

Enantioselective Cobalt-Catalyzed Hydroboration of Fluoroalkyl-Substituted Alkenes to Access Chiral Fluoroalkylboronates

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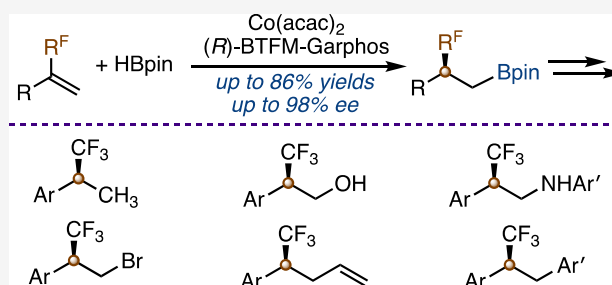
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ABSTRACT: Selective defluoroborylation and asymmetric hydroboration reactions of fluoroalkyl-substituted terminal alkenes with pinacolborane (HBpin) have been developed with cobalt catalysts generated from $\text{Co}(\text{acac})_2$ and bisphosphine ligands. A variety of fluoroalkyl-substituted terminal alkenes undergo this enantioselective hydroboration, affording the corresponding chiral alkylboronates containing fluoroalkyl-substituted stereogenic carbon centers with high enantioselectivity (up to 98% *ee*). This asymmetric hydroboration provides a versatile foundation for the synthesis of a variety of chiral organofluorine compounds containing fluoroalkyl-substituted stereogenic carbon centers.

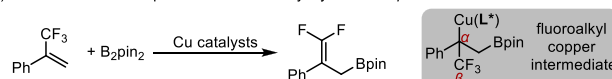


INTRODUCTION

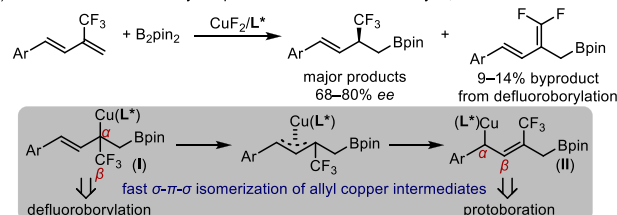
Fluorine-containing molecules have found broad applications in pharmaceutical, agrochemical, and materials sciences due to their unique physicochemical and biological properties.¹ For example, organic compounds with trifluoromethylated stereogenic carbon motifs are widespread in various biologically active compounds.² Therefore, the development of effective catalytic protocols to access chiral molecules containing fluoroalkyl substituents, such as a trifluoromethyl or poly-fluoroalkyl group, is a research field of ever-growing interest.³ In particular, it is highly desirable to achieve asymmetric syntheses of chiral fluoroalkyl compounds containing a functional group with versatile reaction chemistry such as organoboronates, because their subsequent transformations will allow convenient access to a variety of other chiral fluoroalkyl compounds.

Enantioenriched organoboronates are versatile reagents for asymmetric synthesis as they can undergo various stereospecific transformations with no or minimum loss of their enantiopurity.⁴ The installation of boronate functionality into chiral fluoroalkyl compounds will improve their manipulability and enrich their synthetic utility.⁵ Catalytic hydroboration or protoboration of fluoroalkyl-substituted alkenes is one straightforward approach to prepare fluoroalkylated organoboronates.⁶ Asymmetric copper-catalyzed protoboration of α -trifluoromethyl styrene with B_2pin_2 has been attempted to synthesize chiral β -trifluoromethylated alkylboronates,^{6c} but β -fluorine elimination occurs instead to yield *gem*-difluoroallylic boronates as the major product (Figure 1A).⁷ Therefore, the effective suppression of β -fluorine elimination is the key to developing enantioselective addition of Cu-Bpin to CF_3 -substituted $\text{C}=\text{C}$ double bonds. For example, Zhang's group recently developed a Cu-catalyzed asymmetric protoboration

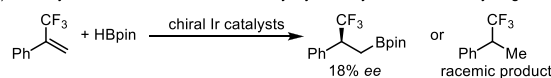
A) The addition of Cu-Bpin to α -trifluoromethylstyrene: fast β -F elimination



B) Enantioselective Cu-catalyzed protoboration of trifluoromethyl 1,3-dienes



C) Ir-catalyzed reactions of α -trifluoromethylstyrene: hydroboration vs hydrogenation



D) Migratory insertion of CF_3 -substituted alkenes to (L)Co-H and (L)Co-Bpin intermediates

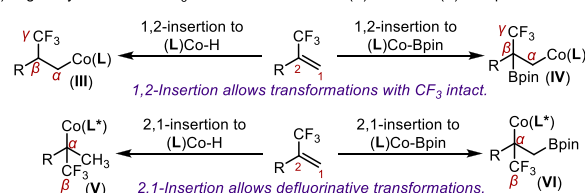


Figure 1. Metal-catalyzed enantioselective protoboration and hydroboration of CF_3 -substituted alkenes.

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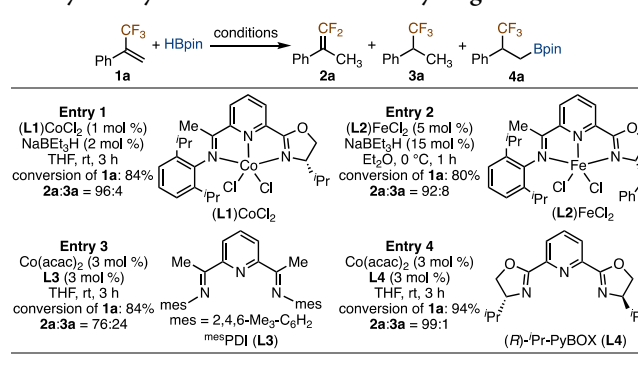
of CF₃-containing 1,3-dienes by taking advantage of fast σ - π - σ isomerization of an allylcopper intermediate (I) with β -fluorine atoms to another allylcopper species (II) that does not have β -fluorine atoms (Figure 1B).⁸ Alternatively, hydroboration of α -trifluoromethyl styrene with HBpin has also been attempted with chiral iridium catalysts,^{6d} but this reaction suffers from either low chemoselectivity or poor enantioselectivity (Figure 1C). Therefore, it still remains a challenge to develop atom-economical and enantioselective approaches to access chiral fluoroalkylated organoboronates from fluoroalkyl-substituted monoalkenes.

In recent years, base metal catalysts, such as chiral cobalt,⁹ iron,¹⁰ and copper complexes,¹¹ have been employed to catalyze enantioselective hydroboration of 1,1-disubstituted alkenes with HBpin to prepare chiral alkylboronates. During our continuous efforts in developing cobalt-catalyzed asymmetric synthesis of alkylboronates,¹² we became interested in identifying chiral cobalt catalysts for asymmetric hydroboration of simple fluoroalkyl-substituted alkenes to access organoboronates containing fluoroalkyl-substituted stereogenic carbon centers. Migratory insertion of fluoroalkyl-substituted alkenes into metal-hydride and metal-boryl intermediates is a fundamental step in metal-catalyzed hydroboration reactions, and possible ways of migratory insertion of a CF₃-substituted alkene into Co-H and Co-Bpin bonds are depicted in Figure 1D. 1,2-Insertion of a CF₃-substituted alkene into a (L)Co-H or (L)Co-Bpin species would generate alkylcobalt intermediates III and IV with fluorine atoms located on their γ -carbon atoms. This helps to suppress fluorine elimination and thus keeps the CF₃ group intact. Alternatively, 2,1-insertion of this alkene into (L)Co-H or (L)Co-Bpin species forms alkylcobalt intermediates V and VI with fluorine atoms located on their β -carbon atoms, and β -fluorine elimination from these alkylcobalt species would allow defluorinative transformations of CF₃-substituted alkenes. Therefore, identifying suitable ligands that can promote the formation of alkylcobalt intermediate III or IV is crucial to develop cobalt-catalyzed hydroboration of fluoroalkyl-substituted alkenes. Herein, we report cobalt-intermediate-dependent defluoroborylation and hydroboration reactions of fluoroalkyl-substituted alkenes, with an emphasis on developing enantioselective hydroboration to access chiral alkylboronates that have fluoroalkylated stereogenic carbon centers. In addition, we also show that the chiral β -CF₃-substituted alkylboronate products can be readily converted, in a stereospecific manner, to various chiral compounds containing CF₃-substituted stereogenic carbon centers.

RESULTS AND DISCUSSION

Evaluation of the Reaction of α -Trifluoromethyl Styrene with HBpin with Chiral Cobalt and Iron Catalysts Previously Reported for Asymmetric Hydroboration of 1,1-Disubstituted Vinylarenes. Cobalt and iron complexes containing iminopyridine oxazoline ligands have been reported to catalyze asymmetric hydroboration of 1,1-disubstituted vinylarenes—for example, α -methyl styrene, with high enantioselectivity.^{9,10} We first evaluated these cobalt and iron catalysts for hydroboration of α -trifluoromethyl styrene **1a** under the reported conditions to determine whether it is necessary to identify new catalysts for asymmetric hydroboration of fluoroalkyl-substituted alkenes. However, the reaction of **1a** with HBpin catalyzed by (L1)CoCl₂ or (L2)FeCl₂ afforded *gem*-difluoroalkene **2a** as the major

Scheme 1. Reaction of α -Trifluoromethyl Styrene **1a with HBpin Catalyzed by N3-Pincer-Ligated Iron and Cobalt Catalysts: Hydrodefluorination and Hydrogenation of **1a****



product, together with (1,1,1-trifluoropropan-2-yl)benzene **3a** as a minor product (entries 1 and 2 in Scheme 1). These results unequivocally show the uniqueness of a CF₃ group, and the replacement of the methyl group on α -methyl styrene with a CF₃ group completely alters the chemoselectivity of its reaction with HBpin under identical conditions.

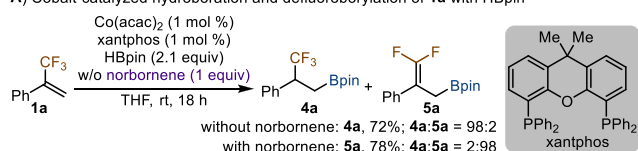
In addition, we also attempted this hydroboration reaction with catalysts generated from Co(acac)₂ and other N3-pincer ligands ^{mes}PDI and (R)-Pr-Pybox, but these two reactions also yielded **2a** as the major product (entries 3 and 4 in Scheme 1). The hydroboration product, fluoroalkylboronate **4a**, was not detected by GC-MS analysis on the crude mixtures of these reactions. The predominant formation of *gem*-difluoroalkene **2a** for the reactions in Scheme 1 suggests that α -trifluoromethyl styrene **1a** tends to undergo 2,1-insertion into an N3-pincer-ligated cobalt-hydride complex to form a cobalt intermediate of type V, as shown in Figure 1D. Therefore, it remains necessary to identify new chiral catalysts for asymmetric hydroboration of fluoroalkyl-substituted alkenes.

Cobalt-Catalyzed Hydroboration and Defluoroborylation of α -Trifluoromethyl Styrene with HBpin. It is known that both the nature of alkenes and metal complexes influences the regioselectivity of insertion of alkenes, 1,2- or 2,1-insertion, into reactive organometallic intermediates. Therefore, we decided to evaluate phosphine-ligated cobalt catalysts for the reaction of **1a** with HBpin. Recently, we have identified the conditions for selective formation of Co-H and Co-Bpin species from Co(acac)₂ and bisphosphine ligands. For example, Co(acac)₂ reacts with HBpin in the presence of xantphos to form a cobalt hydride species, which can be subsequently converted to a cobalt boryl intermediate in the presence of hydrogen acceptors, such as norbornene, cyclooctene, and dicyclopentadiene.^{9b,13} This provides us with an opportunity to test both Co-H and Co-Bpin species for the reaction of fluoroalkyl-substituted alkenes with HBpin. To our delight, we found that the reaction of **1a** with HBpin catalyzed by Co(acac)₂ and xantphos occurred selectively to produce β -trifluoromethyl alkylboronate **4a** in 72% isolated yield, while the corresponding reaction in the presence of norbornene as a hydrogen acceptor selectively afforded *gem*-difluoroallylic boronate **5a** in 78% yield (Scheme 2A).

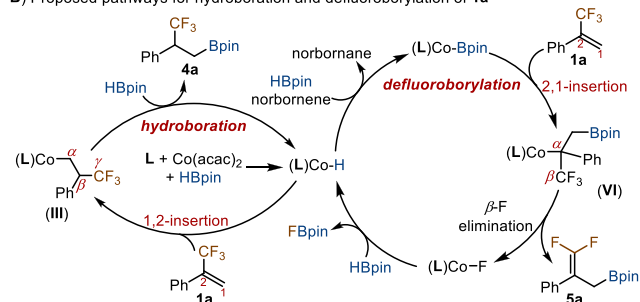
As rationalized in Figure 1D, cobalt species III and VI are key intermediates for the formation of **4a** and **5a**, respectively. A complete depiction of the proposed pathways for cobalt-catalyzed hydroboration and defluoroborylation reactions is shown in Scheme 2B. Compared with N3-pincer ligands in

Scheme 2. Cobalt-Catalyzed Hydroboration and Defluoroborylation of α -Trifluoromethyl Styrene **1a**

A) Cobalt-catalyzed hydroboration and defluoroborylation of **1a** with HBpin



B) Proposed pathways for hydroboration and defluoroborylation of **1a**

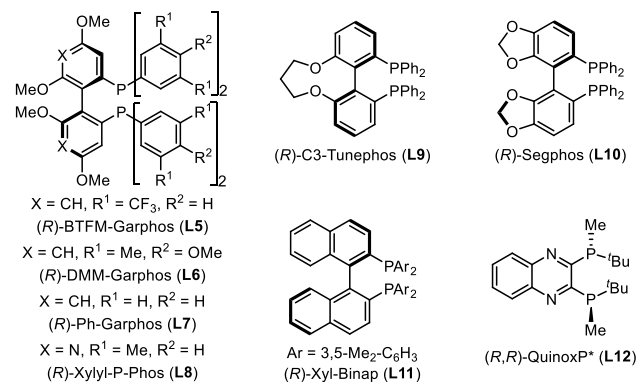


Scheme 1, the xantphos ligand is more sterically demanding due to the two phenyl groups on each of its phosphorus atoms, and the steric repulsion between xantphos and phenyl/ CF_3 groups of **1a** makes 1,2-insertion of **1a** into xantphos-ligated Co-H species more favorable. However, 2,1-insertion of **1a** into xantphos-ligated Co-Bpin species is likely due to the more prominent steric repulsion between the Bpin group and the Ph/ CF_3 groups of **1a**, compared with the steric repulsion between xantphos and the Ph/ CF_3 groups. For defluoroborylation of **1a** with HBpin in the presence of norbornene, FBpin and norbornane were detected by ^{19}F NMR and GC-MS analysis, respectively. As defluoroborylation of CF_3 -substituted alkenes with B_2pin_2 has been studied with various metal catalysts,⁷ we include the scope of CF_3 -substituted alkenes for defluoroborylation reactions with HBpin in the Supporting Information.

Evaluation of Chiral Phosphine Ligands and Conditions for Enantioselective Cobalt-Catalyzed Hydroboration of α -Trifluoromethyl Styrene with HBpin. After establishing conditions for selective hydroboration of α -trifluoromethyl styrene **1a**, we then aimed to identify chiral cobalt catalysts for asymmetric hydroboration of **1a**. After evaluating various chiral phosphine ligands and reaction parameters (Table 1), we found that alkene **1a** reacted smoothly with 1.2 equiv of HBpin in the presence of 3 mol % $\text{Co}(\text{acac})_2$, 4 mol % (*R*)-BTFM-Garphos (**L5**), and 30 mol % $\text{Li}(\text{acac})$ in 2-Me-THF at room temperature, affording chiral alkylboronate **4a** in 82% isolated yield with 98% chemoselectivity and 92% *ee* (entry 1). The reactions employing less sterically demanding Garphos ligands **L6** or **L7** afforded **4a** with lower enantioselectivity (entries 2 and 3). The reactions conducted with cobalt catalysts generated in situ from $\text{Co}(\text{acac})_2$ and other chiral biaryl phosphine ligands, such as (*R*)-Xylyl-P-Phos (**L8**, entry 4), (*R*)-C3-Tunephos (**L9**, entry 5), (*R*)-Segphos (**L10**, entry 6), and (*R*)-Xylyl-Binap (**L11**, entry 7), also occurred to form the desired product **4a** in good yields (68–77%) but with modest enantioselectivity (39–68% *ee*). The reaction catalyzed by the combination of $\text{Co}(\text{acac})_2$ and (*R,R*)-QuinoxP* (**L12**) afforded **4a** in 68% yield with 41% *ee* (entry 8). The removal of $\text{Li}(\text{acac})$ from the reaction conditions led to a slightly decreased enantioselectivity (90% *ee*, entry 9). In general, the reactions catalyzed by $\text{Co}(\text{acac})_2$

Table 1. Evaluation of Conditions for Cobalt-Catalyzed Asymmetric Hydroboration of α -Trifluoromethyl Styrene **1a^a**

entry	variation from the standard conditions	conversion of 1a (%)	ratio of 2a:4a	yield of 4a (%)	<i>ee</i> of 4a (%)
1	none	>99	2:98	82	92
2	L6 instead of L5	>99	12:88	78	78
3	L7 instead of L5	>97	14:86	73	29
4	L8 instead of L5	96	22:78	69	68
5	L9 instead of L5	97	12:88	77	64
6	L10 instead of L5	93	29:71	68	31
7	L11 instead of L5	96	19:81	72	53
8	L12 instead of L5	89	16:84	68	41
9	without $\text{Li}(\text{acac})$	98	2:98	81	90
10	hexane as solvent	86	9:91	71	88
11	toluene as solvent	93	6:94	78	85
12	dioxane as solvent	>99	6:94	80	87
13	THF as solvent	>99	1:99	82	89

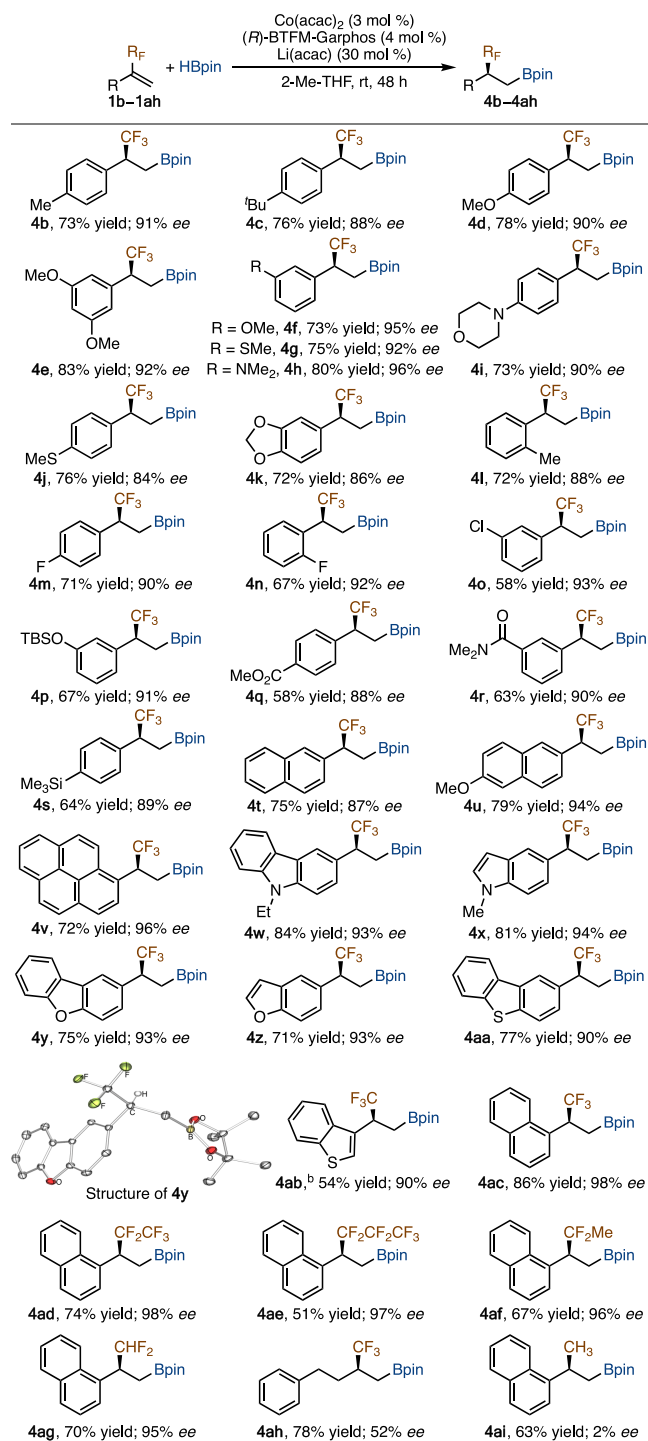


^aConditions: α -trifluoromethyl styrene **1a** (0.100 mmol), HBpin (0.120 mmol), $\text{Co}(\text{acac})_2$ (3.0 μmol), ligand (4.0 μmol), $\text{Li}(\text{acac})$ (30 μmol), 2-Me-THF (0.1 mL) at rt. for 48 h, conversions of **1a**, and ratios of **2a:4a** were determined by GC analysis with tridecane as the internal standard, isolated yields were given, and *ee* values of **4a** were determined by chiral HPLC analysis.

and phosphophine ligands **L6**–**L12** also generated significant amounts of *gem*-difluoroalkene **2a** (entries 2–8). In addition, we also tested various solvents, such as hexane, toluene, dioxane, and THF, for this asymmetric hydroboration reaction, and these reactions occurred with slightly lower enantioselectivity (85–89% *ee*, entries 10–13) compared with the reaction conducted in 2-Me-THF (entry 1).

Substrate Scope of Fluoroalkyl-Substituted Alkenes.

With the identified chiral catalyst and conditions (entry 1 in Table 1), we explored the scope of fluoroalkylated alkenes for this cobalt-catalyzed asymmetric hydroboration, and the results are summarized in Table 2. In general, a wide range of α - CF_3 -substituted vinylarenes (**1b**–**1c**) reacted smoothly with HBpin in the presence of 3 mol % $\text{Co}(\text{acac})_2$ and 4 mol % (*R*)-BTFM-Garphos, affording the corresponding chiral β -trifluoromethylated alkylboronates (**4b**–**4c**) in modest to high yields (54–86%) with high enantioselectivity (84–98% *ee*). Fluoroalkylated alkenes containing other fluoroalkyl groups, such as perfluoroethyl (**1ad**), perfluoropropyl (**1ae**), difluoroethyl (**1af**), and difluoromethyl (**1ag**), also underwent this asymmetric hydroboration reaction to produce β -fluoroalkyl-substituted alkylboronates (**4ae**–**4ag**) in high yields (51–74%) with excellent enantioselectivity (95–98% *ee*). In

Table 2. Scope of Fluoroalkylated Alkenes for Asymmetric Cobalt-Catalyzed Hydroboration^a

^aConditions: alkene (0.200 mmol), HBpin (0.240 mmol), Co(acac)₂ (6.0 μmol), (R)-BTFM-Garphos (8.0 μmol), Li(acac) (60 μmol), 2-Me-THF (0.1 mL), rt, 48 h, yields of isolated products, ee values were determined by chiral HPLC analysis. ^bThis reaction was conducted with 5 mol % Co(acac)₂ and 6 mol % (R)-BTFM-Garphos.

addition, **1ah**, a terminal alkene containing both alkyl and trifluoromethyl substituents, could also react to afford the desired product **4ah** in 78% yield, albeit with modest enantioselectivity. Methyl-substituted vinylarene **1ai** underwent this cobalt-catalyzed hydroboration as well under the

standard conditions, but the alkylboronate product **4ai** was nearly racemic (2% ee).¹⁴ The absolute configuration of alkylboronate **4y** was assigned as (S) by single-crystal X-ray analysis.

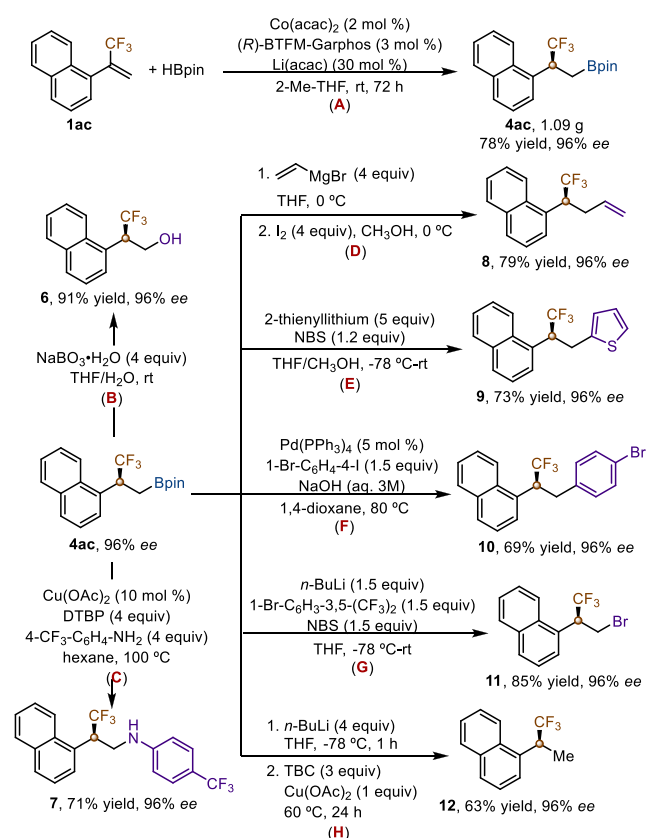
The data in Table 2 show that the substitution pattern on the aryl groups does not have significant influence on the enantioselectivity of this asymmetric hydroboration reaction. For example, the alkenes containing *para*- (**4b**, **4c**, **4d**, **4i**, and **4j**), *meta*- (**4e**–**4h**, **4o**, **4p**, and **4r**), and *ortho*-substituted (**4l** and **4n**) aryl groups reacted with similarly high enantioselectivity. CF₃-substituted alkenes containing polyaryl groups, such as naphthyl (**4t**, **4u**, and **4ac**) and pyrenyl (**4v**), reacted to afford the corresponding β-trifluoromethylated alkylboronates in high yields (72–86%) with high enantioselectivity (87–98% ee). In addition, five-membered nitrogen-, oxygen-, and sulfur-heterocyclic CF₃-substituted alkenes also underwent this asymmetric hydroboration to afford the desired products (**4w**–**4ab**) with high enantioselectivity (90–94% ee). However, hydroboration of 3-(3,3,3-trifluoroprop-1-en-2-yl)pyridine, a Py,CF₃-substituted alkene, proceeded only to less than 5% conversion under the identified conditions. Furthermore, this cobalt-catalyzed asymmetric hydroboration tolerates various functional groups, such as sulfide (**4g** and **4j**), tertiary amine (**4h** and **4i**), fluoro (**4m** and **4n**), chloro (**4o**), silyloxy (**4p**), carboxylic ester (**4q**), carboxylic amide (**4r**), and trimethylsilyl (**4s**) moieties.

Synthetic Utility. To show the synthetic utility of this enantioselective protocol, we conducted a gram-scale asymmetric hydroboration reaction of trifluoromethylated alkene **1ac** with a reduced catalyst loading (2 mol %), and this reaction occurred smoothly to produce chiral alkylboronate **4ac** in 78% yield with 96% ee, although a longer reaction time was required (Scheme 3A). In addition, we showed that trifluoromethylated β-stereogenic alkylboronate **4ac** could undergo various stereospecific transformations without loss of enantiopurity to afford various enantioenriched trifluoromethylated compounds, which are otherwise difficult to access from readily available materials. For example, **4ac** could be oxidized by NaBO₃ to form chiral β-trifluoromethyl alcohol **6** in 91% yield with 96% ee (Scheme 3B).¹⁵ Compound **4ac** could also undergo Chan–Lam coupling with 4-(trifluoromethyl)aniline to form β-stereogenic trifluoromethylated amine **7** in 71% yield with 96% ee (Scheme 3C).¹⁶ Chiral alkylboronate **4ac** could also be employed to construct carbon–carbon bonds. For example, the vinylation of **4ac** with vinylmagnesium bromide in the presence of I₂ afforded chiral alkene **8** in 79% yield with 96% ee (Scheme 3D).¹⁷ The reaction of **4ac** with 2-thienyllithium in the presence of NBS generated compound **9** in 73% yield with 96% ee (Scheme 3E).¹⁸ The Suzuki–Miyaura cross-coupling reaction between **4ac** and 1-bromo-4-iodobenzene occurred smoothly in the presence of 5 mol % Pd(PPh₃)₄ at 80 °C, affording compound **10** in 69% isolated yield with 96% ee (Scheme 3F).¹⁹ Alkylboronate **4ac** could also be converted to chiral alkylbromide **11** in 85% yield with 96% ee (Scheme 3G).¹⁷ Furthermore, protodeborylation of alkylboronate **4ac** could afford compound **12**, which contains a CF₃,CH₃-substituted tertiary stereogenic carbon center, in 63% isolated yield with 96% ee (Scheme 3H).²⁰

CONCLUSIONS

In summary, we have developed cobalt-catalyzed selective defluoroborylation and hydroboration of fluoroalkylated

Scheme 3. Gram-Scale Reaction and Transformations of Chiral Alkylboronate 4ac



terminal alkenes with HBpin. These reactions proceed with different catalytically active cobalt species, with a cobalt-boryl intermediate for the defluoroborylation reaction and a cobalt-hydride species for the hydroboration reaction. Furthermore, we have identified a chiral cobalt catalyst for the asymmetric hydroboration of fluoroalkylated terminal alkenes. A variety of fluoroalkylated alkenes react with HBpin in the presence of Co(acac)₂ and (R)-BTfM-Garphos, forming the corresponding chiral alkylboronates containing fluoroalkylated tertiary stereogenic carbons in high yields with high enantioselectivity. The chiral alkylboronate products from this asymmetric hydroboration reaction can be readily converted, in a stereospecific manner, to various chiral molecules by functional group manipulations of their C–B bonds. Therefore, this enantioselective hydroboration reaction provides a general and versatile foundation for the preparation of various chiral compounds containing fluoroalkylated stereogenic carbon centers.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.2c06488>.

Experimental details, characterization data, and copies of NMR spectra of all compounds (PDF)

Accession Codes

CCDC 2160140 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cam-

bridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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