A New Stereoselective Method for the Preparation of Allylic Alcohols

Eric Oblinger and John Montgomery*

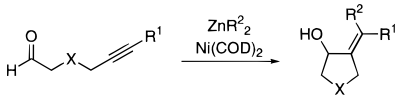
Department of Chemistry, Wayne State University
Detroit, Michigan 48202-3489

Received June 11, 1997

Allylic alcohols are useful building blocks in many synthetic applications including Claisen rearrangements and related sigmatropic processes,[1] enantio-[2] and diastereoselective[3] hydroxyl-directed additions to alkenes, S_N2' displacements with cuprates,[4] palladium-catalyzed π-allyl chemistry,[5] and cationic cyclizations.[6] Allylic alcohols with a tri- or tetrasubstituted alkene component are efficient substrates in many of these applications, and the stereochemical integrity of the alkene is critical to issues involving the creation of stereogenic centers. Prior synthesis of a stereochemically-defined alkenyl iodide followed by metalation/addition or Nozaki/Kishi coupling[7] with an aldehyde are the most commonly employed strategies for the stereoselective preparation of allylic alcohols. However, few general methods exist that allow creation of a tri- or tetrasubstituted alkene and incorporation of an aldehyde in a single operation. In order to address this synthetic challenge, we have initiated the development of a general protocol for the nickel-catalyzed cyclization/alkylation of ynals with organozincs to produce cyclic allylic alcohols and the three-component coupling of alkynes, aldehydes, and organozincs to produce acyclic allylic alcohols with complete control of alkene stereochemistry.

Many powerful methods for reductive and alkylative cyclizations of dienes, enynes, and diynes employing transition metal catalysis have been developed.[8] The corresponding transformations employing enals and ynals to produce alcohol derivatives are also potentially useful. Early transition metal catalysis has proven to be most efficient in cyclizations involving a carbonyl component through the involvement of oxametallacycles, although the strength of the metal−oxygen bond renders catalytic sequences difficult.[9] Recent developments by Buchwald[10] and Crowe[11] demonstrated that σ-bond metathesis of early transition metal oxametallacycles with silyl hydrides provides an efficient mechanism for catalytic turnover in this important class of reactions.[12] Based on our earlier developments in cyclizations of alkynyl enones,[13] we envisioned that nickel-catalyzed couplings of ynals with organozincs could provide an efficient and general entry to allylic alcohols with tri- and tetrasubstituted alkenes. These studies provide, to our knowledge, the first examples of transition metal catalyzed alkylative cyclizations of ynals and related three-component couplings.

Table 1. Ynal Alkylative Cyclizations



entry	X	R^1	R^2	yield (%)[a]
1	CH_2	H	CH_3	70[b]
2	CH_2	H	Ph	72
3	CH_2	H	*n*-Bu	62
4	CH_2	CH_3	Ph	64
5	CH_2	CH_3	*n*-Bu	76
6	CH_2	Ph	CH_3	73
7	CH_2	Ph	Et	67
8	NCOPh	H	CH_3	72

[a] Products were obtained as single stereoisomers by 500 MHz ^{1}H NMR analysis. [b] Isolated as the benzoate ester (two-step yield is reported).

Derivatives of 5-hexynal were first examined in alkylative cyclizations. Upon treatment of 5-hexynal and organozincs with catalytic $Ni(COD)_2$ (5 mol %) at 0 °C in THF, efficient cyclization with stereoselective introduction of the exocyclic trisubstituted alkene was observed (Table 1). The organozincs were generated *in situ* from organolithiums or organomagnesiums and anhydrous zinc chloride. Both sp^2- and sp^3-hybridized organozincs, including those that possess β-hydrogens, were efficiently incorporated without competing β-hydride elimination. Pyrrolidines could also be efficiently prepared by incorporating nitrogen in the tether chain. As expected, the organozinc substituent was always introduced exclusively cis to the alcohol functionality. Direct addition of the organozinc to the aldehyde was not observed. Functionalization of the terminal alkyne (by acetylide alkylation or Sonogashira coupling[14]) followed by nickel-catalyzed alkylative cyclization led to the stereoselective introduction of tetrasubstituted exocyclic alkenes, again with complete and predictable stereocontrol (Table 1). Both isomers of the tetrasubstituted allylic alcohols were conveniently prepared by simply switching the order of substituent introduction. Direct addition of the organozinc to the aldehyde was initially problematic with internal alkynes; however, since the 1,2-addition likely does not involve nickel catalysis, this side reaction could be essentially completely suppressed by employing higher catalyst loadings (20 mol % $Ni(COD)_2$).

Although competing β-hydride elimination was not observed in $Ni(COD)_2$-catalyzed cyclizations employing diethylzinc and dibutylzinc, a complete crossover to reductive cyclization with hydrogen atom introduction was observed simply by pretreating the $Ni(COD)_2$ with PBu_3 (Table 2).[15] Reductive cyclizations were efficient with both terminal and internal alkynes, with the latter allowing completely selective introduction of trisubstituted alkenes of the opposite configuration as those obtained from alkylative cyclizations of terminal alkynes.[16]

The above procedures were also extrapolated to three-component couplings of alkynes, aldehydes, and organozincs

(1) Wipf, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 5, p 827.
(2) (a) Johnson, R. A.; Sharpless, K. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 7, p 389. (b) Charette, A. B.; Marcoux, J. F. *Synlett* **1995**, 1197. (c) Denmark, S. E.; O'Connor, S. P. *J. Org. Chem.* **1997**, *62*, 584.
(3) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.
(4) Lipshutz, B. H.; Sengupta, S. In *Organic Reactions*; Wiley: New York, 1992; Vol. 41, p 135.
(5) Godleski, S. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 4, p 585.
(6) Overman, L. E. *Acc. Chem. Res.* **1992**, *25*, 352.
(7) (a) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644. (b) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048.
(8) (a) For a general review: Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635. (b) For a palladium-catalyzed procedure: Trost, B. M.; Pfrengle, W.; Urabe, H.; Dumas, J. *J. Am. Chem. Soc.* **1992**, *114*, 1923. (c) For a zirconium-catalyzed procedure: Knight, K. S.; Wang, D.; Waymouth, R. M. Ziller, J. *J. Am. Chem. Soc.* **1994**, *116*, 1845.
(9) (a) Hewlett, D. F.; Whitby, R. J. *J. Chem. Soc., Chem. Commun.* **1990**, 1684. (b) For a mid transition metal promoted cyclization, see: Bryan, J. C.; Arterburn, J. B.; Cook, G. K.; Mayer, J. M. *Organometallics* **1992**, *11*, 3965.
(10) Kablaoui, N. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 3182, and references therein.
(11) Crowe, W. E.; Rachita, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 6787.
(12) Related late transition metal cyclizations were reported by Mori, although a mechanism not involving oxametallacycles was proposed: (a) Sato, Y.; Takimoto, M.; Hayashi, K.; Katsuhara, T.; Takagi, K.; Mori, M. *J. Am. Chem. Soc.* **1994**, *116*, 9771. (b) Sato, Y.; Takimoto, M.; Mori, M. *Tetrahedron Lett.* **1996**, *37*, 887.
(13) (a) Montgomery, J.; Savchenko, A. V. *J. Am. Chem. Soc.* **1996**, *118*, 2099. (b) Montgomery, J.; Seo, J.; Chui, H. M. P. *Tetrahedron Lett.* **1996**, *37*, 6839. (c) Montgomery, J.; Oblinger, E.; Savchenko, A. V. *J. Am. Chem. Soc.* **1997**, *119*, 4911. (d) Montgomery, J.; Chevliakov, M. V.; Brielmann, H. L. *Tetrahedron* **1997**, in press.
(14) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467.
(15) Tributylphosphine was found to be far more effective in promoting reductive cyclization than was triphenylphosphine, which was extensively used in our earlier studies with alkynylenones (ref 13).

S0002-7863(97)01918-5 CCC: $14.00

Scheme 1. Proposed Mechanism for Ynal Cyclizations and Three-Component Couplings

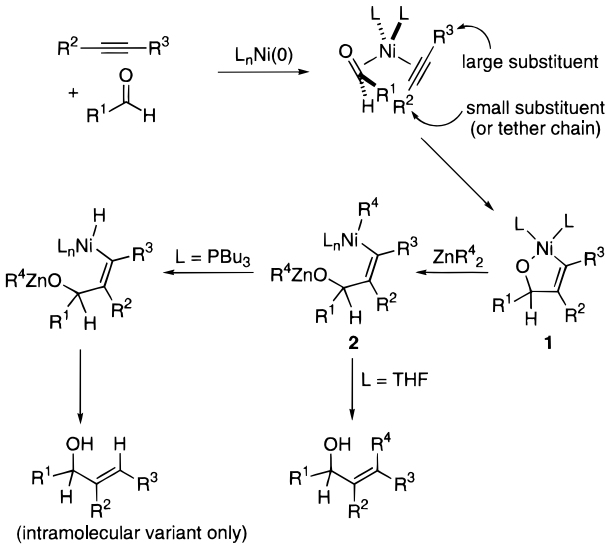
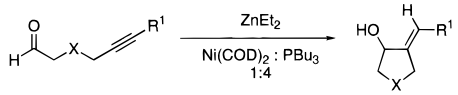


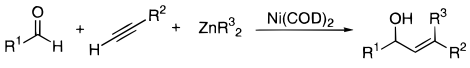
Table 2. Ynal Reductive Cyclizations



entry	X	R^1	yield (%)[a]
1	CH_2	H	74[b]
2	CH_2	CH_3	67[b]
3	CH_2	Ph	62
4	NCOPh	H	70[c]

[a] Products were obtained as single stereoisomers by 500 MHz ^{1}H NMR analysis. [b] Isolated as the benzoate ester (two-step yield is reported). [c] Isolated as a mixture with 9% of the ethyl-substituted alkylative cyclization product.

Table 3. Three-Component Couplings



entry	R^1	R^2	R^3	yield (%)[a]
1	Ph	Ph	Me	60
2	Ph	C_6H_{13}	Me	74
3	Ph	C_6H_{13}	*n*-Bu	71
4	*i*-pr	Ph	Me	21[b]
5	Ph	Ph	$C(CH_3)=CH_2$	0[c]

[a] Products were obtained as single regio- and stereoisomers by 500 MHz ^{1}H NMR analysis. [b] Isolated as the acetate ester (two-step yield is reported). [c] The alcohol derived from isopropenyl addition to benzaldehyde was isolated in 90% yield.

(Table 3).[17,18] Highly chemo-, regio-, and stereoselective addition directly afforded the desired allylic alcohols. Yields were typically highest when the alkyne was introduced as the limiting reagent.[19] Aromatic and aliphatic substitution was tolerated in both the alkyne and aldehyde components, although yields were significantly lower with enolizable aldehydes. sp^3-Hybridized organozincs were tolerated, but diisopropenylzinc underwent direct addition to the aldehyde without alkyne incorporation. In contrast to the efficient reductive cyclizations of ynals in the presence of PBu_3, hydrogen atom incorporation was not observed in intermolecular three-component couplings in the presence of phosphines. The allylic alcohols that would be obtained by intermolecular reductive couplings involving β-hydride elimination are easily obtained by the Wipf procedure involving alkene transfer from hydrozirconation-derived organometallics.[20] The Wipf procedure, however, is not amenable to intramolecular reductive cyclizations (as in Table 2) since aldehyde hydrozirconation proceeds faster than hydrozirconation of alkynes.[21] Thus the Wipf procedure and the methods reported herein are completely complementary.

We speculate that oxametallacycles are involved in the transformations described above and that both reductive and alkylative cyclization products are derived from a common intermediate (Scheme 1).[22] Oxidative cyclization of Ni(0) with an alkyne and an aldehyde would directly afford oxametallacycle **1**.[23,24] Transmetalation of the organozinc would produce vinyl nickel species **2**. Reductive elimination of **2** would afford alkylative cyclization products, whereas β-hydride elimination prior to reductive elimination in the presence of tributylphosphine would afford reductive cyclization products.[25]

In summary, an efficient, general, and stereoselective synthesis of cyclic and acyclic allylic alcohols that possess tri- and tetrasubstituted alkenes has been developed. Significantly, both *E* and *Z* isomers of the alkenes may be obtained in a completely stereoselective fashion from a common intermediate. The above procedures are direct and experimentally simple and are carried out at 0 °C with thermally-stable and readily-accessible reagents. Further methodological refinements, catalytic asymmetric variants, and mechanistic studies are under investigation.

Acknowledgment. J.M. acknowledges receipt of a National Science Foundation CAREER Award (1996−2000) and a New Faculty Award from 3M Pharmaceuticals. Acknowledgment is made to the Donors of The Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

Supporting Information Available: Experimental procedures for all reported compounds and copies of ^{1}H NMR spectra of all new compounds (25 pages). See any current masthead page for ordering and Internet access instructions.

JA9719182

(16) To our knowledge, only one other method allows cyclization and selective formation of either isomer of an exocyclic alkylidene from a common precursor: (a) Martinez-Grau, A.; Curran, D. P. *J. Org. Chem.* **1995**, *60*, 8332. (b) Martinez-Grau, A.; Curran, D. P. *Tetrahedron* **1997**, *53*, 5679. Also, see: (c) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307. (d) Cossy, J.; Pete, J. P.; Portella, C. *Tetrahedron Lett.* **1989**, *30*, 7361.

(17) For related three-component couplings of enones, alkynes, and organozincs, see: (a) Reference 13b. (b) Ikeda, S.; Sato, Y. *J. Am. Chem. Soc.* **1994**, *116*, 5975. (c) Ikeda, S.; Yamamoto, H.; Kondo, K.; Sato, Y. *Organometallics* **1995**, *14*, 5015. (c) Ikeda, S.; Kondo, K.; Sato, Y. *J. Org. Chem.* **1996**, *61*, 8248.

(18) Alkyne carbometalation followed by aldehyde addition accomplishes the same transformation as the three-component couplings reported herein, although chemoselectivity issues generally preclude intramolecular variants (as in Table 1). (a) Okukado, N.; Negishi, E. *Tetrahedron Lett.* **1978**, 2357. (b) Normant, J. F.; Alexakis, A. *Synthesis* **1981**, 841.

(19) See Supporting Information for further details.

(20) (a) Wipf, P.; Xu, W. *Tetrahedron Lett.* **1994**, *35*, 5197. (b) Wipf, P.; Xu, W. *Org. Synth.* **1996**, *74*, 205.

(21) For a discussion of competing reactivity of alkynes and aldehydes with Schwartz's reagent, see: Lipshutz, B. H.; Lindsley, C.; Bhandari, A. *Tetrahedron Lett.* **1994**, *35*, 4669.

(22) A closely related mechanism was proposed by Buchwald and Crowe in titanium-mediated reductive cyclizations, refs 10 and 11.

(23) We are unaware of any fully characterized oxametallacycles of nickel that are exactly analogous to those proposed as intermediates in Scheme 1. However, related nickelacycles prepared from Ni(0), CO_2, and alkenes or alkynes are known. (a) Walther, D.; Dinjus, E.; Sieler, J.; Andersen, L.; Lindqvist, O. *J. Organomet. Chem.* **1984**, *276*, 99. (b) Walther, D.; Bräunlich, G.; Kempe, R.; Sieler, J. *J. Organomet. Chem.* **1992**, *436*, 109. (c) Hoberg, H.; Peres, Y.; Krüger, C.; Tsay, Y. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 771.

(24) For allylic alcohol syntheses based on the stoichiometric generation of early transition metal oxametallacycles: (a) Kataoka, Y.; Miyai, J.; Oshima, K.; Takai, K.; Utimoto, K. *J. Org. Chem.* **1992**, *57*, 1973. (b) Takayanagi, Y.; Yamashita, K.; Yoshida, Y.; Sato, F. *Chem. Commun.* **1996**, 1725. (c) Takagi, K.; Rousset, C. J.; Negishi, E. *J. Am. Chem. Soc.* **1991**, *113*, 1440. (d) Van Wagenen, B. C.; Livinghouse, T. *Tetrahedron Lett.* **1989**, *30*, 3495.

(25) A sequence involving alkyne hydro- or carbometalation followed by addition to the aldehyde cannot be rigorously excluded. Stüdemann, T.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 93.