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Enantioselective Intramolecular [2 + 2 + 2] Cycloaddition of 1,4-Diene-ynes: A New Approach to the Construction of Quaternary Carbon Stereocenters

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Transition-metal-catalyzed cycloaddition is an atom-economical and powerful tool for the synthesis of cyclic carbon skeletons.[1] Various cycloadditions, including more than two alkyne and/or alkene moieties as reaction components, have been reported using transition metal catalysts.[2] In particular, [2 + 2 + 2] cycloaddition is a general protocol for the synthesis of six-membered ring systems,[3] and intramolecular [2 + 2 + 2] cycloaddition gives a tricyclic compound in one pot. The starting material can be classified into three types (Scheme 1): (1) the two reaction components (i.e., alkyne(s) and/or alkene(s)) are connected by a 1,2-disubstituted alkyne and triynes are most commonly used;[4−6] (2) the two reaction components are connected by a 1,2-disubstituted alkene;[7] (3) the two synthetic units are connected by a 1,1-disubstituted alkene. Cycloaddition of the last substrate, a dienyne,[8] is very attractive because it can give strained bridged compounds, which possess two asymmetric carbon centers, including a quaternary carbon stereocenter, at the bridgehead position. Tricyclic compound **A** or **B** would be obtained depending on the direction of olefin insertion. However, to the best of our knowledge, this type of [2 + 2 + 2] cycloaddition has never been reported.

We report here an intramolecular [2 + 2 + 2] cycloaddition of 1,4-diene-ynes for the synthesis of strained bridged compounds. Tricyclic compounds, including a bicyclo[2.2.1]heptene skeleton with two quaternary carbon stereocenters, are enantiomerically obtained by a chiral Rh catalyst. Depending on the substituent on the 1,4-diene moiety, chiral bicyclic cyclohexa-1,3-dienes with a quaternary carbon stereocenter are products.

We chose nitrogen-bridged 1,4-diene-yne **1a** as a model substrate and subjected it to cationic Rh-catalyzed cycloaddition (Table 1).[9] After we screened ligands, BINAP derivatives were found to efficiently activate the Rh complex for the present reaction:[10] 1,4-diene-yne **1a** was completely consumed and tricyclic compound **2a** with two quaternary carbon stereocenters (type **A** in Scheme 1) was the sole detectable product with a very high enantiomeric excess (entry 1). Among BINAP derivatives, tolBINAP was the best chiral ligand, and the minor enantiomer could not be detected by HPLC analysis using a chiral column (entry 2).[11]

Several 1,4-diene-ynes were examined using a Rh−tolBINAP catalyst (Table 2). Butyl-substituted 1,4-diene-yne **1b** required higher reaction temperature, but gave high enantioselectivity (entry 1). A functional group on the alkyne terminus was tolerable (entry 2). 1,4-Diene-ynes with no substituent on the alkyne terminus were also good substrates (entries 3 and 4). In particular, with 1,4-diene-yne **1e**, which has a phenyl group at the 2-position of the 1,4-diene moiety (R^2 = Ph), cycloadduct **2e** with a phenyl group at the quaternary carbon stereocenter was obtained (entry 4), and its structure and absolute configuration were determined by X-ray measurements (Figure 1). Carbon- and oxygen-bridged 1,4-diene-ynes **1f**,**g** were also transformed into the corresponding chiral tricyclic compounds **2f**,**g** with two quaternary carbon stereocenters (entries 5 and 6).

Scheme 1. Types of Substrates for the Intramolecular [2 + 2 + 2] Cycloaddition

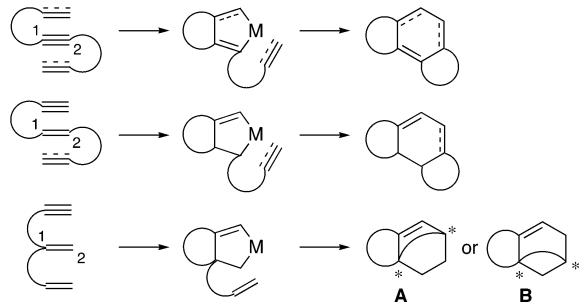
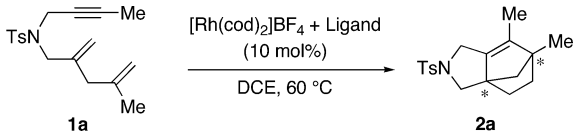
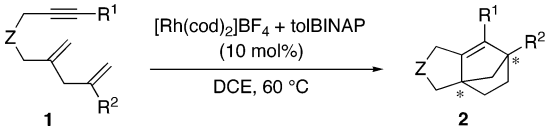


Table 1. Screening of Chiral Ligands



entry	ligand	time/h	yield/%	ee/%
1	(*S*)-BINAP	48	69	97
2	(*S*)-tolBINAP	48	81	>99
3	(*S*)-xylylBINAP	48	82	99
4	(*S*)-H_8-BINAP	36	71	95
5	(*S*)-SEGPHOS	36	69	97

Table 2. Enantioselective [2 + 2 + 2] Cycloaddition for the Construction of Bicyclo[2.2.1]heptene Skeleton



entry	R^1	R^2	Z	dienyne	time/h	yield/%	ee/%
1[a]	Bu	Me	NTs	**1b**	48	46 (**2b**)	>99
2	$BnOCH_2$	Me	NTs	**1c**	48	83 (**2c**)	88
3	H	Me	NTs	**1d**	6	83 (**2d**)	93
4	H	Ph	NTs	**1e**	6	72 (**2e**)	91
5	H	Me	$C(CO_2Bn)_2$	**1f**	48	76 (**2f**)	93
6	Ph	Me	O	**1g**	24	40 (**2g**)	92

[a] The reaction was examined at 80 °C.

We further examined the cycloaddition of 1,4-diene-yne **1h**, which does not have a substituent at the 2-position of the 1,4-diene moiety, under the same reaction conditions. Unexpectedly, bicyclic cyclohexa-1,3-diene **3h** was exclusively obtained with almost perfect enantioselectivity (Table 3, entry 1). When 1,4-diene-yne **1i**, which does not have a substituent on the alkyne terminus, was used, the enantioselectivity exceeded 99% (entry 2). Carbon- and oxygen-bridged 1,4-diene-ynes **1j**−**l** were also suitable substrates (entries 3−5). In all cases, the corresponding bicyclic cyclohexa-

10.1021/ja0639160 CCC: $33.50

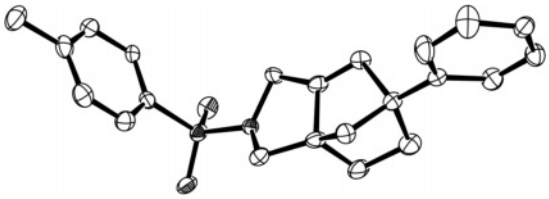
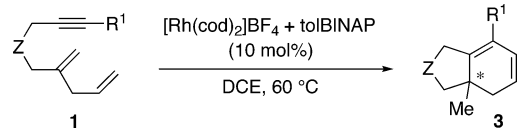


Figure 1. ORTEP diagram of cycloadduct **2e**.

Table 3. Enantioselective [2 + 2 + 2] Cycloaddition for the Synthesis of Bicyclic Cyclohexa-1,3-dienes



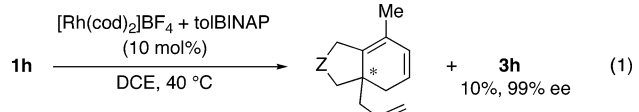
entry	R^1	Z	dienyne	time/h	yield/%	ee/%
1	Me	NTs	**1h**	12	91 (**3h**)	99
2[a]	H	NTs	**1i**	12	79 (**3i**)	>99
3	H	$C(CO_2Bn)_2$	**1j**	6	80 (**3j**)	90
4	Ph	O	**1k**	48	55 (**3k**)	92
5	$Ph(CH_2)_3$	O	**1l**	6	64 (**3l**)	94

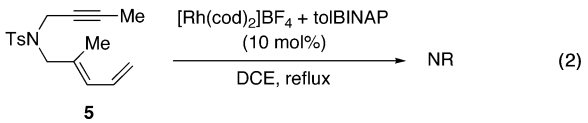
[a] The reaction was examined at 40 °C.

1,3-dienes were obtained with high enantiomeric excess, and tricyclic compounds **2** could not be detected.

The proposed mechanism for the present cycloaddition is shown in Scheme 2. Oxidative coupling of the metal complex to alkyne and alkene moieties of 1,4-diene-yne **1** gives metallacyclopentene **C**, and the intramolecular olefin insertion follows. When R^2 is not hydrogen, tricyclic compound **2** is obtained by reductive elimination from **D**. In contrast, when R^2 is hydrogen, a 1,3-hydrogen shift accompanied by ring cleavage would proceed to provide metallacycloheptadiene **E**, and subsequent reductive elimination gives bicyclic cyclohexa-1,3-diene **3**.[12]

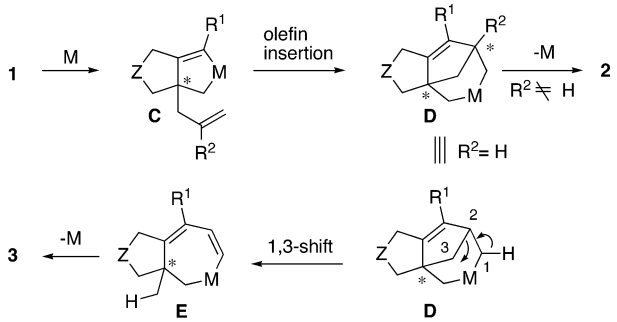
When the reaction of **1h** was examined under acetylene atmosphere, intermolecular [2 + 2 + 2] cycloaddition of enyne and acetylene proceeded to give cyclohexa-1,3-diene **4h** with high enantiomeric excess along with the formation of **3h** (eq 1).[13] The reaction of 1,3-diene-yne **5** did not proceed even under reflux conditions (eq 2). These results suggest that bicyclic cyclohexa-1,3-diene **3** would be formed via metallacyclopentene **C** and is not an intramolecular [4 + 2] cycloadduct of the conjugated 1,3-diene-yne, which could be obtained by double bond isomerization of 1,4-diene-yne **1**.





In conclusion, we have developed an enantioselective intramolecular [2 + 2 + 2] cycloaddition of 1,4-diene-ynes, which provides a new approach to the construction of strained multicyclic compounds with quaternary carbon stereocenters.[14] Therefore, the present protocol is a new synthetic use of [2 + 2 + 2] cycloaddition in asymmetric synthesis, and further applications are under investigation.

Scheme 2. Proposed Mechanism of Formation of **2** and **3**



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Supporting Information Available: Experimental details and spectral data for 1,4-diene-ynes and products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) On the basis of Bredt's rule, [2 + 2 + 2] cycloaddition of yne-ene-yne would be impossible.
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(10) When triphenylphosphine, 1,3-bis(diphenylphosphino)propane, or (*S,S*)-CHIRAPHOS was used as a ligand, almost no reaction proceeded, and cycloadduct **2a** could not be detected under the same reaction conditions.
(11) An opposite enantiomer of cycloadduct **2a** was surely obtained with almost the same yield and enantioselectivity using (*R*)-tolBINAP.
(12) In the course of the reaction of **1h**, the ee was not changed (2 h: 29%, 99% ee; 4 h: 43%, 99% ee; 8h: 79%, 99% ee), and the double bond isomerization of cycloadduct **3h** could not be observed under the same reaction conditions. These results imply that high ee of **3h** is derived from the cycloaddition of **1h**, not from the double bond isomerization of **3h** as a secondary reaction.
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