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Rhodium-catalyzed asymmetric hydroboration of γ,δ-unsaturated amide derivatives: δ-borylated amides‡

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γ,δ-Unsaturated amides in which the alkene moiety bears an aryl or heteroaryl substituent undergo regioselective rhodium-catalyzed δ-borylation by pinacolborane to afford chiral secondary benzylic boronic esters. The results contrast the γ-borylation of γ,δ-unsaturated amides in which the disubstituted alkene moiety bears only alkyl substituents; the reversal in regioschemistry is coupled with a reversal in the sense of π-facial selectivity.

Chiral boronic acid derivatives are useful building blocks for the synthesis of biologically active natural products and pharmaceutical intermediates.[1] Structures in which boron is attached to the same carbon as an aryl or heteroaryl substituent (i.e., benzylic boronic acid derivatives) are of particular synthetic interest. The catalytic asymmetric hydroboration (CAHB) of styrene and related vinyl arenes to yield benzylic boronic esters was first reported in the mid-1980s.[2,3] The observed regioselectivity is often attributed to the formation of a π-benzyl metal intermediate en route to the benzyl borylated product.[3c,d] In spite of its long history and foundational impact on CAHB,[4] the chemistry has largely been limited to simple vinyl arenes; Rh(I)/QUINAZOLINE[5] and Cu(I)/DTBM-SEGPHOS[6] are among a few catalyst systems that exhibit high selectivity for unfunctionalized β-substituted vinyl arenes.

Figure 1 highlights several alternative methods for the preparation of chiral benzylic boron derivatives that have attracted recent interest. Hall,[7] Yun,[8] and Morken[9] independently reported group-selective cross-coupling of chiral *gem*-diboron derivatives. The methods of Hall and Yun exploit stereoretentive Pd-catalyzed cross-coupling of chiral 1,1-diborylalkanes. Morken uses enantiotopic group-selective cross-coupling of achiral 1,1-diborylalkane derivatives using a chiral palladium catalyst. Toste developed a novel three component coupling strategy using an α-olefin, an

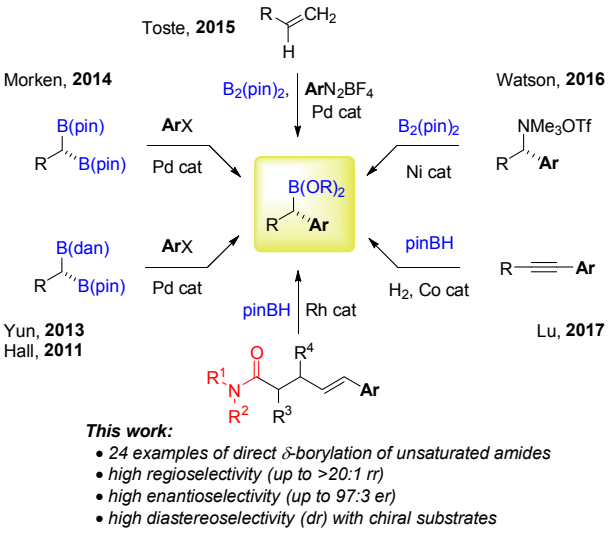

Fig. 1 Recent approaches in preparation of chiral benzylic boronic esters.

aryldiazonium salt, and bis(pinacolato)diboron (B_2pin_2); the enantioselectivity is controlled by a cooperative chiral anion phase transfer catalyst in conjunction with a palladium catalyst.[10] Watson constructed the desired chiral boronic ester derivatives via stereospecific nickel-catalyzed Miyaura borylation of a chiral ammonium salt precursor by B_2pin_2.[11] Most recently, Lu introduced a one-pot cobalt-catalyzed sequential hydroboration/hydrogenation of internal alkynes.[12] Other recently developed methods for the preparation of benzylic boron derivatives include enantioselective conjugate borylation,[13] enantioselective allylic borylation[14] and asymmetric hydrogenation[15] as well as functionalization[16] of vinyl boronates. Herein, we report that γ,δ-unsaturated carbonyl compounds, in which the disubstituted alkene moiety bears an aryl or heteroaryl substituent, undergo efficient CAHB to yield functionalized chiral benzylic boron derivatives.

We have explored rhodium-catalyzed directed-CAHBs of a range of β,γ-unsaturated substrates with varying alkene

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substitution patterns and bearing carbonyl,[17] oxime ether,[18] and phosphonate[19] functionalities. To expand the substrate scope, we are investigating the homologous γ,δ-unsaturated substrates[20] and recently reported that γ,δ-unsaturated amides **1**, in which the alkene moiety bears *only alkyl substituents*, undergo efficient regio- and enantioselective γ-borylation (Fig. 2). For example, benzyl amide **1** (R = $(CH_2)_2$Ph) affords the γ-borylated product **2** (81%) in a >20:1 regioisomer ratio (rr) and a high enantiomer ratio (96.5:3.5 er).[21] We now report that the analogous γ,δ-unsaturated benzyl amide **3a** (R = Ph), in which the alkene moiety instead bears *an aryl substituent*, behaves much differently. Using the same catalyst system, CAHB proceeds with good regiocontrol (>20:1 rr) to give a chiral, secondary benzylic boronic ester, i.e., **4a** (89%, 95:5 er). Unlike product **2**, **4a** is the result of δ-borylation not γ-borylation, and the sense of π-facial selectivity is reversed; pinBH adds to the opposite faces of the π-system in the two substrates.[22]

While we have not carried extensive ligand optimization studies, the series of BINOL-derived phosphoramidites **B1**–**B5** indicate that an *N*-phenyl substituent on the phosphoramidite ligand is needed to achieve good conversion and high levels of regio- and enantioselectivity (Fig. 2).[23] Ligands **B1** and **B2** give the major product **4a** in high yield and enantioselectivity (87–89%, 95:5 er). Ligand **B3**, the corresponding *N*,*N*-diphenyl derivative, also affords **4a** in good yield (87%) and with high regioselectivity (>20:1 rr), but the er is lower in this case (85:15); however, **B3** proves more successful with other substrates (*vide infra*). The *N*,*N*-dibenzyl ligand **B4** and the more rigid indoline- derived phosphoramidite **B5** afford catalysts giving relatively

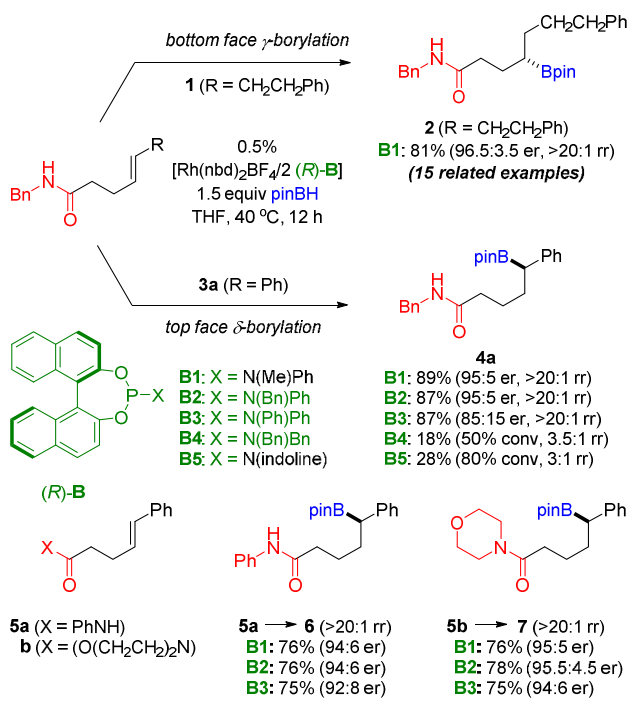

Fig. 2 Regiocontrolled CAHB of γ,δ-unsaturated amides: the effect of aliphatic and aromatic substituents.

low conversion (50–80% after 12 hours), lower regioselectivity (<4:1 rr) and consequently a low isolated yield of **4a** (18–28%).[24] In addition to the *N*-benzyl amide **3a**, the *N*-phenyl amide **5a** and the morpholine-derived tertiary amide **5b** are also good substrates; CAHB affords δ-borylated product **6** (**B1**: 76%, 94:6 er) and **7** (**B2**: 78%, 95.5:4.5 er), respectively.

Figure 3 shows the results obtained under the standard reaction conditions for a series of γ,δ-unsaturated benzyl amides **3**. Using ligands **B1–3**, the most efficient catalyst system varied among the different substrates. For example, although the *N*,*N*-diphenyl ligand **B3** gives relatively low enantioselectivity compared to **B1** and **B2** for substrate **3a**, it gives the highest level of induction for **3b**, a substrate bearing a relatively electron poor aryl substituent (i.e., 4-$CF_3C_6H_4$). CAHB with **B3** affords δ-borylated amide **4b** (78%, 95:5 er); **B1** and **B2** give comparable yields but only 91:9 and 90:10 er, respectively. Substrates **4c** and **4d**, 4-fluorophenyl and 4-chlorophenyl derivatives, undergo CAHB in good yield and enantioselectivity (75–77%, 95:5 er). Aryl derivatives bearing alkoxy group(s) at the *para*- and/or *meta*-positions undergo efficient CAHB (71–80%, >20:1 rr) as illustrated by the 4-methoxyphenyl (**4e**, 96:4 er), 3 methoxyphenyl (**4f**, 97:3 er), 3,5-dimethoxyphenyl (**4g**, 96.5:3.5 er) and 3,4-dialkoxyphenyl (**4h**, 92:8 er) derivatives. The product bearing a 2-methoxyphenyl-substituent (**4i**, 82%, >20:1 rr) is obtained in good yield but with lower enantioselectivity (85:15 er); the corresponding 2-methylphenyl derivative is somewhat more efficient (**4j**, 84%, 93:7 er). A series of four heteroaromatic substrates, although more sluggish to react, undergo CAHB yielding **4k–n** with good regio and enantioselectivity (69–73% yield, 92:8–97:3 er, 11–>20:1 rr); three equivalents of pinBH are employed to achieve complete conversion in 12 hours.

Substrate **8**, chiral by virtue of the stereodefined (*R*)-phenethyl amide moiety, undergoes highly regioselective CAHB (>20:1 rr) (Fig. 4). CAHB/oxidation of **8** using ligand (*R*)-**B1** affords (5*R*)-**9** (82%, 94.5:5.5 dr); the yield and enantioselectivity are comparable to that obtained for the parent substrate **3a**. CAHB using (*S*)-**B1** generates the diastereomer (5*S*)-**9** in similar yield (80%) but with a somewhat diminished diastereomer ratio (91:9 dr) indicating a modest matched/mismatched case of double stereodifferentiation. Chiral substrate **10** also undergoes largely catalyst-controlled diastereoselective δ-borylation. CAHB/oxidation using (*R*)-**B1** gives predominantly (2*R*,5*R*)-**11** (79%, 91:9 dr); (*S*)-**B1** gives predominantly (2*R*,5*S*)-**11** (79%, 92:8 dr). In contrast, the *anti*-β-silyloxybenzyl amide **12** undergoes CAHB/oxidation with lower diastereoselectivity and exhibits a strong matched/mismatched effect. (*R*)-**B2** affords (2*S*,3*S*,5*R*)- **13** (75%, 86:14 dr); the catalyst employing (*S*)-**B2** exhibits lower reactivity (i.e., only 85% conversion after 12 hours) and gives the same major diastereomer of **13** but with much lower diastereoselectivity (67:33 dr).

The question naturally arises, why do **3a** and related substrates afford δ-borylation while **1** gives γ-borylation? The modest, but energetically significant, matched/mismatched change in diastereoselectivity for CAHB of chiral amide **8** (Fig. 4) indicates that the resident stereogenic center is positioned

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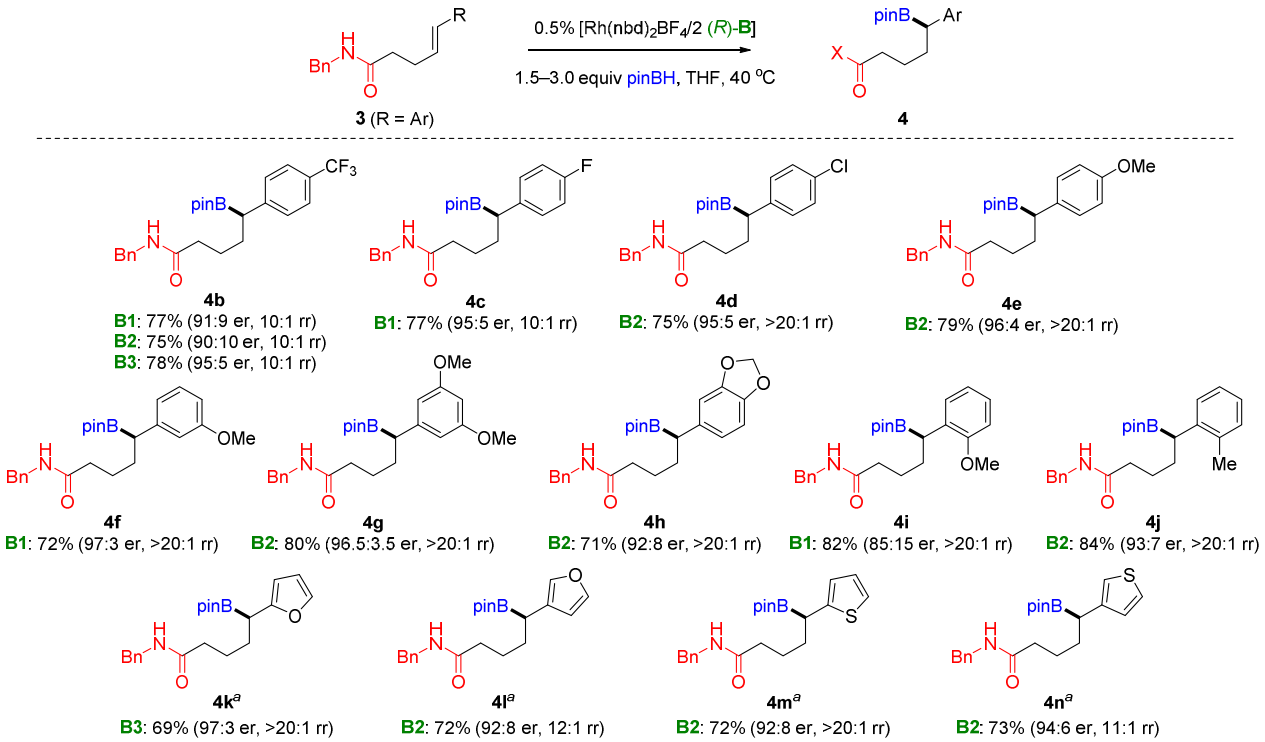

Fig. 3 Substrate scope for CAHB of aryl-substituted γ,δ-unsaturated amides. [a] 3.0 equivalents of pinBH are used.

close to the rhodium-complexed alkene as one would expect in a carbonyl-directed CAHB. The ester moiety in **14** and more so the TIPS ether in **16** are less likely to direct the rhodium-catalyzed reaction. Each undergoes CAHB in good yield and

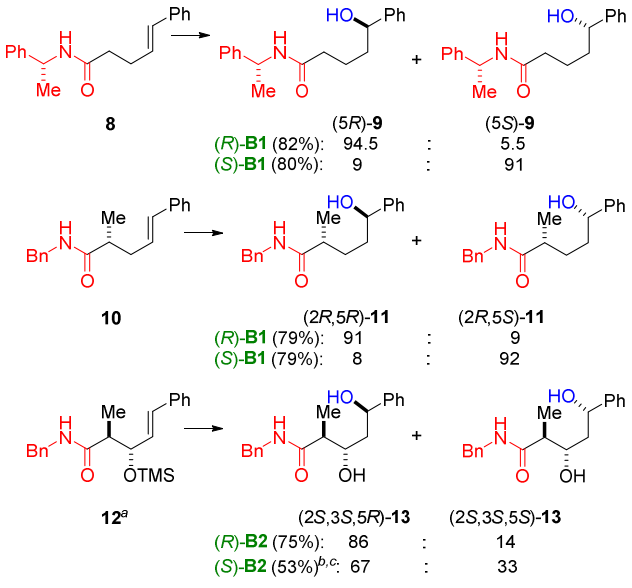

Fig. 4 Diastereoselective CAHB/oxidation of chiral substrates. Unless otherwise noted, the reaction conditions employ 1.0% [Rh(nbd)$_2$BF$_4$/2 **B**], 1.5 pinBH in THF (40 °C, 12 h) followed by oxidation (H_2O_2, aq NaOH, rt, 1 h); the reported yields are for the isolated mixture of inseparable diastereomers. [a] 3.0% [Rh(nbd)$_2$BF$_4$/2 **B**]. [b] NMR yield. [c] ca. 85% conversion.

with high regioselectivity (75–77% yield, >20:1 rr), but compared to amides **3a**, **5a** and **5b,** the level of enantioselectivity is lower, 85:15 for ester **14** and 90:10 er for TIPS ether **16**. Furthermore, in the direct competition between equivalent amounts of **3a** and **16** for a limiting amount of pinBH, **3a** is consumed somewhat faster.[25] The one carbon homologue of **3a**, that is, δ,ε-unsaturated amide **18**, increases the distance between directing group and the alkene; CAHB affords the benzylic, ε-borylated product **19** (78%, >20:1 rr, 90.5:9.5 er). These results seem to indicate that the aryl substituent directs the regiochemistry, but the nature of the directing group is important in determining the level of catalyst-controlled enantioselectivity.

In conclusion, we report the δ-borylation of γ,δ-unsaturated amides bearing an aryl/heteroaryl substituent on the alkene. The results contrast those obtained for CAHB of γ,δ-unsaturated amides bearing only alkyl substituents on the alkene, which differ both in terms of regioselectivity and π-facial selectivity. A brief ligand survey suggests that an *N*-aryl substituent is a necessary feature of the BINOL-derived phosphoramidite ligand. While chiral phosphoramidites[26] and BINOL-derived ligands[27] have found extensive use in asymmetric catalysis, phosphoramidites derived from *N*-aryl amines have less commonly been used; their requirement here is somewhat unusual.[24,28] The reaction exhibits a fairly broad scope with respect to vinyl arene moiety; the successful use of furan and thiophene derivatives and the catalyst-controlled diastereoselective δ-borylation of certain chiral substrates are

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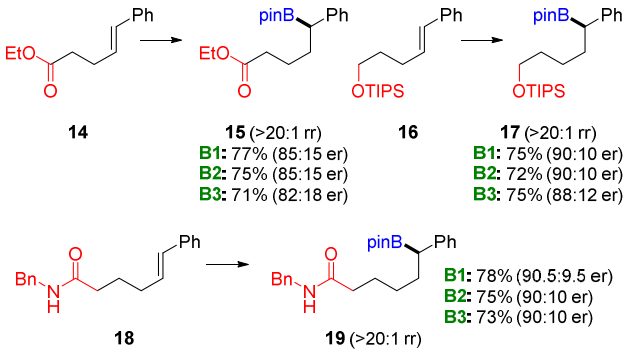

Fig. 5 Other directing groups exhibit lower levels of enantioselectivity.

of particular note. Whether or not δ-borylation is the result of carbonyl-directed CAHB is mechanistically interesting but does not greatly impact the potential utility of the process. Nonetheless, the nature of the directing group is important to the level of enantioselectivity. Further studies on the influence of aryl-substituents on directed-CAHBs are in progress.

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Conflicts of interest

There are no conflicts to declare.

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22 For a rationalization of similarly coupled changes in regioselectivity and π-facial discrimination, see 17a.

23 (*a*) Unless otherwise noted, the isolated yield of the major boronic ester is reported. Enantiomer ratios (er) are determined by chiral HPLC analysis of the corresponding alcohols after oxidation or by ^{19}F NMR analysis of their Mosher esters. Diastereomer ratios are determined by NMR analysis; see the ESI for details. (*b*) A 2:1 ligand-to-metal ratio is employed in this study. A more active catalyst is formed using a 1:1 ratio, but the yield and enantioselectivity are generally diminished by 5–10%.

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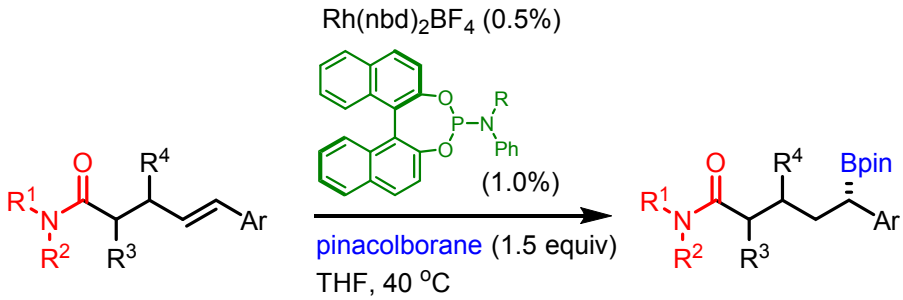

- *24 examples of direct δ-borylation of unsaturated amides*
- *aryl and heteroaryl substituents tolerated*
- *high regioselectivity (up to >20:1 rr)*
- *high enantioselectivity (up to 97:3 er)*
- *high diastereoselectivity (dr) with chiral substrates*