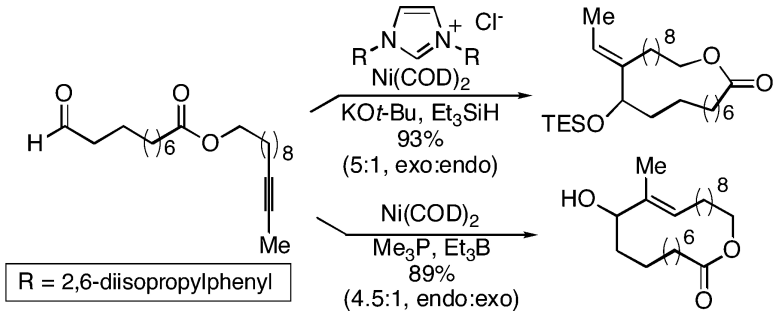
Communication

Access to Macrocyclic Endocyclic and Exocyclic Allylic Alcohols by Nickel-Catalyzed Reductive Cyclization of Ynals

Beth Knapp-Reed, Gireesh M. Mahandru, and John Montgomery

J. Am. Chem. Soc., **2005**, 127 (38), 13156-13157• DOI: 10.1021/ja054590i • Publication Date (Web): 31 August 2005



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 9 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
COMMUNICATIONS

Published on Web 08/31/2005

Access to Macrocyclic Endocyclic and Exocyclic Allylic Alcohols by Nickel-Catalyzed Reductive Cyclization of Ynals

Beth Knapp-Reed, Gireesh M. Mahandru, and John Montgomery*,‡

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

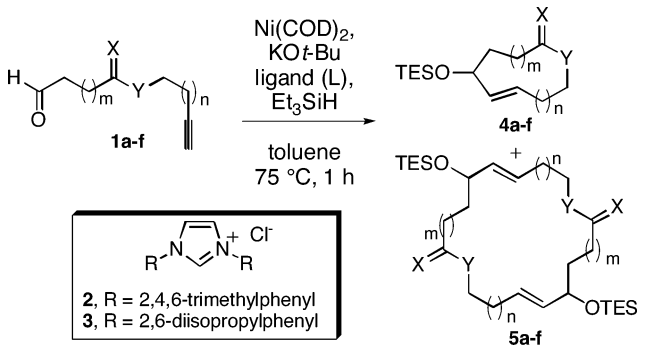
Received July 11, 2005; E-mail: jmontg@umich.edu

Macrocyclic allylic alcohols are a common structural motif in many natural products, and examples of both exocyclic and endocyclic orientations of the alkene unit are frequently observed. Among the known structures, endocyclic allylic alcohols with a 1,2-disubstitution pattern on the alkene are most common. Although many routes to allylic alcohols are known, the reductive coupling of alkynes and aldehydes is perhaps most attractive since the stereogenic center, the alkene stereochemistry, and the carbon−carbon bond that connects the two are simultaneously established.[1−3] Early approaches to the reductive coupling of alkynes and aldehydes involved the stoichiometric hydroboration or hydrozirconation of an alkyne, followed by transmetalation with dimethylzinc and addition to the aldehyde to generate an allylic alcohol.[1] The variant involving hydroboration has recently been applied in macrocyclizations.[1c] Other approaches, which utilize Ti, Zr, and Ta complexes, have also been reported.[2] Our group and Jamison have recently developed nickel-catalyzed methods for the reductive coupling of alkynes and aldehydes, and a broad range of procedures have been reported.[4−9] Alkylative couplings typically involve catalysis with $Ni(COD)_2$, whereas reductive couplings typically involve catalysis with $Ni(COD)_2$ and basic phosphines, such as PBu_3. A particularly challenging subset of this reaction class is the intermolecular reductive coupling of terminal alkynes since $Ni(COD)_2/PBu_3$ efficiently catalyzes the trimerization of terminal alkynes. A recent report from our laboratory illustrates that the use of *N*-heterocyclic carbene ligands largely avoids this limitation and allows efficient reductive couplings of terminal alkynes.[8c]

The strategy of preparing macrocyclic allylic alcohols by the nickel-catalyzed reductive exocyclization of ynals with an internal alkyne was elegantly applied by Jamison in the total syntheses of amphidinolides T1 and T4.[9a] A similar approach was examined in the endocyclization of ynals with internal alkynes in an approach to (−)-terpestacin; however, that strategy was not realized because of the facility of the corresponding exocyclization.[9b] Given the importance of accessing both endo- and exo-manifolds in macrocyclizations, as well as utilizing terminal alkynes to access the important substructure that possesses a 1,2-disubstituted alkene, we have examined macrocyclizations under a modification of our recently reported conditions that involve catalysis with $Ni(COD)_2$ and *N*-heterocyclic carbenes. This study thus provides the first examples of nickel-catalyzed reductive macrocyclizations of ynals that possess terminal alkynes and the first that provides ligand-controlled selectivity for either the endocyclic or exocyclic manifold.

Our study began by examining the cyclization of **1b** using the conditions previously reported for the intermolecular coupling of terminal alkynes and aldehydes.[8c] Treatment of **1b** with a catalyst system derived from $Ni(COD)_2$, **2**,[10] and *n*-BuLi in THF provided the desired 11-membered ring **4b** in 31% yield. While the yield in this initial experiment was modest, we were pleased to observe that these conditions provided endocyclic *E*-olefin **4b** as the sole product. After screening several sets of conditions that varied the base used to generate the carbene, solvent, and temperature, it was determined that the optimal reaction conditions included using a catalyst derived from $Ni(COD)_2$, KO*t*-Bu, and **2**[10] in toluene (Table 1, entry 2).

Table 1. Preparation of Macrocycles



entry	substrate	L	X	Y	*m*	*n*	ring size	yield (**4**:**5**)[a]
1	**1a**	**2**	H_2	CH_2	1	1	9	33% (<1:99)
2	**1b**	**2**	H_2	CH_2	1	3	11	50% (>99:1)
3	**1c**	**2**	H_2	CH_2	1	6	14	62% (>99:1)
4	**1d**	**2**	O	O	7	1	15	69% (>99:1)
5	**1e**	**2**	O	O	7	5	19	70% (>99:1)
6	**1f**	**2**	O	O	7	8	22	67% (>99:1)
7	**1f**	**3**	O	O	7	8	22	67% (>99:1)[b]

[a] Typical reaction conditions: $Ni(COD)_2$ (20 mol %), KO*t*-Bu (20 mol %), **2** or **3** (20 mol %), Et_3SiH (5 equiv), toluene (0.006 M), 1 h. [b] Isolated as a 10:1 ratio of endo- and exocyclic isomers.

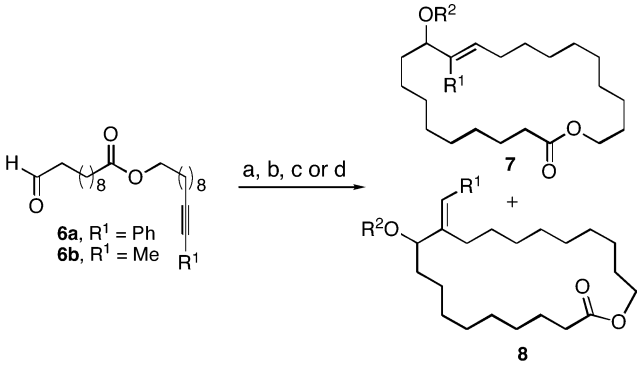
These optimized conditions were then used to generate macrocycles varying in size ranging from 14- to 22-membered rings (Table 1). However, we were unable to form macrocycles smaller than the 11-membered ring originally investigated (**4b**). Under our optimized conditions, alkynal **1a** provided only dimerized product **5a** even when the ynal was added slowly to the catalyst solution via syringe pump (entry 1). These dimerization products were not observed with the longer chains, with the desired monomeric ring being the only discernible product. Only the endocyclic *E*-olefins were observed except when bulkier carbene **3** was employed. Cyclization of **1f** with this ligand produced **4f** as the major product along with a small amount of the exocyclic isomer (entry 7). Other ligand variations were not studied with these substrates since cyclization attempts with phosphine-based catalysts resulted in large amounts of alkyne trimerization byproducts.

The cyclization of internal alkynes was also examined (Table 2). Under the optimized reaction conditions, phenyl-substituted ynal **6a** provided exocyclic olefin **8a** (entry 1). A catalyst system derived from $Ni(COD)_2$ and tributylphosphine was also highly selective for exocyclization (entry 2). Results with methyl-substituted ynal

‡ Correspondence to this author should be addressed to: Department of Chemistry, University of Michigan, 930 N. University, Ann Arbor, MI 48109.

10.1021/ja054590i CCC: $30.25

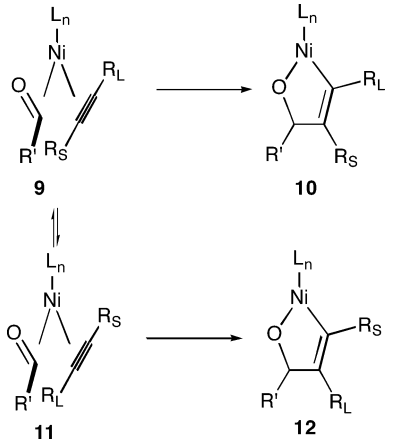
Table 2. Preparation of Macrocycles from Internal Alkynes



entry	substrate	conditions[a]	R^2	product	yield (**7**:**8**)
1	**6a**	a	TES	**8a**	68%
2	**6a**	c	H	**8b**	48%
3	**6b**	a	TES	**7c**/**8c**	60% (1:1)
4	**6b**	b	TES	**7c**/**8c**	93% (1:5)
5	**6b**	c	H	**7d**/**8d**	68% (3:1)
6	**6b**	d	H	**7d**/**8d**	89% (4.5:1)

[a] Conditions: (a) $Ni(COD)_2$ (20 mol %), KO*t*-Bu (20 mol %), **2** (20 mol %), Et_3SiH (5 equiv), toluene (0.006 M), 75 °C, 1 h; (b) $Ni(COD)_2$ (20 mol %), KO*t*-Bu (20 mol %), **3** (20 mol %), Et_3SiH (5 equiv), toluene (0.006 M), 75 °C, 1 h; (c) $Ni(COD)_2$ (20 mol %), Bu_3P (20 mol %), Et_3B (3 equiv), toluene, 60 °C, 16 h; (d) $Ni(COD)_2$ (20 mol %), Me_3P (20 mol %), Et_3B (3 equiv), toluene (0.006 M), 60 °C, 16 h.

Scheme 1. Rationale of Regioselectivity



6b, however, varied depending on the ligand system employed. For example, **6b** produced a 1:1 mixture of products with ligand **2** (entry 3). Switching to a bulkier carbene (**3**) provided the exocyclic olefin as the major product in a 5:1 ratio (entry 4). The combination of tributylphosphine and triethylborane[9] led to a reversal in selectivity, with the endocyclic product **7d** being favored in a 3:1 ratio (entry 5). This selectivity was further improved with trimethylphosphine and triethylborane, which boosted the endocyclic selectivity to 4.5:1 (entry 6).

The inherent electronic and steric biases of terminal and aryl alkynes are only minimally impacted by ligand variation. However, significant variations in regioselectivity with doubly aliphatic-substituted alkynes may be imparted with ligand control.[11] The orientation in which the alkyne complexes to Ni is dependent upon both the steric environment around the aldehyde and that surrounding the ligand (Scheme 1).[12] With a relatively small ligand, such as Me_3P, R_S (Me) is placed proximal to the aldehyde as to minimize interactions between the aldehyde and the alkyne (**9**). This leads to internal olefin products (Table 2, entry 6). As the ligand increases in size, as with **2** and especially **3**, interactions between the ligand and R_L force complexation to occur such that R_L is placed distal to the ligand (**11**), favoring formation of the exocyclization product (entries 3 and 4).

In summary, this communication reports the first examples of Ni-catalyzed macrocyclizations of ynals containing terminal alkynes and the first examples that involve a ligand-controlled reversal in regioselection with internal alkynes. Terminal alkynes and aryl alkynes display substrate control in regioselection that overrides ligand influences. With aliphatic internal alkynes, addition of the most hindered alkyne terminus is favored by bulky ligands, whereas addition of the least hindered alkyne terminus is favored by small ligands. Application of this ligand-directed regioselection in total synthesis will be reported in due course.

Acknowledgment. The authors wish to acknowledge receipt of NIH Grant GM-57014. Mani Chaulagain, Kanicha Sa-ei, and Vanessa Landry are thanked for their contributions.

Supporting Information Available: Full experimental details and copies of NMR spectra (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Oppolzer, W.; Radinov, R. N. *J. Am. Chem. Soc.* **1993**, *115*, 1593. (b) Wipf, P.; Xu, W. *Tetrahedron Lett.* **1994**, *35*, 5197. (c) Oppolzer, W.; Radinov, R. N.; El-Sayed, E. *J. Org. Chem.* **2001**, *66*, 4766.
(2) (a) Crowe, W. E.; Rachita, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 6787. (b) Takayanagi, Y.; Yamashita, K.; Yoshida, Y.; Sato, F. *J. Chem. Soc., Chem. Commun.* **1996**, 1725. (c) Kataoka, Y.; Miyai, J.; Oshima, K.; Takai, K.; Utimoto, K. *J. Org. Chem.* **1992**, *57*, 1973. (d) Buchwald, S. L.; Watson, B. T. *J. Am. Chem. Soc.* **1987**, *109*, 2544. (e) Van Wagenen, B. C.; Huffman, J. C.; Livinghouse, T. *Tetrahedron Lett.* **1989**, *30*, 3495. (f) Bahadoor, A. B.; Flyer, A.; Micalizio, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 3694.
(3) For representative examples of macrocycle formation via carbon−carbon bond formation, see: (a) Tius, M. A.; Reddy, N. S. *Tetrahedron Lett.* **1991**, *32*, 3605. (b) Doi, T.; Takahashi, T. *J. Org. Chem.* **1991**, *56*, 3465. (c) Marshall, J. A.; Wang, X. *J. Org. Chem.* **1991**, *56*, 6264. (d) Kobayashi, S.; Reddy, R. S.; Sugiura, Y.; Sasaki, D.; Miyagawa, N.; Hirama, M. *J. Am. Chem. Soc.* **2001**, *123*, 2887. (e) Wender, P. A.; Beckham, S.; Mohler, D. L. *Tetrahedron Lett.* **1995**, *36*, 209. (f) Elliott, M. R.; Dhimane, A.; Malacria, M. *J. Am. Chem. Soc.* **1997**, *119*, 3427. (g) Furstner, A.; Castanet, A.; Radkowski, K.; Lehmann, C. W. *J. Org. Chem.* **2003**, *68*, 1521. (h) Kigoshi, H.; Kita, M.; Ogawa, S.; Itoh, M.; Uemura, D. *Org. Lett.* **2003**, *5*, 957. (i) Biswas, K.; Lin, H.; Njardarson, J. T.; Chappell, M. D.; Chou, T.; Guan, Y.; Tong, W. P.; He, L.; Horwitz, S. B.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 9825. (j) Furstner, A.; Seidel, G. *J. Organomet. Chem.* **2000**, *606*, 75.
(4) For an overview of the development of this area, see: Montgomery, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3890.
(5) For intramolecular alkylative couplings of ynals, see: (a) Oblinger, E.; Montgomery, J. *J. Am. Chem. Soc.* **1997**, *119*, 9065. (b) Ni, Y.; Amarasinghe, K. K. D.; Montgomery, J. *Org. Lett.* **2002**, *4*, 1743. (c) Lozanov, M.; Montgomery, J. *J. Am. Chem. Soc.* **2002**, *124*, 2106.
(6) For intramolecular reductive couplings of ynals, see refs 5a,c and the following: (a) Tang, X.-Q.; Montgomery, J. *J. Am. Chem. Soc.* **1999**, *121*, 6098. (b) Tang, X.-Q.; Montgomery, J. *J. Am. Chem. Soc.* **2000**, *122*, 6950.
(7) For intermolecular alkylative couplings of alkynes and aldehydes, see refs 5a,b and the following: Qi, X.; Montgomery, J. *J. Org. Chem.* **1999**, *64*, 9310.
(8) For intermolecular reductive couplings of alkynes and aldehydes, see: (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. (c) Mahandru, G. M.; Liu, G.; Montgomery, J. *J. Am. Chem. Soc.* **2004**, *126*, 3698. For a strategy that reverses alkyne regioselection, see: (d) Takai, K.; Sakamoto, S.; Isshiki, T. *Org. Lett.* **2003**, *5*, 653. For an alternate strategy, see: (e) Huddleston, R. R.; Jang, H.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 11488.
(9) For reductive macrocyclizations of ynals with an internal alkyne, see: (a) Colby, E. A.; O'Brien, K. C.; Jamison, T. F. *J. Am. Chem. Soc.* **2005**, *127*, 4297, (b) Chan, J.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 10682.
(10) (a) Arduengo, A. J.; Gamper, S. F.; Calabrese, J. C.; Davidson, F. *J. Am. Chem. Soc.* **1994**, *116*, 4391. For a recent review, see: (b) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290.
(11) Tekavec, T. N.; Arif, A. M.; Louie, J. *Tetrahedron* **2004**, *60*, 7431.
(12) Dorta, R.; Stevens, E. D.; Scott, N. M.; Costabile, C.; Cavallo, L.; Hoff, C. D.; Nolan, S. D. *J. Am. Chem. Soc.* **2005**, *127*, 2485.

JA054590I