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COMMUNICATION

Catalytic asymmetric hydroboration of β , γ -unsaturated Weinreb amides: striking influence of the borane[†][‡]

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Subtle differences in the structure of the borane strongly influence the catalytic efficiency and level of enantioselectivity in the catalytic asymmetric hydroboration of β , γ -unsaturated Weinreb amides.

Chiral organoboranes and organoboronates are widely used as chiral reagents for asymmetric synthesis¹ and, along with organoboronate-derived trifluoroborate salts, are valuable synthetic intermediates for subsequent functional group interconversions.² Several methods have also been developed for their stereospecific conversions to carbon-carbon bonds. For example, carbon-carbon bond formation can be accomplished via the Matteson protocol, which exploits a stereospecific rearrangement to effect the one carbon homologation of organoboronates.³ Alternatively, organoboronates have been shown by Knochel to undergo stereospecific transmetalation to zinc enabling carbon-carbon bond formation.⁴ Recent independent reports by Crudden, Molander, Suginome, and Aggarwal now enable stereospecific carbon-carbon bond formation with chiral organoboronates or organoboronatederived trifluoroborate salts via palladium-catalyzed Suzuki-Miyaura cross-coupling⁵ and rhodium-catalyzed carbonyl addition reactions.⁶ These methods greatly enhance the utility of chiral organoboronates and have generated renewed research interest in their enantioselective synthesis.

Several new catalytic asymmetric reactions afford chiral organoboronates in high enantiopurity.^{7–9} Among these, we reported highly enantioselective catalytic asymmetric hydroborations¹⁰ (CAHB) with recent work focusing on the carbonyl-directed reactions of acyclic β , γ -unsaturated phenyl amides.¹¹ BINOL-derived monophosphoramidite L is among the most successful ligands for the latter reactions. For example, β , γ -unsaturated phenyl amide (*E*)-**1a** undergoes CAHB with PinBH (**B1**) using Rh(nbd)₂BF₄ in conjunction with phosphoramidite L to give β -hydroxyamide (*S*)-**3a** in 78% yield and 93% ee after oxidation (Fig. 1). The high levels of regio- and

enantioselectivity are presumably in part a consequence of efficient two-point binding of the substrate carbonyl and alkene moieties to rhodium. $^{12-14}$

N-Phenyl amides have the advantage of being chemically robust. Weinreb amides, while not as robust, are more readily transformed into other useful functional groups.¹⁵ Replacing the *N*-phenyl amide with the Weinreb amide moiety should still permit the desired two-point binding but afford a product with greater potential synthetic utility. However, rhodiumcatalyzed CAHB of (*E*)-**1b** with PinBH (**B1**) affords, after oxidation, the corresponding β -hydroxyacid product (*S*)-**3b** in good yield but relatively disappointing enantiomeric purity (75%, 83% ee). Unlike amide (*E*)-**1a**, the oxidative workup with hydrogen peroxide both replaces the carbon–boron bond and hydrolyzes the amide (Fig. 1).¹⁶

Recent work by Crudden highlighted the mechanistic importance of the borane in the rhodium-catalyzed hydroboration of internal disubstituted alkenes.¹⁷ In other studies, Crudden, Fernandez, and Brown independently reported that PinBH (**B1**) and catecholborane (CatBH, **B11**) can give products with complementary regio- and/or enantioselectivity under otherwise identical conditions.¹⁸ The use of alternative borane sources for catalytic hydroboration otherwise has been fairly limited.¹⁹ Boranes **B7** (TMDB) and **B9** were mentioned in the original report by Männig and Nöth²⁰ describing



Fig. 1 CAHB-oxidation of β , γ -unsaturated Weinreb amide (*E*)-1b.

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Fig. 2 Structures of boranes (*i.e.*, **B1–B12**) evaluated for the CAHB of (*E*)- and (*Z*)- β , γ -unsaturated Weinreb amides.

rhodium-catalyzed hydroboration but have received little use since.²¹ Consequently, a series of five-membered ring 1,3,2-dioxaborolanes **B1–B5**, six-membered ring 1,3,2dioxaborinanes **B6–B10**, CatBH (**B11**), and the hybrid structure **B12** were evaluated in the CAHB of β , γ -unsaturated Weinreb amides (Fig. 2).

Table 1 summarizes the chemical yield and enantioselectivity as a function of borane for the CAHBs of Weinreb amides (*E*)-1b, (*E*)-4, (*E*)-6 and (*Z*)-6. Focusing on (*E*)-1b, the results

 Table 1
 Efficacy of the borane varies as a function of substrate

MeO、	N N	₹ R ^E	1) 1% [Rh(l)/2 L]BF ₄ 2 equiv B1–B12	но	OH R
	Me	R ^z	THF, 40 °C		
			2) aq. NaOH, $\rm H_2O_2$		
(<i>E</i>)- 1b	$(R^E = {}^nC_4H_5)$	(<i>S</i>)- 3b (R =	= ⁿ C₄H ₉)		
(<i>E</i>)- 4	$(R^E = CH_2C)$	(<i>S</i>)-5 (R = 9	CH ₂ CH ₂ Ph)		
(<i>E</i>)- 6	$(R^{E} = C_{2}H_{5},$	$R^Z = H$)		(<i>S</i>)-7 (R = 0	C ₂ H ₅)
(<i>Z</i>)-6	$(R^E = H, R^Z)$	$= C_2H_5)$			

	% Yield (% ee) for the CAHB of					
Borane	(<i>E</i>)-1b	(<i>E</i>)- 4	(<i>E</i>)-6	(Z)-6		
B1	75 (83)	75 (75)	70 (50)	70 (82)		
B2	79 (84)	50 (85)	40 (88)	40 (87)		
B3	40 (81)	40 (60)	30 (55)	42 (83)		
B4	10 (50)	25 (7)	15 (14)	20 (20)		
B5	16 (14)	5 (6)	25 (5)	10 (3)		
B6	78 (90)	30 (91)	70 (73)	50 (98)		
B7	77 (92)	76 (96)	73 (97)	72 (97)		
(R)- B7	_ ` ´	_ ` ´	71 (96)	_ ` ´		
(S)- B7	_	_	73 (97)			
B 8	81 (97)	40 (88)	11 (60)	20 (96)		
B9	50 (81)	20 (70)	15 (32)	60 (93)		
B10	78 (94)	25 (80)	10 (58)	32 (91)		
B11 ^{<i>a</i>}	16 (15)	20 (10)	15 (15)	12 (20)		
B12 ^{<i>a</i>}	75 (50) ^b	$15(70)^{b}$	79 $(5)^{6}$	75 (44) ^b		

^{*a*} Reaction was carried out at room temperature. ^{*b*} In contrast to other boranes, the (*R*)-enantiomer of the β -hydroxyacid predominates with **B12**.

obtained using the six-membered ring dioxaborinanes **B6–B10** are on average more selective (average of 70% ee) than those obtained using the five-membered ring dioxaborolanes **B1–B5** (average of 49% ee). Comparing specific five- and six-membered ring boranes with similar methyl substitution patterns finds some similarities and some extreme differences. For example, the tetramethyl derivatives, **B1** (PinBH, 83% ee) and **B6** (90% ee), and trimethyl derivatives, **B2** (84% ee) and **B7** (92% ee) afford quite similar results. In contrast, the monomethyl derivatives, **B5** (14% ee) and **B10** (94% ee) differ radically.²²

CatBH (**B11**) was at one time the most commonly used borane for rhodium-catalyzed hydroborations, particularly for the hydroborations of vinylarenes.²³ However, CatBH (**B11**) affords only low levels of asymmetric induction in the CAHB of (*E*)-**1b**. While all other boranes tested give predominantly (*S*)-**3b**, the hybrid borane **B12** produces (*R*)-**3b** as the major enantiomer, albeit the enantiomeric excess (50%) is only modest.²⁴

As shown in Table 1, all four substrates undergo highly selective CAHB-oxidation with TMDB (**B7**). Their corresponding β -hydroxyacids are isolated in good yield (72–77%) and high enantiopurity (92–97% ee). TMDB (**B7**) is chiral and thus raises the possibility of matched/mismatched stereochemical influences in its CAHB reactions. However, this does not appear to be the case. The individual (*R*)- and (*S*)-TMDB reagents were prepared and each found to add to (*E*)-**6** to give (*S*)-**7** with essentially the same efficiency, 71% yield (96% ee) with (*R*)-TMDB and 73% yield (97% ee) with (*S*)-TMDB.

The alkene geometry is important with some of the boranes tested. Both (*E*)- and (*Z*)-6 give (*S*)-7 in comparable enantiomeric excess with **B2** (87–88% ee) and with TMDB (**B7**, 97% ee). In contrast, the tetramethylsubstituted boranes PinBH (**B1**) and **B6** show significant differences; (*Z*)-6 reacts with higher selectivity (82% and 98% ee for PinBH (**B1**) and **B6**, respectively) than (*E*)-6 (50% and 73% ee, respectively). Similarly, the corresponding *gem*-dimethyl substituted borane derivative **B3** affords (*S*)-7 in only 55% ee from (*E*)-6 but in higher selectivity (83% ee) from (*Z*)-6. The corresponding reactions using *gem*-dimethyl derivative **B8** give 60% and 96% ee, respectively, from the (*E*)- and (*Z*)-isomers of **6**.

In addition to the variation in enantioselectivity, the yield of β -hydroxyacid varies widely as a function of borane. PinBH (B1) and TMBD (B7) consistently give good yields (70–77%) across the series of substrates. Other boranes, for example, B3, **B4** and **B5**, consistently give low yields (5–42%) for all substrates. In still other puzzling cases (e.g., B2, B6, B8 and B10), the yield varies widely among the substrates. For example, **B8** gives 96-97% ee in the reactions both of (*E*)-1b and (Z)-6. The yields, however, are 81% for the former and only 20% for the latter. The yield of rhodium-catalyzed hydroboration can be compromised by competing catalyzed disproportionation of the borane.²⁵ This seems to contribute to the low yield of the hydroboration product in at least some of the examples shown in Table 1. For example, the CAHB of (E)-6 was monitored via ¹¹B NMR for selected boranes. It was found that several of the less effective boranes (e.g., B2, B8 and **B10**) are competitively consumed via disproportionation leaving unreacted (E)-6 accompanying the desired hydroborated product.



Scheme 1 (a) KHF₂, MeOH/H₂O (82%); (b) NaBO₃, H₂O/THF (98%); (c) TBSCl, imidazole, DMAP, DMF (82%); (d) DIBAL-H, THF (91%); (e) PhMgBr, THF (94%).

As demonstrated above, the CAHB-oxidation (i.e., workup with basic H₂O₂) of β , γ -unsaturated Weinreb amides can be used to prepare β -hydroxyacids in good yields and excellent levels of enantiopurity. Omitting the harsh oxidative workup by directly subjecting the crude reaction mixture to flash chromatography on silica gel, permits isolation of the chiral organoboronate. For example, 8 is obtained in good yield (79%) from (E)-4. Scheme 1 shows several subsequent transformations to illustrate its synthetic utility. Conversion of 8 to the β -trifluoroborato Weinreb amide 9 is accomplished in 82% yield by treatment with KHF₂. Mild oxidation of **8** with sodium perborate (NaBO₃) proceeds without amide hydrolysis to afford the β -hydroxy Weinreb amide 10 (98% yield). Following TBS-protection (82%), half reduction via treatment with DIBAL-H gives the β -silvloxyaldehyde 11 (91%). Alternatively, addition of phenyl Grignard reagent produces the β -silyloxyketone 12 (94%).

In summary, Weinreb amides are effective substrates for carbonyl-directed CAHB of β , γ -unsaturated alkenes. Large differences in reactivity and selectivity are observed when Weinreb amides are screened across a library of 1,3,2-dioxaborolane and -dioxaborinane derivatives illustrating the importance of the borane in the success of the reaction. It seems clear that the structure of the borane must influence the relative stabilities and/ or reactivities of key intermediates. Mechanistic studies are in progress.

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