Communications to the Editor

Bicyclization of Unsaturated Hydrazones Mediated by Zirconocene Complexes. A New Annulation Strategy Based on the Reductive Cocyclization of Azomethine Linkages with Carbon-Carbon Multiple Bonds

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Received November 17, 1988

Low-valent complexes involving the ligation of unsaturated moieties to zirconocene,[1,3] and other metal centers,[4] have shown considerable promise as intermediates for organic synthesis. In principle, coordinatively unsaturated zirconocene centers should be capable of promoting the reductive coupling of unsaturated carbon-heteroatom linkages with carbon-carbon multiple bonds. Despite the obvious synthetic potential of this reaction, there remains a paucity of examples where successful transformations of this sort have been realized.[2b] In this communication we wish to report the first examples of annulation reactions involving the intramolecular cocyclization of carbon-nitrogen double bonds with alkenes and alkynes (e.g., **1** → **2**).

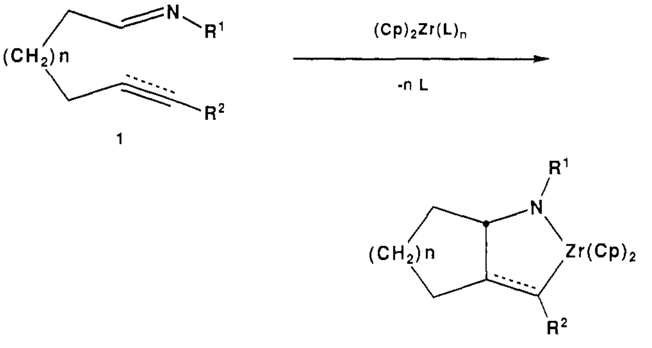

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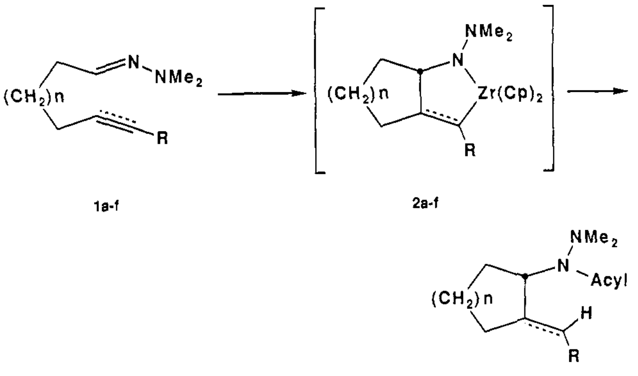
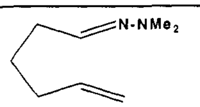
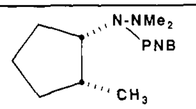
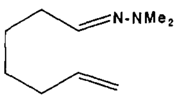
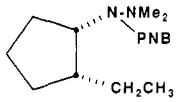
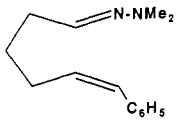
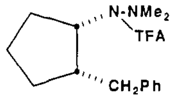
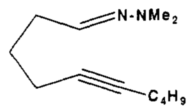
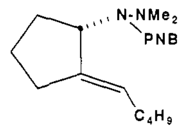
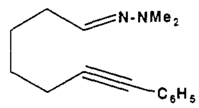
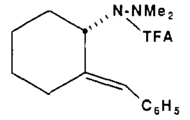
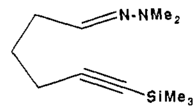
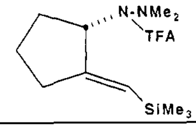
Table I. Bicyclization of Unsaturated Hydrazones Mediated by $(Cp)_2Zr(n\text{-}Bu)_2$



9a-f

	substrate	product (% yield)	
a.			(71 %)
b.			(76 %)
c.			(68 %)[a]
d.			(88 %)
e.			(74 %)
f.			(73 %)

[a] In this instance ca. 8% of the corresponding trans isomer was also formed.

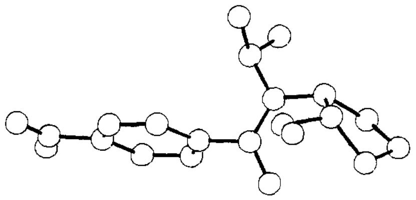


Figure 1. X-ray crystal structure of **9b**.

We initiated our studies by examining potential methods for the direct generation of zirconocene-imine complexes. Negishi and co-workers have reported that the treatment of zirconocene dichloride with 2 molar equiv of *n*-butyllithium provides a convenient source of a "zirconocene" equivalent.[3b] Exposure of *N*-methylbenzaldimine (**3**) (1.0 equiv) to $(Cp)_2Zr(n\text{-}Bu)_2$ (1.1 equiv) in THF [25 °C (75 min)] furnished a solution of the zirconocene-imine complex **4**. Evidence for the intermediacy of **4** was provided by its interception with 3-hexyne (2 equiv, 45 °C), subsequent hydrolysis (aqueous HCl), and acylation (Ac_2O, C_5H_5N) to provide the (*E*)-allyl acetamide **6a** in 67% yield. In an analogous fashion, **4** could be regioselectively trapped with 1-hexyne (2 equiv, 25 °C) to give the (*E*)-allyl amide **6b** in 64% yield after acylation. That the above method could be extended to the intramolecular coupling of imines with carbon-carbon multiple bonds was demonstrated by the following experiment. Cyclization of *N*-methyl-2-(2-butynyloxy)benzaldimine (**7**) in the

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† Fellow of the Alfred P. Sloan Foundation 1989-1991.

(1) (a) Buchwald, S. L.; Watson, B. T.; Lum, R. T.; Nugent, W. A. *J. Am. Chem. Soc.* **1987**, *109*, 7137-7141. (b) Buchwald, S. L.; Watson, B. T. *J. Am. Chem. Soc.* **1987**, *109*, 2544-2546. (c) Buchwald, S. L.; Lum, R. T.; Dewan, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 7441-7442. (d) Buchwald, S. L.; Nielsen, R. B.; Dewan, J. C. *J. Am. Chem. Soc.* **1987**, *109*, 1590-1591.

(2) (a) RajanBabu, T. V.; Nugent, W. A.; Taber, D. F.; Fagan, P. J. *J. Am. Chem. Soc.* **1988**, *110*, 7128-7135. (b) Fagan, P. J.; Nugent, W. A. *J. Am. Chem. Soc.* **1988**, *110*, 2310-2312. (c) Nugent, W. A.; Thorn, D. L.; Harlow, R. L. *J. Am. Chem. Soc.* **1987**, *109*, 2788-2796.

(3) (a) Negishi, E.-i.; Swanson, D. R.; Cederbaum, F. E.; Takahashi, T. *Tetrahedron Lett.* **1987**, 917-920. (b) Negishi, E.-i.; Cederbaum, F. E.; Takahashi, T. *Tetrahedron Lett.* **1986**, 2829-2832. (c) Negishi, E.-i.; Holmes, S. J.; Tour, J. M.; Miller, J. A. *J. Am. Chem. Soc.* **1985**, *107*, 2568-2569.

(4) Two accounts describing the synthetic applications of low-valent niobium-imine complexes have recently appeared: (a) Roskamp, E. J.; Pederson, S. F. *J. Am. Chem. Soc.* **1987**, *109*, 6551. (b) Roskamp, E. J.; Pederson, S. F. *J. Am. Chem. Soc.* **1987**, *109*, 3152.

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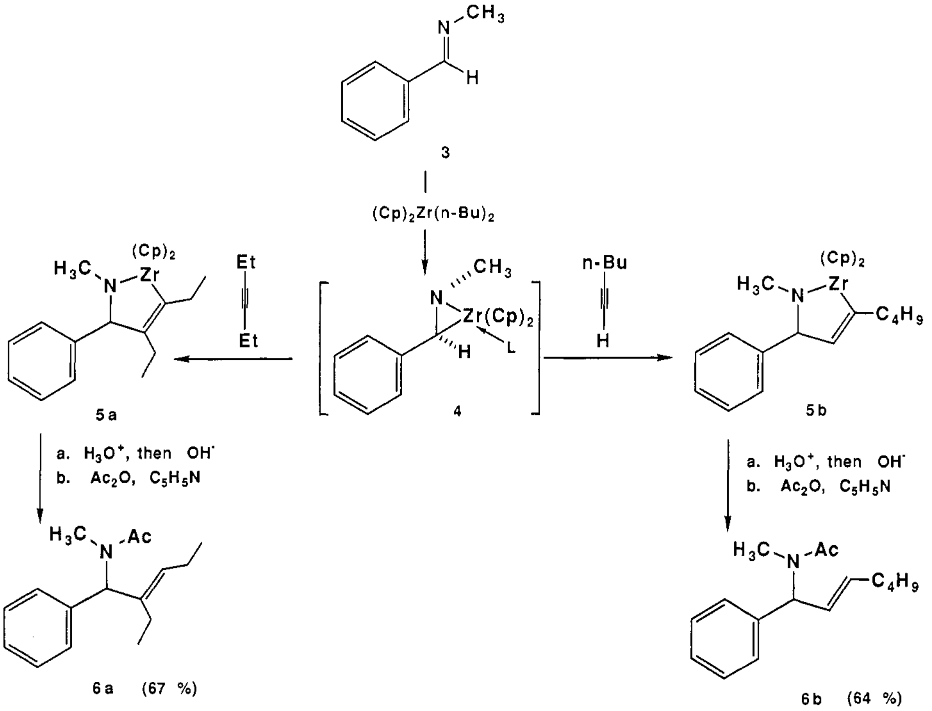
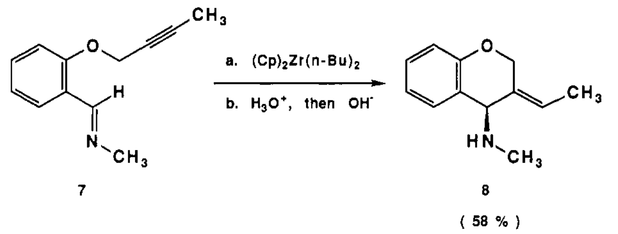
Scheme I

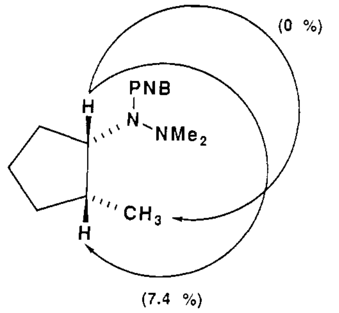


presence of $(Cp)_2Zr(n\text{-}Bu)_2$ [1.35 equiv, 0 °C (3 h) → 25 °C (12 h)] followed by hydrolysis (aqueous HCl) and basification gave the benzotetrahydropyran **8** in 58% chromatographed yield.

It is noteworthy, but not particularly surprising, that the zirconocene-promoted coupling of simple aliphatic aldimines with unsaturated hydrocarbons was found to proceed inefficiently. The lack of generality of zirconium-mediated coupling in these instances can be ascribed to the known predisposition of aliphatic aldimines to undergo facile tautomerization and condensation under ambient conditions.[5] *We now report that the efficiency of cocyclization can be effectively restored by the substitution of N,N-dimethylhydrazones[6] as aldimine equivalents.* Accordingly, a series of unsaturated *N*,*N*-dimethylhydrazones were subjected to bicyclization in the presence of $(Cp)_2Zr(n\text{-}Bu)_2$ (1.35 equiv) to afford the corresponding annulated products **9a–f** in good to excellent yield after chromatographic purification (Table I).[7]



It is of particular interest in a synthetic context that the cyclization of the olefinic hydrazones **1a,b** gave the *cis*-cycloalkylhydrazides **9a,b** with a very high degree of stereoselectivity.[8] Less than 3% of the alternative trans isomers were detectable by capilliary GC mass spectrometry or high field ^{13}C NMR. It is also noteworthy that the reductive cyclization of **1b** gave rise to the rearranged *cis*-2-ethylcyclopentyl hydrazide **96** rather than the anticipated cyclohexyl derivative (Figure 1).[11]



The foregoing results clearly demonstrate the synthetic generality and operational simplicity of this new annulation method. The utilization of chiral hydrazones[9] in enantioselective zirconocene-promoted bicyclizations as well as the application of this methodology to problems of synthetic interest[10] will be the topics of future reports from this laboratory.

Acknowledgments. Support for this research by a grant from the National Institutes of Health is gratefully acknowledged. We are indebted to Ray Larsen for obtaining the X-ray crystal structure of **9b**.

Supplementary Material Available: A representative experimental procedure for the bicyclization of an unsaturated hydrazone with all pertinent spectral data (1 page). Ordering information is given on any current masthead page.

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(5) Campbell, K. N.; Sommers, A. H.; Campbell, B. K. *J. Am. Chem. Soc.* **1944**, *66*, 82–84.

(6) (a) Corey, E. J.; Enders, D. *Tetrahedron Lett.* **1976**, 11–14. (b) Corey, E. J.; Enders, D.; Bock, M. G. *Tetrahedron Lett.* **1976**, 7–10. (c) Corey, E. J.; Enders, D. *Tetrahedron Lett.* **1976**, 3–6.

(7) The reductive conversion of *N*,*N*,*N'*-trisubstituted hydrazines to the corresponding primary amines has been reported previously: Denmark, S. E.; Weber, T.; Piotrowski, D. W. *J. Am. Chem. Soc.* **1987**, *109*, 2224.

(8) Evidence for the cis disposition of the acylamino moiety and the C-2 substituent was provided by NOE difference spectroscopy. Specifically, irradiation of the C-1 methine of **9a** led to a 7.4% enhancement of the C-2 methine and a 0.0% enhancement of the C-2 methyl substituent.

(9) (a) Enders, D.; Shubert, H.; Nubling, C. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1109–1110. (b) Enders, D.; Eichenauer, H.; Baus, U.; Schubert, H.; Kremer, K. A. M. *Tetrahedron* **1984**, *40*, 1345–1359.

(10) (a) The utilization of this method for the elaboration of naturally occurring heterocyclic ring systems is under current pursuit. (b) Preliminary evidence suggests that intermolecular coupling reactions involving *N*,*N*-dimethylhydrazones and unsaturated hydrocarbons proceed in somewhat lower yield than their intramolecular counterparts. Efforts to optimize these reactions are underway.

(11) The mechanism for the conversion of **1b** → **9b** is currently under investigation.