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Nickel-Catalyzed Cyclizations of Alkynyl Enones with Concomitant Stereoselective Tri- or Tetrasubstituted Alkene Introduction

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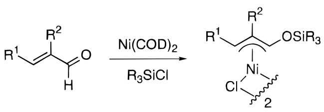
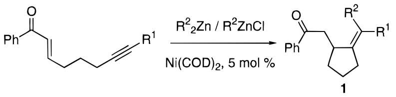
The conjugate addition of main-group and transition-metal organometallics to enones under Ni catalysis is an important method for C−C bond formation.[1] Fully characterized silyloxy π-allyl nickel complexes were recently implicated by Mackenzie as intermediates in conjugate additions of organostannanes to enals in the presence of silyl chlorides (eq 1).[2] Earlier electrochemical studies by Schwartz provided compelling evidence for single-electron-transfer pathways to produce σ-alkyl intermediates in Ni(acac)$_2$/DIBAL-promoted conjugate additions.[3] Despite the postulated intermediacy of related organometallic species in many metal-promoted conjugate addition reactions, including those involving cuprates,[4] few examples exist in which a σ-alkyl or π-allyl organometallic intermediate derived from an enone is intercepted by a reactive functionality in preference to formation of the normal product of conjugate addition.[5] The realization of such a result in an intramolecular sense would allow enones to serve as versatile initiators for a variety of metal-promoted cyclization processes, whereas organic halides, triflates, and alkynes have traditionally been used to initiate such reactions.[6,7] In light of the recent report from Ikeda and Sato that enynes could be produced by the three-component coupling of methyl vinyl ketone, alkynes, and alkynylstannanes,[5] we would like to disclose our results on the cyclizations of alkynyl enones in the presence of Ni(COD)$_2$ and organozincs. The complementary sets of reactions presented provide a highly flexible method for the stereoselective introduction of tri- and tetrasubstituted alkenes to the β-C of cyclic and acyclic enones with concomitant 5-membered ring cyclization.



(1)

The feasibility of cyclizing alkynyl enones in the presence of organozincs and a Ni(0) catalyst was first tested with acyclic, non-enolizable enones (Table 1). Aryl-, alkenyl-, and alkyl-substituted organozincs, including those bearing β-hydrogens, underwent efficient couplings to produce β-alkenyl ketones with complete control of olefin geometry.[8,9] Reactions with organozincs bearing β-hydrogens also resulted in byproducts from reductive cyclization in low yield (entries 2 and 5, Table 1), and the remaining mass balance could generally be accounted for by the formation of dimers of the enone substrates. Direct conjugate addition products were not observed.[1] Both terminal and internal alkynes participated efficiently to produce single isomers of either tri- or tetrasubstituted alkenes, with the organozinc substituent always being delivered cis to the ketone functionality. Significantly, either isomer of the tetrasubstituted alkenes could be selectively produced, depending simply on the order of substituent introduction (compare entries 5 and 6, Table 1).

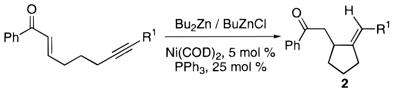
Table 1. Cyclization with Alkylation[a]



entry	R^1	R^2	products (yield, %)
1	H	Me	**1a** (82)
2	H	Bu	**1b** (51) + **2a** (R^2 = H, 11)
3	H	Ph	**1c** (61)
4	H	CH=CH$_2$	**1d** (59) + **2a** (trace)
5	Ph	Bu	**1e** (68) + **2b** (R^2 = H, 8)
6	Bu	Ph	**1f** (38)

[a] All reactions were carried out in THF at 0 °C. All compounds were produced as single isomers by ^{1}H NMR analysis. Isolated yields after silica gel chromatography are provided.

Table 2. Reductive Cyclizations[a]



entry	R^1	products (yield, %)
1	H	**2a** (92)
2	Ph	**2b** (47) + **1e** (19)
3	Bu	**2c** (58) + **1g** (16, R^1,R^2 = Bu)

[a] All reactions were carried out in THF at 0 °C. All compounds were produced as single isomers by ^{1}H NMR analysis. Isolated yields after silica gel chromatography are provided.

Pretreatment of Ni(COD)$_2$ with 5 equiv of triphenylphosphine had an unexpected effect. Instead of cyclization with alkylation, efficient reductive cyclizations occurred in reactions involving dibutylzinc (Table 2).[10,11] Reductive cyclizations with terminal alkynes were the most efficient, but single isomers of trisubstituted alkenes could be obtained in moderate yields from internal alkynes, with hydrogen always being delivered cis to the ketone functionality. The products of cyclization with

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(1) For representative examples, see: (a) Petrier, C.; de Souza Barbosa, J. C.; Dupuy, C.; Luche, J. L. *J. Org. Chem.* **1985**, *50*, 5761. (b) Schwartz, J.; Carr, D. B.; Hansen, R. T.; Dayrit, F. M. *J. Org. Chem.* **1980**, *45*, 3053. (c) Schwartz, J.; Loots, M. J.; Kosugi, H. *J. Am. Chem. Soc.* **1980**, *102*, 1333.

(2) (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.

(3) (a) Dayrit, F. M.; Gladkowski, D. E.; Schwartz, J. *J. Am. Chem. Soc.* **1980**, *102*, 3976. (b) Dayrit, F. M.; Schwartz, J. *J. Am. Chem. Soc.* **1981**, *103*, 4466.

(4) The existence of copper−enone d−π* complexes as intermediates in cuprate additions to enones is fairly well established, but the sequence of events leading from the d−π* complex to products is controversial. For d−π* complex characterization, see: Vellekoop, A. S.; Smith, R. A. J. *J. Am. Chem. Soc.* **1994**, *116*, 2902 and references therein.

(5) For examples of intermolecular insertion of an enone-derived nickel π-allyl intermediate to an alkyne, see: (a) Ikeda, S.; Sato, Y. *J. Am. Chem. Soc.* **1994**, *116*, 5975. (b) After submission of this manuscript, a related process involving dimethylzinc was reported. Ikeda, S.; Yamamoto, H.; Kondo, K.; Sato, Y. *Organometallics* **1995**, *14*, 5015.

(6) For leading references to alkenyl triflate-, alkenyl iodide-, and alkyne-initiated palladium-catalyzed cyclization processes, see: (a) Sugihara, T.; Copéret, C.; Owczarczyk, Z.; Harring, L. S.; Negishi, E. *J. Am. Chem. Soc.* **1994**, *116*, 7923. (b) Overman, L. E. *Pure. Appl. Chem.* **1994**, *66*, 1423. (c) Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1993**, *115*, 9421.

(7) For examples of nickel-promoted cyclization reactions initiated by alkyl or alkenyl halides, see: (a) Knochel, P. *Synlett* **1995**, 393. (b) Solé, D.; Cancho, Y.; Llebaria, A.; Moretó, J. M.; Delgado, A. *J. Am. Chem. Soc.* **1994**, *116*, 12133.

(8) For a mechanistically-distinct palladium-catalyzed alkylative cyclization of enynes initiated by oxidative addition and therefore unsuitable for the introduction of sp^3-hybridized functionality bearing β-hydrogens, see: Trost, B. M.; Pfrengle, W.; Urabe, H.; Dumas, J. *J. Am. Chem. Soc.* **1992**, *114*, 1923.

(9) Carbometalation/capture sequences beginning with oxidative addition of palladium(0) to vinyl iodides and triflates are well documented, but to our knowledge, no examples that tolerate β-hydrogens in the transmetalating agent have been reported. For representative examples, see: (a) Negishi, E. *Pure Appl. Chem.* **1992**, *64*, 323. (b) Brown, A.; Grigg, R.; Ravishankar, T.; Thornton-Pett, M. *Tetrahedron Lett.* **1994**, *35*, 2753.

(10) We use the term "cyclization with alkylation" for processes that introduce a carbon substituent and "reductive cyclization" for processes that introduce hydrogen at the reduced sites. For leading references to reductive cyclizations involving other metals and different substrate classes, see: (a) Kablaoui, N. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1995**, *117*, 6785. (b) Crowe, W. E.; Rachita, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 6787. (c) Trost, B. M.; Rise, F. *J. Am. Chem. Soc.* **1987**, *109*, 3161.

(11) For nickel-catalyzed cycloisomerizations of related substrates without reduction, see: Trost, B. M.; Tour, J. M. *J. Am. Chem. Soc.* **1987**, *109*, 5268.

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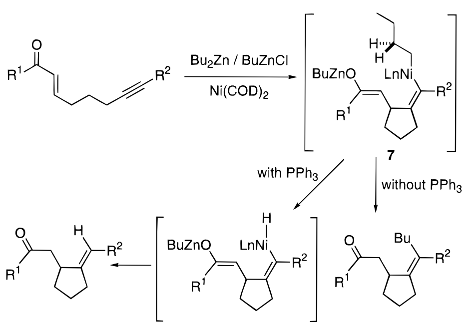
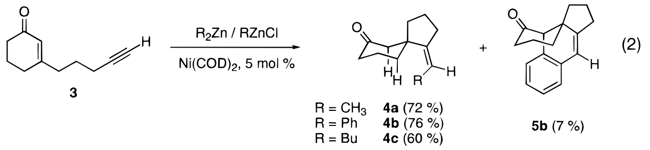
Scheme 1

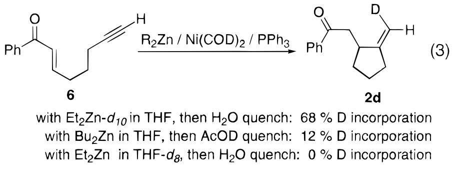


alkylation were generally observed as byproducts in low yield. Thus, either isomer of the trisubstituted alkenes could be selectively produced. Cyclization with alkylation of terminal alkynes in the absence of triphenylphosphine afforded the *Z* isomers, whereas terminal alkyne alkylation, followed by reductive cyclization of the resulting internal alkyne in the presence of triphenylphosphine, afforded the *E* isomers (compare entries 2 and 3, Table 1, with entries 2 and 3, Table 2).

As a test of the methodology in a more complex setting, cyclizations with substrate **3** were investigated (eq 2). With organozincs in the absence of triphenylphosphine, cyclization with alkylation occurred to produce **4a**−**c** as single isomers in 60−76% yield. The reaction with diphenylzinc/phenylzinc chloride also produce the unexpected tetracycle **5b**, derived from spirocyclization followed by ketone α-arylation, in 7% isolated yield. Interestingly, albeit unsurprisingly based on mechanistic considerations, the products derived from cyclizations of **3** are the thermodynamically less stable isomers by virtue of the severe A(1,3) strain associated with the *Z* double bond. The facility with which spirocyclic quaternary centers may be produced from cyclic, enolizable, trisubstituted enones suggests that these procedures should extrapolate nicely to increasingly complex substrates. Attempted reductive cyclizations with dibutylzinc/butylzinc chloride in the presence of triphenylphosphine, however, failed completely with substrate **3**, most likely due to the increased steric demands associated with a phosphine-ligated catalyst. Instead, modest yields of product **4c** along with recovered starting material resulted.



The role of triphenylphosphine in promoting reduction instead of alkylation with unhindered substrates merits discussion. In contrast to the dramatic effect of added phosphine on product distributions in reactions involving dibutylzinc, the addition of triphenylphosphine resulted in virtually no change in reactions with dimethylzinc or diphenylzinc. To confirm the involvement of a β-hydride elimination pathway in the reductive cyclizations with triphenylphosphine, deuterium labeling studies were conducted (eq 3). These experiments indicate that at least two pathways are operative. The major pathway involves β-H elimination, and the minor pathway involves protonation on workup, most likely of an alkenylzinc species.[7a,12]



In light of these results, we speculate that **7** is a common intermediate for all pathways and that triphenylphosphine promotes β-hydride elimination of **7** in preference to reductive elimination (Scheme 1). Reductive elimination of dialkylpalladium and aryl(allyl)palladium complexes is well established to be facilitated by the coordination of electron-deficient alkenes.[13] The π-acceptor properties of the spectator ligand decrease the electron density on the metal center, thus facilitating the reductive process. In the absence of basic phosphine ligands, coordination of unreacted enone to **7** could facilitate reductive elimination either by producing an electron-deficient Ni(II) π-complex[13] or by promoting formal single electron transfer to produce a highly reactive cationic Ni(III) species.[14] In the presence of excess phosphine, however, the alkyl(alkenyl)nickel intermediate **7** would be substantially more electron rich at nickel, and the nonreductive β-hydride elimination could then be favored over reductive elimination.[15] Alternatively, a trans orientation between the alkyl and alkenyl ligands in **7** may be brought about upon addition of phosphine, thus preventing reductive elimination.[16] Studies of product distributions with phosphines and arsines of varying structures and basicities as well as studies toward understanding the mechanism of the formation of **7** are in progress.

In summary, an efficient and general method for the cyclization of alkynyl enones with concomitant stereoselective introduction of tri- or tetrasubstituted alkenes has been developed. This procedure avoids the reagent/substrate compatibility problems generally associated with the intramolecular conjugate addition of alkenyl organometallics to enones.[17,18] More complex methodological studies including intermolecular three-component coupling variants,[19] cyclizations involving different substrate classes, applications in total synthesis, and mechanistic studies are in progress and will reported in due course.

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Supporting Information Available: Experimental procedures and spectral data for **1a**−**g**, **2a**−**d**, **4a**−**c**, and **5b** (7 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(12) Diethylzinc-d_{10} was prepared *in situ* from ethyl iodide-d_5 and *t*-BuLi (2 equiv), followed by addition to zinc chloride. The percent deuterium incorporation was measured by ^1H NMR and confirmed by MS analysis. The experiment involving AcOD quench also resulted in partial incorporation α to the carbonyl. Twelve percent incorporation (by ^1H NMR) at the alkenyl position was observed.

(13) (a) Yamamoto, T.; Yamamoto, A.; Ikeda, S. *J. Am. Chem. Soc.* **1971**, *93*, 3350. (b) Kurosawa, H.; Emoto, M.; Ohnishi, H.; Miki, K.; Kasai, N.; Tatsumi, K.; Nakamura, A. *J. Am. Chem. Soc.* **1987**, *109*, 6333. (c) Temple, J. S.; Riediker, M.; Schwartz, J. *J. Am. Chem. Soc.* **1982**, *104*, 1310. (d) Sustmann, R.; Lau, J.; Zipp, M. *Tetrahedron Lett.* **1986**, *27*, 5207. (e) Binger, P.; Doyle, M. J. *J. Organomet. Chem.* **1978**, *162*, 195.

(14) Reductive elimination of aryl(alkyl)nickel(II) complexes was reported to be accelerated by electron transfer. In the absence of electron-transfer agents, reductive elimination occurred too slowly to be important in the nickel-catalyzed coupling of aryl halides and alkylmetals. Morrell, D. G.; Kochi, J. K. *J. Am. Chem. Soc.* **1975**, *97*, 7262.

(15) For a discussion of the effect of phosphine structure on the relative rates of reductive elimination and β-hydride elimination, see: (a) Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 158. (b) Kumada, M. *Pure Appl. Chem.* **1980**, *52*, 669.

(16) We thank a referee for suggesting this possibility.

(17) For organometallic approaches, see: (a) Bronk, B. S.; Lippard, S. J.; Danheiser, R. L. *Organometallics* **1993**, *12*, 3340. (b) Wender, P. A.; White, A. W. *J. Am. Chem. Soc.* **1988**, *110*, 2218. (c) Cooke, M. P. *J. Org. Chem.* **1992**, *57*, 1495.

(18) For related radical approaches, see: (a) Stork, G.; Mook, R. *J. Am. Chem. Soc.* **1987**, *109*, 2829. (b) Middleton, D. S.; Simpkins, N. S. *Tetrahedron* **1990**, *46*, 545. (c) Marinovic, N. N.; Ramanathan, H. *Tetrahedron Lett.* **1983**, *24*, 1871. (d) Bhaskar, K. V.; Subba Rao, G. S. R. *Tetrahedron Lett.* **1989**, *30*, 225. (e) Janardhanam, S.; Shanmugam, P.; Rajagopalan, K. *J. Org. Chem.* **1993**, *58*, 7782.

(19) Our initial studies have shown that intermolecular three-component couplings are successful. Montgomery, J.; Savchenko, A. V.; Chui, H. *Abstracts of Papers*, 210th ACS National Meeting, Chicago, IL, August 24, 1995; American Chemical Society: Washington, DC, 1995; ORGN 415.