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Letter

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Cu(II)-Catalyzed Enantioselective *β*-Boration of *β*-Trifluoromethyl, *β*,*β*-Disubstituted Enones and Esters: Construction of a CF_3 and Boron Contained Quaternary Stereocenter

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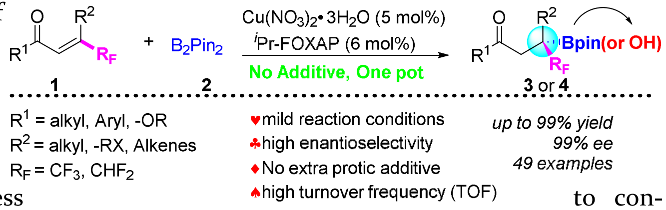
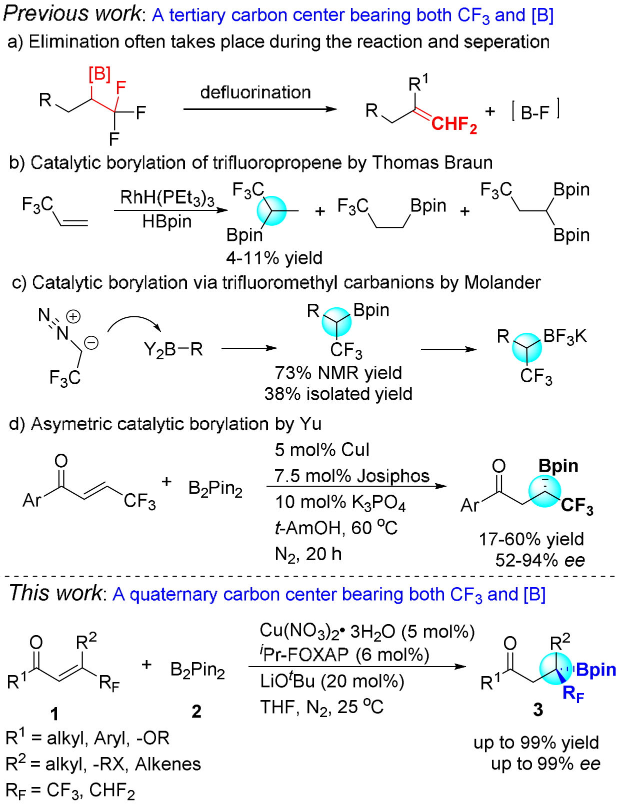
ABSTRACT: A highly enantioselective Cu(II)-catalyzed borylative reaction of *β*-trifluoromethyl *β*,*β*-disubstituted enones was developed, which provide a facile access to a variety of chiral alkylboronic esters with a quaternary stereocenter including both trifluoromethyl and boron group. Meanwhile, CF_3-contained tertiary alcohol derivatives were obtained in high yield with the maintained *ee* value by way of one pot methodology. The reactions proceed smoothly under mild reaction conditions and providing expedient access to construct chiral alkylboronic esters in well functional group toleranced, good yields, diversity conversion and highly enantioselectivities. The appropriate SDE test via achiral chromatography illustrated that the results present here were reliable.



KEYWORDS: *asymmetric copper catalysis, enones, conjugate addition, boration, CF_3-quaternary stereocenter*

Organoboron derivatives are of great importance in organic synthesis, not only for their special characteristics and biological activities,[1] but also for their use as key reagents with broad utility in the field of organic synthesis.[2] Therefore, enantioselective hydroboration,[3] diboration,[4] proto-boryl,[5] rearrangements,[6] reductions,[2e] cross-coupling[2f-g] and conjugate additions[7] of unsaturated compounds have been extensively studied. However, the construction of a CF_3 and boron substituted stereocenter still poses considerable challenge, due to low stablity of the product and potential B-F elimination (Scheme 1a).[8, 9] In 2009, the group of Braun reported the first example of Rh-catalyzed hyroboration of 3,3,3-trifluoroprop-1-ene, giving low yield (4-11%) of CF_3 containing alkylborons (Scheme 1b),[8a] After that, Molander and co-workers reported an alternative method with the use of diazotrifluoroethane and organoboronte (Scheme 1c).[8b] However, the pinacol boronates are susceptible to oxidation during the separation process, in order to solve this problem, the authors converted them into more stable potassium trifluoroborates product. Then, Yu' group developed the first asymmetric synthesis of fluorinated organoboron in 17-60% yield with 52-94% *ee*s (Scheme 1d).[8c] In general, the construction of chiral quaternary carbon stereocenter is much more challenging than that of tertiary carbon stereocenter.[10] During the course of our development of diverse transformations of *β*-CF_3-*β*,*β*-disubstituted enones.[11] we envisaged that the construction of organoboron compounds with a trifuloromethylated chiral

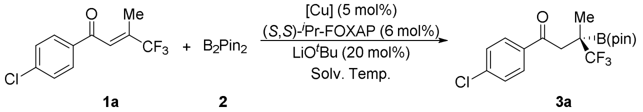


Scheme 1. Methods for the construction of trifluoromethylated organoboron compounds

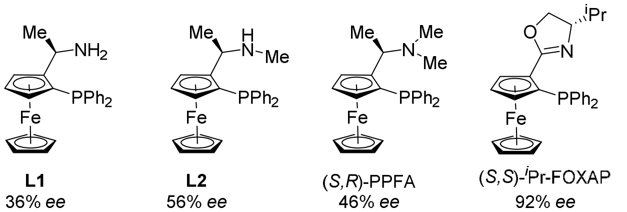
quaternary carbon stereocenter might be achieved by the asymmetric boron conjugate addition. Herein, we disclose the first highly enantioselective Cu-catalyzed borylative reaction of *β*-trifluoromethyl *β*,*β*-disubstituted enones/esters.

Initially, we conducted the reaction of $B_2(pin)_2$ with *β*-trifluoromethyl *β*,*β*-disubstituted enone **1a** in the presence of $Cu(CH_3CN)_4PF_6$ and commercial available ligands (See SI and table 1). Fortunately, chiral adduct **3a** could be obtained in 92% *ee* by the employment of (*S*,*S*)-^{i}Pr-FOXAP as the ligand (Table 1, entry 1). We then investigated a series of copper, such as $Cu(CH_3CN)_4BF_4$, $Cu(CH_3CN)_4ClO_4$, $Cu(OTf)_2$, $Cu(OAc)_2$, $Cu(NO_3)_2\cdot 3H_2O$ (Table 1, entries 2-6). It was found that $Cu(CH_3CN)_4BF_4$, $Cu(OAc)_2$ and $Cu(NO_3)_2\cdot 3H_2O$ could also deliver high yields with 97-98% *ee*. Finally, we choose $Cu(NO_3)_2\cdot 3H_2O$ as the metal catalyst considering the low price. Solvents such as MTBE, Et_2O and toluene did not give better results (Table 1, entries 7-9). Runing the reaction at lower temperature (0 °C) does not improve the enantioselectivity of the reaction (Table 1, entry 10). Overall, the reaction displayed the highest enantioselectivity (98% *ee*) in THF at 25 °C by employing $Cu(NO_3)_2\cdot 3H_2O$/(*S*,*S*)-^{i}Pr-FOXAP as catlyst (Table 1, entry 6).

Table 1. Optimization of Reaction Conditions[a]

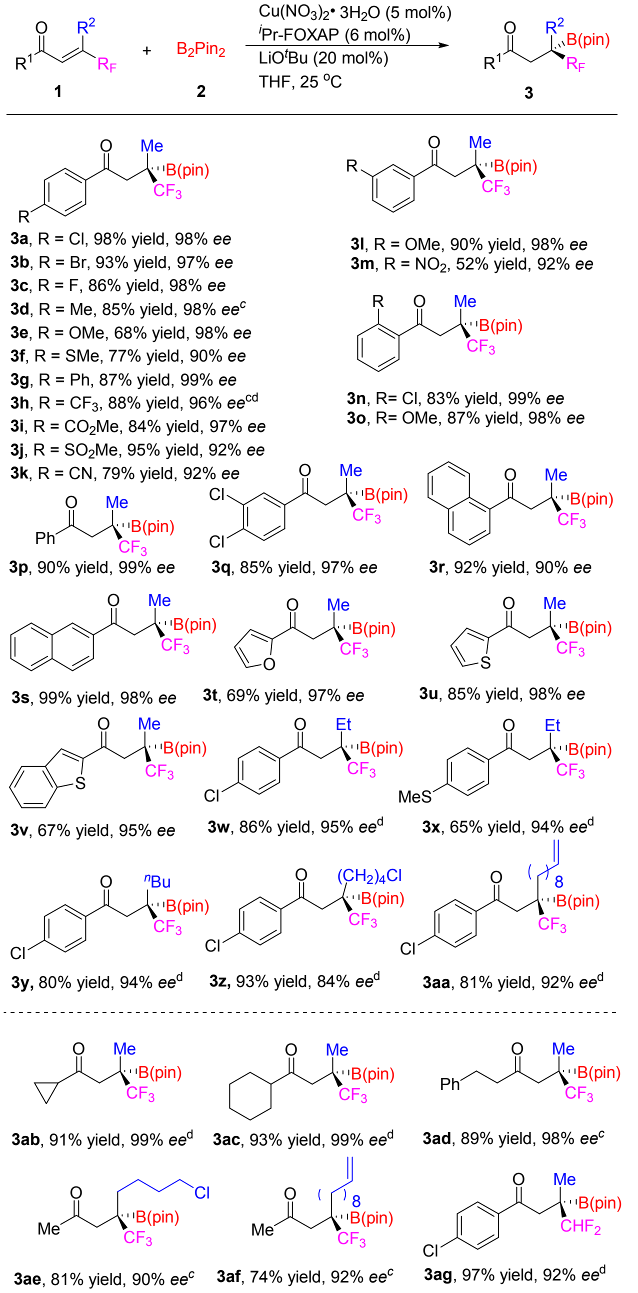


Entry	[Cu]	Sol.	Temp. (°C)	*Ee* (%)[b]
1	$Cu(CH_3CN)_4PF_6$	THF	25	92
2	$Cu(CH_3CN)_4BF_4$	THF	25	97
3	$Cu(CH_3CN)_4ClO_4$	THF	25	88
4	$Cu(OTf)_2$	THF	25	89
5	$Cu(OAc)_2$	THF	25	97
6	**$Cu(NO_3)_2\cdot 3H_2O$**	**THF**	**25**	**98**
7	$Cu(NO_3)_2\cdot 3H_2O$	MTBE	25	97
8	$Cu(NO_3)_2.3H_2O$	Et_2O	25	94
9	$Cu(NO_3)_2\cdot 3H_2O$	Toluene	25	92
10	$Cu(NO_3)_2\cdot 3H_2O$	THF	0	97



[a] Unless otherwise noted, all reactions were carried out with 0.1 mmol of **1**, 0.15 mmol of **2**, 5 mol% of catalyst ([Cu]/L = 1:1.2) in 1.0 mL solvent at 25 °C for 12 h with 100% conversion. [b] The *ee* of **3a** determined by HPLC analysis.

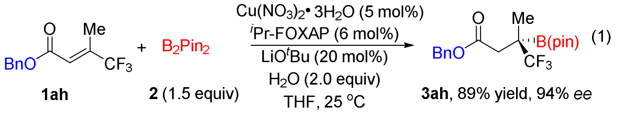
With the optimized reaction conditions in hand, we next investigated the scope of *β*-trifluoromethyl *β*,*β*-disubstituted enones **1** (Scheme 2). A wide variety of electron-donating and withdrawing groups were tolerated at *para*-position of phenyl ring, such as -Cl, -Br, -F, -Me, -OMe, -SMe, -Ph, $-CF_3$, $-CO_2Me$, $-SO_2Me$ and -CN, delivering the desired products **3a-3k** in 68-98% yields with 92-98% *ees*. The reactions also worked well for those enones bearing *ortho*-, *meta*-substituted phenyl group and simple phenyl group (**3l-3q**). Gratifyingly, other aryl enones such as 1-naphthyl (**3r**) and 2-naphthyl (**3s**) and heterocyclic aryl enones, such as furyl, thienyl and ben-



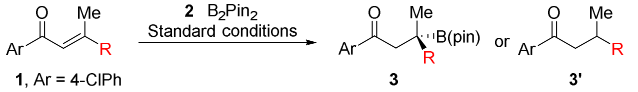
[c] The *ees* of **3** resulting from corresponding alcohol **4** or **7**. [d] 2.0 equiv H_2O was added.

Scheme 2. Substrate Scope Exploration

zothienyl are compatible, delivering the corresponding organoboron products **3t-3v** in high yields with 90-99% *ee*s. Next, we examined the effect of different β-substituted group on the alkene moiety. In addition to methyl, enones with different alkyl or functionalized alkyl substituents at β-position could also give nice results (**3w-3aa**). Remarkably, compared with the aryl enones, the alkyl substituted enones reacted with $B_2(pin)_2$ could aslo afford the corresponding adducts **3ab-3af** in 74-93% yields with 90-99% *ee*s. Unfortunately, the β-aryl, β-CF_3-enone gave a defluorinated product[12] in low yield rather than the desired adduct. The formation of the defluorinated product **9** is presumably attributed to β-fluoride elimination of an in situ generated unstable trifluoroethyl anion.[13] The CF_3 group could be well extended to CHF_2 and the corresponding product **3ag** was obtained in 97% yield with 92% *ee*. The asymmetric boration of β,β-disubstituted α,β-unsaturated ester is especially more challenging compared to enone, because of the relatively low reactivity and poor enantioselectivity.[14] To estimate the reactivity, we set up a competing experiment in which a 1:1 mixture of enone (**1ah**) and ester (**1ah**) with one equivalent of B_2pin_2 under optimized reaction conditions (details in Figure S1). As expected, the enone reacted more than 3 times faster than the ester. Fortunately, even the relative low reactivity, the desired addition product **3ah** was obtained in 89% yield with 94% *ee* (eq 1).



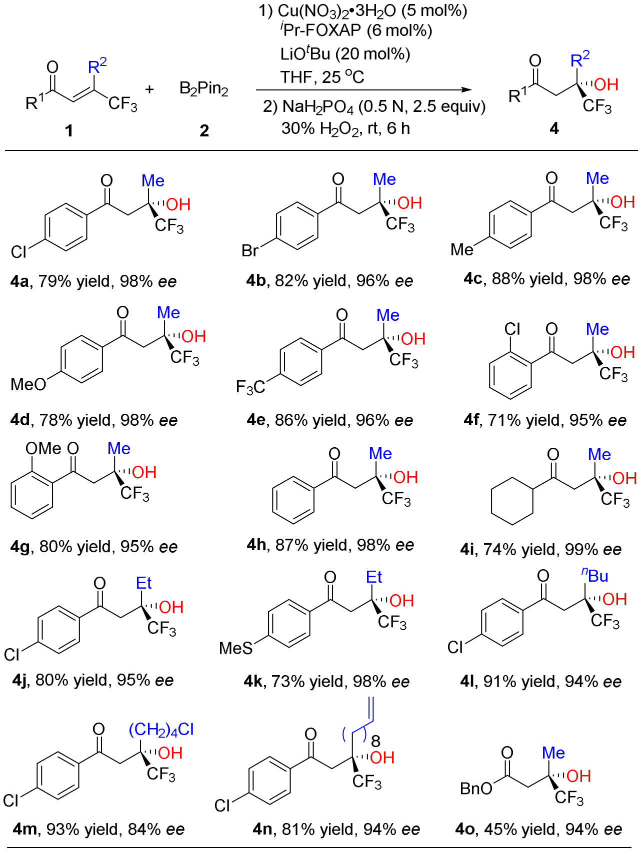
Further investigations revealed that the fluorine substituent of the methyl group in enones had a crucial influence on the reactivity (Table 2). There was no reactivity when CH3-substituted or CCl3-substituted alkenes were used (Table 2, entries 1 and 2). The further extension of the enone to β-ester enone, only hydrogenation product 3' was observed in 96% yield (Table 2, entry 3). When fluorinated substrates were used, the corresponding boron products **3af** and **3a** were obtained in 97 and 98% yields with 92% and 98% *ee*s respectively (Table 2, entries 4 and 5).



Entry	R	Product	Yield (%)	*Ee* (%)[b]
1	CH_3	**3**	NR	-
2	CCl_3	**3**	NR	-
3	CO_2Me	**3'**	96	-
4	CHF_2	**3af**	97	92
5	CF_3	**3a**	98	98

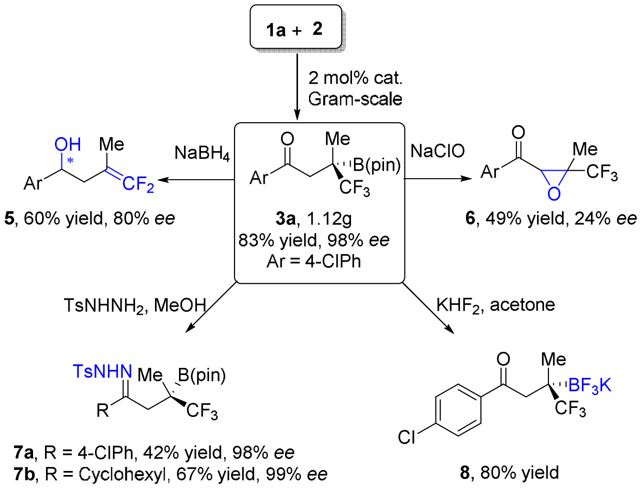
Table 2. The fluoride effect on the reactivity

It should note that optically active tertiary alcohols could be easily obtained with highly enantioselectivity via a 'one pot' sequential asymmetric boration and oxidation strategy (Scheme 3). As shown in Scheme 3, a series of chiral β-hydroxy ketone derivatives **4a-4o**, can be afforded in good yield with 84-99% *ee* values by treatment with NaH_2PO_4 and H_2O_2 after the boration. The absolute configuration of this class of compounds refers to the corresponding literature.[15] To ensure that the results obtained are more believable, we conducted an appropriate SDE[16] (self-disproportionation of enantiomers) test via achiral chromatography (details in Table S2). Fortunately, the data presented here is reliable because of column chromatography does not change the *ee* value of the product.



4a, 79% yield, 98% *ee*
4b, 82% yield, 96% *ee*
4c, 88% yield, 98% *ee*
4d, 78% yield, 98% *ee*
4e, 86% yield, 96% *ee*
4f, 71% yield, 95% *ee*
4g, 80% yield, 95% *ee*
4h, 87% yield, 98% *ee*
4i, 74% yield, 99% *ee*
4j, 80% yield, 95% *ee*
4k, 73% yield, 98% *ee*
4l, 91% yield, 94% *ee*
4m, 93% yield, 84% *ee*
4n, 81% yield, 94% *ee*
4o, 45% yield, 94% *ee*

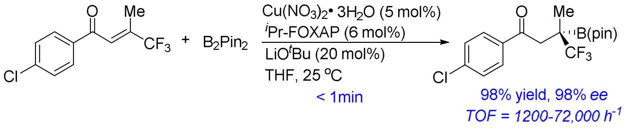
Scheme 3. Synthesis of chiral alcohols



Scheme 4. Gram-Scale Experiment and Transformations of 3a

A gram-scale of **3a** was obtained in 83% yield with 98% *ee* with the use of only 2 mol% catalyst (Scheme 4). Synthetic transformations of **3a** were then carried out. Besides the oxidation reaction to tertiary alcohol showed in Scheme 4, the elimination of B and F was observed during the reduction with $NaBH_4$, furnishing the corresponding chiral homoallyl alcohol **5** with the slightly lower *ee*. Chiral oxirane derivative **6** containing two consecutive stereocenters was obtained by treatment with NaClO at room temperature but unfortunately with only 24% *ee*. The condensation with $TsNHNH_2$ in MeOH for 12 h produced the hydrazones **7a-7b** smoothly without loss of the chirality information. Treatment of **3a** with aqueous KHF_2 could deliver the corresponding potassium trifluoroborate **8** in 80% yield.

Finally, the turnover frequency (TOF) of the asymmetric boration was confirmed to be very high. Borylation product **3a** was obtained in 98% yield with 98% *ee* at rt for less than 1 min in the presence of $Cu(NO_3)_2{\cdot}3H_2O$ (5 mol%), ^{i}Pr-POXAP (6 mol%). Estimated the TOF of the reaction between 1200-72,000 h^{-1}, and the highest value ever reported in an asymmetric boron conjugate addition reaction was 17,600 h^{-1} (Scheme 5).[17]



Scheme 5. Turnover Frequency Test

In summary, we have developed the first highly enantioselective copper-catalyzed boration of *β*-fluoromethyl *β,β*-disubstituted enones and esters under mild conditions. This mild and general protocol provides a rapid access to a variety of chiral alkylboronic esters with a trifluoromethylated quaternary stereocenter. Meanwhile, a series of CF_3-contained tertiary alcohol derivatives with the maintained *ee* value via a one-pot two step strategy. The salient features of the method include good functional group tolerance, good yields, diverse synthetic transformation, high enantioselectivities, inexpensive catalyst and mild conditions. Further studies including synthetic applications of its diversity transformations are underway.

ASSOCIATED CONTENT

Supporting Information: Experimental procedures, spectroscopic data for the substrates and products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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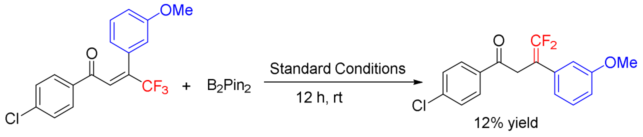

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(17) The TOF was less than 50 h^{-1}, See: Ref 7b, 7c, 7e, 7g. 5580 h^{-1} TOF, see: 7f. 17,600 h^{-1} TOF, see: 10e.

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