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Copper-Catalyzed Enantioselective Formation of C-CF_3 Centers from β-CF_3-Substituted Acrylates and Acrylonitriles.

Pauline Poutrel, Maria V. Ivanova, Xavier Pannecoucke, Philippe Jubault, and Thomas Poisson*

Abstract: The catalytic asymmetric synthesis of β-trifluoromethylated esters or nitriles is reported. The use of an in situ formed chiral Cu-H complex allowed the enantioselective reduction of β-trifluoromethylated acrylates or acrylonitriles. The reaction proceeds smoothly affording the corresponding enantioenriched products in good to excellent yields and outstanding enantioselectivities (up to 98% ee). The mechanism of the reaction was studied and a plausible reaction pathway was suggested accordingly. Finally, the versatility of the products was highlighted through functional group manipulations.

Nowadays, organofluorine chemistry is attracting a lot of interest from the organic chemist community. Indeed, the molecules bearing a fluorine atom or a fluorinated group have a tremendous impact in the discovery of bioactive molecules.[1] For instance, among the 29 small molecules approved by the FDA in 2017, 10 are having at least one fluorine atom on their backbone.[2] As part of the commonly used fluorinated motifs in medicinal chemistry, the trifluoromethyl unit (CF_3) is probably the most popular one and is present on the structure of several blockbusters (*eg*. Januvia®, Tasigna® and Xtandi®).[3] Although, the construction of non-stereogenic C-CF_3 center has been widely studied over the last two decades,[4] the catalytic asymmetric construction of chiral C-CF_3 centers remains less explored. Among the existing methods, the 1,2-addition reactions on carbonyl derivatives or surrogates are the most popular methods.[5] In contrast, the formation of stereogenic C-CF_3 centers α- to a carbonyl derivative has been scarcely studied,[6] while the catalytic asymmetric formation of a remote C-CF_3 stereogenic center remains an unknown transformation. As the catalytic asymmetric 1,4-addition of the CF_3 group remains an elusive goal,[7] alternative methods were elaborated to access chiral β-C-CF_3 centers. The catalytic asymmetric 1,4-addition on β-CF_3-substituted Michael acceptors found a broad range of applications for the introduction of various nucleophiles (Figure 1, eq.1).[8] On the other hand, the chemistry of chiral N-heterocyclic carbene catalysts offered new entries toward the formation of these chiral trifluoromethylated molecules from β-CF_3 enals (*themselves synthesized from the corresponding esters*) (eq. 2).[9] Finally, the catalytic asymmetric reduction of β-CF_3-substituted acrylic acids has been developed using a Rh-catalyst under 20 atm of dihydrogen gas with outstanding enantioselectivities and high yields (eq.3).[10] Complementary to these methods, we thought that the development of a practical catalytic enantioselective method using an inexpensive catalyst along with an excellent functional group tolerance would offer a straightforward access to molecules containing a chiral C-CF_3 center and would tackle the limitations of the existing methods. As part of our research program aiming at offering new Cu-based transformations,[11] we envisioned the catalytic asymmetric reduction of the readily available β-CF_3-substituted Michael acceptors using an in situ formed chiral CuH species. Indeed, CuH-based reductions are well recognized to operate under mild reaction conditions, with a large functional group tolerance and using inexpensive silane as reductive species.[12] Hence, such a transformation would offer a powerful manifold to build up high added value molecules containing C-CF_3 chiral center.

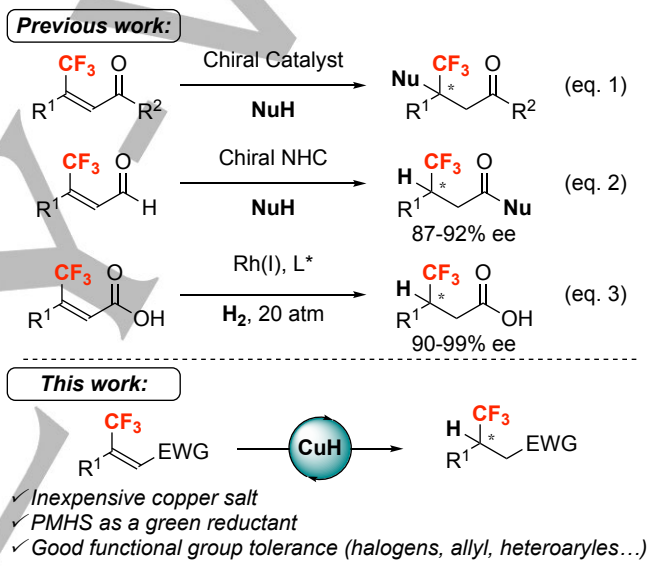

Figure 1. State of the art and present work.

At the outset of the study we chose (*E*)-β-CF_3 ethyl cinnamate **1a** as a model substrate and we evaluated its reduction in the presence of catalytic amount of a Cu salt, a chiral ligand (L) and a silane (R_3SiH) as the reductive species (Table 1).

After a careful examination of all reaction parameters we found that 5 mol% of $Cu(OAc)_2$, chiral ligand **L1** (Josiphos SL-J007-1) and *t*BuONa in the presence of 2 equiv of PMHS and *t*BuOH in toluene at – 20 °C gave the expected product **2a** in 71% isolated yield and an excellent 97% ee (Table 1, entry 1). Note that the reaction performed at RT afforded **2a** in lower yield and ee (entry 2). Chiral ligand **L1** prove to be the most efficient from the Josiphos family (entry 3).[13] During the optimization of the reaction, we found that chiral biaryl diphosphine ligands were less efficient as demonstrated with **L3**, **L4** and **L5**. PMHS proved to be the most efficient silane for this transformation, as showed in entry 7. A decrease of the amount of *t*BuOH from 2 to 1 equiv had a significant impact on the reaction outcome (entry 8). To our delight, we observed that the loading of $Cu(OAc)_2$ and **L1** could be decrease to 2.5 mol% without an alteration of the reaction efficiency (entry 9).

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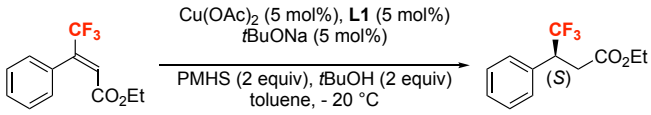
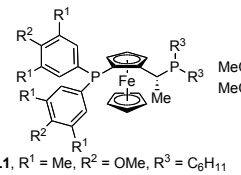
Table 1. Optimization of the catalytic enantioselective reduction of **1a**.[a]



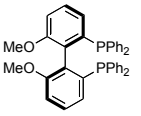
1a **2a**

Entry	Variation from standard conditions	Yield (%)[b]	ee (%)[c]
1	None	71	97
2	at RT	60	89
3	**L2** instead of **L1** at RT	48	73
4	**L3** instead of **L1** at RT	41	44
5	**L4** instead of **L1** at RT	55	72
6	**L5** instead of **L1** at RT	36	64
7	$(EtO)_3SiH$ instead of PMHS	88[d]	93
8	1 equiv of *t*BuOH at RT	51	88
9	2.5 mol% of $Cu(OAc)_2$ and **L1**	85	97
10	Enantiomer of **L1** was used	77	98[e]

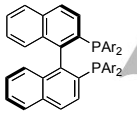
[a] **1a** (0.33 mmol), $Cu(OAc)_2$ (5 mol%), **L1** (5 mol%), *t*BuONa (5 mol%), *t*BuOH (2 equiv), PMHS (2 equiv), toluene (0.25 M), - 20 °C, Ar. [b] Isolated yield. [c] Enantiomeric excess determined by HPLC on a chiral stationary phase. [d] **2a** was contaminated with silane. [e] **(*R*)-2a** was obtained.



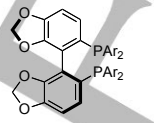
L1, R^1 = Me, R^2 = OMe, R^3 = C_6H_{11}
L2, R^1 = R^2 = H, R^3 = C_6H_{11}



L3



L4, Ar = 3,5-$Me_2C_6H_3$



L5, Ar = 3,5-$Me_2C_6H_3$

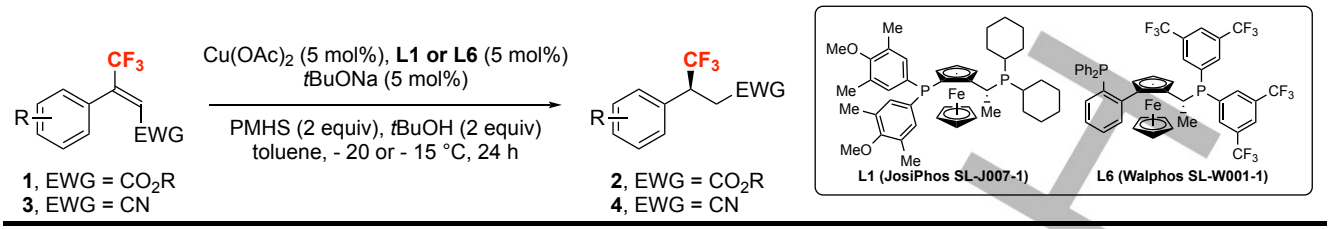
Finally, we demonstrated that the use of the enantiomer of **L1** led to the conversion of **1a** into the opposite enantiomer of **2a**, in similar yield and level of enantioselectivity (entry 10). It is worth to notice that, we did not observe the dehydrodefluorination of the CF_3 group of **2a** into the corresponding α,α-difluoroalkene as observed by Hoveyda during the development of Cu-catalyzed enantioselective hydroboration[14a] and Zhou in the course of the development of the NiH catalyzed reduction of β,β-disubstituted acrylates.[14b]

With these optimization conditions, we then sought to broaden the scope of the transformation to various β-CF_3-cinnamate derivatives (Scheme 1A). First, we demonstrated that the reaction with **1a** could be performed on a larger scale (3.3 mmol) without loss of efficiency as the desired product **2a** was isolated in a quantitative yield with a similar ee (97%). Then, *para*-methyl, *para*-*tert*butyl and *para*-methoxy β-CF_3 cinnamate derivatives **1b**, **1c** and **1d** were readily converted into the corresponding enantioenriched compounds **2b**, **2c** and **2d** in good yields with excellent enantioselectivities (96% - 97%). Interestingly, the *O*-allyl derivative **2e** was obtained in a decent 42% yield and 96% ee and no reduction of the olefin part was observed. This example highlights the functional group tolerance of the method. Then *meta*-substituted aromatic derivatives were evaluated and the desired products **2f** and **2g** were obtained in 87% and 76% yields, respectively. Note that in both cases an excellent level of enantioselectivity was obtained (95% and 97%). Note that, the *ortho*-methyl and the mesitylene derivatives were reluctant in our hands, affording the corresponding products in very low yield (<10%), probably due to steric hindrance. Acrylate **1h**, bearing a 2-naphtyl substituent gave the corresponding product **2h** in moderate yield and excellent ee after an extension of the reaction time to 48 h and an increase of the amount of *t*BuOH to 4 equiv. An allyl ester was tolerated and the product **2i** was obtained in a moderate 50% NMR yield and 94% ee. Aromatic derivatives bearing a halogen (**1j** and **1k**) were also converted into the enantioenriched products **2j** and **2k** in good yields with high enantioselectivities, at the cost of an extension of the reaction time to 48 h. Note that the absolute configuration of **2k** was unambiguously determined as *S*, after X-Ray crystallographic analysis. Trifluoromethyl group, as well as a methyl ester substituents were suitable. The reaction with **1l** and **1m** proved to be highly enantioselective and the products **2l** and **2m** in 97 and 96% ee, respectively, with very good yields. Unfortunately, the aliphatic derivative **1n** was not reactive under out standard conditions and no reduced product was observed.

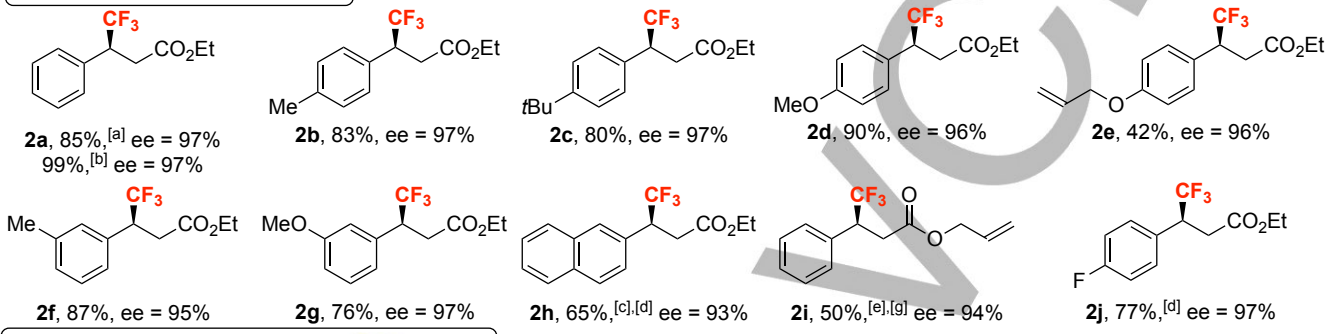
We then thought to extend this transformation to β-CF_3-acrylonitrile derivatives **3** to provide the first general access to chiral β-CF_3-substituted nitrile derivatives **4**.[15] To our delight, after a slight optimization of the reaction conditions, we found that the replacement of **L1** by **L6** (Walphos SL-W001-1) and a slight increase of the reaction temperature from -20 °C to -15 °C allowed the formation of **4a** in high yield (82%) and excellent enantioselectivity (96%) (Scheme 1B).[12] The scope of this transformation was then studied. The presence of a methyl, methoxy or a *tert*butyl group at the *para*-position as well as the *meta*-methoxy substituted aromatic ring did not alter the enantioselectivity of the process (91%, 96% and 98% ee) and afforded the products **4b**, **4c**, **4d** and **4e** in moderate to good isolated yields. The β-trifluoromethylated derivatives **3f** and **3g**, having a halogen (F and Br) at the *para* or *meta* position of the aromatic ring, were readily converted into the corresponding products **4f** and **4g** in good yields and excellent ee. Finally, the reaction was applied to the thiophene derivative **3h**, giving **4h** in 59% yield and 90% ee. Unfortunately, other β-trifluoromethylated Michael acceptor as sulfone and nitro derivatives **5** and **6** were either not reactive or gave poor results in terms of yield and enantioselectivity (Scheme 1C).[16]

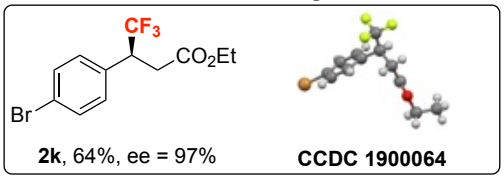
Then, the mechanism of the reaction was studied (Scheme 1). First, a linear dependence of the enantiomeric excess of the product and the enantiomeric excess of the catalyst was observed (Scheme 1D). This result suggested the involvement of a monomeric catalytically active species.[17] Finally, the reaction was carried out with the opposite stereoisomer of the Michael acceptor, the (*Z*)-acrylates **1j** and **1k** and the (*Z*)-acrylonitrile **3b** (Scheme 1E). Interestingly, when **L1** was used the opposite enantiomer was obtained in all cases, with somehow lower enantioselectivities (*ca.* 10% less), as already described by Buchwald and Lipshutz, independently.[18] These results demonstrated that the control of the enantioselectivity seems to be dependent on the geometry of the starting Michael acceptor. Unexpectedly, when the catalytic enantioselective reduction of **(*Z*)-2k** was carried out with the enantiomer of **L1** (Josiphos SL-J007-2), the product having a similar absolute configuration as the one obtained with **L1** (Josiphos SL-J007-1) was obtained, albeit with a moderate 58% ee. Unfortunately, we

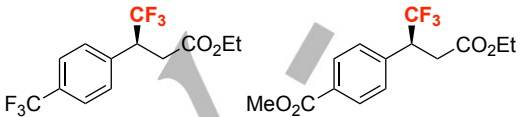
have not been able, so far, to find any clue to explain this reversed enantioselectivity.



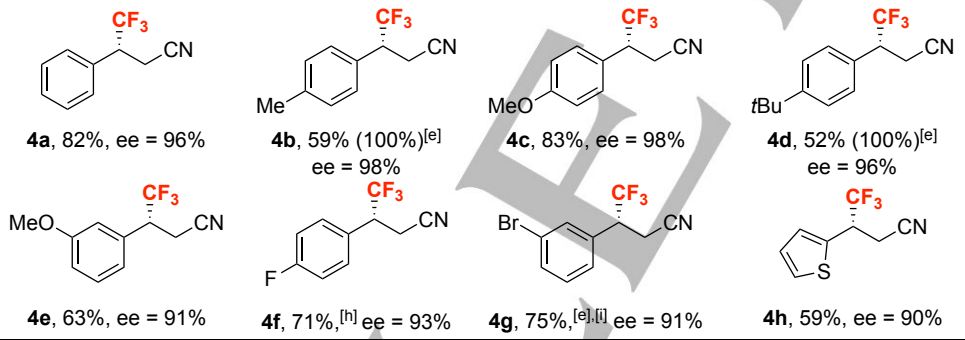
A. EWG = CO_2R with L1 at - 20°C



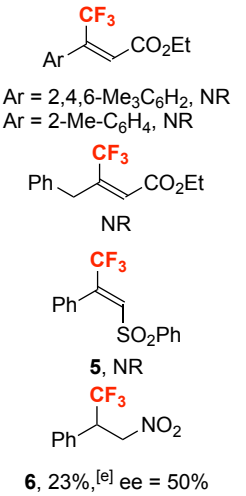




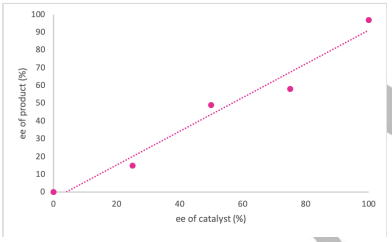
B. EWG = CN with L6 at - 15 °C



C. Reluctant substrates

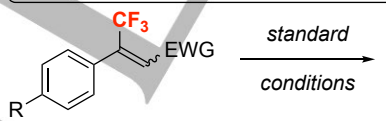


D. Linear effect



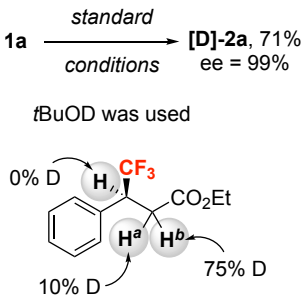
Monomeric catalytically active species

E. Substrate geometry's influence



		EWG	R	Yield (%)	ee (%)
From (*E*)-olefin	(*S*)-2j	CO_2Et	F	77	97
	(*S*)-2k	CO_2Et	Br	64	97
	(*R*)-4b	CN	Me	59	98
From (*Z*)-olefin	(*R*)-2j	CO_2Et	F	66	83
	(*R*)-2k	CO_2Et	Br	75	84
	(*S*)-4b	CN	Me	91	84
with the enantiomer of L1	(*R*)-2k	CO_2Et	Br	87	58[a]

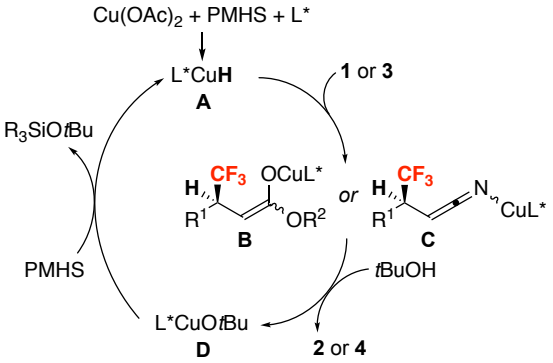
F. [D]-labelling



Scheme 1. Catalytic asymmetric reduction of β-CF_3-acrylates **1** and β-CF_3-acrylonitrile derivatives **3**. Reaction conditions: **1** or **3** (0.5 mmol), $Cu(OAc)_2$ (5 mol%), **L1** or **L6** (5 mol%), *t*BuONa (5 mol%), *t*BuOH (2 equiv), PMHS (2 equiv), toluene (0.25 M), - 20 °C, Ar. Isolated yields were reported unless otherwise stated. The enantiomeric excess (ee) was determined by HPLC on a chiral stationary phase. [a] 2.5 mol% of $Cu(OAc)_2$ and **L1** were used. [b] Reaction was performed on a 3.3 mmol scale (ca. 1g). [c] 4 Equiv of *t*BuOH were used. [d] 48 h reaction time. [e] Determined by ^{19}F NMR analysis on the crude reaction mixture. [f] 7.5 mol% of $Cu(OAc)_2$ and **L1** were used. [g] **L6** was used and the reaction was carried out – 15 °C. [h] Reaction was carried at 0 °C. [i] 64 h reaction time.

Finally, the use of *t*BuOH d-10 with PMHS under the standard reaction conditions demonstrated that the hydride came from the silane (PMHS), while the protonation of the transient copper enolate is performed by the alcohol (Scheme 1F). Moreover, the

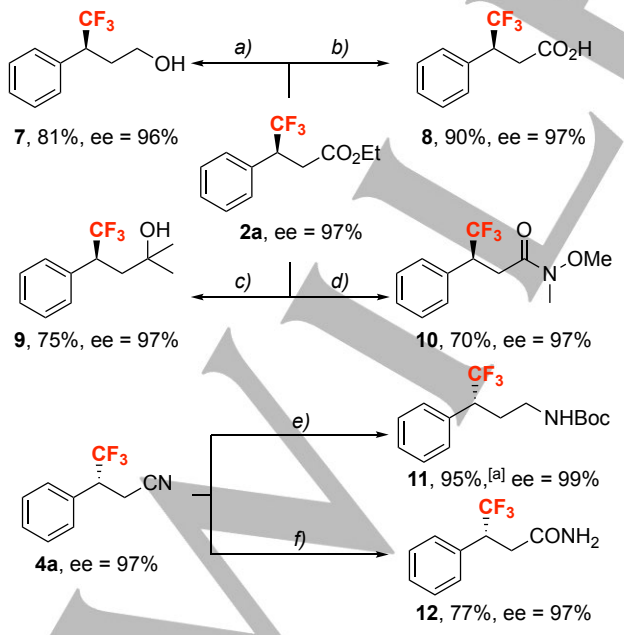
isotopic distribution on **[D]-2a**, resulting from this experiment, revealed that the deuteration reaction on the transient chiral copper enolate is rather diastereoselective. Note that no D incorporation at the β-position was detected, probably due to the low catalyst loading as well as the low reaction temperature.[19] With these experimental observations, we suggested the following mechanism, in agreement with the literature (Scheme 2).[12]



Scheme 2. Suggested mechanism for the formation of the enantioenriched products **2** and **4**.

First, the Cu(II) precatalyst ($Cu(OAc)_2$) is reduced onto the chiral CuH complex **A**,[20] in the presence of PMHS and *t*BuONa. This chiral complex reacts with **1** or **3** to provide, after reduction of the substrate, the chiral Cu-enolate **B** or nitrile anion **C**, which is finally protonated with *t*BuOH to deliver the product **2** or **4**, respectively, along with the formation of the chiral Cu*O*t*Bu complex **D**. The latter reacts with PMHS to regenerate the chiral catalyst **A** (L*CuH).

Finally, the versatility of the products was then highlighted (Scheme 3).



Scheme 3. Synthetically useful transformations of the products **2a** and **4a**. a) $LiBH_4$ (4 equiv), THF, 0 °C to RT. b) $LiOH{\cdot}H_2O$ (3.9 equiv),THF:H_2O (4:1), 0 °C to RT. c) MeMgBr (2.5 equiv), THF, - 78 °C to RT. d) MeO(Me)NH.HCl (1.55 equiv), *i*PrMgCl (3 equiv), THF, 0 °C to RT. e) i. $LiAlH_4$ (2 equiv), THF, 0 °C to RT; ii. Boc_2O (3 equiv), DMAP (10 mol%), Et_3N (3 equiv), DCM, 35 °C. f) $Cu(OAc)_2$ (2 mol%), Et_2NOH (3 equiv), H_2O, 35 °C. The enantiomeric excess was determined by HPLC on a chiral stationary phase. [a] determined by ^{19}F NMR.

First, the ester **2a** was readily reduced into the corresponding alcohol **7** using $LiBH_4$ in good yield without alteration of the enantiomeric excess. Using LiOH in THF, the ester **2a** was converted into the acid **8** in good yield and no erosion of the optical purity of the product was detected. We demonstrated that ester **2a** can react with MeMgBr to give access to the tertiary alcohol **9**, in good yield (75%) and a similar ee as **2a**. In the same vein, **2a** was smoothly converted into the corresponding Weinreb amide **10** in 70% without decrease of the enantiomeric excess. On the other hand, the nitrile **4a** was easily reduced into the corresponding amine and converted into the N-Boc protected derivative **11** in 95% NMR yield. We transformed **4a** into the amide **12** in 77% yield. Note that in both case no alteration of the ee was detected.

In conclusion, we developed an efficient and practical catalytic asymmetric method to build-up chiral C-CF_3 centers using $Cu(OAc)_2$ and **L1** or **L6** in the presence of PMHS. The reaction was applied to α,β-unsaturated esters and nitriles. The corresponding chiral trifluoromethyl compounds were obtained in good yields (42-90%) and excellent enantioselectivities (up to 98% ee). The mechanism of the reaction was studied and demonstrated that the selectivity of the reaction was dependent on the geometry of the starting Michael acceptor. A plausible mechanism and a transition state to explain the stereochemical outcome of the reaction with β-CF_3-acrylates were suggested.

Acknowledgements

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Keywords: Trifluoromethyl Group • Copper • Asymmetric Catalysis • Reduction • Copper Hydride

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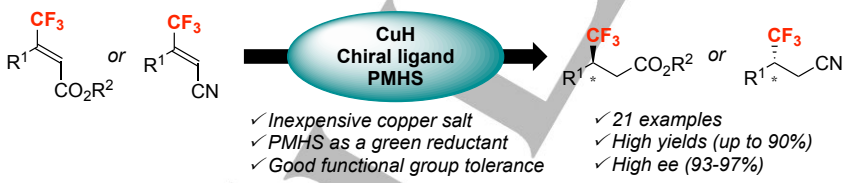

✓ *Inexpensive copper salt*
✓ *PMHS as a green reductant*
✓ *Good functional group tolerance*

✓ *21 examples*
✓ *High yields (up to 90%)*
✓ *High ee (93-97%)*