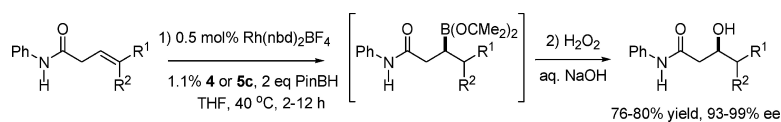


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J. Am. Chem. Soc., **2008**, 130 (12), 3734-3735 • DOI: 10.1021/ja710492q

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Efficient Amide-Directed Catalytic Asymmetric Hydroboration

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Rhodium-catalyzed hydroboration has attracted much interest, in part, because certain substrates react with complementary regio- and diastereoselectivity as compared to the noncatalyzed reaction.¹ The novel regiocontrol is exemplified by the rhodium-catalyzed hydroboration of styrene which introduces boron at the benzylic position yielding, after oxidation, predominately the α -aryl alcohol, 1-phenylethanol. The catalytic asymmetric variant of catalyzed hydroboration is generally limited to the reactions of vinyl arenes.² We recently reported that two simple TADDOL-derived phosphite and phosphoramidite ligands afford high levels of enantioselectivity (90–96% ee) in the rhodium-catalyzed asymmetric hydroborations across a series of styrenes **1** (R = OMe, CH₃, H, CF₃, Cl, F) (Figure 1).^{3,4} We now find that acyclic β,γ -unsaturated amides also undergo regio- and enantioselective rhodium-catalyzed hydroboration with pinacolborane (PinBH) using simple chiral monophosphite or phosphoramidite ligands.

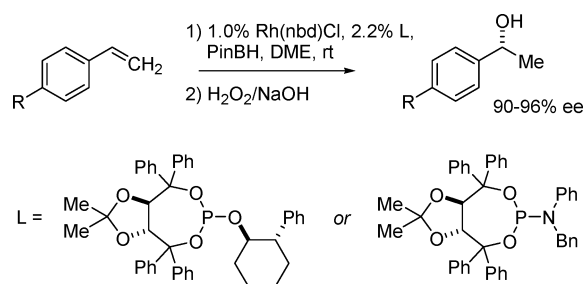


Figure 1. Use of chiral phosphites and phosphoramidites in the rhodium-catalyzed asymmetric hydroboration of 4-substituted styrenes.

Evans and co-workers discovered that rhodium- and iridium-catalyzed hydroborations of certain β,γ -unsaturated amides proceed with novel regiocontrol affording predominantly the β -hydroxy carbonyl derivatives in preference to the γ -isomers.⁵ The observed regiocontrol is attributed to directing by the amide moiety;⁶ that is, the reaction is apparently facilitated by favorable two-point binding of the amide and alkene moieties to rhodium. Two-point substrate binding also plays an important role in rhodium-catalyzed asymmetric hydrogenation,⁷ an important catalytic asymmetric reaction for which simple chiral monophosphites and phosphoramidites are very effective ligands.⁸ Thus, it seemed reasonable that rhodium-catalyzed asymmetric hydroboration also stood a good chance of success using such ligands. Our results bear out this expectation.⁹

After exploring several catalyst systems and reaction conditions,¹⁰ it was found that rhodium-catalyzed hydroboration of (*E*)-**1** with PinBH (0.5 mol % Rh(nbd)₂BF₄, 1.1 mol % BINOL-derived phosphoramidite **4**, THF, 40 °C, 2 h) affords the β -substituted amide **2** (Figure 2). Organoboronates are useful intermediates for a variety of subsequent reactions,¹¹ the most common of course being the oxidative B-to-O conversion to give the corresponding alcohol with a retention of configuration. After oxidation with basic hydrogen

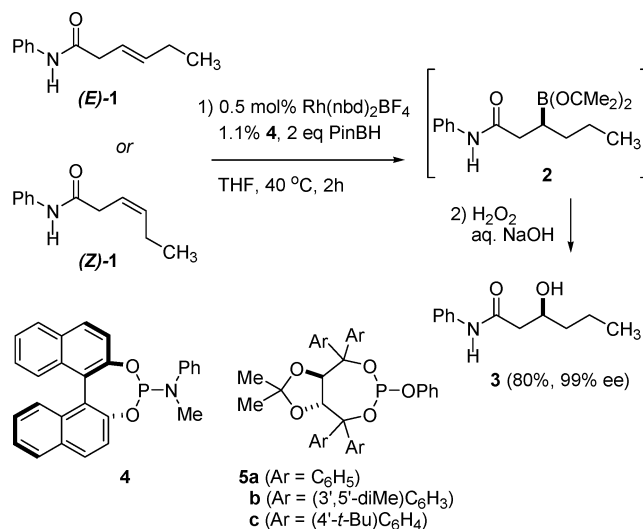
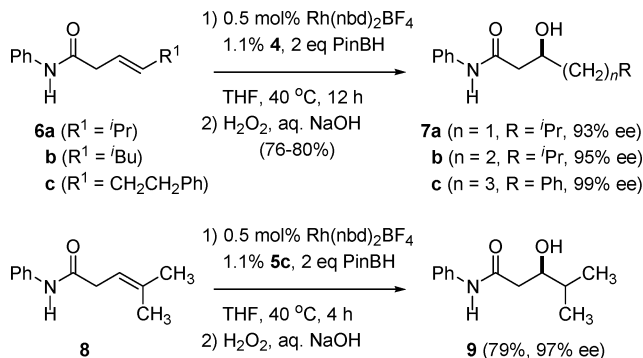


Figure 2. Highly enantioselective amide-directed catalytic asymmetric hydroboration of β,γ -unsaturated amides (*E*)- and (*Z*)-**1**.

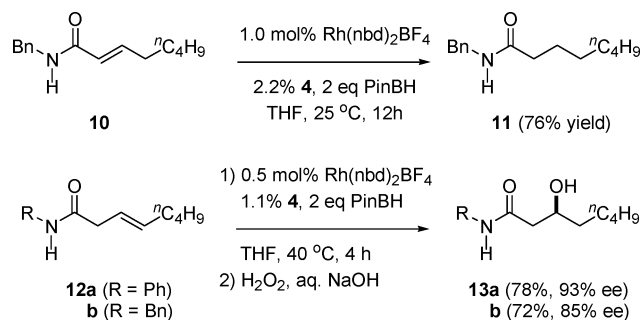
peroxide, intermediate **2** affords β -hydroxy amide (*S*)-**3** in good yield and remarkably high enantiomeric purity (80% yield, 99% ee).¹²

Many catalytic asymmetric reactions prove rather intolerant of changes in the structure of the substrate. It is therefore interesting to find that the diastereomeric (*E*)- and (*Z*)-isomers of **1** afford (*S*)-**3** in the same yield and high enantiomeric purity. The reaction proceeds with good regiocontrol regardless of the alkene geometry; only 3–4% of the γ -hydroxy amide is formed. A variety of BINOL and TADDOL derivatives were examined; the efficiencies and enantioselectivities vary widely (see the Supporting Information). Certain ligands derived from the TADDOL scaffold also afford catalysts that exhibit quite high enantioselectivity. For example, the parent TADDOL-derived phenylphosphite **5a** affords **3** in 85% ee and the corresponding (3',5'-dimethyl)phenyl analogue **5b** gives 93% ee.¹⁴ In the latter case, however, the yield of the β -hydroxyamide is only 60% due to competing formation of the γ -isomer (ca. 20%).

The isopropyl-, isobutyl-, and phenethyl-substituted amides **6a–c** also react with high enantioselectivity using phosphoramidite **4** (93–99% ee) although somewhat longer reaction times are required for these more sterically congested alkenes. Hydroboration of the trisubstituted alkene in amide **8** proceeds to less than 50% conversion under similar reaction conditions. It might be possible to push the reaction to completion by raising the catalyst load or resorting to even longer reaction times; however, a simpler solution was found. The (4'-*tert*-butyl)phenyl analogue, phosphite **5c**, gives a more active catalyst with this substrate. Hydroboration of **8** using **5c** proceeds in good yield (79%) and high enantioselectivity (97% ee). Again, only 3–4% of the γ -isomer is formed under the conditions described for each substrate.

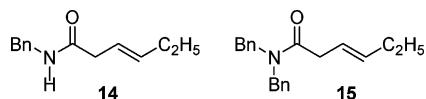


Returning to the observation that the (*E*)- and (*Z*)-isomers of **1** react in nearly identical yield and enantioselectivity, one plausible explanation for their similarity is that the two isomers rapidly interconvert and/or are converted to a common intermediate during the course of the reaction. Sampling and analyzing the reaction mixtures from (*E*)- and (*Z*)-**1** over the course of the reaction reveals no evidence for competing *E/Z* isomerism of the starting material. Alternatively, if isomerization to a common intermediate is an important pathway in the reaction, a likely potential intermediate is the corresponding α,β -unsaturated amide. To explore this latter possibility, α,β -unsaturated amide **10** was prepared. However, treating it with Rh(nbd)₂BF₄, phosphoramidite **4**, and PinBH effects reduction of the alkene not hydroboration.¹⁵ For reference, the data for amides **12a** and **b** are shown below. From sampling and



analyzing aliquots from their reactions, we find that the enantioselectivity is essentially unchanged over the course of the reaction.

Several other factors are important to the success of the reaction as revealed in the course of these preliminary studies. For example, the nature of the acyl substituent is important. In contrast to the *N*-phenyl amide (*E*)-**1**, the corresponding *N*-benzyl amides **12b** and **14** react with somewhat lower regioselectivity, 5–20% of the γ -isomer is formed, and with lower enantioselectivity using ligands **4** or **5b**, 85–87% ee. The *N,N*-dibenzylamide **15** behaves similarly, 87% ee accompanied by 10–25% of the γ -isomer.



The nature of the rhodium(I) catalyst precursor is also important to the success of the reaction. Rh(nbd)₂BF₄ bears a readily dissociable counterion and is an efficient catalyst precursor. In contrast, [Rh(nbd)Cl]₂ gives only low turnover. The nature of the borane is also important. Catecholborane (CatBH) affords product in low yield with poor enantioselectivity under the reaction conditions examined. Furthermore, the reaction of (*E*)-**1** using 1 rather than 2 equiv of PinBH leads to a much diminished yield of the β -hydroxyamide **3** (ca. 30%) along with recovered starting

material; 2 equiv of PinBH are required for complete reaction.¹¹ B NMR experiments suggest that competing formation of borate dimers accounts for the low yield obtained with CatBH and need for excess PinBH under these reaction conditions.¹⁶

In summary, boronate esters are useful intermediates in organic synthesis, but the current routes to chiral boronates in high enantiomeric purity are relatively limited.¹⁷ The efficient catalytic asymmetric hydroboration of β,γ -unsaturated amides adds to the synthetic arsenal as illustrated by their conversion to the β -hydroxycarbonyl derivatives in good yield and high enantiomeric purity. Further studies are in progress.

Acknowledgment. Financial support for this research from the Nebraska Research Initiative and NSF (CHE-0316825) is gratefully acknowledged. We thank T. A. George (UNL Chemistry) for the loan of equipment, S. Koguchi and T. J. Fisher (UNL Chemistry) for some key preliminary experiments, and the NSF (CHE-0091975, MRI-0079750) and NIH (SIG-1-510-RR-06307) for the NMR spectrometers used in these studies carried out in facilities renovated under NIH RR016544.

Supporting Information Available: Experimental details and procedures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- Evans and Fu had previously noted that α,β -unsaturated ketones, esters, and amides undergo efficient rhodium-catalyzed conjugate reduction rather than hydroboration, at least for substrates capable of adopting the *s-cis* geometry. See: Evans, D. A.; Fu, G. C. *J. Org. Chem.* **1990**, *55*, 5678–5680.
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JA710492Q