

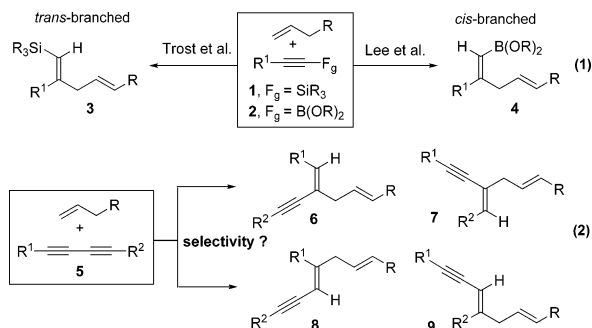
Selectivity in the Ruthenium-Catalyzed Alder Ene Reactions of Di- and Triynes

Eun Jin Cho and Daesung Lee*

Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53706

Received March 20, 2007; E-mail: dlee@chem.wisc.edu

The efficient construction of unsaturated molecular frameworks with desired regio- and stereochemistries remains one of the major challenges in organic chemistry. The metal-catalyzed merger of alkynes and alkenes¹ serves this purpose, albeit the regioselectivity generally suffers in intermolecular processes. Specifically, in the Ru-catalyzed Alder ene reaction,² regioselectivity is unpredictable, leading to the formation of a mixture of linear and branched isomers in varying ratios.³ To improve selectivity, Trost et al.⁴ used silylated alkyne **1** to generate a branched isomer **3**, while Lee et al.⁵ used boronated alkyne **2**, which provided a branched isomer **4** with unusual *cis*-stereochemistry (eq 1).



In search of a new regio-directing element complementary to the silyl and boronate substituents controlling the regio- and stereochemistry of the reaction, we envisioned the use of an alkyne moiety such as in 1,3-diyne **5**,⁶ where the alkyne substituent, attached directly to the reacting alkyne moiety, is expected to exert a strong impact for the favorable formation of one of the pairs of regioisomers **6/7** and **8/9** (eq 2).⁷ Herein, we report the highly regioselective Alder ene reaction of 1,3-diyne (and 1,3,5-triyne) to give **6/7** over **8/9**, where the site-selectivity (a consequence of reactivity difference between the two alkyne moieties in unsymmetrical 1,3-diyne) between **6** and **7** is controlled by judicious selection of R¹ and R².

First, the regioselectivity profile of the Alder ene reaction was examined with symmetrical 1,3-diyne **10a–e** to avoid any potential site-selectivity problem. With 3-butenyl ethyl carbonate in acetone (0.15 M) with a cationic ruthenium complex [RuCp(CH₃CN)₃PF₆],⁸ substrates **10a–e** gave single regioisomeric ene products (branched isomers) **11a–e** in good yields (Table 1, entries 1–5) without contamination of the other regioisomer **11'**. Two salient features of these reactions are the perfect regioselectivity for the branched isomer **11** and the lack of reactivity of its alkyne moiety toward the second Alder ene reaction, thereby giving only monoalkene adducts. The high regioselectivity is the consequence of a strong directing effect of the alkyne moiety, whereas the site-selective reaction of **10** over **11** is probably the result of the higher reactivity of 1,3-diyne than that of the corresponding 3-branched 1,3-enynes.⁹

Having identified the uniform regioselectivity, we next examined the steric and polar heteroatom substituent effect^{3b,10} for site-

Table 1. Regioselectivity with Symmetrical 1,3-Diyne^a

entry		R	yield of 11 (%) ^b	ratio (11 : 11')
1	a	Ph	51	1:0
2	b	CH ₂ OAc	67	1:0
3	c	CH(CH ₃)OAc	70	1:0
4	d	CH(CH ₃)O(<i>p</i> -NO ₂)Bz	72	1:0
5	e	CH(CH ₂ CH ₂ Ph)OAc	68	1:0

^a Reactions performed with 10 mol % of RuCp(CH₃CN)₃PF₆ at 25 °C in acetone (0.15 M) for 5 min. Carbonate protecting group facilitates the isolation of products. Less than 10 mol % of catalyst loading resulted in longer reaction times and incomplete conversion. ^b Isolated yield.

Table 2. Site-Selectivity with Unsymmetrical 1,3-Diyne^a

entry		R ¹	R ²	yield of 13 + 14 (%) ^b	ratio (13 : 14)
1	a	H	Bu	69	1:0
2	b	H	CH ₂ CH ₂ OH	30	1:0
3	c	Bu	CH ₂ OH	60	1:13.4
4	d	Bu	CH ₂ CH ₂ OH	59	1:3.0
5	e	Bu	CH ₂ CH ₂ CH ₂ OH	55	1:1.3
6	f	SiEt ₃	Bu	73	0:1
7	g	SiEt ₃	CH ₂ OH	80	0:1
8	h	SiEt ₃	CH ₂ CH ₂ OH	70	0:1

^a Reactions performed with 10 mol % of RuCp(CH₃CN)₃PF₆ at 25 °C in acetone (0.15 M) for 5 min. ^b Isolated yield.

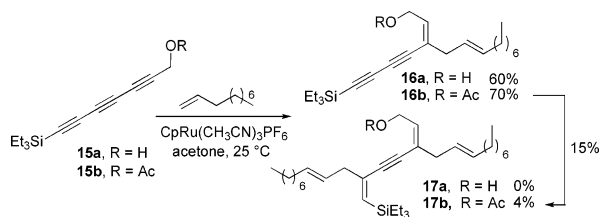
selectivity (Table 2). For terminal 1,3-diyne **12a** and **12b**, the sterically least hindered terminal alkyne moiety participated in the reaction to generate **13a** and **13b** exclusively (entries 1 and 2). On the other hand, the internal 1,3-diyne **12c–e** provided mixtures of **13c–e** and **14c–e** in varying ratio (entries 3–5), which showed clear evidence of the regiochemistry-directing effect of a polar hydroxyl group in a distance-dependent manner. In the case of 1,3-diyne **12f–h** with a silyl group on one of the alkyne moieties, the dominant role of the steric hindrance of the silyl group directed the reaction to occur on the other alkyne, irrespective of the presence or absence of the regiochemistry-directing hydroxyl group, providing single products **14f–h** (entries 6–8).

The generality of regio- and site-selectivity shown in Tables 1 and 2 was further confirmed with reactions between more diverse 1,3-diyne having different steric environments at propargylic sites and various reacting alkene counterparts (Table 3). With diyne **12g**, reactions employing different alkenes did not perturb the efficiency and selectivity (entries 1–4), providing expected products **13k–n**. Replacing propargylic hydroxyl with an acetoxy group in **12j**

Table 3. Selectivity of Reactions with Unsymmetrical 1,3-Diynes^a

Entry	Alkyne	Alkene	Product	Yield (%) ^b
1				81
2				73
3				65
4				80
5				81
6				65 (6.3:1) ^c
7				65 (q:r = 3.5:1)
8				65

^a Reactions performed with 10 mol % of RuCp(CH₃CN)₃PF₆ at 25 °C in acetone (0.15 M) for 5 min. ^b Isolated yield. ^c Ratio between **13p** and its site-selective isomer. ^d The reason for the formation of the minor isomer is unclear at this point.

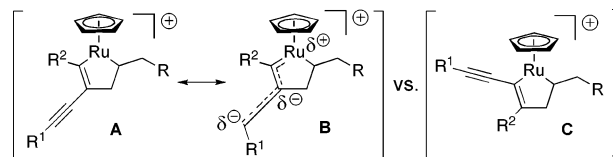
Scheme 1. Ruthenium-Catalyzed Alder Ene Reaction of Triynes

or with Boc in **12k** maintained the yield and selectivity, giving **13o** and **13p**, respectively (entries 5 and 6). Unexpectedly, substrate **12l**, having a tertiary and a primary propargylic acetoxy groups, gave a mixture of **13q** and **13r** with a marginal selectivity (3.5:1), which indicates that the steric factor alone, unless it is a silyl group, might not be enough for high selectivity. A boronate containing diene **12m** showed the same regio- and site-selectivity, generating product **13s** with minor stereochemical scrambling (entry 9).¹¹

Moreover, the regio- and site-selectivity of triynes **15a** and **15b** to generate ene products **16a** and **16b** was found to be identical to that of 1,3-diynes, except for the formation of minor double ene product **17b** (4%). Resubjection of isolated **16b** gave only 15% yield of **17b** with mostly recovered **16b** (Scheme 1).

The observed regioselectivity of Alder ene reactions of 1,3-diynes and 1,3–5-triynes is believed to be the consequence of the favorable formation of metallacyclopentene **A** over **C**. The strong regio-directing effect of the adjacent alkyne moiety is the result of its more effective anion-stabilizing capacity via a conjugated ruthenium carbenoid character, as shown in zwitterionic resonance form **B** compared to that of R₂ in the regioisomeric **C**, as proposed by Trost for the ene reaction between 4-hydroxy-2-alkynoate and terminal alkenes.¹⁰ However, the sense of regioselectivity for the exclusive formation of metallacyclopentene **A** is highly unusual compared

to the general preference for **C** in reactions with Co,^{7b} Ta,^{7c} Zr,^{7d} Ni,^{7g,i} and Rh,^{7h,l} where the di- and triynes enter the metallacycle with the alkynyl substituent α to the metal (biggest lobe of their LUMO β to the metal).^{12,13}



In conclusion, we have realized an unusually high level of regio- and site-selectivity in the Alder reactions of 1,3-diynes and 1,3,5-triynes. The selectivity profile clearly indicates that one of the alkynyl moieties not participating in the reaction determines the regiochemistry, whereas the interplay between steric hindrance and polar substituents at the propargylic sites determines the site-selectivity. The synthetic scope and utility of these reactions,¹⁴ as well as the effect of the alkyne moiety for controlling regiochemistry, is under investigation.

Acknowledgment. We thank the NIH (CA106673) and the Sloan Foundation for partial financial support of this work, as well as the NSF and NIH for NMR and mass spectrometry instrumentation. Dr. Monica Ivancic's help in running an NOE experiment for compound **13o** is greatly acknowledged.

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

References

- Reviews: (a) Trost, B. M.; Toste, F. D.; Pinkerton, A. B. *Chem. Rev.* **2001**, *101*, 2067. (b) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813.
- For a review of Alder ene reaction, see: Trost, B. M.; Frederiksen, M. U.; Rudd, M. T. *Angew. Chem., Int. Ed.* **2005**, *44*, 6630.
- (a) Trost, B. M.; Indolese, A. J. *Am. Chem. Soc.* **1993**, *115*, 4361. (b) Trost, B. M.; Indolese, A. F.; Müller, T. J. J.; Treptow, B. *J. Am. Chem. Soc.* **1995**, *117*, 615. (c) Trost, B. M.; Shen, H. C.; Pinkerton, A. B. *Chem.—Eur. J.* **2002**, *10*, 2341.
- (a) Trost, B. M.; Machacek, M.; Schnaderbeck, M. J. *Org. Lett.* **2000**, *2*, 1761. (b) Trost, B. M.; Machacek, M. R. *Angew. Chem., Int. Ed.* **2002**, *41*, 4693. (c) Trost, B. M.; Machacek, M. R.; Ball, Z. T. *Org. Lett.* **2003**, *5*, 1895.
- Hansen, E. C.; Lee, D. *J. Am. Chem. Soc.* **2005**, *127*, 3252.
- Diynes were synthesized via a CuCl-catalyzed coupling reaction between terminal alkynes and 1-bromoalkynes: Marino, J. P.; Nguyen, H. N. *J. Org. Chem.* **2002**, *67*, 6841.
- For regioselective metal-catalyzed intermolecular reactions involving multiynes, see: (a) Takeda, A.; Ohno, A.; Kadota, I.; Gevorgyan, V.; Yamamoto, Y. *J. Am. Chem. Soc.* **1997**, *119*, 4547. (b) Varela, J.; Castedo, L.; Saá, C. J. *Am. Chem. Soc.* **1998**, *120*, 12147. (c) Boring, E.; Sabat, M.; Finn, M. G.; Grimes, R. N. *Organometallics* **1998**, *17*, 3865. (d) Bredeau, S.; Delmas, G.; Pirio, N.; Richard, P.; Donnadiu, B.; Meunier, P. *Organometallics* **2000**, *19*, 4463. (e) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901. (f) Camacho, D. H.; Saito, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 924. (g) Jeevanandam, A.; Korivi, R. P.; Huang, I.; Cheng, C. *Org. Lett.* **2002**, *4*, 807. (h) Huddleston, R. R.; Jang, H.; Krische, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 11488. (i) Deaton, K. R.; Gin, M. S. *Org. Lett.* **2003**, *5*, 2477. (j) Jiang, M. X.; Rawat, M.; Wulff, W. D. *J. Am. Chem. Soc.* **2004**, *126*, 5970. (k) Kim, M.; Miller, R. L.; Lee, D. *J. Am. Chem. Soc.* **2005**, *127*, 12818. (l) Cho, C.; Krische, M. J. *Org. Lett.* **2006**, *8*, 3873.
- (a) Slugovc, C.; Ruba, E.; Schmid, R.; Kirchner, K.; Mereiter, K. *Monatsh. Chem.* **2000**, *131*, 1241. (b) Trost, B. M.; Older, C. M. *Organometallics* **2002**, *21*, 2544.
- Reactions with 1,3-diynes gave near completion within 5 min as opposed to 1–4 h for enynes: Trost, B. M.; Papillon, J. P. N.; Nussbaumer, T. *J. Am. Chem. Soc.* **2005**, *127*, 17921.
- Trost, B. M.; Müller, T. J. J.; Martinez, J. *J. Am. Chem. Soc.* **1995**, *117*, 1888.
- We believe that the lower reactivity of the borylated alkyne is caused by the electronic deactivation of boronate not by its steric hindrance.
- Stockis, A.; Hoffmann, R. *J. Am. Chem. Soc.* **1980**, *102*, 2952.
- The preferred alkynyl substituent β to a metal in metallacyclobutenes formed from di- and triynes with metal carbenes; see refs 7j and 7k.
- A total synthesis of (3R,9R,10R)-panaxytriol utilizing Alder ene products **13o** and **16b** will be reported elsewhere.

JA0719430