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Highly Enantioselective Construction of a Chiral Spirocyclic Structure by the [2 + 2 + 2] Cycloaddition of Diynes and *exo*-Methylene Cyclic Compounds

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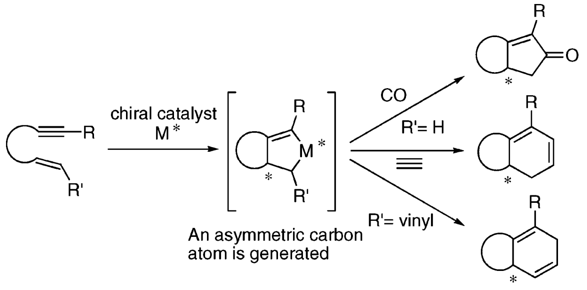
Enantioselective cycloaddition using a chiral transition metal catalyst is a well-established strategy for the synthesis of chiral compounds possessing various cyclic structures. In particular, the cycloaddition of enynes has been comprehensively studied: an oxidative coupling gives a bicyclic metallacyclopentene, in which an asymmetric carbon atom is generated. The following insertion and reductive elimination provides a cyclic compound with a chiral center at the ring-fused carbon. Pauson-Khand-type reaction ([2 + 2 + 1] cycloaddition),[1] [2 + 2 + 2] cycloaddition of an enyne and alkyne,[2] and intramolecular [4 + 2] cycloaddition of a dienyne[3] are the selected examples (Scheme 1).[4,5]

We here propose a new approach for asymmetric induction using a [2 + 2 + 2] cycloaddition of a diyne and an alkene (Scheme 2): an oxidative coupling gives a bicyclic metallacyclopentadiene, in which no asymmetric carbon atom is generated.[6] The following insertion of a 1,1-disubstituted alkene along with reductive elimination induces a chiral quaternary carbon atom on the ring. The [2 + 2 + 2] cycloaddition of diynes and monosubstituted or 1,2-disubstituted alkenes is already reported.[7] However, neither the reaction using 1,1-disubstituted alkenes nor the enantioselective reaction was reported.

We chose an *exo*-methylene cyclic compound as an alkene component because the [2 + 2 + 2] cycloaddition gives a chiral spirocyclic compound, which could never have been obtained by the conventional enantioselective cycloadditions (Scheme 1). We examined a Rh-catalyzed reaction of carbon-tethered symmetric diyne **1a** and α-methylene-γ-butyrolactone (**2a**) under the various reaction conditions (Table 1); when the Rh-BINAP catalyst was used at 60 °C in 1,2-dichloroethane (DCE), diyne **1a** was completely consumed within 3 h, and the desired bicyclic cyclohexa-1,3-diene **3aa**, possessing a spirocyclic system, was obtained in very high enantiomeric excess. However, the yield was moderate because of the formation of a self-coupling cycloadduct of diyne **1a** (entry 1). Dropwise addition of diyne **1a** to a mixture of the chiral catalyst and lactone **2a** at 80 °C over 30 min significantly improved the yield (entry 2). Under the present reaction conditions, several BINAP derivatives were examined as chiral ligands (entries 3−6). As a result, xylylBINAP was the best choice, and almost perfect enantioselectivity was achieved (entry 4). It is also noteworthy that only 3 equiv of alkene **2a** was sufficient to achieve a high yield in the present diyne−alkene coupling.[8]

Scheme 1. Conventional Enantioselective Cycloadditions via a Metallacyclopentene with a Chiral Carbon Stereocenter



Scheme 2. A New Enantioselective Cycloaddition via a Metallacyclopentadiene without a Chiral Carbon Stereocenter

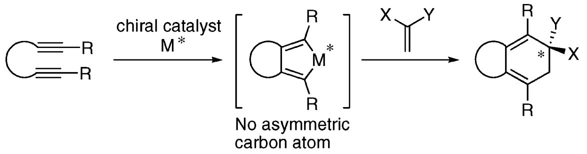
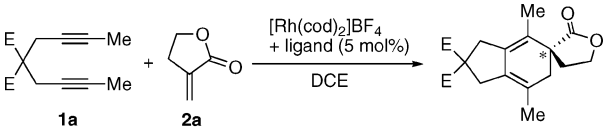


Table 1. Screening of Various Reaction Conditions



1a E = CO$_2$Bn

2a (3 equiv)

3aa

entry	ligand	temp (°C)	time (min)	yield (%)	ee (%)
1	(*S*)-BINAP	60	180	42	97
2	(*S*)-BINAP	80	30[a]	55	96
3	(*S*)-tolBINAP	80	30[a]	62	96
4	(*S*)-xylylBINAP	80	30[a]	84	99
5	(*S*)-H$_8$-BINAP	80	30[a]	64	97
6	(*S*)-SEGPHOS	80	30[a]	49	92

[a] Diyne **1a** was added dropwise over 30 min.

We further examined a preliminarily isolated chiral rhodium complex, [Rh(cod){(*S*)-xylyl-binap}]BF$_4$, and the yield exceeded 90% (Table 2, entry 1). Under the optimal reaction conditions, various symmetric diynes and *exo*-methylene cyclic compounds were subjected to the present enantioselective [2 + 2 + 2] cycloaddition. Lactones **2b**,**c** with six- and seven-membered ring systems also underwent cycloaddition, and the corresponding spirocyclic compounds **3ab** and **3ac** were obtained in excellent enantiomeric excesses (entries 2 and 3). *exo*-Methylene cyclic ketones **2d**,**e** were more reactive, and the reaction proceeded at lower temperature; however, the enantioselectivity decreased (entries 4 and 5). Unsubstituted diyne **1b** was also an appropriate substrate; high yield and enantiomeric excess were achieved without double bond isomerization of the 1,3-diene moiety (entry 6). The reaction of nitrogen- and oxygen-tethered diynes **1c**,**d** and lactones **2a**,**b** also gave spirocyclic compounds with high to excellent enantiomeric excess, but excess amounts of alkenes were needed because heteroatom-tethered diynes are more reactive than carbon-tethered diynes and susceptible to self-coupling (entries 7−9). Cycloadduct **3cb** was determined to be an (*R*)-isomer by X-ray measurements (Figure 1).

Next, we examined the [2 + 2 + 2] cycloaddition of unsymmetric diyne **1e**, which possesses methyl and phenyl groups on its alkyne

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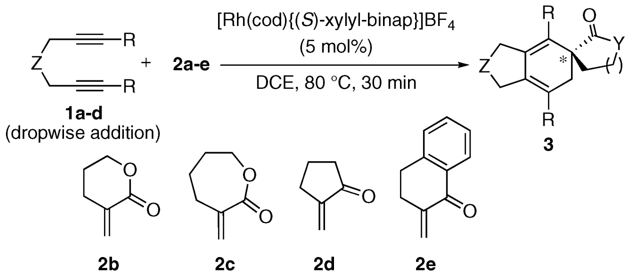
Table 2. Cycloaddition of Various Diynes and *exo*-Methylene Cyclic Compounds



entry	Z	R	diyne	alkene[a]	yield (%)	ee (%)
1	$C(CO_2Bn)_2$	Me	**1a**	**2a**	94 (**3aa**)	99
2	$C(CO_2Bn)_2$	Me	**1a**	**2b**	93 (**3ab**)	98
3	$C(CO_2Bn)_2$	Me	**1a**	**2c**	88 (**3ac**)	97
4[b,c]	$C(CO_2Bn)_2$	Me	**1a**	**2d**	62 (**3ad**)	81
5[b,c]	$C(CO_2Bn)_2$	Me	**1a**	**2e**	72 (**3ae**)	80
6[d]	$C(CO_2Bn)_2$	H	**1b**	**2a**	81 (**3ba**)	95
7	NTs	Me	**1c**	**2a**[e]	92 (**3ca**)	97
8	NTs	Me	**1c**	**2b**[e]	89 (**3cb**)	99
9[b]	O	Et	**1d**	**2a**[f]	50 (**3da**)	92

[a] 3 equiv. [b] At 60 °C. [c] The reaction mixture was stirred for further 2.5 h. [d] At 40 °C. [e] 10 equiv. [f] 20 equiv.

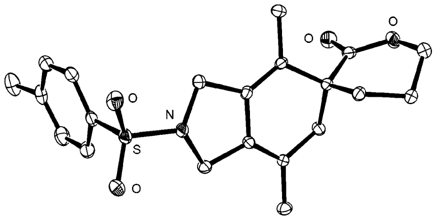
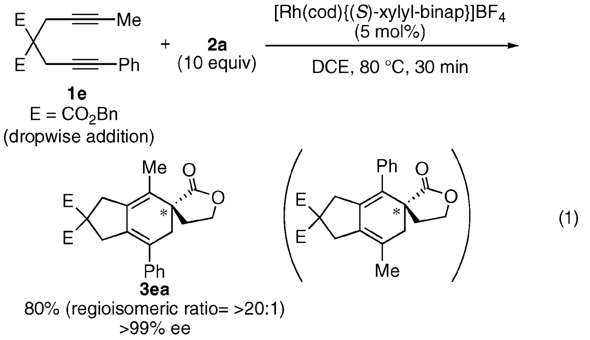


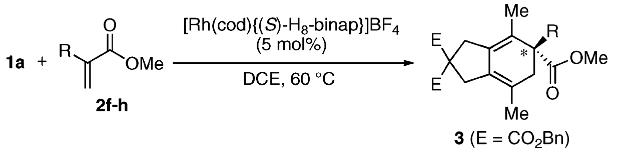
Figure 1. Crystal structure of (*R*)-**3cb**.

termini, with lactone **2a** (eq 1). The regioselectivity of the alkene and enantioselectivity were almost perfect, and cycloadduct **3ea** was the sole isolated spirocyclic compound.



In addition to *exo*-methylene cyclic compounds, *exo*-methylene acyclic compounds were also good coupling partners, and H_8-BINAP was found to be a better chiral ligand (Table 3); the cycloaddition of diyne **1a** with methyl methacrylate (**2f**) gave cycloadduct **3af** in almost perfect enantioselectivity (entry 1). The reaction of methyl 2-phenylacrylate (**2g**) required excess amounts and higher temperature, but a quaternary carbon stereocenter with a phenyl group was generated (entry 2). It is noteworthy that methyl acrylate (**2h**) also gave cycloadduct **3ah**, which is a highly enolizable ester, with high enantiomeric excess.

Table 3. Cycloaddition of Acrylates as Alkenes



entry	R	alkene	equiv	yield (%)	ee (%)
1	Me	**2f**	3	92 (**3af**)	>99
2[a]	Ph	**2g**	10	54 (**3ag**)	93
3	H	**2h**	3	87 (**3ah**)	91

[a] Diyne was added dropwise at 80 °C.

In conclusion, we have developed a Rh-catalyzed highly enantioselective [2 + 2 + 2] cycloaddition of diynes and alkenes. The use of *exo*-methylene cyclic compounds as alkenes realized a new protocol for the catalytic synthesis of a chiral spirocyclic structure.[9] The present enantioselective [2 + 2 + 2] cycloaddition provides access to a new chiral library possessing a quaternary carbon stereocenter, including a spirocyclic system.

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

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