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

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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 Co(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. For example, organic compounds with trifluoromethylated stereogenic carbon motifs are widespread in various biologically active compounds. Therefore, the development of effective catalytic protocols to access chiral alkenes containing fluoroalkyl substituents, such as a trifluoromethyl or polyfluoroalkyl group, is a research field of ever-growing interest. 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. The installation of boronate functionality into chiral fluoroalkyl compounds will improve their manipulability and enrich their synthetic utility. Catalytic hydroboration or protoboration of fluoroalkyl-substituted alkenes is one straightforward approach to prepare fluoroalkylated organoboronates. Asymmetric copper-catalyzed protoboration of α-trifluoromethyl styrene with B₂pin₂ has been attempted to synthesize chiral β-trifluoromethylated alkylboronates, but β-fluorine elimination occurs instead to yield gem-difluoroallylic boronates as the major product (Figure 1A). Therefore, the effective suppression of β-fluorine elimination is the key to developing enantioselective addition of Cu-Bpin to CF₃-substituted C=C double bonds. For example, Zhang’s group recently developed a Cu-catalyzed asymmetric protoboration

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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). 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 (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 gen-difluoroalkene 2a as the major 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, 6e−6dPDI 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 1. Reaction of α-Trifluoromethyl Styrene 1a with HBpin Catalyzed by N3-Pincer-Ligated Iron and Cobalt Catalysts: Hydrodefluorination and Hydrogenation of 1a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Product</th>
<th>Conditions</th>
<th>Conversion</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(L1)CoCl₂ (1 mol %) NaBET(H) (3 mol %)</td>
<td>3a</td>
<td>1,2 Insertion</td>
<td>2a:3a = 64:96</td>
<td>96.4</td>
</tr>
<tr>
<td>2</td>
<td>(L2)FeCl₂ (0.5 mol %)</td>
<td>3b</td>
<td>1,2 Insertion</td>
<td>2b:3b = 92.8</td>
<td>90.0</td>
</tr>
<tr>
<td>3</td>
<td>(L1)CoCl₂ (3 mol %)</td>
<td>4a</td>
<td>1,2 Insertion</td>
<td>L3:Co-H:Co-Bpin = 2a:3a:3b = 79:54</td>
<td>91.5</td>
</tr>
<tr>
<td>4</td>
<td>(L2)FeCl₂</td>
<td>4b</td>
<td>1,2 Insertion</td>
<td>L4:Co-H:Co-Bpin = 2b:3b:3a = 99:1</td>
<td>99.0</td>
</tr>
</tbody>
</table>
Scheme 1, the xanthos ligand is more sterically demanding due to the two phenyl groups on each of its phosphorus atoms, and the steric repulsion between xanthos and phenyl/CF₃ groups of 1a makes 1,2-insertion of 1a into xanthos-ligated Co-H species more favorable. However, 2,1-insertion of 1a into xanthos-ligated Co-Bpin species is likely due to the more prominent steric repulsion between the Bpin group and the Ph/CF₃ groups of 1a, compared with the steric repulsion between xanthos and the Ph/CF₃ groups. For defluoroboration of 1a with HBpin in the presence of norboronene, FBpin and norboronene were detected by ¹⁹F NMR and GC–MS analysis, respectively. As defluoroboration of CF₃-substituted alkenes with Bpin has been studied with various metal catalysts,⁷ we include the scope of CF₃-substituted alkenes for defluoroboration 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 % Co(acac)₂, 4 mol % (R)-BTFM-Garphos (L5), and 30 mol % Li(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 Co(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 Co(acac)₂ and (R,R)-QuinoxP⁸ (L12) afforded 4a in 68% yield with 41% ee (entry 8). The removal of Li(acac) from the reaction conditions led to a slightly decreased enantioselectivity (90% ee, entry 9). In general, the reactions catalyzed by Co(acac)₂ and phosphine ligands L6–L12 also generated significant amounts of gem-difluoralkene 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-CF₃-substituted vinylarenes (1b–1ac) reacted smoothly with HBpin in the presence of 3 mol % Co(acac)₂ and 4 mol % (R)-BTFM-Garphos, affording the corresponding chiral β-trifluoromethylated alkylboronates (4b–4ac) 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).

### Table 1. Evaluation of Conditions for Cobalt-Catalyzed Asymmetric Hydroboration of α-Trifluoromethyl Styrene 1a⁹

<table>
<thead>
<tr>
<th>entry</th>
<th>variation from the standard conditions</th>
<th>conversion of 1a (%)</th>
<th>ratio of 2a:4a</th>
<th>yield of 4a (%)</th>
<th>ee of 4a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>&gt;99</td>
<td>2.98</td>
<td>82</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>L6 instead of L5</td>
<td>&gt;99</td>
<td>12.88</td>
<td>78</td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td>L7 instead of L5</td>
<td>&gt;97</td>
<td>14.86</td>
<td>73</td>
<td>29</td>
</tr>
<tr>
<td>4</td>
<td>L8 instead of L5</td>
<td>96</td>
<td>22.78</td>
<td>69</td>
<td>68</td>
</tr>
<tr>
<td>5</td>
<td>L9 instead of L5</td>
<td>97</td>
<td>12.88</td>
<td>77</td>
<td>64</td>
</tr>
<tr>
<td>6</td>
<td>L10 instead of L5</td>
<td>93</td>
<td>27.97</td>
<td>68</td>
<td>31</td>
</tr>
<tr>
<td>7</td>
<td>L11 instead of L5</td>
<td>96</td>
<td>19.51</td>
<td>72</td>
<td>53</td>
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<tr>
<td>8</td>
<td>L12 instead of L5</td>
<td>89</td>
<td>16.64</td>
<td>68</td>
<td>41</td>
</tr>
<tr>
<td>9</td>
<td>without L(acac)</td>
<td>98</td>
<td>2.98</td>
<td>81</td>
<td>90</td>
</tr>
<tr>
<td>10</td>
<td>hexane as solvent</td>
<td>86</td>
<td>9.91</td>
<td>71</td>
<td>88</td>
</tr>
<tr>
<td>11</td>
<td>toluene as solvent</td>
<td>93</td>
<td>6.94</td>
<td>78</td>
<td>85</td>
</tr>
<tr>
<td>12</td>
<td>dioxane as solvent</td>
<td>&gt;99</td>
<td>8.94</td>
<td>80</td>
<td>87</td>
</tr>
<tr>
<td>13</td>
<td>THF as solvent</td>
<td>&gt;99</td>
<td>1.99</td>
<td>82</td>
<td>89</td>
</tr>
</tbody>
</table>

⁹Conditions: α-trifluoromethyl styrene 1a (0.100 mmol), HBpin (0.120 mmol), Co(acac)₂ (3.0 μmol), ligand (4.0 μmol), Li(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.
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).\(^{16}\) 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 (4i and 4n) aryl groups reacted with similarly high enantioselectivity. CF₃-substituted alkylboronates 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 alkylboronates 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 alkylboronate, proceeded only to less than 5% conversion under the identified conditions. Furthermore, this cobalt-catalyzed asymmetric hydroboration tolerates various functional groups, such as sultide (4g and 4j), tertiary amine (4h and 4i), fluoro (4m and 4n), chloro (4o), siloxy (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).\(^{17}\) Compound 4ac could also underwent 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-isodobenzene 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 CF₃CH₂-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

![Diagram of the reaction and transformations]

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 of 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/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 Cambridge 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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REFERENCES


