

# Palladium-Catalyzed Suzuki–Miyaura Cross-Coupling Reactions of Enantiomerically Enriched Potassium $\beta$ -Trifluoroboratoamides with Various Aryl- and Hetaryl Chlorides

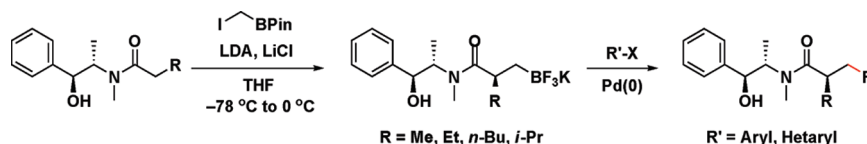
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Received August 9, 2010

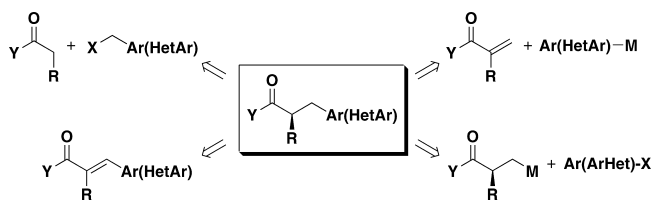
## ABSTRACT



Enantiomerically enriched potassium  $\beta$ -trifluoroboratoamides were synthesized as air-stable solids in greater than 95:5 dr using pseudoephedrine as the chiral auxiliary. With these chiral nucleophiles, Suzuki–Miyaura cross-coupling reactions were carried out with various aryl- and hetaryl chlorides in good to excellent yields. Moreover, the diastereoselectivities were preserved throughout the Suzuki–Miyaura cross-coupling reactions.

$\alpha$ -Chiral  $\beta$ -arylated carbonyl compounds represent an important class of organic molecules. The most common approaches to these materials are benzylation of enolates<sup>1</sup> and conjugate additions of arylmetallics to  $\alpha,\beta$ -unsaturated carbonyl precursors (Scheme 1).<sup>2</sup> Catalytic asymmetric hydrogenation of  $\alpha$ -substituted  $\alpha,\beta$ -unsaturated carbonyl substrates is also a viable entry.<sup>3</sup> With the availability of many chiral auxiliaries, the benzylation approach is a highly attractive one. However, drawbacks include a relative dearth of commercially available benzylic halide precursors and a lack of chemoselectivity toward other embedded functional

**Scheme 1.** Strategies for the Synthesis of  $\alpha$ -Chiral  $\beta$ -Arylated Carbonyls



groups during the alkylation process. The 1,4-addition approach ultimately requires an enantioselective protonation of the enolate, a process that is highly substrate dependent and somewhat variable in its efficacy.<sup>4</sup> Catalytic asymmetric hydrogenation methods have challenges similar to those of the enantioselective protonation and in addition require access to stereodefined trisubstituted alkene substrates.

An alternative approach would derive from the cross-coupling of  $\beta$ -metallo carbonyl substrates with aryl- and

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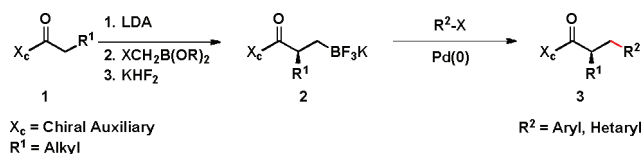
hetaryl halides. Recently, we demonstrated the Suzuki–Miyaura cross-coupling reactions of  $\beta$ -trifluoroborato ketones, esters, and amides, which led to the construction of  $\beta$ -aryl/hetaryl carbonyls.<sup>5</sup> The  $\beta$ -trifluoroborato carbonyl reagents are attractive cross-coupling partners because of their functional group tolerance and minimal toxicity.<sup>6</sup> As a family, potassium organotrifluoroborates have been shown to possess increased stability compared to their boronic acid/boronate counterparts in Suzuki–Miyaura reactions, including an indefinite stability to ambient moisture and a low tendency to protodeboronate during cross-coupling.<sup>7</sup>

Related cross-coupling reagents have been utilized in similar contexts. Thus, Negishi cross-coupling has proven particularly effective for the construction of arylated alanyl derivatives utilizing enantiomerically enriched  $\alpha$ -chiral organozinc coupling partners.<sup>8</sup> However, zinc homoenolates are generally unstable to moisture and air, and consequently they must be prepared in situ and maintained under an inert atmosphere. Furthermore, these organozinc reagents exhibit reactivity with a variety of electrophiles and thus may not be tolerant of other functional groups in desired cross-coupling transformations.<sup>9</sup>

We envisioned that an extension of our previous work on  $\beta$ -trifluoroboratoamides to their enantiomerically enriched counterparts, prepared by employing chiral auxiliaries, would be a valuable tool in asymmetric synthesis. We report herein a protocol for the synthesis of enantioenriched  $\alpha$ -chiral  $\beta$ -trifluoroborato amide substrates and their cross coupling with a variety of aryl- and hetaryl chlorides (Scheme 2). To the best of our knowledge, this chiral reagent class has not previously been prepared or cross-coupled.

One of the concerns in being able to conduct the desired transformation is retention of the stereochemical integrity of the  $\alpha$  stereocenter under the aqueous basic conditions at elevated temperatures required for the organotrifluoroborate cross-coupling. The use of enantiomerically enriched materials in Suzuki–Miyaura cross-coupling reactions where the stereocenter resides  $\alpha$  to a carbonyl is limited to only a few

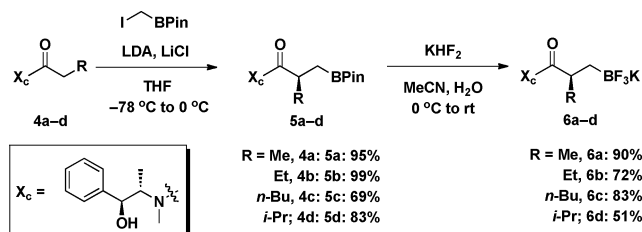
**Scheme 2.** Synthesis and Suzuki–Miyaura Cross-Coupling of Chiral  $\beta$ -Trifluoroboratoamides



examples.<sup>10</sup> In only one of these examples did the stereogenic center reside in the organoboron component.

To prepare the enantiomerically enriched  $\beta$ -trifluoroborato amides **6a–d**, (1*S*,1*S*)-(+)-pseudoephedrine was used as the chiral auxiliary<sup>11</sup> in a modification of a Matteson protocol.<sup>12</sup> Thus the chirality was successfully installed via alkylation of the enolate using iodomethylpinacolboronate. The alkylated products **5a–d** were obtained in relatively high yields. The diastereomeric ratios of **5a–d** were determined to be >95:5 by <sup>1</sup>H NMR of the pinacolboronate intermediate. Subsequent addition of KHF<sub>2</sub> provided enantiomerically enriched potassium trifluoroborato amides **6a–d** in moderate to excellent yields. The prepared  $\beta$ -trifluoroborato amides **6a–d** were moisture- and air-stable solids and thus stored on the bench indefinitely without detectable epimerization or decomposition (Scheme 3).

**Scheme 3.** Preparation of  $\alpha$ -Chiral  $\beta$ -Trifluoroboratoamides



With the enantiomerically enriched  $\beta$ -trifluoroborato amides in hand, we first investigated their application in Suzuki–Miyaura cross-coupling reactions employing **6a** with chlorobenzene to determine optimal conditions. After screening several ligands, bases, solvents, and reaction times, the combination of 5 mol % of Pd(OAc)<sub>2</sub> and 10 mol % of RuPhos in the presence of 3 equiv of K<sub>2</sub>CO<sub>3</sub> in toluene/H<sub>2</sub>O (4:1, 0.25 M) for 22 h emerged as the best conditions, leading to **7a** in 70% isolated yield (Table 1, entry 1).

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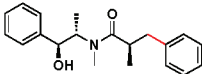
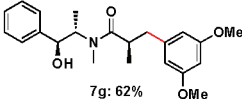
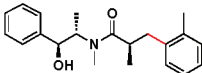
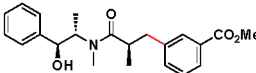
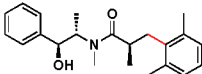
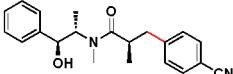
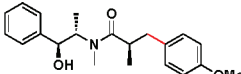
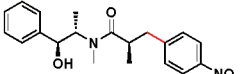
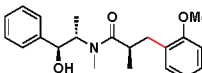
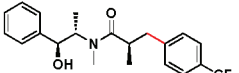
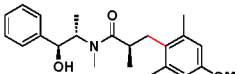
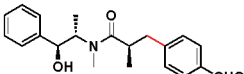
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**Table 1.** Pd-Mediated Cross-Coupling of **6a** with Various Aryl Chlorides

Reaction scheme showing the synthesis of 7a-l from 6a and an aryl chloride (Cl-Ar).

6a: CC(C)(C(=O)N(C)[C@H](O)[C@H](c1ccccc1)C)C(F)(F)F.[K+]

7a-l: CC(C)(C(=O)N(C)[C@H](O)[C@H](c1ccccc1)C)Cc2ccccc2R.[K+]

| entry | product <sup>a</sup><br>yield                                                                             | entry | product <sup>a</sup><br>yield                                                                             |
|-------|-----------------------------------------------------------------------------------------------------------|-------|-----------------------------------------------------------------------------------------------------------|
| 1     | <br>7a: 70%              | 7     | <br>7g: 62%              |
| 2     | <br>7b: 40%              | 8     | <br>7h: 57%              |
| 3     | <br>7c: 38%              | 9     | <br>7i: 75% <sup>b</sup> |
| 4     | <br>7d: 51% <sup>b</sup> | 10    | <br>7j: 75%              |
| 5     | <br>7e: 55%              | 11    | <br>7k: 43%              |
| 6     | <br>7f: 41%             | 12    | <br>7l: 82%             |

<sup>a</sup> 5% Pd(OAc)<sub>2</sub>, 10% RuPhos, 3 equiv of K<sub>2</sub>CO<sub>3</sub>, toluene/H<sub>2</sub>O, 85 °C, 22 h. <sup>b</sup> 5% Pd(OAc)<sub>2</sub>, 10% SPhos, 3 equiv of K<sub>2</sub>CO<sub>3</sub>, toluene/H<sub>2</sub>O, 85 °C, 22 h.

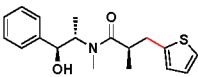
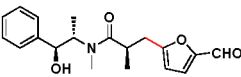
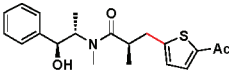
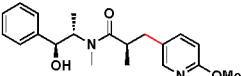
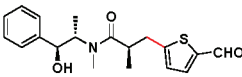
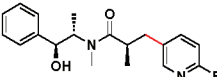
Employing this set of reaction conditions, a variety of aryl chlorides were studied as the coupling partner. Electron-neutral, -donating, and -withdrawing groups on the aryl ring were all tolerated during the cross-coupling reactions. The *ortho*-, *meta*-, and *para*-substituted electrophiles could all be used as suitable coupling partners (Table 1). In certain cases, SPhos was found to be a superior ligand to RuPhos (entries 4 and 9). With increased steric hindrance at the *ortho*-position, the yields dropped dramatically, and generally more hindered electrophiles provided lower yields than less hindered ones (entries 1–3). Electron-rich electrophiles, sometimes known to be poor coupling partners in Suzuki reactions,<sup>13</sup> proceeded well under the same conditions (entries 4–7). Electrophiles containing electron-poor functional groups gave relatively better yields (entries 8–12). Moreover, various functional groups, such as esters, nitriles, nitro groups, and aldehydes, survived the reaction conditions (entries 8–10 and 12). Of note, these functional groups, especially the aldehyde in **7l**, would not be compatible with enolate alkylation routes to the same target structure.

To expand the substrate scope, we also investigated the use of hetaryl chlorides as the coupling partners. Under the

same reaction conditions, nitrogen-, sulfur-, or oxygen-containing hetaryl electrophiles could be cross-coupled with chiral  $\beta$ -trifluoroborato amide **6a** to give the desired products in good to moderate yields (Table 2).

**Table 2.** Pd-Mediated Cross-Coupling of **6a** with Various Hetaryl Chlorides

Reaction scheme showing the conversion of compound **6a** to compound **8a-f** using **HetAr-Cl**.

| entry | product <sup>a</sup><br>yield                                                                        | entry | product <sup>a</sup><br>yield                                                                         |
|-------|------------------------------------------------------------------------------------------------------|-------|-------------------------------------------------------------------------------------------------------|
| 1     | <br><b>8a: 53%</b> | 4     | <br><b>8d: 69%</b> |
| 2     | <br><b>8b: 73%</b> | 5     | <br><b>8e: 55%</b> |
| 3     | <br><b>8c: 60%</b> | 6     | <br><b>8f: 80%</b> |

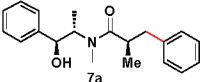
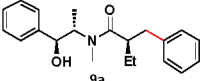
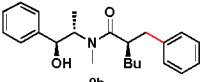
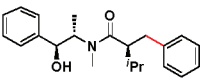
<sup>a</sup> 5% Pd(OAc)<sub>2</sub>, 10% RuPhos, 3 equiv of K<sub>2</sub>CO<sub>3</sub>, toluene/H<sub>2</sub>O, 85 °C, 22 h.

In addition to these studies, Suzuki–Miyaura cross-coupling reactions were conducted with  $\beta$ -trifluoroborato amides **6b–d** possessing different substituents  $\alpha$  to the

**Table 3.** Cross-Coupling Reaction of Various Potassium  $\beta$ -Trifluoroborato Amides with Chlorobenzene

Reaction scheme showing the cross-coupling of 6a-d with chlorobenzene to form products 7a, 9a-c.

Reagents: 5% Pd(OAc)<sub>2</sub>, 10% RuPhos, K<sub>2</sub>CO<sub>3</sub>, toluene/H<sub>2</sub>O, 85 °C.

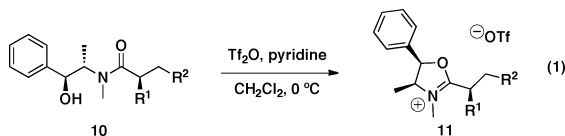
| entry | R            | product                                                                                     | yield            | dr   |
|-------|--------------|---------------------------------------------------------------------------------------------|------------------|------|
| 1     | Me           | <br>7a | 70% <sup>a</sup> | 95:5 |
| 2     | Et           | <br>9a | 70% <sup>a</sup> | 97:3 |
| 3     | <i>n</i> -Bu | <br>9b | 47% <sup>b</sup> | 98:2 |
| 4     | <i>i</i> -Pr | <br>9c | 30% <sup>b</sup> | 98:2 |

<sup>a</sup> 22 h. <sup>b</sup> 48 h.

(13) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 4176.

carbonyl. Again in this series, sterics critically affect the overall yield of the process. As the steric bulk of the substituent at the  $\alpha$ -carbon increased, the reactions required longer times to go to completion, and the yields were dramatically reduced (Table 3).

The degree of stereoretention in the cross-coupled products was determined using the simple one-step protocol developed by Myers employing triflic anhydride-pyridine to form oxazolium triflate derivatives **11** by cyclization of pseudoephedrine amides **10**. The diastereoselectivities of the final products **11** were determined by  $^1\text{H}$  NMR, with the peaks associated with the protons at the  $\alpha$  stereocenter easily detectable (eq 1).<sup>14</sup> For all substituents at the  $\alpha$ -carbon examined, the diastereomeric ratios were greater than 95:5.<sup>15</sup> Unfortunately, the more highly functionalized products displayed in Tables 1 and 2 were incompatible with the triflic acid, and their diastereoselectivities could not be determined in this manner. The stereochemistry of the major diastereomer of **7a** was determined by comparison to the known compound.<sup>11b</sup> The stereochemistry of the remainder of the products was assigned by analogy. Through these studies, we concluded that the diastereoselectivities were preserved throughout the cross-coupling reactions.<sup>14</sup>



In conclusion, the potassium salts of enantiomerically enriched  $\alpha$ -chiral  $\beta$ -trifluoroboratoamides were successfully synthesized using pseudoephedrine as a chiral auxiliary. With these air- and moisture-stable reagents, Suzuki–Miyaura

cross-coupling reactions were studied with various aryl- and hetaryl chlorides, providing an umpolung approach to these valuable materials that is complementary to previously reported protocols. Many of the compounds prepared would be challenging to synthesize by other methods such as direct alkylations with benzylic halides because of the reactivity of the functional groups incorporated (e.g., aldehydes and ketones). Additionally, for alkylation protocols, the relative difficulty in accessing the requisite benzylic halides in both aryl and heteroaryl systems (as compared to the vast array of commercially available aryl- and hetaryl chlorides) also recommends the current procedure. The transformation developed herein provides materials of reliably high diastereoselectivity, a feature that is not always achieved in conjugate addition/enantioselective protonation or asymmetric hydrogenation approaches. The current method thus represents a valuable addition to existing approaches to  $\alpha$ -chiral  $\beta$ -arylated carbonyl target structures.

**Acknowledgment.** We thank the NIGMS (R01 GM035249) for their support of this research. We also acknowledge Dr. Rakesh Kohli (University of Pennsylvania) for obtaining HRMS data.

**Supporting Information Available:** Experimental procedures and spectral data of all compounds synthesized. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(15) See Supporting Information.