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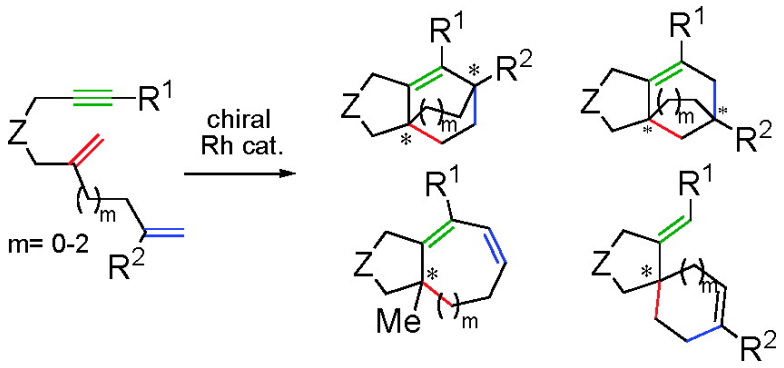

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Enantioselective Syntheses of Various Chiral Multicyclic Compounds with Quaternary Carbon Stereocenters by Catalytic Intramolecular Cycloaddition

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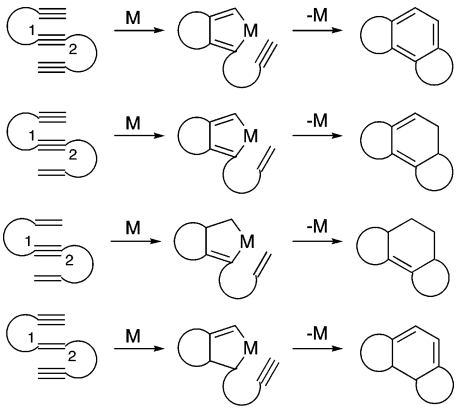
Abstract: The intramolecular cycloaddition of 1,*n*-diene-ynes ($n = 4-6$), where alkyne and alkene moieties are connected by a 1,1-disubstituted alkene, was examined using a chiral rhodium catalyst, and various types of cycloadducts with quaternary carbon stereocenter(s) were obtained in high to excellent enantiomeric excess. In the case of 1,4-diene-ynes, tricyclic, bicyclic, and spirocyclic compounds were obtained depending upon the substituents at the 2-position of the 1,4-diene moiety and those at their alkyne termini. On the other hand, 1,5- and 1,6-diene-ynes gave tricyclic and bicyclic compounds, which included medium-sized ring systems. The mechanistic considerations for different reaction pathways and the synthetic transformation of tricyclic products into functionalized spirocyclic compounds are also described. The reaction of enediynes, where two alkyne moieties are connected by a 1,1-disubstituted alkene, was also examined, and sterically strained tricyclic compounds with two carbon stereocenters were obtained.

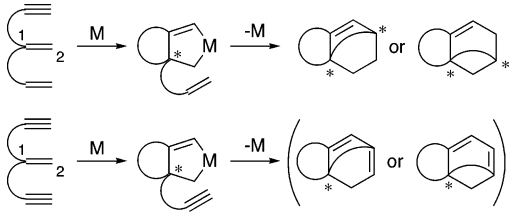
Introduction

The transition-metal-catalyzed [2 + 2 + 2] cycloaddition of C2-unsaturated motifs, such as alkynes and alkenes, is a well-established protocol for the synthesis of carbo- and heterocyclic skeletons.[1] Depending upon the reaction patterns, it can be categorized as an intermolecular, semi-intermolecular, or intramolecular reaction. The latter reaction is very attractive because it gives multicyclic compounds from acyclic substrates in one pot. The intramolecular [2 + 2 + 2] cycloadditions of triynes, where two alkyne moieties are connected by a 1,2-disubstituted alkyne, are most typical, and various transition-metal complexes have been reported to be efficient catalysts.[2] The enantioselective [2 + 2 + 2] cycloaddition of triynes has also been reported: helically chiral helicene derivatives,[3] axially chiral *ortho*-diaryl benzenes,[4] and planarly chiral metacyclophanes[5] have been obtained. The cycloaddition of enediynes and dienynes, where alkyne and alkene or two alkene moieties are connected by a 1,2-disubstituted alkyne, has also been reported.[6−8] The reaction of enediynes, where two alkyne moieties are connected by a 1,2-disubstituted alkene,[9] was reported, and enantioselective variants have recently been published.[10] Compared with these substrates, in which three C2-unsaturated motifs are in a straight chain (Scheme 1), the examples of the cycloaddition of dienynes and enediynes, where the C2-unsaturated motifs are located in a branched chain, are scarce (Scheme 2). The cycloaddition of these substrates is synthetically intriguing because bridged compounds with quaternary carbon stereocenters could be obtained.[11] When enediynes are used, the corresponding products would be further transformed into a more stable skeleton because of the severe strain of tricyclic compounds, which violates Bredt's rule.

Scheme 1. Conventional Mode of Intramolecular Cycloaddition



Scheme 2. New Mode of Intramolecular Cycloaddition



This article presents the full details of the Rh-catalyzed enantioselective and intramolecular cycloaddition of 1,*n*-diene-ynes ($n = 4-6$) and enediynes with branched chains, including

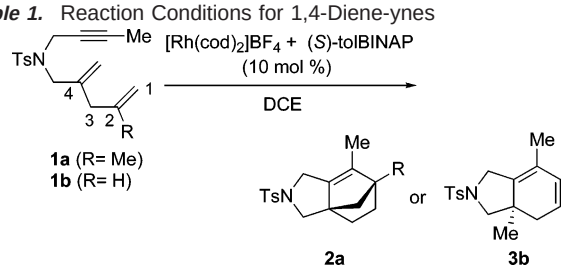
(1) Reviews: (a) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635−662. (b) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813−834. (c) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127−2198. (d) Yamamoto, Y. *Curr. Org. Chem.* **2005**, *9*, 503−519. (e) Kotha, S.; Brahmachary, E.; Lahiri, K. *Eur. J. Org. Chem.* **2005**, 4741−4767. (f) Chopade, P. R.; Louie, J. *Adv. Synth. Catal.* **2006**, *348*, 2307−2327.

mechanistic considerations and synthetic transformation of the products.[12]

Results and Discussion

Reaction of 1,4-Diene-ynes. In a previous communication,[12] we examined various 1,4-diene-ynes using a chiral Rh catalyst at 60 °C in 1,2-dichloroethane (DCE). For example, the reaction of dienyne **1a** with a substituent at the 2-position of the 1,4-diene moiety gave expected tricyclic compound **2a** with two quaternary carbon stereocenters in almost perfect enantioselectivity (Table 1, entry 1).[13] On the other hand, dienyne **1b** with no substituent at that position gave unexpected bicyclic compound **3b** with a quaternary carbon stereocenter at the ring-fused position, also with excellent enantiomeric excess (entry 2).[14] To facilitate the reaction, the same reactions were examined using 1,5-cyclooctadiene (COD)-free Rh catalyst, which was prepared from $[Rh(cod)_2]BF_4$ and (*S*)-tolBINAP, and pretreated with hydrogen gas to exclude COD before use (entries 3 and 4). Dienynes **1a** and **1b** were completely consumed at room temperature within 24 h, and comparable yield and enantioselectivity were achieved. We chose these reaction conditions for further investigation (henceforth, the catalyst, which was prepared using the procedure mentioned above, is referred to as "chiral Rh cat.").

Table 1. Reaction Conditions for 1,4-Diene-ynes

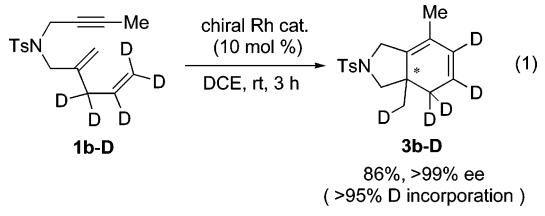


entry	R	dienyne	temp/°C	time/h	yield/%	ee/%[b]
1	Me	**1a**	60	48	81 (**2a**)	>99
2	H	**1b**	60	12	91 (**3b**)	99
3[a]	Me	**1a**	rt	24	88 (**2a**)	>99
4[a]	H	**1b**	rt	24	92 (**3b**)	>99

[a] The catalyst was used after exclusion of COD. [b] The enantiomeric excess was determined by HPLC analysis using a Daicel chiral column (OJ-H for **2a** and **3b**).

Mechanistic Study. The proposed mechanism for different products depending upon the substituents at the 1,4-diene moiety of dienynes is depicted in Scheme 3. Oxidative coupling of the metal complex to the 1,6-enyne moiety of dienyne gives metallacyclopentene **A** as a common intermediate.[15] Steric repulsion between R^2 and the bulky chiral ligand (L_n) on the metal probably controls the direction of intramolecular olefin insertion: when R^2 is not a hydrogen atom, olefin moiety inserts in a direction where R^2 is distant from the metal center to give metallacycle **B**, and subsequent reductive elimination gives tricyclic compound **2**. On the other hand, when R^2 is a hydrogen atom, the olefin inserts in another direction to give metallacycle **C**. Subsequent β-hydrogen elimination and reductive elimination give bicyclic compound **3** with a methyl group at the ring-fusion carbon atom.

To elucidate the mechanism mentioned above, we examined the cycloaddition of deuterated 1,4-diene-yne **1b-D** under the same reaction conditions (eq 1): bicyclic product **3b-D**, which has two deuterated vinylic protons and a monodeuterated methyl group, was obtained, and almost perfect incorporation of the deuteriums was ascertained. These results strongly support the notion that this mechanism includes β-hydrogen elimination and completely exclude the possibility that it includes the intramolecular [4 + 2] cycloaddition of 1,3-diene-yne along with carbon−carbon double bond isomerizations.[16]



(2) Rh: (a) Grigg, R.; Scott, R.; Stevenson, P. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1357−1364. (b) Ojima, I.; Vu, A. T.; McCullagh, J. V.; Kinoshita, A. *J. Am. Chem. Soc.* **1999**, *121*, 3230−3231. (c) Witulski, B.; Alayrac, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3281−3284. (d) Kinoshita, H.; Shinokubo, H.; Oshima, K. *J. Am. Chem. Soc.* **2003**, *125*, 7784−7785. Ni: (e) Bhatarah, P.; Smith, E. H. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2163−2168. Pd: (f) Negishi, E.; Harring, L. S.; Owczarczyk, Z.; Mohamud, M. M.; Ay, M. *Tetrahedron Lett.* **1992**, *33*, 3253−3256. (g) Yamamoto, Y.; Nagata, A.; Arikawa, Y.; Tatsumi, K.; Itoh, K. *Organometallics* **2000**, *19*, 2403−2405. (h) Yamamoto, Y.; Nagata, A.; Nagata, H.; Ando, Y.; Arikawa, Y.; Tatsumi, K.; Itoh, K. *Chem.−Eur. J.* **2003**, *9*, 2469−2483. (i) Pla-Quintana, A.; Roglans, A.; Torrent, A. *Organometallics* **2004**, *23*, 2762−2767. Ru: (j) Peters, J.-U.; Blechert, S. *Chem. Commun.* **1997**, 1983−1984. (k) Hoven, G. B.; Efskind, J.; Rømming, C.; Undheim, K. *J. Org. Chem.* **2002**, *67*, 2459−2463. (l) Yamamoto, Y.; Arakawa, T.; Ogawa, R.; Itoh, K. *J. Am. Chem. Soc.* **2003**, *125*, 12143−12160. Co: (m) Stará, I. G.; Starý, I.; Kollárovič, A.; Teplý, F.; Šaman, D.; Tichý, M. *J. Org. Chem.* **1998**, *63*, 4046−4050. (n) Son, S. U.; Paik, S.-J.; Lee, S. I.; Chung, Y. K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 141−143. (o) Sugihara, T.; Wakabayashi, A.; Nagai, Y.; Takao, H.; Imagawa, H.; Nishizawa, M. *Chem. Commun.* **2002**, 576−577. (p) Teplý, F.; Stará, I. G.; Starý, I.; Kollárovič, A.; Šaman, D.; Vyskočil, Š.; Fiedler, P. *J. Org. Chem.* **2003**, *68*, 5193−5197. Mo: (q) Nishida, M.; Shiga, H.; Mori, M. *J. Org. Chem.* **1998**, *63*, 8606−8608. Fe: (r) Saino, N.; Kogure, D.; Okamoto, S. *Org. Lett.* **2005**, *7*, 3065−3067. (s) Saino, N.; Kogure, D.; Kase, K.; Okamoto, S. *J. Organomet. Chem.* **2006**, *691*, 3129−3136.

(3) Stará, I. G.; Starý, I.; Kollárovič, A.; Teplý, F.; Vyskočil, Š.; Šaman, D. *Tetrahedron Lett.* **1999**, *40*, 1993−1996.

(4) Shibata, T.; Tsuchikama, K.; Otsuka, M. *Tetrahedron: Asymmetry* **2006**, *17*, 614−619.

(5) Tanaka, K.; Sagae, H.; Toyoda, K.; Noguchi, K.; Hirano, M. *J. Am. Chem. Soc.* **2007**, *129*, 1522−1523.

(6) Carbonylative carbocyclization of enediynes was already reported: (a) Ojima, I.; Lee, S.-Y. *J. Am. Chem. Soc.* **2000**, *122*, 2385−2386. (b) Bennacer, B.; Fujiwara, M.; Lee, S.-Y.; Ojima, I. *J. Am. Chem. Soc.* **2005**, *127*, 17756−17767.

(7) (a) Montgomery, J.; Seo, J. *Tetrahedron* **1998**, *54*, 1131−1144. (b) Slowinski, F.; Aubert, C.; Malacria, M. *Tetrahedron Lett.* **1999**, *40*, 5849−5852. (c) Slowinski, F.; Aubert, C.; Malacria, M. *Adv. Synth. Catal.* **2001**, *343*, 64−67. (d) Slowinski, F.; Aubert, C.; Malacria, M. *J. Org. Chem.* **2003**, *68*, 378−386.

(8) Tanaka, D.; Sato, Y.; Mori, M. *J. Am. Chem. Soc.* **2007**, *129*, 7730−7731.

(9) Yamamoto, Y.; Kuwabara, S.; Ando, Y.; Nagata, H.; Nishiyama, H.; Itoh, K. *J. Org. Chem.* **2004**, *69*, 6697−6705.

(10) (a) Shibata, T.; Kurokawa, H.; Kanda, K. *J. Org. Chem.* **2007**, *72*, 6521−6525. (b) Tanaka, K.; Nishida, G.; Sagae, H.; Hirano, M. *Synlett* **2007**, 1426−1430.

(11) *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis;* Christoffers, J., Baro, A., Eds.; Wiley-VCH: Weinheim, Germany, 2005.

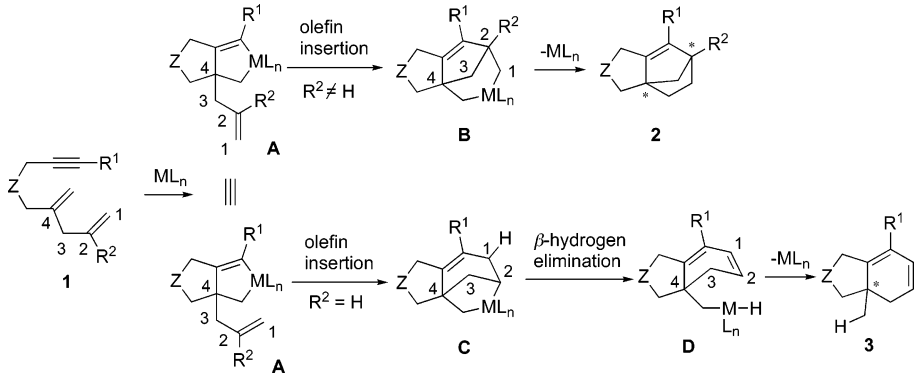
(12) A preliminary communication: Shibata, T.; Tahara, Y. *J. Am. Chem. Soc.* **2006**, *128*, 11766−11767.

(13) The absolute configuration of phenyl-substituted tricyclic compound **2** (R = Ph) was already determined by X-ray measurements (ref 12). That of **2a** (R = Me) could be speculatively assigned because the first metallacycle formation step, where chirality is generated, is common (**A** in Scheme 3).

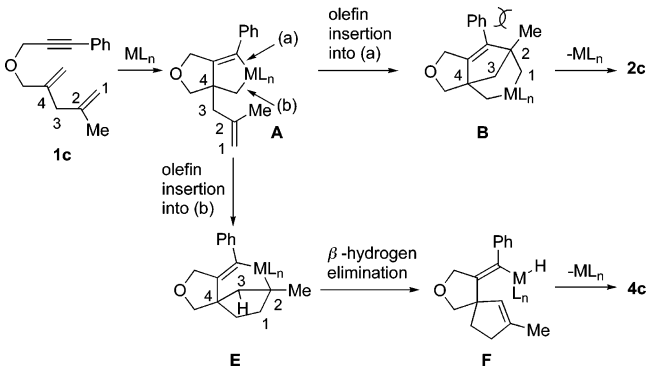
(14) Compound **3b** was already obtained in enantioselective [2 + 2 + 2] cycloaddition of 1,6-enyne and acetylene (ref 14a), and its absolute configuration was speculatively assigned by the comparison of that of a related compound in a related reaction (ref 14b): (a) Shibata, T.; Arai, Y.; Tahara, Y. *Org. Lett.* **2005**, *7*, 4955−4957. (b) Evans, P. A.; Lai, K. W.; Sawyer, J. R. *J. Am. Chem. Soc.* **2005**, *127*, 12466−12467.

(15) Bicyclic metallacyclopentene is a common intermediate to the present reaction and intramolecular Pauson−Khand-type reaction of enynes. Actually, the absolute configuration of the asymmetric carbon atom at the ring-fusion carbon atom is the same when Rh-(*S*)-BINAP derivative catalysts were used: (a) Jeong, N.; Sung, B. K.; Choi, Y. K. *J. Am. Chem. Soc.* **2000**, *122*, 6771−6772. (b) Shibata, T.; Toshida, N.; Takagi, K. *J. Org. Chem.* **2002**, *68*, 7446−7450.

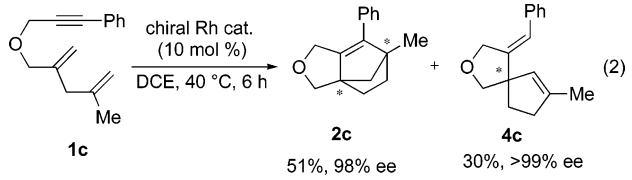
Scheme 3. Proposed Mechanism for the Different Pathways Dependent upon the Substituents



Scheme 4. Proposed Mechanism for the Construction of a Spirocyclic System



Synthesis of Chiral Spirocyclic Compounds. In the screening of various 1,4-diene-ynes, with oxygen-tethered dienyne **1c**, which has a phenyl group at its alkyne terminus, unexpected spirocyclic compound **4c** was obtained as a minor product, albeit with excellent enantiomeric excess, along with tricyclic product **2c** (eq 2).



A proposed reaction mechanism for the formation of a spirocyclic system is shown in Scheme 4: when an intramolecular olefin insertion occurs between the metal center and sp^2 carbon atom (a), tricyclic compound **2c** is obtained via tricyclic intermediate **B**. In contrast, when such an insertion occurs between the metal center and sp^3 carbon atom (b), tricyclic metallacycle **E** would be obtained, and subsequent β-hydrogen elimination and reductive elimination would give spirocyclic compound **4c**. In general, insertion into the metal center-sp^2 carbon atom proceeds more readily than that into a metal center-sp^3 carbon atom;[17] however, steric repulsion between phenyl and methyl groups could induce the latter in the present reaction.

On the basis of the proposed mechanism described above, we hypothesized that the introduction of bulkier substituents to the alkyne terminus could realize the selective formation of spirocyclic compounds and examined the cycloaddition of 1,4-diene-ynes **1d**−**f** with 4-, 3-, and 2-substituted phenyl groups, respectively (Table 2).[18] In the case of dienyne **1d** with a 4-methylphenyl group, the results were almost the same as those with **1c** (entry 1). When dienyne **1e** with a 3-methylphenyl group was used, the formation of spirocyclic compound drastically decreased (entry 2). In contrast, dienyne **1f** with a 2-methylphenyl group gave spirocyclic compound **4f** as the sole detectable product, albeit in low yield (entry 3).

We further examined several 1,4-diene-ynes with an ortho-substituted aryl group at their alkyne termini (Table 3).[18] When a 2-biphenyl group was introduced, spirocyclic compound **4g** was selectively formed in good yield (entry 1). 1-Naphthyl and 9-phenanthryl groups also gave good results, and the corresponding spirocyclic compounds **4h** and **4i** were obtained in excellent enantiomeric excess (entries 2 and 3). Dienyne **1j** with a phenyl group at the olefinic moiety was also a good substrate (entry 4).[19] Nitrogen-tethered dienyne **1k** was also transformed into the corresponding product **4k** in acceptable yield (entry 5).

Cycloaddition of 1,5-Diene-ynes. We next examined 1,5-diene-yne in place of 1,4-diene-yne. Initially, 1,5-diene-ynes with no substituent at the 2-position of 1,5-diene moiety were used under the same reaction conditions (Table 4).[18] From nitrogen-tethered 1,5-diene-yne **5a**, achiral tricyclic product **6a** and chiral bicyclic product **7a** with excellent enantiomeric excess were obtained (entry 1). 1,5-Diene-yne **5b** with no substituent at the alkyne terminus also gave a mixture of achiral compound **6b** and chiral bicyclic product **7b**, which has a 5,7-fused ring system (entry 2). In the case of 1,5-diene-yne **5c** with a phenyl group at its alkyne terminus, achiral tricyclic compound was obtained almost exclusively (entry 3). Carbon- and oxygen-tethered 1,5-diene-ynes **5d** and **5e** were also transformed into two products, and the enantiomeric excess of bicyclic compounds **7d** and **7e** exceeded 99% (entries 4 and 5).

Next, we examined the cycloaddition of 1,5-diene-ynes, which possess a methyl group at the 2-position of the 1,5-diene moiety (Table 5). Both nitrogen- and oxygen-tethered dienynes gave

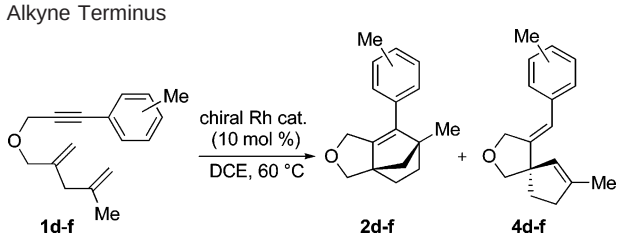
(16) Enantioselective intramolecular [4 + 2] cycloaddition of 1,3-diene-ynes: (a) O'Mahony, D. J. R.; Belanger, D. B.; Livinghouse, T. *Synlett* **1998**, 443−445. (b) Gilbertson, S. R.; Hoge, G. S.; Genov, D. G. *J. Org. Chem.* **1998**, *63*, 10077−10080. (c) Shibata, T.; Takasaku, K.; Takesue, Y.; Hirata, N.; Takagi, K. *Synlett* **2002**, 1681−1682.

(17) Shibata, T.; Koga, Y.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 911−919.

(18) The absolute configuration of the chiral multicyclic products could be speculatively assigned because they were probably formed via the common metallacyclopentene intermediate (**A**).

(19) The substituent at the 2-position of 1,4-diene moiety is apparently important for the induction of the steric repulsion; 1,4-diene-yne with no substituent gave no spirocyclic compound. See ref 12.

Table 2. Effect of Substituents at the Alkyne Terminus

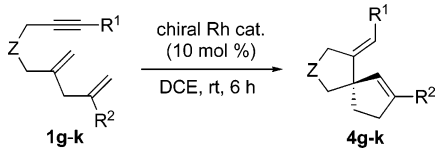


1d-f 2d-f 4d-f

entry	Me	dienyne	time/h	yield of **2**/%	ee of **2**/%[a]	yield of **4**/%	ee of **4**/%[a]
1	4-	**1d**	24	51 (**2d**)	98	29 (**4d**)	97
2	3-	**1e**	3	60 (**2e**)	93	<5 (**4e**)	
3	2-	**1f**	24	<2 (**2f**)		38 (**4f**)	92

[a] The enantiomeric excess was determined by HPLC analysis using a Daicel chiral column (AD-H for **2d** and **2e**, OJ-H for **4d**, and OD-H for **4f**).

Table 3. Enantioselective Synthesis of Spirocyclic Compounds



1g-k 4g-k

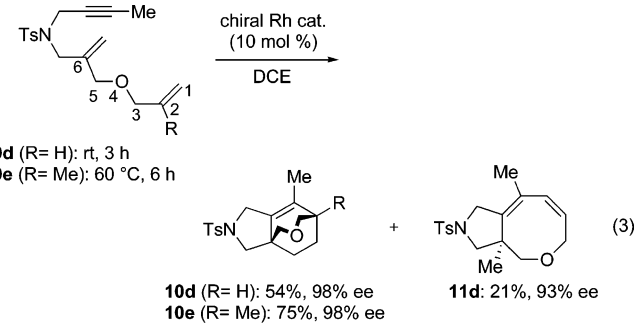
entry	Z	R^1	R^2	dienyne	yield/%	ee/%[b]
1	O	2-PhC_6H_4	Me	**1g**	80 (**4g**)	96
2	O	1-naphthyl	Me	**1h**	82 (**4h**)	97
3	O	9-phenanthryl	Me	**1i**	72 (**4i**)	99
4	O	1-naphthyl	Ph	**1j**	78 (**4j**)	93
5[a]	NTs	1-naphthyl	Me	**1k**	44 (**4k**)	92

[a] The reaction was examined at 60 °C. [b] The enantiomeric excess was determined by HPLC analysis using a Daicel chiral column (OD-H for **4g**, OJ-H for **4h**, IA for **4i** and **4j**, and AD-H for **4k**).

tricyclic compounds, which were achiral (entries 1−3). In contrast to the case of 1,4-diene-ynes with a substituent at the diene moiety (Table 3), the reaction of oxygen-tethered dienynes **5g** and **5h** with phenyl and naphthyl groups, respectively, gave no spirocyclic compounds (entries 2 and 3).

We further examined the reaction of 1,5-diene-ynes with aryl groups at the 2-position of the 1,5-diene moiety (Table 6).[18] When dienyne **5i** with a phenyl group was submitted to the same reaction conditions, chiral tricyclic compound **8i** was obtained with excellent enantiomeric excess as a minor product along with achiral tricyclic compound **6i** (entry 1). 2-Methylphenyl group changed the formation ratio of two products: chiral tricyclic compound **8j** was given as a major product (entry 2). In the case of bulkier 2-biphenyl group, nitrogen- and oxygen-tethered dienynes predominantly provided chiral tricyclic compounds with excellent enantiomeric excess (entries 3 and 4).

Cycloaddition of 1,6-Diene-ynes. To investigate the effect of the length of the carbon chain between two alkene moieties on the ratio of the cycloadducts, we further examined 1,6-diene-ynes (Table 7).[18] Nitrogen-tethered 1,6-diene-yne **9a** was completely consumed under the same reaction conditions as those mentioned above to afford tricyclic compound **10a** predominantly with excellent enantiomeric excess, and only a trace amount of bicyclic compound **11a** with a 5,8-fused ring system could be detected (entry 1). In the case of 1,6-diene-yne **9b** and oxygen-tethered 1,6-diene-yne **9c** with a phenyl group at their alkyne termini, tricyclic compounds **10b** and **10c** with two carbon stereocenters were predominant products, and bicyclic products **11b** and **11c** were nonisolable minor products (entries 2 and 3).



9d (R= H): rt, 3 h
9e (R= Me): 60 °C, 6 h

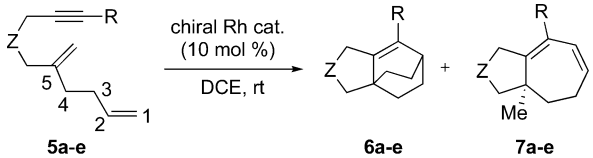
10d (R= H): 54%, 98% ee
10e (R= Me): 75%, 98% ee

11d: 21%, 93% ee

(3)

In contrast, when an oxygen atom was introduced into the carbon chain between two alkene moieties, bicyclic compound

Table 4. Cycloaddition of 1,5-Diene-ynes with No Substituent at the 2-Position of 1,5-Diene Moiety

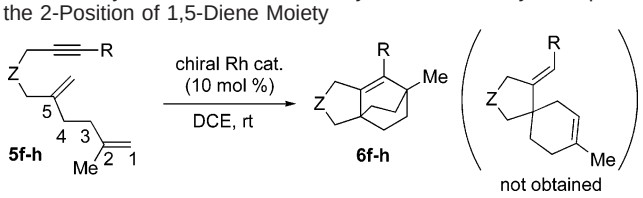


5a-e 6a-e 7a-e

entry	Z	R	dienyne	time/h	total yield/%	**6**/**7**	ee of **7**/%[b]
1	NTs	Me	**5a**	12	>99 (**6a** + **7a**)	2:1	>99
2	NTs	H	**5b**	2	89 (**6b** + **7b**)	1:1	99
3	NTs	Ph	**5c**	24	95 (**6c**)	>20:1[a]	
4	$C(CO_2Bn)_2$	H	**5d**	48	89 (**6d** + **7d**)	1:1[a]	>99
5	O	Me	**5e**	3	61 (**6e** + **7e**)	2:1[a]	>99

[a] The ratio of **6**/**7** was determined by ^1H NMR. [b] The enantiomeric excess was determined by HPLC analysis using a Daicel chiral column (AD-H for **7a**, **7b**, **7d**, and **7e**).

Table 5. Cycloaddition of 1,5-Diene-ynes with a Methyl Group at the 2-Position of 1,5-Diene Moiety



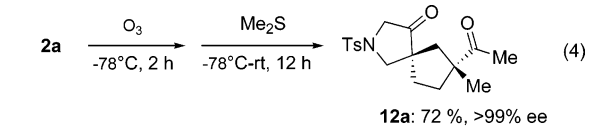
entry	Z	R	dienyne	time/h	yield/%
1	NTs	Me	**5f**	3	88 (**6f**)
2	O	Ph	**5g**	3	82 (**6g**)
3[a]	O	1-naphthyl	**5h**	24	47 (**6h**)

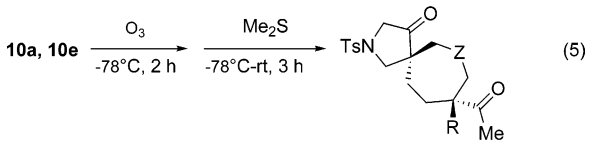
[a] The reaction was examined at 60 °C, but dienyne **5h** was not completely consumed.

11d with a 5,8-fused ring system was obtained (eq 3). Also in this case, a substituent at the 2-position of the diene moiety suppressed the formation of bicyclic compound **11e**, and chiral tricyclic compound **10e** was the sole detectable product.

Consideration of the Reaction Mechanism of 1,5- and 1,6-Diene-ynes. The proposed reaction mechanism of 1,5- and 1,6-diene-ynes is shown in Scheme 5. Bicyclic products **7** and **11** are certainly derived from metallacycle **C′**, which is formed by olefin insertion between the metal center and sp^2 carbon atom (a) in metallacyclopentene **A′**. In contrast, two mechanisms should be considered as the reaction pathway to the formation of tricyclic products **6** and **10**. The pathway via metallacycle **B′** is more reasonable; however, the formation of tricyclic product **6h** from oxygen-tethered dienyne **5h** with a bulky aryl group at its alkyne terminus should be derived from metallacycle **E′** because spirocyclic products were formed from oxygen-tethered 1,4-diene-ynes with a naphthyl group via metallacycle **E** (Scheme 4). The different ring systems could cause different arrangement of the metal center and the β-hydrogen, and thus the spirocyclic compound would not be obtained from **E′** in the case of 1,5- and 1,6-diene-ynes. When R^2 is a bulky group, olefin moiety inserts in another direction because of the steric repulsion between R^2 and the ligand (L_n), and chiral compounds **8** with different tricyclic skeleton are obtained.

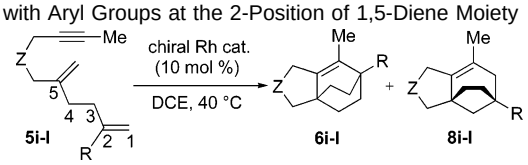
Synthetic Application of Tricyclic Compounds. Some of the obtained tricyclic products were subjected to oxidative cleavage of the carbon−carbon double bond using ozonolysis along with reductive treatment: tricyclic compound **2a** was readily transformed into 2-azaspiro[4.4]nonane **12a** with two quaternary stereocenters (eq 4).[20] Also, from tricyclic compounds **10a** and **10e**, which have a seven-membered ring and/or an oxygen atom among the ring atoms, the corresponding spirocyclic compounds **13a** and **13e** were obtained, respectively (eq 5).[21]





A chiral spirocyclic structure is found in many natural products and biologically active compounds,[22] and its rigid framework acts as an effective chiral ligand.[23] While various

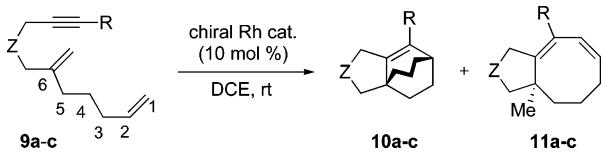
Table 6. Cycloaddition of 1,5-Diene-ynes with Aryl Groups at the 2-Position of 1,5-Diene Moiety



entry	Z	R	dienyne	time/h	total yield/%	**6**/**8**[a]	ee of **8**/%[b]
1	NTs	Ph	**5i**	0.5	95 (**6i** + **8i**)	1.5:1	>99
2	NTs	2-MeC_6H_4	**5j**	1	98 (**6j** + **8j**)	1:2	99
3	NTs	2-PhC_6H_4	**5k**	2	78 (**6k** + **8k**)	1:13	99
4	O	2-PhC_6H_4	**5l**	2	75 (**6l** + **8l**)	1:13	99

[a] The ratio of **6**/**8** was determined by ^{1}H NMR. [b] The enantiomeric excess was determined by HPLC analysis using a Daicel chiral column (IB for **8i**, OD-H for **8j**, and AD-H for **8k** and **8l**).

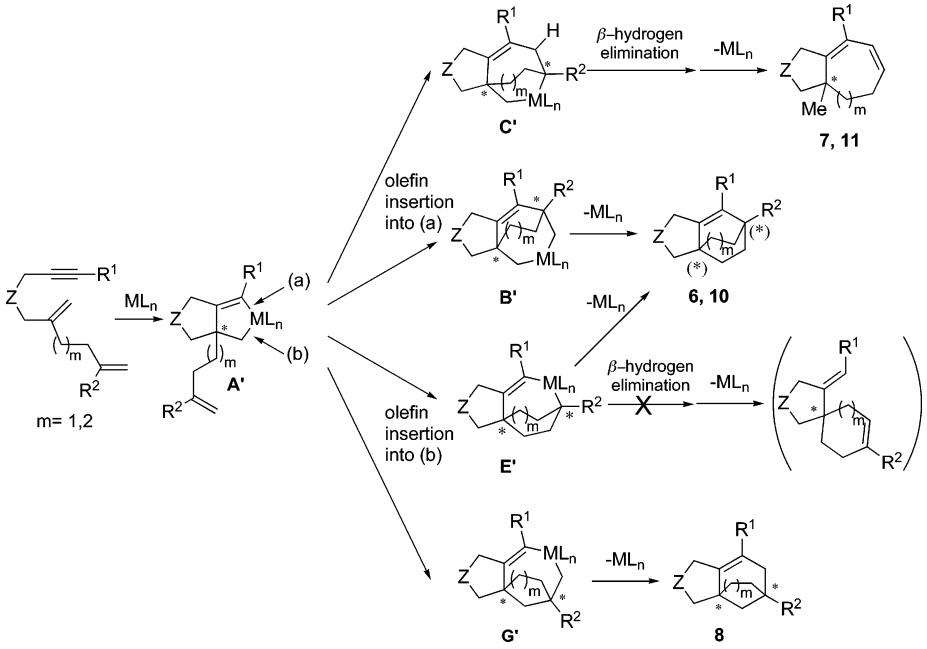
Table 7. Cycloaddition of 1,6-Diene-ynes



entry	Z	R	dienyne	time/h	total yield/%	**10**/**11**[a]	ee of **10**/%[b]
1	NTs	Me	**9a**	24	93 (**10a** + **11a**)	13:1	>99
2	NTs	Ph	**9b**	24	91 (**10b** + **11b**)	14:1	95
3	O	Ph	**9c**	3	63 (**10c** + **11c**)	>20:1	89

[a] The ratio of **10**/**11** was determined by ^{1}H NMR. [b] The enantiomeric excess was determined by HPLC analysis using a Daicel chiral column (OJ-H for **10a**, and AD-H for **10b** and **10c**).

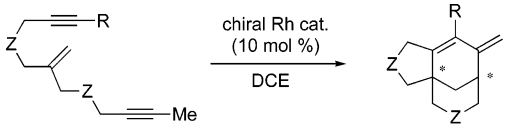
Scheme 5. Possible Explanation for the Cycloaddition of 1,*n*-Diene-ynes ($n = 5, 6$)



methods for the synthesis of chiral spirocyclic compounds have been reported, there are a few transition-metal-catalyzed enantioselective approaches. Overman and co-workers reported a pioneering work on the enantioselective intramolecular Mizoroki−Heck reaction using a chiral Pd catalyst.[24] This was followed by Zr-catalyzed diene cyclization[25] and tandem olefin metathesis.[26] Mikami and co-workers reported a highly enantioselective method using the intramolecular ene-type cyclization of enynes.[27] On the other hand, we recently disclosed an enantioselective [2 + 2 + 2] cycloaddition of diynes and alkenes for the synthesis of spirocyclic compounds.[28] Therefore, the above protocol provides a new cycloaddition-based approach for the generation of a spirocyclic system.

Cycloaddition of Enediynes. Finally, we examined the cycloaddition of enediynes, where two alkyne moieties are connected by a 1,1-disubstituted alkene tether (Table 8). When oxygen-tethered symmetrical enediyne **14a** with methyl groups at its alkyne termini was subjected to the reaction using the same Rh catalyst, tricyclic compound **15a** with two chiral carbon atoms and an *exo*-methylene moiety were obtained in good yield

Table 8. Enantioselective Intramolecular Cycloaddition of Enediynes



entry	Z	R	enediyne	temp/°C	time/h	yield/%	ee/%[b]
1	O	Me	**14a**	rt	6	78 (**15a**)	99
2	NTs	Me	**14b**	60	6	87 (**15b**)	93
3[a]	NTs	H	**14c**	40	24	74 (**15c**)	88

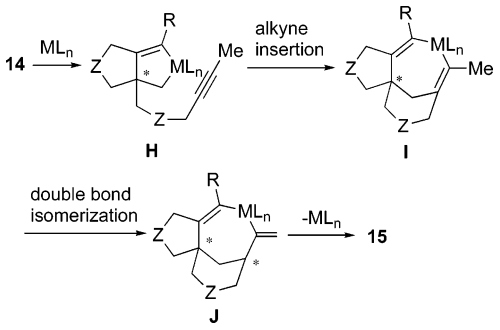
[a] The volume of solvent is ten times as much as that in other entries. [b] The enantiomeric excess was determined by HPLC analysis using a Daicel chiral column (OD-H for **15a**, and IA for **15b** and **15c**).

and excellent enantiomeric excess (entry 1). Nitrogen-tethered symmetrical enediyne **14b** was also transformed into the corresponding tricyclic diene **15b** at an elevated reaction temperature (entry 2). Under the same conditions, however, the reaction of nitrogen-tethered unsymmetrical enediyne **14c**, which has substituted and unsubstituted alkyne termini, gave a complex mixture. Under diluted conditions, which would prevent the intermolecular reaction of the unsubstituted alkyne terminus, tricyclic product **15c** was isolated in good yield (entry 3).

A proposed mechanism for the cycloaddition of enediynes **14** is shown in Scheme 6. In a manner similar to the reaction of dienynes, oxidative coupling of the metal complex to 1,6-enyne moieties gave metallacyclopentene **H** with a chiral center at the ring-fusion carbon atom. Then, the alkyne moiety inserted into the bond between the metal center and the sp^3 carbon atom, probably because insertion into the metal-sp^2 carbon bond is highly strained because of the linearity of the alkyne moiety. The resulting tricyclic intermediate **I** has a carbon−carbon double bond at the bridgehead position and would undergo double-bond isomerization to release the severe strain. At this

(20) The stereospecific transformation was ascertained by the enantiomeric excess of **12a**, and its absolute configuration was speculatively determined by that of chiral tricyclic compound **2a**.
(21) The transformation without racemization was ascertained by NMR analyses of **13a** and **13e**, where only single diastereomers were detected, and their absolute configurations were speculatively determined by that of chiral tricyclic compounds **10a** and **10e**.
(22) A recent review of spirocyclic compounds in nature and the synthesis of spirocyclic structure: Pradhan, R.; Patra, M.; Behera, A. K.; Mishra, B. K.; Behera, R. K. *Tetrahedron* **2006**, *62*, 779−828 and references therein.
(23) (a) Kato, T.; Marubayashi, K.; Takizawa, S.; Sasai, H. *Tetrahedron: Asymmetry* **2004**, *15*, 3693−3697 and references therein. (b) Xie, J.-H.; Zhu, S.-F.; Fu, Y.; Hu, A.-G.; Zhou, Q.-L. *Pure Appl. Chem.* **2005**, *77*, 2121−2132. (c) Guo, Z.; Guan, X.; Chen, Z. *Tetrahedron: Asymmetry* **2006**, *17*, 468−473.
(24) (a) Ashimori, A.; Overman, L. E. *J. Org. Chem.* **1992**, *57*, 4571−4572. (b) Ashimori, A.; Bachand, B.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6477−6487.
(25) Yamaura, Y.; Hyakutake, M.; Mori, M. *J. Am. Chem. Soc.* **1997**, *119*, 7615−7616.
(26) Teng, X.; Cefalo, D. R.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 10779−10784.
(27) (a) Hatano, M.; Mikami, K. *J. Am. Chem. Soc.* **2003**, *125*, 4704−4705. (b) Mikami, K.; Yusa, Y.; Hatano, M.; Wakabayashi, K.; Aikawa, K. *Chem. Commun.* **2004**, 98−99.
(28) Tsuchikama, K.; Kuwata, Y.; Shibata, T. *J. Am. Chem. Soc.* **2006**, *128*, 13686−13687.

Scheme 6. Proposed Mechanism for the Generation of the *exo*-Methylene Moiety



step, the second carbon stereocenter was generated (**J**), and subsequent reductive elimination gave tricyclic compound **15** with an *exo*-methylene moiety.

Conclusions

We have comprehensively studied the Rh-catalyzed enantioselective intramolecular cycloaddition of diene-ynes and enediynes, where alkyne and alkene or two alkyne moieties are connected by a 1,1-disubstituted alkene tether. In the case of 1,*n*-diene-ynes ($n = 4-6$), the choice of the substituent at the 2-position of the 1,*n*-diene moiety and that at the alkyne terminus determined the direction and position of intramolecular alkene insertion into the bicyclic metallacyclopentene intermediate, and three types of multicyclic compounds were obtained: (1) sterically strained tricyclic compounds, which include bicyclo[2.2.1]heptene, bicyclo[2.2.2]octene, bicyclo[3.2.1]octane, and bicyclo[3.2.2]nonene skeletons, (2) bicyclic compounds with a methyl group at the ring-fusion carbon atom, and (3) spirocyclic compounds. In the case of enediynes with two 1,6-enyne moieties, tricyclo[6.3.1.$0^{1,8}$]dodecenes with two stereocenters at the ring-fusion carbon atoms were obtained. All of these products had quaternary carbon stereocenter(s), and their enantiomeric excess was high to excellent. Therefore, the present protocol provides a new family of chiral multicyclic compounds with quaternary carbon stereocenter(s). Further transformations of the functionalized spirocyclic compounds into synthetically useful intermediates are under investigation.

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Supporting Information Available: Spectral data for all new compounds and CIF file of **6a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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