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COMMUNICATIONS

Published on Web 10/11/2006

Catalytic Intermolecular Enal−Alkyne [3 + 2] Reductive Cycloadditions

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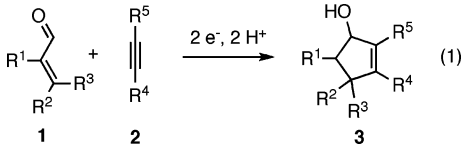
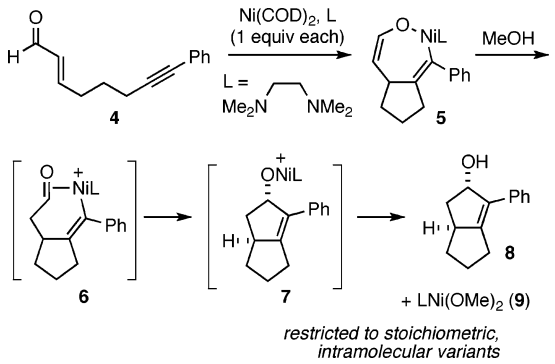
The synthesis of carbocyclic five-membered rings via cycloaddition strategies is complicated by the inability to combine simple stable π-systems such as alkenes, alkynes, and dienes into a five-membered array. Many strategies have been developed to allow access to carbocyclic five-membered rings by [3 + 2] cycloadditions involving 1,3-dipolar reagents or their synthetic equivalents,[1] strained ring precursors,[2] vinyl carbenoid reagents,[3] or species that react as dianion equivalents.[4] Despite the many impressive developments that have been made in such processes, the inherent simplicity of utilizing two simple acyclic π-components that combine to afford a five-membered carbocyclic ring would be attractive for many applications. The assembly of an odd-membered ring from two even-numbered π-systems requires that the cycloaddition is accompanied by a net two electron oxidation or reduction[5] or a hydrogen shift.[6] As an example of this type of strategy, 1,3-functionalization of an enal with an alkyne would allow simple access to a variety of cyclopentenols via a reductive cycloaddition (eq 1).



Advances toward this goal include the use of stoichiometric titanium-promoted addition of tethered alkynes and enoates[7] and the stoichiometric nickel-promoted addition of tethered alkynes and enals.[8] However, these prior approaches do not address the challenge of effecting intermolecular reductive cycloaddition of simple, widely available components, and catalysis was not possible in the previously disclosed variants. Herein, we describe a solution to this challenge in cycloaddition chemistry.

Using our own prior work as an illustration of the limitations of existing methods,[8] our previous efforts involved treatment of alkynyl enal **4** with a stoichiometric quantity of $Ni(COD)_2$ and tmeda to afford metallacycle **5**, which was isolated and characterized by NMR and X-ray (Scheme 1). The addition of methanol to a solution of **5** presumably allows protonation of the enolate to afford vinyl nickel species **6**. The addition of the alkenyl nickel bond to the resulting carbonyl affords nickel alkoxide **7**, which undergoes further protonation to afford product **8**, which is thus formally derived from a reductive [3 + 2] cycloaddition. Intermolecular versions of this process were not possible, and attempts led only to trimerization of the alkyne. Catalytic intramolecular versions were also not possible, largely since a Ni(0) species is required in the reaction, and Ni(II) alkoxides are the final products of the sequence. For a catalytic sequence to be effective, three components must coexist: (i) a Ni(0) catalyst that promotes oxidative cyclization of **4** to **5**, (ii) a Brønsted acid capable of protonating **5** to **6**, and (iii) a reducing agent that converts Ni(II) alkoxide **9** back to Ni(0). No catalytic turnover was noted with common reducing agents such as zinc dust. Additionally, studies from us and from Ikeda had previously demonstrated that species **5** was intercepted by trans-

Scheme 1. Limitations of Stoichiometric Protocol



metallation processes involving common reducing agents such as organozincs,[9] organozirconiums,[10] and organostannanes[11] in an entirely separate class of three-component couplings.[12]

With this backdrop, we were intrigued by two reports that illustrated that Ni(0)-catalyzed reductive processes involving triethylborane were efficient in protic solvents.[13] Although these processes did not require a catalyst reduction step after formation of the organic products, they nonetheless illustrated a combination wherein a Ni(0) species, a reducing agent, and a weak Brønsted acid could all coexist. Upon screening various ligands and conditions in the intermolecular nickel-catalyzed three-component coupling of enals, alkynes, and triethylborane in protic solvents, we were pleased to find that a simple catalytic process involving tributylphosphine as ligand and a methanol/THF cosolvent system allowed the desired reductive cycloadditions to efficiently proceed. As illustrated below (Table 1), a wide range of conjugated enals underwent catalytic, diastereoselective, and regioselective [3 + 2] cycloadditions with 1-phenylpropyne. The reaction tolerates both aryl (entry 1) and alkyl (entry 2) substitution at the enal β-carbon as well as alkyl substitution at the enal α-carbon (entry 3). α,β-Disubstitution was tolerated with both alkyl and aryl substitution patterns (entries 4−5). Additionally, a bicyclic compound was prepared by participation of a cyclic enal in the process (entry 6).

After demonstrating broad scope in enal substitution patterns with 1-phenylpropyne, we also examined the scope tolerated in the alkyne reaction partner (Table 2). Many substitution patterns were suitable in the reaction, including silyl alkynes (entries 1−3), terminal alkynes (entry 4), diaryl alkynes (entries 5−6), and dialkyl alkynes (entry 7). The participation of a β,β-dialkyl enal in a [3 + 2] cycloaddition with a terminal alkyne (entry 4) is noteworthy since 1-phenylpropyne failed to undergo cycloaddition with this hindered substrate. Also noteworthy is the formation of acyclic reductive coupling products, which were seen as minor components of the reaction mixture in several cases and predominated in one case (Table 2, entry 5).[14]

Not only are simple five-membered ring structures available by this catalytic procedure, but more complex structures may also be accessed by intramolecular variants of the process. For instance, catalytic cycloaddition of substrates **10a** and **10b**, under the

10.1021/ja0660249 CCC: $33.50

Table 1. Scope of Enal Structure in [3 + 2] Cycloadditions.

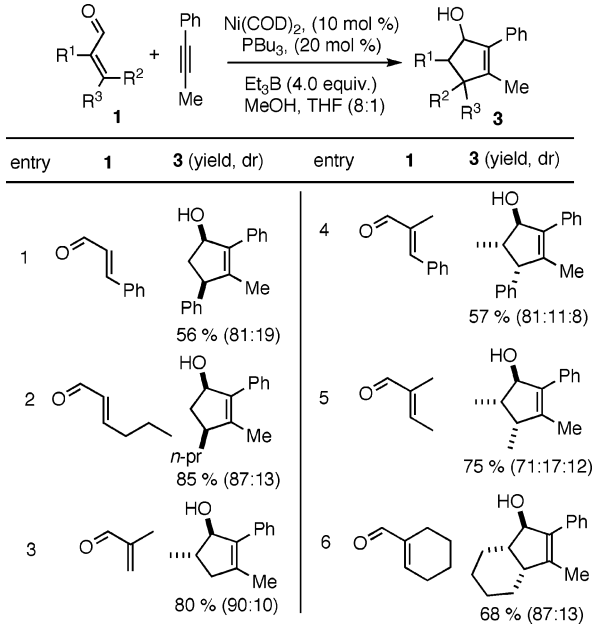
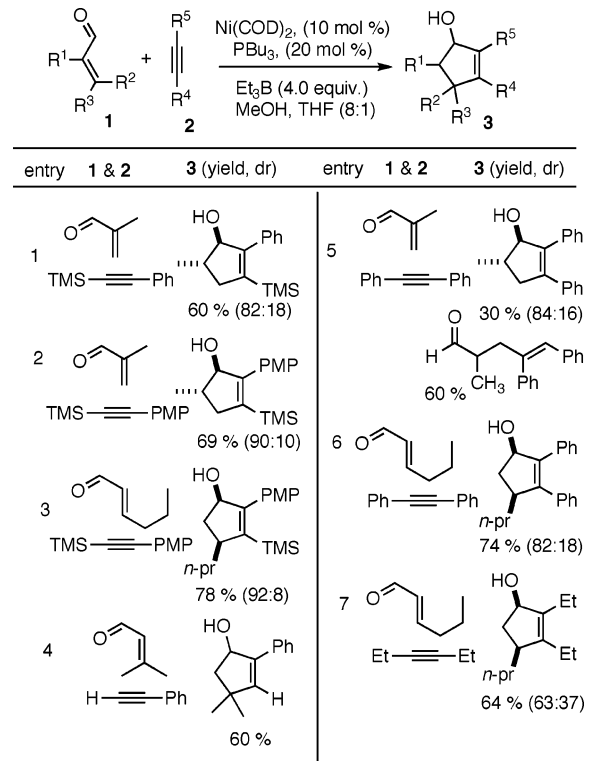
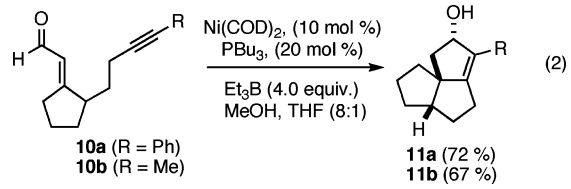


Table 2. Scope of Alkyne Structure in [3 + 2] Cycloadditions.[a]



[a] TMS = trimethylsilyl, PMP = *p*-methoxyphenyl

conditions optimized for intermolecular cycloaddition, proceed smoothly to afford triquinanes **11a** and **11b** in good yield as single diastereomers (eq 2).[8b] Thus, a broad range of [3 + 2] cycloadditions ranging in complexity should likely be available by this procedure.



In summary, a novel method for preparing five-membered carbocyclic rings via a catalytic, intermolecular, reductive [3 + 2] cycloaddition of enals and alkynes has been developed. This work documents the first intermolecular versions and the first catalytic versions of the process. Further exploration of the reactivity features and applications in complex molecule synthesis are in progress.

Acknowledgment. The authors wish to acknowledge receipt of NSF Grant CHE-0553895 in support of this work. Dr. Minsoo Song and Dr. Sanjoy Chowdhury are thanked for helpful advice.

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) For a review of [3 + 2] cycloadditions of propargyl and allyl transition metal complexes, see Welker, M. E. *Chem. Rev.* **1992**, *92*, 97. (b) For a review of trimethylene methane cycloadditions, see Trost, B. M. *Angew. Chem., Int. Ed.* **1986**, *25*, 1. (c) For an anionic [3 + 2] cyclization/elimination, see Beak, P.; Burg, D. A. *J. Org. Chem.* **1989**, *54*, 1647. (d) For a review of allylsilane [3 + 2] cycloadditions, see Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293. (e) For trimethylsilyl allene cycloadditions, see Danheiser, R. L.; Carini, D. J.; Fink, D. M.; Basak, A. *Tetrahedron* **1983**, *39*, 935. (f) For a review of phosphine-based organocatalytic [3 + 2] cycloadditions, see Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035.

(2) (a) Feldman, K. S.; Romanelli, A. L.; Ruckle, R. E.; Miller, R. F. *J. Am. Chem. Soc.* **1988**, *110*, 3300. (b) Liu, L.; Montgomery, J. *J. Am. Chem. Soc.* **2006**, *128*, 5348. (c) Ogoshi, S.; Nagata, M.; Kurosawa, H. *J. Am. Chem. Soc.* **2006**, *128*, 5350.

(3) (a) Davies, H. M. L.; Xiang, B.; Kong, N.; Stafford, D. G. *J. Am. Chem. Soc.* **2001**, *123*, 7461. (b) Davies, H. M. L.; Hu, B. B.; Saikali, E.; Bruzinski, P. R. *J. Org. Chem.* **1994**, *59*, 4535.

(4) (a) Molander, G. A.; Shubert, D. C. *J. Am. Chem. Soc.* **1986**, *108*, 4683. (b) Nakamura, H.; Aoyagi, K.; Singaram, B.; Cai, J.; Nemoto, H.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **1997**, *36*, 367.

(5) We use the term reductive cycloaddition to refer to a process that involves ring formation via cycloaddition of two reagents with a net two-electron reduction. (a) For examples of reductive cycloadditions, see Enholm, E. J.; Kinter, K. S. *J. Am. Chem. Soc.* **1991**, *113*, 7784. (b) Hays, D. S.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 4. (c) Savchenko, A. V.; Montgomery, J. *J. Org. Chem.* **1996**, *61*, 1562. (d) For examples of oxidative cycloadditions, see Snider, B. B.; Han, L.; Xie, C. *J. Org. Chem.* **1997**, *62*, 6978.

(6) For an organocatalytic example in heterocycle synthesis, see Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370.

(7) (a) Suzuki, K.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **1996**, *118*, 8729. (b) Urabe, H.; Suzuki, K.; Sato, F. *J. Am. Chem. Soc.* **1997**, *119*, 10014.

(8) (a) Chowdhury, S. K.; Amarasinghe, K. K. D.; Heeg, M. J.; Montgomery, J. *J. Am. Chem. Soc.* **2000**, *122*, 6775. (b) Mahandru, G. M.; Skauge, A. R. L.; Chowdhury, S. K.; Amarasinghe, K. K. D.; Heeg, M. J.; Montgomery, J. *J. Am. Chem. Soc.* **2003**, *125*, 13481.

(9) Montgomery, J.; Oblinger, E.; Savchenko, A. V. *J. Am. Chem. Soc.* **1997**, *119*, 4911.

(10) Ni, Y.; Amarasinghe, K. K. D.; Montgomery, J. *Org. Lett.* **2002**, *4*, 1743.

(11) Ikeda, S.; Sato, Y. *J. Am. Chem. Soc.* **1994**, *116*, 5975.

(12) For reviews, see (a) Montgomery, J. *Acc. Chem. Res.* **2000**, *33*, 467. (b) Ikeda, S. *Acc. Chem. Res.* **2000**, *33*, 511. (c) Montgomery, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3890.

(13) (a) Kimura, M.; Ezoe, A.; Tanaka, S.; Tamaru, Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 3600. (b) Patel, S. J.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2003**, *42*, 1364.

(14) A detailed description of this process will be reported elsewhere.

JA0660249