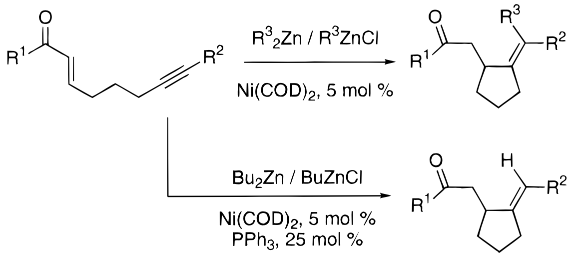
J. Org. Chem. 1996, 61, 1562−1563

Organozinc/Nickel(0)-Promoted Cyclizations of Bis-Enones

Alexey V. Savchenko and John Montgomery*
Department of Chemistry, Wayne State University, Detroit, Michigan 48202-3489

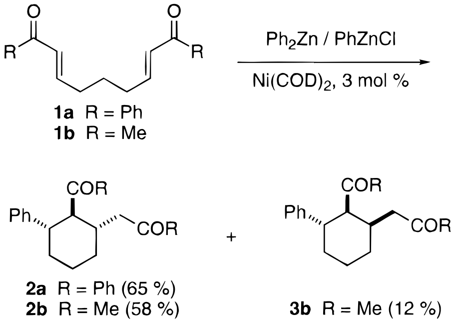
Received January 26, 1996

Recent results from these laboratories demonstrated that alkynyl enones were efficiently cyclized in the presence of Ni(COD)$_2$ and organozincs.[1] The cyclizations were accompanied by either alkylation or reduction, depending on the ligand and organozinc structure.



(1)

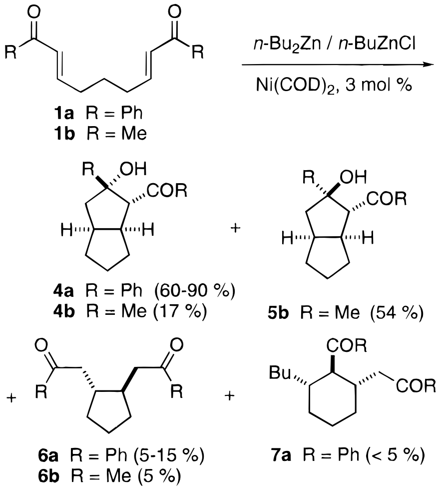
In order to probe the generality of this initial observation, we have examined cyclizations of bis-enones. Two distinct cyclization manifolds were observed during the course of these investigations, with product distributions being highly dependent upon organozinc structure. Our investigations began with bis-enones **1a** and **1b** (eq 2).[2]



(2)

Treatment of **1a** with a mixture of diphenylzinc and phenylzinc chloride in the presence of Ni(COD)$_2$ resulted in the efficient production of the trisubstituted cyclohexane **2a** as a single diastereomer in 65% yield by a mechanism involving sequential conjugate additions.[3,4] Treatment of **1b** under identical conditions resulted in the production of a separable 5:1 mixture of the all-equatorial cyclohexane **2b** and its epimer **3b** in 70% yield. This result contrasts sharply with cyclizations of alkynyl enones, in which direct conjugate addition of the organozinc to the enone was never observed.[1]

Reactions with dibutylzinc, however, followed a different course (eq 3). Instead of conjugate addition of the organozinc, treatment of **1a** with a mixture of dibutylzinc and butylzinc chloride in the presence of Ni(COD)$_2$ resulted in the production of bicyclooctane **4a** as a single isomer in 60−90% yield[5] without incorporation of the butyl moiety. Minor products of the reaction included monocyclic trans isomer **6a** in 5−15% yield, trisubstituted cyclohexane **7a** in <5% yield, and <5% yield of a dimeric byproduct (*vide infra*). Compound **1b** afforded comparable cis/trans selectivity with **4b** and **5b** being produced in 71% yield (as a separable 3:1 mixture of two diastereomers) along with 5% isolated yield of trans isomer **6b**. Interestingly, when commercial diethylzinc was used in place of the usual mixture obtained from a 2:3 stoichiometry of zinc chloride and *n*-butyllithium, a 1:1 mixture of **4a** and **6a** in 84% yield was obtained.[6]



(3)

Related reductive cyclizations of bis-enones recently reported by Enholm employing tributyltin hydride/AIBN produced monocyclic trans isomers such as **6** either predominantly or exclusively depending on the tributyltin hydride concentration.[7a−c] This result was explained by invoking a reversible allylic ketyl cyclization followed by hydrogen atom transfer to ultimately produce the thermodynamic trans isomer. Increasing the concentration of tributyltin hydride increased the proportion of cis-fused

---

(1) Montgomery, J.; Savchenko, A. V. *J. Am. Chem. Soc.* **1996**, *118*, in press.

(2) Montgomery, J.; Savchenko, A. V.; Zhao, Y. *J. Org. Chem.* **1995**, *60*, 5699.

(3) For related tandem Michael additions using other classes of nucleophiles, see: (a) Klimko, P. G.; Singleton, D. A. *Synthesis* **1994**, 979. (b) Shida, N.; Uyehara, T.; Yamamoto, Y. *J. Org. Chem.* **1992**, *57*, 5049. (c) Saito, S.; Hirohara, Y. Narahara, O. Moriwake T. *J. Am. Chem. Soc.* **1989**, *111*, 4533. (d) Yoshii, E.; Hori, K.; Nomura, K.; Yamaguchi, K. *Synlett* **1995**, 568 and references therein.

(4) For representative examples of nickel-promoted conjugate additions, see: (a) Petrier, C.; de Souza Barbosa, J. C.; Dupuy, C.; Luche, J. L. *J. Org. Chem.* **1985**, *50*, 5761. (b) Smith, A. B., III; Leenay, T. L. *J. Am. Chem. Soc.* **1989**, *111*, 5761. (c) Schwartz, J.; Carr, D. B.; Hansen, R. T.; Dayrit, F. M. *J. Org. Chem.* **1980**, *45*, 3053. (d) Schwartz, J.; Loots, M. J.; Kosugi, H. *J. Am. Chem. Soc.* **1980**, *102*, 1333. (e) Flemming, S.; Kabbara, J.; Nickisch, K.; Neh, H.; Westermann, J. *Tetrahedron Lett.* **1994**, *35*, 6075.

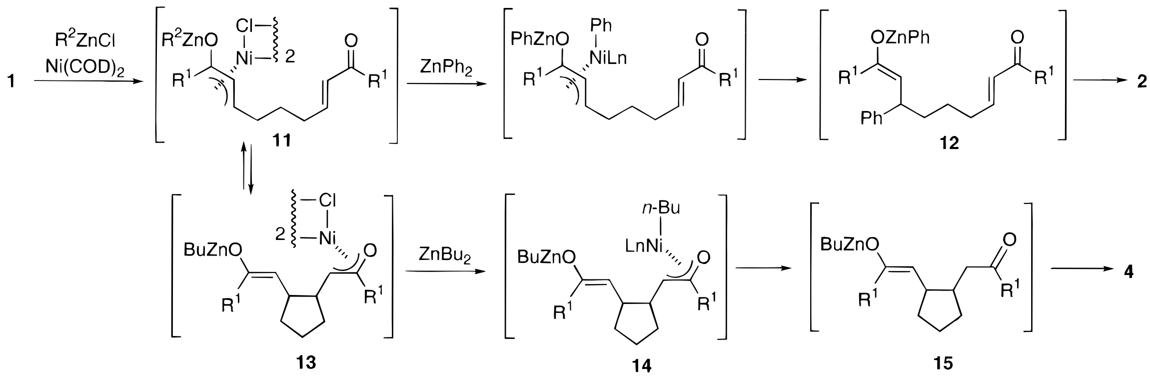
(5) Yields were best when high catalyst loadings (30 mol %) were employed. Catalyst loadings of 3−5 mol % resulted in yields in the lower part of the range given. The structure of **4a** was proven by single-crystal X-ray analysis. A different structure for a compound with ^{1}H and ^{13}C NMR data identical to **4a** was previously reported (see ref 7d). The author has deposited atomic coordinates for **4a** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(6) More complete studies to understand the factors that control stereochemistry are under investigation. Elegant studies by several investigators in related zirconium-catalyzed cyclomagnesiations of dienes demonstrated that cis/trans diastereoselectivities were dependent upon numerous factors including magnesium reagent structure. (a) Knight, K. S.; Wang, D.; Waymouth, R. M. Ziller, J. *J. Am. Chem. Soc.* **1994**, *116*, 1845. (b) Knight, K. S.; Waymouth, R. M. *J. Am. Chem. Soc.* **1991**, *113*, 6268. (c) Taber, D. F.; Louey, J. P.; Wang, Y.; Nugent, W. A.; Dixon, D. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1994**, *116*, 9457. (d) Takahashi, T.; Seki, T.; Nitto, Y.; Saburi, M.; Rousset, C. J.; Negishi, E. *J. Am. Chem. Soc.* **1991**, *113*, 6266. (e) Didiuk, M. T.; Johannes, C. W.; Morken, J. P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1995**, *117*, 7097.

(7) (a) Enholm, E. J.; Kinter, K. S. *J. Org. Chem.* **1995**, *60*, 4850. (b) Enholm, E. J.; Kinter, K, S. *J. Am. Chem. Soc.* **1991**, *113*, 7784. (c) Fu recently reported a radical cyclization procedure that is catalytic in tributyltin hydride: Hays, D. S.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 4. (d) Taniguchi, Y.; Kusudo, T.; Beppu, F.; Makioka, Y.; Takaki, K.; Fujiwara, Y. *J. Chem. Soc. Jpn.* **1994**, 62. (e) Chavan, S. P.; Ethiraj, K. S. *Tetrahedron Lett.* **1995**, *36*, 2281. (f) Schobert, R.; Maaref, F.; Dürr, S. *Synlett* **1995**, 83.

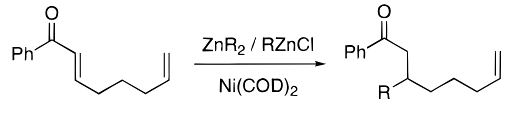
0022-3263/96/1961-1562$12.00/0

Scheme 1



bicyclooctanes (up to a maximum of 20%). The nickel-mediated approach is therefore fully complementary to radical cyclization approaches since the tributyltin hydride/AIBN-mediated process as well as other reported methods for bis-enone reductive cyclizations and mono-enone reductive dimerizations all produce major products with stereochemical outcomes analogous to **6**.[7d–f]

In contrast to the reactivity observed with bis-enones, enones tethered to unactivated alkenes failed to cyclize. Upon exposure of enone **8** to Ni(COD)$_2$ in the presence of either dibutylzinc or diphenylzinc, the products of simple conjugate addition **9a** and **9b** were observed in 75% and 68% yields, respectively (eq 4).[8] The addition of triphenylphosphine resulted in slower reactions and lower yields of conjugate addition products along with recovered enone.

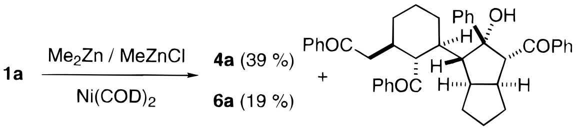


(4)

8

9a R = n-Bu (75 %)
9b R = Ph (68 %)

The diverse reaction manifolds (bicyclooctane vs. cyclohexane formation) observed in bis-enone cyclizations are clearly controlled by zinc reagent structure. To determine if the differences are a function of hybridization of the organozinc ligand or simply a function of the presence or absence of a β-hydrogen on the organozinc ligand, a reaction with dimethylzinc/methylzinc chloride was carried out (eq 5). Interestingly, the reaction products included bicyclooctane **4a** in 39% yield, monocycle **6a** in 19% yield, and the reductive dimerization product **10** in 32% yield as a single diastereomer[9] that was also observed in <5% yield in reactions involving dibutylzinc. A β-hydrogen is not required for the reductive cyclization to occur, but dibutylzinc is more efficient than dimethylzinc in the production of cis-fused bicyclooctanes.[6] Again, this result contrasts sharply with alkynyl enone reductive cyclizations, which were possible only with organozincs bearing β-hydrogens.[1]



(5)

10 (32 %)

A mechanistic scheme that is consistent with all of the above experimental observations is presented in Scheme 1. Oxidative addition of a low valent nickel species to the enone[10,11] would afford π-allyl complex **11**. Transmetalation of an sp^2-hybridized organozinc to nickel, followed by reductive elimination, would afford zinc enolate **12** which could cyclize to produce **2**. Alternatively, if transmetalation of an sp^3-hybridized organozinc is slower, as is the case in most cross-coupling reactions,[12] migratory insertion[13] to produce nickel enolate **13** could occur. Nickel enolate **14** could then be converted to keto enolate **15** either by a β-hydride elimination/reductive elimination sequence or by conversion to a bis-zinc enolate followed by monoprotonation on workup.[14] Intramolecular aldol addition would then afford the observed products.[15]

In summary, these studies provide efficient methods for the synthesis of several classes of mono- and bicyclic ring skeleta in a rapid and highly-stereoselective fashion from common, readily-available precursors and further establish enones as an important functionality for the initiation of nickel-promoted cyclizations. Detailed studies on the scope, mechanism, and synthetic applications of these processes are currently under active investigation in our laboratories.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to Wayne State University for support of this research. Dr. Mary Jane Heeg of Wayne State University is kindly acknowledged for the X-ray crystallographic analysis of **4a**.

Supporting Information Available: Experimental procedures, spectral data, and copies of ^{1}H NMR spectra for compounds **2a**,**b**, **3b**, **4a**, **5b**, **9a**,**b**, and **10** (23 pages).

JO960166B

---

[8] These conjugate additions are considerably slower than additions to enones lacking the pentenyl side chain. Ziegler, F. E.; Wallace, O. B. *J. Org. Chem.* **1995**, *60*, 3626.

[9] The relative stereochemical relationship about the bond connecting the bicyclooctane and cyclohexane moieties of **10** was arbitrarily assigned.

[10] (a) Johnson, J. R.; Tully, P. S.; Mackenzie, P. B.; Sabat, M. *J. Am. Chem. Soc.* **1991**, *113*, 6172. (b) Grisso, B. A.; Johnson, J. R.; Mackenzie, P. B. *J. Am. Chem. Soc.* **1992**, *114*, 5160.

[11] Evidence in support of oxidative addition of a catalytically-active Ni(I) species to enones by a mechanism involving single electron transfer has been provided. Dayrit, F. M.; Schwartz, J. *J. Am. Chem. Soc.* **1981**, *103*, 4466.

[12] Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508.

[13] (a) Ikeda, S.; Sato, Y. *J. Am. Chem. Soc.* **1994**, *116*, 5975. (b) Ikeda, S.; Yamamoto, H.; Kondo, K.; Sato, Y. *Organometallics* **1995**, *14*, 5015.

[14] The latter of these two sequences would be required in cyclizations involving dimethylzinc (eq 5).

[15] A mechanism involving the oxidative cyclization of a nickel(0)/bis-enone complex to a metallacyclopentane intermediate (as in related zirconium-catalyzed reactions, ref 6) cannot be ruled out. However, given that **2a** is formed from diphenylzinc, we favor the mechanism described in Scheme 1. A mechanism involving a radical cyclization also cannot be ruled out. However, the dependence on organozinc structure is more easily explained by the mechanism depicted in Scheme 1.