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Copper-Catalyzed Asymmetric Borylation: Construction of a Stereogenic Carbon Center Bearing Both CF_3 and Organoboron Functional Groups

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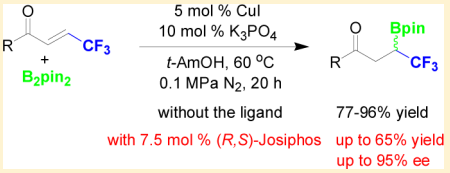
Supporting Information

ABSTRACT: Copper-catalyzed borylation of β-trifluoromethyl-α,β-unsaturated ketones was efficiently achieved by means of bis(pinacolato)diboron (B_2pin_2), affording the enantioenriched products in good yields with high enantioselectivities. CuI and (*R*,*S*)-Josiphos consist of the most efficient catalyst system under mild conditions. In the absence of the chiral ligand, the reactions could be performed more efficiently to form β-ketone derivatives which were directly borylated and indirectly trifluoromethylated at the β-carbon atom of the α,β-unsaturated ketone substrates. The present protocol provides a promising method to access a stereogenic carbon center bearing both CF_3 and organoboron functional groups.



INTRODUCTION

Stereoselective incorporation of a trifluoromethyl unit into organic molecules can lead to significant changes in the physicochemical features and biological properties.[1] Considerable attention has recently been paid to the construction of a chiral center bearing a trifluoromethyl functional group. In this context, two strategies have been employed: (i) direct asymmetric introduction of a CF_3 moiety to a prochiral carbon center through so-called trifluoromethylation;[2] (ii) enantioselective functionalization of prochiral trifluoromethylated compounds.[3] Although the former strategy is straightforward, few examples of asymmetric trifluoromethylation have been documented. To date, the latter has emerged as a powerful tool to obtain optically active trifluoromethylated compounds. β-Trifluoromethyl-α,β-unsaturated ketones can be applied as readily available reagents in asymmetric Michael additions,[4] Diels−Alder reactions,[5] Friedel−Crafts reactions,[6] conjugate additions,[7] and other reactions[8] to enantioselectively synthesize functionalized molecules featuring a CF_3-containing stereogenic carbon center.

Enantioenriched organoboron compounds[9] are potentially applicable for C−O, C−N, and C−C bond formation with retention of their stereogenic centers.[10] Enantioselective conjugate addition of diboron reagents to α,β-unsaturated compounds has been used as one of the most useful methods to access chiral organoboron compounds, in which copper-catalyzed asymmetric borylation is among the most efficient approaches.[9,11] In 2008, Yun et al. reported copper-catalyzed asymmetric borylation of α,β-unsaturated nitriles and esters for the first time.[12] Since then, highly enantioselective additions of diboron reagents to a variety of electron-deficient olefins such as α,β-unsaturated esters,[13] ketones,[14] amides,[15] sulfones,[16] phosphine oxides,[17] and also $\alpha,\beta,\gamma,\delta$-unsaturated compounds,[18] or *p*-quinone methides[19] have been reported under copper catalysis. Other transition-metal-catalyzed systems[20] and organocatalytic methods[21] have also been documented for the same purpose. However, asymmetric conjugate addition of diborons to CF_3-substituted α,β-unsaturated ketones has not yet been reported.[22] During our onging investigation of trifluoromethylation, we became interested in the challenging asymmetric borylation of CF_3-functionalized α,β-unsaturated ketones. Herein, we disclose copper(I)-catalyzed enantioselective borylation of β-trifluoromethyl-α,β-unsaturated ketones with bis(pinacolato)diboron (B_2pin_2) (Scheme 1).

RESULTS AND DISCUSSION

Initially, the reaction of (*E*)-4,4,4-trifluoro-1-*p*-tolylbut-2-en-1-one (**1a**) with B_2pin_2 (**2**) in a 1.0:1.1 molar ratio was carried out to screen the reaction conditions (Table 1). In the presence of 5 mol % CuI as the catalyst, 10 mol % K_3PO_4 as the base, and a stoichiometric amount of methanol (2 equiv) as the hydrogen source in THF at 60 °C, the reaction did not occur to give the target product **3a** within 20 h (Table 1, entry 1). However, the reaction proceeded smoothly in an alcohol solvent. Among the screened alcohols, MeOH, EtOH, and *i*-PrOH facilitated the reaction to give **3a** in 48−58% yields (Table 1, entries 2−4). When the solvent was changed to a bulky alcohol, that is, *t*-BuOH, the yield of **3a** was dramatically enhanced to 93%, and *t*-AmOH was found to improve the reaction further to afford **3a** in 95% isolated yield (Table 1, entries 5 and 6). CuI acted as the most efficient catalyst among

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Scheme 1. Enantioselective Borylation of Electron-Deficient Olefins

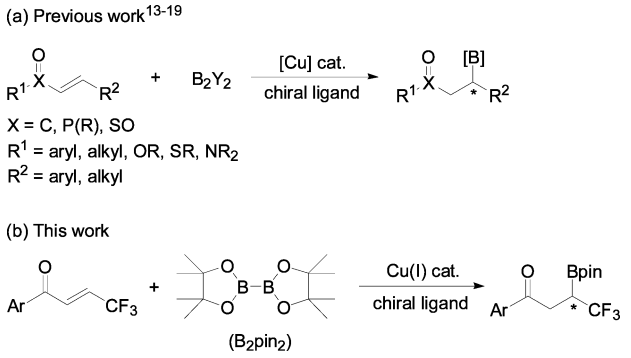
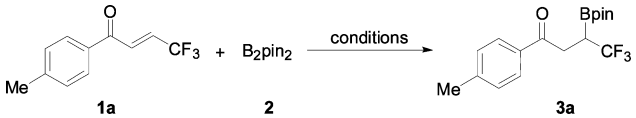


Table 1. Screening of Conditions[a]



entry	[Cu] cat. (mol %)	solvent	temp (°C)	yield[b] (%)
1[c]	CuI (5.0)	THF	60	0
2	CuI (5.0)	MeOH	60	58
3	CuI (5.0)	EtOH	60	48
4	CuI (5.0)	*i*-PrOH	60	57
5	CuI (5.0)	*t*-BuOH	60	93
6	CuI (5.0)	*t*-AmOH	60	99 (95)[d]
7	CuCl (5.0)	*t*-AmOH	60	92
8	CuBr (5.0)	*t*-AmOH	60	94
9	CuI (5.0)	*t*-AmOH	50	93
10[e]	CuI (2.5)	*t*-AmOH	60	94

[a]Conditions: **1a** (0.2 mmol), **2** (0.22 mmol), K_3PO_4 (10 mol %), solvent (2 mL), 60 °C, 0.1 MPa N_2, 20 h. [b]Yield determined by ^1H NMR analysis using CH_2Br_2 as the internal standard. [c]2.0 equiv MeOH were added. [d]Isolated yield given in parentheses. [e]Using 5 mol % K_3PO_4.

the screened copper(I) salts CuX (X = Cl, Br, I) (Table 1, entries 7 and 8). Lowering the temperature to 50 °C or using less catalyst (2.5 mol %) slightly reduced the reaction efficiency (Table 1, entries 9 and 10).

With the optimized conditions in hand, the substrate scope of *β*-trifluoromethyl-*α*,*β*-unsaturated ketones (**1**) was explored (Table 2). Ketones **1** bearing a phenyl or an aryl moiety substituted by electron-donating groups such as methyl and methoxy(s) reacted with **2** to afford the target products **3a**−**3h** in excellent yields (93−96%) (Table 2, entries 1−8). Both the position and number of the substituents on the aromatic ring had no obvious impact on the reaction efficiency. Although 4-fluoro- and 4-chloro-substituted substrates efficiently underwent the reactions to form **3i** (95%) and **3l** (92%) (Table 2, entries 9 and 12), respectively, 3-fluoro, 2-fluoro, and 4-bromo substituents deteriorated the product yields for **3j**, **3k**, and **3m** (77−88%) (Table 2, entries 10, 11, and 13). It is noteworthy that electron-withdrawing substituents demonstrated a negative impact. The reaction of the substrate bearing an ester group with **2** occurred to afford **3n** in 85% yield (Table 2, entry 14), and the strong electron-withdrawing nitro substituent exhibited a remarkably negative substituent effect on the formation of the target product **3o** (<5% yield) (Table 2, entry 15). Bulky 1- and 2-naphthyl *β*-trifluoromethyl-*α*,*β*-unsaturated ketones also exhibited good reactivity to B_2pin_2, and their reactions produced the borylated products **3p** and **3q** in 95% yield (Table 2, entries 16 and 17). 2-Thienyl-functionalized ketone **1r** behaved the same to efficiently react with **2** to generate the target product **3r** (95%) (Table 2, entry 18). In a similar fashion, the alkyl *β*-trifluoromethyl-*α*,*β*-unsaturated ketone, i.e., **1s**, reacted with **2** to form product **3s** in 90% yield (Table 2, entry 19). However, *β*,*β*-disubstituted *β*-CF_3-enone **1t** did not undergo the reaction with **2** presumably due to the steric effect (Table 2, entry 20).

Next, the enantioselective addition of B_2pin_2 (**2**) to *β*-trifluoromethyl-*α*,*β*-unsaturated ketones (**1**) was tested by using **1a** as the model substrate. First, the reaction was conducted under Yun's conditions,[12] that is, using CuCl as the catalyst, (*R*,*S*)-Josiphos as the ligand, and NaO*t*-Bu as the base in the presence of 2 equiv of MeOH in THF. Unexpectedly, the reaction did not occur. However, under the conditions similar to those as shown in Table 2 and in the presence of a chiral ligand, the reaction proceeded smoothly to give the target product **3a** (Table 3). The product yield and stereoselectivity were highly dependent on the chiral ligand employed in the reaction. With an axially chiral bisphosphine ligand such as (*S*)-BINAP (**L1**), **3a** was only obtained in 8% yield (Table 3, entry 1). (*S*,*S*)-Me-Duphos (**L2**) did not promote the desired reaction, but it facilitated the side reaction to form defluoroborane **4** in 25% yield (Table 3, entry 2). Use of (*S*,*S*,*R*,*R*)-Tangphos (**L3**) led to **3a** (35%) with 21% ee as well as **4** (24%) as the byproduct (Table 3, entry 3). Ferrocene-based phosphane ligands were then screened. In the case using (*R*,*S*)-Josiphos (**L4**), a good isolated yield (63%) and excellent enantioselectivity (93%) were achieved (Table 3, entry 4). (*R*)-(*S*)-NMe_2-PPh_2-Mandyphos (**L5**) rendered formation of the product in a higher yield, but the ee value was very low (Table 3, entry 5). (*R*,*R*)-Walphos (**L6**) was not an effective ligand for the asymmetric reaction either (Table 3, entry 6). Use of (*S*,*S*)-Taniaphos (**L7**) led to excellent enantioselectivity (98% ee), while the yield of **3a** was much lower than that obtained by using **L4** as the ligand (Table 3, entry 7). Among the screened copper salt catalysts, CuI promoted the reaction most efficiently (Table 3, entries 4, 8, and 9). K_3PO_4 behaved more effectively than Na_2CO_3, K_2CO_3, or NaO*t*-Bu as the base for the reaction (Table 3, entries 10−12). Variation of temperature to 50 or 80 °C deteriorated the yield of chiral **3a** (Table 3, entries 13 and 14). When the reaction was conducted at ambient temperature (25 °C), the yield of **3a** was sharply decreased to 33% (Table 3, entry 15). It should be noted that, under the stated conditions, formation of the byproduct, that is, compound **4**, led to the chiral product (*S*)-**3a** formed in a yield much lower than that for the corresponding racemic product **3a** (Table 2). It was confirmed that treatment of (*S*)-**3a** in the absence of B_2pin_2 under the optimized conditions resulted in defluoroborane **4** in 26% yield (eq 1). The formation of defluoroborane **4** is presumably attributed to *β*-fluoride elimination of an *in situ* generated unstable trifluoroethyl anion.[22a,23]

The protocol generality for the enantioselective borylation was then investigated under the optimal conditions. The yields and enantioselectivities were obviously affected by the electronic and steric effects from the substituent(s) on the aryl moiety of the ketone substrates. *β*-Trifluoromethyl-*α*,*β*-unsaturated ketones **1** bearing a phenyl or an aryl moiety substituted by a 4- or 3-electron-donating group underwent the asymmetric addition with **2** to yield the target products **3a**−**3f** in good yields (50−63%) with excellent enantioselectivity (91−95%)

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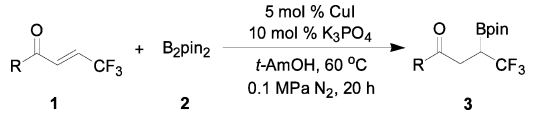
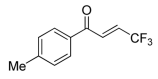
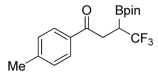
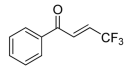
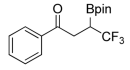
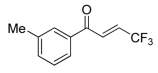
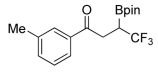
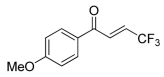
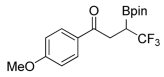
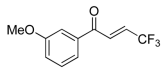
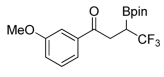
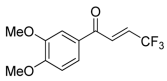
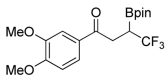
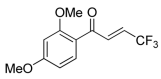
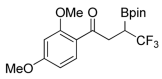
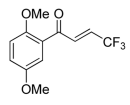
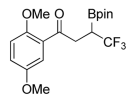
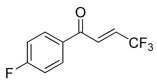
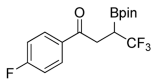
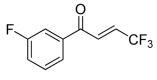
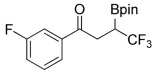
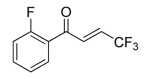
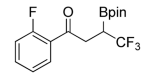
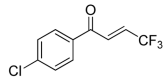
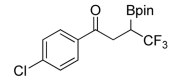
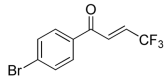
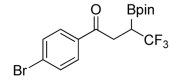
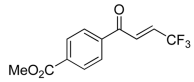
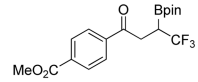
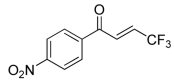
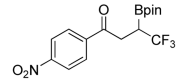
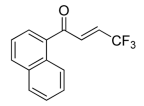
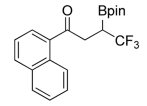
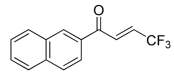
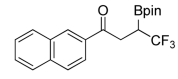
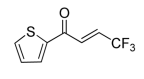
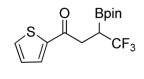
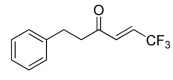
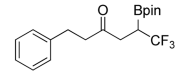
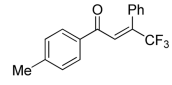
Table 2. Borylation of β-Trifluoromethyl-α,β-unsaturated Ketones (1) with 2[a]



1 2 3

entry	1	3	yield[b] (%)
1	 **1a**	 **3a**	95
2	 **1b**	 **3b**	96
3	 **1c**	 **3c**	96
4	 **1d**	 **3d**	94
5	 **1e**	 **3e**	96
6	 **1f**	 **3f**	94
7	 **1g**	 **3g**	93
8	 **1h**	 **3h**	95
9	 **1i**	 **3i**	95
10	 **1j**	 **3j**	77
11	 **1k**	 **3k**	87
12	 **1l**	 **3l**	92
13	 **1m**	 **3m**	88
14	 **1n**	 **3n**	85
15	 **1o**	 **3o**	<5[c]
16	 **1p**	 **3p**	95
17	 **1q**	 **3q**	95
18	 **1r**	 **3r**	95
19	 **1s**	 **3s**	90
20	 **1t**	**3t**	0

[a]Conditions: **1** (0.2 mmol), **2** (0.22 mmol), *t*-AmOH (2 mL), 60 °C, 0.1 MPa N_2, 20 h. [b]Yield refers to the isolated product. [c]Yield determined by ^{1}H NMR ($CDCl_3$) analysis using CH_2Br_2 as the internal standard.

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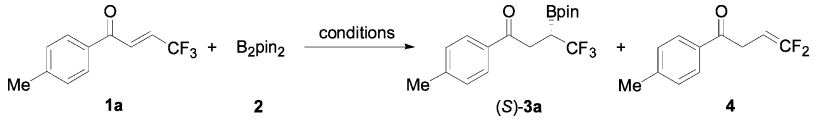
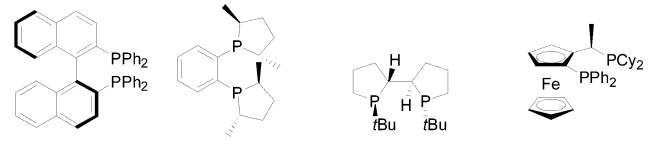
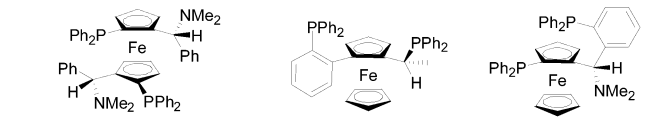
Table 3. Optimization of Conditions for the Enantioselective Borylation of 1a with 2[a]

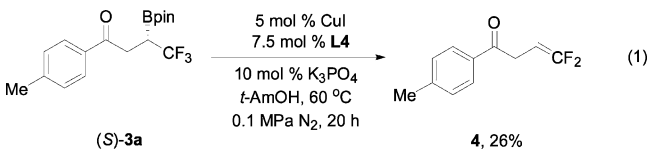


entry	[Cu] cat.	ligand	3a (%)[b]	4 (%)[b]	ee of 3a (%)[c]
1	CuI	**L1**	8	<5	ND
2	CuI	**L2**	<5	25	ND
3	CuI	**L3**	35	24	21
4	CuI	**L4**	65 (63)[d]	35	93
5	CuI	**L5**	68	<5	−6
6	CuI	**L6**	9	<5	ND
7	CuI	**L7**	41	<5	−98
8	CuCl	**L4**	9	<5	ND
9	CuBr	**L4**	58	35	93
10[e]	CuI	**L4**	53	34	93
11[f]	CuI	**L4**	47	35	93
12[g]	CuI	**L4**	26	14	93
13[h]	CuI	**L4**	57	35	93
14[i]	CuI	**L4**	55	32	93
15[j]	CuI	**L4**	33	20	93

[a]Conditions: **1a** (0.2 mmol), **2** (0.22 mmol), [Cu] cat. (5 mol %), ligand (7.5 mol %), K_3PO_4 (10 mol %), *t*-AmOH (2 mL), 60 °C, 0.1 MPa N_2, 20 h. [b]Yield determined by ^1H NMR analysis using CH_2Br_2 as the internal standard. [c]Determined by chiral HPLC analysis using an AD-H column. [d]Isolated yield given in parentheses. [e]Using Na_2CO_3 base. [f]Using K_2CO_3 base. [g]Using NaO*t*-Bu base. [h]50 °C. [i]80 °C. [j]25 °C. ND = Not Determined.

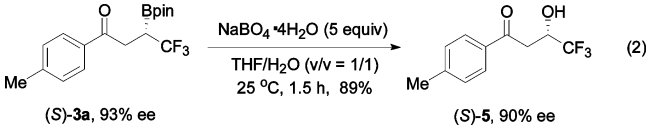






(Table 4, entries 1−6), while the presence of a steric 2-methoxy group lessened the enantioselectivities of **3g** (76%) and **3h** (80%) (Table 4, entries 7 and 8). Electron-withdrawing substituents exhibited a negative substituent effect on the reaction efficiency. Although 4-fluoro-substituted substrate **1i** reacted with **2** to form **3i** in 51% yield with 92% ee (Table 4, entry 9), 3- or 2-fluoro, 4-chloro, and 4-bromo substituents on the aryl moiety deteriorated both the yields and enantioselectivities of the target products **3j**−**3m** (Table 4, entries 10−13). Ketone **1n** bearing an ester substituent exhibited poor reactivity to **2**, and the reaction only afforded (−)-**3n** in 17% yield with 52% ee (Table 4, entry 14). The fused ring-bearing substrates underwent the same type of reactions, furnishing the corresponding products **3p** and **3q** (Table 4, entries 15 and 16). 2-Thienyl-*β*-trifluoromethyl-*α*,*β*-unsaturated ketone also showed good reactivity to **2**, and their reaction gave the target product **3r** (56%) with 94% ee (Table 4, entry 17). Unexpectedly, alkyl *β*-trifluoromethylated-*α*,*β*-unsaturated ketone **1s** did not react with **2** in the presence of chiral ligand **L4** under the standard conditions (Table 4, entry 18), while it reacted well with **2** to form the racemic product **3s** (Table 2, entry 19).

The absolute configurations of the chiral products were determined by derivatization of the resultant product **3a** obtained from the borylation of **1a** with **2** in the presence of chiral ligand (*R*,*S*)-Josiphos (**L4**), that is, conversion of (*S*)-**3a** to the corresponding *β*-hydroxy ketone **5** through oxidation with sodium perborate. Compound **5** was assigned to be (*S*)-configuration by comparison of its optical rotation with the reported data.[24] Thus, chiral **3a** was assigned to be the (*S*)-configuration at its stereocenter (eq 2), and the configurations of other chiral borylation products were assigned by analogy to compound (*S*)-**3a**.



Other transformations of the borylation products were also tried. Treatment of **3a** with BCl_3 followed by addition of benzyl azide in dichloromethane at 0 °C did not generate the BnNH-substituted trifluoromethylated ketone as expected.[25]

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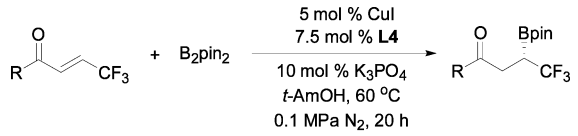
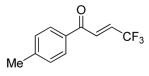
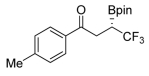
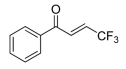
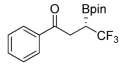
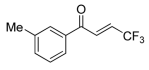
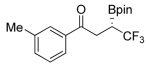
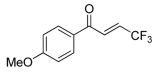
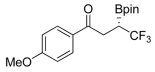
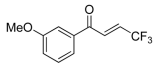
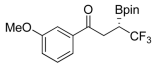
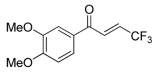
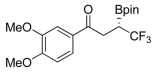
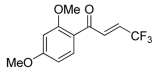
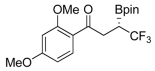
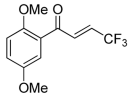
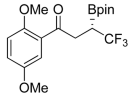
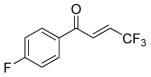
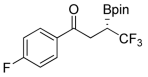
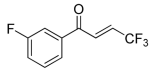
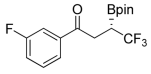
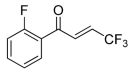
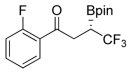
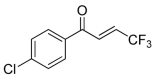
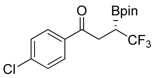
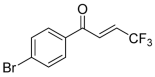
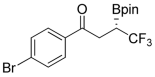
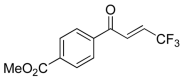
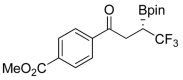
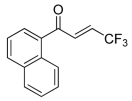
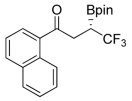
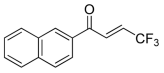
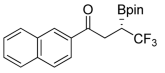
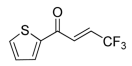
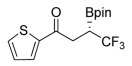
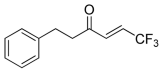
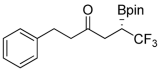
Table 4. Enantioselective Borylation of β-Trifluoromethyl-α,β-unsaturated Ketones (1)[a]



1 2 3

entry	1	3	yield (%)[b]	ee (%)[c]
1	 **1a**	 **(*S*)-3a**	65	93
2	 **1b**	 **(-)-3b**	51	93
3	 **1c**	 **(-)-3c**	58	91
4	 **1d**	 **(-)-3d**	61	95
5	 **1e**	 **(-)-3e**	60	91
6	 **1f**	 **(-)-3f**	50	93
7	 **1g**	 **(-)-3g**	53	76
8	 **1h**	 **(-)-3h**	40	80
9	 **1i**	 **(-)-3i**	51	92
10	 **1j**	 **(-)-3j**	37	72
11	 **1k**	 **(-)-3k**	40	76
12	 **1l**	 **(-)-3l**	35	85
13	 **1m**	 **(-)-3m**	27	86
14	 **1n**	 **(-)-3n**	17	52
15	 **1p**	 **(-)-3p**	52	86
16	 **1q**	 **(+)-3q**	60	92
17	 **1r**	 **(-)-3r**	56	94
18	 **1s**	 **(-)-3s**	0	

[a]Conditions: **1** (0.2 mmol), **2** (0.22 mmol), *t*-AmOH (2 mL), 60 °C, 0.1 MPa N_2, 20 h. [b]Yield refers to the isolated product. [c]Determined by chiral HPLC analysis using an AD-H column.

Reacting **3a** with aqueous KHF_2[15c] afforded the corresponding trifluoroborate **6**, which could not undergo further transformations in toluene or dioxane under the typical Suzuki coupling conditions (Scheme 2). These results may be attributed to the low nucleophilicity of the substrate bearing such a CF_3 group and the undesirable β-fluoride elimination. To overcome these limitations, Molander and co-workers recently developed a photoredox/nickel dual catalytic method for the cross-coupling of α-trifluoromethylated trifluoroborates with aryl bromides.[26] Thus, the reaction of compound **6** with 4-bromobenzonitrile was performed under Molander's conditions. Unfortunately, the reaction did not occur (see the Supporting Information for details). Considering tetrahydroxydiboron ($B_2(OH)_4$) as an atom-economical diboron source as compared to bis(pinacolato)diboron (**2**),[5] the borylation of **3a** with $B_2(OH)_4$ was performed in a similar fashion. In order to facilitate the product isolation and analysis, the resultant boronic acid **8** was directly converted to the corresponding β-hydroxy ketone **5** (30%) by oxidation with $NaBO_4$ (Scheme 3). In this case, tetrahydroxydiboron is inferior to B_2pin_2 as the diboron source.

In conclusion, we have developed copper-catalyzed borylation of β-trifluoromethyl-α,β-unsaturated ketones with

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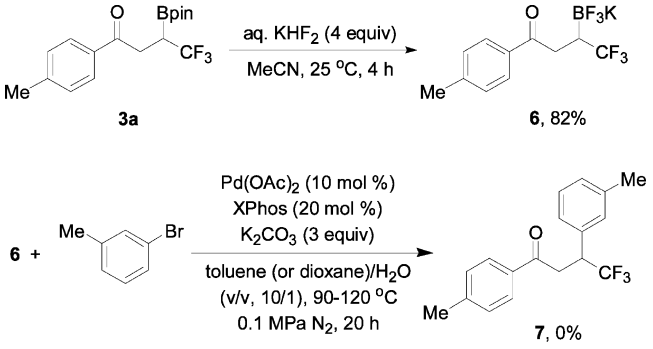
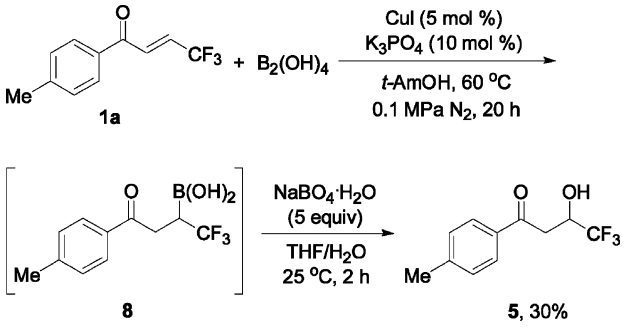
Scheme 2. Synthesis of Trifluoroborate 6 and Its Suzuki Coupling



Scheme 3. Borylation of 3a with Tetrahydroxydiboron



bis(pinacolato)diboron. Under the mild conditions, diverse borylated CF_3-based products could be obtained in high yields. Moreover, the methodology can be extended to an asymmetric version in the presence of a chiral ligand, affording the chiral products with a stereogenic carbon center bearing both CF_3 and orgonoboron functional groups. The present protocol provides a promising method to access enantioenriched organoboron compounds bearing a CF_3 functionality.

EXPERIMENTAL SECTION

General Considerations. The solvents were dried and distilled prior to use by the literature methods. ^{1}H, ^{13}C, ^{19}F, and ^{11}B NMR spectra were recorded on a 400 MHz NMR spectrometer. HRMS data were obtained by ESI on a Q-TOF mass spectrometer. The enantiomeric excess was determined by chiral HPLC analysis. Optical rotations were measured by an olarimeter. All the chemical reagents were purchased from commercial sources and used as received unless otherwise indicated. Compounds **1a**–**1e** and **1i**,[27] **1k**,[6a] **1l**,[27] **1m**,[28] **1n**,[29] **1o**,[27] **1p**,[28] **1q** and **1r**,[27] **1s**,[30] and **1t**[31] were known and prepared as reported.

A Typical Procedure for the Synthesis of 1: Synthesis of 1f. A mixture of trifluoroacetaldehyde ethyl hemiacetal (1.44 g, 10.0 mmol) and pyrrolidine (0.49 g, 7.0 mmol) in THF (20 mL) was stirred at ambient temperature for 30 min. Then 1-(3,4-dimethoxyphenyl)-ethanone (1.80 g, 10.0 mmol) was added to the resultant solution in one portion. Stirring was continued at reflux for 48 h. After cooled to ambient temperature, all the volatiles were evaporated under reduced pressure. The resulting residue was purification by silica gel column chromatography (eluent: petroleum ether (60–90 °C)/EtOAc = 10:1, v/v) to afford 1-(3,4-dimethoxyphenyl)-4,4,4-trifluoro-3-hydroxybutan-1-one as a liquid (1.19 g, 43%). The mixture of 1-(3,4-dimethoxyphenyl)-4,4,4-trifluoro-3-hydroxybutan-1-one (1.19 g, 4.3 mmol), *p*-toluenesulfonic acid (0.57 g, 3.0 mmol), and anhydrous $MgSO_4$ (5 g) in toluene (30 mL) was stirred at reflux for 24 h. After cooling to ambient temperature, the resultant mixture was filtered and rinsed with 10 mL toluene. All the volatiles were evaporated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (eluent: petroleum ether (60–90 °C)/EtOAc = 100:4, v/v) to afford **1f** as a yellow solid (0.92 g, 82%).

(E)-1-(3,4-Dimethoxyphenyl)-4,4,4-trifluorobut-2-en-1-one ***(1f).*** 1.19 g, 43% yield for the first step; 0.92 g, 82% yield for the second step; yellow solid, mp 33–35 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (dd, J = 8.4, 1.9 Hz, 1 H), 7.54–7.50 (m, 2 H), 6.91 (d, J = 8.4 Hz, 1 H), 6.82–6.73 (m, 1 H), 3.95 and 3.93 (s each, 3:3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.2, 154.5, 149.7, 131.0 (q, J = 5.6 Hz), 129.59 (q, J = 34.8 Hz), 129.58, 124.1, 122.8 (q, J = 268.2 Hz), 110.6, 110.2, 56.3, 56.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ −65.0; IR (KBr pellet) 3087, 3002, 2969, 2943, 2842, 1680, 1633, 1604, 1511, 957, 809 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{12}F_3O_3$ $[M + H]^+$ 261.0733, found 261.0730.

(E)-1-(2,4-Dimethoxyphenyl)-4,4,4-trifluorobut-2-en-1-one ***(1g).*** 0.72 g, 26% yield for the first step; 0.37 g, 55% yield for the second step; pale yellow solid, mp 43–45 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.8 Hz, 1 H), 7.53 (dq, J = 15.6, 2.0 Hz, 1 H), 6.62 (dq, J = 15.5, 6.9 Hz, 1 H), 6.54 (dd, J = 8.8, 2.2 Hz, 1 H), 6.44 (d, J = 2.2 Hz, 1 H), 3.87 and 3.85 (s each, 3:3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.4, 165.7, 161.4, 136.4 (q, J = 5.8 Hz), 133.5, 126.6 (q, J = 34.4 Hz), 123.2 (q, J = 268.0 Hz), 120.1, 106.1, 98.4, 55.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −64.8; IR (KBr pellet) 3074, 2981, 2952, 2846, 1676, 1642, 1600, 1502, 890, 830 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{12}F_3O_3$ $[M + H]^+$ 261.0733, found 261.0745.

(E)-1-(2,5-Dimethoxyphenyl)-4,4,4-trifluorobut-2-en-1-one ***(1h).*** 1.28 g, 46% yield for the first step; 0.77 g, 64% yield for the second step; yellow solid, mp 39–41 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (dq, J = 15.6, 1.9 Hz, 1 H), 7.22 (d, J = 3.2 Hz, 1 H), 7.05 (dd, J = 9.0, 3.2 Hz, 1 H), 6.89 (d, J = 9.1 Hz, 1 H), 6.63 (dq, J = 15.6, 6.8 Hz, 1 H), 3.83 and 3.75 (s each, 3:3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.1, 153.83, 153.79, 135.8 (q, J = 5.8 Hz), 127.2 (q, J = 34.6 Hz), 127.1, 123.0 (q, J = 268.1 Hz), 121.7, 114.3, 113.5, 56.1, 55.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ −65.0; IR (KBr pellet) 3083, 3007, 2966, 2950, 2836, 1677, 1638, 1608, 1577, 1500, 805 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{12}F_3O_3$ $[M + H]^+$ 261.0733, found 261.0740.

(E)-4,4,4-Trifluoro-1-(3-fluorophenyl)but-2-en-1-one ***(1j).*** 0.57 g, 24% yield for the first step; 0.21 g, 40% yield for the second step; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85–7.81 (m, 1 H), 7.60–7.55 (m, 1 H), 7.43–7.38 (m, 1 H), 7.28–7.24 (m, 1 H), 7.18–7.13 (m, 1 H), 6.75 (dqd, J = 14.7, 6.7, 1.3 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.4, 162.0 (d, J = 253.5 Hz), 135.8 (d, J = 9.1 Hz), 134.3 (dq, J = 11.5, 5.7 Hz), 131.3 (d, J = 1.8 Hz), 129.8 (q, J = 34.7 Hz), 125.2 (d, J = 12.1 Hz), 125.0 (d, J = 3.3 Hz), 122.7 (q, J = 268.5 Hz), 116.9 (d, J = 22.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −65.3, −109.8; IR (KBr pellet) 3083, 1684, 1650, 1600, 1510, 1415, 735 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_7F_4O$ $[M + H]^+$ 219.0428, found 219.0427.

A Typical Procedure for the Borylation of *β*-Trifluoromethyl-*α,β*-unsaturated Ketones (1) with B_2pin_2 (2): Synthesis of 3a. To a 25 mL Schlenk tube were successively added CuI (1.9 mg, 0.01 mmol), B_2pin_2 (**2**) (56 mg, 0.22 mmol), K_3PO_4 (4.2 mg, 0.02 mmol), and the tube was then evacuated and purged with N_2 three times. *t*-AmOH (1.5 mL) was added, and the mixture was stirred at ambient temperature for 30 min, followed by the addition of (*E*)-4,4,4-trifluoro-1-*p*-tolylbut-2-en-1-one (**1a**) (43 mg, 0.20 mmol) in *t*-AmOH (0.5 mL). The resultant mixture was warmed up to 60 °C and stirred for 20 h. After cooling to ambient temperature, the resultant mixture was filtered through a short pad of Celite and rinsed with 20 mL of EtOAc. All the volatiles were removed under reduced pressure, and the resulting residue was purified by silica gel column chromatography (eluent: petroleum ether (60–90 °C)/EtOAc = 60:1, v/v) to afford **3a** as a white solid (65 mg, 95%).

A Typical Procedure for the Enantioselective Borylation of *β*-Trifluoromethyl-*α,β*-unsaturated Ketones (1) with B_2pin_2 (2): Synthesis of (*S*)-3a. To a 25 mL Schlenk tube were successively added CuI (1.9 mg, 0.01 mmol), (*R,S*)-Josiphos (9.6 mg, 0.015 mmol), and K_3PO_4 (4.2 mg, 0.02 mmol), and the tube was then evacuated and purged with N_2 three times. *t*-AmOH (1.0 mL) was added, and the mixture was stirred at ambient temperature for 30 min, followed by the

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addition of B_2pin_2 (**2**) (56 mg, 0.22 mmol) in *t*-AmOH (0.5 mL). After the mixture was stirred at ambient temperature for 10 min, (*E*)-4,4,4-trifluoro-1-*p*-tolylbut-2-en-1-one (**1a**) (43 mg, 0.20 mmol) in *t*-AmOH (0.5 mL) was then added. The resultant mixture was warmed up to 60 °C to and stirred for 20 h. After cooled to ambient temperature, the reaction mixture was filtered through a short pad of Celite and rinsed with 20 mL of EtOAc. All the volatiles were removed under reduced pressure, and the resulting residue was purified by silica gel column chromatography (eluent: petroleum ether (60−90 °C)/EtOAc = 60:1, v/v) to afford (*S*)-**3a** as a white solid (43 mg, 63%).

*4,4,4-Trifluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-p-tolylbutan-1-one (**3a**).* 65 mg, 95% yield; white solid, mp 78−80 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 8.1 Hz, 2 H), 7.29 (d, J = 8.0 Hz, 2 H), 3.50−3.38 (m, 2 H), 2.44 (s, 3 H), 2.41−2.34 (m, 1 H), 1.32 and 1.27 (s each, 6:6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.4, 144.6, 133.5, 129.5, 128.4, 128.3 (q, J = 275.4 Hz), 84.3, 35.2 (d, J = 2.7 Hz), 24.7, 24.5, 21.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.6; ^{11}B NMR (128 MHz, $CDCl_3$) δ 31.2; IR (KBr pellet) 2985, 2922, 1680, 1608, 1574, 1376, 813 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{23}BF_3O_3$ $[M + H]^+$ 343.1687, found 343.1692.

*(S)-4,4,4-Trifluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-p-tolylbutan-1-one ((S)-**3a**).* 43 mg, 63% yield; 93% ee, $[\alpha]^{20}_D$ = −7.0 (*c* 0.2 $CHCl_3$); HPLC (AD-H, elute: Hexanes/*i*-PrOH = 98/2, detector: 220 nm, flow rate: 0.7 mL/min), t_1 = 6.2 min (maj.), t_2 = 8.7 min.

*4,4,4-Trifluoro-1-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-1-one (**3b**).* 63 mg, 96% yield; white solid, mp 59−61 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, J = 5.2, 3.4 Hz, 2 H), 7.61−7.57 (m, 1 H), 7.49−7.45 (m, 2 H), 3.50−3.37 (m, 2 H), 2.44−2.31 (m, 1 H), 1.30 and 1.25 (s each, 6:6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.8, 136.1, 133.7, 128.8, 128.29 (q, J = 275.3 Hz), 128.28, 84.4, 35.3 (d, J = 2.8 Hz), 24.7, 24.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.6; ^{11}B NMR (128 MHz, $CDCl_3$) δ 31.3; IR (KBr pellet) 3002, 2981, 1686, 1600, 1579, 1385, 759, 690 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{21}BF_3O_3$ $[M + H]^+$ 329.1530, found 329.1531.

*(−)-4,4,4-Trifluoro-1-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-1-one ((−)-**3b**).* 33 mg, 51% yield; 93% ee, $[\alpha]^{20}_D$ = −6.0 (*c* 0.2 $CHCl_3$); HPLC (AD-H, elute: Hexanes/*i*-PrOH = 98/2, detector: 220 nm, flow rate: 0.7 mL/min), t_1 = 5.8 min (maj.), t_2 = 8.0 min.

*4,4,4-Trifluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-m-tolylbutan-1-one (**3c**).* 66 mg, 96% yield; colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77−7.75 (m, 2 H), 7.41−7.33 (m, 2 H), 3.49−3.37 (m, 2 H), 2.41 (s, 3 H), 2.40−2.30 (m, 1 H), 1.30 and 1.25 (s each, 6:6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.9, 138.6, 136.1, 134.4, 128.8, 128.7, 128.3 (q, J = 275.4 Hz), 125.5, 84.4, 35.4 (d, J = 2.7 Hz), 24.7, 24.5, 21.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.6; ^{11}B NMR (128 MHz, $CDCl_3$) δ 31.3; IR (in dichloromethane) 2981, 2928, 1686, 1605, 1586, 1373, 788, 693 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{23}BF_3O_3$ $[M + H]^+$ 343.1687, found 343.1684.

*(−)-4,4,4-Trifluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-m-tolylbutan-1-one ((−)-**3c**).* 40 mg, 58% yield; 91% ee, $[\alpha]^{20}_D$ = −6.5 (*c* 0.2 $CHCl_3$); HPLC (AD-H, elute: Hexanes/*i*-PrOH = 98/2, detector: 220 nm, flow rate: 0.7 mL/min), t_1 = 5.2 min (maj.), t_2 = 6.0 min.

*4,4,4-Trifluoro-1-(4-methoxyphenyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-1-one (**3d**).* 67 mg, 94% yield; white solid, mp 67−69 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 and 6.93 (d each, J = 8.9 Hz, 2:2 H), 3.87 (s, 3 H), 3.44−3.35 (m, 2 H), 2.39−2.27 (m, 1 H), 1.30 and 1.24 (s each, 6:6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 164.0, 130.6, 129.0, 128.4 (q, J = 275.4 Hz), 114.0, 84.3, 55.6, 35.0 (d, J = 2.6 Hz), 24.7, 24.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.6; ^{11}B NMR (128 MHz, $CDCl_3$) δ 30.9; IR (KBr pellet) 2975, 2853, 1678, 1600, 1510, 1376, 843 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{23}BF_3O_4$ $[M + H]^+$ 359.1636, found 359.1639.

*(−)-4,4,4-Trifluoro-1-(4-methoxyphenyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-1-one ((−)-**3d**).* 44 mg, 61% yield; 95% ee, $[\alpha]^{20}_D$ = −4.0 (*c* 0.05 $CHCl_3$); HPLC (AD-H, elute: Hexanes/*i*-PrOH = 98/2, detector: 220 nm, flow rate: 0.7 mL/min), t_1 = 8.3 min (maj.), t_2 = 13.0 min.

*4,4,4-Trifluoro-1-(3-methoxyphenyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-1-one (**3e**).* 69 mg, 96% yield; white solid, mp 70−72 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 7.7 Hz, 1 H), 7.48−7.47 (m, 1 H), 7.38 (t, J = 7.9 Hz, 1 H), 7.13 (dd, J = 8.2, 2.3 Hz, 1 H), 3.85 (s, 3 H), 3.48−3.36 (m, 2 H), 2.43−2.30 (m, 1 H), 1.30 and 1.24 (s each, 6:6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.6, 160.0, 137.4, 129.8, 128.3 (Cq, J = 275.2 Hz), 120.9, 120.1, 112.5, 84.4, 55.6, 35.4 (d, J = 2.8 Hz), 24.7, 24.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.6; ^{11}B NMR (128 MHz, $CDCl_3$) δ 31.4; IR (KBr pellet) 2978, 2847, 1686, 1605, 1582, 1379, 776, 760 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{23}BF_3O_4$ $[M + H]^+$ 359.1636, found 359.1639.

*(−)-4,4,4-Trifluoro-1-(3-methoxyphenyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-1-one ((−)-**3e**).* 43 mg, 60% yield; 91% ee, $[\alpha]^{20}_D$ = −11.0 (*c* 0.2 $CHCl_3$); HPLC (AD-H, elute: Hexanes/*i*-PrOH = 98/2, detector: 220 nm, flow rate: 0.7 mL/min), t_1 = 6.3 min (maj.), t_2 = 7.9 min.

*1-(3,4-Dimethoxyphenyl)-4,4,4-trifluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-1-one (**3f**).* 73 mg, 94% yield; colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 8.4 Hz, 1 H), 7.47 (s, 1 H), 6.87 (d, J = 8.4 Hz, 1 H), 3.92 and 3.90 (s each, 3:3 H), 3.43−3.34 (m, 2 H), 2.37−2.25 (m, 1 H), 1.28 and 1.22 (s each, 6:6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 153.8, 149.1, 129.1, 128.3 (q, J = 275.5 Hz), 123.1, 110. 3, 110.2, 84.2, 56.2, 56.1, 34.8 (d, J = 2.7 Hz), 24.7, 24.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.6; ^{11}B NMR (128 MHz, $CDCl_3$) δ 30.1; IR (KBr pellet) 2978, 2931, 2838, 1668, 1590, 1513, 1376, 808 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{25}BF_3O_5$ $[M + H]^+$ 389.1742, found 389.1745.

*(−)-1-(3,4-Dimethoxyphenyl)-4,4,4-trifluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-1-one ((−)-**3f**).* 39 mg, 50% yield; 93% ee, $[\alpha]^{20}_D$ = −3.5 (*c* 0.2 $CHCl_3$); HPLC (AD-H, elute: Hexanes/*i*-PrOH = 98/2, detector: 220 nm, flow rate: 0.7 mL/min), t_1 = 10.2 min (maj.), t_2 = 12.0 min.

*1-(2,4-Dimethoxyphenyl)-4,4,4-trifluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-1-one (**3g**).* 72 mg, 93% yield; white solid, mp 90−91 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 8.8 Hz, 1 H), 6.51 (dd, J = 8.8, 2.2 Hz, 1 H), 6.43 (d, J = 2.2 Hz, 1 H), 3.88 and 3.84 (s each, 3:3 H), 3.46−3.34 (m, 2 H), 2.26−2.13 (m, 1 H), 1.29 and 1.24 (s each, 6:6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.9, 165.6, 162.0, 133.3, 128.7 (q, J = 275.3 Hz), 118.8, 105.7, 98.2, 83.7, 55.7, 55.6, 40.6 (d, J = 2.4 Hz), 24.7, 24.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.5; ^{11}B NMR (128 MHz, $CDCl_3$) δ 29.6; IR (KBr pellet) 2987, 2945, 2847, 1641, 1600, 1507, 1370, 864, 825 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{25}BF_3O_5$ $[M + H]^+$ 389.1742, found 389.1751.

*(−)-1-(2,4-Dimethoxyphenyl)-4,4,4-trifluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-1-one ((−)-**3g**).* 41 mg, 53% yield; 76% ee, $[\alpha]^{20}_D$ = −5.0 (*c* 0.1 $CHCl_3$); HPLC (AD-H, elute: Hexanes/*i*-PrOH = 98/2, detector: 220 nm, flow rate: 0.7 mL/min), t_1 = 11.0 min (maj.), t_2 = 16.2 min.

*1-(2,5-Dimethoxyphenyl)-4,4,4-trifluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-1-one (**3h**).* 74 mg, 95% yield; pale yellow solid, mp 80−82 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 3.3 Hz, 1 H), 7.05 (dd, J = 9.0, 3.3 Hz, 1 H), 6.91 (d, J = 9.1 Hz, 1 H), 3.87 and 3.77 (s each, 3:3 H), 3.49−3.39 (m, 2 H), 2.34−2.21 (m, 1 H), 1.30 and 1.25 (s each, 6:6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.0, 154.1, 153.5, 128.4 (q, J = 275.4 Hz), 126.5, 121.2, 114.2, 113.2, 84.1, 56.1, 55.9, 40.6 (d, J = 2.6 Hz), 24.7, 24.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.6; ^{11}B NMR (128 MHz, $CDCl_3$) δ 30.9; IR (KBr pellet) 2981, 2951, 2841, 1656, 1614, 1578, 1495, 1368, 816, 730 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{25}BF_3O_5$ $[M + H]^+$ 389.1742, found 389.1750.

*(−)-1-(2,5-Dimethoxyphenyl)-4,4,4-trifluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-1-one ((−)-**3h**).* 31 mg, 40% yield; 80% ee, $[\alpha]^{20}_D$ = −12.0 (*c* 0.1 $CHCl_3$); HPLC (AD-H, elute: Hexanes/*i*-PrOH = 98/2, detector: 220 nm, flow rate: 0.7 mL/min), t_1 = 8.3 min (maj.), t_2 = 11.2 min.

*4,4,4-Trifluoro-1-(4-fluorophenyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-1-one (**3i**).* 66 mg, 95% yield; white solid, mp 48−50 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01−7.97 (m, 2 H), 7.16−7.12 (m, 2 H), 3.46−3.34 (m, 2 H), 2.43−2.30 (m, 1 H), 1.29 and 1.24 (s each, 6:6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.2, 166.2

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(d, J = 253.9 Hz), 132.5 (d, J = 2.8 Hz), 131.0 (d, J = 9.4 Hz), 128.2 (q, J = 275.3 Hz), 116.0 (d, J = 21.8 Hz), 84.5, 35.2 (d, J = 2.8 Hz), 24.7, 24.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.7, −104.3; ^{11}B NMR (128 MHz, $CDCl_3$) δ 31.3; IR (KBr pellet) 2981, 2936, 1683, 1600, 1510, 1384, 841 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{20}BF_4O_3$ $[M + H]^+$ 347.1436, found 347.1430.

*(−)-4,4,4-Trifluoro-1-(4-fluorophenyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-1-one ((−)-**3i**).* 35 mg, 51% yield; 92% ee, $[\alpha]^{20}_D$ = −13.3 (c 0.15 $CHCl_3$); HPLC (AD-H, elute: Hexanes/i-PrOH = 98/2, detector: 254 nm, flow rate: 0.7 mL/min), t_1 = 7.4 min (maj.), t_2 = 9.9 min.

*4,4,4-Trifluoro-1-(3-fluorophenyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-1-one (**3j**).* 53 mg, 77% yield; white solid, mp 43−45 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 7.8 Hz, 1 H), 7.66−7.62 (m, 1 H), 7.49−7.43 (m, 1 H), 7.31−7.27 (m, 1 H), 3.47−3.34 (m, 2 H), 2.44−2.32 (m, 1 H), 1.29 and 1.24 (s each, 6:6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.5, 163.0 (d, J = 246.8 Hz), 138.1 (d, J = 6.5 Hz), 130.5 (d, J = 7.6 Hz), 128.1 (q, J = 275.4 Hz), 124.1 (d, J = 2.9 Hz), 120.7 (d, J = 21.3 Hz), 115.0 (d, J = 22.3 Hz), 84.5, 35.4 (d, J = 2.8 Hz), 24.7, 24.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.7, −111.6; ^{11}B NMR (128 MHz, $CDCl_3$) δ 31.3; IR (KBr pellet) 2981, 2928, 1686, 1594, 1340, 787, 688 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{20}BF_4O_3$ $[M + H]^+$ 347.1436, found 347.1440.

*(−)-4,4,4-Trifluoro-1-(3-fluorophenyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-1-one ((−)-**3j**).* 26 mg, 37% yield; 72% ee, $[\alpha]^{20}_D$ = −4.0 (c 0.1 $CHCl_3$); HPLC (AD-H, elute: Hexanes/i-PrOH = 98/2, detector: 220 nm, flow rate: 0.7 mL/min), t_1 = 5.4 min (maj.), t_2 = 6.4 min.

*4,4,4-Trifluoro-1-(2-fluorophenyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-1-one (**3k**).* 60 mg, 87% yield; white solid, mp 46−48 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 7.7 Hz, 1 H), 7.65−7.63 (m, 1 H), 7.48−7.43 (m, 1 H), 7.31−7.28 (m, 1 H), 3.47−3.33 (m, 2 H), 2.45−2.32 (m, 1 H), 1.29 and 1.24 (s each, 6:6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.6, 163.0 (d, J = 246.7 Hz), 138.2 (d, J = 6.4 Hz), 130.5 (d, J = 7.5 Hz), 128.1 (q, J = 275.4 Hz), 124.1 (d, J = 2.9 Hz), 120.7 (d, J = 21.4 Hz, 115.0 (d, J = 22.2 Hz), 84.6, 35.4 (d, J_{C-F} = 2.8 Hz), 24.7, 24.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.7, −111.6; ^{11}B NMR (128 MHz, $CDCl_3$) δ 31.3; IR (KBr pellet) 2999, 2981, 1686, 1588, 1379, 765 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{19}BF_4NaO_3$ $[M + Na]^+$ 369.1256, found 369.1259.

*(−)-4,4,4-Trifluoro-1-(2-fluorophenyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-1-one ((−)-**3k**).* 28 mg, 40% yield; 76% ee, $[\alpha]^{20}_D$ = −4.0 (c 0.1 $CHCl_3$); HPLC (AD-H, elute: Hexanes/i-PrOH = 98/2, detector: 220 nm, flow rate: 0.7 mL/min), t_1 = 5.5 min (maj.), t_2 = 6.6 min.

*1-(4-Chlorophenyl)-4,4,4-trifluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-1-one (**3l**).* 67 mg, 92% yield; white solid, mp 59−61 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92−7.88 (m, 2 H), 7.46−7.42 (m, 2 H), 3.46−3.32 (m, 2 H), 2.43−2.31 (m, 1 H), 1.29 and 1.23 (s each, 6:6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.6, 140.2, 134.4, 129.7, 129.2, 128.2 (q, J = 275.4 Hz), 84.5, 35.3 (d, J = 2.9 Hz), 24.7, 24.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.7; ^{11}B NMR (128 MHz, $CDCl_3$) δ 31.3; IR (KBr pellet) 2978, 2925, 1689, 1594, 1575, 1380, 829 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{19}BClF_3NaO_3$ $[M + Na]^+$ 385.0960, found 385.0961.

*(−)-1-(4-Chlorophenyl)-4,4,4-trifluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-1-one ((−)-**3l**).* 25 mg, 35% yield; ee 85%, $[\alpha]^{20}_D$ = −5.2 (c 0.25 $CHCl_3$); HPLC (AD-H, elute: Hexanes/i-PrOH = 98/2, detector: 254 nm, flow rate: 0.7 mL/min), t_1 = 5.4 min (maj.), t_2 = 7.2 min.

*1-(4-Bromophenyl)-4,4,4-trifluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-1-one (**3m**).* 71 mg, 88% yield; white solid, mp 73−75 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 8.5 Hz, 2 H), 7.61 (d, J = 8.5 Hz, 2 H), 3.45−3.32 (m, 2 H), 2.44−2.31 (m, 1 H), 1.29 and 1.23 (s each, 6:6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.7, 134.8, 132.2, 129.8, 128.9, 128.2 (q, J = 275.6 Hz), 84.5, 35.2 (d, J = 2.7 Hz), 24.7, 24.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.6; ^{11}B NMR (128 MHz, $CDCl_3$) δ 31.4; IR (KBr pellet) 2979, 2928, 1692, 1594, 1573, 1379, 827 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{20}BBrF_3O_3$ $[M + H]^+$ 407.0635, found: 407.0638.

*(−)-1-(4-Bromophenyl)-4,4,4-trifluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-1-one ((−)-**3m**).* 22 mg, 27% yield; 86% ee, $[\alpha]^{20}_D$ = −2.0 (c 0.1 $CHCl_3$); HPLC (AD-H, elute: Hexanes/i-PrOH = 98/2, detector: 254 nm, flow rate: 0.7 mL/min), t_1 = 5.6 min (maj.), t_2 = 7.4 min.

*Methyl 4-(4,4,4-Trifluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoyl) benzoate (**3n**).* 66 mg, 85% yield; white solid, mp 127−129 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 8.4 Hz, 2 H), 8.01 (d, J = 8.3 Hz, 2 H), 3.95 (s, 3 H), 3.51−3.38 (m, 2 H), 2.46−2.33 (m, 1 H), 1.29 and 1.23 (s each, 6:6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.3, 166.2, 139.3, 134.4, 130.0, 128.2, 128.1 (q, J = 275.5 Hz), 84.6, 52.6, 35.6 (d, J = 2.8 Hz), 24.7, 24.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.6; ^{11}B NMR (128 MHz, $CDCl_3$) δ 31.3; IR (KBr pellet) 2989, 1719, 1678, 1380, 1143, 1087, 870 cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{23}BF_3O_5$ $[M + H]^+$ 385.1585, found: 385.1588.

*(−)-Methyl 4-(4,4,4-Trifluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)- butanoyl)benzoate ((−)-**3n**).* 13 mg, 17% yield; ee 52%, $[\alpha]^{20}_D$ = −17.0 (c 0.1 $CHCl_3$); HPLC (AD-H, elute: Hexanes/i-PrOH = 96/4, detector: 254 nm, flow rate: 0.7 mL/min), t_1 = 9.0 min(maj.), t_2 = 10.9 min.

*4,4,4-Trifluoro-1-(naphthalen-1-yl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-1-one (**3p**).* 72 mg, 95% yield; white solid, mp 86−88 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, J = 8.5 Hz, 1 H), 8.02 (d, J = 8.2 Hz, 1 H), 7.95 (dd, J = 7.2, 0.8 Hz, 1 H), 7.89−7.87 (m, 1 H), 7.62−7.49 (m, 3 H), 3.60 (dd, J = 18.3, 10.5 Hz, 1 H), 3.49 (dd, J = 18.3, 4.8 Hz, 1 H), 2.56−2.43 (m, 1 H), 1.34 and 1.30 (s each, 6:6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.6, 134.6, 134.1, 133.4, 130.3, 128.6, 128.3 (q, J = 275.5 Hz), 128.25, 128.2, 126.7, 125.9, 124.5, 84.5, 38.4 (d, J = 2.7 Hz), 24.8, 24.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.5; ^{11}B NMR (128 MHz, $CDCl_3$) δ 31.4; IR (KBr pellet) 2975, 2931, 1681, 1597, 1570, 1373, 785, 747 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{23}BF_3O_3$ $[M + H]^+$ 379.1687, found 379.1692.

*(−)-4,4,4-Trifluoro-1-(naphthalen-1-yl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-1-one ((−)-**3p**).* 39 mg, 52% yield; 86% ee, $[\alpha]^{20}_D$ = −36.0 (c 0.1 $CHCl_3$); HPLC (AD-H, elute: Hexanes/i-PrOH = 98/2, detector: 220 nm, flow rate: 0.7 mL/min), t_1 = 5.9 min (maj.), t_2 = 10.4 min.

*4,4,4-Trifluoro-1-(naphthalen-2-yl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-1-one (**3q**).* 72 mg, 95% yield; white solid, mp 83−85 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1 H), 8.02 (dd, J = 8.6, 1.6 Hz, 1 H), 7.97 (d, J = 8.0 Hz, 1 H), 7.90−7.87 (m, 2 H), 7.63−7.54 (m, 2 H, 3.65−3.52 (m, 2 H), 2.51−2.39 (m, 1 H), 1.33 and 1.27 (s each, 6:6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.7, 135.9, 133.3, 132.6, 130.1, 129.7, 128.8, 128.7, 128.4 (q, J = 275.7 Hz), 127.9, 127.0, 123.8, 84.4, 35.4 (d, J = 2.8 Hz), 24.7, 24.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.5; ^{11}B NMR (128 MHz, $CDCl_3$) δ 31.4; IR (KBr pellet) 2981, 2933, 1680, 1626, 1594, 1367, 757 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{23}BF_3O_3$ $[M + H]^+$ 379.1687, found 379.1689.

*(+)-4,4,4-Trifluoro-1-(naphthalen-2-yl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-1-one ((+)-**3q**).* 45 mg, 60% yield; 92% ee, $[\alpha]^{20}_D$ = +1.6 (c 0.5 $CHCl_3$); HPLC (AD-H, elute: Hexanes/i-PrOH = 98/2, detector: 220 nm, flow rate: 0.7 mL/min), t_1 = 6.1 min (maj.), t_2 = 8.4 min.

*4,4,4-Trifluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(thiophen-2-yl)butan-1-one (**3r**).* 63 mg, 95% yield; colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76−7.75 (m, 1 H), 7.66 (d, J = 5.0 Hz, 1 H), 7.15−7.13 (m, 1 H), 3.43−3.31 (m, 2 H), 2.49−2.32 (m, 1 H), 1.29 and 1.24 (s each, 6:6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.4, 142.9, 134.1, 132.5, 128.3, 128.1 (q, J = 275.4 Hz), 84.5, 35.5 (d, J = 3.0 Hz), 24.7, 24.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.7; ^{11}B NMR (128 MHz, $CDCl_3$) δ 31.3; IR (in dichloromethane) 2981, 2931, 1668, 1519, 1376, 726 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{19}BF_3O_3S$ $[M + H]^+$ 335.1095, found 335.1096.

*(−)-4,4,4-Trifluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(thiophen-2-yl)butan-1-one ((−)-**3r**).* 37 mg, 56% yield; 94% ee, $[\alpha]^{20}_D$ = −7.0 (c 0.2 $CHCl_3$); HPLC (AD-H, elute: Hexanes/i-PrOH = 98/2, detector: 254 nm, flow rate: 0.7 mL/min), t_1 = 6.4 min (maj.), t_2 = 7.2 min.

*6,6,6-Trifluoro-1-phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexan-3-one (**3s**).* 64 mg, 90% yield; white solid, mp 53−55 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.29 (m, 2 H), 7.27−7.17

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(m, 3 H), 3.00−2.89 (m, 3 H), 2.87−2.73 (m, 3 H), 2.26 (pd, J = 11.5, 4.8 Hz, 1 H), 1.31 and 1.26 (s each, 6:6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.5, 140.8, 128.6, 128.4, 128.0 (q, J = 275.4 Hz), 126.3, 84.5, 43.7, 38.8 (d, J = 2.6 Hz), 29.8, 24.7, 24.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.9; ^{11}B NMR (128 MHz, $CDCl_3$) δ 31.2; IR (KBr pellet) 2987, 2931, 1713, 1600, 1388, 755, 702 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{25}BF_3O_3$ $[M + H]^+$ 357.1849, found 357.1850.

Synthesis of 4. To a 25 mL Schlenk tube were successively added CuI (1.9 mg, 0.01 mmol), (*R*,*S*)-Josiphos (9.6 mg, 0.015 mmol), and K_3PO_4 (4.2 mg, 0.02 mmol), and the tube was then evacuated and purged with N_2 three times. *t*-AmOH (1.5 mL) was added, the mixture was stirred at ambient temperature for 30 min, and (*S*)-**3a** (68 mg, 0.20 mmol) in *t*-AmOH (0.5 mL) was then added. The resultant mixture was warmed up to 60 °C and stirred for 20 h. After cooling to ambient temperature, the reaction mixture was filtered through a short pad of Celite and rinsed with 20 mL of EtOAc. All the volatiles were removed under reduced pressure, and the resulting residue was purified by silica gel column chromatography (eluent: petroleum ether (60−90 °C)/EtOAc = 100:1, v/v) to afford **4** as a white solid (10 mg, 26%).

*4,4-Difluoro-1-p-tolylbut-3-en-1-one (**4**).* 10 mg, 26% yield; white solid, mp 37−39 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 8.2 Hz, 2 H), 7.28 (d, J = 8.1 Hz, 2 H), 4.63 (dtd, J = 25.6, 7.2, 1.8 Hz, 1 H), 3.69 (dt, J = 7.2, 1.7 Hz, 2 H), 2.42 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.7, 158.0 (d, J = 285.6 Hz), 144.5, 133.8, 129.6, 128.4, 72.3 (dd, J = 27.9, 19.2 Hz), 32.4 (d, J = 4.7 Hz), 21.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ −86.5 (d, J = 42.6 Hz), −88.8 (d, J = 42.4 Hz); IR (in dichloromethane): 2925, 2856, 1751, 1683, 1602, 789 cm^{-1}; HRMS (ESI) Calcd for $C_{11}H_{11}F_2O$ $[M + H]^+$ 197.0772, found 197.0775.

Oxidation of (*S*)-3a. Using a modified procedure as reported,[12] a mixture of (*S*)-**3a** (41 mg, 0.12 mmol) and sodium perborate (92 mg, 0.60 mmol) in THF/water (2 mL, v/v = 1:1) was stirred at ambient temperature for 1.5 h. The mixture was then concentrated in vacuo, and the resultant residue was purified by silica gel column chromatography (eluent: petroleum ether (60−90 °C)/EtOAc = 10:1, v/v) to afford (*S*)-**5** as a white solid (25 mg, 89%).

*(S)-4,4,4-Trifluoro-3-hydroxy-1-p-tolylbutan-1-one (**5**).*[23] 25 mg, 89% yield; white solid; 90% ee, $[\alpha]^{20}_D$ = −18.0 (*c* 0.1 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 8.2 Hz, 2 H), 7.30 (d, J = 8.1 Hz, 2 H), 4.73−4.69 (m, 1 H), 3.99 (br, 1 H), 3.39 (dd, J = 17.7, 9.5 Hz, 1 H), 3.27 (dd, J = 17.7, 2.4 Hz, 1 H), 2.44 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.3, 145.3, 133.7, 129.6, 128.5, 125.0 (q, J_{C-F} = 278.8 Hz), 67.1 (q, J_{C-F} = 31.8 Hz), 38.3, 21.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ −79.3; HPLC (AS-H, elute: Hexanes/*i*-PrOH = 95/5, detector: 220 nm, flow rate: 0.7 mL/min), t_1 = 12.4 min (maj.), t_2 = 15.8 min.

Synthesis of Trifluoroborate 6 and Its Suzuki Coupling. A mixture of aqueous KHF_2 (4.0 M, 0.3 mL) and **3a** (103 mg, 0.30 mmol) in MeCN (1.5 mL) was stirred at ambient temperature for 4 h. After all the volatiles were removed under reduced pressure, the resultant residue was extracted with hot CH_3CN (3 × 10 mL), filtered, rinsed with Et_2O (2 × 5 mL), and dried in vacuo to yield potassium 4,4,4-trifluoro-3-(trifluoroborato)-1-*p*-tolylbutan-1-one **6** (79 mg, 82%). To a 25 mL Schlenk tube were added $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), XPhos (19 mg, 0.04 mmol), K_2CO_3 (110 mg, 0.60 mmol), and **6** (64 mg, 0.20 mmol). The tube was evacuated and purged with N_2 three times. Then toluene (1.5 mL), H_2O (0.15 mL), and 1-bromo-3-methylbenzene (51 mg, 0.30 mmol) were added, and the mixture was stirred at 90 °C for 20 h. After cooling to ambient temperature, the reaction mixture was analyzed by TLC and ^{1}H NMR, revealing that no reaction occurred.

*Potassium 4,4,4-Trifluoro-3-(trifluoroborato)-1-p-tolylbutan-1-one (**6**).* 79 mg, 82% yield; white solid, mp 210−213 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 7.88 (d, J = 8.2 Hz, 2 H), 7.29 (d, J = 8.0 Hz, 2 H), 3.09 (dd, J = 17.1, 5.3 Hz, 1 H), 2.98 (dd, J = 17.1, 7.3 Hz, 1 H), 2.83−2.80 (d, J = 13.3 Hz, 1 H), 2.38 (s, 3 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 200.5, 143.9, 136.2, 132.5 (q, J_{C-F} = 275.2 Hz), 129.9, 129.1, 35.6, 21.5; ^{19}F NMR (376 MHz, acetone-d_6) δ −62.5 (d, J = 5.9 Hz), −144.5 (dd, J = 99.6, 47.1 Hz); ^{11}B NMR (128 MHz, acetone-d_6) δ 3.0 (dd, J = 102.6, 50.8 Hz); IR (KBr pellet) 3045, 2926, 1680, 1608, 1321, 805 cm^{-1}; HRMS (ESI) Calcd for $C_{11}H_{10}BF_6O$ $[M - K]^-$ 283.0734, found 283.0728.

Reaction of 1a with Tetrahydroxydiboron. To a 25 mL Schlenk tube were successively added CuI (1.9 mg, 0.01 mmol), $B_2(OH)_4$ (20 mg, 0.22 mmol), and K_3PO_4 (4.2 mg, 0.02 mmol), and the tube was then evacuated and purged with N_2 three times. *t*-AmOH (1.5 mL) was added and stirred at ambient temperature for 30 min, followed by the addition of (*E*)-4,4,4-trifluoro-1-*p*-tolylbut-2-en-1-one (**1a**) (43 mg, 0.20 mmol) in *t*-AmOH (0.5 mL). The resultant mixture was warmed up to 60 °C and stirred for 20 h. After cooling to ambient temperature, all the volatiles were removed under reduced pressure. To the resulting residue were added sodium perborate (153 mg, 1.00 mmol) and THF/water (2 mL, v/v = 1:1), and the mixture was stirred at ambient temperature for 2 h and concentrated under reduced pressure. Purification of the resultant residue by silica gel column chromatography (eluent: petroleum ether (60−90 °C)/EtOAc = 10:1, v/v) afforded **5** as a white solid (14 mg, 30%).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02772.

NMR spectra of the substrates and products; HPLC analysis for racemic and chiral products (PDF)

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Notes

The authors declare no competing financial interest.

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