

## Highly Enantioselective Reductive Cyclization of Acetylenic Aldehydes via Rhodium Catalyzed Asymmetric Hydrogenation

Jong Uk Rhee and Michael J. Krische\*

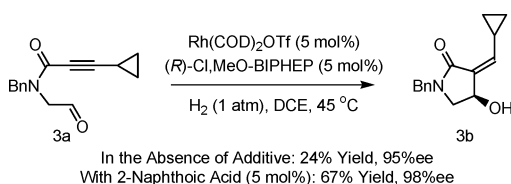
University of Texas at Austin, Department of Chemistry and Biochemistry, Austin, Texas 78712

Received May 30, 2006; E-mail: mkrische@mail.utexas.edu

The invention of catalytic methods for the reductive coupling of alkynes and aldehydes is currently the subject of intensive investigation.<sup>1,2</sup> Seminal contributions to this area include the rhodium-catalyzed reductive cyclization of acetylenic aldehydes reported by Ojima (1994),<sup>3</sup> corresponding titanocene-catalyzed cyclizations disclosed by Crowe (1995),<sup>4</sup> and the nickel-catalyzed reductive cyclization of acetylenic aldehydes reported by Montgomery (1997).<sup>5a–c,e</sup> Through further modification of the nickel based catalysts, corresponding intermolecular couplings have been achieved, as described by Jamison (2000)<sup>6</sup> and Montgomery (2004).<sup>5d</sup> Additionally, intermolecular reductive coupling of conjugated alkynes to vicinal dicarbonyl compounds and  $\alpha$ -iminoacetates may be carried out via rhodium catalyzed hydrogenation, as described by the present author (2003).<sup>7</sup> Asymmetric variants of the intermolecular processes have been devised,<sup>6b,7a,d,e</sup> but are restricted to aryl-substituted acetylenes introduced via syringe pump addition<sup>6b</sup> or use of conjugated alkynes (1,3-enynes and 1,3-diynes).<sup>7a,d,e</sup> Remarkably, catalytic enantioselective methods for the reductive cyclization of acetylenic aldehydes are absent from the literature.<sup>8,9</sup>

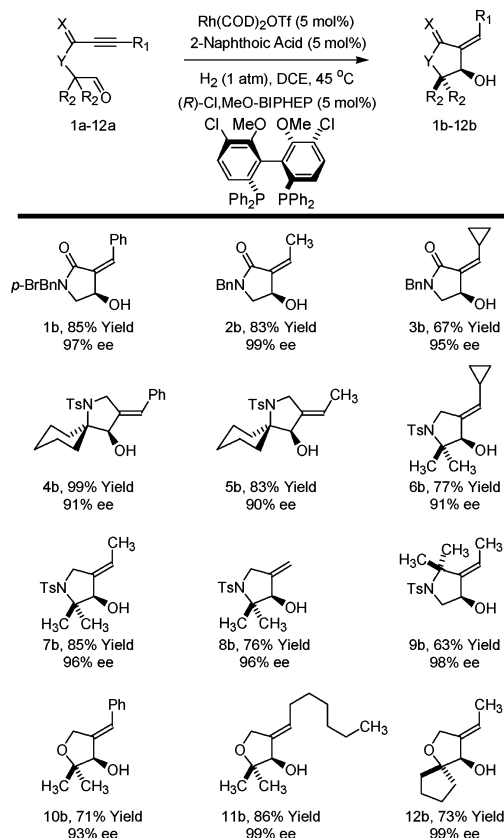
In this account, we disclose that hydrogenation of acetylenic aldehydes using chirally modified cationic rhodium catalysts enables formation of cyclic allylic alcohols in good yield and with exceptionally high levels of asymmetric induction. These transformations are facilitated by our recent finding that Brønsted acid additives greatly enhance both rate and conversion in hydrogen-mediated C–C coupling reactions of alkynes to carbonyl partners.<sup>7d</sup> Additionally, we demonstrate that acetylenic aldehydes possessing preexisting stereogenic centers engage in highly diastereoselective reductive cyclization. These studies represent the first examples of the catalytic enantioselective reductive cyclization of acetylenic aldehydes.

Our initial efforts focused on the hydrogen-mediated cyclization of acetylenic aldehyde **3a**. Exposure of a 1,2-dichloroethane solution (0.1 M) of **3a** to one atmosphere of hydrogen at 45 °C in the absence of a Brønsted acid additive using the cationic catalyst precursor Rh(COD)<sub>2</sub>OTf and (R)-Cl<sub>2</sub>MeO-BIPHEP<sup>10</sup> as ligand resulted in the formation of the cyclized product **3b** in 24% yield and 95% enantiomeric excess. In contrast, in the presence of substoichiometric loadings of 2-naphthoic acid (5 mol %), but under otherwise identical conditions, lactam **3b** is obtained in 67% yield and 98% enantiomeric excess.



These conditions were applied to acetylenic aldehydes **1a–12a**. The  $\alpha,\beta$ -acetylenic amides **1a–3a** provide the corresponding

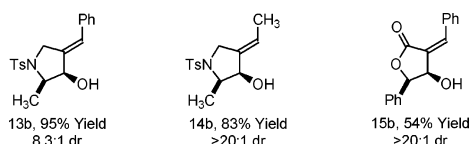
**Table 1.** Enantioselective Reductive Cyclization of Acetylenic Aldehydes via Rhodium Catalyzed Hydrogenation<sup>a</sup>



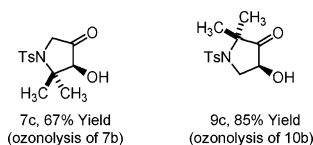
<sup>a</sup> Cited yields are of isolated material and represent the average of two runs. The absolute stereochemical assignment of **1b–12b** is based upon X-ray crystallographic analysis of the 2,4-dinitrobenzolate derived from lactam **1b**. Enantiomeric excess was determined by chiral stationary phase HPLC. See Supporting Information for further details.

lactams **1b–3b** in highly optically enriched form, demonstrating applicability of the cyclization to electron deficient alkynes. Simple unactivated alkynes were explored next. As demonstrated by the formation of **4b–8b**, sulfonamide-tethered acetylenic aldehydes possessing a geminal substituent adjacent to the aldehyde cyclize readily. Aryl, alkyl, and cyclopropyl substituents at the acetylenic terminus are tolerated (**4b–7b**) but are not a prerequisite for efficient cyclization (**8b**). Acetylenic aldehydes that are geminally substituted at the propargylic position also cyclize efficiently with high levels of asymmetric induction (**9b**). As demonstrated by the formation of **10b–12b**, alkylidene furans form readily via hydrogen-mediated cyclization (Table 1).

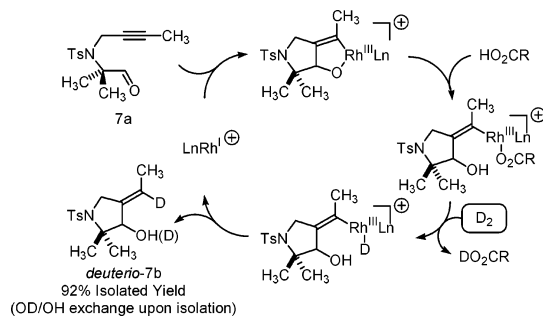
The cyclizations of acetylenic aldehydes that embody preexisting stereogenic centers were conducted using the parent achiral ligand BIPHEP to afford **13b–15b** with good to excellent levels of

**Table 2.** Diastereoselective Reductive Cyclization of Acetylenic Aldehydes via Rhodium Catalyzed Hydrogenation<sup>a</sup>

<sup>a</sup> Cited yields are of isolated material. See Supporting Information for further details.

**Table 3.** Optically Enriched  $\alpha$ -Hydroxy Ketones via Ozonolysis of Reductive Cyclization Products **7b** and **9b**<sup>a</sup>

<sup>a</sup> Cited yields are of isolated material. See Supporting Information for further details.

**Scheme 1.** Plausible Catalytic Cycle as Supported by <sup>2</sup>H-Labeling

diastereoselection (Table 2). Finally, application of this methodology to the synthesis of  $\alpha$ -hydroxy ketones is achieved through ozonolysis of cyclization products **7b** and **9b** (Table 3). The assignment of absolute stereochemistry is based upon X-ray crystallographic analysis of the 2,4-dinitrobenzoate derived from **1b**. Generalization of this assignment to systems that differ significantly in structure should be made with caution. The relative stereochemical assignment of **13b**–**15b** is supported by single-crystal X-ray diffraction analysis of the *p*-bromobenzoate derived from **14b**. Attempted six-membered ring formation provides products of conventional alkyne hydrogenation.

Reductive cyclization of acetylenic aldehyde **7a** under a deuterium atmosphere provides, after chromatographic isolation, *deuterio-7b*. This result is consistent with a catalytic mechanism involving oxidative coupling followed by hydrogenolytic cleavage of the resulting metallacycle via  $\sigma$  bond metathesis. The acidic additive may assist cleavage of the metallacyclic intermediate, as previously proposed.<sup>7d</sup> Alternatively, it may suppress proton loss from cationic rhodium dihydrides to afford neutral monohydride complexes, which appear less prone to engage in oxidative coupling pathways (Scheme 1).<sup>11</sup>

In summary, exposure of acetylenic aldehydes to gaseous hydrogen in the presence of chirally modified rhodium catalysts enables highly enantioselective reductive cyclization. These studies underscore the key role of acidic additives in hydrogen-mediated C–C coupling and support the feasibility of related intermolecular alkyne–electrophile couplings.

**Acknowledgment.** Acknowledgment is made to the Robert A. Welch Foundation, Johnson & Johnson, and the NIH-NIGMS (Grant RO1-GM69445) for partial support of this research. Dr. Ulrich Scholz is thanked for a generous donation of (*R*)-Cl<sub>2</sub>MeO-BIPHEP.<sup>10</sup>

**Supporting Information Available:** Spectral data for all new compounds; scanned images of <sup>1</sup>H and <sup>13</sup>C NMR spectra and chiral stationary phase HPLC traces; single-crystal X-ray diffraction data for the 2,4-dinitrobenzoate derived from compound **1b** and the *p*-bromobenzoate derived from **14b**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

## References

- (1) For selected reviews encompassing intra- and intermolecular direct reductive coupling of alkynes to carbonyl partners, see (a) Ojima, I.; Tzamaroudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635. (b) Montgomery, J. *Acc. Chem. Res.* **2000**, *33*, 467. (c) Montgomery, J.; Amarashinghe, K. K. D.; Chowdhury, S. K.; Oblinger, E.; Seo, J.; Savchenko, A. V. *Pure Appl. Chem.* **2002**, *74*, 129. (d) Ikeda, S.-I. *Angew. Chem., Int. Ed.* **2003**, *42*, 5120. (e) Miller, K. M.; Molinaro, C.; Jamison, T. F. *Tetrahedron Asym.* **2003**, *3619*. (f) Montgomery, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3890. (g) Jang, H.-Y.; Krische, M. J. *Acc. Chem. Res.* **2004**, *37*, 653.
- (2) Alkyne reductive coupling may be achieved indirectly via alkyne hydrometalation using hydroboranes or Cp<sub>2</sub>ZrHCl followed by transmetalation to afford organozinc reagents, which participate in catalyzed enantioselective additions to aldehydes: (a) Oppolzer, W.; Radinov, R. *Helv. Chim. Acta* **1992**, *75*, 170. (b) Oppolzer, W.; Radinov, R. *J. Am. Chem. Soc.* **1993**, *115*, 1593. (c) Soai, K.; Takahashi, K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1257. (d) Wipf, P.; Xu, W. *Tetrahedron Lett.* **1994**, *35*, 5197. (e) Wipf, P.; Xu, W. *Org. Synth.* **1996**, *74*, 205. (f) Wipf, P.; Ribe, S. J. *Org. Chem.* **1998**, *63*, 6454. (g) Oppolzer, W.; Radinov, R. N.; El-Sayed, E. J. *Org. Chem.* **2001**, *66*, 4766. (h) Dahmen, S.; Bräse, S. *Org. Lett.* **2001**, *3*, 4119. (i) Ji, J.-X.; Qiu, L.-Q.; Yip, C. W.; Chan, A. S. C. *J. Org. Chem.* **2003**, *68*, 1589. (j) Lurain, A. E.; Walsh, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 10677. (k) Ko, D.-H.; Kang, S.-W.; Kim, K. H.; Chung, Y.; Ha, D.-C. *Bull. Korean Chem. Soc.* **2004**, *25*, 35. (l) Jeon, S.-J.; Chen, Y. K.; Walsh, P. J. *Org. Lett.* **2005**, *7*, 1729.
- (3) Ojima, I.; Tzamaroudaki, M.; Tsai, C.-Y. *J. Am. Chem. Soc.* **1994**, *116*, 3643.
- (4) Crowe, W. E.; Rachita, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 6787.
- (5) (a) Oblinger, E.; Montgomery, J. *J. Am. Chem. Soc.* **1997**, *119*, 9065. (b) Tang, X.-Q.; Montgomery, J. *J. Am. Chem. Soc.* **1999**, *121*, 6098. (c) Tang, X.-Q.; Montgomery, J. *J. Am. Chem. Soc.* **2000**, *122*, 6950. (d) Mahandru, G. M.; Liu, G.; Montgomery, J. *J. Am. Chem. Soc.* **2004**, *126*, 3698. (e) Knapp-Reed, B.; Mahandru, G. M.; Montgomery, J. *J. Am. Chem. Soc.* **2005**, *127*, 13156.
- (6) (a) Huang, W.-S.; Chan, J.; Jamison, T. F. *Org. Lett.* **2000**, *2*, 4221. (b) Miller, K. M.; Huang, W.-S.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 3442.
- (7) (a) Huddleston, R. R.; Jang, H.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 11488. (b) Jang, H.-Y.; Huddleston, R. R.; Krische, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 4664. (c) Kong, J.-R.; Cho, C.-W.; Krische, M. J. *J. Am. Chem. Soc.* **2005**, *127*, 11269. (d) Kong, J.-R.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 718. (e) Cho, C.-W.; Krische, M. J. *Org. Lett.* **2006**, *8*, 891.
- (8) For rhodium catalyzed enantioselective cycloisomerization, hydrosilylation-cyclization and reductive cyclization of 1,6-enynes, see (a) Ping, C.; Zhang, X. *Angew. Chem., Int. Ed.* **2000**, *39*, 4104. (b) Lei, A.; He, M.; Wu, S.; Zhang, X. *Angew. Chem., Int. Ed.* **2002**, *41*, 3457. (c) Lei, A.; Waldkirch, J. P.; He, M.; Zhang, X. *Angew. Chem., Int. Ed.* **2002**, *41*, 4526. (d) Lei, A.; He, M.; Zhang, X. *J. Am. Chem. Soc.* **2003**, *125*, 11472. (e) Chakrapani, H.; Liu, C.; Widenhoefer, R. A. *Org. Lett.* **2003**, *5*, 157. (f) Jang, H.-Y.; Hughes, F. W.; Gong, H.; Zhang, J.; Brodbelt, J. S.; Krische, M. J. *J. Am. Chem. Soc.* **2005**, *127*, 6174.
- (9) Rhodium catalyzed *arylativ* cyclization of acetylenic carbonyl compounds has been described: (a) Miura, T.; Shimada, M.; Murakami, M. *Synlett* **2005**, 667. (b) Shintani, R.; Okamoto, K.; Otomary, Y.; Ueyama, K.; Hayashi, T. *J. Am. Chem. Soc.* **2005**, *127*, 54. (c) Miura, T.; Shimada, M.; Murakami, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 7598. (d) Matsuda, T.; Makino, M.; Murakami, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4608.
- (10) (a) Laue, C.; Schröder, G.; Arlt, D. Eur. Pat. 749973 A1, 1996. (b) Driesen-Holscher, B.; Kralik, J.; Agel, F.; Steffens, C.; Hu, C. *Adv. Synth. Catal.* **2004**, *346*, 979.
- (11) *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VHC Verlag GmbH & Co.: Weinheim, Germany, 2005.

JA0637954