Catalyzed Cyclization of α,ω-Dienes: A Versatile Protocol for the Synthesis of Functionalized Carbocyclic and Heterocyclic Compounds

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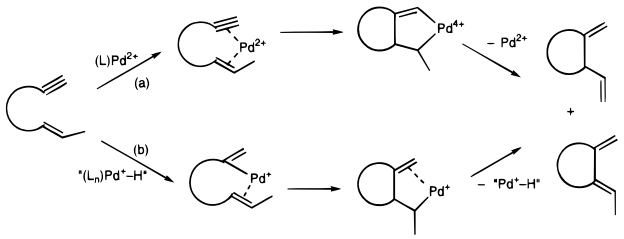
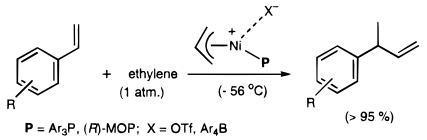
Unactivated olefins and acetylenes have long been recognized as latent functional groups compatible with many traditional methods of C−C bond-forming reactions that use nucleophilic and electrophilic reagents.[1] Since activation of these functionalities for further reactions is best carried out with transition metal reagents, advantages associated with such a process can be brought to bear on the subsequent chemistry even at late stages in a synthesis.[2] In this context, two of the most important attributes relevant to synthetic efficiency are the potential for developing catalytic processes and ligand modification for control of product stereochemistry. One reaction that has received considerable attention is cyclization of eneynes mediated by low valent Zr, Ti, and Pd.[3−5] For the Pd-catalyzed reaction, two principal mechanistic possibilities have been advanced (Scheme 1), (a) involvement of a palladacycle or (b) in situ formation of a [L_n-Pd−H]$^+$ (L = ligand) followed by hydropalladation and subsequent carbapalladation. Ligand-dependent formation of stereo- and regioisomers[4b] as well as an example[6] of enantioselective catalysis of eneyne cycloisomerization have been recorded.

In contrast, very little attention[7] has been paid to the corresponding Ni or Pd-*catalyzed* cyclization of α,ω-dienes, even though the availability of starting materials and the diminished Lewis acidity of these metals (vis-á-vis early transition metals) should make this process a very attractive one for development of highly catalytic reactions.[8] This is especially true for substrates that contain heteroatoms such as O, N, and S, where the use of near-stoichiometric amounts of Ti or Zr catalyst in addition to several equivalents of trapping/reducing agents is routine.[9−11] Recently we have been interested in the applications of well-defined Pd(2+) and Ni(2+) monohydrides olefins. For example, we recently reported a new procedure for asymmetric heterodimerization of ethylene and vinylarenes (Scheme 2).[12] Here we report the first examples of an intramolecular version of this reaction.[13]

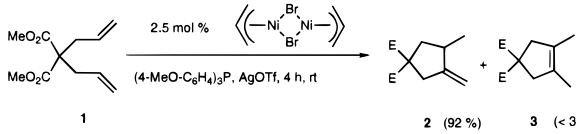
Scheme 1. Metal-Catalyzed Eneyne Cyclization



Scheme 2. [Ni-H]$^+$-Mediated Hydrovinylation of Vinylarenes



Scheme 3. Intramolecular Hydrovinylation of α,ω-Dienes



When a cold CH_2Cl_2 solution of di-*O*-methyl diallylmalonate (**1**) is treated with 0.05 equiv of Ni catalyst prepared from [Ni(allyl)Br]$_2$, tri-4-methoxyphenylphosphine, and AgOTf, excellent conversion of starting material to a methylenecyclopentane **2** ensues (Scheme 3).[14] The cyclization reaction can be carried out with [Pd(allyl)Cl]$_2$ dimer in place of the corresponding Ni salt (Table 1, entry 2). Not surprisingly, the palladium-catalyzed reactions are slower and varying amounts of methylenecyclopentane product **2** and an isomer **3**, in which the double bond has undergone migration to the endocyclic position, are produced in 91% isolated yield. *With regard to functional group compatibility of the present method, it is important to point out that Cp*$_2$YMe(THF) failed to effect cyclization reaction of this substrate*.[7e] Likewise, other methods based on Cp_2Zr,[7d,g,9,11] and Cp_2ScH[7c] are also likely to be incompatible with this and similar substrates with ester groups. Note that the products obtained are similar to those from a Pd-catalyzed *reductive cyclization* of eneynes in the presence of a polymeric silicon hydride.[4b]

Further scope and limitations of the reaction are illustrated in Table 1 with a carefully chosen list of other dienes with sensitive functional groups and heteroatoms. Typically, a number of substituted arylphosphine ligands with both [Pd(allyl)Cl)]$_2$ and [Ni(allyl)Br)]$_2$ were scouted for each reaction. In general, monosubstituted olefins gave the best results, even though under

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(7) For early transition metal-mediated processes, (i) stoichiometric reactions: (a) Nugent, W. A.; Taber, D. F. *J. Am. Chem. Soc.* **1989**, *111*, 1, 6435. (b) Rousset, C. J.; Swanson, D. R.; Lamaty, F.; Negishi, E.-i. *Tetrahedron Lett.* **1989**, *30*, 5105. (ii) Catalytic proceses: (c) Piers, W. E.; Shapiro, P. J.; Bunel, E. E.; Bercaw, J. E. *Synlett* **1990**, 74. (d) Knight, K. S.; Waymouth, R. M. *J. Am. Chem. Soc.* **1991**, *113*, 6268. (e) Molander, G. A.; Hoberg, J. O. *J. Am. Chem. Soc.* **1992**, *114*, 3123. (f) Negishi, E.-i. Takahashi, T. *Acc. Chem. Res.* **1994**, *27*, 124. (g) Dzhemilev, U. M. *Tetrahedron* **1995**, *51*, 4333. (h) Christoffers, J.; Bergman, R. G. *J. Am. Chem. Soc.* **1996**, *118*, 4715. (i) Thiele, S.; Erker, G. *Chem. Ber./Rec.* **1997**, *130*, 201.

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(13) For related diene cyclizations (using Pd and Rh) of limited scope, see: (a) Bright, A.; Malone, J. F.; Nicholson, J. K.; Powell, J.; Shaw, B. L. *J. Chem. Soc., Chem. Commun.* **1971**, 712. (b) Grigg, R.; Malone, J. F.; Mitchell, T. R. B.; Ramasubbu, A.; Scott, R. M. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1745.

(14) See Supporting Information for details of experimental procedures.

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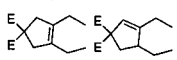
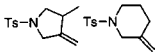
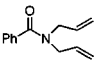
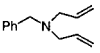
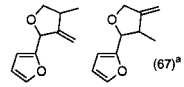
Table 1. Ni- and Pd-Catalyzed Cyclization of 1,6-Dienes

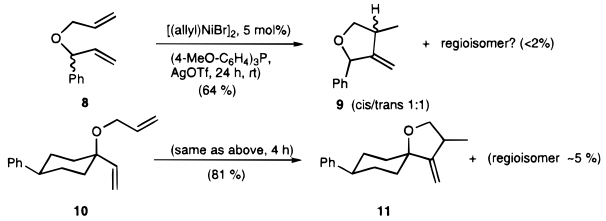
Entry	Substrate	Metal/Conditions	Phosphine	Product(s) (% yield)
1.		 AgOTf, 4 h rt, CH_2Cl_2	(4-MeO-C_6H_4)$_3$P	 (92%)[a,b]
		2.5 mol%		**2**
2.		 AgOTf, 24 h rt, CH_2Cl_2	(2-Me-C_6H_4)$_3$P	**2**  (91%)[a,b]
		5 mol%		(20) **3** (70)
3.		 AgOTf, 72 h rt, CH_2Cl_2	(2-MeO-C_6H_4)PPh_2	
	(Z/E-mixtures)	5 mol%		**4** (1.7) **5** (1) (90%)[a,b]
4.		 AgOTf, 24 h rt, CH_2Cl_2	PPh_3	
	a)	5 mol%		**6** (82) **7** (18) (90%)[a,b]
	b)	5 mol%	(2-Me-C_6H_4)$_3$P	(38) (62) (92%)[a,b]
	c)	 AgOTf, 24 h rt, CH_2Cl_2	(4-MeO-C_6H_4)$_3$P	
		5 mol%		(10)
5.[c]		 AgOTf, 52 h rt, CH_2Cl_2	(2-Me-C_6H_4)$_3$P	 (49)[a]
		10 mol %		
6.		 AgOTf, 24 h rt, CH_2Cl_2	(2-Me-C_6H_4)$_3$P	(no reaction)
		5 mol%		
7.[d]		 AgOTf, 24 h rt, CH_2Cl_2	(4-OMe-C_6H_4)$_3$P	 (64)[a]
	8	5 mol%		**(9**, cis/trans 1:1)
8.[e]		 AgOTf, 72 h rt, CH_2Cl_2	(4-OMe-C_6H_4)$_3$P	 (67)[a]
		5 mol %		(**12**, trans/cis 1/1)[f] (**13**, trans/cis1/1)[f] (**12:13** = 4.5/1)[f]

[a] Isolated yield of pure (GC) product. [b] Ratios determined by GC. [c] No cyclization was observed with Ni catalyst. [d] Substrate yielded mixture of products, with only trace amounts of 5-membered furan product formed when treated with Pd catalyst. [e] Substrate decomposed when treated with Pd catalyst. [f] Ratios determined by ^{1}H NMR.

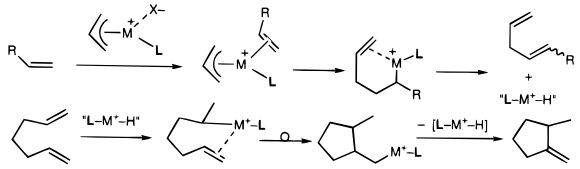
more forcing conditions disubstituted olefins will participate in the reaction (entry 3). It is particularly noteworthy that the Pd-catalyzed reaction is more suitable for *N*-tosyl/*N*-acyl substituted dienes (entries 4 and 5). Depending on the phosphine, both 5- and 6-membered ring heterocycles are produced. Thus, in the case of *N*-tosyldiallylamine, [(allyl)PdCl]$_2$/Ph_3P/AgOTf gave a mixture of 5- and 6-membered heterocycles in a ratio of 82:18. Use of (*o*-tolyl)$_3$P as a ligand under the same conditions gave a ratio of 38:62 of the same compounds (entries 4a and 4b). The corresponding reaction with [(allyl)NiBr]$_2$ gave a lower yield of cyclic 5-membered product (entry 4c). The reaction appears to be sensitive to the amine protecting group and phosphine used. Thus, under the palladium/tri-*o*-tolylphosphine-mediated reaction conditions, the *N*,*N*-diallylbenzamide gave exclusively the methylene derivative (entry 5). Benzyldiallylamine (entry 6) and other tertiary amines failed to undergo cyclization.

The remarkable functional group compatibility of this catalyst system is best illustrated with substrates carrying allyl ether functionality shown in Scheme 4. These reactions are carried out with Ni catalyst, since Pd catalyst gave diminished yields of products.[15] Even though the yields of the reactions are only moderate, it is surprising that the sensitive allyl ether functionality survives the reaction conditions. There are *no known examples* of low-valent Zr-mediated (catalyzed or stoichiometric) cyclization of substrates having an allyloxy group. The highly reducing conditions involving low-valent Cp_2Zr is incompatible with this functional group.[16] Note that the reaction is highly chemo- and regioselective. However, cyclic product **9** is obtained as a mixture of cis and trans (1:1) isomers. Substrate **10** gave an exceptionally clean reaction leading to **11** in 95% isomeric purity. In each case, formation of the indicated regioisomeric product can be rationalized by initial addition of the presumed LNi^+-H intermediate (vide infra) to the less hindered olefin. Even when there is the possibility of an auxiliary coordination, (e.g., entry 8) the expected regioisomer **12** is still the major product.

Scheme 4. Chemo- and Regioselectivity of the Cyclization



Scheme 5. Mechanism of Intramolecular Hydrovinylation



The mechanism of reaction remains speculative at present. One likely scenario[8,17] involves the formation of a metal hydride (Scheme 5), followed by hydrometallation, cyclization, and reductive elimination (see Scheme 1, path b). We have observed that a number of (allyl)Ni(X)(phosphine) complexes used in this study are excellent catalysts for isomerization of terminal olefins[18] to internal olefins, a reaction characteristic of metal hydrides.[19]

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Supporting Information Available: Details of experimental procedures, spectroscopic and chromatographic data of products (48 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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