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Remarkably Facile Borane-Promoted, Rhodium-Catalyzed Asymmetric Hydrogenation of Tri- and Tetrasubstituted Alkenes

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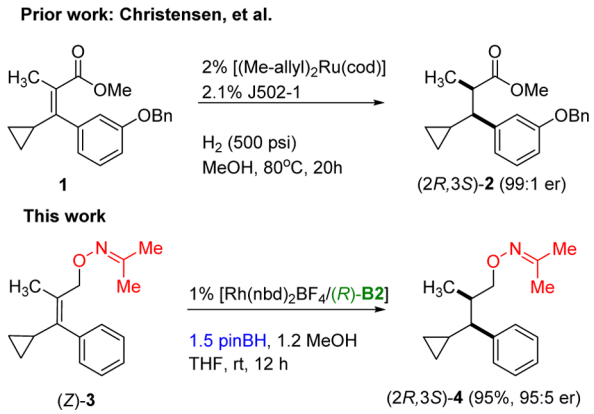
Supporting Information

ABSTRACT: Oxime-directed catalytic asymmetric hydroboration is diverted to catalytic asymmetric hydrogenation (CAH) upon the addition of a proton source, such as MeOH, or by running the reaction under a hydrogen atmosphere. A borane (e.g., pinacolborane) is required to promote CAH. Tri- and tetrasubstituted alkenes, including the challenging all-alkyl tetrasubstituted alkenes, undergo CAH with enantiomer ratios (er) as high as 99:1. The mild reaction conditions, i.e., ambient temperature, moderate reaction times, and the need for only a slight excess of H_2, contrast those used in most state-of-the-art catalysts for related substrates.

Catalytic asymmetric hydrogenation (CAH) is a preeminent example of asymmetric transition metal catalysis and among the most widely used chemical transformations for introducing chirality in the pharmaceutical industry.[1] Given its utility, many chiral catalyst/substrate combinations have been developed to address different structural challenges in asymmetric synthesis;[2] however, relatively few are effective for the CAH of tetrasubstituted alkenes. Furthermore, such catalysts are often limited to substrates wherein the π-system is activated by aromatic substitution[3] or α,β-conjugation with carboxylic acids or esters;[4] certain enamide substrates can also be reduced effectively.[5] Even for these relatively narrowly defined groups of substrates, successful CAH typically requires elevated temperature and high pressure of H_2.

Recently, α-methyl-β-cyclopropyldihydrocinnamates were identified as potentially important pharmacophores. A comprehensive study by Christensen et al.[6] evaluated the CAH of tetrasubstituted cinnamate ester **1** using an extensive collection of catalyst systems. Rhodium catalysts examined in the study are reported to give low yields of **2** due to the lability of the vinyl cyclopropane moiety. However, ruthenium catalysts incorporating Josiphos or JoSPOphos ligands give **2** with high enantiomer ratios (er) as shown in Scheme 1. The reaction conditions employ relatively high pressure (500 psi H_2), elevated temperature (80 °C), and an extended reaction time (20 h). Herein, we report the ability to reduce tri- and tetrasubstituted alkenes under exceptionally mild conditions. For example, 1% [$Rh(nbd)_2BF_4$/(*R*)-**B2**]) catalyzes the CAH of the tetrasubstituted alkene (*Z*)-**3** at ambient temperature to afford (2*R*,3*S*)-**4** (95%, >25:1 dr, 95:5 er). H_2 is presumably generated in stoichiometric amount in situ from pinBH and MeOH.[7]

Scheme 1. Contrasting Reaction Conditions for the CAH of Alkenes Bearing Similar Substituents



The CAH conditions described above evolved from ongoing studies directed toward the preparation of functionalized chiral boronic esters via directed-catalytic asymmetric hydroboration (CAHB).[8] Chiral boronic esters are versatile intermediates[9] and especially useful for diversity-oriented synthesis.[10] Consequently, the development of catalysts for CAHB is receiving much attention.[11] We and others often find varying amounts of the reduced alkene accompany the desired borylated product under the conditions of rhodium- and other metal-catalyzed hydroborations.[12] For example, the formation of chiral tertiary boronic ester **6a** (77%, 94:6 er) via CAHB of trisubstituted alkene (*E*)-**5a** (Scheme 2)[13] is accompanied by the reduced product **7a** (15%, 60:40 er). To the best of our knowledge, the mechanism for formation of the reduced byproduct has never been completely determined. Protodeborylation[14] of an initially formed borylated product is a possibility. The more common assumption is that the reduced product is formed due to the presence of H_2 resulting from adventitious moisture (or other proton source) affecting partial decomposition of the borane (e.g., pinBH).[15]

In support of the proposal that adventitious proton sources enable reduction, we added slightly more than a stoichiometric equivalent of a proton source (1.2 equiv MeOH) to the mixture of substrate (*E*)-**5a**, catalyst, and pinBH (1.5 equiv). The yield of reduced product **7a** increases to near quantitative under those conditions; however, enantiomer ratio (er) remains close to racemic. To improve the enantioselectivity, we screened

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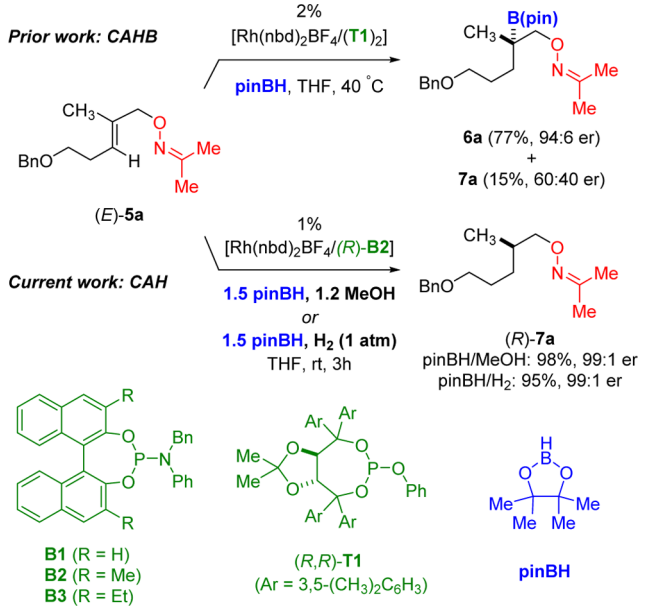
Scheme 2. Oxime-Directed Rhodium-Catalyzed CAH Using pinBH/MeOH or pinBH/H_2



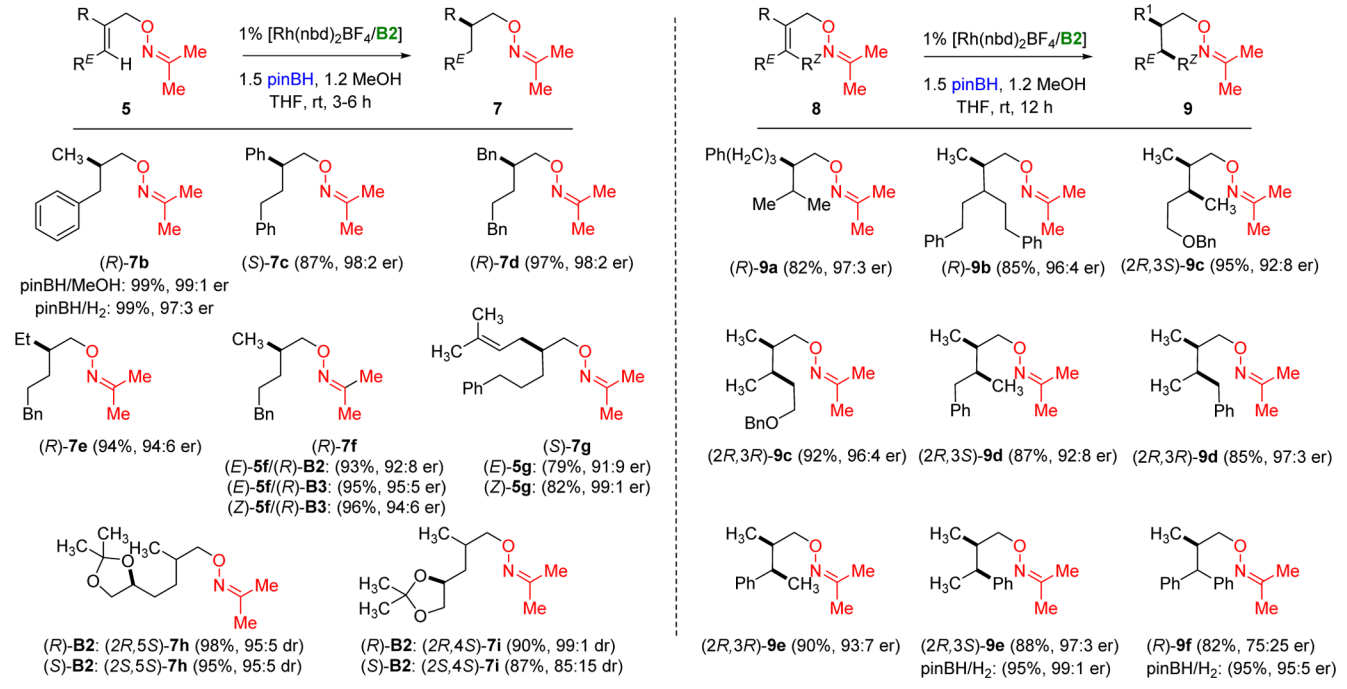
variety of simple, chiral TADDOL- and BINOL-derived phosphite and phosphoramidite ligands[16] finding that (*R*)-**B2** gives (*R*)-**7a** with excellent yield and high enantioselectivity (98%, 99:1 er).[17] Similar results are obtained by omitting MeOH but running the reaction under an atmosphere of H_2.

Scheme 3 illustrates the scope of oxime-directed CAH of trisubstituted and tetrasubstituted alkenes.[18] In each example shown, ([$Rh(nbd)_2BF_4$]/(*R*)-**B2**) is employed using the pinBH/MeOH protocol; in selected cases, results are also reported using the pinBH/H_2 protocol or using (*S*)-**B2**. For example, (*E*)-**5b** (R = Me, R^E = Ph) undergoes CAH using either the pinBH/MeOH or pinBH/H_2 protocol; (*R*)-**7b** is obtained in near quantitative yield and high enantioselectivity (99:1 and 97:3 er, respectively).[19] In contrast, we see no evidence for rhodium-catalyzed reduction of (*E*)-**5b** under H_2 atmosphere up to 50 psi (12 h) without pinBH present.

Other trisubstituted substrates bearing an aryl substituent in the 2-position (i.e., (*E*)-**5c**) or with simple alkyl substituents in both positions (i.e., **5d** and **5e**) similarly give reduced products in high yield (87−97%) and with high levels of enantioselectivity (94:6 er or greater). In the case of substrate **5f**, ligand **B3** gives an improved level of enantioselectivity (95:5 er compared to 92:8 using **B2**). For substrate **5g**, the er improves from 91:9 to 99:1 when starting with the (*Z*)-isomer. Substrate **5g** illustrates another important feature of the chemistry. Although **5g** possesses two trisubstituted alkene moieties, only the double bond proximal to the oxime moiety is reduced. Chiral substrate (5*S*)-**5h** demonstrates good catalyst-controlled reduction. Either (2*R*,5*S*)- or (2*S*,5*S*)-**7h** (95:5 dr) is formed at will by employing the (*R*)- or (*S*)-enantiomer of **B2**, respectively. However, the resident allylic stereocenter in the related chiral acetal (4*S*)-**5i** exerts modest influence leading to a matched (99:1 dr)/mismatched (85:15 dr) case of double stereodifferentiation.

Unactivated, all-alkyl tetrasubstituted alkenes are generally found to be very challenging substrates for CAH. Nevertheless, tetrasubstituted alkenes **8a** and **8b** correspondingly yield **9a** and **9b** with high enantioselectivity using the pinBH/MeOH setting a single stereocenter in the course of hydrogenation. Tetrasubstituted alkenes (*E*)-**8c** and (*Z*)-**8c** demonstrate that hydrogenation proceeds via stereospecific *syn*-addition. The (*E*)-isomer affords (2*R*,3*S*)-**9c** (95%, 92:8 er); the (*Z*)-isomer affords (2*R*,3*R*)-**9c** (92%, 96:4 er). Similar results are obtained for (*E*)- and (*Z*)-**8d**. Aryl substituents are tolerated as illustrated above in the reduction of (*Z*)-**3** to (2*R*,3*S*)-**4** (95%, 95:5 er) (Scheme 1). Using the pinBH/MeOH protocol, (*E*)-**8e** affords (2*R*,3*R*)-**9e** (90%, 93:7 er); (*Z*)-**8e** affords (2*R*,3*S*)-**9e** (88%, 97:3 er). The yield and er are improved for

Scheme 3. CAH of Trisubstituted and Tetrasubstituted Alkenes



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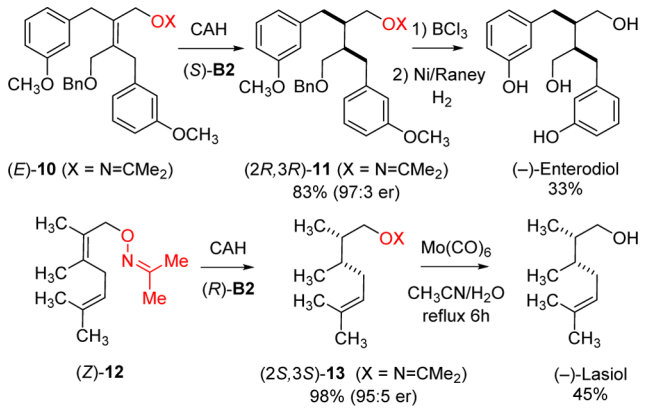
(*Z*)-**8e** using the pinBH/H_2 protocol; (2*R*,3*S*)-**9e** is obtained in 95% yield (99:1 er). The pinBH/H_2 protocol also improves the results obtained with the diaryl substrate **8f**. (*R*)-**9f** is obtained in a 75:25 er (82%) using pinBH/MeOH but in 95:5 er (95% yield) using the pinBH/H_2 protocol.

To demonstrate the synthetic utility of this CAH of tetrasubstituted alkenes two simple natural products, (−)-enterodiol and (−)-lasiol, were prepared, albeit with a major surprise revealed en route to each (Scheme 4). Two syntheses of

Scheme 4. Syntheses of (−)-Enterodiol and (−)-Lasiol

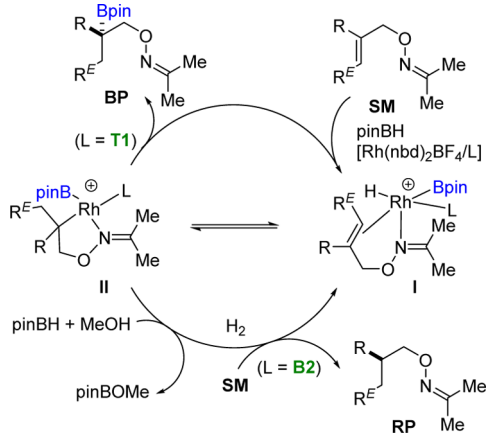


(−)-enterodiol have been published. The Feringa route features the diastereoselective tandem conjugate addition to a chiral alkoxybutenolide,[20] and Sjöholm reported its preparation starting from hydroxymatairesinol.[21] In the present route, CAH of (*E*)-**10** using (*R*)-**B2** and the pinBH/MeOH protocol proceeds in good yield with high diastereo- and enantioselectivity (>25:1 dr, 99:1 er). On the basis of correlations to known compounds for seven of the reduced products shown above, we expected the (*R*)-**B2** catalyst would give (2*R*,3*R*)-**11**; however, in the event, (2*S*,3*S*)-**11** was obtained. We can only speculate that the multiple potential ligating groups in **10** combine to reverse the sense of π-facial discrimination for this substrate. Although mechanistically intriguing, the unexpected enantioswitching[22] is of little consequence from a practical standpoint. Given the simplicity of the ligand used, (*S*)-**B2** is equally accessible and affords (2*R*,3*R*)-**11** (83%, 97:3 er). Cleavage of methyl and benzyl ethers and cleavage of the N−O bond to remove the oxime directing group affords (−)-enterodiol.

Three published routes to (−)-lasiol involve asymmetric catalysis to set one of the two stereocenters: Kobayshi exploited the 1,4-addition to an unsaturated amide;[23] Feringa used enantioselective allylic alkylation followed by a diastereoselective conjugated addition;[24] and Burgess exploited catalyst-controlled CAH of a chiral trisubstituted alkene.[25] Our route is the first wherein the two chiral centers are generated in a single step. CAH of (*Z*)-**12** using the pinBH/MeOH protocol again proceeds with opposite to the expected sense of stereoinduction necessitating the use of (*R*)-**B2** to produce (2*S*,3*S*)-**13** (98%, 95:5 er) as required for the natural product. CAH is selective for the proximal tetrasubstituted alkene in the presence of a trisubstituted double bond. Cleavage of the N−O bond affords (−)-lasiol.

Phosphoramidite ligands have been extensively studied in rhodium-catalyzed CAH both from the synthetic[26] and mechanistic perspectives.[27] Scheme 5 outlines a simple unified

Scheme 5. Potential Competing Pathways for Borane-Promoted CAHB and CAH



model, an "interrupted hydroboration" pathway,[28] to account for the apparent competition between CAH and CAHB[29] under the conditions described herein. Two-point binding of the substrate (**SM**) to Rh and oxidative addition of pinBH gains access to intermediate **I**. Insertion of the alkene into the Rh−H bond would generate a species such as intermediate **II**. Reductive elimination from **II** would afford the borylated product (**BP**) with regeneration of intermediate **I**. Alternately, σ-bond metathesis of rhodium-boryl complex **II** with H_2[30] would generate the reduced product (**RP**) and, in the presence of additional alkene substrate, regenerate intermediate **II** to continue the cycle.

In summary, an unwanted side reaction leading to a reduction byproduct during CAHB is turned into an efficient method for oxime-directed, borane promoted CAH of challenging tri- and tetrasubstituted alkenes. To our knowledge, this report constitutes the first examples using an oxime to direct CAH as well as a new catalyst system for efficient CAH. The mild reduction conditions, short reaction times, and the need for only a slight excess above stoichiometric H_2 contrast those used in state-of-the-art catalysts even for activated tetrasubstituted substrates. Stereospecific *syn*-hydrogenation is enabled via the combination of a simple 1:1 [Rh(I)/chiral phosphoramidite] catalyst system (e.g., [$Rh(nbd)_2BF_4$/(*R*)-**B2**]), pinBH and H_2, the latter either generated in situ or as atmosphere above the reaction mixture. Borane is required for reduction. The method works well for aryl-substituted alkene substrates as well as for the more challenging case of all-alkyl tetrasubstituted alkenes. In substrates bearing an additional double bond, only the proximal alkene with respect to the oxime moiety is reduced; however, the sense of π-facial selectivity can apparently be influenced by remote donor substituents. A simple catalytic cycle in which CAHB is diverted to CAH via σ-bond metathesis of a rhodium−boryl intermediate with H_2 can be drawn; however, the actual mechanism is likely to be more complicated. Further studies and extension of the method to other classes of substrates are in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b02581.

Experimental procedures (PDF)

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Spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(17) The catalyst loading was reduced to 0.5% when run on a 1.3 mmol scale of **5a** without diminishing the yield or enantioselectivity. The parent BINOL-derived phosphoramidite (*R*)-**B1** gives (*R*)-**7a** with promising levels of induction (97% yield, 91:9 er).

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