J|A|C|S
COMMUNICATIONS

Published on Web 03/04/2003

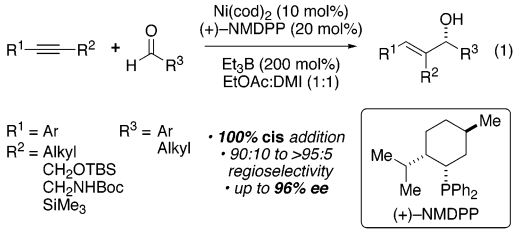
Catalytic Asymmetric Reductive Coupling of Alkynes and Aldehydes: Enantioselective Synthesis of Allylic Alcohols and α-Hydroxy Ketones

Karen M. Miller, Wei-Sheng Huang, and Timothy F. Jamison*

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

Received January 27, 2003; E-mail: tfj@mit.edu

Catalytic asymmetric carbonyl addition reactions are among the most studied and useful methods of enantioselective carbon−carbon bond formation,[1] but very few are catalyzed by complexes of group 10 metals. Examples include Pd(II)- and Pt(II)-catalyzed aldol[2] and ene[3] processes, as well as Ni(II)-catalyzed Nozaki−Hiyama−Kishi reactions[4] and Ni(0)-catalyzed 1,3-dien-ω-al cyclizations.[5,6] Herein we describe a new member of this unusual class of reactions, the first highly enantioselective method for catalytic reductive coupling of alkynes and aldehydes (eq 1).



Allylic alcohols are useful starting materials[7] and are prevalent in complex natural products.[8] Enantioselective methods for their preparation from alkynes and aldehydes that use stoichiometric amounts of transition metals include those of Oppolzer[9] and Wipf,[10] which are particularly effective for preparing (*E*)-disubstituted allylic alcohols from terminal alkynes, and that of Sato, which utilizes a chiral titanium-alkyne complex.[11] Nickel-catalyzed intramolecular[12] and intermolecular[13] reductive coupling of alkynes and aldehydes has been reported, yet asymmetric catalysis has been limited to only a few cases, all of which utilize "alkyl−alkyl" alkynes (alkyl−C≡C−alkyl′) and are of low to moderate regioselectivity and enantioselectivity.[14]

Although (+)-(neomenthyl)diphenylphosphine (NMDPP) was first prepared by Morrison over 30 years ago and is commercially available, this chiral monophosphine has thus far found only limited utility in asymmetric catalysis.[15] Nevertheless, in extensive evaluations of chiral ligands, transition metals, and reducing agents, NMDPP, $Ni(cod)_2$, and triethylborane (Et_3B) consistently provided superior results.[16] Yield and enantioselectivity were improved further by using a solvent composed of equal volumes of ethyl acetate and 1,3-dimethylimidazolidinone (DMI) in conjunction with slow addition of the aldehyde (see Supporting Information). All other solvents and additives reduced efficacy and/or selectivity, as did varying the mode of addition of other components.

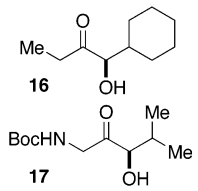
This catalytic system affords trisubstituted allylic alcohols corresponding to exclusive cis addition to the alkyne in excellent regioselectivity and in up to 96% ee (Table 1). Branched aldehydes provide high enantioselectivities in reductive couplings with 1-phenyl-1-propyne, and variation of the alkyne aromatic group (R^1) is tolerated, with 1-naphthyl-1-propyne being particularly effective (entries 5−7). The other alkyne substituent (R^2) can also be varied considerably (entries 8−14), and protected alcohols, protected amines, and $SiMe_3$ groups are accommodated.[17] In contrast to our recent studies with chiral ferrocenyl monophosphines, enantioselectivities are significantly lower using NMDPP in couplings involving alkyl−C≡C−alkyl alkynes (entry 15).[14]

Table 1. Catalytic Asymmetric Reductive Alkyne/Aldehyde Couplings[a]

entry/ product	R^1	R^2	R^3	yield (%), regioselectivity	ee (%)
1	Ph	Me	*i*-Pr	95 (>95:5)	90
2	Ph	Me	*c*-C_6H_{11}	97 (>95:5)	90
3	Ph	Me	Ph	79 (91:9)	73
4	Ph	Me	*n*-Pr	82 (>95:5)	65
5	(*p*-MeO)Ph	Me	*i*-Pr	80 (>95:5)	88
6	(*p*-Cl)Ph	Me	*i*-Pr	75 (>95:5)	83
7	1-naphthyl	Me	*i*-Pr	93 (>95:5)	90
8	Ph	Et	*i*-Pr	81 (>95:5)	93
9[b]	Ph	Et	*c*-C_6H_{11}	78 (>95:5)	89
10	Ph	*n*-Pr	*i*-Pr	74 (>95:5)	92
11	Ph	*i*-Pr	*i*-Pr	58[c] (>95:5)	92
12	Ph	CH_2OTBS	*i*-Pr	59 (>95:5)	85
13	Ph	CH_2NHBoc	*i*-Pr	60 (>95:5)	96
14	Ph	$SiMe_3$	*n*-Pr	43[c] (>95:5)	92
15	*n*-Pr	*n*-Pr	*i*-Pr	35[c] (−)	42

[a] See eq 1. Experimental procedure (see Supporting Information): A solution of $Ni(cod)_2$ (0.05 mmol), (+)-NMDPP (0.10 mmol), and Et_3B (1.0 mmol) in EtOAc/DMI (1:1, total volume 0.50 mL) was cooled to −25 °C. An alkyne (0.50 mmol) was added via syringe, and then an aldehyde (1.0 mmol) was added via syringe over 8 h. The solution was allowed to stir 36 h, and silica gel chromatography afforded allylic alcohols **1**−**15**. Regioselectivity was determined by ^1H NMR; enantioselectivity was determined by chiral GC or HPLC analysis. [b] Performed on 5.0 mmol scale. [c] Some alkylative coupling was observed (transfer of Et group (instead of H) from Et_3B).

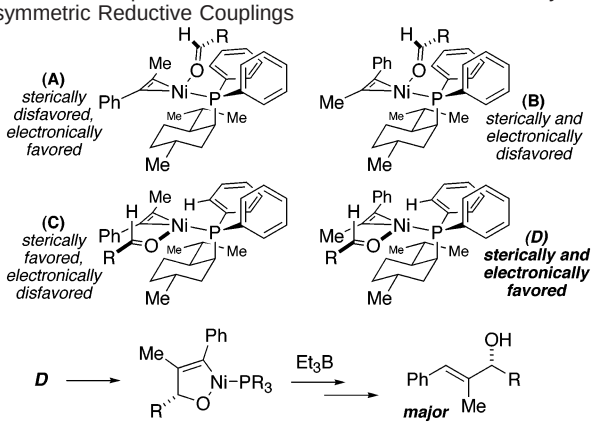
To illustrate the utility of this method further, allylic alcohols **9** and **13** were converted to α-hydroxy ketones via ozonolysis. Enantiomeric purity was preserved in both cases, giving **16** (89% ee), whose TBS ether was developed by Masamune for asymmetric aldol reactions,[18] and **17** (96% ee), whose α-amino-α′-hydroxy pattern is found in molecules targeted against trypanosomes, parasites that cause African sleeping sickness upon transmission from tsetse flies,[19] and in aerothionin natural products with anti-tuberculosis activity.[20] Common methods of α-hydroxy ketone



synthesis via asymmetric catalysis involve dihydroxylation or epoxidation of ketone enolate derivatives.[21] The reductive coupling/ozonolysis approach obviates a regioselective ketone enolization that would be required (and difficult) for cases represented by **16** and **17** and is therefore complementary.[22]

10.1021/ja034366y CCC: $25.00

Scheme 1. Proposed Steric and Electronic Control in Catalytic Asymmetric Reductive Couplings



The sense of asymmetric induction in these couplings is consistent with the model in Scheme 1. Several lines of evidence point to an oxametallocyclopentene intermediate, arising from complexes such as **A**−**D**.[23] Both the axial placement and the orientation of a metal-PPh_2 group over the cyclohexyl ring of NMDPP have been observed in the solid state.[24] Rotation of one of the phenyl groups to avoid interaction with the isopropyl group places a C−H bond in the ligand plane on one side, disfavoring aldehyde complexation (**A** and **B**). Coordination of the aldehyde to the less encumbered side (**C** or **D**) by way of the electron pair cis to the aldehyde H and placement of the aldehyde R group away from the metal center appear to minimize steric interactions.

The high enantioselectivity uniquely provided by NMDPP in these couplings can thus be explained by a cooperative effect between steric properties of the ligand and electronic differences of the alkyne substituents. Two of four modes of aldehyde coordination (**A** and **C**) are inconsistent with the sense and degree of regioselectivity, and one of the remaining two is more accessible (**D**) and leads to the major enantiomer observed. This framework suggests that increased steric differentiation of the two aldehyde coordination sites might further enhance enantioselectivity. Finally, the general strategy of tandem electronic and steric control of enantioselectivity presented here may be applicable to related reactions involving alkynes, such as those described by our group and others.[4−6,12a,23,25]

Acknowledgment. We thank the National Institute of General Medical Sciences (GM-063755), the NSF (CAREER CHE-0134704), Merck Research Laboratories, Pfizer, Boehringer-Ingelheim, Bristol-Myers Squibb, 3M, Johnson & Johnson, the donors of the Petroleum Research Fund, and MIT for financial support. We are grateful to Robert D. Jackson, Chudi O. Ndubaku, Justin P. Cohen, and Elizabeth A. Colby for experimental assistance. The NSF (CHE-9809061 and DBI-9729592) and NIH (1S10RR13886-01) provide partial support for the MIT Department of Chemistry Instrumentation Facility.

Supporting Information Available: Experimental procedures and data for compounds **1**−**17** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999. (b) *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000.

(2) (a) Gorla, F.; Togni, A.; Venanzi, L. M.; Abinati, A.; Lianza, F. *Organometallics* **1994**, *13*, 1607−1616. (b) Sodeoka, M.; Ohrai, K.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 2648−2649. (c) Fujimura, O. *J. Am. Chem. Soc.* **1998**, *120*, 10032−10039. (d) Motoyama, Y.; Kawakami, H.; Shimozono, K.; Aoki, K.; Nishiyama, H. *Organometallics* **2002**, *21*, 3408−3416.

(3) (a) Hao, J.; Hatano, M.; Mikami, K. *Org. Lett.* **2000**, *2*, 4059−4062. (b) Koh, J. H.; Larsen, A. O.; Gagné, M. R. *Org. Lett.* **2001**, *3*, 1233−1236.

(4) Choi, H. W.; Nakajima, K.; Demeke, D.; Kang, F. A.; Jun, H. S.; Wan, Z. K.; Kishi, Y. *Org. Lett.* **2002**, *4*, 4435−4438.

(5) Sato, Y.; Saito, N.; Mori, M. *J. Am. Chem. Soc.* **2000**, *122*, 2371−2372.

(6) Bercot, E. A.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 174−175.

(7) (a) Brückner, R. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 6, Chapter 4.6, pp 873−908. (b) Hill, R. K. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 5, Chapter 7.1, pp 785−826. (c) Wipf, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 5, Chapter 7.2, pp 827−873. (d) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307−1370.

(8) (a) Barchi, J. J., Jr.; Moore, R. E.; Patterson, G. M. L. *J. Am. Chem. Soc.* **1984**, *106*, 8193−8197. (b) Bollag, D. M.; McQueney, P. A.; Zhu, J.; Hensens, O.; Koupal, L.; Liesch, J.; Goetz, M.; Lazarides, E.; Woods, C. M. *Cancer Res.* **1995**, *55*, 2325−2333. (c) Oka, M.; Iimura, S.; Tenmyo, O.; Sawada, Y.; Sugawara, M.; Ohkusa, N.; Yamamoto, H.; Kawano, K.; Hu, S.-L.; Fukagawa, Y.; Oki, T. *J. Antibiot.* **1993**, *46*, 367−373.

(9) Oppolzer, W.; Radinov, R. N. *Helv. Chim. Acta* **1992**, *75*, 170−173.

(10) Wipf, P.; Ribe, S. *J. Org. Chem.* **1998**, *63*, 6454−6455.

(11) Takayanagi, Y.; Yamashita, K.; Yoshida, Y.; Sato, F. *Chem. Commun.* **1996**, 1725−1726.

(12) (a) Oblinger, E.; Montgomery, J. *J. Am. Chem. Soc.* **1997**, *119*, 9065−9066. (b) See also: Crowe, W. E.; Rachita, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 6787−6788.

(13) Huang, W.-S.; Chan, J.; Jamison, T. F. *Org. Lett.* **2000**, *2*, 4221−4223.

(14) Colby, E. A.; Jamison, T. F. *J. Org. Chem.* **2003**, *68*, 156−166.

(15) (a) Morrison, J. D.; Burnett, R. E.; Aguiar, A. M.; Morrow, C. J.; Philips, C. *J. Am. Chem. Soc.* **1971**, *93*, 1301−1303. (b) Blum, J.; Eisen, M.; Schumann, H.; Gorella, B. *J. Mol. Catal.* **1989**, *56*, 329−337. (c) Lee, S.; Hartwig, J. F. *J. Org. Chem.* **2001**, *66*, 3402−3415. (d) Recent chiral monophosphine review: Komarov, I. V.; Börner, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 1197−1200.

(16) Most monophosphines formed catalytically active complexes, but all ee's were lower than 25% (R^1 = Ph, R^2 = Me, R^3 = *n*-Pr). For example: (*S*)-ferrocenylmethylphenylphosphine[14] (15% ee); [(*S*)-(*R*)-PPF−OMe] (5% ee); (*R*,*R*)-2,5-dimethyl-1-phenylphospholane (0% ee). Nickel complexes incorporating diphosphines (e.g., BINAP, BPE, DuPHOS) did not catalyze the reaction. Couplings utilizing 200 mol % aldehyde were of much higher yield than those with 100 mol %; reactions employing an NMDPP/Ni ratio of 2:1 gave slightly higher yields than those with a 1:1 ratio. Kimura and Tamaru have also observed that a combination of a nickel catalyst and Et_3B effects reductive carbonyl additions; see, for example: Kimura, M.; Ezoe, A.; Shibata, K.; Tamaru, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4033−4034.

(17) The allylic alcohol derived from phenylacetylene and isobutyraldehyde (R^1 = Ph, R^2 = H, R^3 = *i*-Pr) was afforded in 75% ee, >95:5 regioselectivity, and 15% yield. Alkyne cyclotrimerization is competitive with reductive coupling under these conditions.

(18) (a) Masamune, S.; Choy, W.; Kerdesky, F. A. J.; Imperiali, B. *J. Am. Chem. Soc.* **1981**, *103*, 1566−1568. (b) Masamune, S.; Hirama, M.; Mori, S.; Ali, S. A.; Garvey, D. S. *J. Am. Chem. Soc.* **1981**, *103*, 1568−1571.

(19) (a) Eisenthal, R.; Game, S.; Holman, G. D. *Biochim. Biophys. Acta* **1989**, *985*, 81−89. (b) Azéma, L.; Bringaud, F.; Blonski, C.; Périé, J. *Bioorg. Med. Chem.* **2000**, *8*, 717−722.

(20) Ciminiello, P.; Costantino, V.; Fattorusso, Magno, S.; Mangioni, A.; Pansini, M. *J. Nat. Prod.* **1994**, *57*, 705−712.

(21) (a) Hashiyama, T.; Morikawa, K.; Sharpless, K. B. *J. Org. Chem.* **1992**, *57*, 5067−5068. (b) Zhu, Y.; Tu, Y.; Yu, H.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 7819−7822. (c) Davis, F. A.; Chen, B. C. *Chem. Rev.* **1992**, *92*, 919−934.

(22) See also: (a) Trost, B. M.; Pinkerton, A. B. *J. Am. Chem. Soc.* **2002**, *124*, 7376−7389. (b) Dünkelmann, P.; Kolter-Jung, D.; Nitsche, A.; Demir, A. S.; Siegert, P.; Lingen, B.; Baumann, M.; Pohl, M.; Müller, M. *J. Am. Chem. Soc.* **2002**, *124*, 12084−12085.

(23) Patel, S. J.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2003**, *42*, in press, and references therein.

(24) Whittall, I. R.; Humphrey, M. G.; Samoc, M.; Luther-Davies, B.; Hockless, D. C. R. *J. Organomet. Chem.* **1997**, *544*, 189−196.

(25) Reviews: (a) Tamaru, Y. *J. Organomet. Chem.* **1999**, *576*, 215−231. (b) Montgomery, J. *Acc. Chem. Res.* **2000**, *33*, 467−473. (c) Ikeda, S.-i. *Acc. Chem. Res.* **2000**, *33*, 511−519. (d) Houpis, I. N.; Lee, J. *Tetrahedron* **2000**, *56*, 817−846. Recent examples involving alkynes: (e) Ni, Y.; Amarasinghe, K. D.; Montgomery, J. *Org. Lett.* **2002**, *4*, 1743−1745. (f) Lozanov, M.; Montgomery, J. *J. Am. Chem. Soc.* **2002**, *124*, 2106−2107. (g) Ikeda, S.-i.; Miyashita, H.; Taniguchi, M.; Kondo, H.; Okano, M.; Sato, Y.; Odashima, K. *J. Am. Chem. Soc.* **2002**, *124*, 12060−12061.

JA034366Y