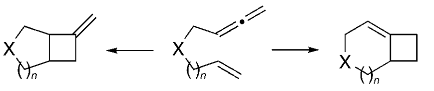
DOI: 10.1002/anie.200501413

Thermal Intramolecular [2+2] Cycloaddition of Allenenes and Allenynes: Diastereoselective Access to Bicyclic Nitrogen Heterocycles**

Hiroaki Ohno, Tsuyoshi Mizutani, Yoichi Kadoh, Kumiko Miyamura, and Tetsuaki Tanaka**

Cycloaddition reactions that occur without the use of reagents or catalysts and without creating any waste have attracted much attention in recent years as an ideal process in terms of atom economy.[1] Considerable research efforts have been particularly focused on the development of cycloaddition of allenes,[2] on account of the current interest in the reactions of allenes with an additional multiple bond, including transition-metal-catalyzed carbocyclizations.[3,4] The [2+2] cycloaddition reactions[5] between allenes and alkenes are extremely useful for the synthesis of methylenecyclobutane derivatives.[6] Especially, intramolecular cycloaddition constitutes a versatile method for the stereoselective synthesis of a variety of bicyclic compounds having a strained bicyclo[*n*.2.0] framework (Scheme 1).[7] In most reported intramolecular [2+2] cycloaddition reactions of simple unactivated allenes, the proximal 2π component of the allene moiety participates in the cycloaddition to form bicyclic products **2**.[2] Only limited examples of the intramolecular [2+2] reaction of the distal allenic double bond to give **3** have been reported to date, which used a special class of allenes such as allene carboxylates,[8] allenyl sulfones,[9] difluoroallenes,[10] β-lactam-tethered allenes,[11] or diyne-diallenes.[12]

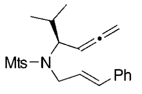
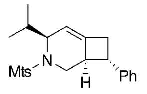
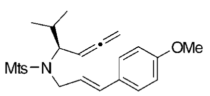
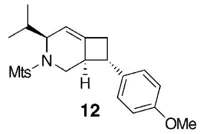
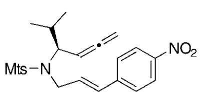
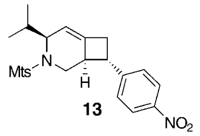
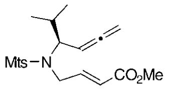
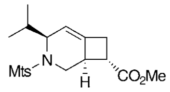
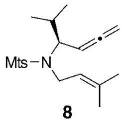
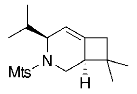
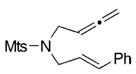
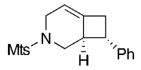
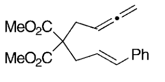
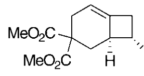


Scheme 1. Intramolecular [2+2] cycloaddition of allenenes.

In the course of our efforts toward the development of a new methodology for the synthesis of heterocyclic compounds by the transition-metal-catalyzed cyclization of allenes,[4,13] we found that the thermal cycloaddition of simple allenes with an additional multiple bond proceeds by simply heating the allenenes or allenynes in the absence of any catalyst. Herein, we present an intramolecular [2+2] cycloaddition of unactivated allenes to form distal adducts of type **3**, which constitute an important class of compounds in synthetic[14] and natural product chemistry.[15]

Various allenenes **4–10** (Table 1) were prepared according to the reported procedure[4d] and their thermal cycloaddition reaction was investigated. First, the [2+2] cycloaddition of allenene **4** was examined under various reaction conditions. Among the solvents employed, dioxane and dimethylformamide (DMF) were the solvents of choice leading to 3-azabicyclo[4.2.0]oct-5-ene derivative **11** in 89 and 96 % yields, respectively, as the sole isolable isomer (Table 1, entries 1 and 2). The structure and configuration of **11** were confirmed by

Table 1: Thermal [2+2] cycloaddition of allenenes.[a]

Entry	Substrate	*t* [h]	Product	Yield [%][b]
1	 Mts–N, Ph **4**	65[c]	 Mts, N, H, Ph **11**	89
2		3		96
3	 Mts–N, OMe **5**	3	 Mts, N, H, OMe **12**	71
4	 Mts–N, NO2 **6**	1	 Mts, N, H, NO2 **13**	93
5	 Mts–N, CO2Me **7**	2	 Mts, N, H, CO2Me **14**	73
6	 Mts–N **8**	24[d]	 Mts, N, H **15**	82
7	 Mts–N, Ph **9**	19[d]	 Mts, N, H, Ph (±)-**16**	68
8	 MeO2C, MeO2C, Ph **10**	30	 MeO2C, MeO2C, H, Ph (±)-**17**	69

[a] Unless otherwise stated, reactions were carried out in DMF at 150 °C. [b] Yields of isolated products. [c] Reaction was carried out in dioxane under reflux conditions. [d] Reaction was carried out in DMF under reflux conditions. Mts = 2,4,6-trimethylphenylsulfonyl.

---

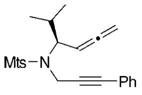
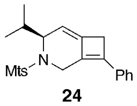
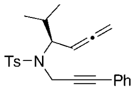
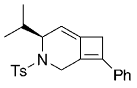
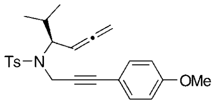
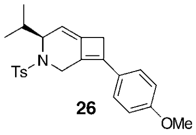
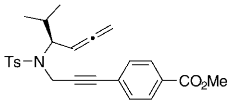
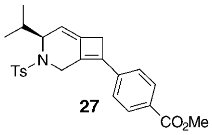
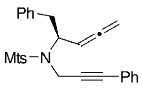
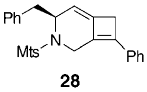
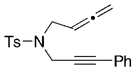
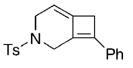
[*] Dr. H. Ohno
Graduate School of Pharmaceutical Sciences
Kyoto University
Sakyo-ku, Kyoto 606-8501 (Japan)
Fax: (+81) 7-5753-4570
E-mail: hohno@pharm.kyoto-u.ac.jp
T. Mizutani, Y. Kadoh, K. Miyamura, Prof. Dr. T. Tanaka
Graduate School of Pharmaceutical Sciences
Osaka University
1-6 Yamadaoka, Suita, Osaka 565-0871 (Japan)
Fax: (+81) 6-6879-8214
E-mail: t-tanaka@phs.osaka-u.ac.jp

[**] We thank Dr. S. Aoki, Graduate School of Pharmaceutical Sciences, Osaka University, for NMR spectroscopic analyses. This work was supported by a Grant-in-Aid for Encouragement of Young Scientists from the Ministry of Education, Culture, Sports, Science, and Technology of Japan and Mitsubishi Chemical Corporation Fund, which are gratefully acknowledged.

heteronuclear multiple quantum correlation (HMQC) and NOESY analysis of the corresponding hydrogenated derivatives. The reaction in dioxane under reflux was rather slow (Table 1, entry 1), and therefore the cycloaddition of the other allenenes **5**–**10** was conducted in DMF. All the allenenes were successfully converted into the corresponding bicyclic products in good to excellent yields, with complete regioselectivity. The reaction of the allenene **5** bearing an electron-donating aryl group gave **12** in relatively low yield (71 %, Table 1, entry 3), whereas the allenene **6** with an electron-withdrawing group afforded **13** in 93 % yield within a shorter reaction time (1 h, Table 1, entry 4). Allene **7** with an α,β-unsaturated ester group showed sufficient reactivity to give the cycloadduct **14** in 73 % yield. Allenene **8** with a geminal dimethyl group on the olefinic carbon atom (Table 1, entry 6), α-unsubstituted allene derived substrate **9** (Table 1, entry 7), and dimethyl malonate derived allenene **10** (Table 1, entry 8) gave the distal cycloadducts **15**–**17** in 68–82 % yields, although prolonged reaction times were required.

Next, the thermal cycloaddition of allenynes **18**–**23** (Table 2) was investigated, which were easily prepared by the N-arylpropargylation of known amino allenes. In contrast to the cycloaddition of allenenes **4** (Table 1, entries 1 and 2), the reaction of the allenyne **18** was complete within 2 h in dioxane under reflux conditions to give 3-azabicyclo[4.2.0]octa-1(8),5-diene derivative **24** in 92 % yield (Table 2, entry 1). In the reaction of N-tosylated allenyne derivatives **19**–**21**, the effect of the electron-donating and -withdrawing aryl group on the reactivity was not dramatic (Table 2, entries 2–4). More important is the α substituent of the allene: the reaction of the allenyne **22** bearing a smaller substituent at the α position was complete in 8 h, whereas the cycloaddition of α-unsubstituted allene derivative **23** required a prolonged reaction time (117 h) to give **29** in 94 % yield.

Table 2: Thermal [2+2] cycloaddition of allenynes.[a]

Entry	Substrate	*t* [h]	Product	Yield [%][b]
1	 **18**	2	 **24**	92
2	 **19**	3	 **25**	70
3	 **20**	2	 **26**	61
4	 **21**	2	 **27**	67
5	 **22**	8	 **28**	91
6	 **23**	117	 **29**	94

[a] All reactions were carried out in dioxane under reflux conditions. [b] Yields of isolated products. Mts = 2,4,6-trimethylphenylsulfonyl; Ts = *p*-toluenesulfonyl.

The related [2+2] thermal reactions of allenes are thought to proceed by a two-step mechanism, that is, via a diradical intermediate.[2, 9b,c, 16] In the present [2+2] cyclization of simple allenenes and allenynes, the substituent on the double or triple bond, which effectively stabilizes the radical intermediate, is essential for successful conversion: the corresponding allenenes or allenynes without the radical-stabilizing group were completely inert to the thermal [2+2] cycloaddition. This experimental result supports the diradical mechanism; however, further study is necessary to elucidate the reaction mechanism.

In conclusion, a stereoselective route to bicyclo[4.2.0]octane derivatives has been developed by using thermal [2+2] cycloaddition of allenes with an additional multiple bond. This study first demonstrated that unactivated allenenes and allenynes can regioselectively undergo intramolecular [2+2] cycloaddition of the distal double bond of the allene moiety. This simple and environmentally benign process would extend the potential application of fused bicyclic cyclobutane derivatives in synthetic and medicinal chemistry.

Received: April 25, 2005
Published online: July 20, 2005

Keywords: allenes · bicyclic compounds · cycloaddition · nitrogen heterocycles · regioselectivity

---

[1] a) B. M. Trost, *Acc. Chem. Res.* **2002**, *35*, 695–705; see also, b) B. M. Trost, *Science* **1991**, *254*, 1471–1477.

[2] For excellent reviews, see: a) D. J. Pasto, *Tetrahedron* **1984**, *40*, 2805–2827; b) M. Murakami, T. Matsuda in *Modern Allene Chemistry*, *Vol. 2* (Eds.: N. Krause, A. S. K. Hashmi), Wiley-VCH, Weinheim, **2004**, pp. 727–815.

[3] a) S. Shin, T. V. RajanBabu, *J. Am. Chem. Soc.* **2001**, *123*, 8416–8417; b) C. H. Oh, S. H. Jung, C. Y. Rhim, *Tetrahedron Lett.* **2001**, *42*, 8669–8671; c) J. Franzén, J. Löfstedt, I. Dorange, J.-E. Bäckvall, *J. Am. Chem. Soc.* **2002**, *124*, 11246–11247; d) J. Franzén, J.-E. Bäckvall, *J. Am. Chem. Soc.* **2003**, *125*, 6056–6057; e) C. H. Oh, S. H. Jung, D. I. Park, J. H. Choi, *Tetrahedron Lett.* **2004**, *45*, 2499–2502.

[4] a) H. Ohno, K. Miyamura, Y. Takeoka, T. Tanaka, *Angew. Chem.* **2003**, *115*, 2751–2754; *Angew. Chem. Int. Ed.* **2003**, *42*, 2647–2650; b) H. Ohno, Y. Takeoka, K. Miyamura, Y. Kadoh, T. Tanaka, *Org. Lett.* **2003**, *5*, 4763–4766; c) H. Ohno, Y. Takeoka, Y. Kadoh, K. Miyamura, T. Tanaka, *J. Org. Chem.* **2004**, *69*, 4541–4544; d) H. Ohno, K. Miyamura, T. Mizutani, Y. Kadoh, Y. Takeoka, H. Hamaguchi, T. Tanaka, *Chem. Eur. J.* **2005**, *11*, 3728–3741.

[5] For some recent examples of [2+2] cycloaddition, see: a) B. M. Trost, M. Yanai, K. Hoogsteen, *J. Am. Chem. Soc.* **1993**, *115*, 5294–5295; b) F. Marion, J. Coulomn, C. Courillon, L. Fensterbank, M. Malacria, *Org. Lett.* **2004**, *6*, 1509–1511; c) K. Villeneuve, W. Tam, *Angew. Chem.* **2004**, *116*, 620–623; *Angew. Chem. Int. Ed.* **2004**, *43*, 610–613; d) R. F. Sweis, M. P. Schramm, S. A. Kozmin, *J. Am. Chem. Soc.* **2004**, *126*, 7442–7443; e) K.

Inanaga, K. Takasu, M. Ihara, *J. Am. Chem. Soc.* **2005**, *127*, 3668 – 3669; f) J. D. Winkler, E. C. McLaughlin, *Org. Lett.* **2005**, *7*, 227 – 229.

[6] For some recent examples, see: a) Y. Gu, T. Hama, G. B. Hammond, *Chem. Commun.* **2000**, 395 – 396; b) T. Akiyama, K. Daidouji, K. Fuchibe, *Org. Lett.* **2003**, *5*, 3691 – 3693; c) Y. Horino, M. Kimura, S. Tanaka, T. Okajima, Y. Tamaru, *Chem. Eur. J.* **2003**, *9*, 2419 – 2439.

[7] For recent examples, see: a) M. S. Shepard, E. M. Carreira, *J. Am. Chem. Soc.* **1997**, *119*, 2597 – 2605; b) T. Tsuno, K. Sugiyama, *Bull. Chem. Soc. Jpn.* **1999**, *72*, 519 – 531; for transition-metal-catalyzed [2+2] cycloadditions, see: c) S.-K. Kang, T.-G. Baik, A. N. Kulak, Y.-H. Ha, Y. Lim, J. Park, *J. Am. Chem. Soc.* **2000**, *122*, 11 529 – 11 530; d) M. Murakami, S. Ashida, T. Matsuda, *J. Am. Chem. Soc.* **2004**, *126*, 10 838 – 10 839.

[8] a) M. Yoshida, M. Hiromatsu, K. Kanematsu, *Heterocycles* **1986**, *24*, 881 – 884; b) M. Yoshida, Y. Hidaka, Y. Nawata, J. M. Rudziñski, E. Õsawa, K. Kanematsu, *J. Am. Chem. Soc.* **1988**, *110*, 1232 – 1238; for a related reaction of cumulenes, see: c) J. G. Garcia, B. Ramos, L. M. Pratt, A. Rodríguez, *Tetrahedron Lett.* **1995**, *36*, 7391 – 7394.

[9] a) K. Kanematsu, N. Sugimoto, M. Kawaoka, S. Yeo, M. Shiro, *Tetrahedron Lett.* **1991**, *32*, 1351 – 1354; b) A. Padwa, M. A. Filipkowski, M. Meske, S. H. Watterson, Z. Ni, *J. Am. Chem. Soc.* **1993**, *115*, 3776 – 3777; c) A. Padwa, M. Meske, S. S. Murphree, S. H. Watterson, Z. Ni, *J. Am. Chem. Soc.* **1995**, *117*, 7071 – 7080; d) A. Padwa, H. Lipka, S. H. Watterson, S. S. Murphree, *J. Org. Chem.* **2003**, *68*, 6238 – 6250.

[10] Q. Shen, G. B. Hammond, *J. Am. Chem. Soc.* **2002**, *124*, 6534 – 6535.

[11] B. Alcaide, P. Almendros, C. Aragoncillo, *Org. Lett.* **2003**, *5*, 3795 – 3798.

[12] Recently, in their study of the molybdenum-mediated allenic Pauson–Khand reaction, Cook and co-workers observed the formation of distal adducts in 30–40% yield, by heating of conformationally restricted diyne-allenes in toluene at 100 °C in the absence of any catalyst. As far as we are aware, this is the first example of thermal [2+2] cycloaddition between unactivated allenes and alkynes. See: a) H. Cao, J. Flippen-Anderson, J. M. Cook, *J. Am. Chem. Soc.* **2003**, *125*, 3230 – 3231; b) H. Cao, S. G. Van Ornum, J. Deschamps, J. Flippen-Anderson, F. Laib, J. M. Cook, *J. Am. Chem. Soc.* **2005**, *127*, 933 – 943.

[13] a) H. Ohno, A. Toda, Y. Miwa, T. Taga, E. Osawa, Y. Yamaoka, N. Fujii, T. Ibuka, *J. Org. Chem.* **1999**, *64*, 2992 – 2993; b) H. Ohno, M. Anzai, A. Toda, S. Ohishi, N. Fujii, T. Tanaka, Y. Takemoto, T. Ibuka, *J. Org. Chem.* **2001**, *66*, 4904 – 4914; c) H. Ohno, *Yakugaku Zasshi* **2001**, *121*, 733 – 741; d) H. Ohno, H. Hamaguchi, M. Ohata, T. Tanaka, *Angew. Chem.* **2003**, *115*, 1791 – 1795; *Angew. Chem. Int. Ed.* **2003**, *42*, 1749 – 1753; e) H. Ohno, H. Hamaguchi, M. Ohata, S. Kosaka, T. Tanaka, *J. Am. Chem. Soc.* **2004**, *126*, 8744 – 8754; f) H. Hamaguchi, S. Kosaka, H. Ohno, T. Tanaka, *Angew. Chem.* **2005**, *117*, 1537 – 1541; *Angew. Chem. Int. Ed.* **2005**, *44*, 1513 – 1517.

[14] For example, see: a) E. Piers, Y.-F. Lu, *J. Org. Chem.* **1989**, *54*, 2267 – 2268; b) H. Suginome, T. Takeda, M. Itoh, Y. Nakayama, K. Kobayashi, *J. Chem. Soc. Perkin Trans. 1* **1995**, 49 – 61; c) M. T. Crimmins, S. Huang, L. E. Guise-Zawacki, *Tetrahedron Lett.* **1996**, *37*, 6519 – 6522.

[15] a) J. T. Naik, P. G. Mantle, R. N. Sheppard, E. S. Waight, *J. Chem. Soc. Perkin Trans. 1* **1995**, 1121 – 1125; b) A. Carotenuto, M. R. Conte, E. Fattorusso, V. Lanzotti, S. Magno, *Tetrahedron* **1995**, *51*, 10 751 – 10 758; c) K. Kurata, K. Taniguchi, Y. Agatsuma, M. Suzuki, *Phytochemistry* **1998**, *47*, 363 – 369; d) Y. Kashiwada, K. Yamazaki, Y. Ikeshiro, T. Yamagishi, T. Fujioka, K. Mihashi, K. Mizuki, L. M. Cosentino, K. Fowke, S. L. Morris-Natschke, K.-H. Lee, *Tetrahedron* **2001**, *57*, 1559 – 1563.

[16] a) S.-H. Dai, W. R. Dolbier, Jr., *J. Am. Chem. Soc.* **1972**, *94*, 3946 – 3952; b) R. D. Froese, G. L. Lange, J. D. Goddard, *J. Org. Chem.* **1996**, *61*, 952 – 961; c) M. Schmittel, M. Maywald, M. Strittmatter, *Synlett* **1997**, 165 – 166; d) Y. Yang, J. L. Petersen, K. K. Wang, *J. Org. Chem.* **2003**, *68*, 8545 – 8549.