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J. Am. Chem. Soc., **2005**, 127 (17), 6174-6175• DOI: 10.1021/ja042645v • Publication Date (Web): 06 April 2005

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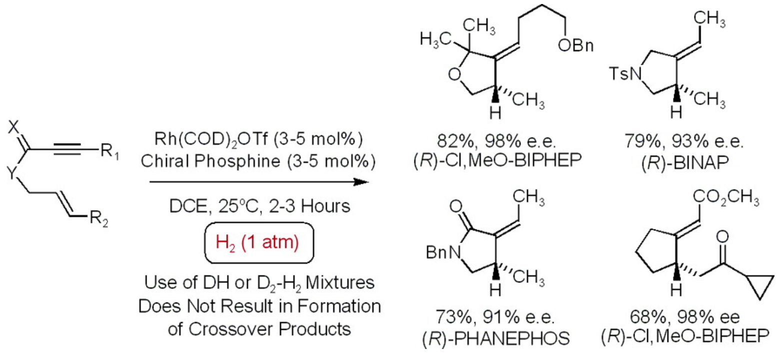

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Published on Web 04/06/2005

Enantioselective Reductive Cyclization of 1,6-Enynes via Rhodium-Catalyzed Asymmetric Hydrogenation: C−C Bond Formation Precedes Hydrogen Activation

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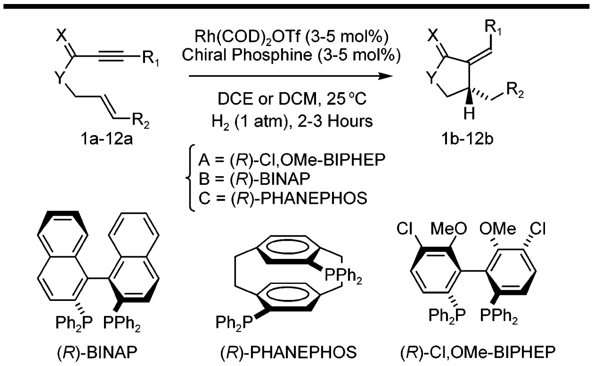
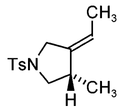
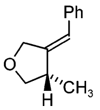
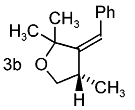
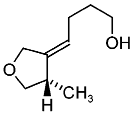
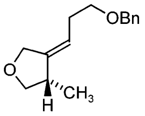
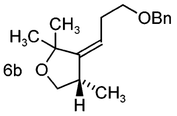
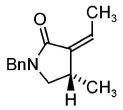
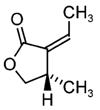
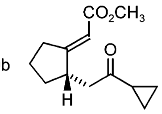
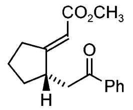
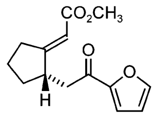
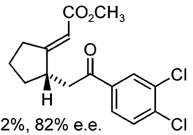
Although elemental hydrogen is the cleanest and most cost-effective reductant available, the capture of organometallic species generated via hydrogenation has, until recently, only been achieved through migratory insertion of carbon monoxide (alkene hydroformylation and the Fischer−Tropsch reactions).[1] The principal challenge posed by hydrogen-mediated C−C bond formation involves partitioning of conventional hydrogenation and reductive coupling manifolds. Initial studies from our lab on hydrogen-mediated reductive aldol coupling demonstrate that conventional hydrogenation pathways are suppressed through the use of cationic rhodium precatalysts and mild basic additives. Such conditions are believed to induce heterolytic hydrogen activation.[2,3] Subsequently developed reductive couplings of α-keto aldehydes to 1,3-dienes, 1,3-enynes, and 1,3-diynes retain the requirement of a cationic rhodium precatalyst, yet proceed in the absence of basic additives, suggesting heterolytic hydrogen activation may not be operative.

In connection with our studies on hydrogen-mediated C−C bond formation,[1] an enantioselective variant of the hydrogen-mediated reductive cyclization of 1,6-enynes was sought. While enantioselective cycloisomerizations and hydrosilylative cyclizations of 1,6-enynes are known, simple enantioselective reductive cyclizations have not been described.[4−7] Here, we report that asymmetric hydrogenation of 1,6-enynes at ambient temperature and pressure using chirally modified rhodium catalysts promotes highly enantioselective reductive cyclization to afford a diverse range of alkylidene-substituted carbocycles and heterocycles with complete atom economy. Related hydrogen−deuterium crossover experiments suggest oxidative cyclization to form a metallocyclic intermediate occurs in advance of hydrogen activation.

Initial studies focused on the enantioselective reductive cyclization of 1,6-enyne **1a**. Gratifyingly, hydrogenation of **1a** at ambient pressure and temperature using $\mathrm{Rh(COD)_2OTf}$ (5 mol %) as precatalyst and (*R*)-BINAP (5 mol %) as a chiral inducing element gave the desired reductive cyclization product **1b** in 69% yield and 94% ee. These reaction conditions proved to be applicable across a structurally diverse set of 1,6-enynes **1a**−**12a**. Interestingly, a striking dependence of chemical yield and enantiomeric excess upon the structural features of the chiral phosphine ligand is observed; while **1a**−**6a** and **9a**−**12a** cyclize in good yield and excellent enantiomeric excess using (*R*)-Cl,OMe-BIPHEP and (*R*)-BINAP, (*R*)-PHANEPHOS delivers a complex distribution of conventional hydrogenation products, yet (*R*)-PHANEPHOS is unique in its ability to promote highly enantioselective cycloreduction of enynes **7a**−**8a**.

Table 1. Enantioselective Hydrogen-Mediated Reductive Cyclization of 1,6-Enynes **1a**−**12a** Catalyzed by Rhodium[a]



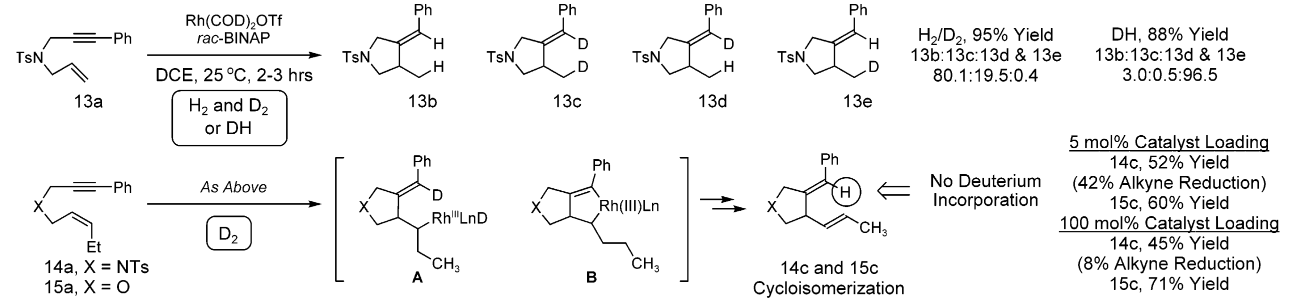
1b  A: 69%, 94% e.e. B: 79%, 93% e.e. C: multiple products	2b  A: 84%, 95% e.e. B: 80%, 97% e.e. C: multiple products	3b  A: 85%, 84% e.e. B: 76%, 82% e.e. C: multiple products
4b  A: 77%, 95% e.e. B: 75%, 95% e.e. C: multiple products	5b  A: 75%, 98% e.e. B: 77%, 98% e.e. C: multiple products	6b  A: 82%, 98% e.e. B: 64%, 98% e.e. C: multiple products
7b  A: 40%, 26% e.e. B: 24%, 10% e.e. C: 73%, 91% e.e.	8b  A: 89%, 6% e.e. B: 79%, 20% e.e. C: 73%, 94% e.e.	9b  A: 68%, 98% e.e. B: 63%, 90% e.e. C: complete reduction
10b  A: 78%, 88% e.e. B: 66%, 96% e.e. C: complete reduction	11b  A: 65%, 95% e.e. B: 72%, 96% e.e. C: complete reduction	12b  A: 72%, 82% e.e. B: 63%, 94% e.e. C: complete reduction

[a] Procedure: To a solution of enyne **1a** (100 mol %) in DCE or DCM (0.1 M) at 25 °C were added rhodium catalyst and ligand. In the case of substrates **1a**−**5a** and **9a**−**12a**, 5 mol % of catalyst and ligand was employed. In the case of substrates **6a**−**8a**, 3 mol % of catalyst and ligand was employed. The system was purged with H_2 (g), and the reaction was allowed to stir under 1 atm of H_2 (g) until complete consumption of **1a** was observed (2−3 h), at which point the reaction mixture was evaporated onto silica gel and the product purified by silica gel chromatography.

Reductive cyclization products **1b**−**12b** incorporate two *nonexchangeable* hydrogen atoms. Homolytic and heterolytic hydrogen activation pathways may now be discriminated on the basis of hydrogen−deuterium crossover experiments. Reductive cyclization of **13a** under a mixed atmosphere of H_2 and D_2 or under an atmosphere of DH does not provide crossover products, in accordance with homolytic hydrogen activation. Exposure of **14a**

10.1021/ja042645v CCC: $30.25 © 2005 American Chemical Society

Scheme 1 [a]



[a] (Top) Reductive cyclization of **13a** under a mixed atmosphere of H_2 and D_2 or under an atmosphere of DH does not provide crossover products. (Bottom) Exposure of **14a** and **15a** to identical conditions under a D_2 atmosphere provides cycloisomerization products **14c** and **15c** *without* deuterium incorporation, even at stoichiometric catalyst loadings, thus suggesting hydrometallative pathways en route to **14c** and **15c** are not operative.

or **15a** to identical conditions under a D_2 atmosphere does not induce reductive cyclization. Rather, cycloisomerization products **14c** and **15c** are formed.[7] A hydrometallative mechanism for cycloisomerization would be initiated by D_2 oxidative addition and propagated by rhodium hydrides derived upon β-hydride elimination from intermediate **A**. Deuterium incorporation should occur in the first turnover of the catalytic cycle, yet deuterium incorporation is not observed, even at stoichiometric catalyst loadings. The extent of deuterium incorporation for **13b**−**e**, **14c**, and **15c** is established by ESI−MS analysis with isotopic correction and is corroborated by ^{1}H NMR analysis (Scheme 1).

Acquisition of **14c** and **15c** without deuterium incorporation is inconsistent with a hydrometallative mechanism. This fact, along with the absence of conjugated cycloisomerization products, suggests β-hydride elimination from metallocycle **B**. If indeed oxidative cyclization occurs initially, subsequent hydrogenolytic cleavage must occur via (a) hydrogen oxidative addition, or (b) hydrogen activation via σ-bond metathesis. Rh(I)-mediated oxidative coupling of 1,6-enynes to form Rh(III) metallocycles is well established.[8] Additionally, an increasing body of evidence supports participation of organorhodium(III) complexes in σ-bond metathesis pathways,[9] including reactions with hydrogen.[10c] Whereas hydrogen oxidative addition to a Rh(III) metallocycle would afford a Rh(V) intermediate, hydrogen activation via σ-bond metathesis would not. *In either case, C−C bond formation occurs in advance of hydrogen activation*. Hydrogen oxidative addition followed by rhodium(V) metallocycle formation is unlikely and, to our knowledge, without precedent. As hydrogen oxidative addition is rate-determining for asymmetric hydrogenations catalyzed by cationic rhodium complexes,[10] it is reasonable to suggest that oxidative cyclization is faster than hydrogen activation. Finally, it is worth noting that the ^{1}H NMR ratio of **13d**:**13e** is 1:2.1, suggesting hydrogen activation is rate-determining for reductive cyclization.

While hydrogen-mediated enone couplings require basic additives and, hence, may involve formal heterolytic hydrogen activation, the present hydrogen−deuterium crossover experiments suggest related reductive couplings under base-free conditions proceed through rhodium(III) metallocycles, which form in *advance* of homolytic hydrogen activation. This oxidative coupling−hydrogenolytic cleavage motif should play a key role in the design of related hydrogen-mediated couplings.

Acknowledgment. Acknowledgment is made to the Research Corporation Cottrell Scholar Award, the Sloan Foundation, the Dreyfus Foundation, the Welch Foundation, Eli Lilly, Johnson & Johnson, and Merck. Dr. Ulrich Scholz of Bayer Chemicals is thanked for the generous donation of (*R*)-Cl,OMe-BIPHEP. Our reviewers are thanked for helpful comments.

Supporting Information Available: Spectral data for new compounds, absolute stereochemical assignments, and ESI−MS data. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA042645V