J|A|C|S
COMMUNICATIONS

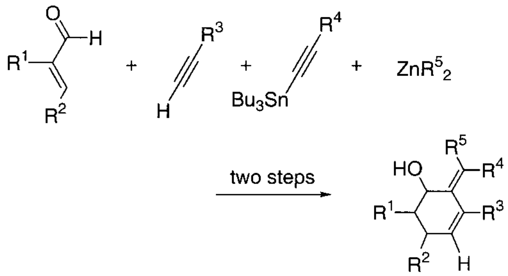
A New Two-Step Four-Component Synthesis of Highly Functionalized Cyclohexenols by Sequential Nickel-Catalyzed Couplings

Mario Lozanov and John Montgomery*

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

Received November 21, 2001; Revised Manuscript Received January 21, 2002

The development of new multicomponent coupling processes has attracted intense interest in recent years.[1] Such processes allow the efficient construction of complex molecules from simple precursors in a minimum number of steps, and many are ideally suited for the generation of structurally diverse libraries of small molecules. The development of tandem reactions that utilize the same catalyst for more than one step has recently been recognized as an efficient strategy for effecting multicomponent coupling processes.[2] Our group has developed several classes of nickel-catalyzed reactions that involve either enones or aldehydes as one of the reactive components.[3] Therefore, we envisioned that enals could be particularly attractive as substrates in multicomponent reactions since initial nickel-catalyzed functionalization of the β-carbon of an enal produces an aldehyde functionality, which could itself then be further functionalized in a second nickel-catalyzed reaction. Implementation of this strategy has allowed the development of a new two-step, four-component coupling of enals, alkynes, acetylenic tin reagents, and either organozincs or organoboranes to produce highly functionalized cyclohexenols (eq 1).



(1)

A central challenging requirement for the development of the desired sequential process is that an acetylenic functionality must be consumed in an initial coupling process with an enal at the same time that a second acetylenic functionality is introduced. That second acetylenic functionality must then undergo cyclization with the saturated aldehyde that is generated during the initial enal/alkyne coupling. Important exploratory investigations from Ikeda suggested that the nickel-catalyzed coupling of enones, alkynes, and acetylenic tin reagents possessed the critical features outlined above.[4] We have, therefore, explored the scope of enal, alkyne, acetylenic tin couplings and found that the process is indeed exceptionally attractive for the generation of ynals **1** that are poised for further nickel-catalyzed cyclizations. The optimum conditions involved generation of the active catalyst by reduction of Ni(acac)$_2$ with DIBAL, followed by the addition of the acetylenic tin, alkyne, enal, and trimethylsilyl chloride. As demonstrated in Table 1, each of the three components can be varied to allow access to a broad range of functionalized enynals. For instance, the enal may be unsubstituted (entries 1−2, 5) or substituted at the α-(entry 3) or β-(entries 4, 6−7) positions. The alkyne may be unsubstituted (entries 2−3, 5−6) or substituted with simple (entries 1,7) or functionalized (entry 4) groups. Finally, the acetylenic tin reagent may be substituted with aromatic (entries 1−3, 5−6) or aliphatic (entries 4, 7) groups. The combination of these variations suggests that quite a broad range of substituted enynals should be available by this coupling process.

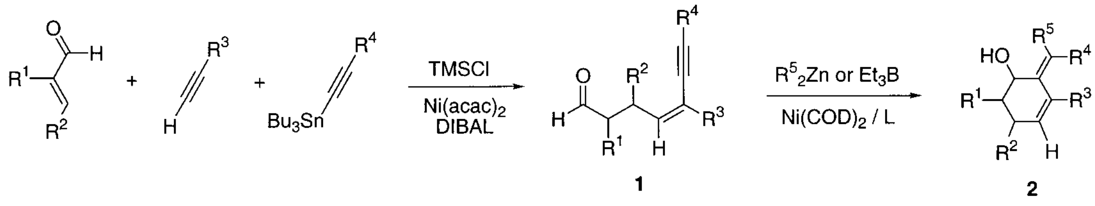
A critical feature of the three-component coupling process is that the aldehyde and alkyne functional groups are introduced in a cis orientation, which is required for the second nickel-catalyzed coupling event. Accordingly, treatment of product **1** from the initial nickel-catalyzed coupling with catalytic Ni(COD)$_2$ and an organozinc afforded good yields of cyclohexenol **2**, which is thus derived from the coupling of the aldehyde, alkyne, and organozinc components. Only simple organozincs (Me, entries 3, 5, 6 and Et, entry 2) were examined, although we anticipate that more complex organozincs may be incorporated. Prior investigations from our laboratory demonstrated that ligand structure could be varied to promote either ethyl group incorporation or hydrogen atom incorporation during ynal cyclizations with diethylzinc.[3] However, the presence of the internal double bond in substrate **1** completely suppresses the hydrogen incorporation pathway, irrespective of ligand structure.

Since hydrogen atom substitution would be advantageous in some applications, we screened other reducing agents and found that the use of triethylborane leads to clean hydrogen atom incorporation if tributylphosphine is employed as a ligand. Triethylborane has been successfully used as a reducing agent by Tamaru and Kimura[5] and Jamison[6] in related nickel-catalyzed couplings. The completely selective incorporation of an ethyl group from diethylzinc and a hydrogen atom from triethylborane under otherwise identical conditions was fortunate, albeit surprising. Cyclization of substrate **1** under these modified conditions with triethylborane and tributylphosphine thus led cleanly to hydrogen atom introduction in each case examined (entries 1, 4, 7).[7] The seemingly similar reactions that employ either triethylborane or diethylzinc may indeed proceed by different mechanisms.[8]

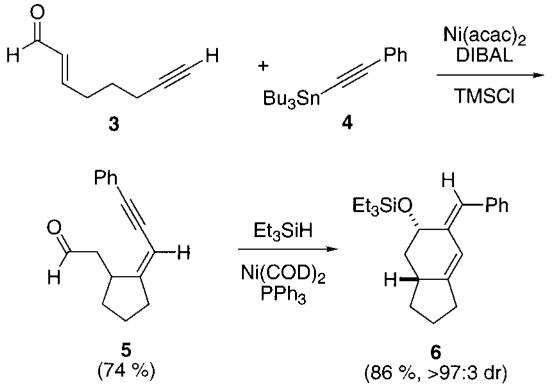
A partially intramolecular variant of the process was next examined utilizing substrate **3** (eq 2). Treatment of enal **3** with acetylenic tin **4** in the presence of trimethylsilyl chloride and catalytic Ni(acac)$_2$/DIBAL cleanly afforded product **5**. Cyclization of **5** with either triethylborane or triethylsilane as the reducing agent in the presence of catalytic Ni(COD)$_2$/PPh$_3$ cleanly afforded bicyclononenol **6**. Whereas Et$_3$B was the best reducing agent in cyclizations of **1**, Et$_3$SiH afforded better yield and diastereoselectivity in cyclizations of cyclic template **5**.

10.1021/ja0175845 CCC: $22.00 © 2002 American Chemical Society

Table 1. Synthesis of Cyclohexenols

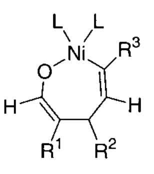


entry	R^1	R^2	R^3	R^4	R^5 (reagent)	L	% yield of **1**	% yield of **2** (dr)
1	H	H	*n*-hexyl	Ph	H (Et_3B)	PBu_3	69	85
2	H	H	H	Ph	Et (Et_2Zn)	PPh_3	68	81
3	CH_3	H	H	Ph	Me (MeLi/$ZnCl_2$)	none	63	74 (2.7:1)
4	H	CH_3	$(CH_2)_3COPh$	*n*-hexyl	H (Et_3B)	PBu_3	49	73 (1.7:1)
5	H	H	H	Ph	Me (MeLi/$ZnCl_2$)	none	68	71
6	H	CH_3	H	Ph	Me (MeLi/$ZnCl_2$)	none	67	80 (5.3:1)
7	H	CH_3	*n*-hexyl	CH_3	H (Et_3B)	PBu_3	51	72 (1.2:1)

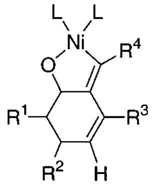


(2)

An interesting feature of the overall four-component transformation is that close mechanistic parallels exist between the two nickel-catalyzed additions. Notably, oxidative cyclization of Ni(0) with an enal and alkyne in the first step would afford intermediate **7** en route to **1**, whereas a closely related oxidative cyclization of Ni(0) with an aldehyde and alkyne in the second step would afford intermediate **8** en route to **2**. Future studies will be devoted to better understanding the mechanistic details and the divergent reactivity of organozincs and organoboranes, but metallacycle-based pathways nonetheless provide a useful working mechanistic model for the design of new transformations such as the two-step sequence delineated in this work.[7]



7



8

In summary, two sequential, multicomponent, nickel-catalyzed processes provide a two-step, four-component entry to highly substituted cyclohexenol derivatives which can serve as versatile building blocks in organic synthesis. Variation is allowed in each of the four components, thus making a wide range of products accessible. Future studies will include extending the scope of the process as well as developing new procedures for utilizing the novel products obtained.

Acknowledgment. We thank the National Institutes of Health (GM 57014) and the Johnson and Johnson Focused Giving Program for support of this research.

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

References

(1) (a) Wipf, P.; Kendall, C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2001**, *123*, 5122. (b) Neumann, H.; von Wangelin, A. J.; Gördes, D.; Spannenberg, A.; Beller, M. *J. Am. Chem.* Soc. **2001**, *123*, 8398. (c) Trost, B. M.; Pinkerton, A. B. *J. Am. Chem. Soc.* **2000**, *122*, 8081.

(2) (a) Bielawski, C. W.; Louie, J.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 12872. (b) Louie, J.; Bielawski, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 11312. (c) Evans, P. A.; Robinson, J. E. *J. Am. Chem. Soc.* **2001**, *123*, 4609.

(3) (a) Montgomery, J. *Acc. Chem. Res.* **2000**, *33*, 467. (b) Oblinger, E.; Montgomery, J. *J. Am. Chem. Soc.* **1997**, *119*, 9065. (c) Montgomery, J.; Oblinger, E.; Savchenko, A. V. *J. Am. Chem. Soc.* **1997**, *119*, 4911.

(4) (a) Ikeda, S. *Acc. Chem. Res.* **2000**, *33*, 511. (b) Ikeda, S.; Kondo, K.; Sato, Y. *J. Org. Chem.* **1996**, *61*, 8248. (c) Ikeda, S.; Sato, Y. *J. Am. Chem. Soc.* **1994**, *116*, 5975.

(5) (a) Kimura, M.; Ezoe, A.; Shibata, K.; Tamaru, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4033. (b) Kimura, M.; Fujimatsu, H.; Ezoe, A.; Shibata, K.; Shimizu, M.; Matsumoto, S.; Tamaru, Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 397. (c) Shibata, K.; Kimura, M.; Shimizu, M.; Tamaru, Y. *Org. Lett.* **2001**, *3*, 2181.

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

(7) For mechanistic discussions of related processes, see: (a) Amarasinghe, K. K. D.; Chowdhury, S. K.; Heeg, M. J.; Montgomery, J. *Organometallics* **2001**, *20*, 370. (b) Tang, X. Q.; Montgomery, J. *J. Am. Chem. Soc.* **1999**, *121*, 6098.

(8) Kimura and Tamaru noted a different type of divergent reactivity of diethylzinc and triethylborane in nickel-catalyzed couplings (ref 5b).

JA0175845