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

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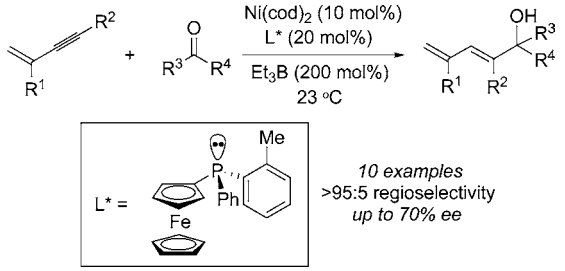
ABSTRACT



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 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 alkynes[2i]) 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

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(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. *Tetrahedron: Asymmetry* **2003**, *14*, 3619−3625. (g) Miller, K. M.; Luanphaisarnnont, T.; 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. *Angew. 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.

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(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.

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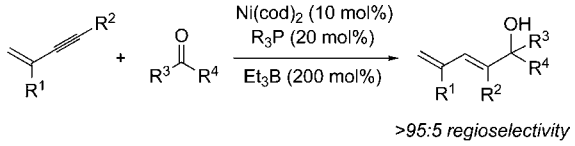
efficiently in high regioselectivity and modest enantioselectivity when conducted in the presence of catalytic amounts of a *P*-chiral, ferrocenyl monodentate phosphine ligand (Scheme 1).

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 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 (Et_3B) as a stoichiometric reductant and catalytic amounts of both $Ni(cod)_2$ and tricyclopentylphosphine (Cyp_3P), 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*-methoxyphenyl)phosphine ($(o\text{-anisyl})_3P$, entry 2) and cyclohexyldiphenylphosphine ($CyPPh_2$, 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).

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

entry	R^1	R^2	R_3P	yield (%), regioselectivity[b]	ee[c] (%)
1	H	*n*-Hex (**1**)	Cyp_3P	<2 (n.d.)	
2	H	*n*-Hex (**1**)	$(o\text{-anisyl})_3P$	<2 (n.d.)	
3	H	*n*-Hex (**1**)	$CyPPh_2$	<2 (n.d.)	
4	H	*n*-Hex (**1**)	(+)-NMDPP	68 (>95:5)	17
5	H	*n*-Hex (**1**)	$FcPPh_2$	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), R_3P (0.1 mmol), acetophenone (1.0 mmol), and Et_3B (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 $NaBH_4$ at 0 °C. n.d. = not determined.

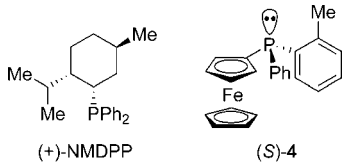


Figure 1. Chiral monodentate phosphines effective at promoting the catalytic reductive coupling of 1,3-enynes and ketones.

P-Chiral, ferrocenyl monodentate phosphines are effective in catalytic asymmetric coupling reactions of alkynes with both aldehydes[2] and imines.[5b] Accordingly, we evaluated this family of phosphines in the ketone coupling reaction described above. Unlike the other achiral ligands evaluated,

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(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.

(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.

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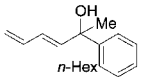
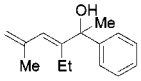
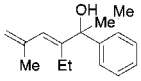
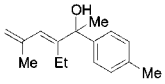
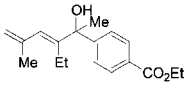
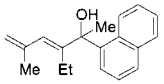
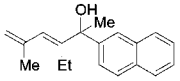
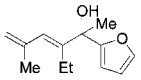
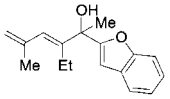
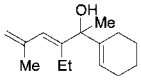
(16) (a) Li, H.; Walsh, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 6538−6539. (b) Anaya de Parrodi, C.; Walsh, P. J. *Synlett* **2004**, 2417−2420.

(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.

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

entry	product		yield (%),[b] regioselectivity[c]	ee (%)[d]
1[e]		**2**	62 (>95:5)	60
2		**5**	69 (>95:5)	64[f]
3		**6**	52 (>95:5)	47
4		**7**	71 (>95:5)	64
5[g]		**8**	60 (>95:5)	58
6		**9**	77 (>95:5)	46
7[g]		**10**	65 (>95:5)	62
8[g]		**11**	58 (>95:5)	40
9[g]		**12**	58 (>95:5)	42
10		**13**	39 (>95:5)	70

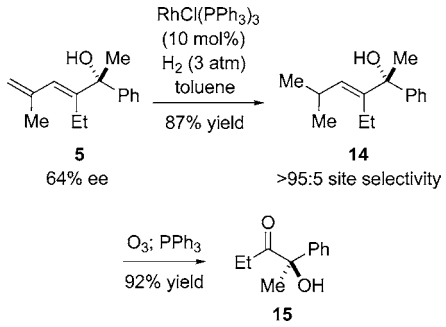
[a] See Scheme 1 and the Supporting Information for details. Standard procedure: To $Ni(cod)_2$ (0.05 mmol), (*S*)-**4** (0.1 mmol), the ketone (1.0 mmol), and Et_3B (1.0 mmol) at 23 °C, the enyne (0.5 mmol) was added dropwise over 6 h. After an additional 12 h, the reaction was stirred 30 min open to air to promote oxidation of the catalyst and treated with $NaBH_4$ (1.0 mmol) at 0 °C. [b] Isolated yield (SiO_2 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 ($FcPPh_2$) 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 $FcPPh_2$, 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-enynes 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-

Scheme 2



(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).

(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;

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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.

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