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Rh-Catalyzed Enantioselective [2 + 2] Cycloaddition of Alkynyl Esters and Norbornene Derivatives

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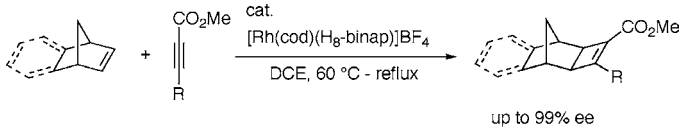
ABSTRACT



The enantioselective [2 + 2] cycloaddition of alkynes possessing an ester functionality and norbornene derivatives proceeded efficiently using a chiral rhodium catalyst. The chiral tri- and tetracyclic cyclobutenes were obtained in moderate to high ee.

Transition-metal-catalyzed cycloaddition of unsaturated motifs, such as alkynes, alkenes, etc., which is represented by [*m* + *n*] or [*l* + *m* + *n*] cycloaddition, is an atom-economical and reliable protocol for the synthesis of carbo- and heterocyclic skeletons.[1] Various types of cycloadditions have been reported for the construction of complex multicyclic compounds.[2] The advantage of transition-metal-catalyzed cycloaddition is that it can be readily applied as an asymmetric version because direct coordination of the reaction site to the chiral transition-metal complex gives high enantioselectivity. Our group has also described highly enantioselective [2 + 2 + 1] and [2 + 2 + 2] cycloadditions using chiral Ir and Rh complexes as catalysts.[3]

We report here the Rh-catalyzed enantioselective [2 + 2] cycloaddition of alkynyl esters and norbornene derivatives for the synthesis of chiral cyclobutenes.[4] There are a few examples of the transition-metal-catalyzed [2 + 2] cycloaddition of alkynes and alkenes, compared with other types of cycloadditions: ever since a pioneering work on the Ru-catalyzed [2 + 2] cycloaddition of alkynes with ester functionalities and norbornene derivatives,[5] only Pd-,[6] Ni-,[7] and Co-catalyzed[8] reactions have been described.[9] Recently, Ru-catalyzed [2 + 2] cycloaddition of various alkynes has been studied comprehensively,[10] including a diastereoselec-

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(4) To the best of our knowledge, there has been no example of Rh-catalyzed [2 + 2] cycloaddition of an alkyne and an alkene for the construction of cyclobutene skeleton; however, Rh-catalyzed dimerization of norbornene, which is [2 + 2] cycloaddition of alkenes, was reported: Mrowca, J. J.; Katz, T. J. *J. Am. Chem. Soc.* **1966**, *88*, 4012.

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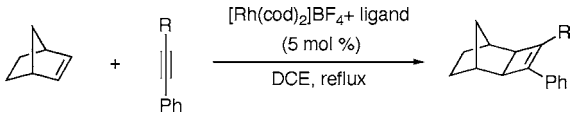
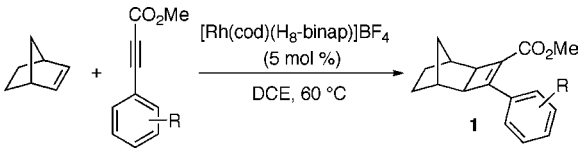
Table 1. Screening of Various Reaction Conditions



entry[a]	R	ligand[b]	time/h	yield/%	ee/%
1	CO_2Me	BINAP	9	93	66
2	CO_2Me	tolBINAP	9	87[c]	65
3	CO_2Me	xylylBINAP	6	quant	51
4	CO_2Me	H_8-BINAP	9	quant	73
5	CO_2Me	SEGPHOS	9	ca. 30[c]	67
6	CO_2Bn	H_8-BINAP	4	82	48
7	CO_2-*t*-Bu	H_8-BINAP	9	61[c]	32
8	C(O)Me	H_8-BINAP	12	94	14
9	CH_2OMe	H_8-BINAP	60	59[c]	26

[a] Alkyne/norbornene is 1/5. [b] *S*-Isomers were used as chiral ligands. [c] Alkynes were not completely consumed.

Table 2. [2 + 2] Cycloaddition of Various Arylpropiolates



entry[a]	R	time/h	yield/%	ee/%
1	H	24	85 (**1a**)	80
2[b]	4-OMe	6	98 (**1b**)	90
3	3-OMe	18	96 (**1c**)	78
4	2-OMe	72	quant (**1d**)	55
5	4-Me	24	97 (**1e**)	86
6[b]	3-Me	4	92 (**1f**)	82
7[b]	4-Br	24	91 (**1g**)	74
8	4-CO_2Et	24	83 (**1h**)	58
9	2,3-benzo	96	54 (**1i**)	63

[a] Alkyne/norbornene is 1/5. [b] The amount of catalyst is 10 mol %.

tive [2 + 2] cycloaddition using chiral alkynes.[11] However, to the best of our knowledge, there has been no example of a catalytic and enantioselective [2 + 2] cycloaddition for the synthesis of chiral cyclobutenes, except for only two examples of the chiral Lewis acid catalyzed [2 + 2] cycloadditions of alkynyl sulfides and electron-deficient alkenes.[12]

During our study of enantioselective transition-metal-catalyzed cycloadditions using alkynes as unsaturated motifs, we considered that active Rh complexes could be used to realize [2 + 2] cycloaddition: for comparison with previous examples, we chose the reaction of an alkynyl ester and norbornene and examined various rhodium complexes. As a result, cationic Rh complexes with phosphine ligands were found to be efficient catalysts[13] (Table 1): in the presence of chiral Rh catalyst, which was prepared in situ from [Rh(cod)$_2$]BF_4 and BINAP, the [2 + 2] coupling of methyl 3-phenylpropiolate with norbornene proceeded in refluxed 1,2-dichloroethane (DCE), and a chiral cyclobutene **1a** was obtained in high yield with moderate ee[14] (entry 1). Among the chiral diphosphine ligands of BINAP derivatives that we examined, H_8-BINAP was the best choice (entries 1−5).[15] In the case of benzyl and *tert*-butyl esters, the enantioselectivity apparently decreased (entries 6 and 7). Moreover, the reaction of alkynyl ketone proceeded to give a cycloadduct in high yield, but the ee was very poor. (entry 8). On the contrary, the reaction of propargyl ether sluggishly proceeded; however, the ee was slightly improved (entry 9). These results suggest that the electron-deficient moiety on an alkyne terminus is important to promote the [2 + 2] cycloaddition and that etheric oxygen atom plays a pivotal role in asymmetric induction in the present Rh-catalyzed enantioselective [2 + 2] cycloaddition.

Next, the chiral catalyst [Rh(cod)(H_8-binap)]BF_4 was isolated and subjected to the enantioselective [2 + 2] cycloaddition of methyl 3-phenylpropiolate and norbornene: cyclobutene **1a** was obtained at 60 °C with a higher ee of 80% (Table 2, entry 1).[16] Under the present reaction conditions, various methyl 3-arylpropiolates were examined as a coupling partner for norbornene. A 4-methoxyphenyl substituent on an alkyne terminus realized further higher enantioselectivity, and the corresponding cyclobutene **1b** was obtained almost quantitatively with 90% ee using 10 mol % catalyst (entry 2). The reactions of 3-methoxyphenyl- and 2-methoxyphenyl-substituted alkynes also proceeded to give cycloadducts in excellent yield; however, the ee was not sufficiently high (entries 3 and 4). An electron-donating group at the para position apparently induced better enantioselectivity, and the coupling of methyl 3-(4-methylphenyl)-propiolate gave cycloadduct **1e** in higher ee (entry 5). Methyl 3-(3-methylphenyl)propiolate also gave cycloadduct **1f** in good ee (entry 6). Electron-withdrawing groups, such as bromo and ethoxycarbonyl groups, could be tolerated as a substituent on the benzene ring, and chiral cyclobutenes **1g**, **h** were obtained in good to high yield with moderate ee (entries 7, 8). The reaction of alkynyl naphthalene was very

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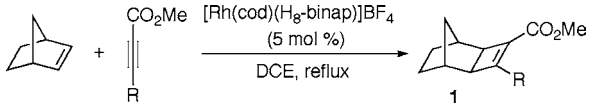
(13) Cationic rhodium complexes are efficient catalysts for various types of cycloadditions: Robinson, J. E. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, 2005; Chapter 12, p 241.

(14) The obtained ester **1a** was reduced to the corresponding alcohol, whose absolute configuration was determined by the comparison of the sign of the optical rotation (ref 11b), because it was derived from a chiral amide with a chiral auxiliary, whose absolute configuration was determined by the X-ray analysis; see: Lough, A. J.; Villeneuve, K.; Tam, W. *Acta Crystallogr.* **2004**, *E60*, o1566.

(15) BDPP (ca. 10%, 13% ee) and MeDUPHOS (ca. 5%, 4% ee) were inappropriate chiral ligands for the present reaction.

(16) **Typical Experimental Procedure.** Under an atmosphere of argon, [Rh(cod)((*S*)-H_8-binap)]BF_4 (9.3 mg, 0.010 mmol) was stirred in degassed 1,2-dichloroethane (0.4 mL) at room temperature to give a yellow solution. Then methyl 3-phenylpropiolate (32.0 mg, 0.20 mmol) and norbornene (94.2 mg, 1.00 mmol) in 1,2-dichloroethane (1.6 mL) were added to the solution, and the reaction mixture was stirred at 60 °C for 24 h. The solvent was removed under reduced pressure, and the crude products were purified by thin-layer chromatography (EtOAc/hexane = 1:20) to give pure cycloadduct **1a** (43.1 mg, 85%). The ee was determined to be 80% by HPLC analysis using a chiral column.

Table 3. [2 + 2] Cycloaddition of Alkyl-Substituted Propiolates



entry[a]	R	time/h	yield/%	ee/%
1	Me	1	55 (**1j**)	99
2[b]	Me	1	64 (**1j**)	93
3[b]	Bu	2	87 (**1k**)	73

[a] Alkyne/norbornene is 1/2. [b] The quadruple volume of solvent (8 mL) was used (see ref 16).

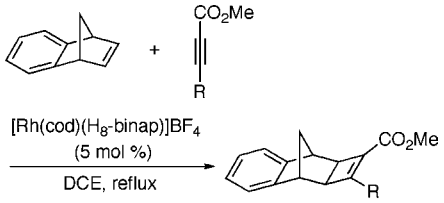
slow, but the corresponding cycloadduct **1i** was obtained in moderate ee (entry 9).

We further examined alkyl-substituted propiolates as a coupling partner for norbornene (Table 3). The [2 + 2] cycloaddition of methyl but-2-ynoate proceeded under reflux conditions using Rh−H_8-BINAP catalyst to give cyclobutene **1j** with almost perfect enantioselectivity (entry 1). The [2 + 2 + 2] cycloadducts of two but-2-ynoates and norbornene, including three regioisomers, were obtained as byproducts. The diluted conditions improved the yield; however, a slight decrease in ee was observed (entry 2). Methyl hept-2-ynoate was also a substrate, and cycloadduct **1k** was obtained in higher yield with acceptable ee (entry 3).

The reaction of benzonorbornadiene required a higher temperature (Table 4). As in the case of norbornene, 3-(4-methoxyphenyl)propiolate achieved higher enantioselectivity than 3-phenylpropiolate (entries 1 and 2). In the reaction of but-2-ynoate, the enantioselectivity exceeded 90% (entry 3).

In conclusion, we developed the Rh-catalyzed [2 + 2] cycloaddition of alkynyl esters and norbornene derivatives,

Table 4. [2 + 2] Cycloaddition of Benzonorbornadiene



entry[a]	R	time/h	yield/%	ee/%
1	C_6H_5	10	92 (**2a**)	79
2[b]	4-$MeOC_6H_4$	5	95 (**2b**)	87
3	Me	2	68 (**2j**)	94

[a] Alkyne/benzonorbornadiene is 1/2. [b] The amount of catalyst is 10 mol %.

and various tri- and tetracyclic cyclobutenes were obtained in good to excellent yield. The chiral Rh−H_8-BINAP catalyst realized moderate to high enantioselectivity. This present reaction provides a new and facile protocol for the construction of chiral cyclobutenes.

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Supporting Information Available: Spectral data for cycloadducts. This material is available free of charge via the Internet at http://pubs.acs.org.

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