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

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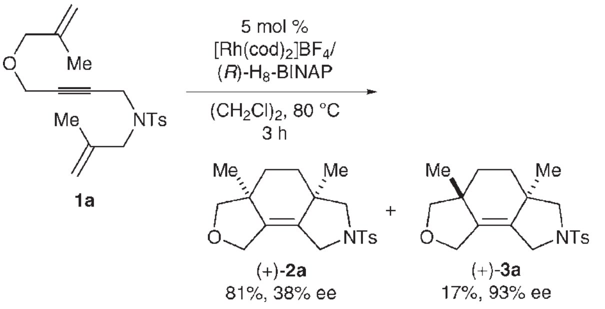
A cationic rhodium(I)/(*R*)-H$_8$-BINAP or (*R*)-Segphos complex catalyzes an intramolecular [2 + 2 + 2] cycloaddition of unsymmetrical dienynes, leading to fused tri- and tetracyclic cyclohexenes bearing two tertiary or quaternary carbon centers in high yields with high enantio- and diastereoselectivity.

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)).



(+)-**2a**
81%, 38% ee

(+)-**3a**
17%, 93% ee

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

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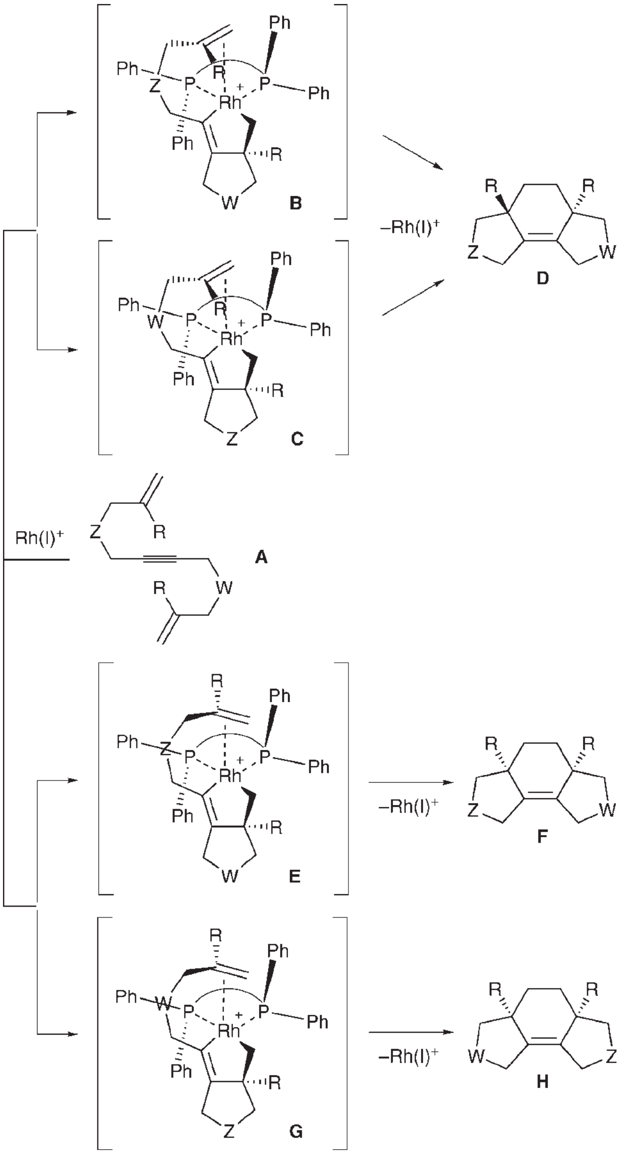


Scheme 1 Possible mechanism for the formation of *trans*- and *cis*-fused tricyclic cyclohexenes.

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

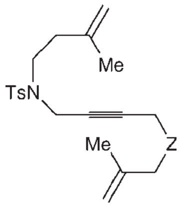
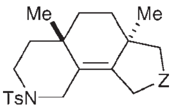
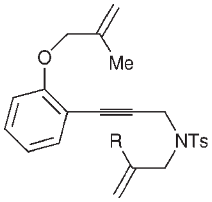
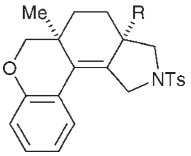
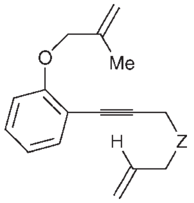
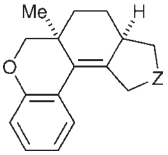
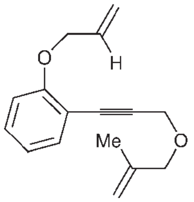
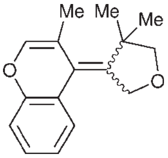
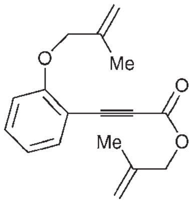
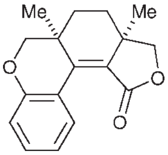
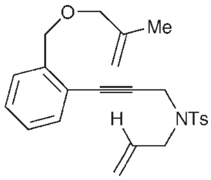
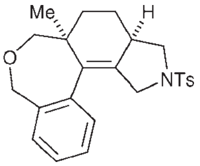
Entry	Dienyne **1**	Conditions	Product [**2** (*cis*)/**3** (*trans*)], yield (%)[b] {*cis* : *trans*}, ee (%)
			
1	**1b** (Z = NTs)	80 °C, 3 h	**2b**/**3b**, >99 {1 : 2.4}, 4/99,
2	**1c** (Z = O)	rt, 16 h	(+)-**2c**, 24, 45 (3a*R*,5a*S*)-(+)-**3c**, 75, >99
			
3[cd]	**1d** (R = Me)	rt, 64 h	(+)-**2d**, 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_2Et)$_2$]	rt, 16 h	(+)-**2f**, 87, 97
8	**1f** [Z = C(CO_2Et)$_2$]	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

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_2Cl_2 (rt–40 °C) or $(CH_2Cl)_2$ (80 °C) (2.0 mL) were used. [b] Isolated yield. [c] Ligand: (*R*)-Segphos. [d] Catalyst: 20 mol%. [e] Catalyst: 10 mol%.

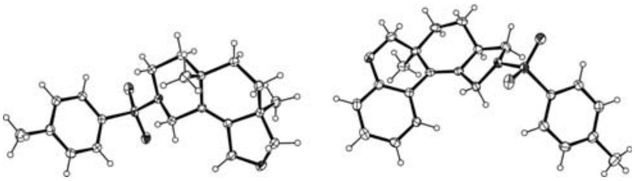


Fig. 1 ORTEP drawings of *trans*-cyclohexene (3a*R*,5a*S*)-**3c** (left) and *cis*-cyclohexene (3a*R*,5a*S*)-**2e** (right).

(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.

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Notes and references

‡ **General procedure:** under an Ar atmosphere, a CH_2Cl_2 (1.0 mL) solution of (*R*)-H_8-BINAP or (*R*)-Segphos (0.010–0.040 mmol) was added to a CH_2Cl_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_2Cl_2 (rt–40 °C) or $(CH_2Cl)_2$ (80 °C) (0.5 mL). To this solution was added a CH_2Cl_2 or $(CH_2Cl)_2$ (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**.

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