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## Enantioselective Desymmetrization via Carbonyl-Directed Catalytic Asymmetric Hydroboration and Suzuki-Miyaura Cross-Coupling

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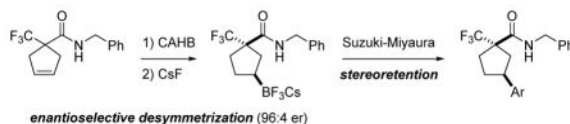
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### Abstract



The rhodium-catalyzed enantioselective desymmetrization of symmetric  $\gamma,\delta$ -unsaturated amides via carbonyl-directed catalytic asymmetric hydroboration (directed CAHB) affords chiral secondary organoboronates with up to 98% ee. The chiral  $\gamma$ -borylated products undergo palladium-catalyzed Suzuki-Miyaura cross-coupling via the trifluoroborate salt with stereoretention.

Chiral organoboronates are useful intermediates in organic synthesis,<sup>1,2</sup> and consequently, a number of research groups are developing enantioselective methods for their preparation.<sup>3–10</sup> We reported the rhodium-catalyzed carbonyl-directed catalytic asymmetric hydroborations (directed CAHBs) of certain (*E*)- and (*Z*)-disubstituted and -trisubstituted  $\beta,\gamma$ -unsaturated amides **1** and 1,1-disubstituted (i.e., methylidene)  $\beta,\gamma$ -unsaturated amides and *tert*-butyl esters **3**.<sup>11</sup> Simple chiral catalyst systems have been identified to give chiral  $\beta$ - and  $\gamma$ -borylated carbonyl compounds with high regio- and  $\pi$ -facial selectivity (Figure 1). We now report the efficient CAHB of symmetric  $\gamma,\delta$ -unsaturated amides **5**. For example, **5a** undergoes carbonyl-directed CAHB with 4,4,6-trimethyl-1,3,2-dioxaborinane (tmdBH, ( $\pm$ )-

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Supporting Information

Experimental procedures and compound characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

**B1**) using  $\text{Rh}(\text{nbd})_2\text{BF}_4$  in conjunction with  $(\text{BINOL})\text{PN}(\text{Bn})\text{Ph}$  (**L1b**) to give the cis- $\gamma$ -borylated amide (*1R,3S*)-**6a** in 80% yield and 94% ee (determined after oxidation) via enantioselective desymmetrization.<sup>12</sup> Asymmetric desymmetrization is a widely used method for generating chiral substances;<sup>13</sup> however, few examples employ CAHB.<sup>14</sup>

Varying the nature of the ligand used (i.e., **L1–L5**) for rhodium-catalyzed CAHB of **5a** by **tmdBH** (**B1**) reveals a number of interesting effects on the sense and degree of enantioselectivity (Figure 2). BINOL-derived phosphoramidites **L1a–b** in combination with **tmdBH** (**B1**) give the most selective catalysts for the formation of (*1R,3S*)-**6a** (93–94% ee). Catalysts formed from TADDOL phenyl phosphites **L2a–L5a** are also quite selective (83–92% ee); small changes in the TADDOL backbone only incrementally affect enantioselectivity. In contrast to the TADDOL-derived phenyl phosphites **L2a–L5a** and BINOL-derived phosphoramidites **L1a/b**, TADDOL-derived phosphoramidites afford catalysts that are much less selective with **tmdBH**; the products obtained are near racemic for most combinations of **L2–5** possessing substituents **b–e**.

The enantioselectivity obtained for CAHB by **pinBH** (**B2**) with catalysts derived from BINOL-derived phosphoramidites **L1a** and **b** and the series of phenyl phosphites **L2a–L5a** is significantly lower (55–81% ee) than obtained with **tmdBH** (Figure 2). However, **pinBH** generally affords higher levels of enantioselectivity with TADDOL-derived phosphoramidites **L2–5b–e**. Furthermore, these phosphoramidites generally give the enantiomeric product compared to that obtained with corresponding phenyl phosphite; enantioselectivity as high as 78% ee for (*1S,3R*)-**6a** is found using **L3c**. The results are in qualitative agreement with our previous report of exceptionally high levels of enantioswitching<sup>15</sup> with the acyclic substrate **1**.<sup>11d</sup>

Using the most promising catalyst system identified in our brief ligand/borane survey (i.e., [**(L1b)**]<sub>2</sub> $\text{Rh}(\text{nbd})\text{BF}_4$ ) with **tmdBH**, a series of  $\gamma,\delta$ -unsaturated amides **5a–I** varying in their amide- and  $\alpha$ -substituents are converted via the  $\gamma$ -borylated intermediate to their chiral cyclopentanols **7a–I** (Table 1 and Figure 3). Phenyl amides **5a–d**, a series of substrates bearing  $\alpha$ -H, -alkyl, -aryl, and  $-\text{CF}_3$  substituents, gave the respective  $\gamma$ -alcohol in good yield and high enantiomeric excess (i.e., **7a–d**, 96:4 to 97:3 er) (entries 1–4). Substituting benzyl for phenyl as the amide substituent gave **7e–h** in comparable yields but slightly lower enantioselectivity; enantiomer ratios ranged from 92:8 to 96:4 (entries 5–8). Chiral substrates **5i** and **5j** bear a chiral phenethyl substituent on the amide nitrogen and were included in the screening to confirm structural assignments (vide infra). These chiral substrates undergo CAHB with somewhat lower stereoselectivity compared to the corresponding phenyl and benzyl amides and exhibit a modest matched/mismatched diastereomer effect (entries 9 and 10).

Two derivatives shown in Figure 3 highlight unusual group-selectivity in the CAHB. Substrates **5k** and **5l** each contain two alkene moieties ostensibly positioned equidistant from the carbonyl directing group, one endocyclic double bond and an unsaturated side chain substituent on the ring. The side-chain alkene is *trans*-disubstituted in the case of **5k** and a methyldene derivative in the case of **5l**. Both substrates undergo CAHB selectively with the endocyclic double bond to give the monounsaturated  $\gamma$ -alcohol [i.e., (*1S,3S*)-**7k** and

**7i**, respectively] in good yield (75–80%) and high enantioselectivity (99:1 and 97:3 er, respectively). We speculate that the preferred orientation of the carbonyl oxygen and/or somewhat greater reactivity for the endocyclic double bond might account for the observed product.

The CAHB of chiral amide **5i** proved useful in unambiguously assigning the absolute configuration of the product and thereby the stereochemical course of the reaction. The intermediate organoboronate generated upon CAHB was converted to the cesium<sup>17</sup> or potassium<sup>18</sup> trifluoroborate by the reported methods. The latter gave crystals of the major diastereomer suitable for x-ray crystallographic analysis; the structure of (1*R*,3*S*)-**8i** (M = K) is shown in Figure 4.

The cross-coupling reactions of chiral, secondary organoboronates have recently attracted a great deal attention.<sup>19</sup> Several examples illustrating successful Suzuki-Miyaura cross-coupling of the benzyl and chiral phenethyl amide derivatives of (1*R*,3*S*)-**8i** (M = Cs) using Buchwald's palladium-precatalyst **10**<sup>20</sup> are summarized in Table 2.<sup>21</sup>

Understanding the stereochemical course of the Suzuki-Miyaura reaction has recently attracted considerable attention.<sup>19</sup> Spectral data obtained for products **9a** and **b** indicate that the cross-coupling is highly diastereoselective. For example, the <sup>19</sup>F NMR spectrum of **9b** shows a single major resonance with no minor peak integrating for more than 6% abundance. As first demonstrated by Crudden,<sup>1g,2</sup> Suzuki-Miyaura cross-couplings of  $\alpha$ -chiral alkylboron compounds possessing adjacent  $\pi$ -systems proceed with stereoretention. However, substrates similar to those used here by Molander<sup>22</sup> and Suginome,<sup>23</sup> as well as other substrates reported by Biscoe,<sup>1a</sup> Morken<sup>4b</sup> and Hall,<sup>24</sup> proceed with stereoinversion. For example, the borylated amides **17** and **19** undergo palladium-catalyzed cross-coupling with near complete *stereoinversion* (Figure 5). The intermediate  $\gamma$ -borylated amide (1*R*,3*S*)-**8i** was coupled with 2-methoxy-5-chloropyridine (**15**); product **9g** was isolated and subsequently converted to its tetrafluoroborate salt **21** (66% overall). The latter gives crystals suitable for x-ray analysis which confirms the structure as (1*R*,3*S*)-**21** and establishes that palladium-catalyzed cross-coupling proceeds with *stereoretention*.

Substrate reactivity is another aspect of the cross-coupling chemistry that has attracted recent attention.<sup>25</sup> For example, Molander<sup>19</sup> proposed that intramolecular hemi-labile  $\pi$ -complexation of palladium by a suitably disposed benzyl substituent was a key element facilitating cross-coupling with stereoretention. In contrast to the corresponding benzyl and phenethyl amides, phenyl amide **22** (M = K or Cs), gives little or no cross-coupling product under the conditions used in Table 2. For example, the attempted cross-coupling of phenyl amide **22** with 1-bromonaphthalene gives only 20% (based on limiting aryl bromide) of the cross-coupled product **23**; in addition, **7c** is isolated in 85% yield (based on the amount of **22**) from the reaction mixture after oxidation with Oxone<sup>®</sup> (Figure 6). The reproducible, low yield of cross-coupled product initially suggested that the greater rotational freedom and reach available to benzyl amides was a necessary feature for efficient cross-coupling. However, the direct competition of equal amounts of phenyl amide **22** and **8i** (R<sup>1</sup> = Ph, R<sup>2</sup> = (*R*)-CH(Me)Ph) for a limiting amount of 1-bromonaphthalene **11** gave surprising results and raise doubt about that explanation (Figure 6). The total yield of cross-coupled products is

high (90% based on the limiting aryl bromide) and a near 1:1 mixture of **23** (48%) and **9c** (42%) is obtained along with commensurate amounts of the respective alcohols **7c** and **7i** resulting from oxidation of the two residual starting materials.

In summary, carbonyl-directed CAHB of  $\gamma,\delta$ -unsaturated substrate **5** proceeds with efficient  $\pi$ -facial discrimination to introduce boron cis with respect to the amide functional group consistent with two-point binding of the substrate as described in a prior computational study;<sup>12</sup> efficient *re/si*-site selectivity by the chiral catalyst controls enantioselectivity. The ligand and the borane employed have striking effects on the level and sense of enantioinduction including in some cases enantioswitching. Unusual group-selectivity is seen in the CAHBs of the doubly  $\gamma,\delta$ -unsaturated substrates **5k** and **5l** for which the endocyclic alkene preferentially undergoes reaction. The chiral  $\gamma$ -trifluoroborates produced via CAHB undergo palladium-catalyzed Suzuki-Miyaura cross-coupling with stereoretention. The amide substituent influences the efficiency of the cross-coupling reaction under the conditions examined, although the reasons are not clear. Further studies are in progress.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

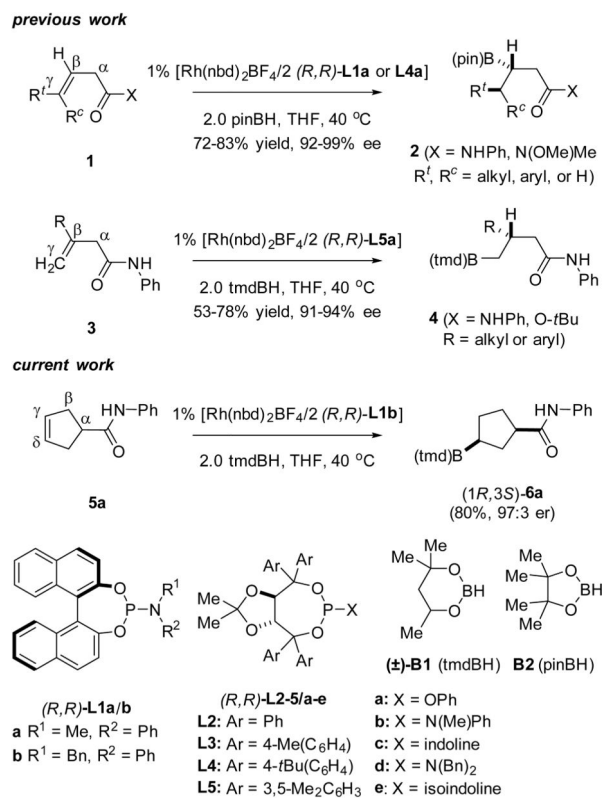
## Acknowledgments

We gratefully acknowledge financial support for these studies from the NIH (GM100101). The crystal structures reported herein were determined by V.W. Day at the KU Small-Molecule X-ray Crystallography Lab using instrumentation purchased with funds from the NSF (CHE-0923449) and the University of Kansas.

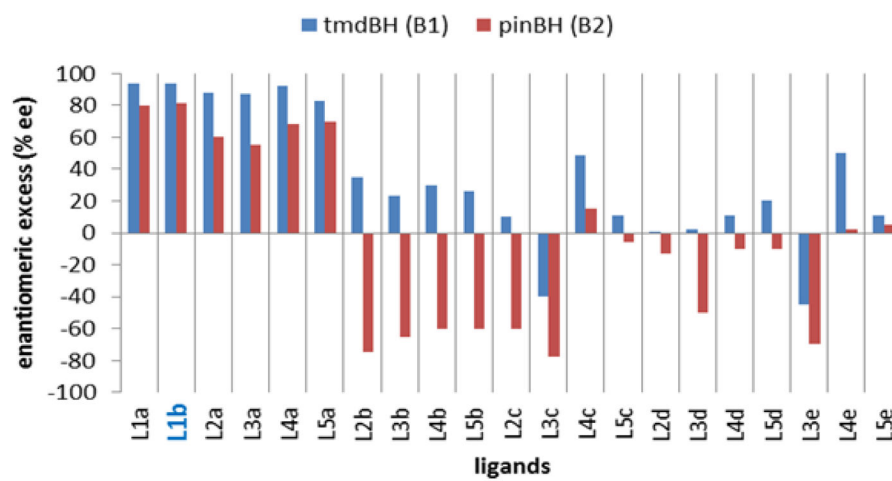
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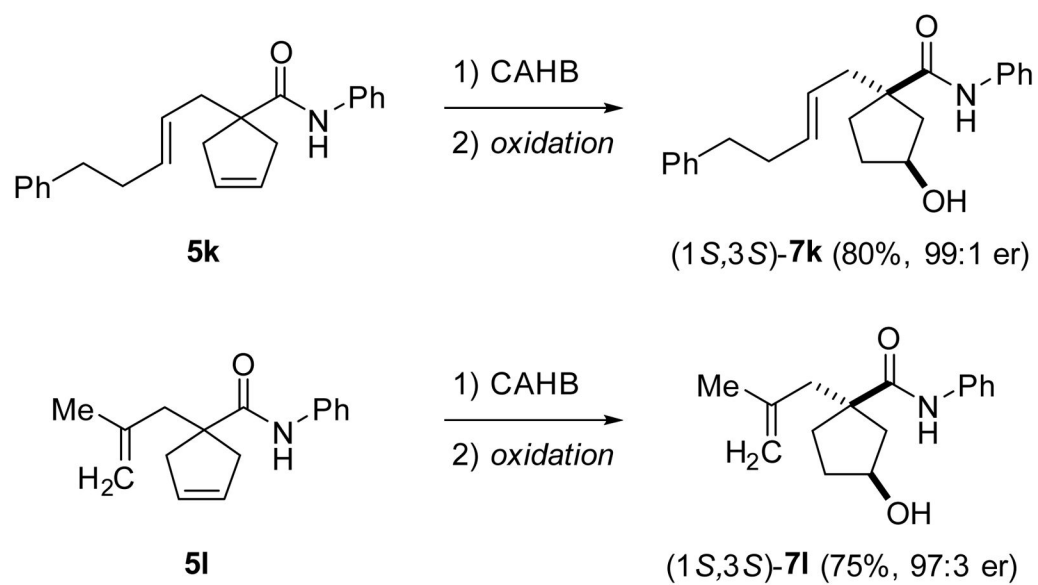
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**Figure 1.** Carbonyl-directed CAHB exploits  $\pi$ -facial selectivity for  $\beta,\gamma$ -unsaturated substrates **1** and **3** and *re/si*-site selectivity for the enantioselective desymmetrization of  $\gamma,\delta$ -substrate **5a**.

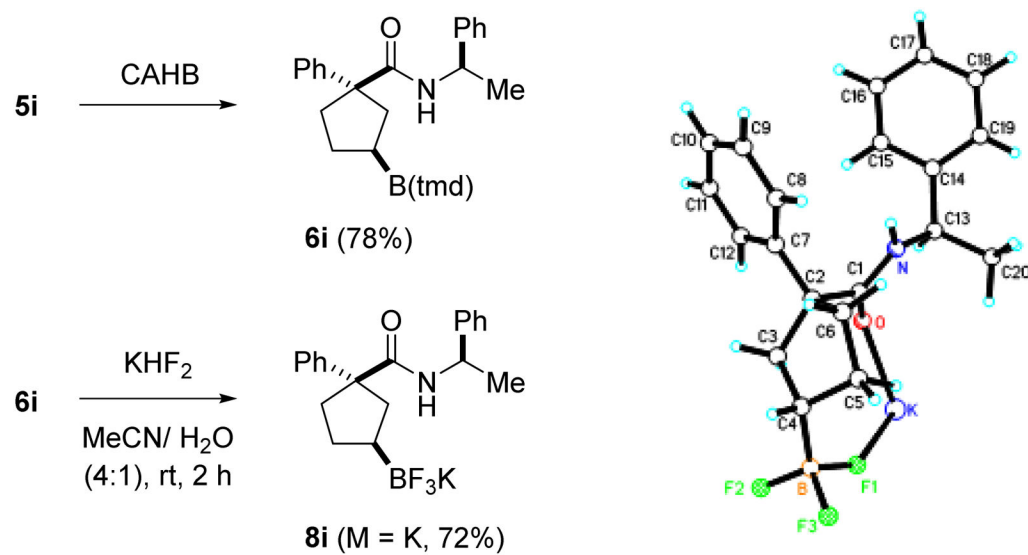


**Figure 2.** Varying the boranes and ligands employed strikingly affects the enantioselectivity for the CAHB of **5a**.<sup>16</sup>

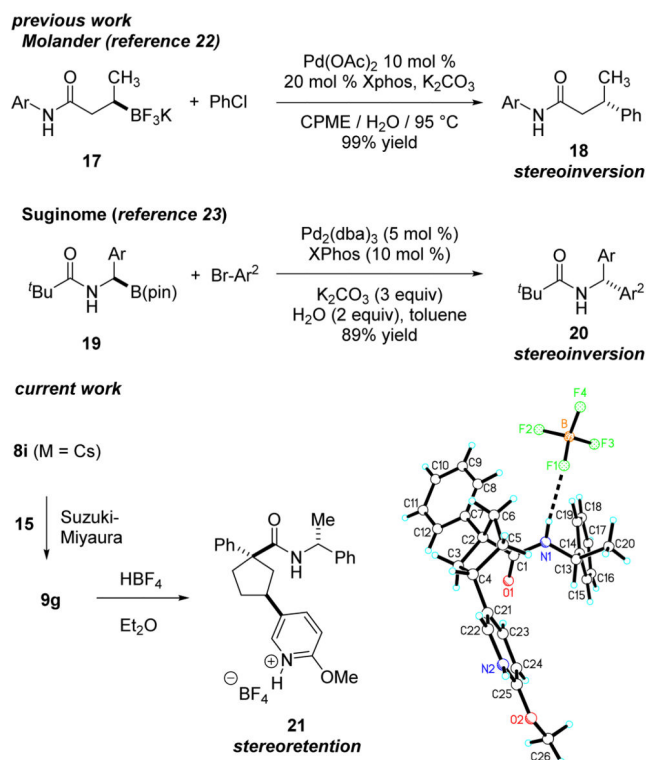


**Figure 3.**  
Group-selective enantioselective desymmetrization.

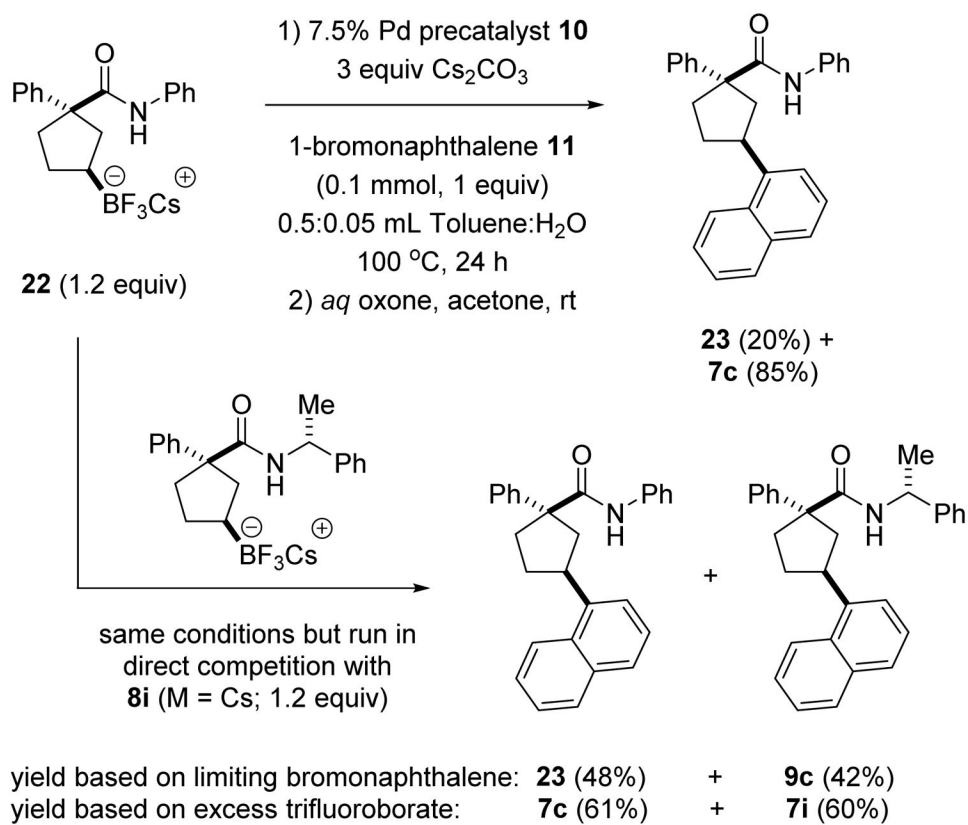




**Figure 4.**  
Preparation and crystal structure of **8i** (M = K).



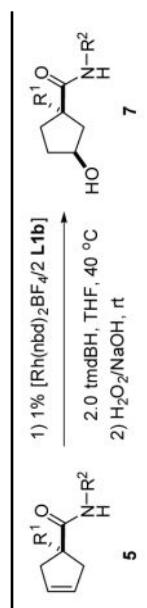
**Figure 5.** In contrast to recent examples of  $\beta$ -borylated amides, palladium-catalyzed cross-coupling of  $\gamma$ -borylated amide (1*R*,3*S*)-**8i** proceeds with stereoretention.



**Figure 6.** Unexpected influence of the amide substituent on the facility of palladium-catalyzed cross-coupling.

Table 1

Enantioselective desymmetrization via CAHB.



entry	5	R <sup>1</sup>	R <sup>2</sup>	yield <sup>a</sup>	er/dr <sup>b</sup>
1	<b>a</b>	H	Ph	80	97:3
2	<b>b</b>	Me	Ph	65	96:4
3	<b>c</b>	Ph	Ph	72	96:4
4	<b>d</b>	CF <sub>3</sub>	Ph	78	97:3
5	<b>e</b>	H	Bn	69	94:6
6	<b>f</b>	Me	Bn	62	92:8
7	<b>g</b>	Ph	Bn	70	93:7
8	<b>h</b>	CF <sub>3</sub>	Bn	71	96:4
9 <sup>c</sup>	<b>i</b>	Ph	( <i>R</i> )-CH(Me)Ph	76	88:12
10 <sup>c</sup>	<b>j</b>	Ph	( <i>S</i> )-CH(Me)Ph	74	20:80

<sup>a</sup> Isolated yields, an average of three experiments generally exhibiting a spread of ±2%.<sup>b</sup> Enantiomer ratio (er) determined by chiral HPLC analysis or diastereomer ratio (dr) determined by <sup>1</sup>H NMR.<sup>c</sup> 2% catalyst loading.

Table 2

Palladium-catalyzed cross-coupling of cesium tri-fluoroborate salt **8i**.

entry	<b>8</b>	<b>R<sup>1</sup></b>	<b>R<sup>2</sup></b>	aryl halide	<b>9</b>	yield <sup>a</sup>
1 <sup>b</sup>	<b>8g</b>	Ph	Bn	<b>11</b>	<b>a</b>	69
2 <sup>b</sup>	<b>8h</b>	CF <sub>3</sub>	Bn	<b>11</b>	<b>b</b>	63
3	<b>8i</b>	Ph	( <i>R</i> )-CH(Me)Ph	<b>11</b>	<b>c</b>	86
4	<b>8i</b>	Ph	( <i>R</i> )-CH(Me)Ph	<b>12</b>	<b>d</b>	66
5	<b>8i</b>	Ph	( <i>R</i> )-CH(Me)Ph	<b>13</b>	<b>e</b>	66
6	<b>8i</b>	Ph	( <i>R</i> )-CH(Me)Ph	<b>14</b>	<b>f</b>	71
7	<b>8i</b>	Ph	( <i>R</i> )-CH(Me)Ph	<b>15</b>	<b>g</b>	75 <sup>c</sup>
8	<b>8i</b>	Ph	( <i>R</i> )-CH(Me)Ph	<b>16</b>	<b>h</b>	70

<sup>a</sup> Isolated yields based on limiting aryl halide, an average ( $\pm 2\%$ ) of two runs.

<sup>b</sup> Cross-coupling proceeds with high diastereoselectivity (ca. 94:6 dr).

<sup>c</sup> 5 equiv of CsOH replaces Cs<sub>2</sub>CO<sub>3</sub>.