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Skeletal Reorganization of Enynes Catalyzed by $InCl_3$

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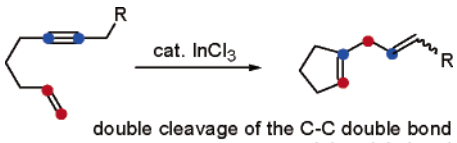
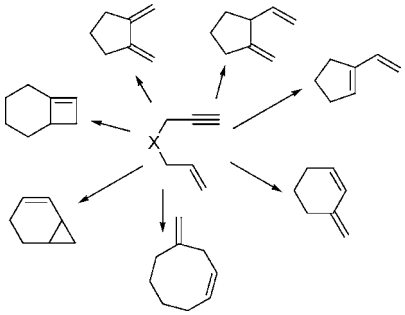
ABSTRACT



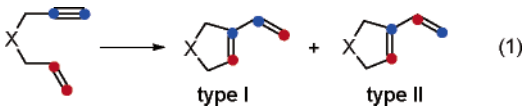
The skeletal reorganization of enynes is achieved by the presence of $InCl_3$ as the catalyst. The reaction of enynes having a terminal acetylenic moiety proceeds in a stereospecific manner to give 1-vinylcycloalkenes. The reaction of enynes containing an alkyl group on the acetylenic terminal carbon resulted in a new type of skeletal reorganization to give 1-allylcycloalkenes, formation of which involves a double cleavage of the C–C double bond and the triple bond.

The catalytic cycloisomerization of enynes has been extensively studied because of the diversity of products that can be accessed with this method by means of a simple operation (Scheme 1).[1] The course of the reaction is significantly affected by the structure of the substrates and the nature of the catalysts and additives used.

Scheme 1. Cycloisomerization of Enynes



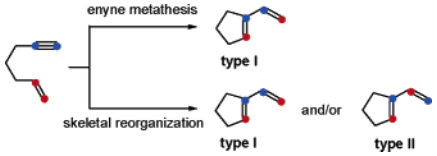
Not only from a synthetic point of view but also from a mechanistic point of view, the skeletal reorganization of enynes leading to 1-vinylcycloalkenes is a most interesting reaction among cycloisomerization reactions because two possible products, type **I** and **II** products, can be formed (eq 1).[2] The formation of the type **II** product involves a double cleavage of the C−C double bond and the triple bond.



A variety of electrophilic transition metal halides or cation complexes are known to trigger the skeletal reorganization of enynes.[3,4] The first example of such a skeletal reorganiza-

(1) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813−834. Lloyd-Jones, G. C. *Org. Biomol. Chem.* **2003**, *1*, 215−236. Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317−1382. Añorbe, L.; Domínguez, G.; Pérez-Castells, J. *Chem. Eur. J.* **2004**, *10*, 4938−4943. Bruneau, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 2328−2334.

(2) Two transformations, enyne metathesis and skeletal reorganization, should be differentiated, although both reactions give 1-vinylcycloalkenes. Catalysts which can be used and the reaction mechanism are totally different. Enyne metathesis appears to proceed through a metal alkylidene mechansim, and only type **I** products are obtained. In addition, enyne metathesis involves an intermolecular process (see: Lloyd-Jones, G. C.; Margue, R. G.; de Vries, J. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 7442−7447).



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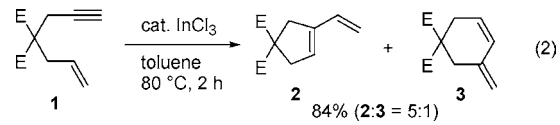
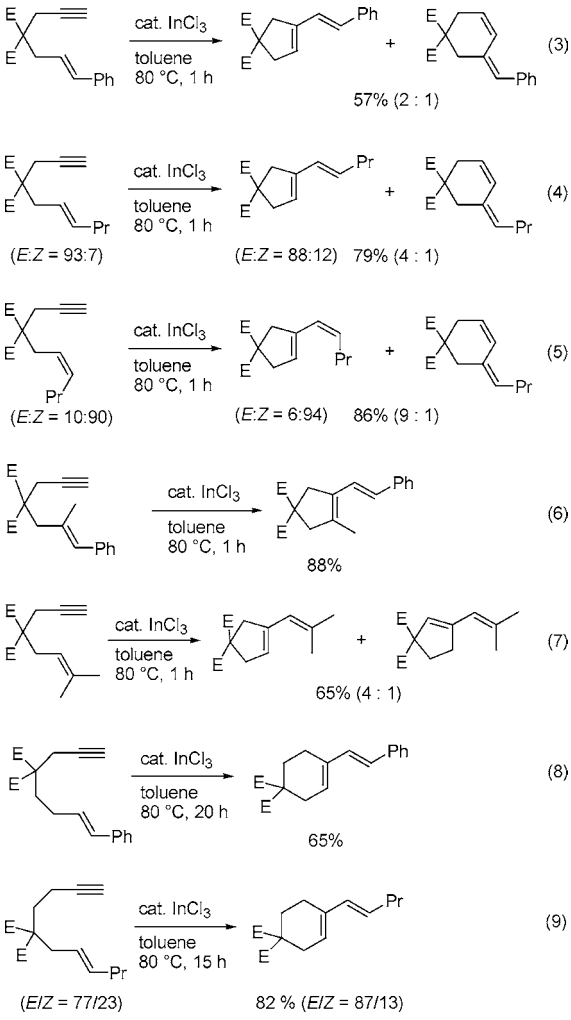
tion was reported by Trost, who used Pd(II), palladacycles, as the catalyst.[4a] When enynes bearing an ester group on the acetylenic carbon and a cis substituent on the terminal olefinic carbon were used, type **I** products were selectively formed. In the case of a terminal alkyne entity, a mixture of types **I** and **II** was obtained. We subsequently found that even more practical and simple metal halides, such as $[RuCl_2(CO)_2]_2$, show a high catalytic activity for the skeletal reorganization of enynes having a terminal acetylenic moiety leading to type **I** products.[3a] Since this report, various metal halides or cation complexes have been used in the skeletal reorganization. Substrates applicable to the skeletal reorganization depend on the nature of catalysts. Enynes having an alkyl or phenyl group on the acetylenic carbon can be used only with Pt complexes. The Pt-catalyzed reaction of enynes bearing a substituent, such as methyl or phenyl, on the acetylenic carbon gave type **I** product as a main product, and the substitution of an ester group gave type **II** product selectively.[6b] Several mechanisms have been proposed, including a nonstabilized carbene mechanism and a nonclassical carbocation mechanism,[5] and various types of new cycloisomerization reactions have been explored on the basis of these reaction mechanisms. Proposed carbene intermediates were trapped by intramolecular olefins.[4l,n,6] The skeletal reorganization of enynes was extended to the cycloisomerization of yne-benzenes.[7] Other new types of reactions which are initiated by electrophilic interaction of metal halides with alkynes have recently been studied mostly with $PtCl_2$ or $AuCl_3$.[8] The driving force for the catalysis is the high electrophilic affinity of the metal complexes toward an acetylene moiety. $InCl_3$ has recently been reported to have a high affinity toward acetylenic bonds.[9] This prompted us to examine its use as a catalyst in the cycloisomerization reactions of enynes. We wish to report here on an unusual type of skeletal reorganization of enynes catalyzed by $InCl_3$.

In an initial investigation, it was found that $InCl_3$ can also be used to effect skeletal reorganization. Treatment of **1** with $InCl_3$ (10 mol %) in toluene at 80 °C resulted in a skeletal reorganization to give 1-vinylcyclopentene **2** along with a six-membered cycloisomerization product **3** (eq 2).



(2)

The reactions of some 1,6- and 1,7-enynes with terminal acetylenic moieties were next examined (eqs 3−9).[10] The reaction proceeded smoothly to afford the expected skeletal reorganization products in good to high yields.[3,4] In the case of 1,6-enynes, six-membered cycloisomerization products were also formed.[11] On the other hand, no corresponding seven-membered cycloisomerization products were formed in the case of 1,7-enynes (eqs 8 and 9). The reaction of enynes containing a mono-substituent at the olefinic carbon was found to proceed in a stereospecific manner with respect to the geometry of the olefin moiety (eqs 4, 5, 8, and 9).



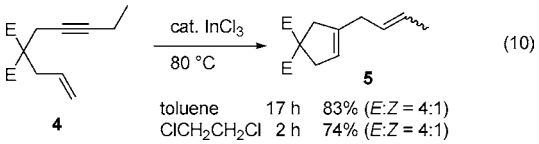
Surprisingly, an unusual type of product was obtained when enynes containing an alkyl group on the acetylenic carbon were employed. The reaction of ethyl-substituted

(3) (a) Ru(II): Chatani, N.; Morimoto, T.; Muto, T.; Murai, S. *J. Am. Chem. Soc.* **1994**, *116*, 6049−6050. (b) Pt(II): Chatani, N.; Furukawa, N.; Sakurai, H.; Murai, S. *Organometallics* **1996**, *15*, 901−903. (c) Ir(I): Chatani, N.; Inoue, H.; Morimoto, T.; Muto, T.; Murai, S. *J. Org. Chem.* **2001**, *66*, 4433−4436. (d) Ga(III): Chatani, N.; Inoue, H.; Kotsuma, T.; Murai, S. *J. Am. Chem. Soc.* **2002**, *124*, 10294−10295.

(4) Pd: (a) Trost, B. M.; Tanoury, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 1636−1638. (b) Trost, B. M.; Trost, M. K. *J. Am. Chem. Soc.* **1991**, *113*, 1850−1852. Pt: (c) Trost, B. M.; Chang, V. K. *Synthesis* **1993**, 824−832. (d) Fürstner, A.; Szillat, H.; Gabor, B.; Mynott, R. *J. Am. Chem. Soc.* **1998**, *120*, 8305−8314. (e) Trost, B. M.; Doherty, G. A. *J. Am. Chem. Soc.* **2000**, *122*, 3801−3810. (f) Fürstner, A.; Szillat, H.; Stelzer, F. *J. Am. Chem. Soc.* **2000**, *122*, 6785−6786. (g) Fürstner, A.; Stelzer, F.; Szillat, H. *J. Am. Chem. Soc.* **2001**, *123*, 11863−11869. (h) Oi, S.; Tsukamoto, I.; Miyano, S.; Inoue, Y. *Organometallics* **2001**, *20*, 3704−3709. (i) Oh, C. H.; Bang, S. Y.; Rhim, C. Y. *Bull. Korean Chem. Soc.* **2003**, *24*, 887. (j) Mamane, V.; Gress, T.; Krause, H.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 8654−8655. (k) Bajracharya, G. B.; Nakamura, I.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 892−897. Au: (l) Nieto-Oberhuber, C.; Muñoz, M. P.; Bunuel, E.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2402−2406. (m) Mézailles, N.; Ricard, L.; Gagosz, F. *Org. Lett.* **2005**, *7*, 4133−4136. (n) Nieto-Oberhuber, C.; Muñoz, M. P.; López, S.; Jiménez-Núñez, E.; Nevado, C.; Herrero-Gómez, E.; Raducan, M.; Echavarren, A. M. *Chem. Eur. J.* **2006**, *12*, 1677−1693. Ru: (o) Madhushaw, R. J.; Lo, C.-Y.; Hwang, C.-W.; Su, M.-D.; Shen, H.-C.; Pal, S.; Shaikh, I. R.; Liu, R.-S. *J. Am. Chem. Soc.* **2004**, *126*, 15560−15565.

(5) (a) Echavarren, A. M.; Nevado, C. *Chem. Soc. Rev.* **2004**, *33*, 431−436. (b) Soriano, E.; Ballesteros, P.; Marco-Contelles, J. *Organometallics* **2005**, *24*, 3172−3181. (c) Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Cárdenas, D. J.; Buñuel, E.; Nevado, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6146. (d) Soriano, E.; Marco-Contelles, J. *J. Org. Chem.* **2005**, *70*, 9345−9353. See also refs 3d and 4f.

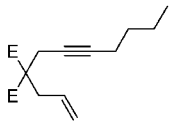
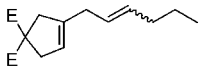
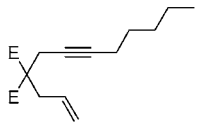
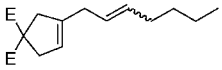
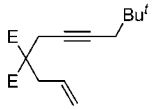
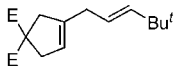
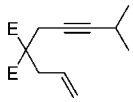
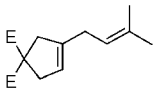
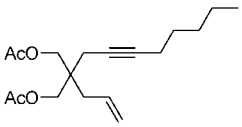
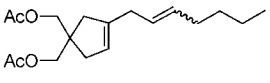
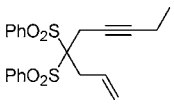
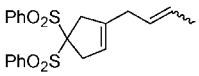
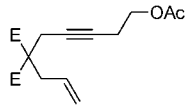
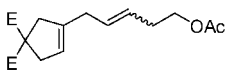
enynes **4** in the presence of 10 mol % of $InCl_3$ in toluene gave 3-buten-2-ylcyclopent-3-ene-1,1-dicarboxylic acid diethyl ester (**5**) in 83% yield (eq 10).[12] We examined the



(10)

solvent effect. It was found that the use of 1,2-dichloroethane as a solvent dramatically shortened the reaction time. Although various transition metal halides are known to be active in the skeletal reorganization of enynes, enynes with substituents, such as alkyl or phenyl groups, on the acetylenic carbon are not suitable substrates for most catalysts, except for $PtCl_2$.[3b,4h]

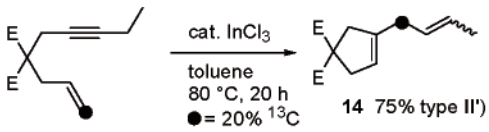
Table 1. Skeletal Reorganization of Enynes to 1-Allylcyclopentenes[a]

enyne	product [b]
	 **6** 82% (*E*:*Z* = 4:1) 80 °C, 2 h
	 **7** 81% (*E*:*Z* = 4:1) 80 °C, 2 h
	 **8** 49% 100 °C, 20 h
	 **9** 38% 100 °C, 7 h
	 **10** 83% (*E*:*Z* = 4:1) 80 °C, 15 h
	 **11** 55% (*E*:*Z* = 10:1)[c] 100 °C, 20 h
	 **12** 44% (*E*:*Z* = 14:1) 80 °C, 20 h

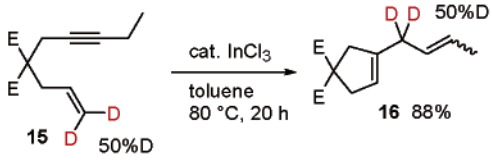
[a] Reaction conditions: enyne (0.5 mmol), $InCl_3$ (0.05 mml), 1,2-dichloroethane (2.5 mL) under N_2. [b] The *E*/*Z* ratio was determined by GC. [c] The *E*/*Z* ratio was determined by ^1H NMR.

The reaction of some enynes with a substituent on the acetylenic carbon was also examined. Alkyl-substituted enynes gave the corresponding 1-allylcyclopentene derivatives in good yields (Table 1). Thus, some functional groups can be tolerated.

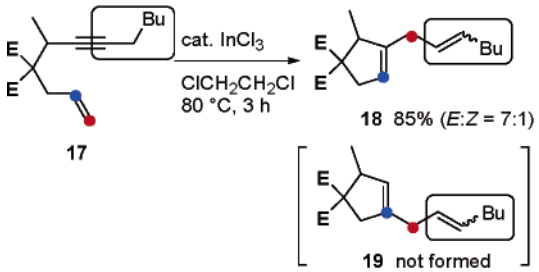
To gain an insight into the reaction mechanism, a ^{13}C-labeled experiment was performed with **13** in which the terminal olefinic carbon was labeled with ^{13}C. The result shows that the bond connection of the ^{13}C-labeled product **14** is the same as that of the type **II** product (eq 11), but that double bond migration has occurred to generate an allyl group (type **II′**) rather than a vinyl group. In addition, to exclude the possibility of group migration, indicated by black circles, to the olefinic terminal carbon, the reaction of **17** was also examined. The reaction of **17** gave **18**, and **19** was not formed (eq 13). These results indicate that the terminal olefinic carbon migrates into the acetylenic carbons. The results on the reaction of deuterated enyne **15** and **20** also support the insertion of the terminal olefinic carbon into the acetylenic carbon (eqs 12 and 14). Furthermore, the result in eq 14 indicates that the formation of the unusual product **14** does not involve double-bond isomerization of the usual product, 1-but-1-enylcyclopentene.



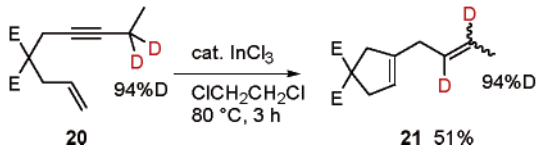
(11)



(12)

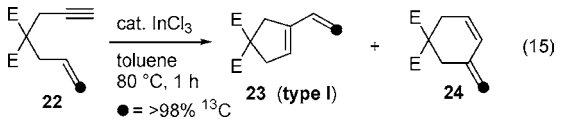


(13)



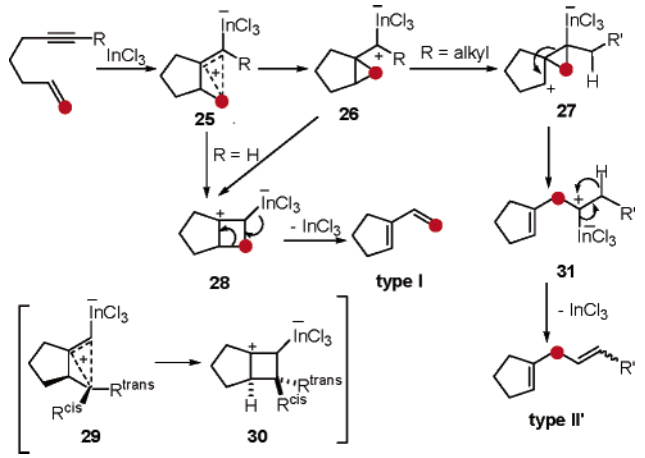
(14)

In contrast to **13**, a ^{13}C-labeling experiment with the simple enyne **22** revealed that cyclization to the type **I** product takes place exclusively. As a result, the acetylenic bond is not cleaved (eq 15). This result is in sharp contrast to the previously reported reaction of **22**, in which the type **II** product was obtained exclusively.[3a,b,4h] These results interestingly show that the course of the reaction is significantly dependent on the substituent on the acetylenic carbon and the catalyst used.



A possible mechanism for the reaction is shown in Scheme 2. The electrophilic interaction of $InCl_3$ with an alkyne gives

Scheme 2. Proposed Mechanism



25.[3d,4f] If R = H, **28** is formed with the formation of a cyclobutane ring, and **28** undergoes electrocyclic ring-opening to give type **I** product. The retention of stereochemistry of the terminal olefinic carbon, as in **29** and **30**, agrees with the stereospecificity observed. When R = an alkyl group, **26** is generated from **25** because the cation is stabilized by the R group. Then, **26** is converted to **27**, which undergoes ring-opening to give the type **II′** product.[4h,13,14]

In summary, $InCl_3$ is also an efficient catalyst for the skeletal reorganization of enynes. The reaction of 1,6-enynes with an alkyl group at the acetylenic carbon results in a new type of skeletal reorganization to give 1-allyl-1-cyclopentenes, in which a terminal olefinic carbon migrates between the acetylenic carbons. Labeling experiments indicate that two mechanistic paths operate, and the path is dependent on the pattern of substitution for the enynes.

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

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