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

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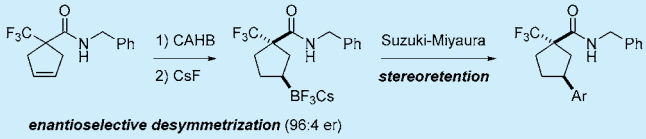
Supporting Information

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



Chiral organoboronates are useful intermediates in organic synthesis,[1,2] and consequently, a number of research groups are developing enantioselective methods for their preparation.[3−10] We reported the rhodium-catalyzed carbonyl-directed catalytic asymmetric hydroborations (directed CAHBs) of certain (*E*)- and (*Z*)-disubstituted and -trisubstituted β,γ-unsaturated amides **1** and 1,1-disubstituted (i.e., methylidene) β,γ-unsaturated amides and *tert*-butyl esters **3**.[11] Simple chiral catalyst systems have been identified to give chiral β- and γ-borylated carbonyl compounds with high regio- and π-facial selectivity (Figure 1). We now report the efficient CAHB of symmetric γ,δ-unsaturated amides **5**. For example, **5a** undergoes carbonyl-directed CAHB with 4,4,6-trimethyl-1,3,2-dioxaborinane (tmdBH, (±)-**B1**) using $Rh(nbd)_2BF_4$ in conjunction with (BINOL)PN(Bn)Ph (**L1b**) to give the cis-γ-borylated amide (1*R*,3*S*)-**6a** in 80% yield and 94% ee (determined after oxidation) via enantioselective desymmetrization.[12] Asymmetric desymmetrization is a widely used method for generating chiral substances;[13] however, few examples employ CAHB.[14]

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 (1*R*,3*S*)-**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 the corresponding phenyl phosphite; an enantioselectivity as high as 78% ee for (1*S*,3*R*)-**6a** is found using **L3c**. The results are in qualitative agreement with our previous report of exceptionally high levels of enantioswitching[15] with the acyclic substrate **1**.[11d]

Using the most promising catalyst system identified in our brief ligand/borane survey (i.e., $[(\mathbf{L1b})_2Rh(nbd)BF_4]$ with tmdBH), a series of γ,δ-unsaturated amides **5a**–**l** varying in their amide- and α-substituents are converted via the γ-borylated intermediate to their chiral cyclopentanols **7a**–**l** (Table 1 and Figure 3). Phenyl amides **5a**–**d**, a series of substrates bearing α-H, -alkyl, -aryl, and $-CF_3$ substituents, gave the respective γ-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

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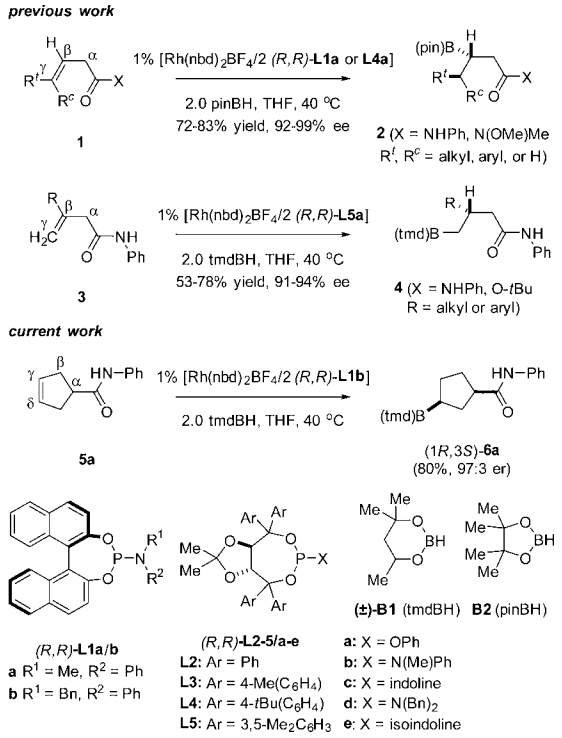


Figure 1. Carbonyl-directed CAHB exploits π-facial selectivity for β,γ-unsaturated substrates **1** and **3** and *re*/*si*-site selectivity for the enantioselective desymmetrization of γ,δ-substrate **5a**.

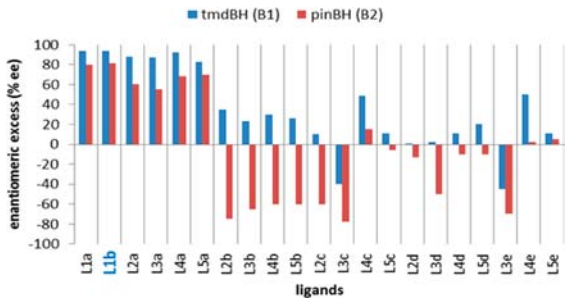


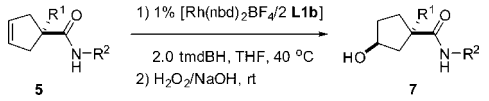
Figure 2. Varying the boranes and ligands employed strikingly affects the enantioselectivity for the CAHB of **5a**.[16]

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 methylidene derivative in the case of **5l**. Both substrates undergo CAHB selectively with the endocyclic double bond to give the monounsaturated γ-alcohol [i.e., (1*S*,3*S*)-**7k** and **7l**, 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

Table 1. Enantioselective Desymmetrization via CAHB



entry	5	R^1	R^2	yield[a]	er/dr[b]
1	**a**	H	Ph	80	97:3
2	**b**	Me	Ph	65	96:4
3	**c**	Ph	Ph	72	96:4
4	**d**	CF_3	Ph	78	97:3
5	**e**	H	Bn	69	94:6
6	**f**	Me	Bn	62	92:8
7	**g**	Ph	Bn	70	93:7
8	**h**	CF_3	Bn	71	96:4
9[c]	**i**	Ph	(*R*)-CH(Me)Ph	76	88:12
10[c]	**j**	Ph	(*S*)-CH(Me)Ph	74	20:80

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

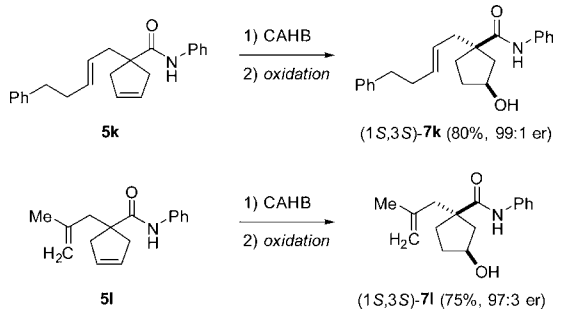


Figure 3. Group-selective enantioselective desymmetrization.

organoboronate generated upon CAHB was converted to the cesium[17] or potassium[18] 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.

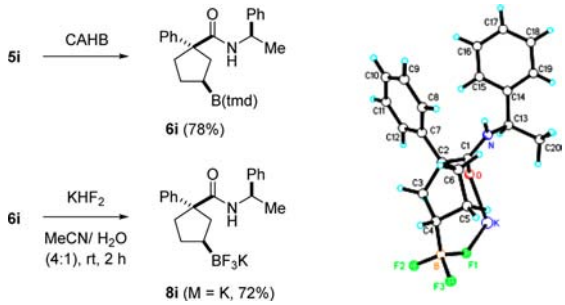


Figure 4. Preparation and crystal structure of **8i** (M = K).

The cross-coupling reactions of chiral, secondary organoboronates have recently attracted a great deal attention.[19] 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**[20] are summarized in Table 2.[21]

Understanding the stereochemical course of the Suzuki−Miyaura reaction has recently attracted considerable attention.[19] Spectral data obtained for products **9a** and **b** indicate that the

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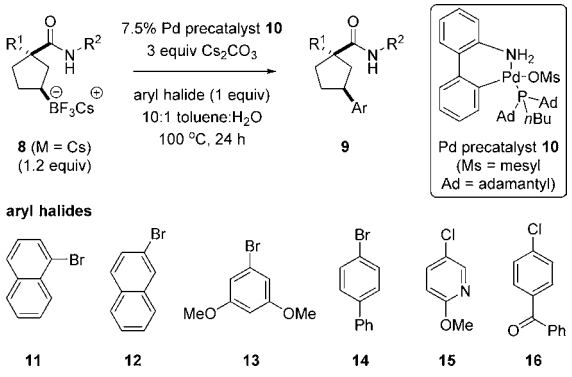
Table 2. Palladium-Catalyzed Cross-Coupling of Cesium Trifluoroborate Salt 8i



entry	8	R^1	R^2	aryl halide	9	yield[a]
1[b]	**8g**	Ph	Bn	**11**	**a**	69
2[b]	**8h**	CF_3	Bn	**11**	**b**	63
3	**8i**	Ph	(*R*)-CH(Me)Ph	**11**	**c**	86
4	**8i**	Ph	(*R*)-CH(Me)Ph	**12**	**d**	66
5	**8i**	Ph	(*R*)-CH(Me)Ph	**13**	**e**	66
6	**8i**	Ph	(*R*)-CH(Me)Ph	**14**	**f**	71
7	**8i**	Ph	(*R*)-CH(Me)Ph	**15**	**g**	75[c]
8	**8i**	Ph	(*R*)-CH(Me)Ph	**16**	**h**	70

[a]Isolated yields based on limiting aryl halide, an average (±2%) of two runs. [b]Cross-coupling proceeds with high diastereoselectivity (ca. 94:6 dr). [c]CsOH (5 equiv) replaces Cs_2CO_3.

cross-coupling is highly diastereoselective. For example, the ^{19}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,[1g,2] Suzuki–Miyaura cross-couplings of α-chiral alkylboron compounds possessing adjacent π-systems proceed with stereoretention. However, substrates similar to those used here by Molander[22] and Suginome,[23] as well as other substrates reported by Biscoe,[1a] Morken,[4b] and Hall,[24] proceed with stereoinversion. For example, the borylated amides **17** and **19** undergo palladium-catalyzed cross-coupling with near complete *stereoinversion* (Figure 5). The intermediate γ-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.[25] For example, Molander[19] proposed that intramolecular hemilabile π-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 (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^1 =

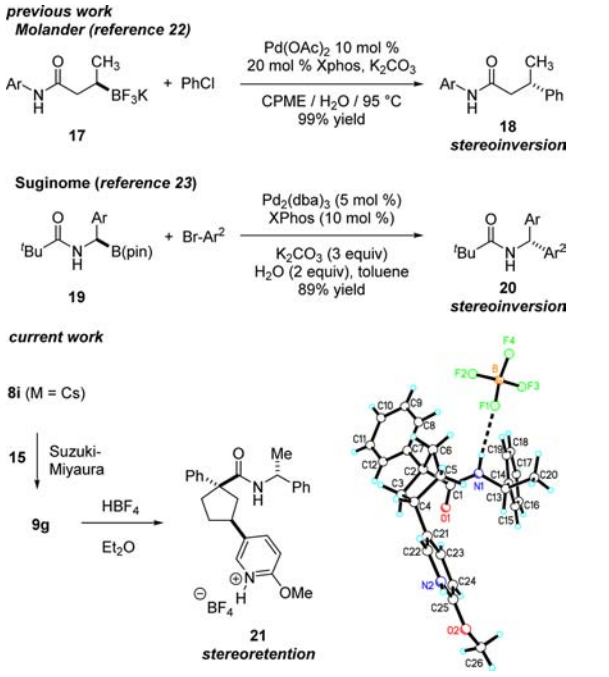


Figure 5. In contrast to recent examples of β-borylated amides, palladium-catalyzed cross-coupling of γ-borylated amide (1*R*,3*S*)-**8i** proceeds with stereoretention.

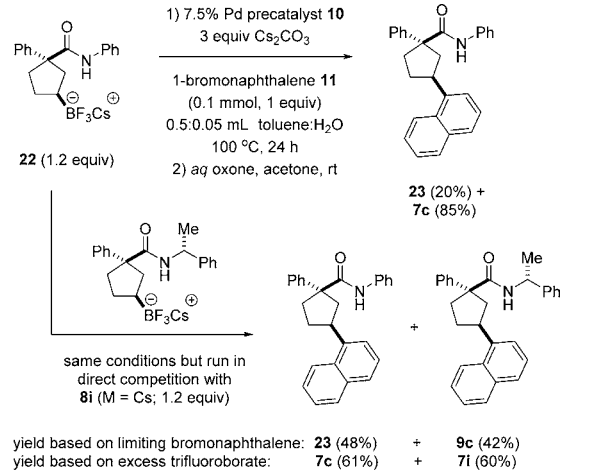


Figure 6. Unexpected influence of the amide substituent on the facility of palladium-catalyzed cross-coupling.

Ph, R^2 = (*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 γ,δ-unsaturated substrate **5** proceeds with efficient π-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;[12] 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.

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Unusual group selectivity is seen in the CAHBs of the doubly γ,δ-unsaturated substrates **5k** and **5l** for which the endocyclic alkene preferentially undergoes reaction. The chiral γ-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.

■ ASSOCIATED CONTENT

Supporting Information

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

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Notes

The authors declare no competing financial interest.

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(16) Conditions: 1% [L_2Rh(nbd)BF_4], 2 equiv **B1** or **B2**, 40 °C, THF; % ee determined by chiral HPLC analysis after oxidation and is an average of two experiments exhibiting a spread of ±1% ee.

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(21) The cesium salt gives higher overall yields in the CAHB/Suzuki-Miyaura cross-coupling sequence, mostly due to higher yields in forming the salt. Data on the corresponding potassium salts are given in the Supporting Information, Figure S1.

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