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Enantioselective Construction of Quaternary Carbon Centers by Catalytic [2 + 2 + 2] Cycloaddition of 1,6-Enynes and Alkynes

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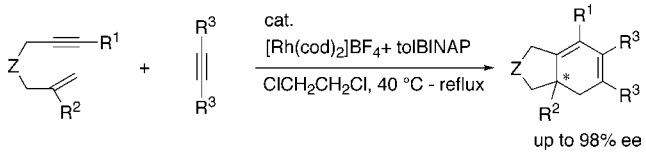
ABSTRACT



The enantioselective [2 + 2 + 2] cycloaddition of 1,6-enynes and alkynes using chiral rhodium catalysts gave cycloadducts containing quaternary carbon stereocenters. Both symmetrical and unsymmetrical alkynes and acetylene could be used as coupling partners, and the corresponding bicyclic cyclohexa-1,3-dienes were obtained in good to excellent ee.

The catalytic and enantioselective construction of various stereocenters is of great importance in organic synthesis.[1] The synthesis of compounds that contain asymmetric quaternary carbon centers is particularly valuable because they are found in many naturally occurring compounds. Indeed, various approaches have been reported as efficient protocols,[2] including the enantioselective aldol, alkylation, Diels−Alder, and Heck reactions. Nonetheless, the development of a new strategy for the synthesis of asymmetric quaternary carbon centers is still an intriguing topic.[3]

We report here an enantioselective [2 + 2 + 2] cycloaddition of 1,6-enynes and alkynes as a new approach for the synthesis of chiral compounds possessing a quaternary carbon stereocenter. Transition-metal-catalyzed [2 + 2 + 2] cycloaddition of unsaturated motifs is a reliable and atom-economical protocol for the construction of six-membered ring systems.[4] The synthesis of cyclohexa-1,3-dienes by the [2 + 2 + 2] cycloaddition of two alkynes and an alkene is also a well-known procedure.[5] However, to the best of our knowledge there is no reported example in which it has been

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(2) Reviews: (a) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388. (b) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591. (c) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105. (d) Shibasaki, M.; Vogl, E. M.; Ohshima, T. *Adv. Synth. Catal*. **2004**, *346*, 1533. (e) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363.

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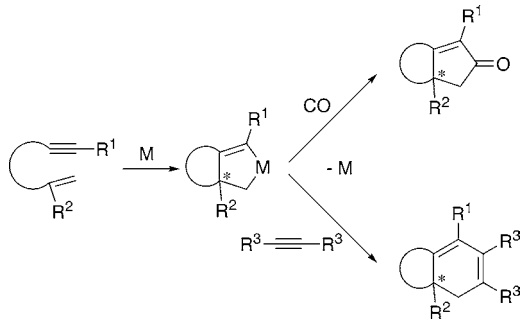
used for the enantioselective synthesis of an asymmetric quaternary carbon.[6,7]

We have studied the enantioselective carbonylative coupling of an alkyne and alkene, i.e., a Pauson−Khand-type reaction, using chiral Ir or Rh complexes.[8] The asymmetric carbon center would be generated by the oxidative coupling of enynes, and this is followed by carbonyl insertion and reductive elimination of the metal catalyst (Scheme 1). We

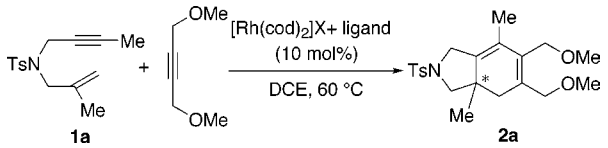
Scheme 1



considered that the enantioselective coupling of an enyne with 1,1-disubstituted olefin as an alkene moiety along with alkyne insertion could provide a chiral bicyclic 1,3-diene with a quaternary carbon stereocenter.

We chose nitrogen-bridged enyne **1a** and 1,4-dimethoxybut-2-yne as a model enyne and alkyne, respectively, and examined the enantioselective [2 + 2 + 2] cycloaddition under various reaction conditions using chiral rhodium and iridium complexes with BINAP as a chiral ligand. The coupling proceeded smoothly and enantioselectively with a cationic rhodium complex in hot 1,2-dichloroethane (DCE) (Table 1, entry 1).[9] The counteranion of the metal catalyst slightly affected both the yield and ee, and BF_4 gave the best results (entries 1−3). Chiral diphosphines possessing a binaphthyl scaffold generally gave good results,[10,11] and we further examined this reaction using tolBINAP, which resulted in the best yield and ee (entries 4−7). While it took a longer reaction time, 1.5 equiv of alkyne also gave a good yield and high ee (entry 8).

Table 1. Screening of Various Reaction Conditions



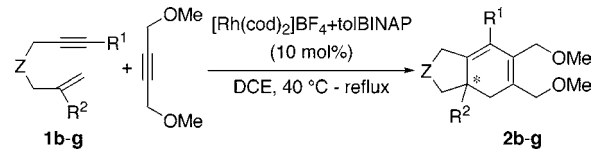
1a 2a

entry[a]	X	ligand[b]	time/h	yield/%	ee/%
1	BF_4	BINAP	9	77	93
2	SbF_6	BINAP	12	71	87
3	OTf	BINAP	12	62	89
4	BF_4	tolBINAP	12	81	97
5	BF_4	xylylBINAP	24	36	91
6	BF_4	H_8-BINAP	6	83	95
7	BF_4	SEGPHOS[c]	6	72	94
8[d]	BF_4	tolBINAP	24	80	96

[a] Enyne **1a**/alkyne is 1/2 if otherwise noted. [b] *S*-Isomers were used as a chiral ligand. [c] (4,4′-Bi-1,3-benzodioxole)-5,5′-diylbis(diphenylphosphine). [d] Enyne **1a**/alkyne is 1/1.5.

Various enynes were subjected to the enantioselective [2 + 2 + 2] cycloaddition (Table 2).[12] The reaction of enyne

Table 2. Cycloaddition of Various Enynes and an Alkyne



1b-g 2b-g

entry[a]	Z	R^1	R^2	*T*/°C	time/h	yield/%	ee/%
1[b]	NTs	Ph	Me	reflux	4	96 (**2b**)	88
2[b]	NTs	Me	Ph	reflux	24	61 (**2c**)	89
3	NTs	H	Me	40	13	41 (**2d**)	97
4	NTs	H	Me	40	15	72 (**2d**)	98
5	NTs	H	Ph	40	30	44 (**2e**)	95
6	NTs	H	Ph	80	2	52 (**2e**)	92
7	$C(CO_2Me)_2$	H	Me	40	12	60 (**2f**)	92
8	O	H	Me	40	5	38 (**2g**)	92
9[c]	O	H	Me	80	1	65 (**2g**)	97

[a] Enyne/alkyne is 1/2 for entries 1−3. Enyne/alkyne is 1/10 for entries 4−9. [b] The volume of solvent is half as much as that in other entries (ref 12). [c] Enyne was added dropwise over 1 h.

1b, which has a phenyl group on its alkyne terminus, proceeded sluggishly, and a higher reaction temperature and concentration were needed to consume enyne **1b** completely; a high yield and ee were achieved (entry 1). A phenyl group on the alkene moiety could also be tolerated and enyne **1c** was transformed into bicyclic diene **2c** in high ee (entry 2). Enyne **1d**, which has no substituent on its alkyne terminus, was a good substrate, and a higher ee of 97% was achieved. However, it was too reactive and the yield of the cross-

(6) Cobalt-mediated asymmetric [2 + 2 + 2] cycloaddition for the synthesis of chiral cyclohexa-1,3-dienes using chiral auxiliaries or chiral alkynes: (a) Halterman, R.; Vollhardt, K. P. C. *Organometallics* **1988**, *7*, 883. (b) Slowinski, F.; Aubert, C.; Malacria, M. *Tetrahedron Lett.* **1999**, *40*, 5849.

(7) A pioneering work of catalytic and enantioselective synthesis of chiral cyclohexa-1,3-dienes by [2 + 2 + 2] cycloaddition of two alkynes and an alkene using chiral nickel catalysts (up to 62% ee): Ikeda, S.; Kondo, H.; Arii, T.; Odashima, K. *Chem. Commun.* **2002**, 2422.

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(9) 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, pp 241−262.

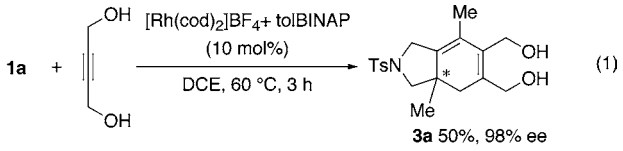
(10) A recent review of chiral biaryl-type biphosphine ligands: Shimizu, H.; Nagasaki, I.; Saito, T. *Tetrahedron* **2005**, *61*, 5405.

(11) Only a trace amount of cycloadduct **2a** was obtained using 1,2-bis(2,5-dimethylphospholano)benzene (MeDUPHOS) as a chiral ligand under the same reaction conditions.

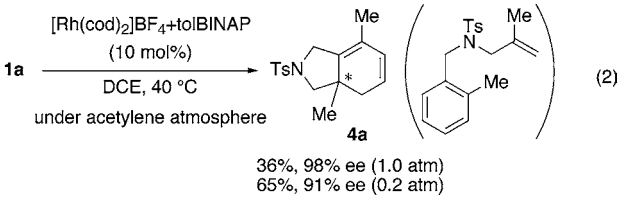
(12) Typical experimental procedure: Under an atmosphere of argon, tolBINAP (6.8 mg, 0.010 mmol) and $[Rh(cod)_2]BF_4$ (4.1 mg, 0.010 mmol) were stirred in 1,2-dichloroethane (0.25 mL) at room temperature to give a yellow solution. Then, 1,4-dimethoxybut-2-yne (22.8 mg, 0.20 mmol or 114.1 mg, 1.00 mmol) and an enyne (0.10 mmol) in 1,2-dichloroethane (0.75 mL) were added to the solution and the mixture was stirred at the appropriate temperature (cited in Table 2). After completion of the reaction, the solvent was removed under reduced pressure, and the crude products were purified by thin-layer chromatography to give a chiral cycloadduct. The ee was determined by HPLC analysis using a chiral column.

coupling product **2d** was moderate due to the formation of a self-coupling product of enyne **1d** (entry 3). The use of excess amounts of 1,4-dimethoxybut-2-yne suppressed the formation of a self-coupling product, and the yield of **2d** was increased (entry 4). With enyne **1e**, the reaction proceeded with high enantioselectivity (entries 5 and 6). Not only nitrogen-bridged enynes but also carbon- and oxygen-bridged enynes **1f** and **1g** reacted with 1,4-dimethoxybut-2-yne, and the corresponding cycloadducts **2f** and **2g** were obtained in high ee (entries 7 and 8). However, the self-coupling of enyne **1g** dominantly proceeded even with the use of excess amounts of the monoalkyne, and cycloadduct **2g** was obtained in only moderate yield (entry 8). Dropwise addition of enyne **1g** to a solution of the chiral catalyst and the monoalkyne at a higher reaction temperature improved the yield without any loss of ee (entry 9).

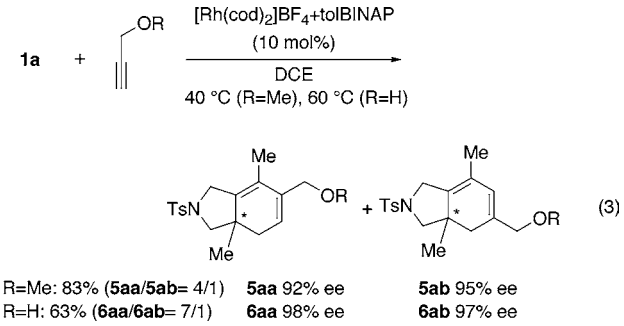
We also found that protection of the diol was unnecessary: but-2-yne-1,4-diol acted as a coupling partner and the corresponding chiral diol **3a** was obtained in moderate yield with excellent ee (eq 1).



Next, we examined the reaction of enyne **1a** under an atmospheric pressure of acetylene. While the desired cycloadduct **4a** was obtained in high ee, the intermolecular trimerization of two acetylenes and an alkyne moiety of enyne **1a** was a major pathway. A decrease of the partial pressure of acetylene gas to 0.2 atm improved the yield with a slight decrease in ee (eq 2).



Methyl propargyl ether, an unsymmetrical alkyne, also reacted with enyne **1a** under the same reaction conditions. While the regioselectivity of the alkyne was not very high, both regioisomers were obtained in high ee (eq 3). In the case of propargyl alcohol, while a higher reaction temperature was needed, better regioselectivity and excellent enantioselectivities were realized.



In conclusion, we developed a highly enantioselective [2 + 2 + 2] cycloaddition of 1,6-enynes and alkynes. This catalytic reaction provides a new and facile protocol for the construction of quaternary carbon stereocenters. Recently, we[13] and other groups[14] independently reported catalytic enantioselective [2 + 2 + 2] cycloadditions of diynes and monoalkynes for the synthesis of axially chiral biaryl compounds. The present report proposes another use of transition-metal-catalyzed [2 + 2 + 2] cycloaddition in asymmetric synthesis.

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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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