Highly Regioselective, Catalytic Asymmetric Reductive Coupling of 1,3-Enynes and Ketones

Karen M. Miller and Timothy F. Jamison*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

tfj@mit.edu

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ABSTRACT



Highly regioselective, catalytic asymmetric reductive coupling reactions of 1,3-enynes and ketones have been achieved using catalytic amounts of Ni(cod)₂ and a *P*-chiral, monodentate ferrocenyl phosphine ligand. These couplings represent the first examples of catalytic, intermolecular reductive coupling of alkynes and ketones, enantioselective or otherwise, and afford synthetically useful 1,3-dienes possessing a quaternary carbinol stereogenic center in up to 70% ee.

Catalytic, stereoselective, multicomponent coupling reactions facilitate the efficient construction of complex organic molecules by forming multiple bonds in a single synthetic operation.¹ Examples of such reactions include transition metal catalyzed intermolecular reductive or alkylative coupling of alkynes with common functional groups, such as aldehydes,^{2,3} epoxides,⁴ and imines.⁵ In contrast, due to their greatly attenuated reactivity relative to aldehydes, the use of *ketones* as coupling partners in reactions of this type has

10.1021/ol051075g CCC: \$30.25 © 2005 American Chemical Society Published on Web 06/09/2005 yet to be reported.^{6–9} In fact, ketones have been employed as electrophiles only rarely in *any* catalytic multicomponent coupling reactions,¹⁰ and the vast majority of these are intramolecular processes.^{11–13}

We recently reported catalytic reductive couplings of aldehydes and 1,3-enynes^{2g} (and other alkynes²ⁱ) in which a pendant alkene enhanced both the reactivity and selectivity of the alkyne. We now disclose that catalytic intermolecular reductive couplings of 1,3-enynes and ketones also proceed

^{(1) (}a) *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim, Germany, 2005. (b) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602–1634.

⁽²⁾ Nickel: (a) Oblinger, E.; Montgomery, J. J. Am. Chem. Soc. 1997, 119, 9065–9066. (b) Huang, W.-S.; Chan, J.; Jamison, T. F. Org. Lett. 2000, 2, 4221–4223. (c) Colby, E. A.; Jamison, T. F. J. Org. Chem. 2003, 68, 156–166. (d) Takai, K.; Sakamoto, S.; Isshiki, T. Org. Lett. 2003, 5, 653–655. (e) Miller, K. M.; Huang, W. S.; Jamison, T. F. J. Am. Chem. Soc. 2003, 125, 3442–3443. (f) Miller, K. M.; Molinaro, C.; Jamison, T. F. J. Am. Chem. Soc. 2004, 126, 4130–4131. (h) Mahandru, G. M.; Liu, G.; Montgomery, J. J. Am. Chem. Soc. 2004, 126, 3698–3699. (i) Miller, K. M.; Jamison, T. F. J. Am. Chem. Soc. 2004, 126, 15342–15343. (j) Review: Montgomery, J. Amgew. Chem., Int. Ed. 2004, 43, 3890–3908.

⁽³⁾ Rhodium: (a) Huddleston, R. R.; Yang, H.-Y.; Krische, M. J. J. Am. Chem. Soc. 2003, 125, 11488–11489. (b) Jang, H.-Y.; Huddleston, R. R.; Krische, M. J. J. Am. Chem. Soc. 2004, 126, 4664–4668. (c) Review: Jang, H.-Y.; Krische, M. J. Acc. Chem. Res. 2004, 37, 653–661.

⁽⁴⁾ Molinaro, C.; Jamison, T. F. J. Am. Chem. Soc. 2003, 125, 8076-8077.

^{(5) (}a) Patel, S. J.; Jamison, T. F. Angew. Chem., Int. Ed. 2003, 42, 1364– 1367. (b) Patel, S. J.; Jamison, T. F. Angew. Chem., Int. Ed. 2004, 43, 3941–3944.

⁽⁶⁾ For an example of the nickel-catalyzed intramolecular reductive coupling of an alkyne and a ketone, see: Chan, J.; Jamison, T. F. J. Am. Chem. Soc. **2004**, *126*, 10682–10691.

⁽⁷⁾ For a recent report of nickel-catalyzed intermolecular alkyne insertions into cyclobutanones, see: Murakami, M.; Ashida, S.; Takanori, M. J. Am. Chem. Soc. **2005**, *127*, 6932–6933.

efficiently in high regioselectivity and modest enantioselectivity when conducted in the presence of catalytic amounts of a *P*-chiral, ferrocenyl monodentate phosphine ligand (Scheme 1).



The enantioselective generation of quaternary stereocenters is generally a formidable challenge. Recently, several catalytic, asymmetric methods that achieve this goal have been developed,¹⁴ and addition reactions to ketones have attracted significant attention, as they provide access to enantiomerically enriched tertiary alcohols.¹⁵ Walsh has reported highly enantioselective, catalytic additions of alkenylzirconium reagents (prepared by in situ hydrozirconation of a terminal alkyne) to ketones.^{16,17} The catalytic, asymmetric reductive coupling of alkynes and ketones reported herein allows for the use of internal alkynes and affords a

(10) For example, see: (a) Tejedor, D.; Garcia-Tellado, F.; Marrero-Tellado, J. J.; de Armas, P. *Chem. Eur. J.* **2003**, 3122–3131. (b) Bharadwaj, A. R.; Scheidt, K. A. *Org. Lett.* **2004**, *6*, 2465–2468.

(11) Titanocene-catalyzed intramolecular alkene-ketone cyclocarbonylation: (a) Kablaoui, N. M.; Hicks, F. A.; Buchwald, S. L. J. Am. Chem. Soc. **1997**, *119*, 4424–4431. (b) Mandal, S. K.; Amin, S. R.; Crowe, W. E. J. Am. Chem. Soc. **2001**, *123*, 6457–6458.

(12) Catalytic intramolecular allene-ketone cyclizations: (a) Kang, S.-K.; Yoon, S.-K. *Chem. Commun.* **2002**, 2634–2635. (b) Kang, S.-K.; Ha, Y.-H.; Ko, B.-S.; Lim, Y.; Jung, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 343–345. (c) Kang, S.-K.; Hong, Y.-T.; Lee, J.-H.; Kim, W.-Y.; Lee, I.; Yu, C.-M. *Org. Lett.* **2003**, *5*, 2813–2816.

(13) Rh-catalyzed carbometallative aldol cycloreduction: (a) Cauble, D.
F.; Gipson, J. D.; Krische, M. J. J. Am. Chem. Soc. 2003, 125, 1110–1111. (b) Bocknack, B. M.; Wang, L.-C.; Krische, M. J. Proc. Natl. Acad. Sci. U.S.A. 2004, 101, 5421–5424.

(14) Reviews: (a) Fuji, K. Chem. Rev. 1993, 93, 2037-2066. (b) Corey,
E. J.; Guzmán-Pérez, A. Angew. Chem., Int. Ed. 1998, 37, 388-401. (c)
Christoffers, J.; Mann, A. Angew. Chem., Int. Ed. 2001, 40, 4591-4597.
(d) Denissova, I.; Barriault, L. Tetrahedron 2003, 59, 10105-10146. (e)
Ramón, D. J.; Yus, M. Curr. Org. Chem. 2004, 8, 149-183. (f) Douglas,
C. J.; Overman, L. E. Proc. Natl. Acad. Sci. U.S.A. 2004, 101, 5363-5367.

(15) Review: Ramón, D. J.; Yus, M. Angew. Chem., Int. Ed. 2004, 43, 284–287.

(16) (a) Li, H.; Walsh, P. J. J. Am. Chem. Soc. 2004, 126, 6538–6539.
(b) Anaya de Parrodi, C.; Walsh, P. J. Synlett 2004, 2417–2420.

(17) For diastereoselective additions of alkenylzirconocenes to ketones and α -keto esters, respectively, see: (a) Chavez, D. E.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2001**, *40*, 3667–3670. (b) Wipf, P.; Stephenson, C. R. J. *Org. Lett.* **2003**, *5*, 2449–2452.

more direct approach, as both alkyne reduction and C-C bond formation occur in the same catalytic pathway and the stoichiometric use of a transition metal is avoided.

Initial attempts to promote the catalytic reductive coupling of 1-decen-3-yne (1) and acetophenone using triethylborane (Et₃B) as a stoichiometric reductant and catalytic amounts of both Ni(cod)₂ and tricyclopentylphosphine (Cyp₃P), a ligand that had proven particularly effective in promoting reductive couplings of 1,3-enynes and aldehydes, were completely unsuccessful. Only a trace of the desired coupling product was observed, even at elevated temperature (Table 1, entry 1). Similar results were obtained with both tris(o-

 Table 1.
 Ligand Evaluation in Catalytic Reductive Couplings of 1,3-Enynes and Acetophenone^a

entry	\mathbb{R}^1	\mathbb{R}^2	R_3P	yield (%), regioselectivity ^b	ee ^c (%)
1	н	$n ext{-Hex}(1)$	Cyp ₃ P	<2 (n.d.)	
2	н	$n ext{-Hex}\left(1\right)$	(o-anisyl) ₃ P	<2 (n.d.)	
3	н	$n ext{-Hex}\left(1\right)$	$CyPPh_2$	<2 (n.d.)	
4	н	$n ext{-Hex}\left(1\right)$	(+)-NMDPP	68 (>95:5)	17
5	Η	$n ext{-Hex}\left(1 ight)$	$FcPPh_2$	44 (>95:5)	
6	Me	Et (3)	$FcPPh_2$	79 (>95:5)	
7^d	Me	Et (3)	(S)- 4	89 (>95:5)	58
8^{e}	Me	Et(3)	(S)- 4	69 (> 95:5) ^f	64

^{*a*} See Scheme 1. Standard procedure: To Ni(cod)₂ (0.05 mmol), R₃P (0.1 mmol), acetophenone (1.0 mmol), and Et₃B (1.0 mmol) at 50 °C was added dropwise the enyne (0.5 mmol) over 6 h. After an additional 12 h, silica gel chromatography afforded dienols **2** and **5** as mixtures with acetophenone. ^{*b*} Yield and regioselectivity determined by ¹H NMR integration. ^{*c*} Determined by HPLC analysis, Chiralcel OJ column. ^{*d*} Reaction conducted at 35 °C. ^{*e*} Reaction conducted at 23 °C. ^{*f*} Isolated yield of **5** following treatment of crude reaction mixture with NaBH₄ at 0 °C. n.d. = not determined.

methoxyphenyl)phosphine ((o-anisyl)₃P, entry 2) and cyclohexyldiphenylphosphine (CyPPh₂, entry 3). To our delight, however, the use of (+)-neomenthyldiphenylphosphine (NMDPP, Figure 1) led to an efficient catalytic reductive





coupling, affording the desired dienol 2 in 68% yield and >95:5 regioselectivity, albeit in only 17% ee (entry 4).

P-Chiral, ferrocenyl monodentate phosphines are effective in catalytic asymmetric coupling reactions of alkynes with both aldehydes² and imines.^{5b} Accordingly, we evaluated this family of phosphines in the ketone coupling reaction described above. Unlike the other achiral ligands evaluated,

⁽⁸⁾ Transition metal mediated reductive coupling of alkynes and ketones (stoichiometric in transition metal): (a) Buchwald, S. L.; Watson, B. T.; Huffman, J. C. *J. Am. Chem. Soc.* **1987**, *109*, 2544–2546. (b) Kataoka, Y.; Miyai, J.; Oshima, K.; Takai, K.; Utimoto, K. *J. Org. Chem.* **1992**, *57*, 1973–1981. (c) Takahashi, T.; Xi, C.; Xi, Z.; Kageyama, M.; Fischer, R.; Nakajima, K.; Negishi, E. J. Org. Chem. **1998**, *63*, 6802–6806. (d) Ozerov, O. V.; Brock, C. P.; Carr, S. D.; Ladipo, F. T. Organometallics **2000**, *19*, 5016–5025.

⁽⁹⁾ Reductive cyclizations of alkynes and ketones promoted by samarium diiodide. Reviews: (a) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29–68. (b) Edmonds, D. J.; Johnston, D.; Procter, D. J. *Chem. Rev.* **2004**, *104*, 3371–3403. Examples: (c) Molander, G. A.; Kenny, C. J. Am. Chem. Soc. **1989**, *111*, 8236–8246. (d) Berndt, M.; Gross, S.; Hölemann, A.; Reissig, H.-U. Synlett **2004**, 422–438. (e) Hölemann, A.; Reissig, H.-U. *Synlett* **2004**, 2732–2735.

 Table 2.
 Catalytic Asymmetric Reductive Coupling of 1,3-Enynes and Ketones^a

entry	product		yield (%), ^b regioselectivity ^c	ee (%) ^d
1 ^e	OH Me n-Hex	2	62 (>95:5)	60
2	OH Me Me Et	5	69 (>95:5)	64 ^ŕ
3	OH Me Me Me Et	6	52 (>95:5)	47
4	OH Me Et Me	7	71 (>95:5)	64
5 ^g	OH Me Et CO2Et	8	60 (>95:5)	58
6	OH Me Me Et	9	77 (>95:5)	46
7 ^g	OH Me Me Et	10	65 (>95:5)	62
8 ^g	OH Me Me Et	11	58 (>95:5)	40
9 ^g	OH Me Me Et	12	58 (>95:5)	42
10	OH Me Me Et	13	39 (>95:5)	70

^{*a*} See Scheme 1 and the Supporting Information for details. Standard procedure: To Ni(cod)₂ (0.05 mmol), (*S*)-**4** (0.1 mmol), the ketone (1.0 mmol), and Et₃B (1.0 mmol) at 23 °C, the enyne (0.5 mmol) was added dropwise over 6 h. After an additional 12 h, the reaction was stirred 30 min open to air to promote oxidation of the catalyst and treated with NaBH₄ (1.0 mmol) at 0 °C. ^{*b*} Isolated yield (SiO₂ chromatography). ^{*c*} Determined by ¹H NMR. ^{*d*} Determined by HPLC analysis (Chiralcel OJ or Chiralpak AD-H column). ^{*e*} (*R*)-**4** (0.1 mmol) was employed. ^{*f*} Absolute configuration determined to be *S* by conversion to the known α-hydroxy ketone **15** (Scheme 2). ^{*g*} Toluene (0.2 mL) was added as a cosolvent.

ferrocenyldiphenylphosphine (FcPPh₂) was effective at promoting the catalytic reductive coupling of **1** and acetophenone (entry 5), and the yield of the reaction of the commercially available 2-methyl-1-hexen-3-yne (**3**) under the same conditions was significantly higher (entry 6). The introduction of a methyl group at the ortho position of one of the phenyl rings of FcPPh₂, i.e., *P*-chiral ferrocenyl phosphine **4**,^{2c} not only improved the reaction yield, but also afforded the corresponding dienol **5** in 58% ee (entry 7).¹⁸ The enhanced reactivity observed with phosphine **4** allowed this coupling reaction to be conducted efficiently at room temperature, affording a further increase in enantioselectivity (64% ee, entry 8).¹⁹

In addition to acetophenone, a variety of aromatic and heteroaromatic ketones undergo efficient catalytic asymmetric reductive coupling with 2 under these conditions (Table 2).²⁰ Electron-donating substituents (entries 3 and 4) and electron-withdrawing aromatic esters are compatible (entry 5). Both 1- and 2-acetylnaphthalene couple effectively (entries 7 and 8), although ortho substitution leads to somewhat diminished enantioselectivity (entries 3 and 7). Heteroaromatic ketones 2-acetylfuran and benzofuran-2-yl methyl ketone can also be employed (entries 9 and 10). Interestingly, an α,β -unsaturated ketone, 1-acetyl-1-cyclohexene, affords the best enantioselectivity observed (70% ee), albeit in moderate yield (entry 12).²¹ The unique reactivity of 1,3-envnes relative to other classes of alkynes and the high regioselectivity in these reactions suggests that these transformations may be directed by the neighboring alkene.2g,22

The products of these coupling reactions are enantiomerically enriched chiral 1,3-dienes, a class of compounds whose utility in Diels–Alder cycloaddition reactions has been intensively studied.^{23,24} As shown in Scheme 2, a site-



selective Rh-catalyzed hydrogenation of these dienols previously reported in our laboratory^{2g} provides access to enan-

(19) Superior yields were typically obtained in these reactions when conducted in the absence of an additional solvent. However, when solid ketones were employed, toluene was used as a cosolvent.

(20) Ketones containing two alkyl substituents, such as cyclohexyl methyl ketone or cyclopropyl methyl ketone, afforded coupling products in very low yield (<10%), and α -keto esters were completely ineffective.

(21) The yield was improved by conducting this reaction at 35 °C: 55% yield, >95:5 regioselectivity, 63% ee.

(22) Alkynes that lack an alkenyl substituent, such as 1-phenyl-1-propyne or 4-octyne, and 1,3-enynes bearing an aromatic substituent, such as 1-phenyl-3-buten-1-yne, did not undergo coupling under these conditions.

(23) For leading references on related chiral 1,3-dienes in intermolecular Diels-Alder reactions, see: (a) Tripathy, R.;. Franck, R. W.; Onan, K. D. J. Am. Chem. Soc. 1988, 110, 3257-3262. (b) Fisher, M. J.; Hehre, W. J.; Kahn, S. D.; Overman, L. E. J. Am. Chem. Soc. 1988, 110, 4625-4633. (c) Datta, S. C.; Franck, R. W.; Tripathy, R.; Quigley, G. J.; Huang, L.; Chen, S.; Sihaed, A. J. Am. Chem. Soc. 1990, 112, 8472-8478. (d) Adam, W.; Glaser, J.; Peters, K.; Prein, M. J. Am. Chem. Soc. 1995, 117, 9190-9193. (e) Barriault, L.; Thomas, J. D. O.; Clement, R. J. Org. Chem. 2003, 68, 2317-2323;

(24) In intramolecular Diels–Alder reactions, see: (a) Bols, M.; Skrydstrup, T. *Chem. Rev.* **1995**, *95*, 1253–1277. (b) Keck, G. E.; Romer, D. R. *J. Org. Chem.* **1993**, *58*, 6083–6089. (c) Shiina, J.; Nishiyama, S. *Tetrahedron* **2003**, *59*, 6039–6044;

⁽¹⁸⁾ *P*-Chiral ferrocenyl phosphines with other substitution patterns on this aromatic ring displayed reduced efficacy (e.g., 2-biphenyl, 28% yield, 18% ee; 2,5-dimethylphenyl, 76% yield, 50% ee; 2-*i*-Pr-phenyl, 13% yield, 70% ee).

tiomerically enriched, trisubstituted allylic alcohols such as **14** that possess a quaternary carbinol stereogenic center, a class of allylic alcohols not previously accessible via any catalytic method (Scheme 2).²⁵ Ozonolysis of these compounds affords α -hydroxy ketones such as **15**, the TMS ether of which has been employed by Masamune in asymmetric aldol reactions.²⁶ This two-step procedure also allowed assignment of the configuration of the major enantiomer of dienol **5** as *S*.²⁷

In summary, we have developed the first catalytic asymmetric reductive coupling of alkynes and ketones, a transformation in which 1,3-enynes are uniquely effective substrates. This transformation is highly regioselective and affords synthetically useful 1,3-dienes with an adjacent quaternary carbinol stereogenic center in moderate enantioselectivity. Finally, the *P*-chiral monodentate ferrocenyl phosphine that promotes this coupling reaction may find use in other asymmetric, nickel-catalyzed transformations. Our efforts toward this end will be described in due course.

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Supporting Information Available: Detailed experimental procedures and characterization data for compounds 2 and 5–15. This material is available free of charge via the Internet at http://pubs.acs.org.

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⁽²⁵⁾ For the singular example of the preparation of such compounds via antibody-catalyzed resolution, see: List, B.; Shabat, D.; Zhong, G.; Turner, J. M.; Li, A.; Bui, T.; Anderson, J.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **1999**, *121*, 7283–7291.

⁽²⁶⁾ Masamune, S.; Ali, S. A.; Snitman, D. L.; Garvey, D. S. Angew. Chem., Int. Ed. Engl. 1980, 19, 557–558.

⁽²⁷⁾ Harder, T.; Lohl, T.; Bolte, M.; Wagner, K.; Hoppe, D. *Tetrahedron Lett.* **1994**, *35*, 7365–7368.