Rhodium-catalyzed enantio- and diastereoselective intramolecular [2 + 2 + 2] cycloaddition of unsymmetrical dienynes†

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A cationic rhodium(I)/(R)-H$_8$-BINAP or (R)-Segphos complex catalyzes an intramolecular [2 + 2 + 2] cycloaddition of unsymmetrical dienynes, leading to fused tri- and tetracyclic cyclohexenes bearing two tertiary or quaternary carbon centers in high yields with high enantio- and diastereoselectivity.

Transition-metal-catalyzed enantioselective [2 + 2 + 2] cycloadditions involving alkenes are efficient synthetic methods for the rapid construction of chiral six-membered carbocycles.[1,2] Catalytic enantioselective [2 + 2 + 2] cycloadditions of two monoynes and an alkene,[3] 1,6-diyne and alkene,[4] 1,6-enyne and monoyne,[5] and enediyne[4b,6] using Ni[2] and Rh[4–6] complexes have been reported. However, catalytic enantioselective [2 + 2 + 2] cycloadditions of one alkyne unit and two alkene units are scarce.[7,8] Sato and co-workers recently reported the synthesis of *cis*-fused tricyclic cyclohexenes by a Ru-catalyzed intramolecular [2 + 2 + 2] cycloaddition of both symmetrical and unsymmetrical dienynes.[9] Independently, we have also reported that an intramolecular [2 + 2 + 2] cycloaddition of a symmetrical dienyne in the presence of a cationic rhodium(I)/(R)-H$_8$-BINAP complex proceeded to give the corresponding *cis*- and *trans*-fused tricyclic cyclohexenes in quantitative yield, while the achiral *meso*-isomer (*cis*-fused cyclohexene) was obtained as the major product.[4b,10,11] Thus, we examined a [2 + 2 + 2] cycloaddition of unsymmetrical dienyne 1a bearing two different tethers, which would furnish two chiral tricyclic cyclohexenes 2a and 3a possessing two quaternary-substituted carbon centers.[12] Although the reaction proceeded in high yield by using the same rhodium catalyst, and the minor product (+)-3a was obtained with high ee, the major product (+)-2a was obtained with low ee (eqn (1)).

A possible mechanism for the formation of *trans*- and *cis*-fused tricyclic cyclohexenes using the cationic rhodium(I)/(R)-H$_8$-BINAP complex as a catalyst is shown in Scheme 1. We proposed that intermediates B and C furnish the same enantiomer D of the *trans*-fused cyclohexene, and intermediates E and G furnish an enantiomeric pair of *cis*-fused cyclohexenes F and H. One of the stereocenters is constructed

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by the reaction of a more reactive enyne moiety of dienyne A with rhodium due to the steric repulsion between the Rh–CH$_2$
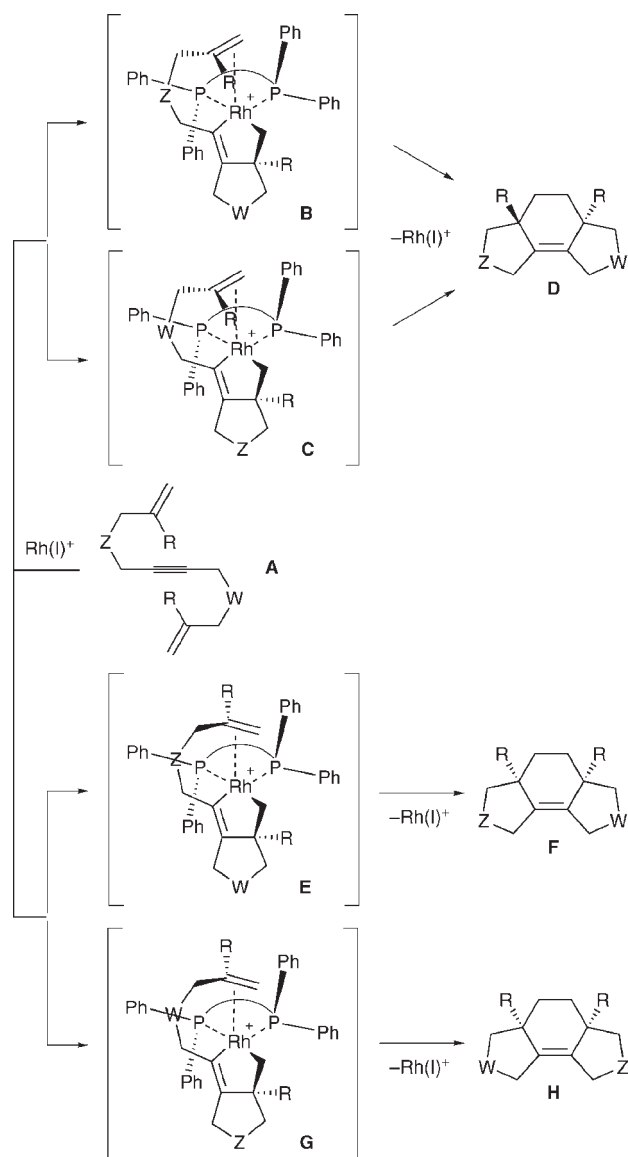

$$(1)$$
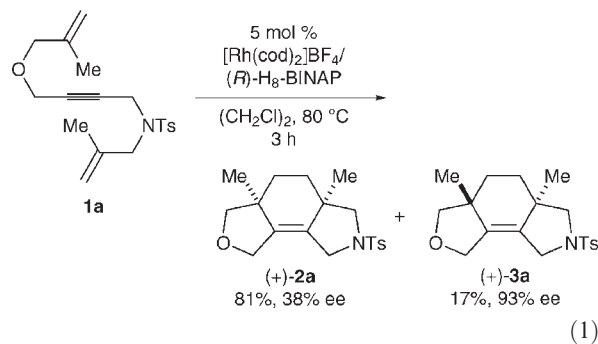
moiety and the equatorial P–Ph group of (R)-H$_8$-BINAP. Subsequently, the other stereocenter is constructed by the coordination of another double bond of dienyne A to rhodium due to the steric repulsion between the tether or R group and the axial P–Ph group of (R)-H$_8$-BINAP. Although *trans*-fused cyclohexene (+)-3a was obtained with high ee, a similar reactivity of the two enyne moieties of 1a toward rhodium causes the low ee of *cis*-fused cyclohexene (+)-2a, presumably due to the formation of both intermediates E and G. According to the above-mentioned mechanism, a *trans*-selective coordination mode of the double bond shown in intermediate B or C would be favorable by employing dienyne A with the longer tether, which results in increased yield of *trans*-fused cyclohexene D. On the other hand, a large difference in the reactivity between the two enyne moieties of dienyne A toward rhodium would induce the selective formation of either intermediate E or G, which results in improved ee of *cis*-fused cyclohexene F or H, respectively.

Thus, the reaction of unsymmetrical dienyne 1b bearing different tether lengths was examined in the presence of the cationic rhodium(I)/(R)-H$_8$-BINAP complex (5 mol%).[13] Fortunately, the reaction proceeded to give the corresponding chiral tricyclic cyclohexenes 2b and 3b in quantitative yield (Table 1, entry 1).‡ In this reaction, *trans*-isomer 3b was obtained as the major product with high ee, while *cis*-isomer 2b was obtained as the minor product with low ee. The reaction of dienyne 1c bearing an ether-linked 1,6-enyne moiety proceeded to give *trans*-isomer (+)-3c as the major product with high ee and *cis*-isomer (+)-2c as the minor product with moderate ee (entry 2). These results might show that the reactivity of 1,6- and 1,7-enyne moieties toward

Scheme 1 Possible mechanism for the formation of *trans*- and *cis*-fused tricyclic cyclohexenes.

Table 1 Rhodium-catalyzed enantio- and diastereoselective [2 + 2 + 2] cycloaddition of unsymmetrical dienynes **1b–1j**[a]

Entry	Dienyne 1	Conditions	Product [2 (*cis*)/3 (*trans*)], yield (%)[b] {*cis* : *trans*}, ee (%)
1	**1b** (Z = NTs)	80 °C, 3 h	**2b/3b**, >99 {1 : 2.4}, 4/99, (+)-**2c**, 24, 45 (3a*R*,5a*S*)-(+)-**3c**, 75, >99
2	**1c** (Z = O)	rt, 16 h	
3[cd]	**1d** (R = Me)	rt, 64 h	(+)-**2d**, 98, 94
4[ce]	**1d** (R = Me)	40 °C, 40 h	(+)-**2d**, 94, 86
5[e]	**1e** (R = H)	rt, 16 h	(3a*R*,5a*S*)-(+)-**2e**, 89, 99
6	**1e** (R = H)	80 °C, 3 h	(3a*R*,5a*S*)-(+)-**2e**, 82, 98
7[e]	**1f** [Z = C(CO$_2$Et)$_2$]	rt, 16 h	(+)-**2f**, 87, 97
8	**1f** [Z = C(CO$_2$Et)$_2$]	80 °C, 3 h	(+)-**2f**, 88, 93
9	**1g** (Z = O)	80 °C, 3 h	(+)-**2g**, 95, 93
10	**1h**	80 °C, 3 h	**4**, 70 {*E*/*Z* = 1 : 3.3}
11	**1i**	80 °C, 3 h	**2i/3i**, 57 {14 : 1}, 96/>99

rhodium is not different enough to allow the selective formation of intermediate **E** or **G**. The absolute configuration of *trans*-fused cyclohexene (+)-**3c** was unambiguously determined by X-ray crystallographic analysis (Fig. 1), which is indeed consistent with that derived from our proposed intermediates **B** and **C**.

We anticipated that the reaction of phenol-linked dienyne **1d** would selectively provide *cis*-fused cyclohexene **2d** with high ee through intermediate **E** (W = NTs). The phenol-linked 1,7-enyne moiety may be much less reactive to rhodium than the 1,6-enyne moiety, the double bond of which may not coordinate to rhodium with *trans*-selectivity due to the rigid structure of the phenol-linked tether. As expected, **1d** cleanly cyclized at room temperature to give (+)-**2d** as a sole product in high yield with high ee, although a high catalyst loading (20 mol%) was required (entry 3).[14] By conducting the reaction at elevated temperature (40 °C), the catalyst loading could be reduced to 10 mol% with slight erosion of the yield and ee

Table 1 (*continued*)

Entry	Dienyne 1	Conditions	Product [2 (*cis*)/3 (*trans*)], yield (%)[b] {*cis* : *trans*}, ee (%)
12[e]	**1j**	80 °C, 16 h	(+)-**2j** 81, 98

[a] [Rh(cod)$_2$]BF$_4$ (0.010 mmol), (*R*)-H$_8$-BINAP (0.010 mmol), **1b**–**1j** (0.20 mmol), and CH$_2$Cl$_2$ (rt–40 °C) or (CH$_2$Cl)$_2$ (80 °C) (2.0 mL) were used. [b] Isolated yield. [c] Ligand: (*R*)-Segphos. [d] Catalyst: 20 mol%. [e] Catalyst: 10 mol%.
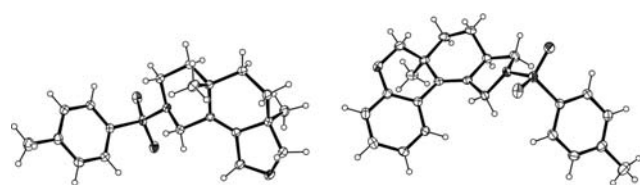
Fig. 1 ORTEP drawings of *trans*-cyclohexene (3a*R*,5a*S*)-**3c** (left) and *cis*-cyclohexene (3a*R*,5a*S*)-**2e** (right).

(entry 4). Interestingly, the reactions of dienynes **1e**–**1g** bearing monosubstituted 1,6-enyne moieties proceeded to give the desired cyclohexenes (+)-**2e**–**2g** in high yields with high ees (entries 5–9). Furthermore, these reactions could be conducted with lower catalyst loadings than those for dienyne **1d** bearing a geminally disubstituted 1,6-enyne moiety. However, the reaction of dienyne **1h** bearing a monosubstituted 1,7-enyne moiety furnished an *E*/*Z* mixture of diene **4** presumably through β-hydride elimination of the rhodacycle intermediate (entry 10). Finally, ester-linked cyclohexene **2i** and cyclohexene (+)-**2j** containing a seven-membered ring were also obtained with high ees from the corresponding dienynes **1i** and **1j**, respectively (entries 11 and 12). The absolute configuration of *cis*-fused cyclohexene (+)-**2e** was unambiguously determined by X-ray crystallographic analysis (Fig. 1), which is again consistent with that derived from our proposed intermediate **E** (W = NTs).

In conclusion, we have determined that a cationic rhodium(I)/(*R*)-H$_8$-BINAP or (*R*)-Segphos complex catalyzes an intramolecular [2 + 2 + 2] cycloaddition of rationally designed unsymmetrical dienynes, leading to fused tricyclic and tetracyclic cyclohexenes possessing two tertiary or quaternary carbon centers in high yields with high enantio- and diastereoselectivity.

Notes and references

‡ **General procedure:** under an Ar atmosphere, a CH$_2$Cl$_2$ (1.0 mL) solution of (*R*)-H$_8$-BINAP or (*R*)-Segphos (0.010–0.040 mmol) was added to a CH$_2$Cl$_2$ (1.0 mL) solution of [Rh(cod)$_2$]BF$_4$ (0.010–0.040 mmol, 5–20 mol% Rh), and the solution was stirred at room temperature for 5 min. H$_2$ (1 atm) was introduced to the resulting solution in a Schlenk tube. After stirring at room temperature for 0.5 h, the resulting solution was concentrated to dryness and the residue was dissolved in CH$_2$Cl$_2$ (rt–40 °C) or (CH$_2$Cl)$_2$ (80 °C) (0.5 mL). To this solution was added a CH$_2$Cl$_2$ or (CH$_2$Cl)$_2$ (1.5 mL) solution of **1** (0.200 mmol). The solution was stirred at rt–80 °C for 3–64 h. The resulting solution was concentrated and purified by preparative TLC, which furnished **2** and/or **3**.

1 For recent reviews of transition-metal-catalyzed [2 + 2 + 2] cycloadditions, see: (*a*) N. Agenet, O. Buisine, F. Slowinski, V. Gandon, C. Aubert and M. Malacria, *Org. React.*, 2007, **68**, 1; (*b*) P. R. Chopade and J. Louie, *Adv. Synth. Catal.*, 2006, **348**, 2307; (*c*) V. Gandon, C. Aubert and M. Malacria, *Chem. Commun.*, 2006, 2209; (*d*) S. Kotha, E. Brahmachary and K. Lahiri, *Eur. J. Org. Chem.*, 2005, 4741; (*e*) Y. Yamamoto, *Curr. Org. Chem.*, 2005, **9**, 503.

2 For pioneering works on transition-metal-catalyzed enantioselective [2 + 2 + 2] cyclizations, see: (*a*) Y. Sato, T. Nishimata and M. Mori, *J. Org. Chem.*, 1994, **59**, 6133; (*b*) I. G. Stara, I. Stary, A. Kollarovic, F. Teply, S. Vyskocil and D. Saman, *Tetrahedron Lett.*, 1999, **40**, 1993.

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

4 (*a*) K. Tsuchikama, Y. Kuwata and T. Shibata, *J. Am. Chem. Soc.*, 2006, **128**, 13686; (*b*) K. Tanaka, G. Nishida, H. Sagae and M. Hirano, *Synlett*, 2007, 1426; (*c*) T. Shibata, A. Kawachi, M. Ogawa, Y. Kuwata, K. Tsuchikama and K. Endo, *Tetrahedron*, 2007, **63**, 12853.

5 (*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.

6 T. Shibata, H. Kurokawa and K. Kanda, *J. Org. Chem.*, 2007, **72**, 6521.

7 For a Rh(I)$^+$/modified-BINAP-catalyzed enantioselective [2 + 2 + 2] cycloaddition of 1,4-diene-ynes, see: T. Shibata and Y. Tahara, *J. Am. Chem. Soc.*, 2006, **128**, 11767.

8 For a Ni-catalyzed non-asymmetric [2 + 2 + 2] cycloaddition of 1,6-enynes with alkenes, see: J. Seo, H. M. P. Chui, M. J. Heeg and J. Montgomery, *J. Am. Chem. Soc.*, 1999, **121** 476.

9 D. Tanaka, Y. Sato and M. Mori, *J. Am. Chem. Soc.*, 2007, **129**, 7730.

10 For our first discovery of the cationic Rh(I)/BINAP-type bis-phosphine complex-catalyzed [2 + 2 + 2] cycloadditions, see: K. Tanaka and K. Shirasaka, *Org. Lett.*, 2003, **5**, 4697.

11 For our accounts of cationic Rh(I)/BINAP-type bis-phosphine complex-catalyzed [2 + 2 + 2] cycloadditions, see: (*a*) K. Tanaka, *Synlett*, 2007, 1977; (*b*) K. Tanaka, G. Nishida and T. Suda, *J. Synth. Org. Chem., Jpn.*, 2007, **65**, 862.

12 For recent reviews of catalytic asymmetric methods that generate quaternary-substituted carbon centers, see: (*a*) B. M. Trost and C. Jiang, *Synthesis*, 2006, 369; (*b*) C. J. Douglas and L. E. Overman, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5363; (*c*) I. Denissova and L. Barriault, *Tetrahedron*, 2003, **59**, 10105.

13 In favor of this approach, the cationic Rh(I)/H$_8$-BINAP complex can catalyze an intramolecular [2 + 2 + 2] cycloaddition of triynes bearing a long tether to give enantioenriched [*n*]metacyclophanes with high enantioselectivity, see: (*a*) K. Tanaka, H. Sagae, K. Toyoda, K. Noguchi and M. Hirano, *J. Am. Chem. Soc.*, 2007, **129**, 1522; (*b*) K. Tanaka, H. Sagae, K. Toyoda and M. Hirano, *Tetrahedron*, 2008, **64**, 831.

14 In this case, the use of (*R*)-Segphos as a ligand furnished the cycloaddition product with higher ee than that using (*R*)-H$_8$-BINAP.