Reactivity and Selectivity of 1,3-Diyn-6-enes in Electrophilic Transition Metal-Catalyzed Reactions
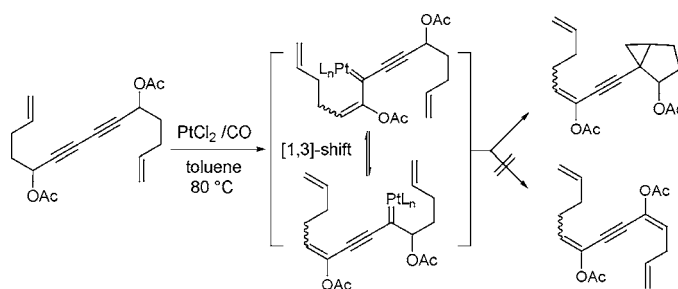
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ABSTRACT

1,3-Diyne is an excellent source of alkynyl metal carbene species upon activation with an electrophilic metal catalyst. The products from this bond reorganization process suggest that the metal carbene species, generated from the preferential participation of an acetate over an alkene in the first step, undergo an efficient metallotropic [1,3]-shift followed by termination via cyclopropanation.

The metal-catalyzed reactions of 1,*n*-enynes (*n* = typically 5−7) are versatile synthetic tools whereby unsaturated cyclic molecular frameworks can be generated efficiently.[1] One topical subject of research involving enynes of type **1** is their activation by an electrophilic metal catalyst. When the alkyne is not terminal (R = alkyl or aryl group), allenyl acetate **3** is the most frequently observed final product or intermediate for the subsequent reaction, which is believed to proceed through an intermediate **2** via the [1,3]-migration of an acetate (Scheme 1).[2] On the other hand, when the alkyne is

terminal (R = H), a pathway leading to product **5** is generally preferred. The formation of **5** is the consequence of two possible reaction pathways that involve alkylidene species **4** and **7**. Although evidence from theoretical calculations[3]

Scheme 1
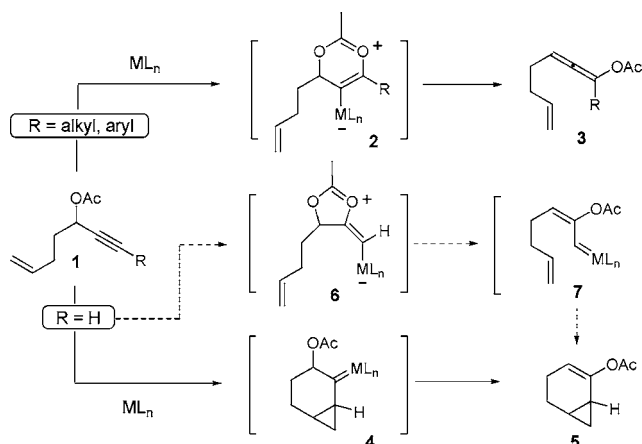
(1) Reviews: (a) Bruneau, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 2328. (b) Echavarren, A. M.; Nevado, C. *Chem. Soc. Rev.* **2004**, *33*, 431. (c) Lloyd-Jones, G. C. *Org. Biomol. Chem.* **2003**, *1*, 215. Reviews for gold-catalyzed reactions: (d) Ma, S.; Yu, S.; Gu, Z. *Angew. Chem., Int. Ed.* **2006**, *45*, 200. (e) Hashimi, A. S. K. *Angew. Chem., Int. Ed.* **2005**, *44*, 6990. (f) Höffmann-Röder, A.; Krause, N. *Org. Biomol. Chem.* **2005**, *3*, 387. (g) Hashimi, A. S. K. *Gold Bull.* **2004**, *37*, 51. (h) Dyker, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 4237.

(2) Formation of allene as a final product or an intermediate, see: (a) Marion, N.; Diez-Gonzalez, S.; de Fremont, P.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2006**, *45*, 3647. (b) Zhang, L.; Wang, S. *J. Am. Chem. Soc.* **2006**, *128*, 1442. (c) Buzas, A.; Istrate, F.; Gagosz, F. *Org. Lett.* **2006**, *8*, 1957. (d) Zhao, J.; Hughes, C. O.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 7436. (e) Zhang, L. *J. Am. Chem. Soc.* **2005**, *127*, 16804. (f) Cariou, K.; Mainetti, E.; Fensterbank, L.; Malacria, M. *Tetrahedron* **2004**, *60*, 9745.

and experiments[4] favorably suggests the involvement of intermediate **4** over that of **6/7**, the preference among these reaction pathways should depend on the interplay of many factors,[5] the most important of which seems to be the nature of the R substituent.[6] Given the cationic charge development on the alkyne moiety upon complexation of electrophilic metals, the role of R as an electron-releasing group seems to be pivotal in determining the fate of the initially formed alkyne−metal complex, generating intermediates **2**, **4**, or **6**. This hypothesis is further supported by the reactions of related enynes of type **8**, where the nature of X determines the formation of intermediates **9** and **11**, which eventually generate products **10/10′** and **12**, respectively (Scheme 2).[7]

Scheme 2
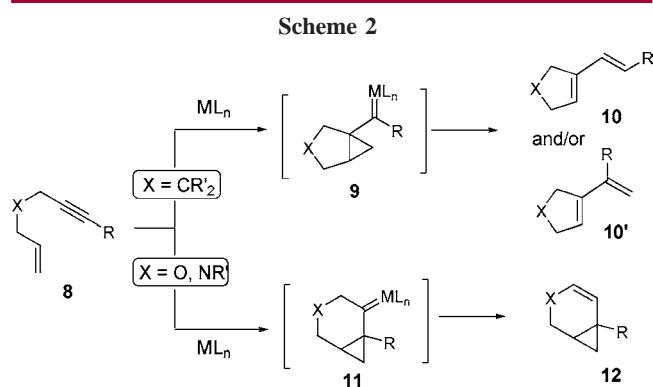
We envisioned that the use of 1,3-diyne moiety in **1**, where R = alkyne, would not only bias the electronics of the reacting alkyne to form metal carbenes but also allow these initially formed alkylidene intermediates to undergo metal-lotropic [1,3]-shift,[8] thereby promoting the mode of reaction pathway not available for the monoalkyne-containing enyne **1**. Herein we report a unique selectivity profile of 1,3-diynes

(3) (a) Soriano, E.; Ballesteros, P.; Marco-Contelles, J. *Organometallics* **2005**, *24*, 3182. (b) Nieto-Oberhuber, C.; Paz Muñoz, M.; Buñuel, E.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem.*, *Int. Ed.* **2005**, *44*, 6146.
(4) (a) Fürstner, A.; Hannen, P. *Chem. Eur. J.* **2006**, *12*, 3006. For a slightly different mechanistic interpretation, see: (b) Fehr, C.; Galindo, J. *Angew. Chem.*, *Int. Ed.* **2006**, *45*, 2901.
(5) For the Rautenstrauch reaction involving 3-acetoxy-1,4-enynes, see: (a) Faza, O. N.; Lopez, C. S.; Alvarez, R.; de Lera, A. R. *J. Am. Chem. Soc.* **2006**, *128*, 2434. (b) Shi, X.; Gorin, D. J.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 5802. (c) Rautenstrauch, V. *J. Org. Chem.* **1984**, *49*, 950.
(6) For reactions of 3-acetoxy-1,4- and 1,5-enynes with electron-withdrawing carboxylate substituent, see: (a) Prasad, B. A. B.; Yoshimoto, F. K.; Sarpong, R. *J. Am. Chem. Soc.* **2005**, *127*, 12468. (b) Reference 2f.
(7) For a theoretical calculations for divergent skeletal rearrangement of 1,6-enynes, see ref 3b.
(8) [1,3]-Shift: (a) Kim, M.; Lee, D. *J. Am. Chem. Soc.* **2005**, *127*, 18024. (b) Kim, M.; Miller, R. L.; Lee, D. *J. Am. Chem. Soc.* **2005**, *127*, 12818. (c) Barluenga, H.; de la Ruá, R. B.; de Sáa, D.; Ballesteros, A.; Tomás, M. *Angew. Chem.*, *Int. Ed.* **2005**, *44*, 4981. (d) van Otterlo, W. A. L.; Ngidi, E. L.; de Koning, C. B.; Fernandes, M. A. *Tetrahedron Lett.* **2004**, *45*, 659. (e) Padwa, A.; Austin, D. J.; Gareau, Y.; Kassir, J. M.; Xu, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 2637. [1,1,5]-Shift: (f) Casey, C. P.; Dzwiniel, T. L. *Organometallics* **2003**, *22*, 5285. (g) Casey, C. P.; Dzwiniel, T. L.; Kraft, S.; Guzei, I. A. *Organometallics* **2003**, *22*, 3915. (h) Ortin, Y.; Sournia-Saquet, A.; Lugan, N.; Mathieu, R. *Chem. Commun.* **2003**, 1060. (i) Casey, C. P.; Kraft, S.; Powell, D. R. *J. Am. Chem. Soc.* **2000**, *122*, 3771. (j) Casey, C. P.; Kraft, S.; Powell, D. R. *Organometallics* **2001**, *20*, 2651. (k) Casey, C. P.; Kraft, S.; Kavana, M. *Organometallics* **2001**, *20*, 3795. (l) Casey, C. P.; Kraft, S.; Powell, D. R. *J. Am. Chem. Soc.* **2002**,

Table 1. Reactivity of Alkene vs Acetate as the Initiator[a]

entry	substrate	product	yield (*Z:E*)[b,c,d]
1	**13a**	**14a**	88% (2.5:1)
2	**13b**	**14b**	92% (6.5:1)
3	**13c**	**14c**	87% (2.7:1)
4	**13d**	**14d**	82% (4.7:1)
5	**13e**	**14e**	98%
6	**13f**	**14f**	90%

[a] With 5 mol % catalyst loading under balloon pressure of CO. [b] All yields are isolated yields after 4 h of total reaction time. [c] The *E/Z* ratios were determined by ^{1}H NMR before purification. [d] The *E/Z* ratios change during the purification.

upon electrophilic metal activation to form alkynyl alkylidenes and their subsequent facile metallotropic [1,3]-shift.

First, the reactivity of 1,3-diynes **13a**[9] that contain both the competing tethered alkene and propargylic acetoxy group was examined with several different metal complexes.[10] From a brief screening, a platinum-based catalyst system PtCl$_2$/CO in toluene at 80 °C, a condition used by Fürstner for the reactions of enynes of type **1**,[11,12] was found to be most

124, 2584. Also see recent examples of the closely related bond shift of free alkynyl carbenes: (m) Bowling, N. P.; Halter, R. J.; Hodges, J. A.; Seburg, R. A.; Thomas, P. S.; Simmons, C. S.; Stanton, J. F.; McMahon, R. J. *J. Am. Chem. Soc.* **2006**, *128*, 3291 and references therein.
(9) For the preparation of diynes, see the Supporting Information.
(10) Pt- and Au-catalyzed rearrangement of 1,3-diynes, see: (a) Cho, E. J.; Kim, M.; Lee, D. *Eur. J. Org. Chem.* **2006**, 3074. See also [RuCl$_2$(CO)$_3$]$_2$-catalyzed reaction: (b) Miki, K.; Ohe, K.; Uemura, S. *J. Am. Chem. Soc.* **2006**, *128*, 9270.
(11) Representative examples of PtCl$_2$-catalyzed reactions with/without CO: (a) Fürstner, A.; Davies, P. W.; Gress, T. *J. Am. Chem. Soc.* **2005**, *127*, 8244. (b) Mamane, V.; Gress, T.; Krause, H.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 8654. (c) Harrak, Y.; Blaszykowski, C.; Bernard, M.; Cariou, K.; Mainetti, E.; Mouriès, V.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *J. Am. Chem. Soc.* **2004**, *126*, 8656. (d) Nevado, C.; Ferrer, C.; Echavarren, A. M. *Org. Lett.* **2004**, *6*, 3191. (e) Mainetti, E.; Mouriès, V.; Fensterbank, L.; Malacria, M.; Marco-Contelles, J. *Angew. Chem.*, *Int. Ed.* **2002**, *41*, 2132. (f) Fürstner, A.; Szillat, H.; Stelzer, F. *J. Am. Chem. Soc.* **2000**, *122*, 6785. (g) Chatani, N.; Furukawa, N.; Sakurai, H.; Murai, S. *Organometallics* **1996**, *15*, 901.
(12) The current reaction resulted in a low conversion without CO.

Table 2. Selectivity of 5-Exo vs 6-Endo Ring Closure[a]

entry	substrate	product	yield (%)[b]
1	15a	16a	96
2	15b	16b	6.3
		17b	23
3	15c	16c	25
		17c	trace
4	15d	17d	63

[a] With 5 mol % catalyst loading. [b] All yields are isolated yields.

Table 3. Differential Reactivity of Alkene vs Acetate[a]

entry	substrate	product	yield (Z:E)[b,c]
1	18a	19a	80% (1.3:1)
2	18b	19b	67% (1.2:1)
3	18c	19c	33% (3.5:1)
		19c'	57% (2.2:1)
4	18d	19d	50% (2.5:1)

[a] With 5 mol % catalyst loading. [b] All yields are isolated yields. [c] The ratios were determined by ^{1}H NMR before purification.

effective, generating **14a** in 88% yield with $Z/E = 2.5$:1 (entry 1, Table 1). Under the same conditions, substrate **13b** containing a phenyl instead of methyl group gave better yield and selectivity (entry 2). Heteroatom substituents in the tether of **13c** and **13d** are tolerant, providing comparable yields and selectivity for **14c** and **14d**, respectively (entries 3 and 4). Substrates **13e** and **13f** with a tertiary *p*-nitrobenzoate provided excellent yields of products **14e** and **14f** (entries 5 and 6). The formation of bicyclo[3.1.0]hexane moieties in products **14a**−**f** strongly indicates that the acetate/benzoate should be the kinetically more reactive initiating functionality, directing these reactions to occur following the path similar to **1** → **6** → **7** in Scheme 1. If the reaction initially occurred via the participation of the tethered alkene, the final products **14c**, **14d**, and **14f** from substrates **13c**, **13d**, and **13f** should have contained bicyclo[4.1.0]heptene moiety based on the general reactivity pattern (via intermediate **11**) shown in Scheme 2.

To confirm our belief that transformation of **13a**−**f** involved an initial acetate or benzoate participation rather than the alkene, as well as to gain further insight into the role of diynes in 5-*exo*/6-*endo* type ring closure selectivity in Scheme 2, symmetrical diynes **15a**−**d** were examined (Table 2).[13] Treatment of substrate **15a** with PtCl₂/CO in

toluene at 80 °C provided exclusively the 5-*exo*-product **16a** in 96% yield after 12 h without any formation of the 6-*endo*-product (entry 1).[14] However, **15b** gave a mixture of 5-*exo*-product **16b** and 6-*endo*-product **17b** in 6.3% and 23% yield at 30% conversion (entry 2), while **15c** gave **16c** and **17c** in 25% and trace amount, respectively (entry 3).[15] The *N*-toluensulfonyl group-containing substrate **15d** gave only 6-*endo*-product **17d** (entry 4). The observed product distribution clearly showed the role of the heteroatom substituent to affect the reaction course of 1,3-diyne substrates **15a**−**d** to form **16a**−**c** and **17b**−**d**, which follows the general trend depicted in Scheme 2. Furthermore, this result strongly supports the notion that the reactions in Table 1 should involve the initial acetate and benzoate participation rather than the alkene.[16]

Next, the selectivity between propargylic polar functional groups (acetate or bromide) and the tethered alkenes for the carbenoid reaction in the termination step was examined (Table 3). Symmetrical substrate **18a** containing two acetates and two alkenes provided an Z/E mixture of products **19a** in 80% yield (Z/E = 1.3:1) (entry 1). Similarly, substrate **18b** gave exclusive formation of **19b** with slightly lower yield

(13) The reaction of **15a,b** with PtCl₂, AuCl₃, Ph₃PAuCl, PdCl₂(PhCN)₂, and [Rh(OAc)₂]₂ gave low conversion.

(14) A gold-catalyzed reaction of **15a** to generate **16a** was reported recently, see: Lopez, S.; Herrero-Gomez, E.; Perez-Galan, P.; Nieto-Oberhuber, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 6029.

(15) Unstable enol ether **17b** could be isolated only when the reaction was stopped at low conversion; however, **17c** was too unstable to be isolated under the reaction conditions.

(16) The preferential participation of acetate in these reactions is the opposite to the reactivity observed and predicted by that of monoynes with propargylic acetates, see refs 3a and 4a.

(67%) ($Z/E = 1.2{:}1$) (entry 2). The reaction of substrate **18c** that contains two different acetates provided **19c** and **19c′** in 33% and 57% yield, respectively (entry 3). Product **19c** is the result of initiation of the reaction from the left-hand side acetate of **18c** followed by metallotropic [1,3]-shift and termination with the other acetate, whereas product **19c′** is the consequence of initiation from the right-hand side acetate followed by metallotropic [1,3]-shift and the termination of the putative alkylidene intermediate via cyclopropanation. Reaction of substrate **18d** containing a bromide provided **19d** as a sole product in marginal yield, which we believe is the consequence of the initiation from the acetate and termenation by the alkene via cyclopropanation (entry 4).

The observed product distribution clearly suggests that acetates preferentially participate at the initial formation of carbenoid intermediates whereas the tethered alkenes participate in the termination step favorably. The general reactivity and selectivity trend is illustrated with substrate **18a** in Scheme 3. The formation of Z/E-mixtures of the vinyl
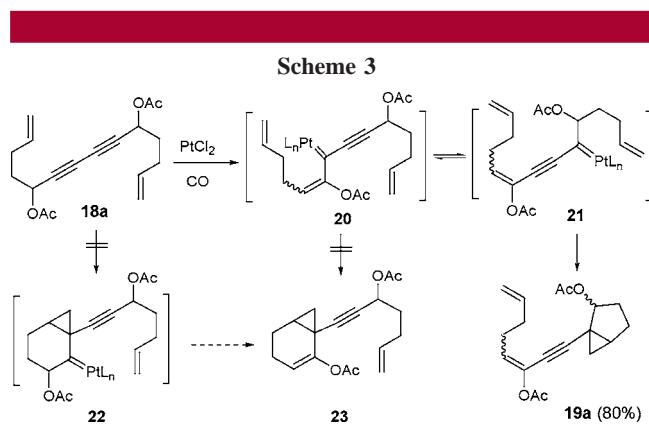
acetate moiety in these products endorses this conclusion, where the vinyl acetate formed during the formation of carbenoid intermediates generally gives a mixture of Z/E-stereochemistry, while that formed from the termination step selectively generates E-stereochemistry.[10a]

In conclusion, we have demonstrated that 1,3-diynes behave in predictable yet distinctive manners compared to simple enynes under electrophilic transition metal-mediated reaction conditions. This characteristic behavior of 1,3-diynes is presumably caused by the slightly electron-withdrawing nature of the alkynyl substituent, which not only renders the preferred formation 5-*exo*-type alkylidenes (similar to **9**) but also allows for the subsequent [1,3]-metallotropic shift. Several salient features of reactions with this functionality include the following: (a) an acetate is more reactive than the tethered alkene as an initiator, generating [1,2]-acetate migrated alkylidene intemediate whereas an alkene is a better terminator than an acetate/bromide to generate the cyclopropane moiety, (b) allene products are not formed at all under current reaction conditions, (c) 5-*exo*/6-*endo* type alkylidene formation depends on the heteroatom substiuent in the tether, and (d) facile metallotropic [1,3]-shift of the intermediate alkylidenes occurred whenever possible.

Supporting Information Available: General procedures and characterization data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

Scheme 3