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An Efficient [4 + 2 + 1] Entry to Seven-Membered Rings

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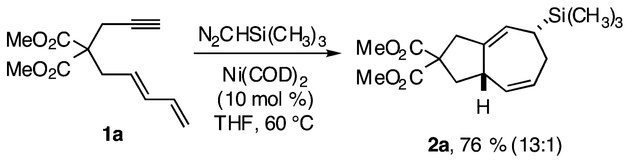
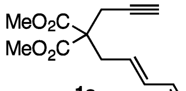
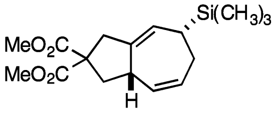
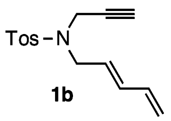
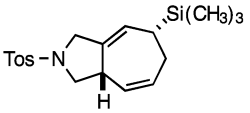
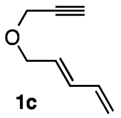
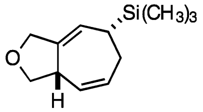
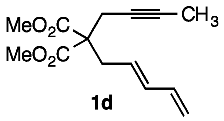
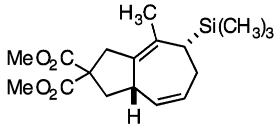
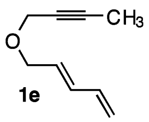
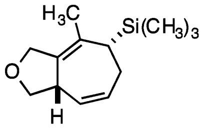
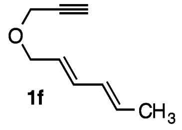
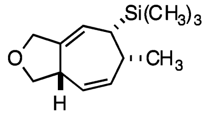
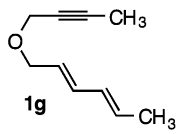
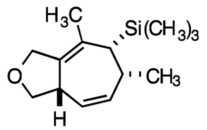
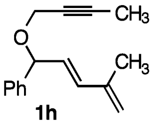
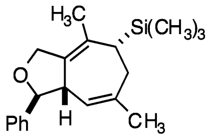
Transition metal catalysis provides many elegant entries to medium ring systems via cycloadditions that are either unavailable or inefficient by noncatalyzed thermal counterparts. For example, efficient metal-catalyzed or promoted [4 + 4], [5 + 2], [6 + 2], [6 + 4], [4 + 2 + 2], [5 + 2 + 1], and [2 + 2 + 2 + 1] cycloadditions have been developed in recent years.[1] Wender recently reported the first examples of a new [4 + 2 + 1] cycloaddition process involving alkynes, dienes, and carbon monoxide, although yields were low since [4 + 2] and [2 + 2 + 1] pathways predominated.[2] The stoichiometric [4 + 2 + 1] cycloaddition of molybdenum Fischer carbene complexes to dienes tethered with alkynes is known, although there are considerable substrate restrictions with both reaction partners.[3] Related [4 + 3] catalytic cycloadditions involving diazoacetates have been extensively developed,[4] and two examples of fully intramolecular catalytic [4 + 2 + 1] diazoacetate-mediated cycloadditions have been reported.[5] To our knowledge, the only partially intermolecular, catalytic [4 + 2 + 1] cycloadditions known are the studies from Wender that afforded < 20% yield of seven-membered ring products as minor components of the reaction mixture.[2]

To fill this void in the synthesis of seven-membered rings, we have explored the development of catalytic [4 + 2 + 1] cycloadditions of diazoalkanes with dienes tethered to alkynes. Given our longstanding interest in nickel chemistry[6] and the paucity of useful synthetic procedures that involve carbene insertions with nickel catalysis,[7−9] we examined the behavior of Ni(COD)$_2$ in the desired [4 + 2 + 1] transformation. Thus, exposure of a mixture of unsaturated precursor **1a** and trimethylsilyldiazomethane (2 equiv) to 10 mol % Ni(COD)$_2$ in THF at 60 °C led to the efficient production of bicyclo-[3.5.0]-decane **2a** in 76% yield as a 13:1 mixture of diastereomers. Remarkable selectivity for production of the [4 + 2 + 1] adduct over alternate [4 + 2], [4 + 1], [2 + 1], [2 + 2 + 1], [2 + 2 + 2], [4 + 4], or [4 + 2 + 2] cycloaddition modes was noted.[1] Given the exquisite chemoselectivity of this transformation, we have carried out a preliminary study of the scope of this new reaction.



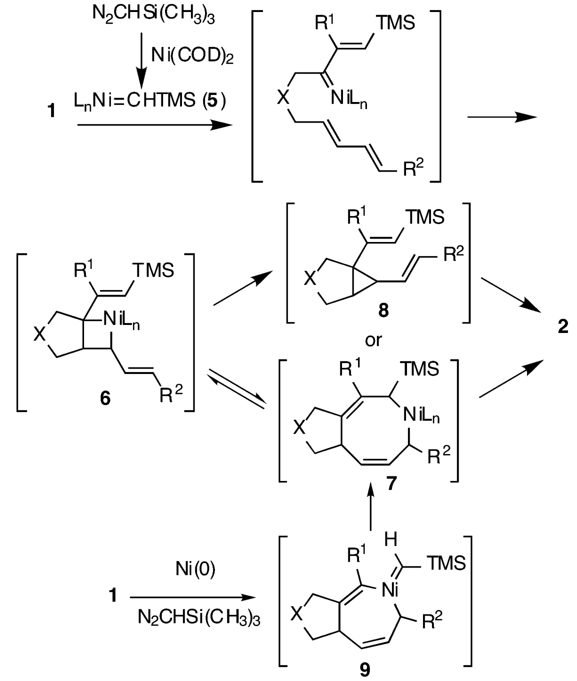
Our initial studies have focused exclusively on the use of TMS diazomethane given its ease of handling and the synthetic utility of the product allyl silanes (Table 1). In addition to a malonate-derived substrate (entry 1), we examined the preparation of heterocyclic structures. Nitrogen-containing substrate **1b** generated product **2b** in 68% yield in greater than 95:5 dr (entry 2), and oxygen-containing substrate **1c** generated product **2c** in 65% yield as a 10:1 ratio of diastereomers (entry 3). Internal alkynes were also effective participants, as evidenced by the generation of products **2d**, **2e**, **2g**, and **2h** (entries 4, 5, 7, 8). Substitution on either the diene terminus (entries 6 and 7) or an internal position of the diene (entry 8) was acceptable. Substitution within the tether chain was also tolerated with excellent resulting diastereoselectivity (entry 8).

Table 1

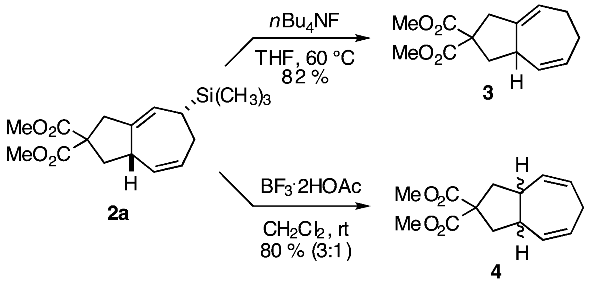
entry	substrate	product, yield (dr)
1	 **1a**	 **2a**, 76 % (13:1)
2	 **1b**	 **2b**, 68 % (>95:5)
3	 **1c**	 **2c**, 65 % (10:1)
4	 **1d**	 **2d**, 78 % (>95:5)
5	 **1e**	 **2e**, 62 % (16:1)
6	 **1f**	 **2f**, 45 % (4:1)
7	 **1g**	 **2g**, 49 % (>95:5)
8	 **1h**	 **2h**, 74 % (>95:5)

10.1021/ja046147y CCC: $27.50

Scheme 1



The allyl silane handle installed in the cycloaddition process is potentially useful in a variety of post-cycloaddition manipulations. However, in this initial study, we have only examined simple desilylation. Interestingly, n-Bu_4NF-mediated desilylation proceeds without alkene migration to generate product **3**,[10a] whereas protodesilylation of **2a** with BF_3/HOAc proceeds with allylic transposition to generate product **4**.[10b] Thus, desilylated products **3** and **4** may be selectively prepared according to the reaction conditions chosen, although product **4** was prepared as a 3:1 ratio of isomers favoring the cis isomer.



The mechanism of this novel cycloaddition process is unclear at this stage. In analogy to stoichiometric molybdenum carbene-mediated dienyne cyclizations[3,11] and catalytic ruthenium-mediated cyclizations of enynes,[12] the mechanism could involve formation of a nickel carbene intermediate **5**, followed by a metathesis cascade to generate metallacyclobutane **6**. Rearrangement of **6** to **7** would allow direct production of **2** upon reductive elimination. Alternatively, reductive elimination of **6** to produce **8**, followed by Cope rearrangement, would afford product **2**.[3−5,13] In a completely distinct mechanism, oxidative cyclization of nickel(0) with dienyne **1** could allow production of metallacycloheptadiene **9**.[14] Carbene insertion into either metal carbon bond of **9** to generate metallacycle **7** (or its regioisomer) followed by reductive elimination would afford product **2**. Further study will be directed toward elucidating these mechanistic issues.

In summary, a novel, nickel-catalyzed [4 + 2 + 1] cycloaddition of a diazoalkane, diene, and alkyne has been developed, and a preparatively useful, chemoselective entry to seven-membered rings is provided. Although numerous mechanistic issues have yet to be established, these studies suggest that nickel carbene intermediates may be useful mediators of cascade metathesis entries to functionalized medium rings. We are actively pursuing further developments in this area.

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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.

References

(1) (a) For [4 + 4] reactions: Wender, P. A.; Ihle, N. C. *J. Am. Chem. Soc.* **1986**, *15*, 4678. (b) For [5 + 2] reactions: Wender, P. A.; Takahashi, H.; Witulski, B. *J. Am. Chem. Soc.* **1995**, *117*, 4720. (c) For [6 + 2] reactions: Rigby, J. H.; Henshilwood, J. A. *J. Am. Chem. Soc.* **1991**, *113*, 5122. (d) For [6 + 4] reactions: Rigby, J. H.; Ateeq, H. S.; Charles, N. R.; Cuisiat, S. V.; Ferguson, M. D.; Henshilwood, J. A.; Krueger, A. C.; Ogbu, C. O.; Short, K. M.; Heeg, M. J. *J. Am. Chem. Soc.* **1993**, *115*, 1382. (e) For [4 + 2 + 2] reactions: Evans, P. A.; Robinson, J. E.; Baum, E. W.; Fazal, A. N. *J. Am. Chem. Soc.* **2002**, *124*, 8782. (f) Gilbertson, S. R.; DeBoef, B. *J. Am. Chem. Soc.* **2002**, *124*, 8784. (g) For [5 + 2 + 1] reactions: Wender, P. A.; Gamber, G. G.; Hubbard, R. D.; Zhang, L. *J. Am. Chem. Soc.* **2002**, *124*, 2876. (h) For [2 + 2 + 2 + 1] reactions: Ojima, I.; Lee, S.-Y. *J. Am. Chem. Soc.* **2000**, *122*, 2385.

(2) Wender, P. A.; Deschamps, N. M.; Gamber, G. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 1853.

(3) (a) Harvey, D. F.; Lund, K. P. *J. Am. Chem. Soc.* **1991**, *113*, 5066. (b) Harvey, D. F.; Grenzer, E. M.; Gantzel, P. K. *J. Am. Chem. Soc.* **1994**, *116*, 6719. (c) See also: Herndon, J. W.; Chatterjee, G.; Patel, P. P.; Matasi, J. J.; Tumer, S. U.; Harp, J. J.; Reid, M. D. *J. Am. Chem. Soc.* **1991**, *113*, 7808.

(4) (a) Davies, H. M. L.; McAfee, M. J.; Oldenburg, C. E. M. *J. Org. Chem.* **1989**, *54*, 930. (b) Davies, H. M. L.; Doan, B. D. *J. Org. Chem.* **1999**, *64*, 8501. (c) Davies, H. M. L.; Calvo, R. L.; Townsend, R. J.; Ren, P.; Churchill, R. M. *J. Org. Chem.* **2000**, *65*, 4261.

(5) Padwa, A.; Krumpe, K. E.; Gareau, Y.; Chiacchio, U. *J. Org. Chem.* **1991**, *56*, 2523.

(6) (a) Montgomery, J. *Acc. Chem. Res.* **2000**, *33*, 467. (b) Montgomery, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3890.

(7) For representative reports of well-characterized nickel carbene complexes, see: (a) Mindiola, D. J.; Hillhouse, G. L. *J. Am. Chem. Soc.* **2002**, *124*, 9976. (b) Gabor, B.; Krüger, C.; Marczinke, B.; Mynott, R.; Wilke, G. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1666. (c) Arduengo, A. J.; Gamper, S. F.; Calabrese, J. C.; Davidson, F. *J. Am. Chem. Soc.* **1994**, *116*, 4391. (d) Hou, H.; Gantzel, P. K.; Kubiak, C. P. *Organometallics* **2003**, *22*, 2817.

(8) For representative reports of reactions that involve incorporation of a nickel carbene unit into the organic product, see: (a) Barluenga, J.; Barrio, P.; López, L. A.; Tomás, M.; García-Granda, S.; Alvarez-Rúa, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 3008. (b) Nakamura, A.; Yoshida, T.; Cowie, M.; Otsuka, S.; Ibers, J. A. *J. Am. Chem. Soc.* **1977**, *99*, 2108. (c) Gai, Y.; Julia, M.; Verpeaux, J.-N. *Synlett* **1991**, 269. (d) Waterman, R.; Hillhouse, G. L. *J. Am. Chem. Soc.* **2003**, *125*, 13350.

(9) For representative reports of nickel-catalyzed processes that involve *N*-heterocyclic carbene ligands, see: (a) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290. (b) Mahandru, G. M.; Liu, G.; Montgomery, J. *J. Am. Chem. Soc.* **2004**, *126*, 3698. (c) Zuo, G.; Louie, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 2277. (d) Louie, J.; Gibby, J. E.; Farnworth, M. V.; Tekavec, T. N. *J. Am. Chem. Soc.* **2002**, *124*, 15188. (e) Sato, Y.; Sawaki, R.; Mori, M. *Organometallics* **2001**, *20*, 5510. (f) Dible, B. R.; Sigman, M. S. *J. Am. Chem. Soc.* **2003**, *125*, 872. (g) Blakey, S. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 6046.

(10) (a) Hulme, A. N.; Henry, S. S.; Meyers, A. I. *J. Org. Chem.* **1995**, *60*, 1265. (b) Knölker, H.-J.; Baum, E.; Graf, R.; Jones, P. G.; Spiess, O. *Angew. Chem., Int. Ed.* **1999**, *38*, 2583.

(11) (a) Korkowski, P. F.; Hoye, T. R.; Rydberg, D. B. *J. Am. Chem. Soc.* **1988**, *110*, 2676. (b) Hoye, T. R.; Rehberg, G. M. *J. Am. Chem. Soc.* **1990**, *112*, 2841.

(12) Monnier, F.; Castillo, D.; Dérien, S.; Toupet, L.; Dixneuf, P. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 5474.

(13) (a) Wender, P. A.; Filosa, M. P. *J. Org. Chem.* **1976**, *41*, 3490. (b) Marino, J. P.; Browne, L. J. *Tetrahedron Lett.* **1976**, 3245. (c) Piers, E.; Nagakura, I. *Tetrahedron Lett.* **1976**, 3237. (d) Lee, J.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1995**, *117*, 9919. (e) Hudlicky, T.; Fan, R.; Reed, J. W.; Gadamesetti, K. G. *Org. React.* **1992**, *41*, 1.

(14) Intermediate **9** is directly analogous to that proposed in nickel-catalyzed [4 + 2] cycloadditions of alkynes and dienes: (a) Wender, P. A.; Jenkins, T. E. *J. Am. Chem. Soc.* **1989**, *111*, 6432. (b) Wender, P. A.; Smith, T. E. *Tetrahedron* **1998**, *54*, 1255.

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