Catalytic Asymmetric Construction of CF_3-Substituted Chiral sp^3 Carbon Centers

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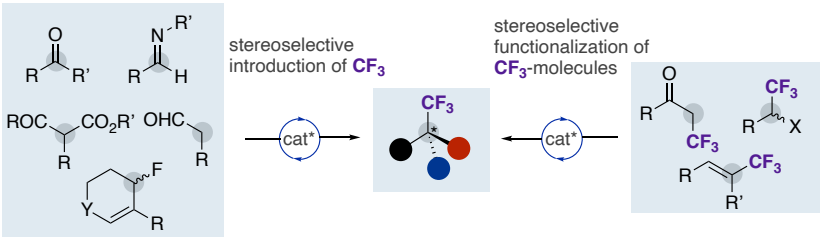

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Abstract Due to the unique steric and electronic nature of fluorine atom, organofluorine compounds have received significant attention in the fields of pharmaceuticals and agrochemicals. In particular, the CF_3 group is frequently found in biologically active compounds. However, compared to aryl- and alkenyl-CF_3-containing molecules, the construction of sp^3 carbon-based alkyl-CF_3-containing molecules, particularly via catalytic enantioselective synthesis, remains a considerable challenge in spite of their high potential in medicinal applications. This short review focuses on recent advances in this research area, and the reported strategies are categorized according to reaction types and starting substrates. In addition, chiral catalysts, substrate scope, and reaction mechanisms are briefly summarized.

Key words addition, asymmetric catalysis, fluorine, substitution, trifluoromethyl group

1 Introduction

Owing to the unique steric and electronic characteristics of the fluorine atom, its introduction into parent organic molecules often improves their biological activities. Accordingly, organofluorine compounds have received significant attention in the design of new drug candidates and agrochemicals.[1] In particular, the trifluoromethyl group (CF_3) is the most frequently occurring fluorinated organic group in biologically active compounds.[2] Thus, the development of efficient synthetic protocols for the preparation of CF_3-substitued molecules has been a long-standing research subject within the synthetic community. The synthesis of sp^2 carbon-based aryl- and alkenyl-CF_3-containing molecules has witnessed remarkable progress as a result of the efforts of many synthetic chemists.[3] On the other hand, the construction of sp^3 carbon–CF_3 bonds, particularly via catalytic asymmetric process, remains underdeveloped, despite the fact that such motifs are found in several bioactive molecules, as exemplified by Alpelisib,[4] Lansoprazole,[5] Efavirenz,[6] Befloxatone,[7] and Odanacatib[8] (Figure 1). In this short review, recent advances on the catalytic asymmetric construction of CF_3-substituted chiral sp^3 carbon centers are described. The reported strategies are divided into two sections, namely, (1) stereoselective introduction of a CF_3 group, and (2) stereoselective functionalization of CF_3-substituted molecules. In each section, the developed protocols are categorized according to the starting substrates employed. Additionally, chiral catalysts, substrate scope, and reaction mechanisms are briefly summarized.

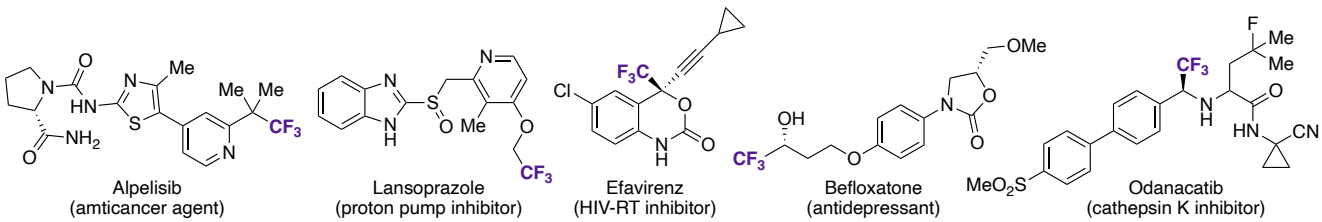
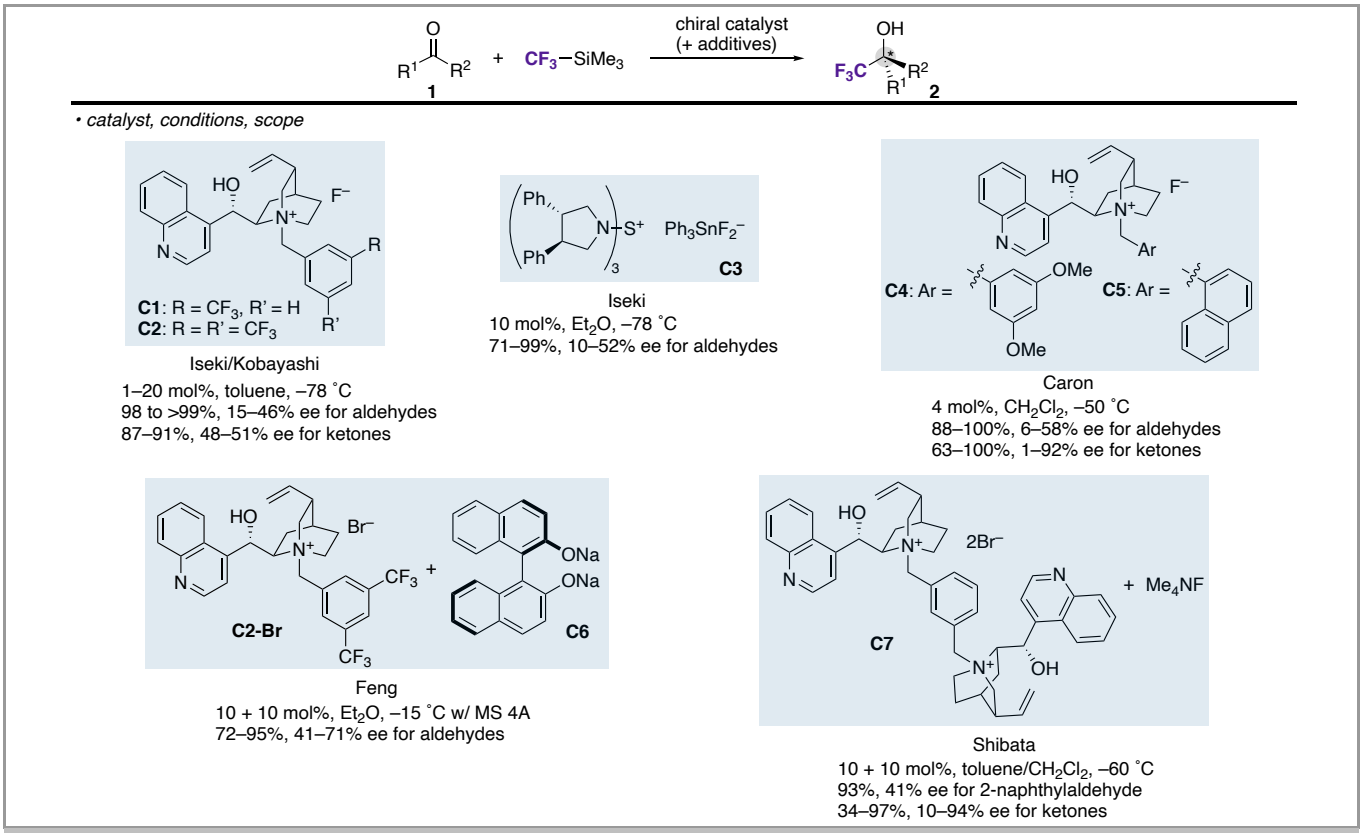


Figure 1 Examples of CF_3-substituted sp^3 carbon centers in bioactive molecules



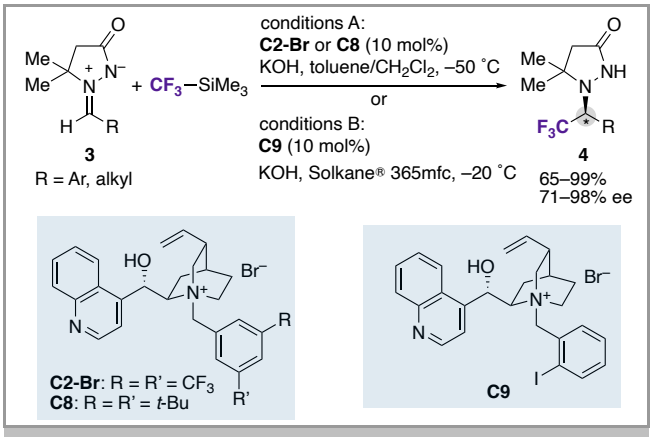
Scheme 1 Asymmetric nucleophilic addition of CF_3-$SiMe_3$ to carbonyls catalyzed by cinchonine-derived quaternary ammonium salts

2 Stereoselective Introduction of a CF_3 Group

2.1 Nucleophilic Addition to Carbonyls and Imines

Since the reports of the preparation and synthetic application of CF_3-$SiMe_3$ as a CF_3 anion by Rupport[9a] and Prakash,[9b] the fluoride-mediated nucleophilic addition reaction of CF_3-$SiMe_3$ to electrophilic carbonyls and imines has been widely studied for the synthesis of α-CF_3 alcohols and amines. However, the catalytic asymmetric equivalent is still somewhat challenging. A breakthrough was reported by Iseki and Kobayashi, where the cinchonine-derived *N*-benzylated quaternary ammonium fluorides **C1** and **C2** served as chiral catalysts to deliver the optically active α-CF_3 alcohols **2** from aldehydes/ketones **1** (Scheme 1).[10] The same research group subsequently developed the related chiral triaminosulfonium fluorostannate **C3**.[11] The observed enantiomeric excess (ee) was generally low to moderate, but these seminal works clearly demonstrated the high potential of chiral ammonium and sulfonium fluoride catalysts in the asymmetric nucleophilic addition reaction with CF_3-$SiMe_3$. Caron extensively investigated the substituent effect on the nitrogen of the cinchoninium salt, leading to the development of the more active ammonium fluoride catalysts **C4** and **C5**.[12] Feng reported the interesting synergy effect of chiral BINOL sodium salt **C6** with the cinchonine-based catalyst **C2-Br**.[13] In 2007, Shibata elegantly designed the linked cinchoninium bromide **C7** and accomplished the highly enantioselective trifluoromethylation of ketones by using a combination of **C7** and Me_4NF.[14]

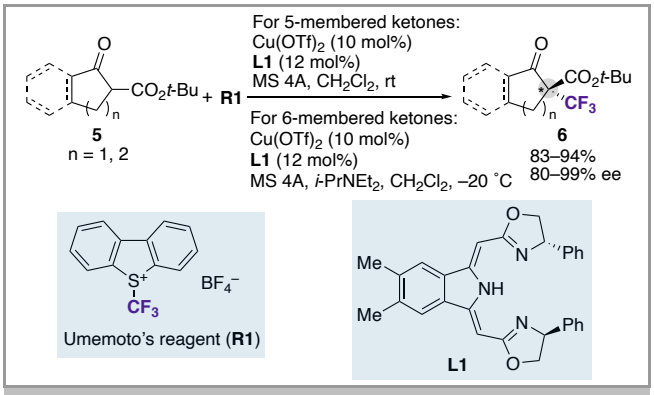
Cinchonine-based quaternary ammonium catalysts were also applicable to the asymmetric trifluoromethylation of imines. Shibata reported the first successful example of the catalytic asymmetric addition of CF_3-$SiMe_3$ to the azomethine imines **3** in a toluene/CH_2Cl_2 mixed solvent system with **C2-Br** or its *t*-Bu-analogue **C8** as the catalyst and KOH additive as an additive (Scheme 2, conditions A).[15a] The same reaction was possible in the non-toxic, environmentally benign fluorous solvent, Solkane® 365mfc (1,1,1,3,3-pentafluorobutane), by using catalyst **C9** possessing an *ortho*-iodo substituent (conditions B).[15b]



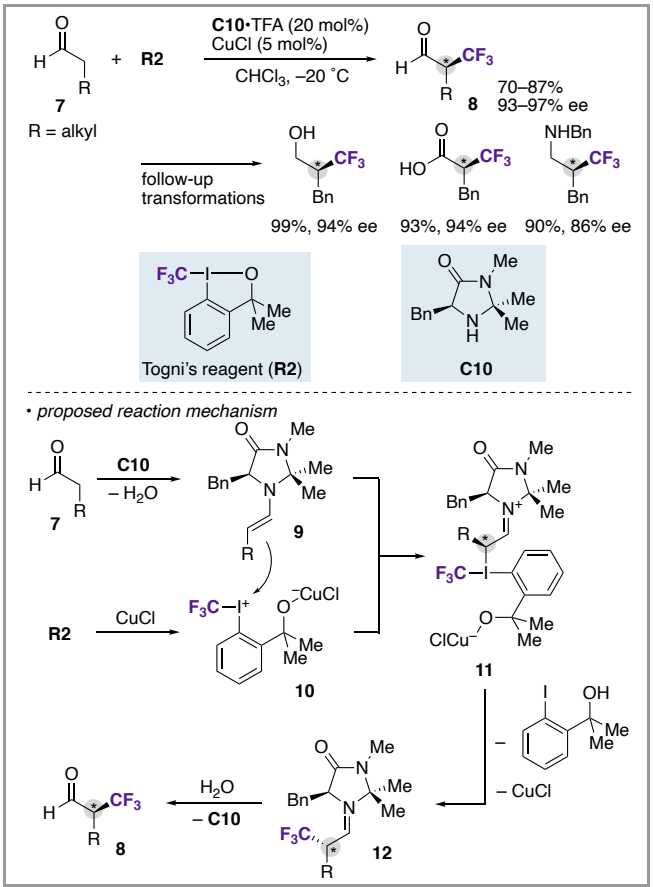
Scheme 2 Asymmetric nucleophilic addition of CF_3-$SiMe_3$ to imines catalyzed by cinchonine-derived quaternary ammonium salts

2.2 Electrophilic Substitution at the α Position of Carbonyls

The development of electrophilic trifluoromethylation agents of the type CF_3^+, such as Umemoto[16] and Togni[17] reagents, has allowed the enolizable carbonyl compounds to be adopted in trifluoromethylation reactions at the α position. The catalytic asymmetric α-trifluoromethylation of relatively acidic β-ketoesters **5** with Umemoto's reagent (**R1**) was achieved in the presence of a $Cu(OTf)_2$ catalyst and the *N,N,N*-pincer-type chiral ligand **L1** to construct the CF_3-substituted quaternary carbon center (Scheme 3).[18] Although the substrate was limited to a cyclic system, the five- and six-membered α-CF_3 ketones **6** were obtained in good yields and high enantioselectivities.



Scheme 3 Asymmetric electrophilic trifluoromethylation of β-ketoesters catalyzed by a Cu/*N,N,N*-pincer ligand complex



Scheme 4 Asymmetric electrophilic trifluoromethylation of aldehydes catalyzed by a CuCl/chiral imidazolidinone dual system

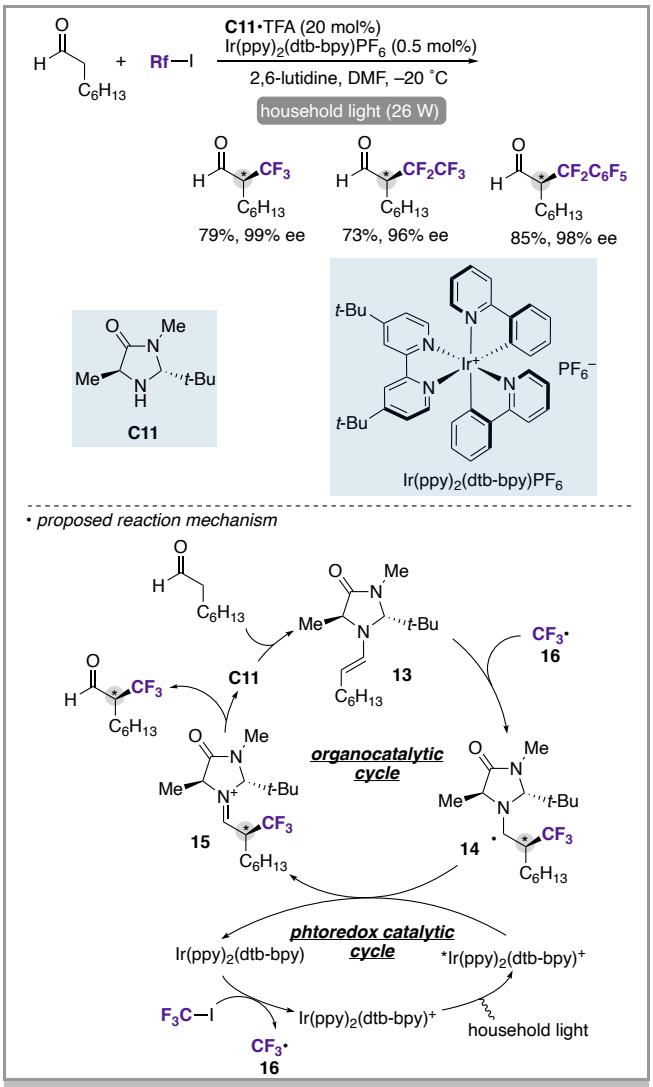
The readily available simple aliphatic aldehydes **7** also underwent asymmetric α-trifluoromethylation with Togni's reagent (**R2**) under CuCl/MacMillan chiral imidazolidinone **C10** dual catalyst system (Scheme 4).[19] The obtained α-CF_3 chiral aldehyde **8** could be converted to the corresponding alcohol, carboxylic acid, and amine only with negligible to minor erosion of enantiomeric excess. The proposed reaction mechanism includes: (1) the formation of enamine intermediate **9** by dehydration of the aldehyde **7** with **C10**, (2) enantioselectivity-determining electrophilic attack of CuCl-activated, ring-opening hypervalent iodine reagent **10**, (3) C–CF_3 forming reductive elimination from **11** to deliver **12**, and finally (4) hydrolysis to give **8** along with regeneration of the starting imidazolidinone **C10**.

A similar enantioselective α-trifluoromethylation of aldehyde with CF_3-I was also possible by the combination of chiral imidazolidinone **C11** and the photoredox catalyst $Ir(ppy)_2(dtb\text{-}bpy)PF_6$ (Scheme 5).[20] A feature of this protocol is its successful application to more general fluoroalkylation with easily available and sometimes commercial fluoroalkyl iodides, which is a significant synthetic advantage compared to the aforementioned electrophilic trifluoromethylations with Umemoto and Togni reagents (see Schemes 3 and 4). The reaction is considered to proceed via the merger of a **C11**-based organocatalytic cycle and an Ir-promoted photoredox catalytic cycle. The photo-irradiated excited $*Ir(ppy)_2(dtb\text{-}bpy)^+$ catalyst initially accepts single electron transfer from a sacrificial quantity of the in situ generated enamine intermediate **13** to form reduced $Ir(ppy)_2(dtb\text{-}bpy)$. Its

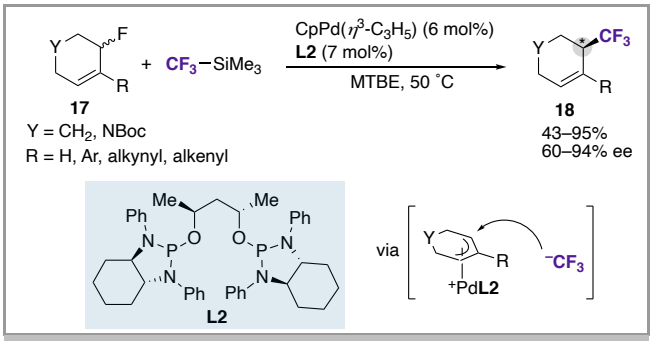
strongly reducing nature enables the one-electron reduction of CF_3-I to generate the CF_3 radical **16** and $Ir(ppy)_2(dtb\text{-}bpy)^+$ in the ground state. The electrophilic radical addition of **16** to the enamine **13** occurs in an enantioselective manner to give the stereodefined α-amino alkyl radical **14**. Subsequent one-electron oxidation with the excited $^*Ir(ppy)_2(dtb\text{-}bpy)^+$ species is followed by hydrolysis to afford the enantioenriched α-CF_3 aldehyde along with regeneration of the imidazolidinone catalyst **C11**. The concurrently formed $Ir(ppy)_2(dtb\text{-}bpy)$ enters the second single-electron transfer with CF_3-I to complete the photoredox catalytic cycle.

2.3 Allylic Nucleophilic Substitution

The palladium-catalyzed allylic substitution reaction proceeding via a π-allyl palladium species, the so-called Tsuji-Trost reaction, has been widely studied and applied to the synthesis of complex natural products and bioactive molecules.[21] Now, various allylic electrophiles and external nucleophiles can be successfully employed in this type of reaction. However, there was no successful use of a CF_3 nucleophile until Trost reported the asymmetric allylic substitution of allylic fluorides **17** with CF_3-$SiMe_3$ under Pd/originally developed diamidophosphite bidentate ligand **L2** catalysis in 2019 (Scheme 6).[22] The key to success is the fluoride leaving group as well as the specific chiral ligand: other common leaving groups, such as carbonate, acetate, and chloride, did not provide the trifluoromethylated product **18** at all. Only six-membered cyclic substrates were applicable, but this protocol can construct a CF_3-substituted chiral sp^3 carbon center without any proximal directing heteroatoms. The reaction is considered to proceed via a common outer-sphere mechanism,[21] involving an electrophilic π-allyl Pd intermediate and an externa CF_3 anion nucleophile.

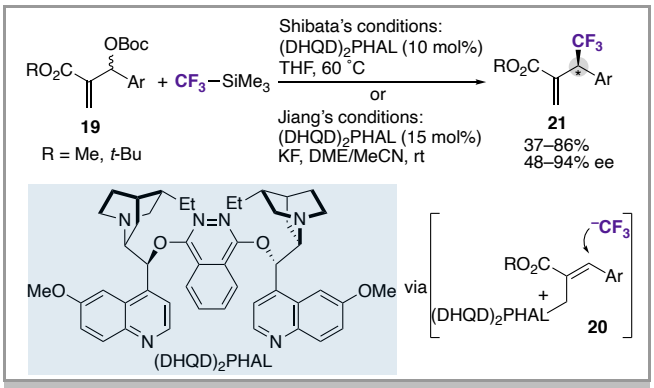


Scheme 5 Asymmetric electrophilic trifluoromethylation of aldehydes via merger of organocatalytic and photoredox catalytic cycles



Scheme 6 Pd-catalyzed asymmetric allylic trifluoromethylation of allylic fluorides with CF_3-$SiMe_3$

While somewhat specific, Shibata[23] and Jiang[24] independently reported the enantioselective allylic trifluoromethylation of Morita-Baylis-Hillman (MBH)-type allyl electrophiles **19** with CF_3-$SiMe_3$ by using $(DHQD)_2PHAL$ as the nucleophilic chiral organocatalyst (Scheme 7). The racemic MBH adduct **19** initially undergoes an S_N2' reaction with $(DHQD)_2PHAL$ and is converted to the activated allylic intermediate **20**. A subsequent face-selective second S_N2' reaction with CF_3-$SiMe_3$ furnishes the net S_N2-type product **21** in enantioenriched form.



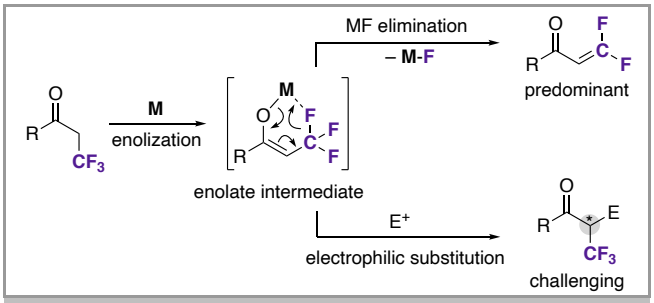
Scheme 7 Organocatalytic asymmetric allylic trifluoromethylation of MBH adducts

3 Stereoselective Functionalization of CF_3-Substituted Molecules

Since CF_3-carbonyls, -imines, and their derivatives are readily prepared, enantioselective reductions and addition-type reactions toward optically active α-CF_3 alcohols and amines have been actively studied by many synthetic chemists. In addition, comprehensive review articles covering these studies have already appeared,[25] hence this short review thus does not discuss the stereoselective functionalization of CF_3-carbonyls and imines.

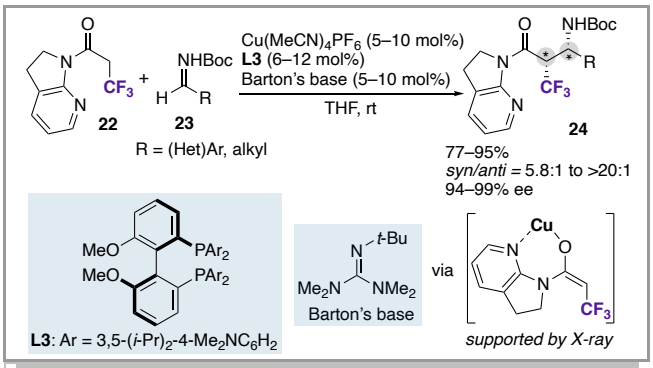
3.1 Electrophilic Substitution of α-CF_3 Carbonyls

The preparation of α-CF_3 carbonyl compounds is also relatively easy, but their application in the metal-catalyzed asymmetric electrophilic substitution at the α position is generally difficult because of the propensity for metal fluoride (MF) elimination from the metal enolate intermediate via an intramolecular metal-fluorine interaction (Scheme 8).[26]



Scheme 8 α-CF_3 metal enolate: metal fluoride elimination vs electrophilic substitution

In this context, Kumagai and Shibasaki elegantly designed the α-CF_3 amide **22** that bears a 7-azaindoline directing group and successfully performed a Cu-catalyzed asymmetric Mannich-type reaction with high diastereo- and enantioselectivity (Scheme 9).[27] The key to success was coordination of the 7-azaindoline nitrogen to the Cu center, to suppress the possible metal fluoride elimination, which was supported by X-ray crystallographic analysis of the Cu/**22** complex. Subsequently, the same research group extended this strategy to asymmetric α-allylation with the allyl carbonate **25** by utilizing a Cu/Pd dual catalyst system (Scheme 10).[28] Both the α-CF_3 chiral Cu enolate nucleophile and achiral π-allyl Pd electrophile are generated in a catalytic manner and successfully underwent cross-coupling to form the enantioenriched product **26**.

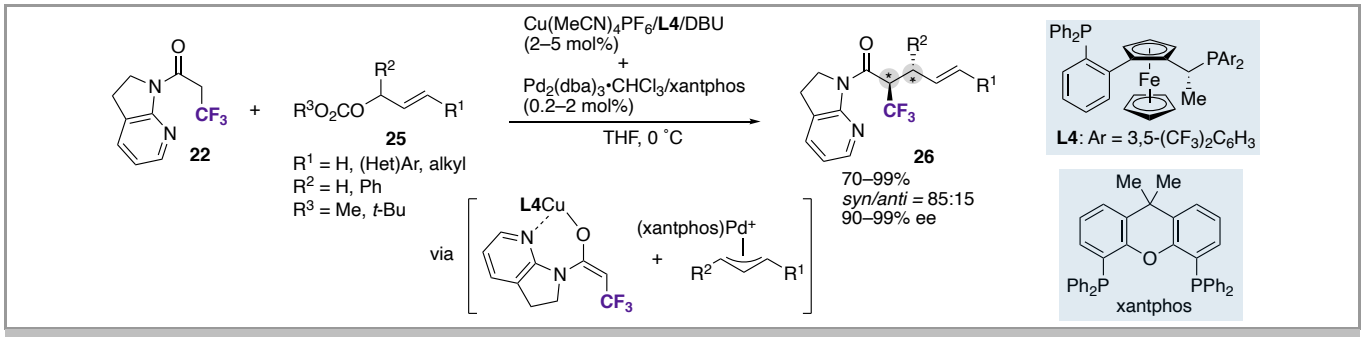


Scheme 9 The Cu-catalyzed, 7-azaindoline-directed asymmetric Mannich-type reaction of an α-CF_3 amide with imines

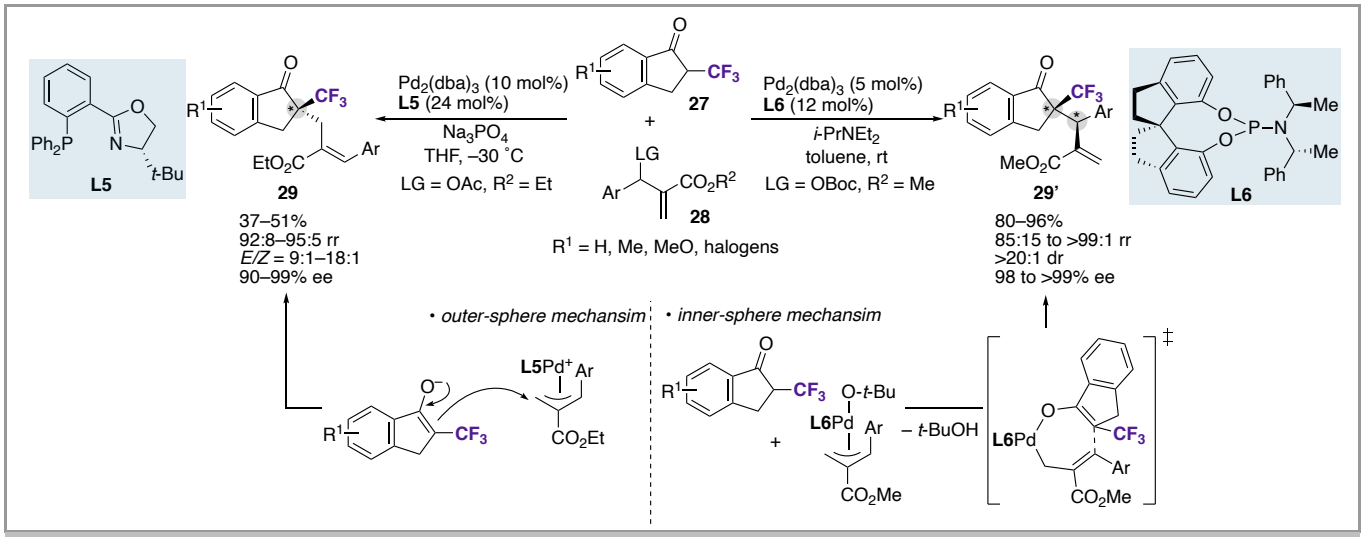
The aforementioned work in Schemes 9 and 10 effectively promoted electrophilic substitution at the α position of the α-CF_3 carbonyl over the undesired fluoride elimination, but the tedious attachment and detachment of the 7-azaindoine auxiliary is unavoidable. In 2021, Wang and Xue reported the Pd-catalyzed asymmetric α-allylation of simple α-CF_3 cyclic ketones **27** with MBH adducts **28** without any directing groups (Scheme 11).[29] Moreover, the ligand-controlled regiodivergent allylation was also achieved: the phox-type ligand **L5** selectively afforded the less hindered liner-type product **29**, whereas the branched and more congested regioisomer **29'** was formed predominantly in the presence of phosphoramidite ligand **L6**. The observed divergent regioselectivity can be explained by the ligand-dependent outer- and inner-sphere mechanism switch.[30] Namely, the allyl fragment of the **L5**-ligated π-allyl Pd species undergoes the relatively common outer-sphere substitution reaction[21] with the in-situ generated enolate from **27** at the more sterically accessible terminal position to deliver the linear-type product **29**. On the other hand, in the case of the **L6**-coordinated π-allyl Pd intermediate, ligand exchange with the parent **27** on Pd is followed by a [3,3'] sigmatropic reductive elimination[31] to afford the branched isomer **29'**.

3.2 Substitution of α-Halo CF_3 Compounds

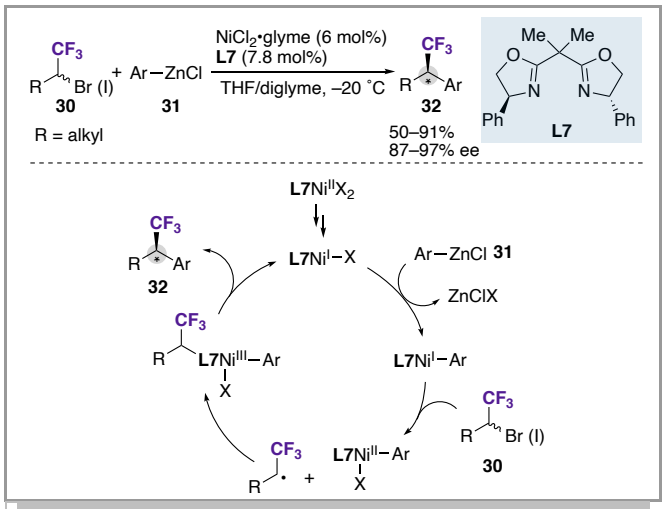
The metal-catalyzed enantioconvergent C–C cross-coupling reaction of racemic α-halo CF_3 compounds with organometallic reagents is a powerful method to generate a chiral CF_3-substituted sp^3 carbon center without the need of any proximal heteroatoms. Fu reported the seminal work on the Ni/box-



Scheme 10 The Cu/Pd-co-catalyzed, 7-azaindoline-directed asymmetric α-allylation of an α-CF_3 amide with allyl carbonates



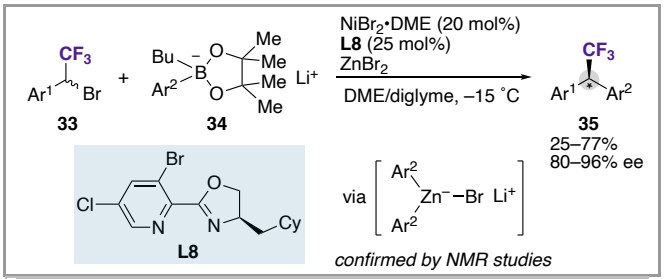
Scheme 11 Pd-catalyzed, ligand-controlled regiodivergent asymmetric α-allylation of α-CF_3 ketones



Scheme 12 Ni-catalyzed enantioconvergent cross-coupling of α-halo CF_3 compounds with arylzinc reagents

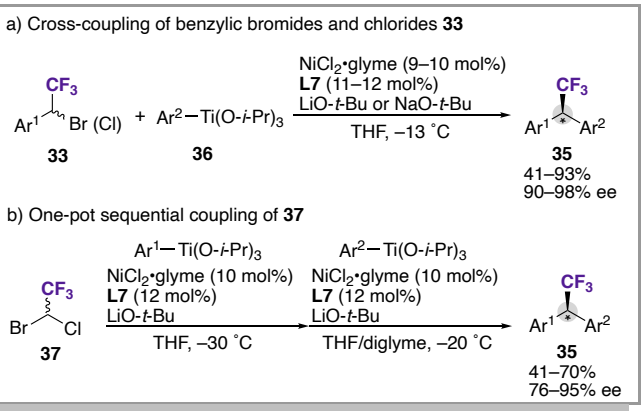
type ligand **L7**-catalyzed enantioconvergent cross-coupling of racemic α-Br and -I CF_3 compounds **30** with arylzinc reagents **31** (Scheme 12).[32] A radical-involved, organometallic Ni(I)/(II)/(III) redox mechanism was originally proposed, which was later supported experimentally and theoretically by the authors themselves and other research groups.[33] The ArNi(I) species generated by transmetalation with **31** undergoes single-electron transfer (SET) to **30** to form ArNi(II) and an alkyl radical intermediate, where the stereochemical information of starting **30** is lost. Subsequent radical rebound to ArNi(II) is followed by reductive elimination from ArNi(III) to deliver the target product **32** with regeneration of Ni(I)X to complete the catalytic cycle. The enantioselectivity can be determined in the radical rebound or reductive elimination step.[34]

Shen subsequently developed the related Ni/pyridine-oxazoline ligand **L8**-catalyzed enantioconvergent cross-coupling of racemic CF_3 benzyl bromides **33** with arylborates **34**, generated from the parent arylboronates and BuLi (Scheme 13).[35] Notably, $ZnBr_2$ was a crucial additive, which dramatically accelerated the transmetalation process via formation of the corresponding arylzincate species. The successful use of benzylic halides **33** is complementary to the reaction with the alkyl halides **30** described in Scheme 12.



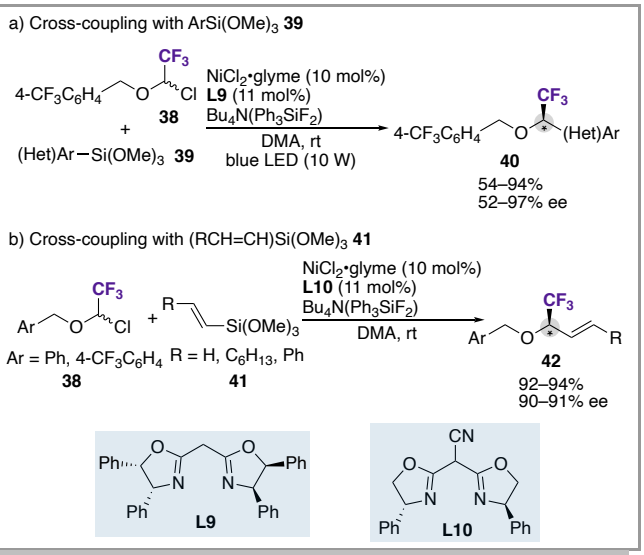
Scheme 13 Ni-catalyzed enantioconvergent cross-coupling of α-halo CF_3 compounds with arylboron reagents

Aryltitanates **36** could also be employed in a similar Ni-catalyzed enantioconvergent cross-coupling reaction of compounds **33** (Scheme 14a).[36] A feature of the titanate-based process is the applicability of less reactive but stable and cheap benzylic chlorides as well as bromides. The successful conversion of the benzylic chloride allowed 1-bromo-1-chloro-2,2,2-trifluoroethane (**37**), a readily available anesthetic, to be adopted in one-pot sequential cross-coupling reaction with two different aryltitanates, directly giving products **35** in good yields (Scheme 14b).



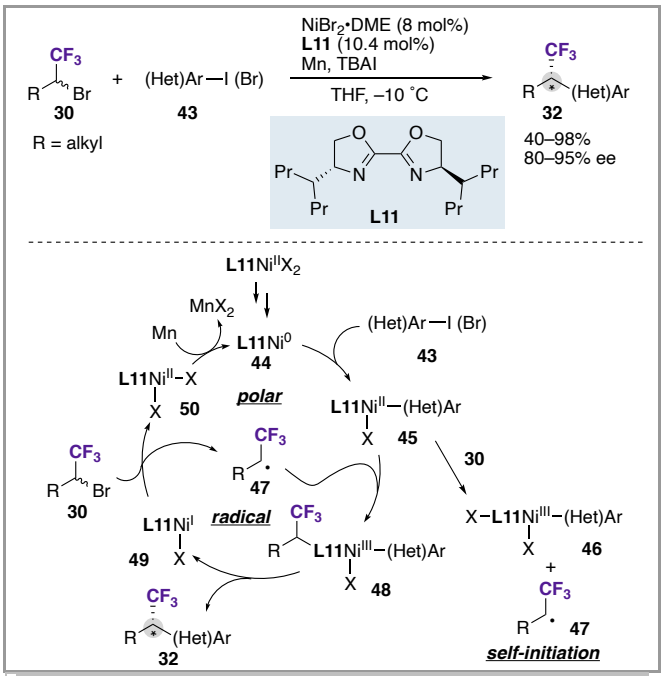
Scheme 14 Ni-catalyzed enantioconvergent cross-coupling of α-halo CF_3 compounds with aryltitanate reagents

While viable substrates were limited to the somewhat specialized ether derivatives **38**, Gandelman reported the Hiyama-type cross-coupling of (Het)ArSi(OMe)$_3$ **39** with the assistance of blue LED irradiation (Scheme 15a).[37] The reaction itself proceeded with the same enantioselectivity even under dark conditions, but the reaction time was prolonged. The synthetic advantage of the Si-based Hiyama reaction is the accommodation of not only (Het)ArSi(OMe)$_3$ **39** but also (RCH=CH)Si(OMe)$_3$ **41** (Scheme 15b).



Scheme 15 Ni-catalyzed enantioconvergent cross-coupling of α-halo CF_3 ethers with organosilicon reagents

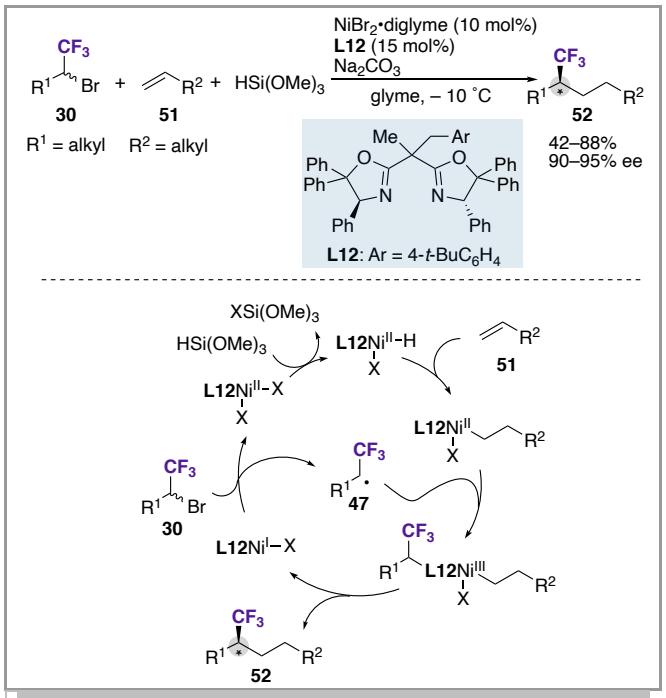
These cross-coupling reactions are quite useful for the convergent synthesis of chiral CF_3-containing molecules, but one disadvantage is the prior preparation of organometallic reagents, which is sometimes difficult and problematic. Recently, Wang developed the Ni-catalyzed enantioselective reductive cross-coupling reaction (Scheme 16).[38] Without any preactivation, α-halo CF_3 compounds **30** and (hetero)aryl iodides/bromides **43** were directly cross-coupled in the presence of metallic manganese (Mn) as the terminal reductant, delivering the enantioenriched products **32**. By taking advantages of the ready availability of various aryl halides, complicated fluorinated molecules can also be easily accessed. The authors did not mention a detailed mechanism, but the Ni(0)/(I)/(II)/(III)-involved, polar-radical-combined mechanism is believed to operate, which was originally developed by Weix in the related reductive cross-coupling of aryl halides and nonfluorinated alkyl halides.[39] The starting point is the in situ generated Ni(0) species **44**, which undergoes a two-electron redox oxidative addition with **43**. The formed ArNi(II) species **45** initially reacts with **30** to generate ArNi(III) **46** and alkyl radical **47**; this step is a so-called self-initiation process. The radical **47** then combined with ArNi(II) **45** to afford ArNi(III) species **48**. Reductive elimination furnishes **32** and Ni(I) **49**, and the latter then enters into a single-electron reduction with **30**, giving the radical **47** and Ni(II) **50**. The catalytic cycle is closed by the two-electron reduction of **50** with Mn.



Scheme 16 Ni-catalyzed enantioconvergent reductive cross-coupling of α-halo CF_3 compounds and aryl halides

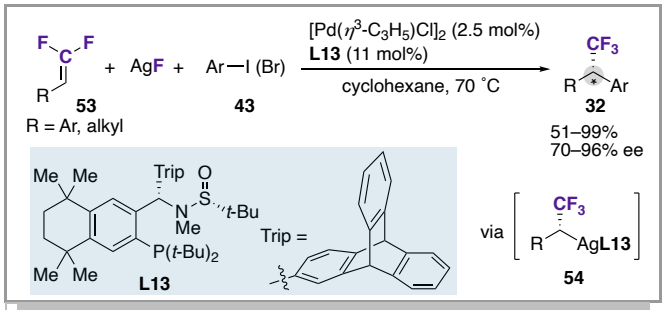
Another approach to avoid the stoichiometric preparation of organometallic reagents is via the NiH-catalyzed asymmetric hydroalkylation of terminal alkene **51** with compounds **30** (Scheme 17).[40] A catalytically generated alkylnickel species from alkene **51** and HSi(OMe)$_3$ undergoes an enantioselective cross-coupling reaction with **30** to form products **52** with high ee values. The proposed reaction mechanism involves SET-promoted alkyl radical intermediates and Ni(I)/(II)/(III) organometallic species, which is similar to the aforementioned pathways in Schemes 12 and 16. It should be noted that the

asymmetric Ni catalysis can control the point chirality at the CF_3-substituted sp^3 carbon center with two different simple alkyl substituents, which is difficult by other means.



Scheme 17 Ni-catalyzed enantioselective hydroalkylation of terminal alkenes with α-halo CF_3 compounds and a hydrosilane

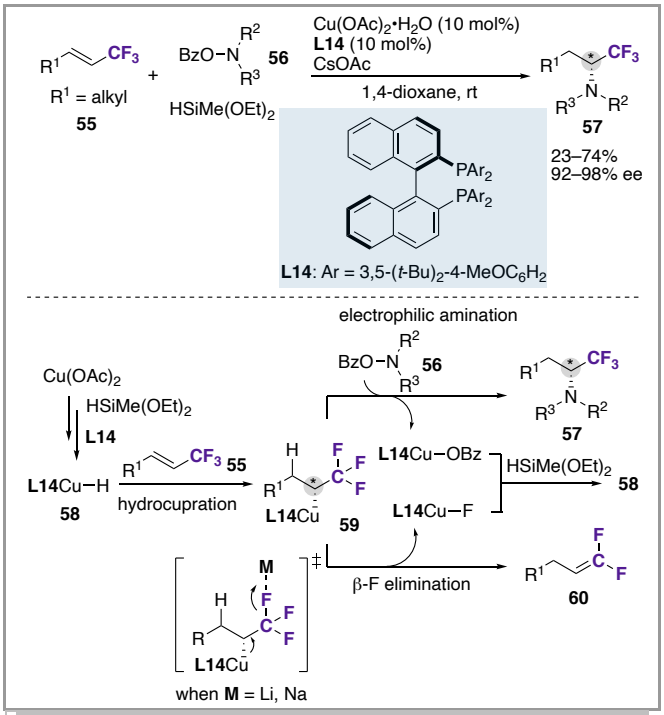
While somewhat differently categorized, the related umpolung-type strategy using the α-CF_3 alkylsilver **54**, generated in situ from *gem*-difluoroalkenes **53** and AgF, was reported by Li and Zhang (Scheme 18).[41] In the presence of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ cas the atalyst and the originally developed chiral sulfinamide phosphine ligand **L13**, the aryl halides **43** were converted into the desired products **32** with high enantioselectivities.



Scheme 18 Pd-catalyzed asymmetric three-component-coupling of *gem*-difluoroalkenes, AgF, and aryl halides

3.3 Addition-type Reactions with CF_3-Substituted Alkenes

CF_3-substitted alkenes are potentially useful starting platforms for the preparation of chiral CF_3-containing molecules, because the stereoselective functionalization of alkene moiety enables the rapid construction of CF_3-substituted chiral sp^3 carbon centers. However, almost all the reported procedures relied on the presence of additional electron-withdrawing groups such as carbonyl and aromatic rings, which increase the reactivity and feasibility of the stereocontrolled process.[42] The first successful example using simple CF_3-substituted aliphatic alkenes **55** was reported by Hirano and Miura (Scheme 19), where the CsOAc-assisted, CuH/**L14**-catalyzed asymmetric hydroamination with hydroxylamines **56** and $HSiMe(OEt)_2$ was in operation.[43] The optically active α-CF_3 amines **57** were obtained with high enantiomeric excess values. The reaction proceeds via (1) regio- and enantioselective hydrocupration of **55** with the **L14**CuH species **58** obtained from $Cu(OAc)_2$ and $HSiMe(OEt)_2$, (2) electrophilic amination of the stereodefined α-CF_3 alkylcopper **59** with **56** in a stereoretentive manner to give enantioenriched **57**, and (3) regeneration of **L14**CuH **58** by σ-bond metathesis of concurrently formed **L14**CuOBz with $HSiMe(OEt)_2$. The conceivable byproduct is the *gem*-difluoroalkene **60**, obtained by β-fluoride elimination from **59**, which is similar to the metal fluoride elimination from the α-CF_3 metal enolate mentioned in Scheme 8. Actually, when fluorophilic alkaline metal bases such as Li and Na were employed instead of CsOAc, the undesired β-fluoride elimination predominantly occurred via intermolecular metal (M) to F interaction.[44] Thus, the lower fluorophilicity of the Cs base[45] is the key to success for functionalization at the α position relative to CF_3.

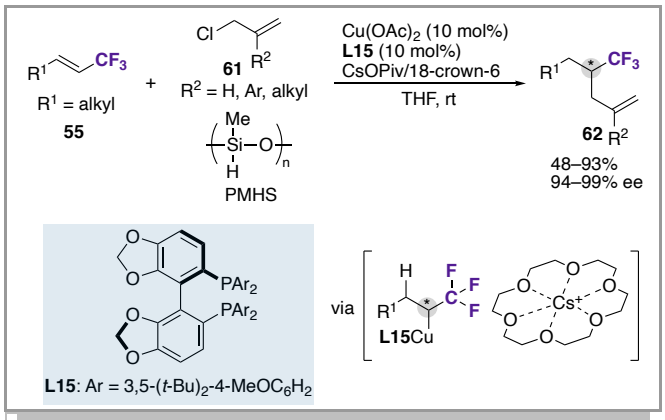


Scheme 19 Cu-catalyzed, CsOAc-assisted asymmetric hydroamination of CF_3-substituted aliphatic alkenes with hydroxylamines and a hydrosilane

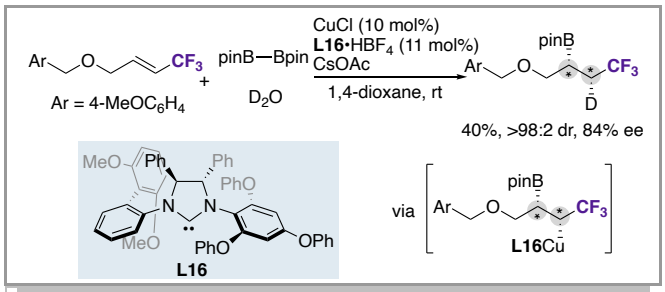
The same authors subsequently developed a related Cu-catalyzed asymmetric hydroallylation with allylic chlorides **61** instead of the hydroxylamine **56** (Scheme 20).[46] In this case, the use of 18-crown-6 was crucial for the disruption of Cs-F interaction[47] to suppress the undesired β-F elimination. This is one of the few successful examples of catalytic asymmetric construction of non-allylic and non-benzylic CF_3-substituted sp^3 chiral carbon centers.

In addition to the CuH species, CuBpin also undergoes the enantioselective addition reaction with simple CF_3-substituted

aliphatic alkenes. Hoveyda reported the Cu-catalyzed enantioselective deuterioboration with pinB–Bpin and D_2O in the presence of the originally developed chiral NHC ligand **L16** (Scheme 21),[48] albeit with only one successful example.

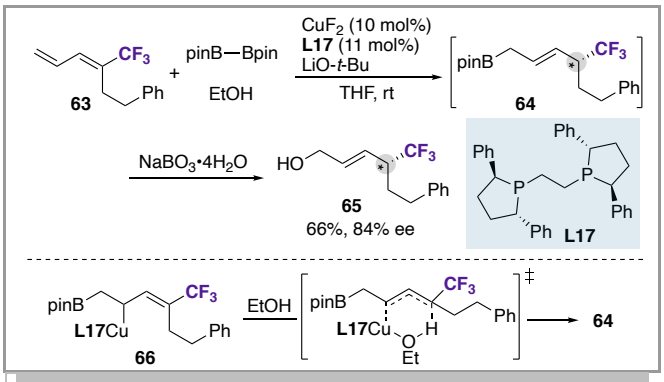


Scheme 20 Cu-catalyzed, 18-crown-6-Aasisted asymmetric hydroallylation of CF_3-substituted aliphatic alkenes with allyl chlorides and a hydrosilane



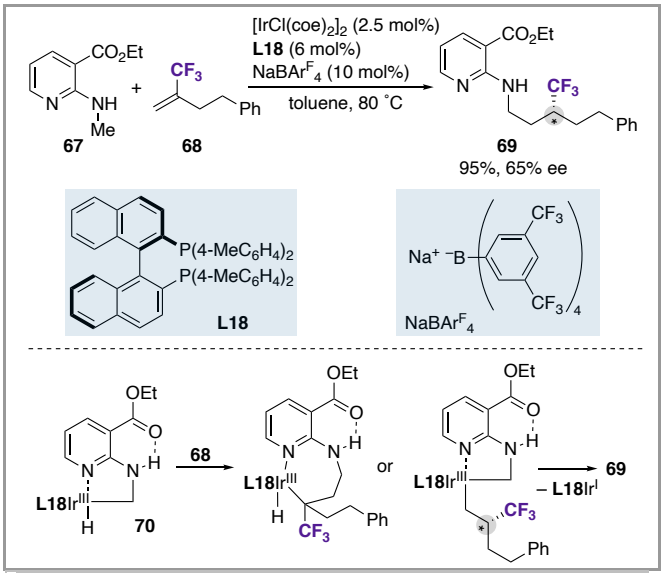
Scheme 21 Cu-catalyzed asymmetric deuterioboration of CF_3-substituted aliphatic alkenes with a diboron and D_2O

Recently, Huang and Zhang reported the Cu/**L17**-catalyzed enantioselective protoboration of CF_3-substituted 1,3-dienes with pinB–Bpin and EtOH.[49] Electronically activated, aryl-substituted dienes were mainly employed, but successful application to the aliphatic substrate **63** was also shown (Scheme 22). After oxidative follow-up treatment of initially formed **64** with $NaBO_3$•$4H_2O$, the corresponding alcohol **65** bearing a chiral CF_3-substituted sp^3 carbon center was obtained with good enantioselectivity. The proposed reaction mechanism is as follows: the in-situ generated **L17**CuBpin species adds to **63** regioselectively at the more sterically accessible terminal position to generate the allyl Cu intermediate **66**. The observed protoborated product is produced by subsequent enantioselective S_N2'-type protonation with EtOH. Also in this catalytic process, the fluoride elimination reaction potentially occurs, but DFT calculations suggest that it is an energetically higher and kinetically less favored pathway.



Scheme 22 Cu-catalyzed asymmetric protoboration of a CF_3-substituted aliphatic 1,3-diene with with a diboron and EtOH

Another successful application of unactivated CF_3-substituted aliphatic alkenes is in the Ir-catalyzed asymmetric C–H addition reaction of 2-(methylamino)pyridine derivative **67** (Scheme 23), as reported by Nishimura.[50] Under Ir/**L18** asymmetric catalysis, 1,1-disubstituted CF_3 substrate **68** was converted to the enantioenriched amine **69** possessing a chiral CF_3-substituted sp^3 carbon center. A plausible reaction mechanism includes the pyridine-directed, oxidative addition of the *N*-Me C–H to Ir(I), in which the ester moiety at the C3 position of the pyridine ring plays an important role in the regulation of the substrate configuration (**70**). The CF_3 alkene **68** then undergoes insertion into C–Ir or Ir–H bond of **70,** and final reductive elimination affords the asymmetric hydroalkylation product **69**. Although the enantioselectivity was still moderate, this protocol receives more attention because metalated and halogenated starting substrates are not needed.



Scheme 23 Ir-catalyzed asymmetric hydroalkylation of a CF_3-containing 1,1-disubstituted aliphatic alkene with a 2-(aminomethyl)pyridine derivative

4 Conclusion and Outlook

Recent development on chiral metal catalysts, organocatalysts, and trifluoromethylation reagents, as well as the rational design of reactions and substrates, has enabled significant progress on the catalytic asymmetric construction of CF_3-substituted chiral sp^3 carbon centers. Given the prevalence of CF_3 groups in recent

marketed drugs, the aforementioned advance are expected to find wide application in more concise and stereoselective synthesis of chiral CF_3 drug molecules. However, almost all the reported protocols still require prefunctionalization, such as halogenation, metalation, introduction of reactive functional groups, or preinstallation of CF_3, of the starting substrates. On the other hand, the direct sp^3 C–H trifluoromethylation has recently been described by several research groups.[51] Although the reaction conditions and site-selectivity still need to be improved, the direct substitution of simple and unactivated aliphatic C–H bonds with a CF_3 group is possible without any preactivation steps, and thus requires additional attention from a synthetic point of view. The further development of mild reaction conditions and highly site- and enantioselective catalysts is expected to enable the asymmetric sp^3 C–H trifluoromethylation of simple substrates and late-stage asymmetric introduction of CF_3, which can open the door to the discovery of new drug candidates based on CF_3-substituted chiral sp^3 carbon centers.

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Conflict of Interest

The author declares no conflict of interest.

References

(1) (a) Swallow, S. In *Fluorine in Pharmaceutical and Medicinal Chemistry: From Biophysical Aspects to Clinical Applications*; Gouverneur, V. Müller, K., Eds.; Imperial College Press: London, 2012; p 141. (b) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (c) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. *J. Med. Chem.* **2015**, *58*, 8315. (d) Ogawa, Y.; Tokunaga, E.; Kobayashi, O.; Hirai, K.; Shibata, N. *iScience* **2020**, *23*, 101467.

(2) (a) Wishart, D. S.; Feunang, Y. D.; Guo, A. C.; Lo, E. J.; Marcu, A.; Grant, J. R.; Sajed, T.; Johnson, D.; Li, C.; Sayeeda, Z.; Assempour, N.; Iynkkaran, I.; Liu, Y.; Maciejewski, A.; Gale, N.; Wilson, A.; Chin, L.; Cummings, R.; Le, D.; Pon, A.; Knox, C.; Wilson, M. *Nucleic Acids Res.* **2018**, *46*, D1074. (b) Meanwell, N. A. *J. Med. Chem.* **2018**, *61*, 5822.

(3) (a) Yang, X.; Wu, T.; Phipps, R. J.; Toste, F. D. *Chem. Rev.* **2015**, *115*, 826. (b) Alonso, C.; de Marigorta, E. M.; Rubiales, G.; Palacios, F. *Chem. Rev.* **2015**, *115*, 1847.

(4) André, F.; Ciruelos, E.; Rubovszky, G.; Campone, M.; Loibl, S.; Rugo, H. S.; Iwata, H.; Conte, P.; Mayer, I. A.; Kaufman, B.; Yamashita, T.; Lu, Y.-S.; Inoue, K.; Takahashi, M.; Pápai, Z.; Longin, A.-S.; Mills, D.; Wilke, C.; Hirawat, S.; Juric, D. *N. Engl. J. Med.* **2019**, *380*, 1929.

(5) Takagi, T.; Naito, Y.; Okada, H.; Ishii, T.; Mizushima, K.; Akagiri, S.; Adachi, S.; Hanada, O.; Kokura, S.; Ichikawa, H.; Itoh, K.; Yamamoto, M.; Matsui, H.; Yoshikawa, T. *J. Pharmacol. Exp. Ther.* **2009**, *331*, 255.

(6) Young, S. D.; Britcher, S. F.; Tran, L. O.; Payne, L. S.; Lumma, W. C.; Lyle, T. A.; Huff, J. R.; Anderson, P. S.; Olsen, D. B.; Carroll, S. S.; Pettibone, D. J.; O'Brien, J. A.; Ball, R. G.; Balani, S. K.; Lin, J. H.; Chen, I.-W.; Schleif, W. A.; Sardana, V. V.; Long, W. J.; Byrnes, V. W.; Emini, E. A. *Antimicrob. Agents Chemother.* **1995**, *39*, 2602.

(7) Curet. O.; Damoiswau, G.; Aubin, N.; Sontag, N.; Jarreau, F. X. *J. Pharmacol. Exp. Ther.* **1996**, *277*, 253.

(8) Masarachia, P. J.; Pennypacher, B. L.; Pickarski, M.; Scott, K. R.; Wesolowski, G. A.; Smith, S. Y.; Samadfam, R.; Goetzmann, J. E.; Scott, B. B.; Kimmel, D. B.; Duong, L. T. *J. Bone Miner. Res.* **2012**, *27*, 509.

(9) (a) Rupport, I.; Schlich, K.; Volbach, W. *Tetrahedron Lett.* **1984**, *25*, 2195. (b) Parakash, G. K. S.; Krishnamurti, R.; Olah, G. A. *J. Am. Chem. Soc.* **1989**, *111*, 393.

(10) Iseki, K.; Nagai, T.; Kobayashi, Y. *Tetrahedron Lett.* **1994**, *35*, 3137.

(11) Kuroki, Y.; Iseki, K. *Tetrahedron Lett.* **1999**, *40*, 8231.

(12) Caron, S.; Do, N. M.; Aroin, P.; Larivée, A. *Synthesis* **2003**, 1693.

(13) Zhao, H.; Qin, B.; Liu, X.; Feng, X. *Tetrahedron* **2007**, *63*, 6822.

(14) Mizuta, S.; Shibata, N.; Akiti, S.; Fujimoto, H.; Nakamura, S.; Toru, T. *Org. Lett.* **2007**, *9*, 3703.

(15) (a) Kawai, H.; Kusuda, A.; Nakamura, S.; Shiro, M.; Shibata, N. *Angew. Chem. Int. Ed.* **2009**, *48*, 6324. (b) Okusu, S.; Kawai, H.; Xu, X.-H.; Tokunaga, E.; Shibata, N. *J. Fluorine Chem.* **2012**, *143*, 216.

(16) Umemoto, T.; Ishihara, S. *J. Am. Chem. Soc.* **1993**, *115*, 2156.

(17) Kieltsch, I.; Eisenberger, P.; Togni, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 754.

(18) Deng, Q.-H.; Wadepohl, H.; Gade, L. H. *J. Am. Chem. Soc.* **2012**, *134*, 10769.

(19) Allen, A. E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 4986.

(20) Nagib, D. A.; Scott, M. E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 10875.

(21) (a) Tsuji, J.; Minami, I. *Acc. Chem. Res.* **1987**, *20*, 140. (b) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921. (c) Trost, B. M.; Machacek, M. R.; Aponick, A. *Acc. Chem. Res.* **2006**, *39*, 747. (d) Trost, B. M. *Tetrahedron* **2015**, *71*, 5708. (e) Tsuji, J. *Tetrahedron* **2015**, *71*, 6330.

(22) Trost, B. M.; Gholami, H.; Zell, D. *J. Am. Chem. Soc.* **2019**, *141*, 11446.

(23) Furukawa, T.; Nishimine, T.; Tokunaga, E.; Hasegawa, K.; Shiro, M.; Shibata, N. *Org. Lett.* **2011**, *13*, 3972.

(24) Li, Y.; Liang, F.; Xu, Y.-c.; Wang, Q.-R.; Jiang, L. *Org. Lett.* **2011**, *13*, 6082.

(25) (a) Nie, J.; Guo, H.-C.; Cahard, D.; Ma, J.-A. *Chem. Rev.* **2011**, *111*, 455. (b) Onyeagusi, C. I.; Malcolmson, S. J. *ACS Catal.* **2020**, *10*, 12507.

(26) Itoh, Y.; Yamanaka, M.; Mikami, K. *J. Am. Chem. Soc.* **2004**, *126*, 13174.

(27) Yin, L.; Brewitz, L.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2014**, *136*, 17958.

(28) Saito, A.; Kumagai, N.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2017**, *56*, 5551.

(29) Zhu, Y.; Ni, Y.; Lu, C.; Wang, X.; Wang, Y.; Xue, X.-S.; Pan, Y. *Org. Lett.* **2021**, *23*, 2443.

(30) Bai, D.-C.; Yu, F.-L.; Wang, W.-Y.; Chen, D.; Li, H.; Liu, Q.-R.; Ding, C.-H.; Chen, B.; Hou, X.-L. *Nat. Commun*. **2016**, *7*, 11806.

(31) (a) Méndez, M.; Cuerva, J. M.; Gómez-Bengoa, E.; Cárdenas, D. J.; Echavarren, A. M. *Chem. Eur. J.* **2002**, *8*, 3620. (b) Zhang, P.; Brozek, L. A.; Morken, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 10686.

(32) Liang, Y.; Fu, G. C. *J. Am. Chem. Soc.* **2015**, *137*, 9523.

(33) (a) Jones, G. D.; Martin, J. L.; McFarland, C.; Allen, O. R.; Hall, R. E.; Haley, A. D.; Brandon, R. J.; Konovalova, T.; Desrochers, P. J.; Pulay, P.; Vicic, D. A. *J. Am. Chem. Soc.* **2006**, *128*, 13175. (b) Lin, X.; Phillips, D. L. *J. Org. Chem.* **2008**, *73*, 3680. (c) Schley, N. D.; Fu, G. C. *J. Am. Chem. Soc.* **2014**, *136*, 16588.

(34) Gutierrez, O.; Tellis, J. C.; Primer, D. N.; Molander, G. A.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2015**, *137*, 4896.

(35) Huang, W.; Hu, M.; Wan, X.; Shen, Q. *Nat. Commun*. **2019**, *10*, 2963.

(36) Varenikov, A.; Shapiro, E.; Gandelman, M. *Org. Lett.* **2020**, *22*, 9386.

(37) Gandelman, M.; Varenikov, A. *Nat. Commun.* **2018**, *9*, 3566.

(38) Min, Y.; Sheng, J.; Yu, J.-L.; Ni, S.-X.; Ma, G.; Gong, H.; Wang, X.-S. *Angew. Chem. Int. Ed.* **2021**, *60*, 9947.

(39) Biswas, S.; Weix, D. J. *J. Am. Chem. Soc.* **2013**, *135*, 16192.

(40) Guo, W.; Cheng, L.; Ma, G.; Tong, W. Wu, F. *Org. Lett.* **2022**, *24*, 1796.

(41) Lin, T.-Y.; Pan, Z.; Tu, Y.; Zhu, S.; Wu, H.-H.; Liu, Y.; Li, Z.; Zhang, J. *Angew. Chem. Int. Ed.* **2020**, *59*, 22957.

(42) For examples, see ref. 25 and: (a) Dong, K.; Li, Y.; Wang, Z.; Ding, K. *Angew. Chem. Int. Ed.* **2013**, *52*, 14191. (b) Massolo, E.; Benaglia, M.; Orlandi, M.; Rossi, S.; Celentano, G. *Chem. Eur. J.* **2015**, *21*, 3589. (c) Zhu, Y.; Li, X.; Chen, Q.; Su, J.; Jia F.; Qiu, S.; Ma, M.; Sun, Q.; Yan, W.; Wang, K.; Wang, R. *Org. Lett.* **2015**, *17*, 3826. (d) Zhu, Y.; Dong, Z.; Cheng, X.; Zhong, X.; Liu, X.; Shen, Z.; Yang, P.; Li, Y.; Wang, H.; Yan, W.; Wang, K.; Wang, R. *Org. Lett.* **2016**, *18*, 3546. (e) Holmes, M.; Nguyen, K. D.; Schwartz, L. A.; Luong, T.; Krische, M. J. *J. Am. Chem. Soc.* **2017**, *139*, 8114. (f) Pan, X.; Wang, Z.; Kan, L.; Mao, Y.; Zhu, Y.; Liu, L. *Chem. Sci.* **2020**, *11*, 2414.

(43) Takata, T.; Hirano, K.; Miura, M. *Org. Lett.* **2019**, *21*, 4284.

(44) (a) Corberán, R.; Mszar, N. W.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2011**, *50*, 7079. (b) Kojima, R.; Akiyama, S.; Ito, H. *Angew. Chem. Int. Ed.* **2018**, *57*, 7196. (c) Sakaguchi, H.; Uetake, Y.; Ohashi, M.; Niwa, T.; Ogoshi, S.; Hosoya, T. *J. Am. Chem. Soc.* **2017**, *139*, 12855. (d) Sakaguchi, H.; Ohashi, M.; Ogoshi, S. *Angew. Chem. Int. Ed.* **2018**, *57*, 328. (e) Kojima, Y.; Takata, T.; Hirano, K.; Miura, M. *Chem. Lett.* **2020**, *49*, 637. (f) For a related review, see: Wang, M.; Shi, Z. *Chem. Lett.* **2021**, *50*, 553.

(45) Mikami, K.; Itoh, Y.; Yamanaka, M. *Chem. Rev.* **2004**, *104*, 1.

(46) Kojima, Y.; Miura, M.; Hirano, K. *ACS Catal.* **2021**, *11*, 11663.

(47) Goff, C. M.; Matchette, M. A.; Shabestary, N.; Khazaeli, S. *Polyhedron* **1996**, *15*, 3897.

(48) Paioti, P. H. S.; del Pozo, J.; Mikus, M. S.; Lee, J.; Koh, M. J.; Romiti, F.; Torker, S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2019**, *141*, 19917.

(49) Wu, J.; Wu, H.; Li, X.; Liu, X.; Zhao, Q.; Huang, G.; Zhang, C. *Angew. Chem. Int. Ed.* **2021**, *60*, 20376.

(50) Yamaguchi, D.; Nakamura, I.; Nishimura, T. *Chem. Commun.* **2021**, *57*, 11787.

(51) (a) Guo, S.; AbuSalim, D. I.; Cook, S. P. *J. Am. Chem. Soc.* **2018**, *140*, 12378. (b) Sarver, P. J.; Bacauanu, V.; Schults, D. M.; DiRocco, D. A.; Lam, Y.-h.; Shere, E. C.; MacMillan, D. W. C. *Nat. Chem.* **2020**, *12*, 459. (c) He, J.; Nguyen, T. N.; Guo, S.; Cook, S. P. *Org. Lett.* **2021**, *23*, 702.

Biosketches

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