Highly diastereo- and enantioselective construction of both central and axial chiralities by Rh-catalyzed [2 + 2 + 2] cycloaddition†

Takanori Shibata,* Mayumi Otomo, Yu-ki Tahara and Kohei Endo

Received 12th August 2008, Accepted 30th September 2008
First published as an Advance Article on the web 15th October 2008
DOI: 10.1039/b814014f

The cationic Rh–SEGPHOS complex catalyzed an intermolecular [2 + 2 + 2] cycloaddition of enynes, possessing an *ortho*-substituted aryl group on their alkyne terminus, with acetylenedicarboxylates. Bicyclic cyclohexa-1,3-dienes with both central and axial chiralities were obtained in extremely highly diastereo- and enantioselective manner.

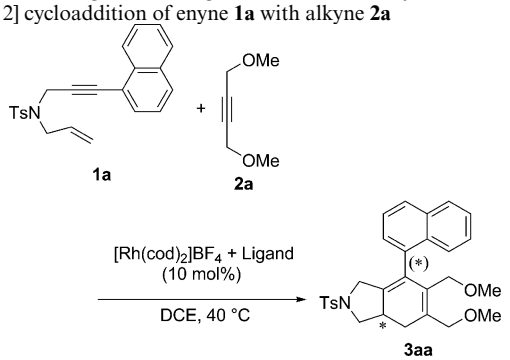
Catalytic asymmetric synthesis has made remarkable progress in recent years, and chiralities have been efficiently induced in a highly enantioselective manner: various approaches to the construction of central, axial, facial and helical chiralities were reported.[1] In general, a chiral motif is only generated in a reaction using a chiral catalyst, such as the asymmetric alkylation of carbonyl compounds. In some examples, multiple chiral motifs were formed in a multiple bond-forming reaction, however, the induction of different kinds of chiral motifs in a reaction has been scarcely reported. On the contrary, there are many compounds possessing both central and axial chiralities,[2] and some of them are used as efficient chiral ligands and catalysts.[3] Chirality transfer from central to axial chirality[4] and *vice versa*[5] are known procedures but we here disclose the generation of two different kinds of chiralities in a reaction, namely a highly diastereo- and enantioselective construction of both central and axial chiralities.

Transition metal-catalyzed [2 + 2 + 2] cycloaddition of two alkyne and an alkene moieties is an established protocol for the synthesis of cyclohexa-1,3-diene.[6] A Co-catalyzed diastereoselective reaction using chiral alkynes[7] and a Ni-catalyzed enantioselective reaction[8] are pioneering works of asymmetric variants. Evans *et al.* and we independently reported a highly enantioselective [2 + 2 + 2] cycloaddition of enynes and alkynes using chiral cationic Rh catalysts, where a central chirality was generated at the ring-fused position.[9] We assume that axial chirality can be further constructed by introduction of a bulky *ortho*-substituted aryl group on the alkyne terminus of enynes. The generation of axial chirality in a biaryl system by [2 + 2 + 2] cycloaddition of alkynes was already reported by us and other groups,[10] but that in aryl–diene system has not been reported as far as we know.

We chose the reaction of nitrogen-tethered enyne **1a** with a naphthyl group on its alkyne terminus and 1,4-dimethoxybut-2-yne (**2a**) as a model reaction, and examined several chiral phosphorus ligands for the cationic Rh complex in 1,2-dichloroethane at 40 °C (Table 1). When BINAP was used, [2 + 2 + 2] cycloadduct **3aa** was obtained in high yield, and the enantiomeric excess of minor diastereomer exceeded 90% but diastereoselectivity was low (Entry 1). In the case of tolBINAP, which was the best ligand for the intermolecular [2 + 2 + 2] cycloaddition of enynes with alkyne **2a** for the construction of a central chirality,[9b] the enyne was smoothly consumed but yield and enantioselectivities decreased (Entry 2). XylylBINAP and H_8-BINAP gave poorer results (Entries 3 and 4). On the contrary, SEGPHOS (5,5′-bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole) resulted in the best yield within 1 h and the ee of minor diastereomer exceeded 99% (Entry 5). But the diastereoselectivity remained low despite using several phosphorus ligands.

We further investigated the reaction conditions to improve diastereoselectivity (Table 2). When tetrakis(3,5-ditrifluoromethylphenyl)borate (BARF) was used as a counter anion for the Rh-complex, the catalytic activity drastically increased (Entries 1 and 2): enyne **1a** was completely consumed within 10 min at 40 °C and within 1 h even at room temperature, however, diastereoselectivity was not improved. Solvent screening using toluene and tetrahydrofuran affected the ee of the major diastereomer but diastereoselectivity was low (Entries 3 and 4). We next focused on the choice of alkynes: when more bulky TBS-protected but-2-yne-1,4-diol **2b** was used, the ratio of major isomer against minor one was dramatically improved but its ee

Table 1 Screening of chiral ligands in the Rh-catalyzed intermolecular [2 + 2 + 2] cycloaddition of enyne **1a** with alkyne **2a**



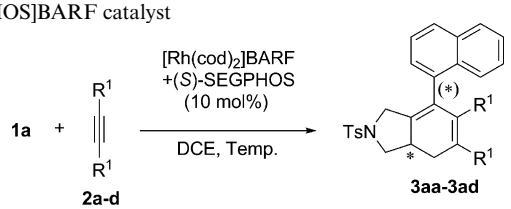
Entry[a]	Ligand[b]	Time/h	Yield (%)	dr[c]	ee (%)[d]
1	BINAP	24	85	2 : 1	84, 94
2	tolBINAP	6	69	2 : 1	60, 82
3	xylylBINAP	48	44	2 : 1	38, 82
4	H_8-BINAP	48	59	2 : 1	31, 95
5	**SEGPHOS**	**1**	**96**	**2 : 1**	**80, >99**

[a] **1a** : **2a** = 1 : 2. [b] *S* isomers were used. [c] Diastereomeric ratio was determined by integration of ^{1}H-NMR spectra. [d] Enantiomeric excess of major and minor diastereomers.

Department of Chemistry and Biochemistry, School of Advanced Science and Engineering, Waseda University, 3-4-1, Okubo, Shinjuku, Tokyo, 169-8555, Japan. E-mail: tshibata@waseda.jp; Fax: +81 352868098

† Electronic supplementary information (ESI) available: Experimental procedure and full characterization of enynes and cycloadducts. CCDC reference number 696283. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b814014f

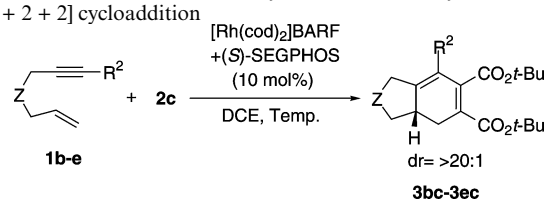
Table 2 Effect of the alkynes on the diastereoselectivity using [Rh–SEGPHOS]BARF catalyst



Entry[a]	R^1	Temp./°C	Time/h	Yield (%)	dr[b]	ee (%)[c]
1	CH_2OMe (**2a**)	40	0.2	88 (**3aa**)	2 : 1	73, 98
2	CH_2OMe (**2a**)	rt	1	71 (**3aa**)	2 : 1	79, >99
3[d]	CH_2OMe (**2a**)	rt	5	76 (**3aa**)	1 : 1	69, >99
4[e]	CH_2OMe (**2a**)	rt	24	15 (**3aa**)	1 : 1	94, >99
5	CH_2OTBS (**2b**)	rt	1	97 (**3ab**)	10 : 1	75, —
6	CO_2t-Bu (**2c**)	rt	1	48 (**3ac**)	10 : 1	ND[f]
7[g]	**CO_2t-Bu (2c)**	**60**	**0.25**	**93 (3ac)**	**>20 : 1**	**>99, —**
8[g]	CO_2Me (**2d**)	80	0.25	97 (**3ad**)	7 : 1	>99, —

[a] **1a** : **2a–d** = 1 : 2. [b] Diastereomeric ratio was determined by integration of ^{1}H-NMR spectra. [c] Enantiomeric excess of major and minor diastereomers. [d] Toluene was used as a solvent. [e] THF was used as a solvent. [f] Not determined. [g] Alkyne was added dropwise.

Table 3 Examination of several enynes in the Rh-catalyzed intermolecular [2 + 2 + 2] cycloaddition



Entry[a]	R^2	Z	Enyne	Temp/°C	Time/h	Yield (%)	ee (%)
1	2-MePh	NTs	**1b**	60	0.25	91 (**3bc**)	>99
2	2-biphenyl	NTs	**1c**	60	2	33 (**3cc**)[b]	99[c]
3[d]	2-biphenyl	NTs	**1c**	rt	24	48 (**3cc**)[e]	>99[c]
4[d,f]	2-biphenyl	NTs	**1c**	rt	3	98 (**3cc**)	>99
5[d]	1-naphthyl	O	**1d**	rt	0.3	85 (**3dc**)	98
6	1-naphthyl	CE_2[g]	**1e**	60	0.25	34 (**3ec**)	99
7[f]	1-naphthyl	CE_2[g]	**1e**	60	0.25	95 (**3ec**)	99

[a] **1b–e** : **2c** = 1 : 2. Alkyne was added dropwise. [b] Diastereomeric ratio is 2 : 1. [c] Enantiomeric excess of major diastereomer. [d] Both enyne and alkyne were added simultaneously and dropwise. [e] Diastereomeric ratio is 6 : 1. [f] **1c** or **1e** : **2c** = 1.2 : 1. The yield was based upon the amount of alkyne **2c**. [g] E = CO_2Me.

was moderate, which could be speculated from the results above (Entry 5). As bulky substituents on the alkyne, we installed *tert*-butoxycarbonyl groups (Entry 6): The high diastereoselectivity was also achieved but the yield was low because enyne **1a** was recovered. In order to consume the enyne and to prevent the trimerization of the alkyne, the reaction was examined at 60 °C along with the dropwise addition of acetylene dicarboxylate **2c** (Entry 7): enyne **1a** was completely consumed within 15 min and the minor diastereomer was not detected by NMR analysis.[11,12] Moreover, the ee of the single diastereomer exceeded 99%. When dimethyl acetylenedicarboxylate **2d** was used, an excellent yield and enantioselectivity were accomplished but diastereoselectivity significantly decreased (Entry 8). These results imply that the bulkyness of alkynes controlled the diastereoselectivity.

Several enynes were submitted to the reaction with alkyne **2c** using Rh–SEGPHOS complex as a chiral catalyst (Table 3): when an *o*-tolyl group was introduced to the alkyne terminus, the corresponding cycloadduct **3bc** was obtained in high yield with excellent diastereo- and enantioselectivities (Entry 1). On the contrary, in the reaction of enyne **1c**, product **3cc** was afforded in low yield with low diastereomeric ratio and unidentified by-products were formed (Entry 2). When the reaction was examined at room temperature, and both enyne and alkyne were added simultaneously and dropwise, yield and diastereoselectivity were improved but the yield was moderate (Entry 3). When a slight excess of enyne was used, the reaction smoothly proceeded and cycloadduct **3cc** was obtained in high yield as a single diastereomer with excellent ee (Entry 4). The structure of cycloadduct **3cc** was determined by X-ray analysis, and the central and axial chiralities were determined to be the *S* and *R* form, respectively (Fig. 1). Oxygen-tethered enyne **1d** was reactive and good results were attained at room temperature (Entry 5). On the contrary, carbon-tethered enyne **1e** was inactive: diastereo- and enantioselectivity were extremely high, but the yield was low probably because of the formation of a [2 + 2 + 2] cycloadduct derived from two alkynes and the alkyne moiety of **1e** (Entry 6). Also in this case, the use of a slight excess amount of the enyne improved the yield:

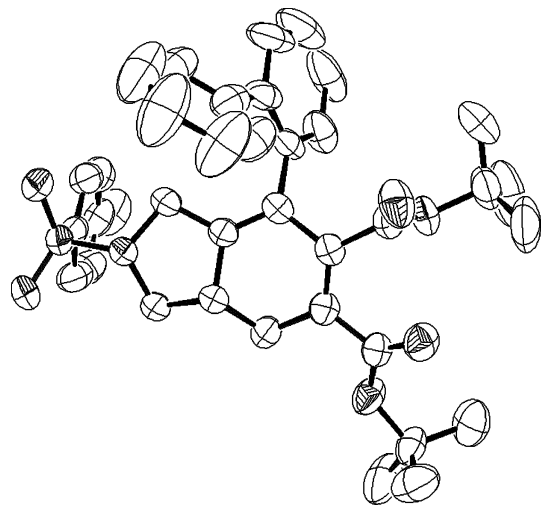
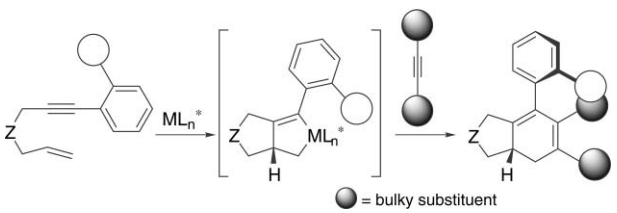


Fig. 1 Ortep diagram of cycloadduct **3cc**.

the excellent yield was achieved with the same stereoselectivity (Entry 7).

Scheme 1 shows the asymmetric induction of two different chiralities: a central chirality is generated at the ring-fused position of the bicyclic metallacyclopentene intermediate by the oxidative coupling of the metal center with an enyne. We assume that axial chirality cannot be completely controlled at this stage, but the following reaction with an alkyne induces the axial chirality.



Scheme 1 Induction of central and axial chiralities.

In conclusion, we have developed a [Rh–SEGPHOS]BARF complex-catalyzed [2 + 2 + 2] cycloaddition with excellent diastereo- and enantioselectivities. The intermolecular reaction of enynes, possessing an *ortho*-substituted aryl group on their alkyne terminus, with di(*tert*-butyl) acetylenedicarboxylate gave the bicyclic cyclo-1,3-dienes with both central and axial chiralities. As far as we know, this is the first example of generation of two different chiral motifs in the transition metal-catalyzed cycloaddition.

We thank Takasago International Corp. for the gift of SEGPHOS and H_8-BINAP. This research was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Notes and references

1 (*a*) *Comprehensive Asymmetric Catalysis II*, ed. E. N. Jacobsen, A. Pfaltz and H. Yamamoto, Springer-Verlag, Berlin, 1999; (*b*) *Catalytic Asymmetric Synthesis*, ed. I. Ojima, Wiley-VCH, New York, 2nd edn, 2000; (*c*) *Comprehensive Asymmetric Catalysis: Supplement 1*, ed. E. N. Jacobsen, A. Pfaltz and H. Yamamoto, Springer-Verlag, Berlin, 2003; (*d*) *Methodologies in Asymmetric Catalysis*, ed. S. V. Malhotra, American Chemical Society, Washington, DC, 2004.

2 (*a*) D. J. Edwards, D. House, H. M. Sheldrake, S. J. Stone and T. W. Wallace, *Org. Biomol. Chem.*, 2007, **5**, 2658; (*b*) G. Arnott and R. Hunter, *Tetrahedron*, 2006, **62**, 992; (*c*) K. Beattie, C. Elsworth, M. Gill, N. M. Milanovic, D. P. -Putra and E. Raudies, *Phytochemistry*, 2004, **65**, 1033; (*d*) O. Baudoin, A. Decor, M. Cesario and F. Gueritte, *Synlett*, 2003, 2009; (*e*) Y. Wang, X. Li and K. Ding, *Tetrahedron Lett.*, 2002, **43**, 159; (*f*) Y. Yamamoto, R. Hattori, T. Miwa, Y. Nakagai, T. Kubota, C. Yamamoto, Y. Okamoto and K. Itoh, *J. Org. Chem.*, 2001, **66**, 3865.

3 (*a*) D.-Y. Wang, X.-P. Hu, J.-D. Huang, J. Deng, S.-B. Yu, Z.-C. Duan, X.-F. Xu and Z. Zheng, *Angew. Chem., Int. Ed.*, 2007, **46**, 7810; (*b*) W.-L. Duan, Y. Imazaki, R. Shintani and T. Hayashi, *Tetrahedron*, 2007, **63**, 8529; (*c*) V. A. Soloshonok, H. Ueki, J. L. Moore and T. K. Ellis, *J. Am. Chem. Soc.*, 2007, **129**, 3512; (*d*) I. Mikhael, C. Goux-Henry and D. Sinou, *Tetrahedron: Asymmetry*, 2006, **17**, 1853; (*e*) L. Qiu, F. Y. Kwong, J. Wu, W. H. Lam, S. Chan, W.-Y. Yu, Y.-M. Li, R. Guo, Z. Zhou and A. S. C. Chan, *J. Am. Chem. Soc.*, 2006, **128**, 5955; (*f*) T. Fekner, H. Muller-Bunz and P. J. Guiry, *Org. Lett.*, 2006, **8**, 5109; (*g*) S. E. Denmark, Y. Fan and M. D. Eastgate, *J. Org. Chem.*, 2005, **70**, 5235; (*h*) A. Patti, S. Pedotti, A. Forni and G. Casalone, *Tetrahedron: Asymmetry*, 2005, **16**, 3049; (*i*) A. V. Malkov, M. Bell, M. Orsini, D. Pernazza, A. Massa, P. Herrmann, P. Meghani and P. Kocovsky, *J. Org. Chem.*, 2003, **68**, 9659; (*j*) O. Tissot, M. Gouygou, J.-C. Daran and G. G. A. Balavoine, *Chem. Commun.*, 1996, **19**, 2287; (*k*) A. Kless, J. Holz, D. Heller, R. Kadyrov, R. Selke, C. Fischer and A. Boerner, *Tetrahedron: Asymmetry*, 1996, **7**, 33; (*l*) Y. Nishibayashi, J. D. Singh, S. Fukuzawa and S. Uemura, *J. Chem. Soc., Perkin Trans. 1*, 1995, **22**, 2871; (*m*) K. H. Doetz, C. Christoffers, J. Christoffers, D. Boettcher, M. Nieger and S. Kotila, *Chem. Ber.*, 1995, **128**, 645.

4 (*a*) A. V. Vorogushin, W. D. Wulff and H. -J. Hansen, *Tetrahedron*, 2008, **64**, 949; (*b*) G. Stavrakov, M. Keller and B. Breit, *Eur. J. Org. Chem.*, 2007, 5726; (*c*) Y. Nishii, K. Wakasugi, K. Koga and Y. Tanabe, *J. Am. Chem. Soc.*, 2004, **126**, 5358; (*d*) T. Hattori, M. Date, K. Sakurai, N. Morohashi, H. Kosugi and S. Miyano, *Tetrahedron Lett.*, 2001, **42**, 8035; (*e*) F. Fabris, O. De, Lucchi and V. Lucchini, *J. Org. Chem.*, 1997, **62**, 7156; (*f*) M. Tichy, J. Gunterova and J. Zavada, *Collect. Czech. Chem. Commun.*, 1997, **62**, 1080; (*g*) R. W. Baker, T. W. Hambley, P. Turner and B. J. Wallace, *Chem. Commun.*, 1996, 2571; (*h*) A. I. Meyers and D. G. Wettlaufer, *J. Am. Chem. Soc.*, 1984, **106**, 1135.

5 (*a*) Y. Zhang, Y. Wang and W.-M. Dai, *J. Org. Chem.*, 2006, **71**, 2445; (*b*) M. Ogasawara, K. Ueyama, T. Nagano, Y. Mizuhata and T. Hayashi, *Org. Lett.*, 2003, **5**, 217; (*c*) A. V. Vorogushin, W. D. Wulff and H.-J. Hansen, *J. Am. Chem. Soc.*, 2002, **124**, 6512; (*d*) M. Tichy, M. Budesinsky, J. Gunterova, J. Zavada, J. Podiaha and I. Cisarova, *Tetrahedron*, 1999, **55**, 7893; (*e*) K. Ohmori, M. Kitamura and K. Suzuki, *Angew. Chem., Int. Ed.*, 1999, **38**, 1226; (*f*) M. Amadji, D. Cahard, J.-D. Moriggi, L. Toupet and J.-C. Plaquevent, *Tetrahedron: Asymmetry*, 1998, **9**, 1657; (*g*) M. Bertrand, M. L. Roumestant and P. Sylvestre-Panthet, *Tetrahedron Lett.*, 1981, **22**, 3589.

6 (*a*) C.-A. Chang, J. A. Jr, King and K. P. C. Vollhardt, *J. Chem. Soc., Chem. Commun.*, 1981, 53; (*b*) R. Grigg, R. Scott and P. Stevenson, *J. Chem. Soc., Perkin Trans. 1*, 1988, 1365; (*c*) B. M. Trost and G. J. Tanoury, *J. Am. Chem. Soc.*, 1987, **109**, 4753; (*d*) H.-Y. Rhyoo, B. Y. Lee, H. K. B. Yu and Y. K. Chung, *J. Mol. Catal.*, 1994, **92**, 41; (*e*) C. H. Oh, H. R. Sung, S. H. Jung and Y. M. Lim, *Tetrahedron Lett.*, 2001, **42**, 5493; (*f*) Y. Yamamoto, S. Kuwabara, Y. Ando, H. Nagata, H. Nishiyama and K. Itoh, *J. Org. Chem.*, 2004, **69**, 6697; (*g*) S. Kezuka, T. Okado, E. Niou and R. Takeuchi, *Org. Lett.*, 2005, **7**, 1711.

7 (*a*) R. Halterman and K. P. C. Vollhardt, *Organometallics*, 1988, **7**, 883; (*b*) F. Slowinski, C. Aubert and M. Malacria, *Tetrahedron Lett.*, 1999, **40**, 5849.

8 S. Ikeda, H. Kondo, T. Arii and K. Odashima, *Chem. Commun.*, 2002, 2422.

9 (*a*) P. A. Evans, K. W. Lai and J. R. Sawyer, *J. Am. Chem. Soc.*, 2005, **127**, 12466; (*b*) T. Shibata, Y. Arai and Y. Tahara, *Org. Lett.*, 2005, **7**, 4955.

10 (*a*) A. Gutnov, B. Heller, C. Fischer, H.-J. Drexler, A. Spannenberg, B. Sundermann and C. Sundermann, *Angew. Chem., Int. Ed.*, 2004, **43**, 3795; (*b*) T. Shibata, T. Fujimoto, K. Yokota and K. Takagi, *J. Am. Chem. Soc.*, 2004, **126**, 8382; (*c*) K. Tanaka, G. Nishida, A. Wada and K. Noguchi, *Angew. Chem., Int. Ed.*, 2004, **43**, 6510.

11 When adduct **3ac** was heat at 80 °C in DCE for 1 h, a significant decrease of diastereomeric ratio was observed (from 10 : 1 to 5 : 1).

12 As a reference experiment, the cycloaddition of alkynes **2a** and **2c** with a diyne, in place of enynes, was examined under the same reaction conditions: the reaction of alkyne **2c** achieved much higher enantioselectivity than that of **2a** (details in supplemental information†). These results suggest that diastereoselectivity was determined by the induction of axial chirality at the stage of alkyne insertion.

