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Preparation of Homoallylic Alcohols by Nickel-Catalyzed Cyclizations of Allenyl Aldehydes

John Montgomery* and Minsoo Song

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

jwm@chem.wayne.edu

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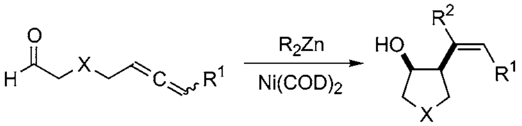
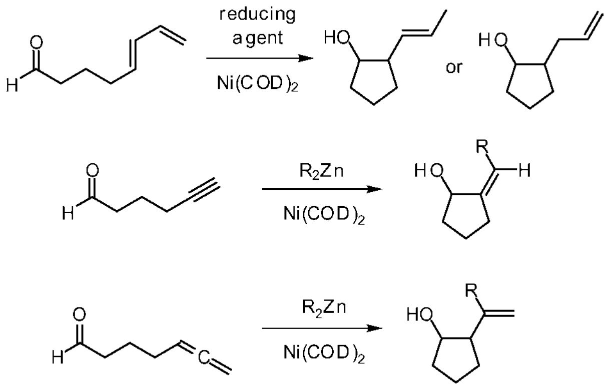
ABSTRACT



The direct cyclization of allenyl aldehydes with organozincs in the presence of Ni(COD)$_2$ provides synthetically versatile homoallylic alcohols. Both monosubstituted and 1,3-disubstituted allenes participate in the process, with the latter allowing preparation of stereochemically defined trisubstituted alkenes.

Homoallylic alcohols are versatile substructures that are typically prepared by the addition of allylmetals to aldehydes[1] or carbonyl ene reactions.[2] In addition to these more classical methods, nickel-catalyzed processes for the production of homoallylic and bis-homoallylic alcohols have recently been developed by Mori and Kimura/Tamaru.[3] These nickel-catalyzed methods rely on the inter- or intramolecular reductive coupling of aldehydes and dienes with silanes, organoboranes, or organozincs. Related studies from our laboratory have demonstrated that nickel-catalyzed couplings of aldehydes and alkynes efficiently provide allylic alcohols.[4] On the basis of these reports, we envisioned that the nickel-catalyzed coupling of aldehydes and allenes with organozinc reagents would provide a useful entry to homoallylic alcohols that is fully complementary to the methods cited above (Scheme 1).[5]

Scheme 1



The cyclization of allenic ketones and aldehydes by SET pathways were first reported by Pattenden and Crandall.[6] Those studies demonstrated that carbonyl-derived radical anions undergo efficient cyclizations with allenes to generate allylic or homoallylic alcohols depending on the substrate structure and tether length. More recent studies from Kang demonstrated that allenic aldehydes undergo a variety of

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(1) Roush, W. R. Allyl Organometallics. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, p 1.

(2) (a) Snider, B. B. The Prins and Carbonyl Ene Reactions. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, p 527. (b) Aggarwal, V. K.; Vennall, G. P., Davey, P. N.; Newman, C. *Tetrahedron Lett.* **1998**, *39*, 1997. (c) Sarkar, T. K.; Nandy, S. K. *Tetrahedron Lett.* **1996**, *37*, 5195. (d) Snider, B. B.; Karras, M.; Price, R. T.; Rodini, D. J. *J. Org. Chem.* **1982**, *47*, 4538. (e) Andersen, N. H.; Hadley, S. W.; Kelly, J. D.; Bacon, E. R. *J. Org. Chem.* **1985**, *50*, 4144.

(3) (a) Sato, Y.; Takimoto, M.; Mori, M. *J. Am. Chem. Soc.* **2000**, *122*, 1624. (b) Sato, Y.; Takanashi, T.; Mori, M. *Organometallics* **1999**, *18*, 4891. (c) Shibata, K.; Kimura, M.; Shimizu, M.; Tamaru, Y. *Org. Lett.* **2001**, *3*, 2181. (d) Kimura, M.; Fujimatsu, H.; Ezoe, A.; Shibata, K.; Shimizu, M.; Matsumoto, S.; Tamaru, Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 397. (e) Kimura, M.; Ezoe, A.; Shibata, K.; Tamaru, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4033.

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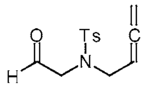
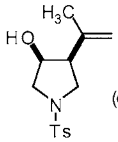
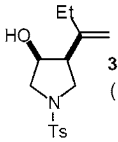
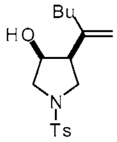
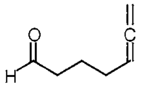
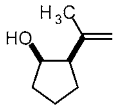
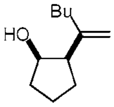
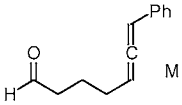
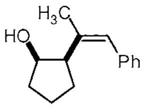
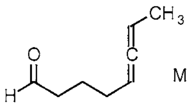
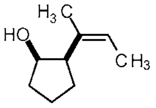
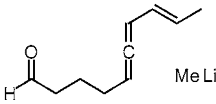
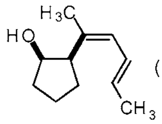
palladium-catalyzed cyclizations to generate functionalized homoallylic alcohols.[7] The opportunity to effect allenyl aldehyde cyclizations in which an organozinc substituent is introduced during the cyclization would provide a strategy for homoallylic alcohol preparation that is complementary to the above cyclization methods, and we disclose here our initial studies in the development of such a strategy.[8]

Cyclizations of aldehydes tethered to monosubstituted allenes were first examined. The reactions proceeded at 0 °C in THF or ether with 10−20 mol % Ni(COD)$_2$. This substrate class affords 1,1-disubstituted alkenes within a homoallylic alcohol framework. *N*-Tosyl pyrrolidines **2**−**4** were readily prepared from substrate **1** via cyclization with dimethylzinc, diethylzinc, or BuLi/ZnCl$_2$ (Table 1, entries 1−3).[9] Notably, either commercial organozincs or organozincs generated in situ from the requisite organolithium and zinc chloride participated cleanly in the reactions. The corresponding carbocyclic frameworks **6** and **7** were also prepared by cyclization of **5** with MeLi/ZnCl$_2$ or BuLi/ZnCl$_2$ (Table 1, entries 4 and 5). In all cases, the cis isomer was selectively formed, although small amounts of the trans isomer were noted in two cases (entries 3 and 5).

Table 1. Allenyl Aldehyde Cyclizations

entry	allenyl aldehyde	organozinc	product (yield)
1	 **1**	$ZnMe_2$	 **2** (70 %) (dr > 97:3)
2	**1**	$ZnEt_2$	 **3** (64 %)$^{ref 9}$ (dr > 97:3))
3	**1**	BuLi / $ZnCl_2$	 **4** (52 %) (dr 75:25)
4	 **5**	MeLi / $ZnCl_2$	 **6** (69 %)[a] (dr > 97:3)
5	**5**	BuLi / $ZnCl_2$	 **7** (69 %) (dr 91:9)
6[b]	 **8**	MeLi / $ZnCl_2$	 **9** (71 %) (cis:trans >97:3) (*Z*:*E* > 97:3)
7[b]	 **10**	MeLi / $ZnCl_2$	 **11** (77 %) (cis:trans >97:3) (*Z*:*E* = 80:20)
8[b]	 **12**	MeLi / $ZnCl_2$	 **13** (68 %) (cis:trans >97:3) (*Z*:*E* = 84:16)

[a] Isolated as the benzoate ester; two-step yield (cyclization and protection) is reported. [b] Racemic allenes were used.

The involvement of 1,3-disubstituted allenes in the cyclizations provides the opportunity to prepare trisubstituted alkenes within the homoallylic alcohol framework. Thus, we examined cyclizations of allenes that bear aromatic, aliphatic, and alkenyl substitution at the allene terminus (Table 1, entries 6−8). Cyclization of aromatic allene **8** with MeLi/ZnCl$_2$ provided alcohol **9** in 71% yield in greater than 97:3 diastereomeric purity. Alternatively, selectivities were lower with methyl and propenyl substituted allenes **10** and **12**, respectively. In these instances, a second isomer was obtained that maintained the cis disubstitution about the cyclopentanol ring but possessed the opposite stereochemistry of the trisubstituted alkene. Substrate **10** provided product **11** in 77% yield as an 80:20 mixture of (*Z*)- and (*E*)-isomers, and substrate **12** provided product **13** in 68% yield as an 84:16 ratio of (*Z*)- and (*E*)-isomers. The (*Z*)- and (*E*)-isomers of **11** and **13** were obtained as inseparable mixtures, and evidence for the minor isomer stereochemistry was obtained by Swern oxidation of the mixture of alcohols to an *E*:*Z* mixture of ketones of the identical isomeric composition as the starting alcohols.[10]

Ligand effects were not extensively studied, but an interesting effect that was noted is the role of basic phosphines. In analogy to observations made in ynal cyclizations,[4] pretreatment of Ni(COD)$_2$ with PBu$_3$ allowed reductive cyclizations with diethylzinc, in which H atom transfer predominantly occurred along with small amounts of ethyl transfer (eq 1). Yields and selectivities were lower

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[4] (a) Montgomery, J. *Acc. Chem. Res.* **2000**, *33*, 467. (b) Oblinger, E.; Montgomery, J. *J. Am. Chem. Soc.* **1997**, *119*, 9065. (c) Tang, X. Q., Montgomery, J. *J. Am. Chem. Soc.* **1999**, *121*, 6098. (d) Tang, X. Q.; Montgomery, J. *J. Am. Chem. Soc.* **2000**, *122*, 6950. (e) Lozanov, M.; Montgomery, J. *J. Am. Chem. Soc.* **2002**, *124*, 2106. (f) Ni, Y.; Amarasinghe, K. K. D.; Montgomery, J. *Org. Lett.* **2002**, *4*, 1743. See also: (g) Huang, W.-S.; Chan, J.; Jamison, T. F. *Org. Lett.* **2000**, *2*, 4221. (h) Takimoto, M.; Shimizu, K.; Mori, M. *Org. Lett.* **2001**, *3*, 3345.

[5] A related nickel-catalyzed enone−allene cyclization was recently carried out as a key step in the total synthesis of kainic acid. See: Chevliakov, M. V.; Montgomery, J. *J. Am. Chem. Soc.* **1999**, *121*, 11139.

[6] (a) Pattenden, G.; Robertson, G. M. *Tetrahedron* **1985**, *41*, 4001. (b) Crandall, J. K.; Mualla, M. *Tetrahedron Lett.* **1986**, *27*, 2243. (c) Gillmann, T. *Tetrahedron Lett.* **1993**, *34*, 607.

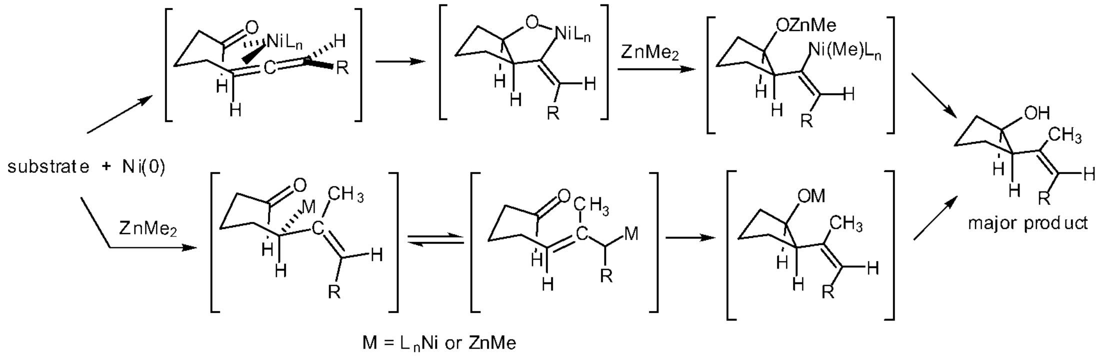
[7] (a) Kang, S.-K.; Ha, Y.-H.; Ko, B.-S.; Lim, Y.; Jung, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 343. (b) Ha, Y. H.; Kang, S.-K. *Org. Lett.* **2002**, *4*, 1143. (c) Kang, S.-K.; Lee, S.-W.; Jung, J.; Lim, Y. *J. Org. Chem.* **2002**, *67*, 4376.

[8] The first example of this new transformation was reported as the key step in the total synthesis of testudinariol A: Amarasinghe, K. K. D.; Montgomery, J. *J. Am. Chem. Soc.* **2002**, *124*, 9366.

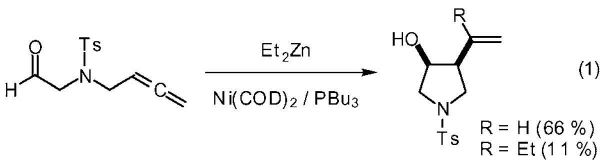
[9] Small amounts (<10%) of six-membered products derived from addition to the internal allene carbon were observed in one instance (entry 2). See Supporting Information for details.

[10] For a discussion of the role of allene structure in metal complexation in zirconium-catalyzed allenic Pauson−Khand reactions, see: Brummond, K. M.; Wan, H.; Kent, J. L. *J. Org. Chem.* **1998**, *63*, 6535.

Scheme 2



with PPh_3 or $P(OMe)_3$ in place of PBu_3. It should be noted that selective ethyl transfer occurred in the absence of a phosphine ligand (Table 1, entry 2).



(1)

The mechanism of the alkylative cyclizations could proceed by several potential pathways. Mechanisms that seem most probable involve either (a) formation of a nickel metallacycle followed by organozinc transmetalation or (b) carbozincation or carbonickelation of the allene followed by addition to the aldehyde[7] (Scheme 2). Although simple allenes lacking an aldehyde undergo rapid oligomerization when exposed to $Ni(COD)_2$, no evidence for allene carbometalation was noted when simple allenes were treated with organozincs and $Ni(COD)_2$ under the standard conditions. The metallacycle-based mechanism is perhaps more consistent with this observation, and it should be noted that other classes of related transformations developed in our labs also appear to proceed by a similar mechanism.[11]

In summary, nickel-catalyzed allenyl aldehyde cyclizations with organozincs provide a novel entry to homoallylic alcohols. The available substitution patterns and stereochemical relationships of the products are complementary to alternative procedures. Future studies will include expansion of the scope of the process, mechanistic studies, and applications in complex molecule synthesis.

Acknowledgment. We thank Mr. K. K. D. Amarasinghe for helpful suggestions and for experimental assistance. We thank the National Institutes of Health (GM 57014) for financial support of this work.

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

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[11] For a discussion of a related mechanism in enone/alkyne cyclizations, see: Amarasinghe, K. K. D.; Chowdhury, S. K.; Heeg, M. J.; Montgomery, J. *Organometallics* **2001**, *20*, 370.