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Copper-catalyzed diastereoselective synthesis of β-boryl-α-quaternary carbon carboxylic esters†

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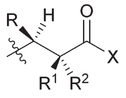
Cu(I)-Catalyzed diastereoselective carboboration of α-alkyl-substituted α,β-unsaturated carboxylic esters to produce β-boryl-α-quaternary carbon esters was developed. The carbon skeletons of dialkyl sulfates, primary allyl halides, and benzyl bromides were transferred to the α-position of the substrates to provide products in moderate to good yields with a diastereoselectivity of >95% in most cases. Substrates bearing a β-(hetero)aryl substituent gave higher diastereoselectivities than those bearing a linear β-alkyl substituent. The crystal structure of the potassium trifluoroborate derivative shows that the reactions probably go through a copper(I) enolate intermediate and the diastereoselectivity arises from the electrophilic attack of electrophiles to the less hindered side of the enolates.

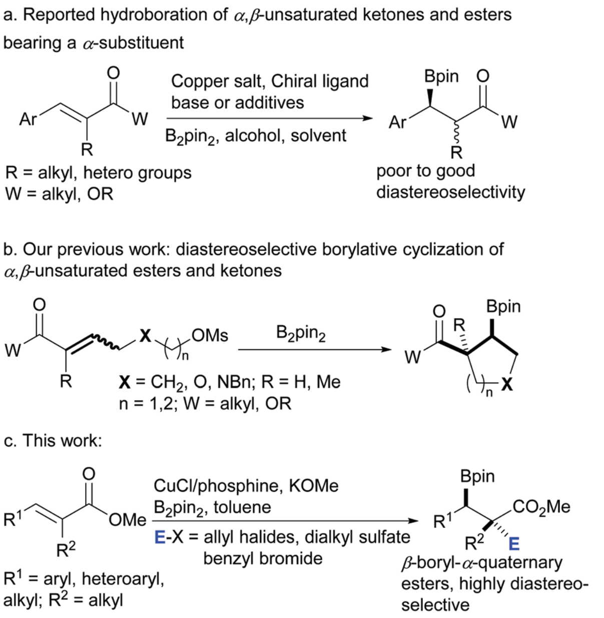
Introduction

Construction of quaternary carbon stereogenic centers remains one of the most significant challenges in modern synthetic chemistry.[1] Carbonyl compounds bearing a β-functional and α-quaternary carbon center are versatile building blocks in organic synthesis (Chart 1), and numerous methods have been developed to access the corresponding β-hydroxyl and amino compounds.[2] Boronyl is a versatile functional group that can be transferred to hydroxyl, amino, aryl, vinyl, and many others. Copper-catalyzed hydroboration of α,β-unsaturated carbonyl compounds is the most widely used procedure to access β-boron functionalized carbonyl compounds.[3] However, hydroboration of α-functionalized α,β-unsaturated carbonyl substrates typically results in two tertiary carbon centers (Scheme 1a).[4] Although there are many reports on copper-catalyzed carboboration of alkenes and alkynes,[5] the examples of copper-catalyzed carboboration of α-functionalized α,β-unsaturated carbonyl substrates leading to a α quaternary carbon center are rare.[6] Carboboration of unsaturated compounds is associated with several potential challenges because of the use of a stoichiometric amount of base additive. One is



R = hydroxyl, amino, boryl. etc.

Chart 1



Scheme 1 Copper-catalyzed borylation of α,β-unsaturated compounds.

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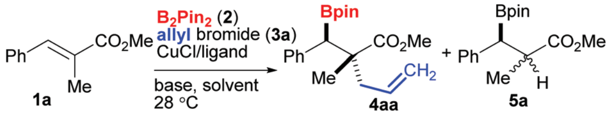
the hydroboration reaction of the substrate.[7] Other two side reactions are transesterification between a methyl ester substrate and base,[8] and nucleophilic substitution between an electrophile and base. A skillful choice of a base and electrophile is crucial to access the carboboration product efficiently.

We previously reported intramolecular carboboration of α,β-unsaturated esters and ketones to produce *cis*-boryl-substituted cycloalkyl esters and ketones, respectively (Scheme 1b).[9] Herein, we report the first copper-catalyzed diastereoselective carboboration of α-alkyl-substituted α,β-unsaturated esters to synthesize β-boryl-α,α-disubstituted esters (Scheme 1c). The presence of an ester and an allyl on the quaternary center as well as a boryl on the neighboring carbon offers many possibilities for further transformations.

Results and discussion

Carboboration of **1a** by bis(pinacolato)diboron (**2**) and allyl bromide (**3a**) (as the electrophile) was carried out in the presence of CuCl/Xantphos/KOMe (Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene) in toluene at 28 °C. In addition to the carboboration product **4aa** (58% yield), the hydroboration product **5a** is produced in 27% yield as a mixture of diastereoisomers (Table 1, entry 1). **5a** cannot be transformed to **4aa** under the reaction conditions.[10] As we encountered in our previous study,[7] hydroboration is the main side reaction in the copper-catalyzed carboboration of unsaturated compounds.[11] Thus, a series of phosphine ligands were screened to improve the selectivity of **4aa** (Table 1, entries 2–11). As indicated in Table 1, 1,1′-bis(diphenylphosphino)ferrocene (dppf, entry 3), 1,4-bis(diphenylphosphino)ethane (dppe, entry 5), and 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (Sphos, entry 7) yield **4aa** in higher yields (66–70%) with improved selectivity. In contrast, 1,1-bis(diphenylphosphino)methane (dppm, entry 4) and tris(2,4-di-*tert*-butylphenyl)phosphite (entry 10) do not produce **4aa** at all. NaOMe (entry 12) decreases the yield, while LiOMe (entry 13) is not active for carboboration. The use of either KO-*t*-Bu or NaO-*t*-Bu should be avoided because it will result in transesterification between the bases and **1a.**[12] The reactions in DMF and THF were also conducted (entries 14 and 15). **4aa** was not observed by ^{1}H NMR when DMF was used as a solvent.

Table 1 Screening of reaction conditions[a]



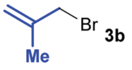
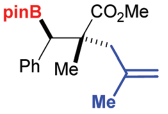
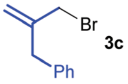
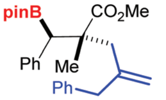
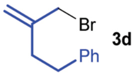
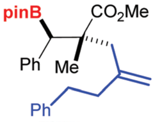
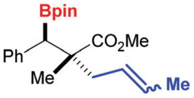
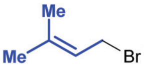
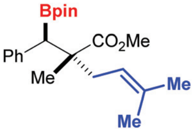
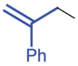
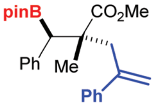
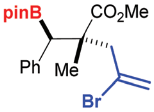
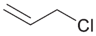
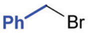
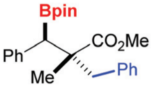
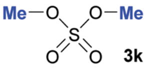
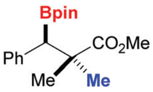
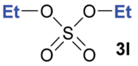
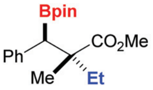
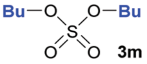
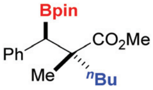
Entry	Ligand	Base	Solvent	Yield[b] (%) **4aa** [c]	Yield[b] (%) **5a** [d]
1	Xantphos	KOMe	Toluene	58	27
2	BINAP	KOMe	Toluene	36	24
3	dppf	KOMe	Toluene	66	34
4	dppm	KOMe	Toluene	0	13
5	dppe	KOMe	Toluene	66	32
6	dppp	KOMe	Toluene	57	27
7	Sphos	KOMe	Toluene	70	29
8	Xphos	KOMe	Toluene	25	20
9	PCy_3	KOMe	Toluene	50	45
10	L1[e]	KOMe	Toluene	0	16
11	L2[f]	KOMe	Toluene	50	40
12	Sphos	NaOMe	Toluene	36	30
13	Sphos	LiOMe	Toluene	0	6
14	Sphos	KOMe	THF	64	28
15	Sphos	KOMe	DMF	0	7

[a] Reaction conditions: **1a** (0.4 mmol), **2** (0.44 mmol), **3a** (0.8 mmol), CuCl (0.02 mmol), ligand (entries 1–6, 0.02 mmol; entries 7–13, 0.04 mmol), base (0.4 mmol), toluene (0.8 mL), 3 h. B_2Pin_2 = bis(pinacolato)diboron. [b] Determined by ^{1}H NMR analysis. [c] The relative configuration of **4aa** was determined by X-ray single crystal structure analysis of its derivatives (see Fig. 1). The diastereoselectivities of **4aa** are >99 : 1 in all cases. [d] **5a** was produced as a mixture of diastereoisomers with dr = 71 : 29–26 : 74. [e] L1 = tris(2,4-di-*tert*-butylphenyl)phosphite. [f] L2 = 1,1′-bis(di-*tert*-butylphosphino)ferrocene.

The scope of electrophiles was studied using **1a** as the substrate (Table 2). The reactions using 2-substituted allyl bromides (entries 1–3) provide the corresponding borylallylation products **4ab**, **4ac**, and **4ad** in yields of 42–45%, with a dr of >98 : 2, 91 : 9, and >99 : 1, respectively. In addition, 3-methyl- and 3,3-dimethyl-substituted allyl bromides are also effective electrophiles (entries 4 and 5). However, the reactions using 2-phenyl- and 2-bromoallyl bromides do not produce the desired products, but rather *ca.* 10% yield of side product **5a** (entries 6 and 7). Allyl chloride (**3i**) also reacts with **1a** to produce **4aa** in 63% yield (entry 8, 80 °C, 30 min). Considering the similar reactivity of benzyl bromide (**3j**) to that of allyl bromide in an S_N2 substitution reaction, the electrophile was subjected to the reaction with **1a** to produce **4aj** in 45% yield (entry 9). Dialkyl sulfates are other types of electrophiles widely used in alkylation reactions. Indeed, dialkyl sulfates **3k**, **3l**, and **3m** are effective electrophiles because they produce **4ak**, **4al**, and **4am**, respectively, in 80–84% yields (entries 10–12). Perhaps the balance between reactivity and resistance to the side reaction of dialkyl sulfates is responsible for the high yields.

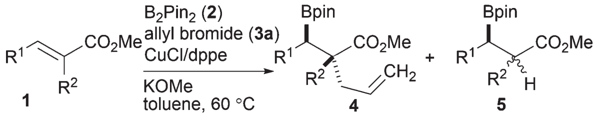
The reaction of α-substituted α,β-unsaturated esters (**1**) with **3a** was also studied, and the results are shown in Table 3. First, the effect of different substituents on the R^1 group was studied (**4ba–4ga**). Substrates bearing *p*-MeO, *p*-Br, and *p*-Cl on R^1 afforded products in 53% (**4ba**), 63% (**4ca**), and 60% (**4da**) yields, respectively, accompanied by the formation of side product **5** in 10–16% yields. Improved yield and suppressed side reaction are achieved when there is an *o*-Cl in **1e** (**4ea**, 67%; **5e** < 1%). When Cl is situated at the *meta* position, the yield of side product **5f** increases to 7%. For the substrate with a *p*-nitro group, no products (**4ga** and **5g**) are formed.[4b] For the substrate with an α-butyl group (**1h**), **4ha** is obtained in 66% yield. We also studied the carboboration of the substrate with a β-2-furyl group (**1i**). In this case, **4ia** is produced in 35% yield with a diastereomeric ratio (dr) of 98 : 2. The steric effect of the β-substituent of the substrate on diastereoselectivity is illustrated when a substrate with a β-2-phenylethyl group (**1j**) is used. Owing to the smaller size of the β group in **1j**, **4ja** is gen-

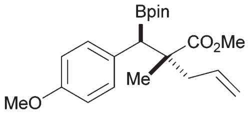
Table 2 Copper-catalyzed carboboration of methyl (2*E*)-2-methyl-3-phenylacrylate (**1a**)[a]

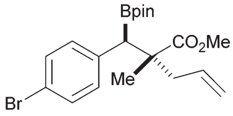
Entry	3	4[b]
1	 **3b**	 **4ab**, 42%, dr > 98:2 (36%)
2	 **3c**	 **4ac**, 45%, dr = 91:9 (18%)
3	 **3d**	 **4ad**, 42%, dr > 99:1 (36%)
4[c]	 E/Z = 83:17 **3e**	 **4ae**, 76% *E/Z* = 90:10 dr > 99:1 (16%)
5	 **3f**	 **4af**, 48%, dr > 99 (15%)
6	 **3g**	 **4ag**, 0% (13%)
7	 **3h**	 **4ah**, 0% (8%)
8[d]	 **3i**	**44aa**, 63%, dr > 99 : 1 (16%)
9	 **3j**	 **4aj**, 45%, dr > 99:1 (18%)
10	 **3k**	 **4ak**, 80% (20%)
11	 **3l**	 **4al**, 80%, dr > 98:2 (16%)
12	 **3m**	 **4am**, 84%, dr > 99:1 (7%)

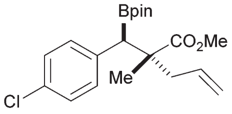
[a] Reaction conditions: **1a** (0.4 mmol), **2** (0.44 mmol), **3** (0.8 mmol), CuCl (0.02 mmol), Sphos (0.04 mmol), KOMe (0.4 mmol), toluene (0.8 mL), 28 °C, 3 h. [b] Isolated yields. The dr ratio of **4** is determined by ^{1}H NMR analysis based on the percentage decrease of the integral area of ester methyl or the β proton close to boron, after purification. The yield of **5a** is determined by ^{1}H NMR analysis of crude products and is shown in parentheses. [c] **3e** is an isomeric mixture consisting of (*E*)-1-bromobut-2-ene (73%), (*Z*)-1-bromobut-2-ene (14.6%), and 3-bromobut-1-ene (12.4%). [d] The reaction was conducted at 60 °C.

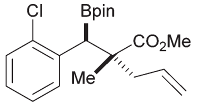
Table 3 Copper-catalyzed allylboration of methyl(2*E*)-2-alkyl-3-arylacrylate (**1**) with B_2Pin_2 (**2**) and allyl bromide (**3a**)[a]

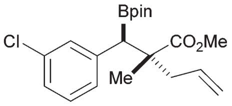


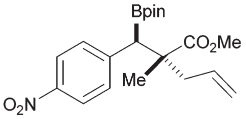

4ba, 53%, dr > 99:1
5b, 14%, dr = 60:40

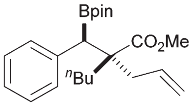

4ca, 63%, dr = 95:5
5c, 10%, dr = 53:47

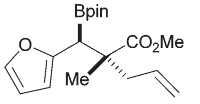

4da, 60%, dr = 99:1
5d, 16%, dr = 58:42

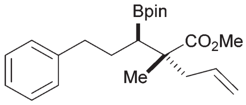

4ea, 67%, dr = 95:5
5e, <1%

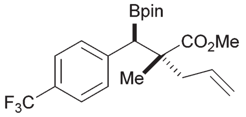

4fa, 48%, dr = 97:3
5f, 7%, dr = 72:28


4ga, 0%; **5g**, 0%


4ha, 66%, dr = 99:1
5h, 8%, dr = 50:50


4ia, 35%, dr = 98:2
5i, <1%

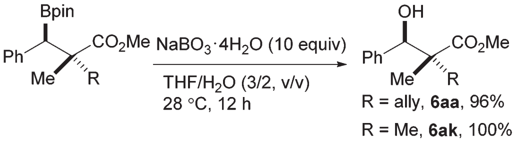

4ja, 27%, dr = 74:26
5j, 22%, dr = 50:50


4ka, 87%, dr = 96:4
5k, 10%, dr = 60:40

[a] Reaction conditions: **1** (0.4 mmol), **2** (0.44 mmol), **3a** (0.8 mmol), CuCl (0.04 mmol), dppe (0.04 mmol), KOMe (0.4 mmol), toluene (0.8 mL), 60 °C, 30 min. Isolated yields are shown for **4** and yields of **5** were determined by ^{1}H NMR analysis of crude products. The dr ratio of **4** is determined by ^{1}H NMR analysis based on the percentage decrease of the integral area of ester methyl or the β proton close to boron, after purification. The dr ratio of **5** is determined by the ^{1}H NMR integral area ratio of ester methyls or β protons close to boron.

erated at a lower dr of 74 : 26. We are pleased to find that substrate **1k**, which contains an electron-withdrawing 4-CF_3 substituent, produces **4ka** in 87% yield (dr = 96 : 4).

In order to illustrate the derivatization of the products, **4aa** and **4ak** are oxidized to the corresponding alcohols **6aa** and **6ak** in 96% and 100% yields, respectively, using $NaBO_3 \cdot H_2O$ in THF/H_2O at 28 °C (eqn (1)). The high yields are probably due to the high stability of the alcohols lacking an α-proton. Using KHF_2 in MeCN/H_2O at 28 °C, **4aa** is transferred to potassium alkyl trifluoroborate (**7**) in 93% yield (eqn (2)). The crystal structure of **7** was studied by single-crystal X-ray structural analysis, and the results indicated that the relative configurations of the two chiral carbons are (2*SR*, 3*RS*) (Fig. 1).



(1)

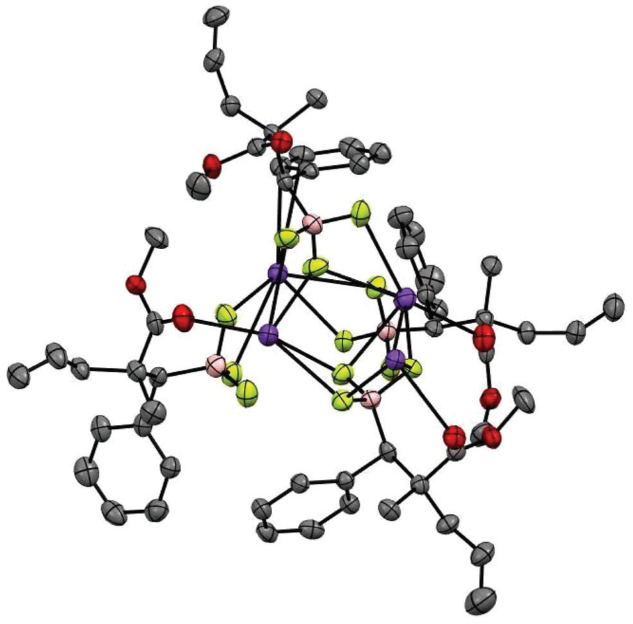
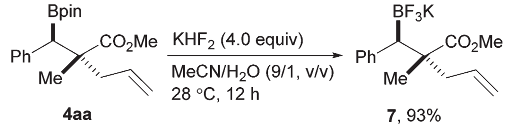
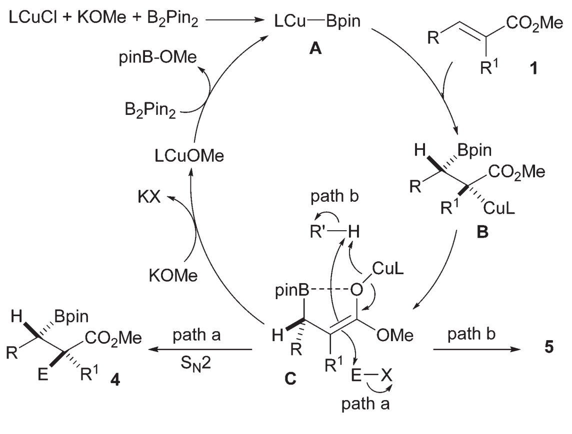


Fig. 1 The asymmetric unit of **7**, with 50% probability displacement ellipsoids. Hydrogen atoms are omitted for clarity.

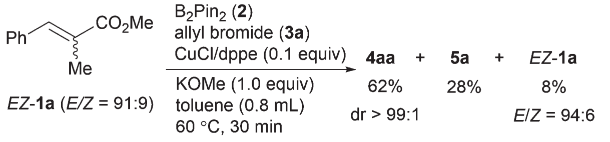


(2)

On the basis of the experimental results and crystal structure of **7**, a plausible reaction mechanism of carboboration is proposed (Scheme 2). The *syn* addition of borylcopper (**A**, formed *in situ* from LCuCl, KOMe, and **2**) to the double bond of substrate **1** produces adduct **B**, which then undergoes a fast tautomerization process to form intermediate **C**. Enolation is facilitated by the α-substituent of **1**. An interaction between boron and the enolate oxygen presumably keeps **C** in a rigid conformation. There are two possible pathways for product formation from **C**. Path a involves an S$_N$2 attack of the less sterically hindered side of **C** by the electrophile E-X (*e.g.*, allyl bromide) to form product **4** and LCuOMe. When the R group in **1** is an aryl group, the large steric hindrance makes an S$_N$2 attack on the opposite side more favorable and only one diastereoisomer is formed. However, when R is a linear alkyl group, such as 2-phenylethyl in **1j**, there is less steric difference between the two sides of **C**, which results in decreased diastereoselectivity. Path b is the protonation of the C- or O-terminal of the enolate, which produces side product **5**.



Scheme 2 A plausible reaction mechanism.



Scheme 3 The effect of *Z*-isomer in **1a** on the diastereoselectivity.

According to the proposed catalytic cycle (Scheme 2), *E*-**1a** and *Z*-**1a** should produce the same diastereoisomer **4aa**. An *EZ* mixture of **1a** (*EZ*-**1a**, *E*/*Z* = 91 : 9) was synthesized and applied to the reaction (Scheme 3). **4aa** is produced in 62% yield with a dr of >99 : 1. *EZ*-**1a** is recovered in 8% yield with *E*/*Z* = 94 : 6. This result provides an additional support for the mechanism.

Conclusions

In summary, we successfully developed Cu-catalyzed, diastereoselective carboboration of α-substituted α,β-unsaturated carboxylic esters.[13] The reaction affords β-boryl-α-quaternary carbon esters in moderate to good yields using a widely available catalyst system under mild reaction conditions. The reaction proceeds through an enolate intermediate, whose less sterically hindered side is attacked by the electrophile to produce the major diastereoisomer. Primary allyl bromides and chlorides, dialkyl sulfates, and benzyl bromides are effective electrophiles in this reaction. The diastereoselectivity of the reaction remarkably depends on the steric effect of the β-substituent of the substrate, that is, a larger substituent leads to higher diastereoselectivity. The major side reaction is hydroboration of the substrate, which is affected by both the substrate and catalyst. A detailed mechanistic study will be helpful in the development of an effective method to further reduce side product formation.

Experimental

General procedure for the copper-catalyzed reaction

In a glovebox, a 5 mL screw-capped reaction vial was charged with CuCl (4.0 mg, 0.04 mmol), Sphos (33 mg, 0.08 mmol), KOMe (30 mg, 0.4 mmol), B$_2$(Pin)$_2$ (122 mg, 0.044 mmol), **1** (0.04 mmol), toluene (0.8 mL), and a stirrer bar. The vial was sealed and moved out of the glove box and heated at 80 °C until the solution changed to a brownish red or black color.

After the temperature was cooled to 28 °C (Tables 1 and 2) or 60 °C (Table 3), the electrophile (**3**, 0.8 mmol) was added through a micro syringe. The reaction mixture was stirred for a specified time (changed to pale yellow). Then the reaction mixture was diluted with DCM and then passed through a short silica gel column (eluent DCM). After evaporation under reduced pressure, the residue was purified by silica gel column chromatography to obtain the desired product.

Derivatization of 4aa and 4ak to 6aa, 6ak

The reaction was conducted according to a reported procedure.[14] A 5 mL vial was charged with **4** (0.5 mmol), $NaBO_3 \cdot 4H_2O$ (5 mmol, 770 mg), THF (0.6 mL), H_2O (0.4 mL), and a stirrer bar. The mixture was stirred at 28 °C for 12 h. The mixture was extracted with ethyl acetate (4 × 1 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography.

Methyl (*SR*)-2-((*SR*)-hydroxy(phenyl)methyl)-2-methylpent-4-enoate (6aa)[15]

6aa was obtained as a colorless viscous liquid (111 mg, 96%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.37–7.21 (m, 5H), 5.75–5.60 (m, 1H), 5.05 (m, 2H), 4.87 (s, 1H), 3.69 (s, 3H), 3.15 (d, *J* = 2.8 Hz, 1H), 2.50 (dd, *J* = 13.5, 7.1 Hz, 1H), 2.00 (dd, *J* = 13.5, 7.5 Hz, 1H), 1.07 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.78, 140.22, 133.35, 127.96, 127.95, 127.70, 118.63, 78.43, 52.10, 51.98, 41.47, 16.24. HRMS (ESI) *m*/*z* calcd for $C_{14}H_{17}O_2$ $(M - OH)^+$ 217.1229, found 217.1235.

Methyl 3-hydroxy-2,2-dimethyl-3-phenylpropanoate (6ak)[16]

6ak was obtained as a white solid (106 mg, 100%), m.p. = 60–62 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 7.41–7.21 (m, 5H), 4.89 (d, *J* = 3.7 Hz, 1H), 3.72 (s, 3H), 3.07 (d, *J* = 3.9 Hz, 1H), 1.14 (s, 3H), 1.11 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.29, 140.12, 127.90, 127.78, 78.85, 52.21, 47.88, 23.16, 19.23.

Methyl (*RS*)-2-methyl-2-((*RS*)-phenyl(trifluoro-boranyl)methyl)pent-4-enoate, potassium salt (7). A 5 mL vial was charged with **4aa** (103 mg, 0.3 mmol), KHF_2 (94 mg, 1.2 mmol), MeCN (2 mL), H_2O (270 μL), and a stirrer bar. The mixture was stirred at 28 °C for 12 h. Then the mixture was concentrated at reduced pressure. The residue was washed with hexane (3 × 1 mL) (discarded). Then the solid residue was washed with MeCN (4 × 1 mL). The MeCN solution was evaporated under reduced pressure and **7** was obtained as a white solid (90 mg, 93%). M.p. = 204–208 °C. Crystals suitable for X-ray structure analysis are prepared by recrystallization from MeCN/Et_2O solution. ^1H NMR (500 MHz, DMSO) δ 7.17 (d, *J* = 7.3 Hz, 1H), 7.08 (t, *J* = 7.4 Hz, 1H), 6.98 (t, *J* = 7.2 Hz, 1H), 5.48 (td, *J* = 17.0, 8.2 Hz, 1H), 4.82 (d, *J* = 9.2, 1H), 4.77 (d, *J* = 17.2, 1H), 3.43 (s, 3H), 2.26 (dd, *J* = 13.3, 6.3 Hz, 1H), 2.05 (d, *J* = 4.5 Hz, 1H), 1.62 (dd, *J* = 13.3, 8.3 Hz, 1H), 1.09 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 177.61, 145.80, 131.43, 126.43, 123.50, 116.22, 78.91 (d, *J* = 33.4 Hz), 50.39, 47.77, 44.19, 19.00.

Conflicts of interest

There are no conflicts of interest to declare.

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8 See the ESI for details. The copper-catalyzed carboboration of the produced tert-butyl ester provide 11% desired product and 80% hydroboration side product. A further study using this reactant was not continued.†

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10 A reaction of **5a** with allyl bromide in the presence of MeOK (1 equiv.) and CuCl (0.05 equiv.) in toluene at 28 °C for 3 h was conducted and no **4aa** was detected by ^{1}H NMR.

11 A control reaction was conducted in the absence of allyl bromide under the otherwise same conditions given in Table 2, and **5a** was produced in 83% yield.

12 See ref. 8.

13 Unsaturated ketones and nitriles were also subjected to the reaction. (*E*)-3-Methyl-4-phenylbut-3-en-2-one and 2-benzylidenebutanenitrile (E/Z = 50 : 50) produce no desired products under the conditions shown in Table 3. The ketone produced a complicated mixture with 35% conversion, and the nitrile was recovered quantitatively.

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