selective C−H functionaliztion, affording the desired 1,2,3-oxathiazinane 2,2-dioxide scaffolds **374** efficiently. A mechanism involving nitrene transfer was proposed. Further, the use of radical inhibitor, dihydroanthracene (DHA) made the yield decrease dramatically (Scheme 130).[213]

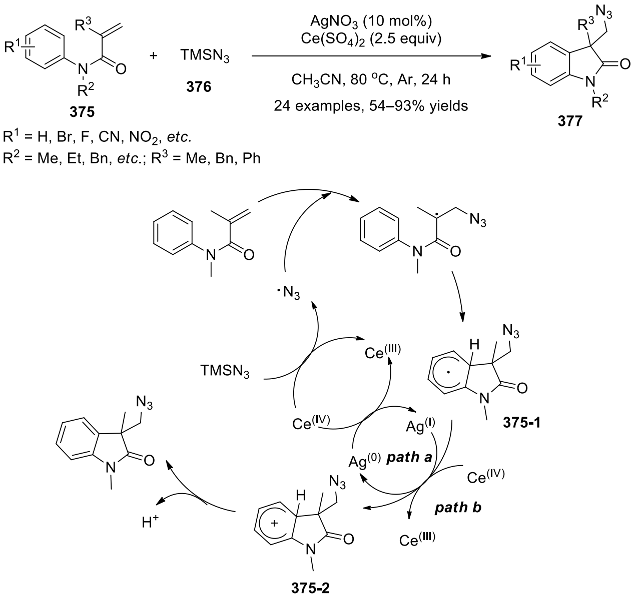


AG = alkynyl, Ar, alkenyl

Scheme 130. Amination of propargylic, benzylic, and allylic C−H bonds.

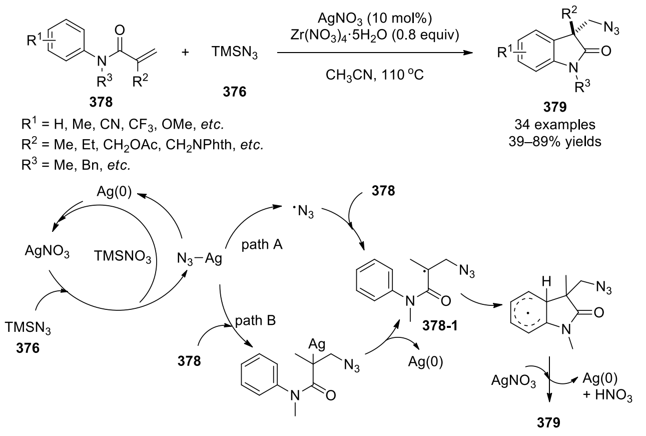
3.2 N_3 Radical

Azido compounds are a class of very useful synthetic intermediates and building blocks in organic synthesis. Although some attractive approaches of catalytic C–N formation *via* C–H activation have been reported, the direct C–H azidation still remains challenging.[214] Inspired by the tandem radical addition/C–H functionalization process to achieve oxindoles, in 2013 the Jiao group developed an efficient silver(I)-promoted azido-carbocyclization of activated alkenes **375** with trimethylsilyl azide ($TMSN_3$) **376**. *N*-protected-*N*-arylmethacrylamides **375** bearing an electron-rich/poor group at the aryl ring could be smoothly converted into the desired azido oxindoles **377** in moderate to excellent yields. 2.5 equivalents of Ce(IV) salts were essential to work as radical initiation and terminal oxidation. The single-electron oxidative process (**375-1** → **375-2**) was suggested *via* two pathways containing Ce(IV/III) circle with/without Ag(0/I) (path a and b), which were also confirmed by obtaining moderate yield without $AgNO_3$ (path a). Considering the nature of azido compounds, azido oxindole products **377** were readily transformed to the corresponding amine, as well as occurred click reaction with phenylacetylene (Scheme 131).[215]



Scheme 131. AgNO3-promoted azido-carbocyclization of activated alkenes.

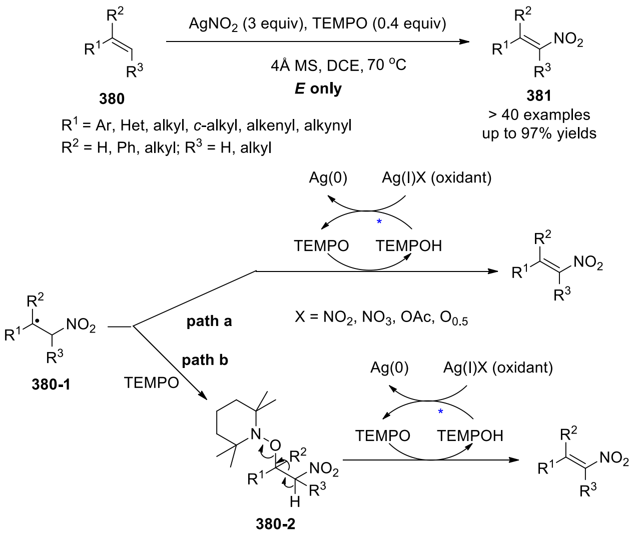
Simultaneously, Yang *et al.* also disclosed a similar method to prepare various azido oxindoles by employing the combination of $AgNO_3$ and $Zr(NO_3)_4\cdot5H_2O$. A wide range of *N*-protected arylacrylamides **378** with broad reaction scope and good functional-group compatibility were applized, leading to the oxindoles **379** in 39–89% yields. Moreover, 3,4-dihydroquinolin-2(1*H*)-one derivatives was also formed under these reaction conditions. Whereas, heteroaromatics attached to *N*-atom, such as pyridine, quinoline, and pyrimidine were inapplicable. With BHT as radical inhibitor, N_3 radical was captured and detected by GC–MS. The intermediate AgN_3 generated from $TMSN_3$ **376** was pivotal. The transformation of AgN_3 into alkyl radical **378-2** possibly had two pathways (path A and B). AgN_3 first performs cleavage to give the N_3 radical that is then incorporated into arylacrylamide **378** forming radical **378-1**. Another possibility to achieve alkyl radical **378-1** involves the direct addition of AgN_3 to alkene and homolysis C–Ag bond with the elimination of Ag(0). The generated radical **378-1** follows an intramolecular radical substitution and a SET step providing the final product **379**. In line with the previous reports, the Ag(0) is oxidized to Ag(I) in the presence of HNO_3 to realize the catalytic cycling (Scheme 132).[216]



Scheme 132. Synthesis of azide oxindoles from *N*-protected arylacrylamides.

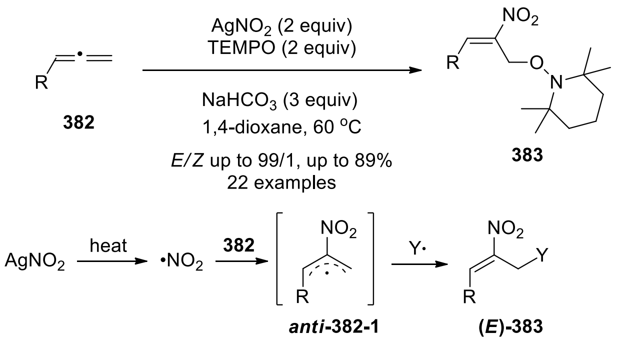
3.2 NO_2 Radical

Nitroolefins[217] are building blocks for generating molecules of biological and pharmaceutical relevance. Its synthesis from olefin *via* directly incorporation of a nitro group is generally limited by the formation of undesirable mixture of E/Z isomers, harsh conditions and poor substrate scope. Development of an efficient and practical method of regio- and stereoselective nitration of olefin is highly desirable. In 2013, Maiti group did a progress for C–H nitration of olefins **380** by employing $AgNO_2$/TEMPO under ambient conditions.[218] A wide array of *E*-nitroolefins **381** was generated from aromatic, aliphatic, and heteroaromatic olefins **380** in highly regio- and stereoselectives. The order of reactivity of olefins is shown as follows: mono- substituted > di-substituted > tri-substituted. This strategy was extended to complex molecule synthesis, *i.e.* cholestan-3-one, pregnenolone and testosterone, even gram-scale reaction. Mechanically, the initially generated nitroalkane radical **380-1** with olefin would undergo subsequent transformations *via* two paths, leading to the desired nitroolefin **381** in a stereoselective manner. $AgNO_2$ acted as source of nitro radical and stoichiometric oxidant. In path b, TEMPO could intercept the radical **380-1** to form a TEMPO−alkane−NO_2 intermediate **380-2**, which was confirmed by X-ray crystallography. *anti*-Elimination of intermediate **380-2** would generate nitroolefin stereoselectively. TEMPOH is generated upon abstraction of H-atom either directly from intermediate **380-1** (path a) or from intermediate **380-2** (path b) (Scheme 133). Further, (*E*)-nitroolefins can be achieved *via* stereoselective nitration of olefins under metal-free conditions.[219]



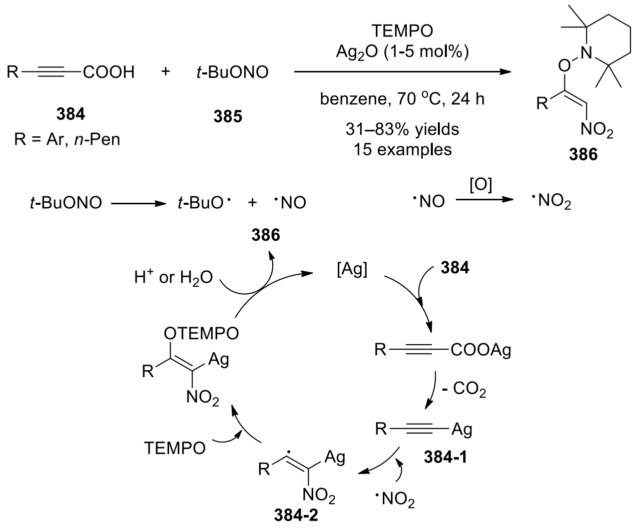
Scheme 133. Silver(I)-based C–H nitration of olefins.

Afterwards, Fu and Ma *et al.* developed a highly regio- and stereoselective (up to 99/1) nitro-oxoamination reaction of mono-substituted allenes **382**, leading to a series of useful nitroolefin derivatives **383** with potential bioactivity. In the presence of $AgNO_2$ and a free radical trap TEMPO, a new C–N bond and a C–O bond were formed in a single-pot manner. An array of allenes **382** with substituted (hetero)aryl group and alkyl group were compatible, which could be easily prepared from terminal alkynes, formaldehyde, and amines. Mechanically, the addition of nitro radical with allenes forms a relatively more stable allylic radical intermediate *syn*-**382-1** or *anti*-**382-1**, which may be directly captured by TEMPO, fixing two functional groups in one-pot procedure. Considering the steric effect, thermodynamics and kinetics stability in the radical addition process, intermediate *anti*-**382-1** should be favored and afforded (*E*)-isomer **383** as the major product (Scheme 134).[220]



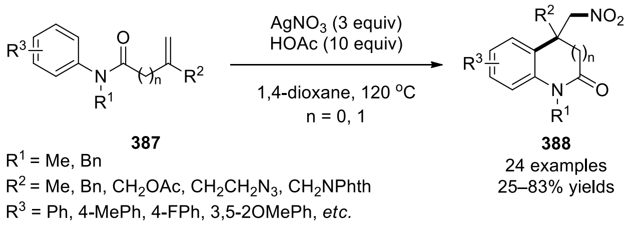
Scheme 134. Nitro-oxoamination reaction of mono-substituted allenes.

Further, a stereoselective strategy for the generation of (*E*)-β-nitroolefinic alkoxyamines **386** was achieved through silver-catalyzed decarboxylative nitroaminoxylation reaction of phenylpropiolic acids **384** with *tert*-butyl nitrite (*t*-BuONO) **385** as nitro source. All the products **386** showed single *trans*-configuration with moderate to good yields. When $AgNO_3$, Ag_2CO_3 and AgOAc were used instead of Ag_2O, slight decreased yields were obtained. The loading of Ag_2O (as low as 5 mol% to 1 mol%) had a significant effect on the yield because both too much and too little loading of Ag_2O brought negative influences. It was found that long-chain alkyl propiolic acids were efficient, whereas short-chain alkyl propiolic acids were incompatible. The authors suggested that the *t*-BuONO **385** generated a *tert*-butyl radical and a NO radical. Meanwhile Ag–acetylide **384-1** was formed by decarboxylation with silver(I). The *in situ* generated NO_2 radical subsequently reacted with Ag–acetylide intermediate **384-1**. Finally, TEMPO trapped sp^2 C-centered radical **384-2** to deliver the expected product (Scheme 135).[221]



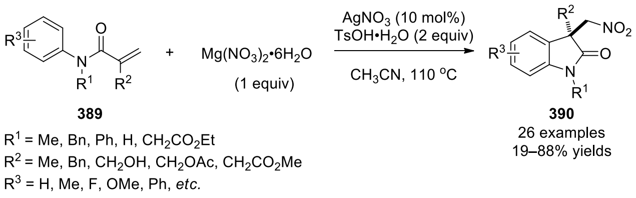
Scheme 135. Synthesis of (*E*)-β-nitroolefinic alkoxyamines with phenylpropiolic acids.

Inspired by transition metal-catalyzed difunctionalization of simple alkenes for forming oxindole skeletons, in 2014, Li *et al.* developed an efficient arylnitration of alkenes **387** by nitration and C–H functionalization cascade process in the presence of $AgNO_3$ (3.0 equiv.) and HOAc (10 equiv.) in 1,4-dioxane at 120°C. A series of structurally diverse nitro-containing oxindoles and dihydroquinolin-2(1*H*)-ones **388** were received in good yields with significant functional-group tolerance. A probable mechanism involving a free-radical process (NO_2 radical) was proposed (Scheme 136).[222]



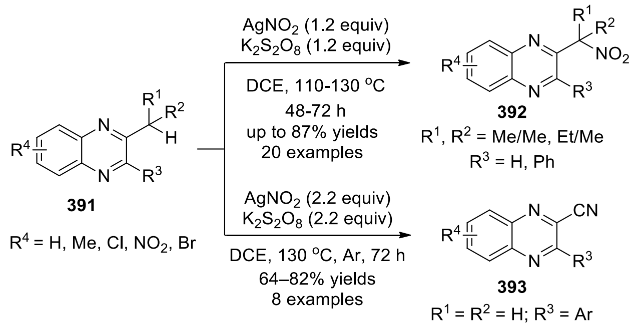
Scheme 136. $AgNO_3$-mediated arylnitration of activated alkenes.

Further, Yang and colleagues successfully improved the difunctionalization of arylacrylamides **389** for synthesizing nitro-group-containing oxindoles **390** to a catalytic process with the incorporation of $AgNO_3$ and $Mg(NO_3)_2$. Remarkably, representative oxindole derivatives such as horsfiline, CR TH2 receptor antagonist, and alstonisine could be easier produced from nitrating oxindoles (Scheme 137).[223]



Scheme 137. Silver(I)-catalyzed arylnitration of alkenes.

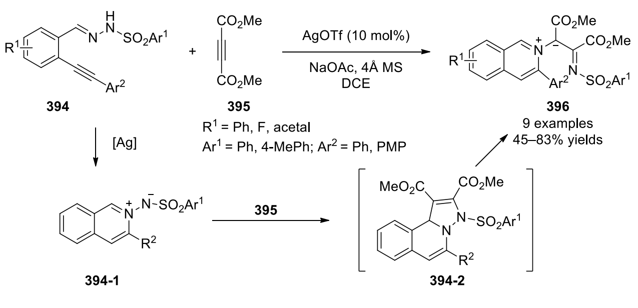
In contrast to the much developing C(sp^2)–H nitration of arenes, the selective nitration of aliphatic C–H bonds is awkward. The usual requirement of high temperatures for the nitration process of aliphatic hydrocarbons will cause undesired C–C bond scissions, thus leading to poor selectivities and adding difficulties for the product separation. In 2014, Liu *et al.* made an advancement *via* the direct nitration of the quinoxaline tertiary C–H bond **391** promoted by the combination of $AgNO_2$ and $K_2S_2O_8$. A range of quinoxalines with 3° benzylic C–H bond were tolerated and delivered the nitration products **392** in good yields. Whereas, *N*-containing heterocycles, *i.e.* quinolone and benzo[*d*]thiazole frameworks failed to form the nitration products. The process was the first example of transition metal-involved C(sp^3)–H nitration. The authors found that with catalytic amount of $AgNO_2$ and 1.2 equiv. KNO_2 acceptable yields was obtained. On the basis of the mechanistic experiments, a radical process was revealed. Further, the extension of quinoxalines with 1° or 2° benzylic C–H bond was discussed. It was demonstrated 2-quinoxaline nitriles **393** were achieved with 1° benzylic C–H bonds **391** directly, while 2° benzylic C–H bond favored ketonization process. Moreover, the direct transformations of methyl arenes into aryl nitriles remain scarely developed. A possible reaction mechanism for the direct formation of nitriles from 1° benzylic C–H bond and ketonization of the 2° benzylic C–H bond **391** might involve the formation of a NO radical (Scheme 138).[224]



Scheme 138. Nitration of aliphatic C–H bonds.

3.3 Homolysis Cleavage of N–N, N–O Bonds

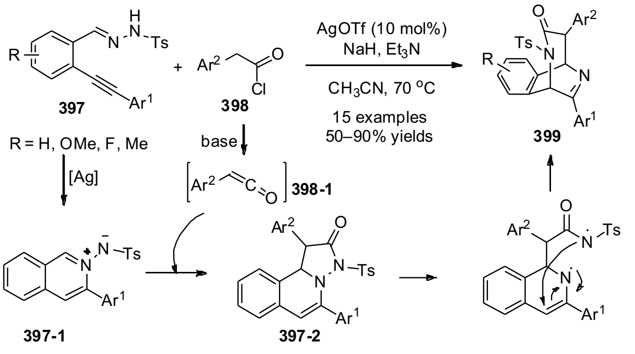
The cycloisomerization of *N*'-(2-alkynylbenzylidene)hydrazides or 2-alkynylbenzaldoximes has been widely developed, affording a large library of functionalized isoquinoline derivatives. In this mode, a mechanism involving tandem 6-*endo*-cyclization, [3+2] cycloaddition and intramolecular rearrangement process is proposed, which contains a N–N or N–O bond homolysis cleavage.[225] The Wu group has made a systematical study. In 2009, the group described a silver triflate-catalyzed tandem reaction of *N*'-(2-alkynylbenzylidene)hydrazides **394** with dimethyl acetylenedicarboxylate (DMAD) **395**, providing an efficient approach for the synthesis of isoquinoline-based azomethine ylides **396** in moderate to high yields. The initial iminium intermediate **394-1** occurred [3+2] cycloaddition with DMAD **395** to form azomethine ylide **396** as final product rather than the expected fused dihydroisoquinoline **394-2** (Scheme 139).[226] Afterwards, the strategy was extended to three-component reaction. A series of 1-(isoquinolin-1-yl)guanidine derivatives were formed from 2-alkynylbenzaldehydes, sulfonohydrazides, and carbodiimides.[227]



Scheme 139. Synthesis of 1-(isoquinolin-1-yl)guanidines.

The authors reasoned that the tandem reaction pathway could be extended to ketenes with *N*'-(2-

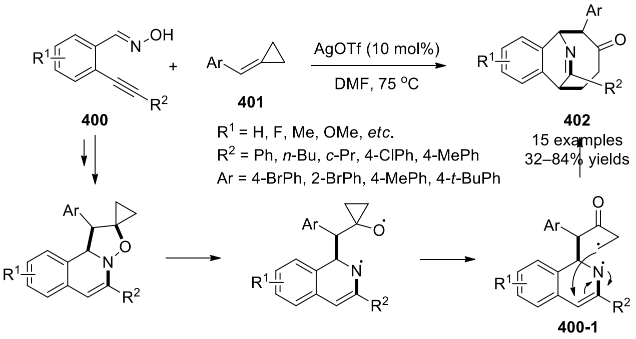
alkynylbenzylidene)hydrazides. A spectrum of 2,6-diaza-bicyclo[3.2.2]non-6-en-3-ones **399** were obtained in 50–90% yields with the formation of four bonds in a one-pot procedure. The authors argued that the ketenes **398-1** would be produced *in situ* when acetyl chlorides **398** were treated with a base, which would react with isoquinolinium-2-yl amide **397-1** *via* [3+2] cycloaddition to afford intermediate **397-2**. The intermediate **397-2** underent N–N bond cleavage and a subsequent intramolecular radical addition to yield the final product **399** (Scheme 140).[228] On the basis of the strategy, a tandem reaction of *N*'-(2-alkynylbenzylidene)hydrazides with 2-chloropyridyne as C2 synthon was achieved, providing complex molecular 6,11-dihydro-5*H*-11,6-(azenometheno)benzo[*e*]pyrido[4,3-*b*]azepines.[229]



Scheme 140. Synthesis of 2,6-diaza-bicyclo[3.2.2]non-6-en-3-ones with ketenes.

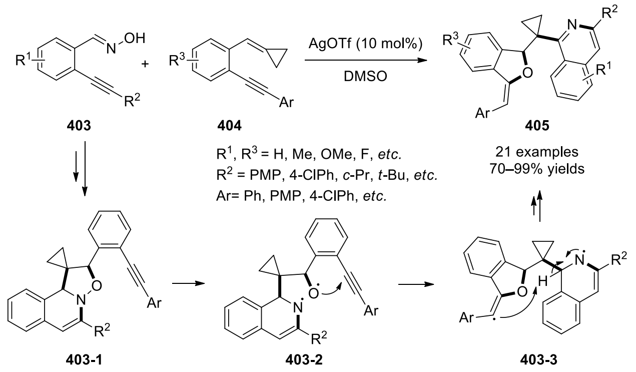
Similarly, 2-alkynylbenzaldoximes can used as 1,3-dipole precursor for [3+2] cycloaddition. In 2009, Wu *et al.* reported the tandem reaction of 2-alkynylbenzaldoximes with isocyanides co-catalyzed by AgOTf and Bi(OTf)$_3$.[230] In line with *N*'-(2-alkynylbenzylidene)hydrazide system, components such as carbodiimides, arynes, isothiocyanates, α,β-unsaturated carbonyl compounds, and ketenes were employed as dipolarphiles respectively, participating the [3+2] cycloaddition reaction with isoquinoline-*N*-oxide intermediate and intramolecular rearrangement in sequence under silver(I) catalysis.[231]

Components with multifunctional groups were discussed as well. In 2012, the Wu group extended the silver(I)-catalyzed tandem reaction of alkylidenecyclopropanes **401** with 2-alkynylbenzaldoximes **400**, providing an efficient entry towards benzo-7-azabicyclo[4.2.2]dec-7-en-4-ones **402** in moderate to good yields. Remarkably, the carbon radical **400-1** was generated *via* a N–O bond cleavage/rearrangement process, which was finally converted to the corresponding heterocyclic compounds **402**. The complexity and diversity could be easily incorporated with the formation of three bonds during the process (Scheme 141).[232]



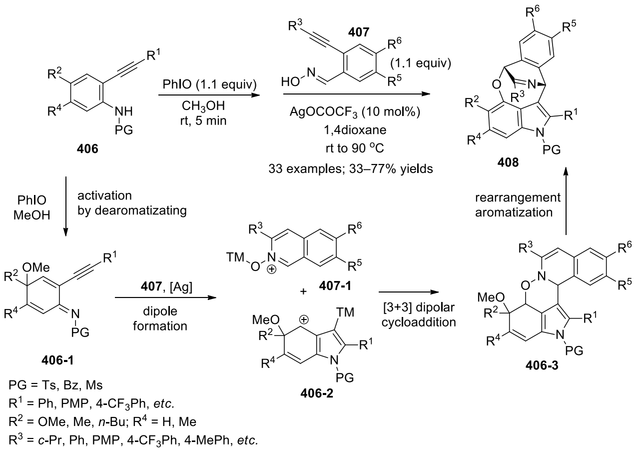
Scheme 141. AgOTf-catalyzed tandem reaction of alkylidenecyclopropanes with 2-alkynylbenzaldoximes.

Further, a facile transformation was modified to 1-((cyclopropylidenemethyl)-2-alkynyl)arenes **404** with 2-alkynylbenzaldoximes **403**, delivering various 1-((1,3-dihydroisobenzofuran-1-yl)methyl)isoquinolines **405** in good to excellent yields. A radical inhibition with TEMPO was uncovered an involvement of radical species. Mechanistically, substrates **403** and **404** performed the initial cyclization and [3+2] cycloaddition to form isoquinoline **403-1**, followed by a ring-opening step yielding the radical species **403-2**. The radical **403-2** subsequently proceeded an intramolecular *O*-annulation with alkynyl bond to furnish the intermediate **403-3**, and transfered to the corresponding isoquinoline finally (Scheme 142).[233]



Scheme 142. Synthesis of 1-((1,3-dihydroisobenzofuran-1-yl)methyl)isoquinolines.

Although a plethora of cyclization or cascade cyclization/coupling reactions of 2-alkynylanilines have been developed for the synthesis of 2-substituted or 2,3-disubstituted indoles, methods that allow rapid access to 3,4-fused indoles from 2-alkynylanilines still remain scarce. Recently, He and Fan *et al.* developed a one-pot stepwise procedure for construction of multisubstituted oxocino[4,3,2-*cd*]indoles **408** in moderate to good yields starting from a wide range of 2-alkynylanilines **406** and 2-alkynylbenzaldoximes **407** with well functional-group tolerance. Initial screening of various metal salts revealed that only silver salts are effective catalysts for the [3+3] dipolar cycloaddition. Among silver catalysts tested, silver trifluoroacetate (CF_3COOAg) proved to be the best catalyst to achieve cycloaddition product. The protocol involved a tandem process including PhIO-mediated oxidative dearomatization of 2-alkynylanilines **406**, silver-catalyzed [3+3] cycloaddition with 2-alkynylbenzaldoximes **407**, and subsequent thermal radical skeletal rearrangement and aromatization. The main challenge to implementation of this strategy was the realization of an efficient [3+3] dipolar cycloaddition. From preliminary investigations a mechanism involving the radical skeletal rearrangement followed by the aromatization reaction was proposed. Moreover, the subsequent rearrangement and aromatization step were revealed as thermal processes (Scheme 143).[234]

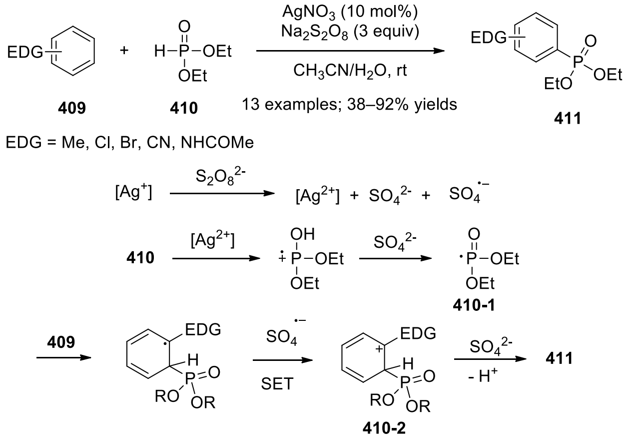


Scheme 143. Formation of oxocino[4,3,2-*cd*]indoles form 2-alkynylanilines and 2-alkynylbenzaldoximes.

4. Phosphinyl Radicals

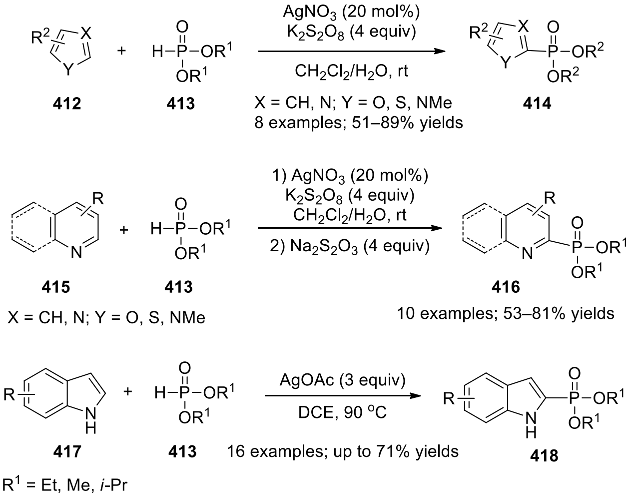
4.1 Cross-Dehydrogenative-Coupling Reactions

In the past few decades, considerable advances have been made to construct C–P bonds. Among them, one of the most atom economical and attractive strategies is the direct hydrophosphinylation of alkenes.[235] In 1985, Effenberger reported the formation of C–P bonds by coupling arenes **409** and diethyl phosphite **410** with the combination of $AgNO_3$ and $Na_2S_2O_8$, but only arenes bearing electron-donating groups (EDGs) were suitable. A possible mechanism involving radical substitution was proposed.[236] Generally, P-centered free radical **410-1** is formed by the single-electron oxidation of the (O)P–H **410** followed by a deprotonation. A subsequent addition of the phosphinyl radical **410-1** to a C–C double bond and hydrogen abstraction from the (O)P–H **410-2** lead to the hydrophosphinylation product **411** and regenerate the phosphinyl radical (Scheme 144).[237]



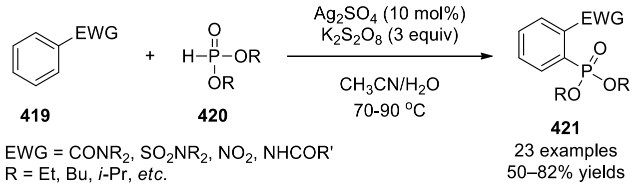
Scheme 144. Coupling reaction of electron-donating arenes with diethyl phosphite.

However the reaction was stagnant for a few deceades. Until 2012, with dialkyl phosphites **413**, substituted heteroarenes including furans, thiophenes, thioazoles, and pyrroles **412** successfully allowed the corresponding phosphonated products **414** with good regioselectivities and in 51–89% yields under silver catalysis. Moreover, an advance in constructing pyridine phosphonates **416** was conducted through the coupling of pyridines **415** with phosphites **413** and a reduction with $Na_2S_2O_3$, ortherwise the side product *N*-oxide of pyridine-2-phosphonates were present.[238] A large array of indoles **417**, for the first time, furnished the corresponding 2-substituted dialkylphosphoryl-substituted indoles **418** by using 3.0 equivalent AgOAc at 90°C (Scheme 145).[239]



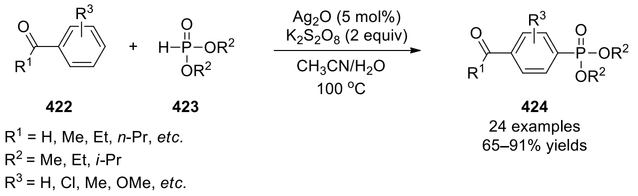
Scheme 145. Silver-catalyzed coupling of heteroarenes with dialkyl phosphites.

In 2013, Zhu and Cheng *et al.* extended the reaction scope to electron-withdrawing arenes, furnishing a broad range of coupling products **421** in good yields and with excellent regioselectivity under $Ag_2SO_4/K_2S_2O_8$ conditions. It was the first example for CDC reaction of phosphites **420** with strongly electron-deficient arenes **419** (Scheme 146).[240]



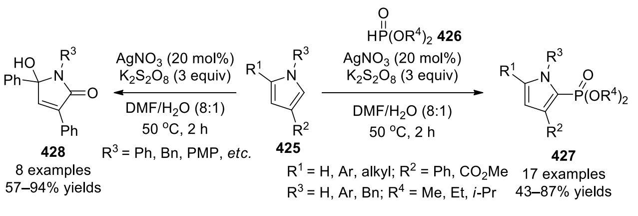
Scheme 146. CDC reaction of strongly electron-deficient arenes with dialkyl phosphites.

Recently, aromatic aldehydes or ketones were extended to react with phosphites **423**, while complex mixtures were obtained under manganese-catalysis. The CDC reaction tolerated many functional groups, and resulted in a series of *p*-formyl and *p*-acylphenylphosphonates **424** in high yields and with excellent para regioselectivities which should be important building blocks to access versatile arylphosphonate derivatives (Scheme 147).[241]



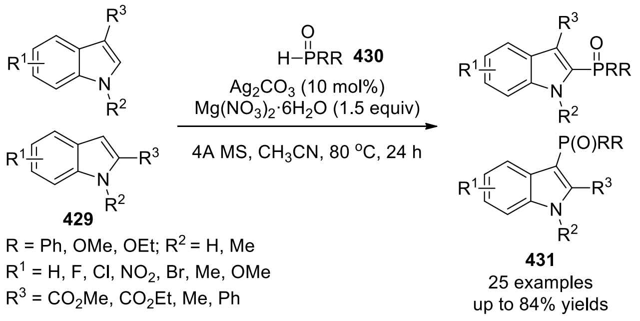
Scheme 147. CDC reaction of aromatic aldehydes or ketones with dialkyl phosphites.

Considering the restriction that very simple and limited number of pyrroles in direct oxidative coupling with (O)P–H, Kim *et al.* realized a variety of pyrroles **425** with dialkyl phosphites **426** to produce pyrrole-2-phosphonates **427** under AgNO$_3$/K$_2$S$_2$O$_8$ conditions in DMF/H$_2$O (V/V = 8:1). Whereas, 3-phosphonate substituted pyrroles could not be obtained owing to the many intractable side products and sluggish reactivity. In the absence of dialkyl phosphites, γ-hydroxy-γ-butyrolactam derivatives **428** were obtained in good yields. Moreover, other heterocyclic compounds, such as indole, furan, thiophene scaffolds were explored under the conditions, albeit some of them demonstrated low yields and even unreacted (Scheme 148).[242]



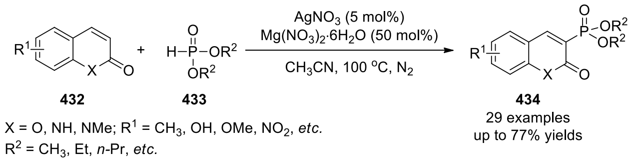
Scheme 148. Formation of pyrrole-2-phosphonates and γ-hydroxy-γ-butyrolactams.

Zeng and Zou *et al.* modified the C(sp^2)−H phosphorylation of indoles **429** with organophosphorus **430** to a catalytic reaction by using magnesium nitrate and 4Å MS as additive. While without 4Å MS, a significant reduction of yields was observed. This protocol provides an efficient and general method to access 2- and 3-phosphorylated indoles **431** in moderate to good yields (Scheme 149).[243] Biologically active heterocycles thiazolo[3,2-*b*]-1,2,4-triazoles were also applized and afforded the regioselective C(sp^2)–H phosphonated products in high yields under silver catalysis.[244]



Scheme 149. Formation of 2- and 3-phosphorylated indoles.

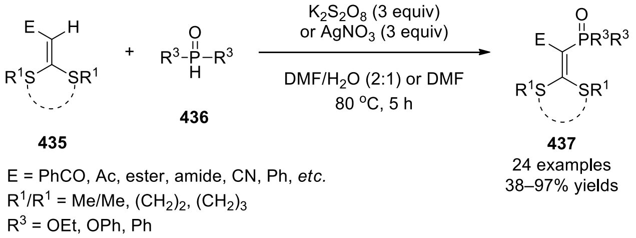
With C(sp^2)–H radical phosphorylation procedure, 3-phosphorylated coumarins and other phosphorylated heteroarenes such as 3-phosphorylated quinolinone derivatives **434** were achieved from a library of substituted coumarins **432** and *H*-phosphites **433** in high yields under AgNO$_3$ and Mg(NO$_3$)$_2$·6H$_2$O cocatalysis (Scheme 150).[245]



Scheme 150. C(sp^2)–H radical phosphorylation of coumarins with *H*-phosphites.

Although the C−P coupling of aromatic C−H has been developed, the C−H phosphorylation of the alkene C−H bond has not been reported because of the low reactivity of the alkene C−H bond (especially for internal alkenes) and the strong coordination of the phosphorus reagents to transition metal catalysts. In 2015, Xu and Wang *et al.* disclosed the first example of C(sp^2)−H phosphorylation of ketene dithioacetals **435** with diaryl phoshine oxides **436** under transition-metal-free conditions. An electron-donating dithioalkyl group of ketene dithioacetals

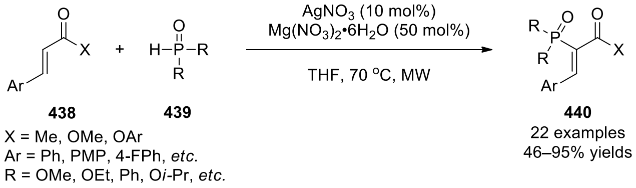
435 was utilized to activate the inert C−H bond of the internal alkene, while stoichiometric amounts of $AgNO_3$ were required in the cases of *H*-phosphonate. On the basis of KIE reactions, ESI-HRMS measurement, *etc*., a radical pathway about phosphinyl radical was proposed. Moreover, the phosphorylation products **437** are useful synthon, such as an application in palladium-catalyzed cross-coupling with aryl boronic acid to give the tetrasubstituted alkenes (Scheme 151).[246]



E = PhCO, Ac, ester, amide, CN, Ph, *etc.*
R^1/R^1 = Me/Me, $(CH_2)_2$, $(CH_2)_3$
R^3 = OEt, OPh, Ph

Scheme 151. C(sp^2)−H phosphorylation with diaryl phoshine oxides.

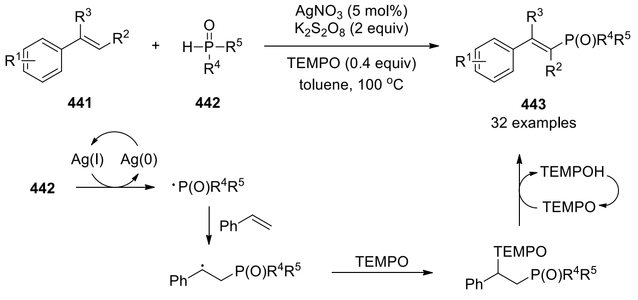
Alkenylphosphonates serve as important building blocks in organic chemistry. Very recently, Yuan and Qu *et al.* reported a microwave-promoted radical phosphonation of β-aryl-α,β-unsaturated carbonyl compounds **438** with *H*-phosphites **439**, affording substituted alkenylphosphonates **440** with highly *trans*-selectivity in moderate to excellent yields. The α-position of the conjugated alkene plausibly had a higher electron density, as well as the addition of electrophilic phosphonyl radical to α-position was energetically favorable, which resulted in the formation of *E*-isomer (Scheme 152).[247]



X = Me, OMe, OAr
Ar = Ph, PMP, 4-FPh, *etc.*
R = OMe, OEt, Ph, O*i*-Pr, *etc.*

Scheme 152. Formation alkenylphosphonates with β-aryl-α,β-unsaturated carbonyl compounds.

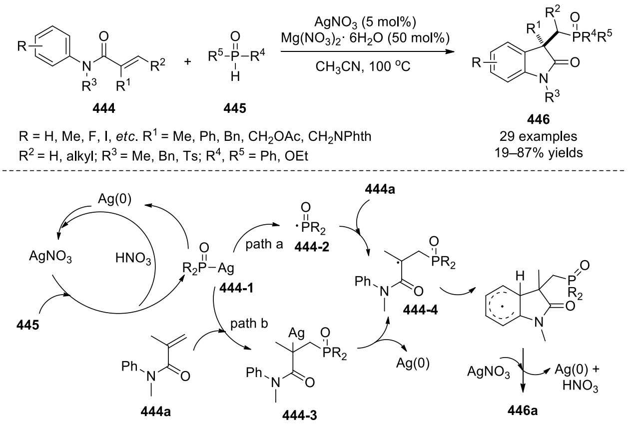
Moreover, the simple and available aryl-substituted olefins **441** also underwent the C(sp^2)−H CDC reaction with phosphine oxides **442**, leading to the production of vinylphosphonates **443** in generally high yields. In light of direct C–H nitration of the Maiti research group, the reaction performed in the presence of TEMPO as radical interceptor under silver(I)/peroxysulphate oxidative conditions. A broad substrate scope and excellent functional-group compatibility were displayed (Scheme 153).[248]



Scheme 153. C(sp^2)–H CDC reaction to access vinylphosphonates.

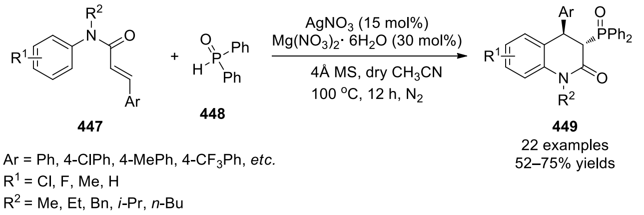
4.2 Radical Tandem Reactions

Recently, transition metal-catalyzed difunctionalization of alkenes provides a powerful strategy for the synthesis of various organic compounds. In 2013, the Yang laboratory developed a radical entry for the synthesis of various phosphorylated oxindoles **446** from *N*-alkyl-*N*-arylacrylamides **444**. A cheap, nontoxic silver salt was employed in catalyzing the hydrophosphorylation of alkenes for the first time. A series of α-substituted olefins **444** bearing different functional groups, such as phenyl, benzyl, ester, and phthalimide groups were compatible and provided the desired products **446** in moderate to high yields. With $AgNO_3$ optimal, 0.5 equivalent of $Mg(NO_3)_2$•$6H_2O$ was added to decrease the amount of $AgNO_3$. The silver-catalyzed difunctionalization of alkenes occurred through radical carbon phosphorylation/C–H functionalization cascade process. In the carbon phosphorylation, the formation of the $R_2(O)PAg$ **444-1** was significant. Learning from the ESI/MS analysis, the generation of $R_2(O)PAg$ **444-1** form phosphine oxide **445** occurred *via* two paths, $R_2(O)PAg$ **444-1** produced the phosphoryl radical **441-2** that subsequently reacted with arylacrylamides **444a** to give the alkyl radical **444-4** or $R_2(O)PAg$ was incorporated with arylacrylamides to form the silver(I) species **444-3** which then gave **444-4**. The resulting alkyl radical **444-4** underwent the second step as participated in an intramolecular radical substitution and a subsequent SET to silver(I). Finally, the product **446a** was released along with HNO_3 and silver(0). The silver(0) was regenerated to silver(I) by HNO_3. Deuterium-labeled experiments indicated that the C–H bond cleavage was not the turnover-limiting step (Scheme 154).[202c, 202d]



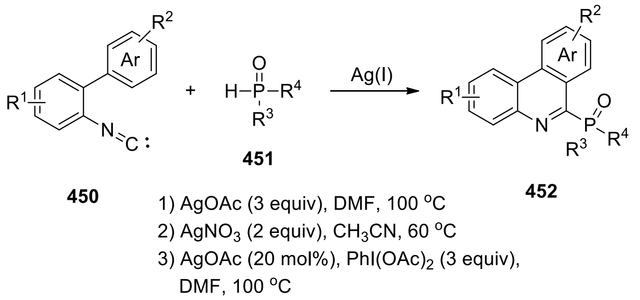
Scheme 154. Silver-catalyzed radical arylphosphorylation of alkenes.

By contrast, Zhu *et al.* provided an efficient and straightforward route to access a set of functionalized 3,4-dihydroquinolin-2(1H)-ones **449** starting from *N*-methyl-*N*-phenyl-cinnamamides **447** *via* the $AgNO_3/Mg(NO_3)_2·6H_2O$ catalytic system with diphenylphosphine oxide **448**. The reaction allowed a 6-*endo-trig* pathway for the construction of dihydroquinolin-2(1*H*)-one framworks (Scheme 155).[249]



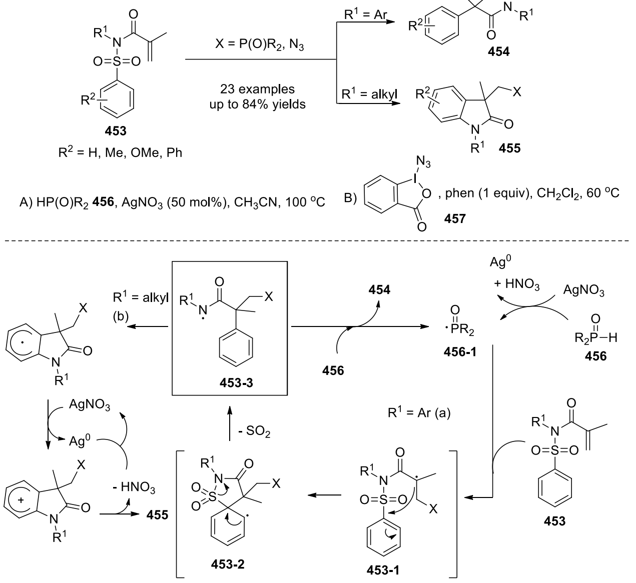
Scheme 155. Formation of 3,4-dihydroquinolin-2(1H)-ones from *N*-methyl-*N*-phenyl-cinnamamides.

Recently, aryl isonitriles have gained renewed attention as radical acceptors in cascade reactions for the construction of heteroarenes. Studer and co-workers demonstrated the first example of P-centered radicals for delivering 6-phosphorylated phenanthridines **452**, starting from readily prepared 2-isocyanobiphenyls **450** and phosphine oxides **451** with the aid of 3.0 equivalent of AgOAc at 100 °C. Substrates bearing electron-rich/poor substituents at the aryl group were acceptable and a heteroarene such as pyridine, benzo[*d*][1,3]dioxole was also tolerated in the biaryl moiety. Mechanically, the cascade reaction comprised addition of an oxidatively generated P-centered radical to the isonitrile functionality and subsequent C(sp^2)–H functionalization. Moreover, the phenanthridine skeleton is common in many natural products for their biological activities.[250] Later, Yang *et al.* reported a similar reaction to prepare 6-phosphorylated phenanthridines by employing less silver salts and at a decreased temperature.[251] Considering drawback of reports of Studer's group and Yang's group utilizing stoichiometric amounts of silver salts, Wang and Ji *et al.* disclosed a catalytic process for the construction of 6-phosphorylated phenanthridines utilizing an additional oxidant $PhI(OAc)_2$. The desired 6-phosphorylated phenanthridine derivatives **452** might be used as N,P,O-ligand (Scheme 156).[252]



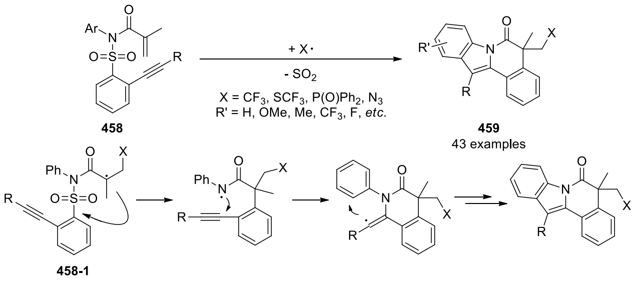
Scheme 156. Construction of 6-phosphorylated phenanthridines.

In 2013, Nevado and co-workers reported the CF_3 radical initiated an aryl migration/desulfonylation sequence of tosyl acrylamides under copper catalysis[202a]. In light of the reaction, two radical-mediated processes of activated alkenes, *N*-aryl substituted tosyl acrylamides **453**, namely arylphosphonylation and arylazidation were disclosed. The arylphosphonylation of *H*-phosphonates **456** progressed with 50 mol% $AgNO_3$ in CH_3CN, while arylazidation of N_3-iodine(III) reagent **457** performed in the presence of stoichiometic amount of phenanthroline as additive in CH_2Cl_2. With *N*-aryl substituted acrylamides **453**, this transformation underwent by radical addition, 1,4-aryl migration, desulfonylation, and *H*-abstraction in sequence thus generated α-aryl-β-heterofunctionalized amides **454** bearing a quaternary stereocenter. However, in the case of *N*-alkyl substituted substrates, heterooxindoles or spirobicycles **455** could be obtained in a completely regioselective manner. The phosphonyl radical **456-1** was revealed as the active intermediate, rather than the [$Ph_2P(O)Ag$] complex recommended in previous reports. Deuterium labelling experiments showed $Ph_2P(O)H$ **456** plausibly offered the key hydrogen source, whereas in the arylazidation reaction, adventitious traces of water in the medium resulted in the formation of the N–H bond probaly. As a result, a self-propagating radical cycle operated without the need to further invoke a metal or a [$Ph_2P(O)Ag$] complex, was in contrast to previously described oxidative phosphonylation reactions. It should be mentioned that *ipso*-cyclization/desulfonylation (**453-1** to **453-3**) were the rate-determining step of these transformations. The presence of an alkyl group on the nitrogen atom (R^1 = alkyl) generated a more nucleophilic amidyl radical **453-3**, thus easily underwent a direct C–H functionalization to form a cycle ring **455** (Scheme 157).[202b]



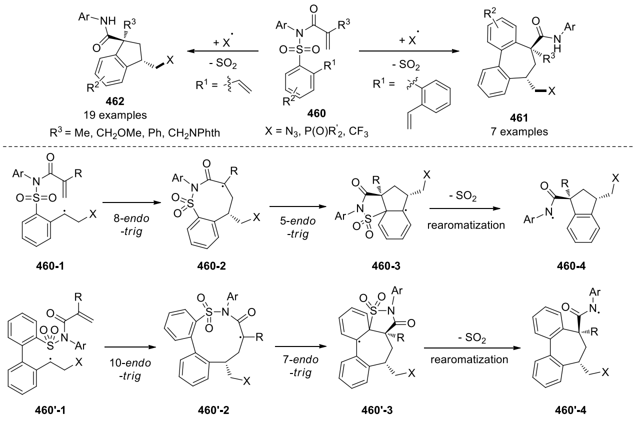
Scheme 157. Radical reaction cascades of *N*-aryl substituted acrylamides to access amides and heterooxindoles.

The authors hypothesized that the amidyl radical intermediates **453-3** generated *in situ* could be engaged in additional bond-forming events in the presence of adequate partners, such as with alkynyl and vinyl group. As a result, they described a regioselective one-pot synthesis of CF$_3$-, SCF$_3$-, Ph$_2$(O)P-, and N$_3$-containing indolo[2,1-a]isoquinolin6(5*H*)-ones **459** from *N*-[(2-ethynyl)arylsulfonyl]acrylamides **458** through a multi-step radical reaction cascade. For example, the desired SCF$_3$-, phosphonyl-substituted isoquinolinone derivatives were generated by using AgSCF$_3$/K$_2$S$_2$O$_8$/HMPA (hexamethylphosphoramide) and AgNO$_3$/Ph$_2$P(O)H systems, respectively. Control experiments unraveled the key intermediates and the sequence of individual steps involved in these transformations. The approach highlighted a one-pot formation of four new bonds (one C−X, two C−C, and one C−N), a formal 1,4-aryl migration, and a desulfonylation procedure of the starting materials. The amidyl radical intermediates **458-1** were generated *via* Smiles rearrangement, followed by additional radical cyclizations to construct new C−N and C−C bonds. Besides, the reactivity of amidyl radicals **458-1** could be varied by changing the substituents directly attached to the *N*-atom (alkyl *vs* aryl), which were influenced by both electronic and steric factors (Scheme 158).[133]



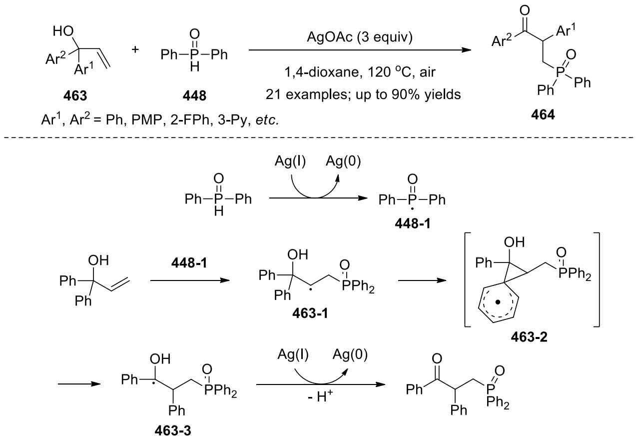
Scheme 158. Radical reaction cascades to access indolo[2,1-*a*]isoquinolin6(5*H*)-ones.

Further, the same group presented two highly stereoselective radical cascades that produced densely functionalized indanes **461** and dibenzocycloheptadienes **462** from *ortho*-vinyl- and *ortho*-vinylaryl-substituted *N*-(arylsulfonyl)acrylamides **460**, respectively. The indane core is common in natural products and dibenzocycloheptadiene is the main scaffold of colchicine alkaloids of significant pharmaceutical activities. Control experiments suggested the chemoselective addition of *in situ* generated heteroatom-centered radicals (N$_3$, P(O)RR, and CF$_3$ radicals) into the styrenic olefin as a trigger of an unprecedented sequence of steps, resulting in the formation of a new C–X and two new C–C bonds. In the first step, benzylic radicals (**460-1** and **460’-1**) generated upon the combination of carbon or heteroatom centered radicals and the styrene system, underwent an 8- or 10-*endo-trig* cyclization to give radical **460-2** and **460’-2**, constructing a new C(sp^3)–X bond and a new C(sp^3)–C(sp^3) bond together. Then, a second 5- or 7-*ipso* cyclization of radical **460-2** and **460’-2** onto the carbon atom of the C(sp^2)–SO$_2$ group occurred in a highly stereoselective manner. Subsequently, a formal 1,4-aryl migration and desulfonylation step of the radical **460-3** and **460’-3** resulted in an amidyl radical intermediates **460-4** and **460’-4**, which finally performed *H*-abstraction to yield the expected carbocyclic products with a 5- or 7-membered ring **461** and **462**, respectively. Acrylamides with substituents at the terminal positions of both alkene moieties, and *N*-alkyl-substituted moieties proved to be unreactive under these conditions. In addition, Ph$_2$POAg was also unraveled that did not participate as a productive intermediate (Scheme 159).[253]



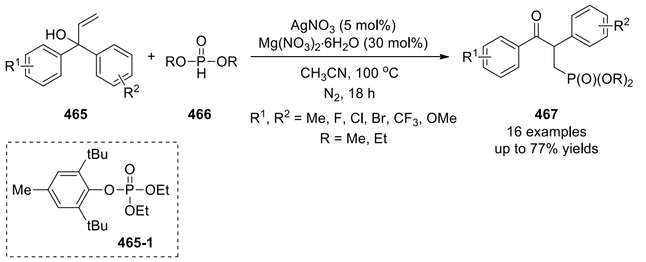
Scheme 159. Stereoselective radical cascades to access functionalized indanes and dibenzocycloheptadienes.

Although diverse C(sp^3)–P, C(sp^2)–P bond forming reactions *via* transition metal-catalyzed phosphination have proven to be efficient in the past few decades, new types of C–P formation are still highly desirable and present a considerable challenge. In 2014, Xu and Ji *et al.* developed a novel silver(I)-promoted phosphinylation reaction of α,α-diaryl allylic alcohols **463**. The strategy allowed the formation of new C(Ar)–C(sp^3) and C(sp^3)–P bonds in one step, involving a 1,2-aryl migration process. A variety of α-aryl-β-phosphinylated carbonyl ketones **464** were obtained in moderate to excellent yields, which are useful intermediates for the formation of substituted ketones, cyclopropanes, and alkenes. Under the optimal conditions, both symmetrical and asymmetrical α,α-diaryl allylic alcohols **463** were compatible for the reaction. It was also found that electron-poor aryl groups migrate preferentially. Mechanically, P-centered radical **448-1** generated from phosphine oxide **448** inserted into C=C bond of allylic alcohol **463** to afford an alkyl radical **463-1**. Subsequently, the radical **463-1** performed an intramolecular addition to the aromatic ring to generate the spiro[2,5]octadienyl radical **463-2**, followed by migration of the electron-deficient aryl group, thus releasing radical **463-3**. Finally, a single-electron transfer (SET) from **463-3** to Ag(I) produced the desired product **464** along with loss of a proton. A silver mirror was observed during the reaction, which reinforced a SET process for the reaction (Scheme 160).[254]



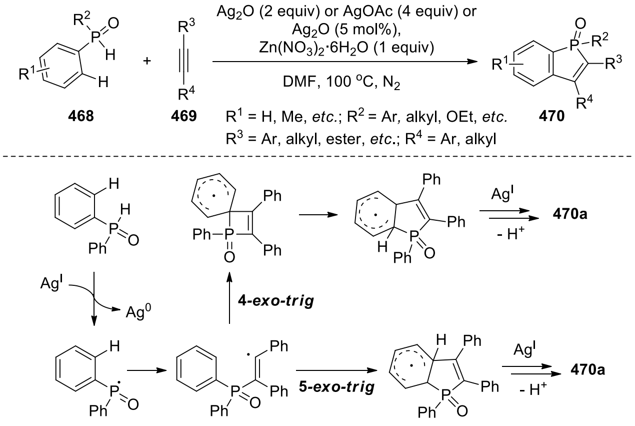
Scheme 160. AgOAc-promoted phosphinylation reaction of α,α-diaryl allylic alcohols.

Afterwards, Huang and Wu *et al.* extended the reaction scope to *H*-phosphonates **466** in which Ji's report were unreacted. A range of γ-ketophosphonates **467** with different substituents were readily provided from allylic alcohols **465** by using the combination of $AgNO_3$ and $Mg(NO_3)_2\cdot 6H_2O$. The nitrate ion is essential for the reaction efficiency and made it a catalytic process. An adduct of diethyl *H*-phosphonate with BHT **465-1** was detected by ESI-MS, which was confirmed the formation of phosphonyl radical (Scheme 161).[255]



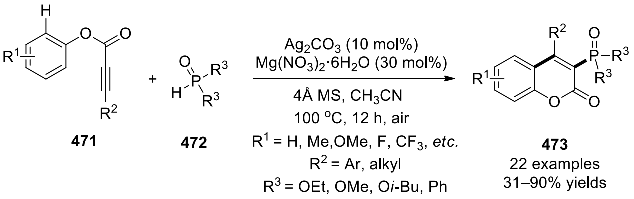
Scheme 161. Formation of γ-ketophosphonates with dialkyl *H*-phosphonates.

In addition to olefins and isonitriles, alkynes also can be used as radical acceptor for constructing of highly complex organophosphorus compounds. In 2013, two reports for silver-mediated dehydrogenative annulation of arylphosphine oxides **468** with internal alkynes **469** were developed by Duan group as well as Satoh and Miura *et al.* Promoted by stoichiometric amount of AgOAc or Ag_2O, a library of benzo[*b*]phosphole oxides **470** ere obtained efficiently.[256] Moreover, the addition of nitrate made it a catalytic process. Notably, the asymmetrical alkynes with diphenylphosphine oxide regioselectively resulted in single regioisomers, whereas the asymmetrical diarylphosphine oxides with different aryl substituents or one aryl group with two annulated sites generally produced a mixture of regioisomers. Mechanistically, a radical process was proposed by both research groups involving two possible 4-*exo-trig* and 5-*exo-trig* annulation pathways (Scheme 162). Additionally, a similar P–H/C–H functionalization for the synthesis of benzo[*b*]phosphole oxides was presented by Ackermann and co-workers with excess AgOAc in DMSO at 120 °C.[257]



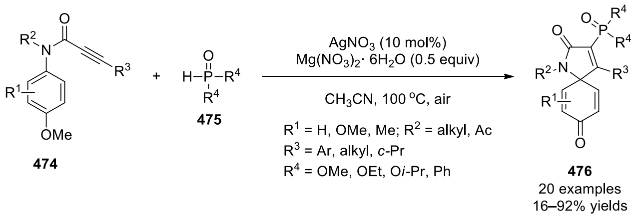
Scheme 162. Dehydrogenative annulation of arylphosphine oxides with internal alkynes.

The tandem radical phosphonation/C–H functionalization protocol was further expanded by Wang and Wu *et al.*, who reported the silver(I)-catalyzed difunctionalization of aryl alkynoates **471** with *H*-phosphonates **472**, furnishing a new C–P and a C–C bond in one pot. An array of 3-phosphonated coumarin derivatives **473** were obtained in 31–90% yields. The authors proposed that $Mg(NO_3)_2•6H_2O$ participated the generation of HNO_3 that subsequently performed the redox of silver(0/I). (Scheme 163).[258]



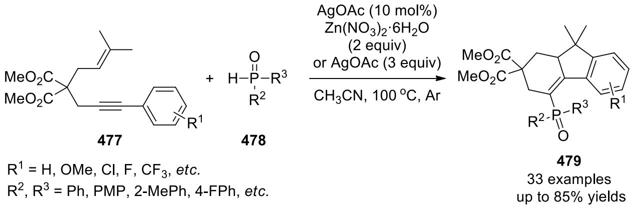
Scheme 163. Ag_2CO_3-catalyzed difunctionalization of aryl alkynoates with *H*-phosphonates.

The Liang research group extended this radical tandem annulation to *N*-(*p*-methoxyaryl)propiolamides **474**, providing phosphorylated aza-decenones **476** in moderate to excellent yields under silver(I) catalysis conditions. *H*-phosphonates as well as diphenylphosphine oxide **475** were acceptable. A reaction mechanism involving intermolecular phosphonation, intramolecular 5-*exo*-cyclization, and dearomatization in subsequence was recommended (Scheme 164).[259]



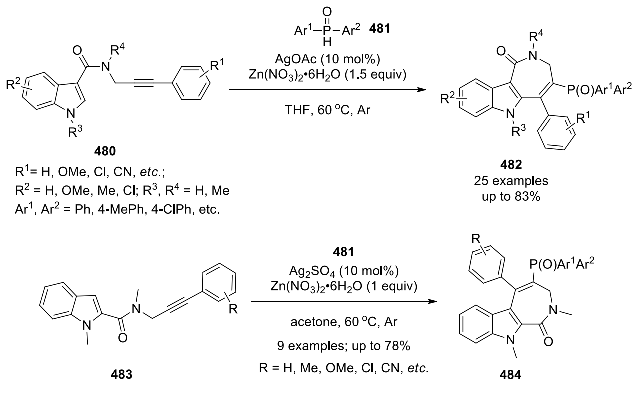
Scheme 164. Construction of phosphorylated aza-decenones.

Moreover, Liang and co-workers group developed a radical tandem reaction of 1,6-enynes **477** with phosphine oxides **478** with the aid of AgOAc (10 mol%) and $Zn(NO_3)_2·6H_2O$ (2 equiv), providing a sequence of functionalized fluorene derivatives **479** with high regioselectivity. Notably, 3.0 equivalent of silver salts were required when 1,6-enynes **477** bearing an un-/mono-substituted olefin moiety were used, without $Zn(NO_3)_2$. However, this reaction was limited to diaryl-substituted phosphine oxides **478** (Scheme 165).[260]



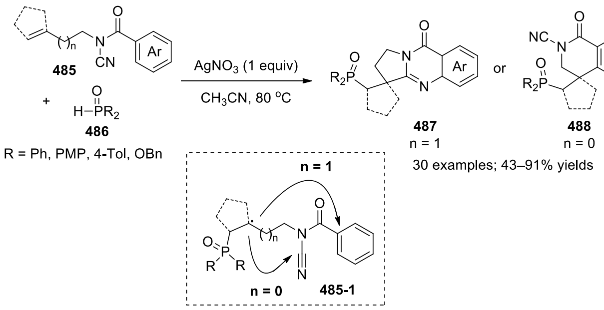
Scheme 165. AgOAc-catalyzed annulation of 1,6-enynes with phosphine oxides.

Further, the authors extended the reaction scope to 2- or 3-propargylamide-substituted indoles **480** and **483** with diarylphosphine oxides **481** under silver(I) catalysis. The reaction presented a novel, simple, and practical approach for the synthesis of various phosphorated indoloazepinone derivatives **482** and **484** with moderate to good yields, which are common building blocks in many natural products and pharmaceutical drugs. This difunctionalization of alkynes with diarylphosphine oxides **481** successfully formed a seven-membered ring in a one-pot sequence *via* a radical cyclization process (Scheme 166).[261]



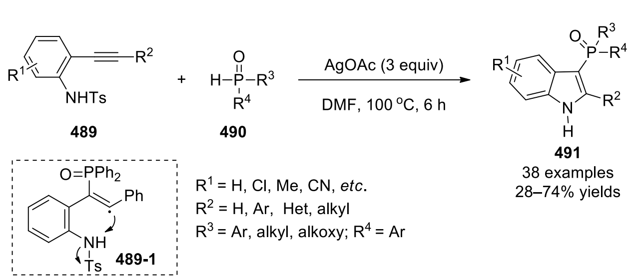
Scheme 166. Silver-catalyzed oxidative cyclization reaction of 2- or 3-propargylamide-substituted indoles.

Very recently, the Cui group reported an efficient $AgNO_3$-promoted divergent tandem reaction of *N*-cyanamide alkenes **485** for the formation of phosphorus 4-quinazolinones **487** or dihydroisoquinolinones **488** in moderate to excellent yields, respectively. The final construction of the products was depended on the chain of the substrates **485**. On the basis of previous reports, a radical phosphorylation/cyclization process was proposed. In line with Baldwin's rule, the initially formed radical **485-1** underwent an *exo-dig* cyclization to give a new iminyl radical which subsequently underwent an aromatic substitution, or a direct aromatic substitution to form the heterocycles. Both terminal and internal *N*-cyanamide alkenes **485** were applicable under the optimal conditions (Scheme 167).[262]



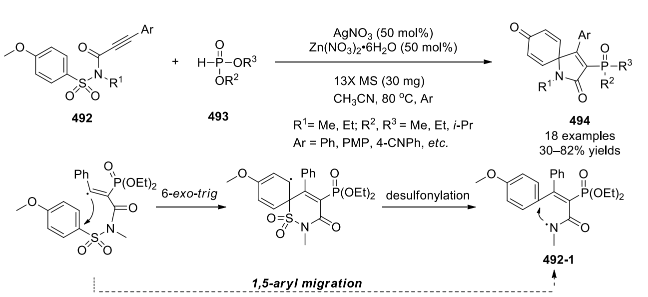
Scheme 167. Synthesis of phosphorus 4-quinazolinones or dihydroisoquinolinones.

3-Phosphinoylindole derivatives play important roles as pharmaceutical drugs and ligands. Zhao *et al.* developed an efficient radical protocol for the preparation of a broad spectrum of 3-phosphinoylindoles **491** in high yields starting from *N*-tosyl-2-alkynylaniline derivatives **489** and *H*-phosphine oxides **490**. The current method took place *via* tandem radical phosphinoylation to access radical **489-1**, cyclization, and desulfonylation in sequence, which underwent with the aid of AgOAc (3.0 equiv.). A new C−P and a C−N bond was formed directly (Scheme 168).[263]



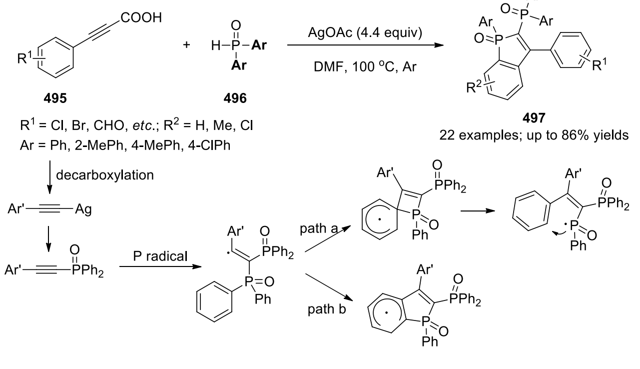
Scheme 168. Formation of 3-phosphinoylindoles with *N*-tosyl-2-alkynylanilines.

A range of phosphorylated azaspiro[4.5]decenones **494** could be synthesized by a silver-promoted oxidative cascade cyclization of *N*-(phenylsulfonyl)-*N*-methyl-3-phenylpropiolamides **492** with *H*-phosphonates **493**. The reaction progressed through radical phosphorylation, 1,5-aryl migration, desulfonylation, and dearomatization process in sequence. The cinnamamidyl radical **492-1** played a key role in this reaction, which is rarely reported before (Scheme 169).[264]



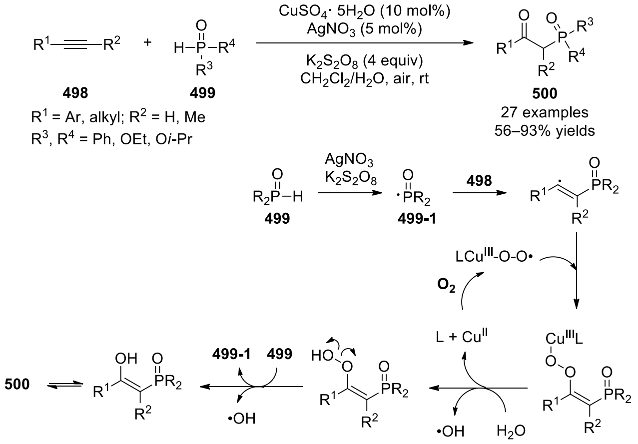
Scheme 169. $AgNO_3$-catalyzed oxidative cascade cyclization of *N*-(phenylsulfonyl)-*N*-methyl-3-phenylpropiolamides.

Gao and colleagues successfully developed the first facile and efficient silver(I)-mediated radical cascade reaction of readily available arylpropiolic acids **495** with diarylphosphine oxides **496**, affording a range of 2-phosphinobenzo[*b*]phosphole oxide compounds **497** with excellent functional-group compatibility. Preliminary mechanistic studies revealed that this synthetic protocol involved a decarboxylative C–P bond cross-coupling and a subsequent intermolecular C–H/P–H functionalization with another *H*-phosphine oxide. Among thesse, both 4-*exo-trig* and 5-*exo-trig* annulation pathways might be involved. Moreover, the generated π-conjugated products **497** bearing P–C–P backbones could be further transformed to valuable 2-phosphinobenzo[*b*]-phospholes and 2-phosphinobenzo[*b*]phosphole sulfides by ready reduction and sulfur oxidation (Scheme 170).[265]



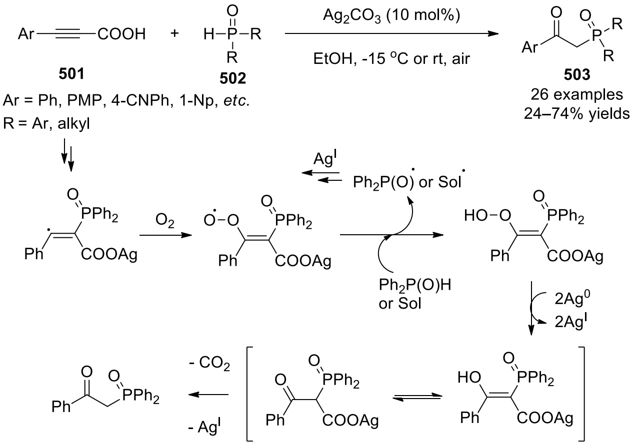
Scheme 170. Synthesis of 2-phosphinobenzo[*b*]phosphole oxides from arylpropiolic acids.

A library of terminal/internal alkynes **498** was employed for the oxyphosphorylation reaction with phosphine oxides **499** under silver/copper-cocatalysis in air conditions, leading to the corresponding β-ketophosphonates **500** in 56–93% yields. Diphenyl/ethyoxyl phenyl substituted phosphine oxides, and dialkyl *H*-phosphonates **499** were acceptable for the current strategy. Based on the radical trapping and control experiments, Zhao co-workers proposed a plausible mechanism involving a phosphite radical **499-1** and oxygen-activated copper complex. In the course, Ag(I/II) with $K_2S_2O_8$ as the oxidant and Cu(II/III) with oxygen catalytic circle were probably involved (Scheme 171).[266]



Scheme 171. Silver/copper-catalyzed direct oxyphosphorylation of alkynes.

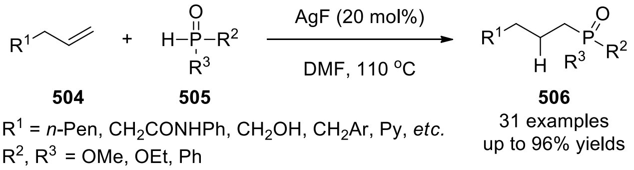
By constrast, a sequence of functionalized β-oxophosphine oxides **503** was synthesized starting from arylpropiolic acids **501**. A set of diaryl and dialkyl-substituted *H*-phosphine oxides **502** were suitable for this Ag_2CO_3-catalyzed oxidative decarboxylative coupling reaction, even underwent in gram-scale synthesis, whereas dialkyl *H*-phosphonates caused poor yields. ^{18}O-labeled reaction were conducted and unraveled the carbonyl oxygen atom was originated from molecular oxygen which functioned as the terminal oxidant (Scheme 172).[267]



Scheme 172. Ag_2CO_3-catalyzed oxidative decarboxylative coupling reaction with arylpropiolic acids.

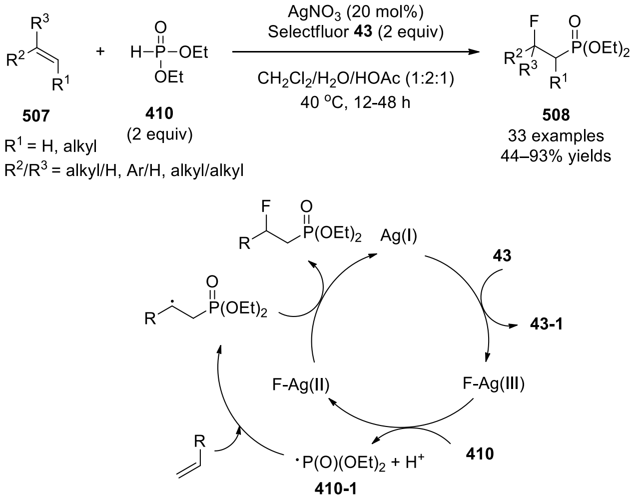
4.3 Miscellaneous Reactions

Recently, Liu *et al.* reported an efficient and scalable AgF-catalyzed intermolecular hydrophosphinylation of unactivated alkenes **504**. Phosphine oxides with different substituent groups **505** were incorporated with the highly functionalized terminal alkenes **504**, furnishing completely *anti*-Markovnikov addition products **506** in good yields. Mechanistic studies including electron-spin-resonance (ESR) and radical clock experiments supported a free radical process. In addition, styrene and its derivatives were not effective in this system.[268]



Scheme 173. AgF-catalyzed hydrophosphinylation of unactivated alkenes.

The silver(I)/Selectfluor system serves not only as an oxidant but also as a fluorine atom transfer agent in fluorodecarboxylation of aliphatic carboxylic acids and in intramolecular radical aminofluorination of unactivated alkenes, presumably *via* Ag(III)F and Ag(II)F as intermediates. Based on these, Li *et al.* successfully developed the first example of catalytic phosphonofluorination of unactivated alkenes **507**, providing a set of β-fluorinated alkylphosphonates **508** of great biological activities under mild conditions. With diethyl phosphite **410** and Selectfluor **43**, the reaction displayed good stereoselectivity, extensive alkene scopes and wide functional-group compatibility. Notably, all three co-solvents ($CH_2Cl_2/H_2O/HOAc$) as well as the silver catalyst were required for the reaction. The acetic acid or TFA was used as the co-solvent, which might enhanced the stability of the proposed Ag(III)F and/or Ag(II)F intermediates in acidic medium. A mechanism involving silver-catalyzed oxidative generation of phosphonyl radical **410-1** and silver-assisted fluorine atom transfer was proposed. While studying the scope of alkenes, electron-deficient alkenes such as methyl acrylate and alkenes with easily oxidized groups were observed inappropriate. Importantly, the combination of silver-catalyzed oxidative generation of electrophilic radicals and the silver-assisted fluorine atom transfer to nucleophilic alkyl radicals offers an entry to access fluorinated molecules.[269]



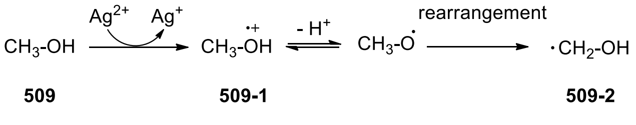
Scheme 174. Silver-catalyzed phosphonofluorination of unactivated alkenes.

5. Oxygen Radicals

O-centered radiacals, such as alkoxy radicals (RO•) or acyloxyl radicals (RCOO•), suffer from the competition with other pathways, in particular allylic hydrogen abstraction and β–fragmentation in the case of alkoxy radicals or decarboxylation of acyloxyl radicals, thus make transformations into C-centered radicals.[2a]

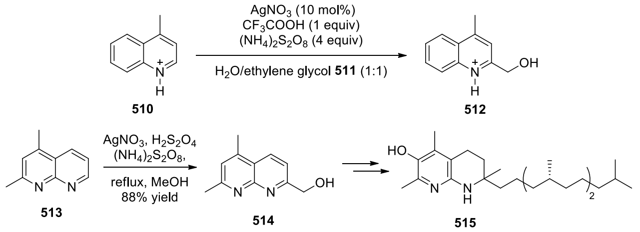
5.1 Alcohols

Simple Alcohols. Alkoxy radicals can be formed in the presence of peroxysulphate with silver(I) salts. In general the mechanism is similar with the decarboxylation pathway *via* Ag(I/II) cycle. The methanol molecule **509** is oxidized to its radical cation **509-1** by Ag(I)/$S_2O_8^{2-}$, followed by a dehydrogenation and a rearrangement to form a new carbon-centered radical (•CH_2OH) **509-2** (Scheme 175).[25, 28, 270]



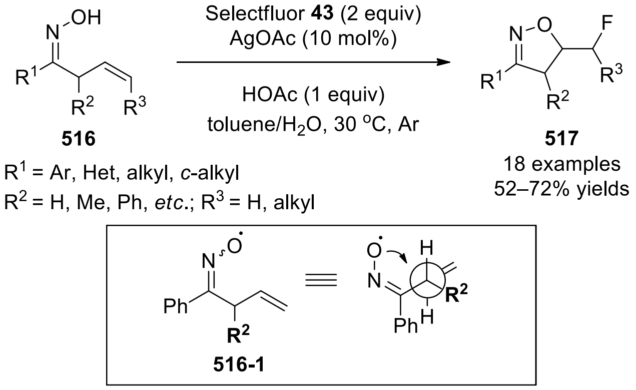
Scheme 175. Generation of hydroxymethyl radical.

In 2004, Minisci group demonstrated the hydroxymethyl radical (•CH_2OH) **509-2** could be merged into heteroaromatics such as quinolines **510** in refluxing ethylene glycol/H_2O under silver(I)/persulphate/trifluoroacetic acid system, which offered a practical approach for the assembly of hydroxymethylated compounds **512**.[271] The importance of the β-scission of the alkoxyl radical intermediate was emphasised. By comparison with methanol, ethylene glycol **511** owned a better selectivity without oxidation into aldehyde.[272] With methanol as the source of •CH_2OH, the hydroxymethylation procedure was employed in the formation of tetrahydro-1,8-naphthyridol analogues of α-tocopherol that function as antioxidants of lipid peroxidation. The 1,8-naphthyridols may be valuable owing to to lipid peroxidation has association with pathologies such as cardiovascular disease, neurodegeneration and cancer. For instance, in the synthesis of a key compound known as *N*-TOH **515**, a naphthyridine **513** underwent selective hydroxymethylation process in refluxing methanol, and furnished the expected (1,8-naphthyridin-2-yl)methanol compound **514** in 88% yield (Scheme 176).[273]



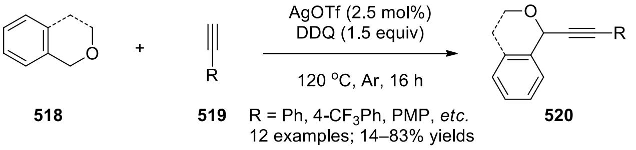
Scheme 176. Silver-catalyzed hydroxymethylation of heteroaromatics.

Based on the aminofluorination,[201] a new oxyfluorination of unactivated alkenes under silver(I)/Selectfluor oxidative conditions was demonstrated, which provided a new access to 5-(fluoromethyl)-4,5-dihydroisoxazoles **517** in 52–72% yields, constructing a C–O and a C–F bond in one pot. This silver-catalyzed alkene radical difunctionalization strategy offered a general and available route to synthesize the Δ^2-isoxazoline compounds **517**, whereas the previous methods suffer severely from restricted substrate scope, unsatisfactory regioselectivity or harsh conditions. A radical mechanism involving a generation of oxygen radical **516-1** was proposed, which plausibly attacked toward the carbon-carbon double bond from the back-side of the R^2 group. The diastereoselectivity of products **517** was highly relyed on the properties of the R^2 group, especially the steric effect. In addition, the corresponding products **517** efficiently underwent ring-opening process to provide the other fluorine-containing compounds (Scheme 177).[274]



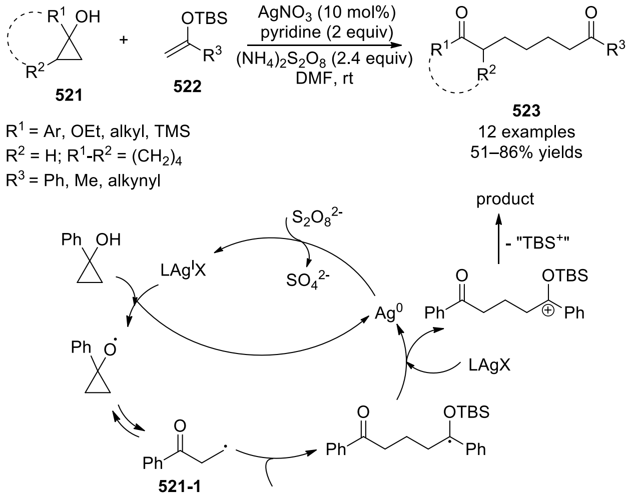
Scheme 177. AgOAc-catalyzed oxyfluorination to access Δ^2-isoxazolines.

Transition metal-catalyzed C–C bond formation through direct C–H bond activation has attracted considerable attention in recent years. A set of propargyl ethers **520** were derived from terminal alkynes **519** and benzylic ethers **518**, using 2,3-dichloro-5,6-dicyanoquinone (DDQ) as an oxidant at 120 °C under an argon atmosphere, which was reported by the Li group in 2010. The key benzoxy cation radical was possibly generated from benzylic ether **518** by a single electron transfer of ether **518** to DDQ and a *H*-radical abstraction (Scheme 178).[275]



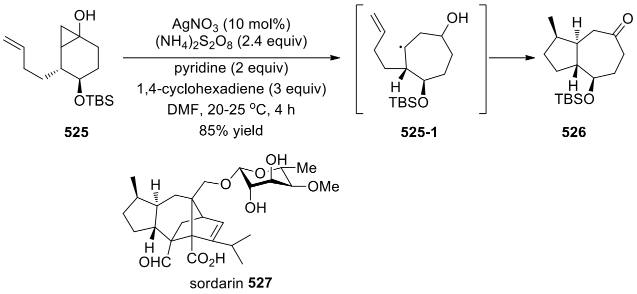
Scheme 178. CDC reaction of terminal alkynes and benzylic ethers.

Cyclopropanol derivatives. In 2006, Narasaka *et al.* reported a catalytic β-keto radical formation from cyclopropanol derivatives **521** under silver(I)/persulphate/pyridine system, which was improved to a catalytic process in contrast to the manganese(III)-promoted conditions. Under the optimal conditions, the generated β-keto radicals **521-1** coupled with terminal silyl enol ethers **522** to yield the desired addition products **523**. Unfortunately, the reaction of trisubstituted alkenes provided low yields. In comparision, other *N*-bases, such as 2,6-lutidine, 2,2-bipyridine, and DBU were less effective for this reaction. Pyridine worked as a base during the oxidation and also as a ligand coordinating to Ag(I). Different from the Ag(I)-Ag(II) cycle with persulphate oxidation under harsh conditions (*i.e.*, refluxing in water), this catalytic reaction presumably occured *via* Ag(I)-Ag(0) cycle for milder conditions. The Ag(II) species was sufficient to oxidate silyl enol ethers **522** because of the strong oxidizability.[276] Moreover, three-component coupling of cyclopropanols, electoron-deficient and rich alkenes were carried out, which was initially started by nucleophilic β-keto radicals attack electron-deficient alkenes (Scheme 179).[277]



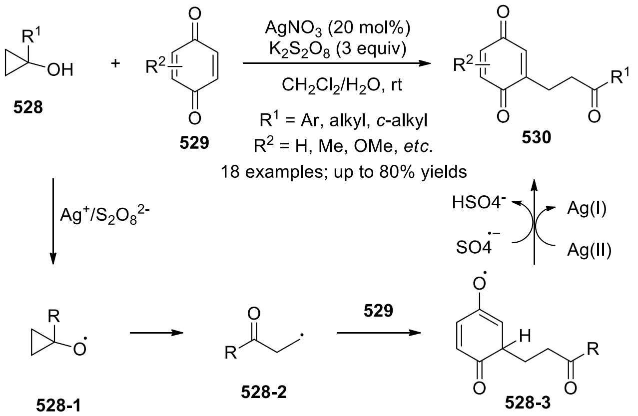
Scheme 179. Coupling reaction of cyclopropanols with terminal silyl enol ethers.

The methodology that radical C–C bond cleavage of cycloalkanolsinto carbon-radical[278] was applied to the total synthesis of polycyclic terpene (–)-sordarin **527**. Treatment of bicyclo[4.1.0]heptan-1-ol tethered 3-butenyl group **525** with a $AgNO_3$-$(NH_4)_2S_2O_8$-pyridine system produced the β-keto radical intermediate **525-1**, followed by an intramolecular cyclization process and yielded the optically active bicyclo[5.3.0]-decan-3-one derivative **526** stereoselectively (Scheme 180).[279]



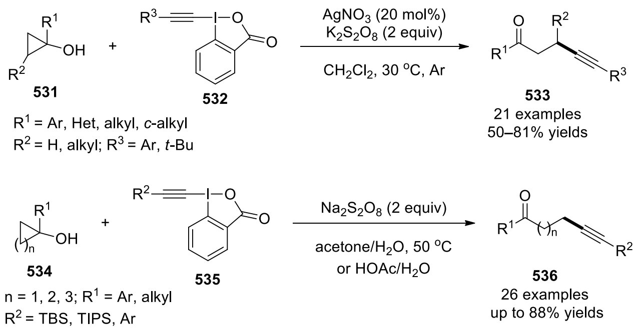
Scheme 180. Radical C–C bond cleavage of cycloalkanols.

Using cyclopropanols as a radical source, a mild and convenient method for the assembly of highly substituted γ-carbonyl quinones **530** has been developed by Ilangovan and colleagues *via* C–H functionalization of quinones **529**. A series of γ-carbonyl quinones **530** were obtained in high yields with wide range of substrate scope and excellent functional groups. Quinones with electron-withdrawing groups delivered poor yields. The mechanism was proposed involving an oxidative ring opening of cyclopropanols **528** and a radical addition to quinones **529** *via* Ag(I)–Ag(II) catalytic cycle. The cyclopropanol forms a radical **528-1** under Ag(I)/persulfate conditions, which performs C–C bond cleavage to form β-keto radical **528-2**. The radical **528-2** reacts with a quinone **529** forming a radical intermediate **528-3** which subsequently occurs reoxidation with Ag(II) to yield the final product **530** and regenerates Ag(I) (Scheme 181).[280] Additionally, this method was utilized for the synthesis of cytotoxic natural products, as exemplified by 4,6-dimethoxy-2,5-quinodihydrochalcone and evelynin.[281]



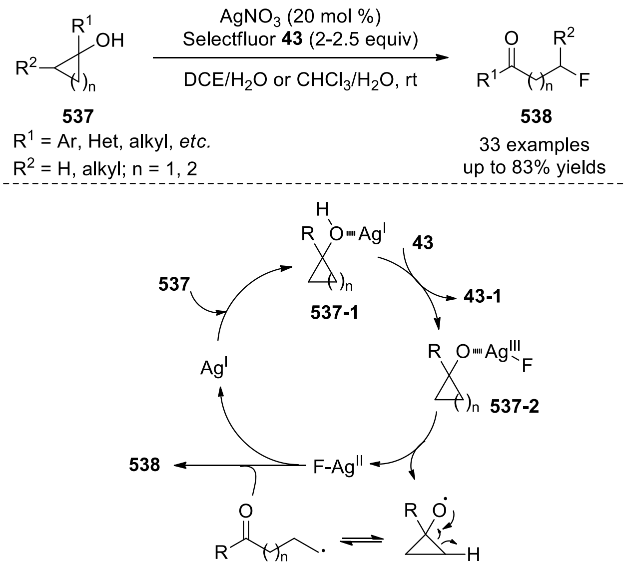
Scheme 181. Synthesis of γ-carbonyl quinones with quinones.

Learning from the silver-catalyzed decarboxylative alkynylation reported by Li group,[24h] Xie and Li *et al.* revealed that cyclopropanols **531** allowed the silver-promoted oxidative ring opening/alkynylation with ethynylbenziodoxolones (EBXs) **532** for the synthesis of alkylated alkynes **533** in 50–81% yields. An array of aryl- and alkyl-substituted EBXs **532** was compatible, and provided a mild and practical route to produce the functionalized γ-carbonyl alkynes **533**. Control experiments showed that both $AgNO_3$ and $K_2S_2O_8$ have twofold roles, namely serving as not only catalysts but also oxidants for in ring opening and alkynylation step.[282] In comparison, a very similar report without metal catalysts has been developed, but excess amount of acetic acid was required. And silyl and aryl-substituted alkynes **535** were appropriate for the reaction. Moreover, the less strained tertiary cyclopentanols **534** were also applicable and led to the desired δ-alkynylated ketones **536** in moderate yields catalyzed by 10 mol% $AgNO_3$ (Scheme 182).[283]



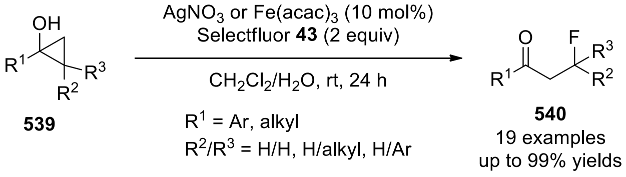
Scheme 182. Synthesis of alkylated alkynes from cyclopropanols with EBXs.

Direct fluorination on alkyl groups to generate $C(sp^3)-F$ bonds is relatively less investigated. In contrast to the easy access of α-fluorinated ketones, the practically direct fluorination for regioselectively synthesize distal (β, γ, δ, *etc.*) fluorinated ketones is rarely reported.[284] Given this, Zhu *et al.* made progress in developing a ring-opening strategy for the synthesis of fluoroketones **538** with the combination of silver(I) and Selectfluor **43** under mild conditions. The transformation exhibits good functional-group compatibility, including electron-rich and -deficient aryl groups, heteroaryl and alkyl groups at α-carbon of alcohols **537**. Starting from tertiary cyclopropanols and cyclobutanols **537**, a variety of β- and γ-fluorinated ketones **538** were obtained in good regioselectivities, respectively. $AgNO_3$ gave a better outcome with cyclopropanols, while cyclobutanols performed the reaction under $AgBF_4$ catalysis preferably. This fluorination process was readily applized for the construction of complexly fluorine-incorporated molecules. Learning from the mechanism experiments and previous reports, a radical mechanism was plausibly involved. Moreover, the reaction of a single diastereomer alcohol resulted in a couple of isomers in a 1.5:1 ratio rather than retention of C-center configuration, which was inconsistent with the product *via* sequence of C−C bond insertion and reductive elimination. In light of the results, a radical-mediated sequential C−C bond cleavage and C−F bond formation pathway was suggested, in which Ag(I) **537-1** was oxidated to Ag(III) **537-2** by Selectfluor (Scheme 183).[285]



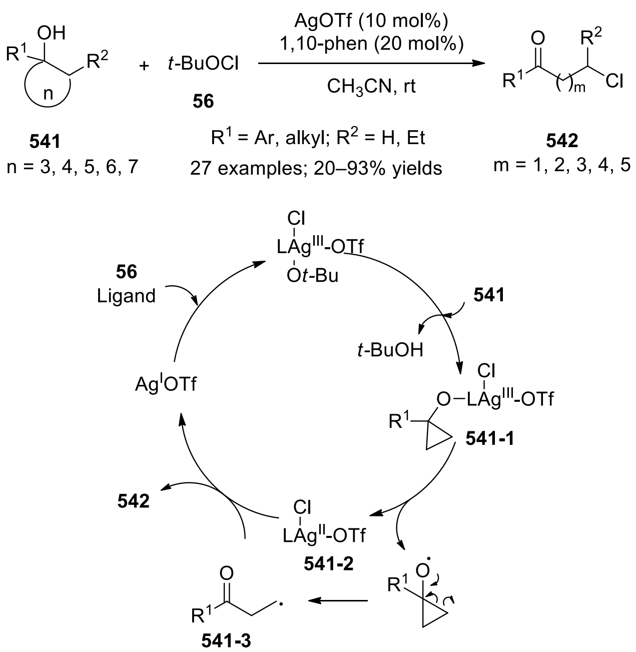
Scheme 183. Ring opening for the synthesis of fluoroketones with Selectfluor.

Meanwhile, Feng and Loh *et al*. reported a similar method for the preparation of β-fluoroketone **540** under $AgNO_3$ or $Fe(acac)_3$ catalysis. This reaction also performs efficiently and delivers the desired β-fluoroketones **540** from a library of highly functionalized cyclopropanols **539** in good to excellent yields. With respect to alkyl and electron-deficient or sterically hindered aryl derived cyclopropanols, catalyst $AgNO_3$ was proved to be superior to $Fe(acac)_3$. A further extension to cyclobutanols and cyclopentanols were conducted and delivered the γ- or δ-fluoroketones efficiently (Scheme 184).[286]



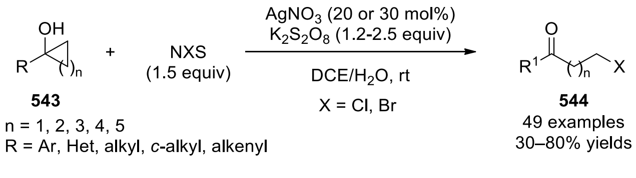
Scheme 184. Synthesis of β-fluoroketone by $AgNO_3$ or $Fe(acac)_3$ catalysis.

An analogous and facile approach that silver(I)-catalyzed ring-opening chlorination of cycloalkanols **541** was developed by Qi and Zhang *et al*., leading to a wide range of β-, γ-, δ-, ε-, and even ζ- chlorinated ketones **542** in moderate to excellent yields. Mechanically, Ag(III) species **541-1** was possibly formed from cycloalkanols **541** in the presence of AgOTf, *t*BuOCl **56** as oxidant and 1,10-phen as ligand, which subsequently evolved to the Ag(II) species **541-2** and β-keto radical **541-3** (Scheme 185).[287]



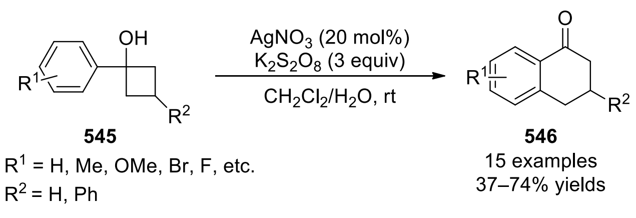
Scheme 185. Silver(I)-catalyzed ring-opening chlorination of cycloalkanols with *t*BuOCl.

With *N*-cholosuccinimide (NCS) as chlorinating regant, a broad spectrum of β, γ, δ, and even more remotely chlorinated ketones **544** were efficiently synthesized under mild reaction conditions. The reaction was carried out under silver(I)/$S_2O_8^{2-}$ system without ligands and even in gram-scale. While using *N*-bromosuccinimide (NBS), the distal bromination reaction of cycloalkanols **543** progressed smoothly as well and furnished the corresponding brominated products (Scheme 186).[288] Similarily, a library of cycloalkanols underwent the oxidative trifluoromethylthiolation reaction delivering distally trifluoromethylthiolated ketones in good yields in the presense of $AgSCF_3$ and $K_2S_2O_8$.[289]



Scheme 186. Synthesis of distally chlorinated/brominated ketones.

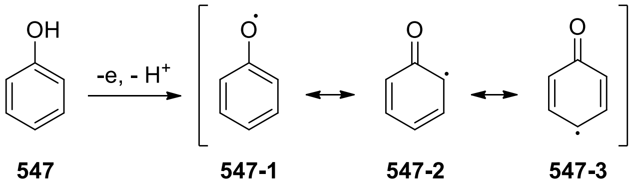
A series of α-aryl substituted cyclobutanols **545** were designed for the tandem oxidative C–C bond cleavage/intramolecular annulation reaction, thus led to the corresponding 1-tetralones **546** in moderate to good yields under mild conditions. The preliminary experimental and DFT studies also revealed a radical pathway is involved (Scheme 187).[290]



Scheme 187. Synthesis of 1-tetralones from cyclobutanols.

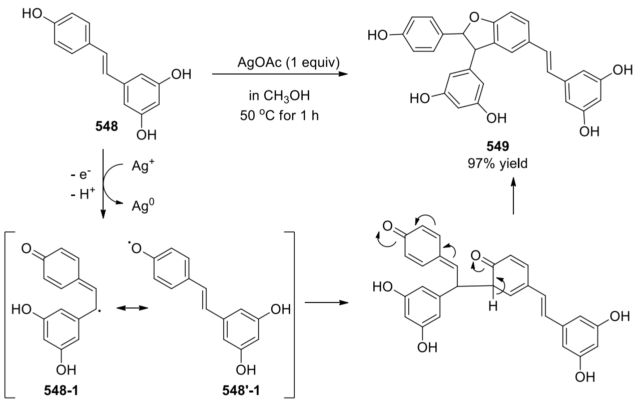
5.2 Phenoxyl Radicals:

Numerous natural products can be constructed *via* different oxidative phenol couplings, including homo-coupling at the same site, homo-coupling at different sites, and cross-coupling of different phenols. Hence, the chemo- and regioselective oxidation of phenols **547** have been gained much attention and widely studied, especially in biomimetic synthesis. Whereas it still remains a challenge in organic chmistry due to they are unstable and susceptible to being oxidized, and have multiple reaction sites of the resonance isomers. With silver salts, phenol and its derivatives **547** can be oxidized to access phenoxyl radicals and their resonance isomers (**547-1→547-3**), which can be readily applized for the C–C or C–O bond formation, as shown in Schem 188. For a long time silver salts has been known to oxidize hydroquinone into benzoquinone.[291]



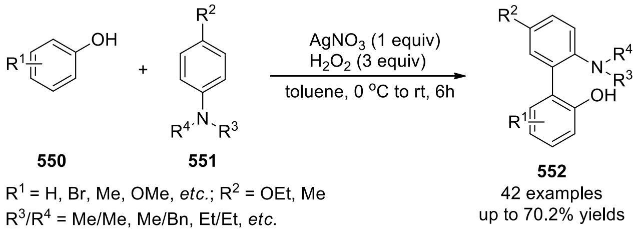
Scheme 188. Phenoxyl radicals and their resonance isomers.

For instance, promoted by stoichiometric amount of AgOAc, a series of 4-hydroxystyrene derivatives furnished the dehydrodimers in high yields and stereoselectivities. This oxidative dimerization method was applicable to access dihydrobenzofuran framworks possessing various types of biological activities **549**, such as resveratrol and *E*-viniferin (*E*)-dehydrodimers. The phenoxyl radical and its resonance isomer **548-1** and **548’-1** were probably generated from 4-hydroxystyrene **548** to induce the coupling reaction (Scheme 189).[292]



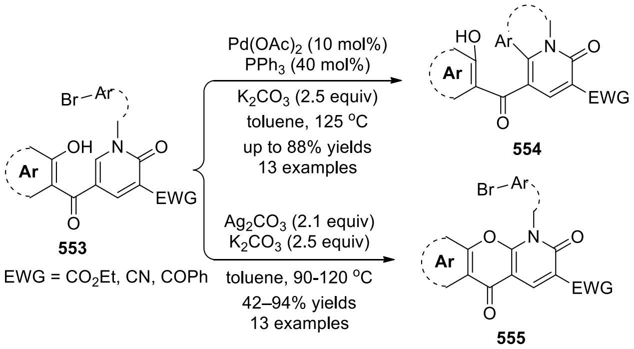
Scheme 189. Formation of dihydrobenzofurans with 4-hydroxystyrene derivatives.

A regioselective oxidative DCC reaction between a broad range of available phenols **550** and aniline derivatives **551** has been developed, affording the expected biphenyl analogous **552** under mild conditions, which is promoted by $AgNO_3$ in the presence of H_2O_2. It should be noted that this was one of the rare reports which have extension scope to simple phenol derivatives **550**. The reaction initiated with the formation of a silver(I)–phenol complex followed by one electron oxidation resulting in a electrophilic carbon radical intermediate, which was then merged into aniline (Scheme 190).[293]



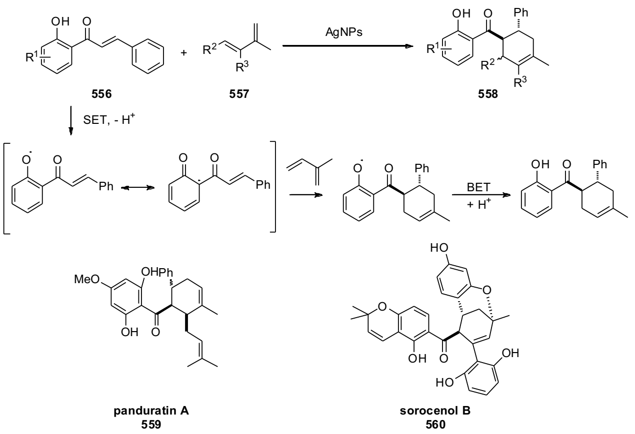
Scheme 190. DCC reaction between phenols and anilines.

Recently, Lawson and co-workers found an interesting selective C–C or C–O bond coupling reaction of *N*,3,5-trisubstituted pyridones **553**. A wide range of *C*-arylated and *O*-arylated pyridones of biological interest were received efficiently and selectively. 1,6-*C*-annulated pyridones **554** were generally achieved in good yields with excellent chemoselectivity under Pd(0)/PPh_3 catalytic conditions. Whereas, with simple Ag_2CO_3 medium, full C6-regioselective C(sp^2)-aryloxylation reaction was conducted and resulted in 5,6-*O*-annulated pyridones **555** in 42–94% yields, which was proposed through a radical cyclization mechanism (Scheme 191).[294]



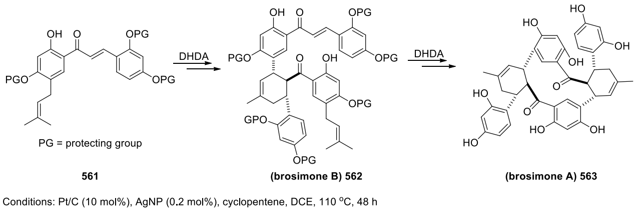
Scheme 191. Selective C–C or C–O bond coupling of *N*,3,5-trisubstituted pyridones.

It is known that nanocatalysts have special and high catalytic activity. Their application in the synthesis of complex natural products still need further development, which potentially open up new direction and allow reactions for the total synthesis.[295] The first report for the prodution of complex compounds under silver nanoparticles catalysis was reported by Porco *et al.* in 2010.[296] A cycloaddition reactions between chalcone derivatives **556** and dienes **557** catalyzed by silica-supported AgNPs generally resulted in the endo Diels–Alder cycloadducts **558** with high levels of yields and regioselectivities, and even unsymmetrical dienes were used. Notably, the use of supported AgNPs at a loading of as low as 0.01 mol% Ag still offered a nearly quantitative yield with increasing the reaction temperature and prolonged reaction times. More importantly, the AgNPs system could be applied in the total synthesis of natural product panduratin A **559** *via* the key Diels–Alder reaction. In this case, AgNPs likely functioned as electron shuttles and redox catalysts (Scheme 192). Another application of the nanosilver-catalyzed Diels–Alder cycloaddition as key step was demonstrated for the assembly of sorocenol B **560**.[297] Similarly, the Rahman group applied AgOTf/Bu$_4$BH$_4$ as the precursor of AgNPs for the catalytic [4 + 2] cycloaddition of chalcone derivatives with dienes. Although the authors did not regard the reaction as a AgNPs-promoted natural product synthesis, the AgNPs were usually prepared from silver salts in the presence of reductants (such as Bu$_4$BH$_4$).[298]



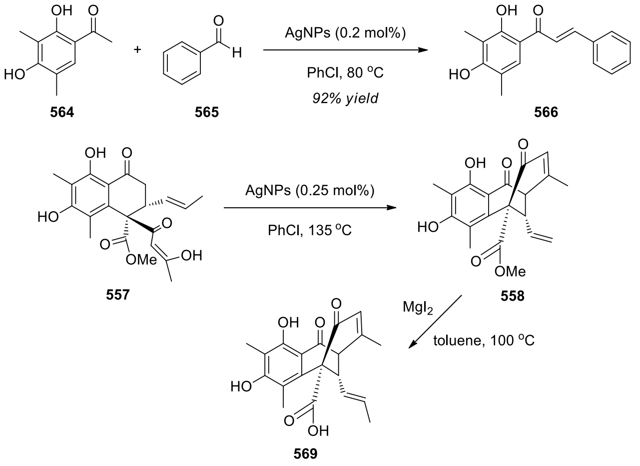
Scheme 192. Synthesis of natural product panduratin A and sorocenol B.

Afterwards, the Porco Jr. group developed a concise method for the synthesis of the natural product brosimone B **562** and brosimone A **563**, which highlighted the involvment of biomimetic, dehydrogenative Diels–Alder (DHDA) cycloadditions with chalcones **561**. On the basis of thermodynamic calculation, the energetics of AgNP-catalyzed cycloadditions was unveiled and showed the lowest barriers for the process involving one electron oxidation/phenol deprotonation/complexation of the resultant radical with Ag(I) on the surface of the AgNPs. Experiments were unveiled the kinetic *exo-endo* diastereomer of a protected form of brosimone A could be converted to the thermodynamic *exo-exo* isomer using AgNPs at higher temperature (Scheme 193).[299]



Scheme 193. Synthesis of the natural product brosimone B and brosimone A.

While studying the nanosilver catalyst for natural product synthesis, silver nanoparticle-mediated aldol condensation was shown as the key step, thus the Porco Jr. group carried out the model aldol condensation of 2’,4’-dihydroxyacetophenone **564** and benzaldehyde **565** under silver nanoparticle catalysis. The mechanistic studies indicated that a radical process was involved in the aldol process for the construction of chalcone **566**. Treatment of substrate **567** with AgNP catalyst afforded a 72% yield of the cyclized product **568**, which further evolved into sorbiterrin A **569** in 85% yield with the aid of MgI$_2$ (Scheme 194).[300]



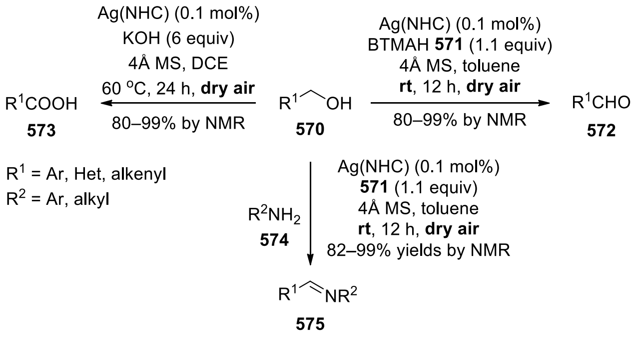
Scheme 194. Formation of sorbiterrin A.

5.3 Oxidation

The oxidation reaction is a fundamental process in nature and one of the most important transformations in organic chemistry. Silver salts/complexes have been used as classic oxidizing agent.[7a] In the past decades, the catalytic activity of silver-based alloys or heterogeneous silver-based catalyst systems in oxidation reactions (heterogeneous oxidation and dehydrogenation reaction) has been widely discussed, which have been applied in industrial production.

Besides, considering the excess use of silver salts, modifications silver-based oxidation reactions to catalytic mode have been focused. Therefore, alternative oxidants like the green and low-cost H_2O_2 has been widely utilized. For instance, a variety of carboxylic acid derivatives were obtained from the corresponding aromatic, aliphatic and conjugated aldehydes by the combination of 30% H_2O_2 (5 equiv.) with $AgNO_3$ catalyst.[301] Moreover, molecular oxygen is the most ideal oxidant owing to its environmental and economic benefits. Thus, oxygen aerobic oxidation is one of the hot topics in organic synthesis. Ag(II) species is derived *via* the incorporation of oxygen with Ag(I).[302]

Although many Ag-NHC complexes have been studied as catalysts, however, their potential in aerobic oxidation has not been fully elucidated. In 2014, Jiang *et al.* presented that Ag-NHC complexes catalyzed aerobic oxidation of a wide spectrum of alcohols **570**. In the presence of NHC-Ag(I) as catalyst, BTMAH (tetramethylammonium hydroxide) **571** or KOH as base, the oxidation was performed aerobically to produce aldehydes **572** or carboxylic acids **573** in excellent yields. Further, a one-pot process with an amine **574** was developed and furnished imines **575** with high yields and wide range of substrate scope. A plausible mechanism involving molecular oxygen activation for the formation of a triplet Ag^{II} complex bearing a peroxy radical was proposed on the basis of the *in situ* ESI-MS (Scheme 195).[303]



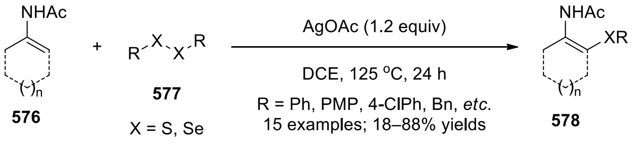
Scheme 195. NHC-Ag(I)-catalyzed aerobic oxidation of alcohols.

6. S-centered Radicals

6.1 Thiol and sulfonyl radicals

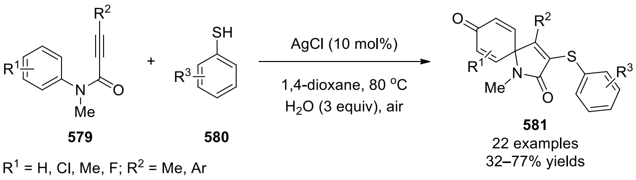
Many of the transition metal catalyzed C−S cross-couplings depend on harsh reaction conditions such as high reaction temperature, the necessity of strong base, and use of expensive ligand, and they always suffer from limited substrate scope. Moreover, catalyst poisoning by the sulfide is one of the limiting factors in these approaches. And considering reactions of S-centered radicals,[235c] thiol radical is feasibly oxidized under silver-based oxidative conditions.

Due to the rapid progress of direct C–H functionalization, numerous transition-metal catalyzed/mediated C(sp^2)–H sulfenylations have been reported for the synthesis of diaryl sulfides. However, very few of them can be applied to the vinylic C–H bond. Yang and Deng *et al.* made a contribution to describe a Ag-mediated oxidative vinylic C–H sulfenylation of enamides **576** with diaryl disulfides **577**, furnishing biologically important arylvinyl sulfides **578** in 36–88% yields in a consice and efficient way. Components such as 1,2-dibenzyldisulfane and 1,2-dibenzyldiselane were extended, albeit in low isolated yields due to their low conversion. A plausible non-chain radical mechanism that vinyl radical facilitates the homolytic cleavage of the diaryl disulfide to form arylthiol radical was proposed based on the preliminary mechanistic studies (Scheme 196).[304] _ENREF_68



Scheme 196. Oxidative vinylic C–H sulfenylation.

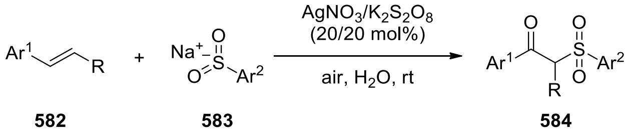
In 2015, Wei and Wang *et al.* reported the AgCl-catalyzed oxidative spirocyclization of *N*-arylpropiolamides **579** producing a set of functionalized 3-thioazaspiro-[4,5]trienone compounds **581** of synthetic and pharmaceutical importance in 32–77% yields. The radical trapping reaction with TEMPO unraveled the generation of thiol radicals from thiophenols **580**. $H_2{}^{18}O$ experiments indicated the carbonyl oxygen atom of the products was originated by a nucleophilic addition of water and oxidation in sequence (Scheme 197).[305]



R¹ = H, Cl, Me, F; R² = Me, Ar
R³ = H, Cl, Br, OMe, *etc.*

Scheme 197. Oxidative spirocyclization of *N*-arylpropiolamides.

Transition metals used for dioxygen activation and radical initiation is an exciting as well as a challenging strategy for the development of new synthetically important reactions. In 2014, Yadav's group developed the first example of catalytic oxysulfonylation of alkenes **582** with sodium arenesulfinate salts ($ArSO_2Na$) **583** to synthesize β-keto sulfones **584**. The procedure underwent with dioxygen at room temperature using $AgNO_3/K_2S_2O_8$ catalyst system in aqueous medium.[306] Moreover, the $ArSO_2$• generated *in situ* could efficiently undergo the silver-catalyzed tandem radical addition/C–H functionalization reaction with *N*-arylacrylamides, thus led to the corresponding sulfonated products (Scheme 198).[190]

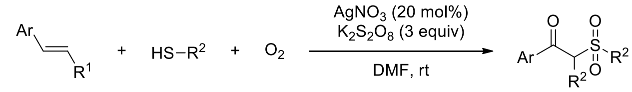


582 **583** **584**
23 examples
62–96% yields

Ar¹ = Ph, PMP, 4-CNPh, *etc.*
Ar² = Ph, PMP, 2-Np, 4-ClPh, *etc.*
R = H, Me, Et

Scheme 198. Oxysulfonylation of alkenes with sodium arenesulfinate salts.

Yadav and co-workers also demonstrated β-ketosulfones **587** could be achieved *via* oxysulfonylation of alkenes **585** with thiophenols/thiols **586** as sulfonylation precursors, providing the first case for the thiophenols acting as sulfonyl source in a dioxygen activation based radical process. Tiophenol radical was generated *in situ* and added to the C=C bond, followed by oxidation of dioxygen. Aryl-substituted terminal or internal alkenes **585** were suitable and allowed the oxysulfonylated products in good yields. Moreover, β-hydroxysulfides were formed in 94% yield under $AgNO_3$ catalysis at room temperature without the use of oxidation reagents ($K_2S_2O_8/O_2$) (Scheme 199).[307]

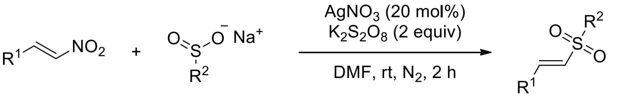


585 **586** **587**
21 examples
75–95% yields

Ar = Ph, PMP, 2-Np, *etc.*; R¹ = H, Me
R² = Ph, 4-ClPh, PMP, 2-Np, *n*-Pr, *etc.*

Scheme 199. Oxysulfonylation of alkenes with thiophenols/thiols.

Very recently, the first report of denitrative radical cross-coupling of β-nitrostyrenes **588** and sodium sulfinates **589** based on silver catalysis was developed, leading to the highly stereoselective synthesis of (*E*)-vinyl sulfones **590** under mild reaction conditions. A mechanism involving a sulfonyl radical addition and NO_2 group elimination process was suggested to form a new C(sp²)–S bond (Scheme 200).[308]



588 **589** **590**
23 examples
69–94% yields

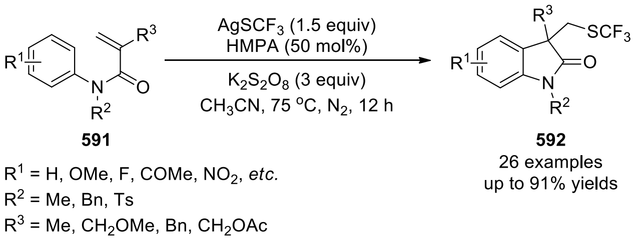
R¹ = Ph, PMP, 4-NO₂Ph, 2-Th, *etc.*
R² = PMP, 4-CF₃Ph, 2-Th, Et, *c*-Pr, *etc.*

Scheme 200. Synthesis of (*E*)-vinyl sulfones from β-nitrostyrenes.

6.2 SCF_3 Radicals

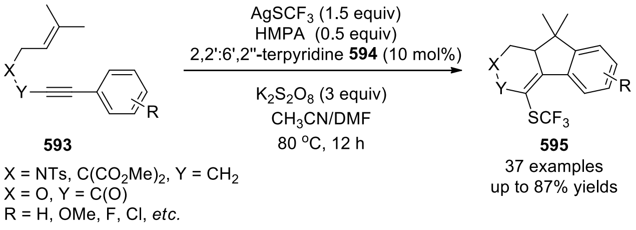
The trifluoromethylthiol group (CF_3S) has attracted increasing attention because of its special biological properties, such as enhancement of membrane permeability and absorption rate, and improvement of the stability of parent molecules, due to its lipophilicity and high electronegativity.[309] Considering the limitations of classical methodologies, such as harsh reaction conditions and the requirement of prefunctionalization, the more general and straightforward methods for C−SCF_3 bond construction are highly desirable. Previously CF_3S sources were limited to toxic and gaseous (or volatile) CF_3SH, CF_3SCl, and CF_3SSCF_3.[310] In subsequent research, silver(I) trifluoromethanethiolate ($AgSCF_3$) has been advocated as the trifluoromethylthiolation reagent that is commercially available, stable, maneuverable and chemically well-studied.

Learning from the tandem radical insertion/C–H functionalization strategy, Wang *et al.* in 2014 provided the first example of silver-mediated radical cyclization for the synthesis of various valuable SCF_3-containing oxindoles **592** in moderate to good yields, constructing the C(sp³)–SCF_3 bond and C–C bond in a one-pot procedure. The F$_3$CS radical was formed *via* a combination of AgSCF$_3$ and oxidant. The hexamethylphosphoramide (HMPA) acted as a base as well as a possible ligand to improve the solubility and stability of AgSCF$_3$. The coordination between HMPA and AgSCF$_3$ might lower the redox potential of the high valent silver species, thus preventing the oxidative decomposition of starting materials and products. Besides, in the presence of 1.5 equiv. of tetrabutylammonium iodide (TBAI), the yield decreased dramatically which indicated that silver(I) was critical (Scheme 201).[311] By mean of the AgSCF$_3$/K$_2$S$_2$O$_8$/HMPA system, Nevado and co-workers introduced CF$_3$S• to *N*-[(2-ethynyl)arylsulfonyl]acrylamides, providing a variety of functionalized indolo[2,1-*a*]isoquinolin6(5*H*)-ones *via* a tandem process featured with a 1,4-aryl migration, desulfonylation and 5-*exo-trig* cyclization.[133]



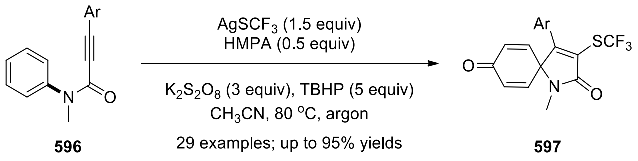
Scheme 201. Synthesis of SCF$_3$-containing oxindoles.

Simultaneously, Liang and co-workers disclosed that a broad spectrum of trifluoromethylthio-substituted fluorene derivatives **595** were achieved in good yields through the radical trifluoromethylthiolation reaction of 1,6-enynes **593**. The active C−C triple bond was first applized as primary acceptor for the tandem radical strategy. An argon atmosphere and 2,2':6',2''-terpyridine **594** as a base were required for the reaction. Mechanistic studies, like free radical inhibition and kinetic isotope experiments, proposed a radical process. It was disclosed that rate-limiting step was neither the SET process triggered by a free radical or the C−H cleavage step. Additionally, the corresponding trifluoromethylthiolated products **595** bearing a 2-pyrone moiety, potentially have great applications in pharmaceutics (Scheme 202).[312]



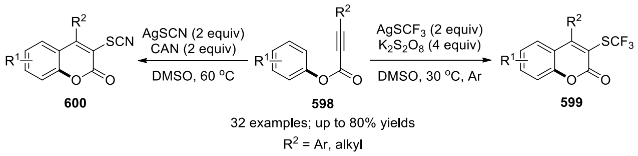
Scheme 202. Synthesis of trifluoromethylthio-substituted fluorene derivatives.

With the utilization of AgSCF$_3$/HMPA/K$_2$S$_2$O$_8$ conditions, diverse SCF$_3$-substituted spiro[4,5]trienone derivatives **597** were synthesized by radical functionalized trifluoromethythiolation and dearomatization in sequence, starting from propiolamides **596**. The methodology offered a direct entry to deliver a C–SCF$_3$ bond, a C–C bond, and a C–O double bond in a one-pot procedure (Scheme 203).[313]



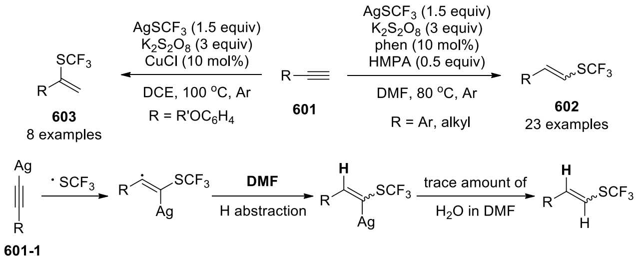
Scheme 203. Synthesis of SCF$_3$-substituted spiro[4,5]trienone derivatives.

An array of 3-trifluoromethylthiolated and 3-thiocyanated coumarins **599** and **600** was obtained *via* the oxidative radical cyclization of aryl alkynoate esters **598**, using AgSCF$_3$ and AgSCN as the functionalized reagents, respectively. This reaction developed by Wang *et al.* highlighted readily available starting material, excellent functional-group tolerance and good yields. Preliminary mechanistic studies, sucn as radical trapping experiments and KIE study suggested a radical insertion and subsequent 6-*endo*-cyclization pathway were involved (Scheme 204). _ENREF_81[314]



Scheme 204. Synthesis of 3-trifluoromethylthiolated and 3-thiocyanated coumarins from aryl alkynoate esters.

Very recently, the Cao group developed the first direct hydrotrifluoromethylthiolation for the preparation of vinyl trifluoromethyl thioethers **602** and **603**. The *anti*-Markovnikov hydrotrifluoromethylthiolated products **602** were obtained from terminal aryl- and alkyl-substituted alkynes **601** in the presence of AgSCF$_3$/HMPA/K$_2$S$_2$O$_8$/phen system. Mechanistic studies, *e.g.*, KIE experiments, and deuterated experiments unveiled an involvement of acetylene silver **601-1** and SCF$_3$ radical, and the rate-limiting step was plausibly the cleavage of the C−H bond of DMF. While under AgSCF$_3$/CuCl/K$_2$S$_2$O$_8$ conditions, Markovnikov products **603** were obtained derived from electronic-rich arylacetylenes (Scheme 205). _ENREF_339[315]



Scheme 205. Hydrotrifluoromethylthiolation of terminal alkynes.

7. Conclusion and Perspectives

Considering silver as a SET oxidant, the deployment of silver compounds has been discussed and employed in the contemporary radical chemistry. They have displayed exceptional ability to generate radicals from diverse compounds, such as carboxylic acids, α-keto acids, aldehydes, ketones, boronic acids, and organophosphates, *etc.* which subsequently undergo addition/coupling reactions with other radicals or neutral molecules. For instance, the combination of silver(I) and peroxydisulphate, known as Minisci reaction, have been widely studied and applized in organic synthesis and pharmacochemistry, which offered a direct and efficient entry to access substituted (hetero)arene compounds, as exemplified by alkylation, acylation, arylation, and phosphorylation. For decarboxylation reaction, silver(I) have displayed high efficiency, compared with copper and gold catalysts. Hence, a variety of decarboxylative functionalization such as alkynylation, fluorination, chlorination, azidation, trifluoromethylthiolation, *etc.* has been revealed. Importantly, the system of silver(I)/Selectflour provides an entry to produce diverse chemicals with fluorine. Radical cascade transformations have been a versatile tool in organic chemistry. Particularly, the silver-catalyzed radical initiated aryl migration/desulfonylation sequence of tosyl acrylamides, in which an amidyl radical intermediate is formed, deliver new C–C and C–heteroatom bonds in a one-pot procedure. The vital CF_3 or perfluoroalkyl radicals can be produced *via* different compounds, such as Langlois's reagent, trifluoroacetic acid, and AgF with fluorinated materials. Although substantial progress has been achieved so far, the free radical reaction based on silver is still evolving. Especially, by contrast with flourishing C-centered radicals, the investigations of other heteroatom centered radicals are indeed underdeveloped, such as N, O, S-centered radicals. A thorough exploration to improve the efficiency/consumption of the catalyst, yields and selectivities, and broaden scope of radical precursors, with detailed studies of the mechanisms and limitations, can advance this field to a more complete and practical level. A revolution to develop highly efficient, atom economic, environmentally friendly synthestic methodologies are still onging.

Acknowledgements

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