Enantioselective Intramolecular [2+2+2] Cycloaddition of Dienynes for the Construction of Adjacent Three Chiral Centers

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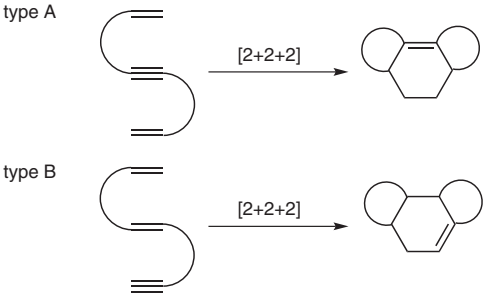
Abstract: A chiral rhodium catalyst realized the first intramolecular [2+2+2] cycloaddition of yne–ene–enes, and chiral multicyclic cyclohexenes with adjacent three chiral centers were afforded with high to excellent ee.

Key words: catalysis, chirality, cycloaddition, rhodium, multicyclic

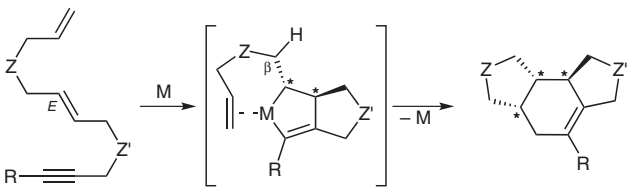
Intramolecular reaction of substrates with multi-reaction sites is synthetically very important because it realizes the construction of multicyclic skeleton in one-pot with complete regioselectivity. Actually, transition-metal-catalyzed intramolecular [2+2+2] cycloaddition of unsaturated motifs, such as alkyne and alkene, has been comprehensively studied, and various types of reactions were reported[1] including asymmetric variants.[2] Especially, enantioselective cycloaddition of triynes was used for the construction of helical,[3] axial,[4] and planar chiralities.[5] In the cycloaddition of enediynes, palladium-catalyzed reactions of yne–yne–enes and yne–ene–ynes were reported,[6] and chiral rhodium-catalyzed enantioselective reaction of yne–ene–ynes was also reported.[7] On the contrary, as for the cycloaddition of dienynes (Scheme 1), ruthenium-catalyzed[8] and chiral rhodium-catalyzed reactions[9] of ene–yne–enes (type A) were reported, however, the cycloaddition of yne–ene–enes (type B) was not reported. The transformation of yne–ene–enes into tricyclic cyclohexenes was realized by palladium-catalyzed cycloisomerization along with thermal Diels–Alder reaction[10] and radical cyclization,[11] but no asymmetric variant was reported.[12]

We examined an intramolecular [2+2+2] cycloaddition of yne–ene–enes: oxidative coupling of enyne moiety, which is more active than diene moiety, proceeds with a metal catalyst, and the following alkene insertion provides a tricyclic cyclohexene with adjacent three chiral centers (Scheme 2). The most expected side reaction is the β-hydrogen elimination from the metallacyclopentene intermediate, which gives the ene-type product.[13]

We chose dienyne **1a** with two nitrogen tethers as a model substrate and submitted to the reaction using rhodium-chiral diphosphine ligand (Table 1). In the case of BINAP, dienyne **1a** was completely consumed within 2 hours at room temperature, and the desired tricyclic product **2a** was obtained in good yield with high ee, however, the mixture of ene type product **2a′** and its isomerized product **2a″** was also obtained in significant yield (entry 1). After screening several BINAP derivatives, H_8-BINAP gave the best results but the β-elimination could not be completely restrained (entries 2–5).[14]



Scheme 1 [2+2+2] Cycloadditions of ene–yne–ene and yne–ene–ene



Scheme 2 Generation of adjacent three chiral centers

Under the optimal reaction conditions, we examined several dienynes (Table 2). In place of nitrogen tether, carbon and oxygen tethers could be introduced into the enyne moiety (entries 1 and 2). Especially, carbon-tethered dienyne **1b** was a good substrate, and the corresponding tricyclic product **2b** was selectively obtained with excellent ee. As a substituent on the alkyne terminus, phenyl group was also possible and chiral cyclohexenes **2d** and **2e** were obtained in high ee (entries 3 and 4).[15] On the contrary, when carbon and oxygen tethers were introduced into the diene moiety, the corresponding [2+2+2] cycloadducts could not be obtained (entries 5 and 6).[16]

We next examined *o*-phenylene-tethered dienynes under the same reaction conditions (Scheme 3). In the reaction of phenyl-substituted substrate **1h**, almost perfect enantio-

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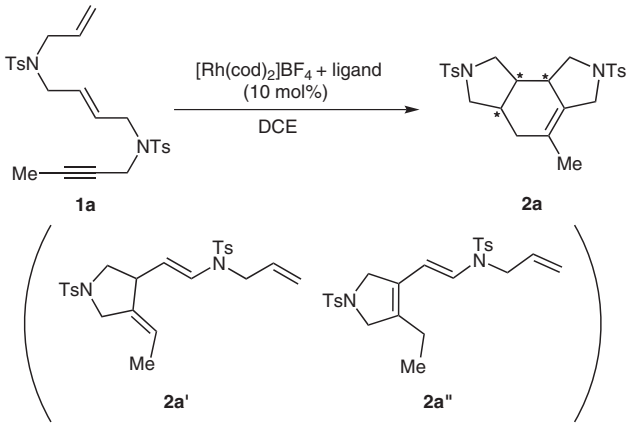
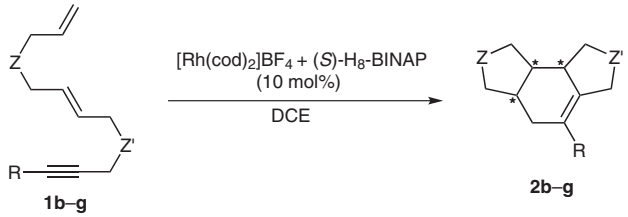
Table 1 Screening of Chiral Ligands for Cycloaddition of Dienyne **1a**



Entry	Chiral ligand[a]	Temp (°C)	Time (h)	Yield of **2a** (%)	ee of **2a** (%)	Yield of **2a′** + **2a″** (%)
1	BINAP	r.t.	2	72	80	19
2	tolBINAP	60	4	63	77	37
3	H_8-BINAP	r.t.	0.5	74	87	13
4	DM-H_8-BINAP	80	5	55	–68	25
5	SEGPHOS	r.t.	24	64	46	24

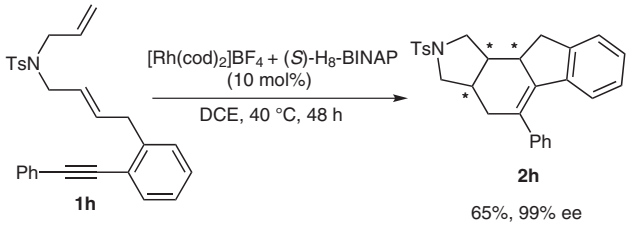
[a] H_8-BINAP: bis(diphenylphospino)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl, DM-H_8-BINAP: bis[di-(3,5-xylyl)phosphino]-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl, SEGPHOS: 5,5′-bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole. *S*-Isomers were used except DM-H_8-BINAP.

Table 2 Examination of Dienynes with Various Tethers



Entry	Z	Z′	R		Temp, time	Yield (%)	ee (%)
1	NTs	CE_2[a]	Me	**1b**	r.t., 1 h	79 (**2b**)	95
2	NTs	O	Me	**1c**	40 °C, 24 h	54 (**2c**)	73
3	NTs	NTs	Ph	**1d**	80 °C, 15 min	54 (**2d**)	86
4	NTs	CE_2[a]	Ph	**1e**	80 °C, 30 min	55 (**2e**)	92
5	CE_2[a]	NTs	Me	**1f**	80 °C, 24 h	–	–
6	O	NTs	Me	**1g**	r.t., 2 h	–	–

[a] E = CO_2Me



Scheme 3 Reaction of *o*-phenylene-tethered dienyne **1h**

selectivity was achieved, and its absolute configuration was determined by X-ray diffraction (Figure 1).[17]

We examined ester-tethered dienyne **1i**, which never undergoes cycloisomerization by β-elimination, but almost no reaction proceeded (Figure 2). In the case of dienynes **1j** and **1k**, which have 1,1- and 1,2-disubstituted alkene moiety, respectively, cycloisomerization predominantly proceeded.

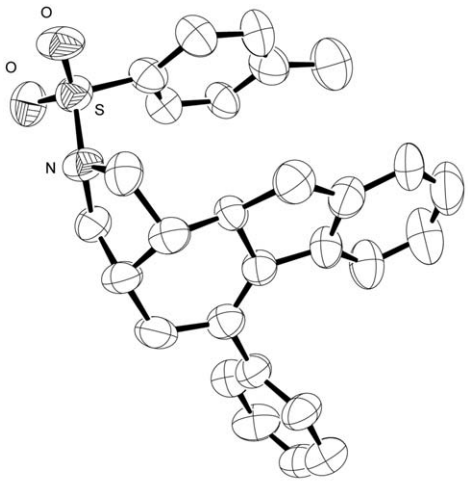


Figure 1 ORTEP diagram of cycloadduct **2h**

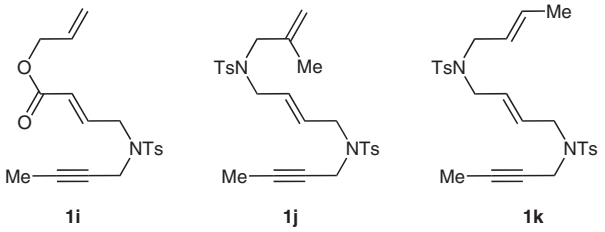
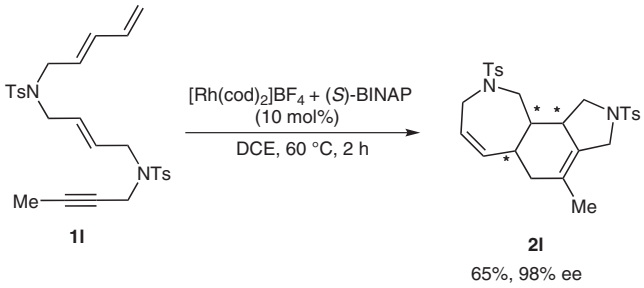


Figure 2 Inappropriate substrates

On the contrary, yne–ene–diene system was available (Scheme 4). Trienyne **1l** possessing active conjugate diene moiety was transformed into tricyclic compound **2l** in 98% ee using Rh-BINAP catalyst, which means chiral 5,6,7-tricyclic ring system was constructed in one pot along with excellent enantioselectivity.



Scheme 4 Reaction of yne–ene–diene **1l**

In conclusion, we developed an enantioselective [2+2+2] cycloaddition of dienynes using a chiral rhodium-catalyst. The present reaction is the first example of intramolecular cycloaddition of yne–ene–ene system, and multicyclic cyclohexenes with adjacent three chiral centers were obtained with good to excellent enantioselectivity. It is noteworthy that a chiral 5,6,7-tricyclic ring system could be constructed in one pot in the reaction of trienyne.

Under an atmosphere of argon, H_8-BINAP (6.3 mg, 0.010 mmol) and $[Rh(cod)_2]BF_4$ (4.1 mg, 0.010 mmol) were stirred in CH_2Cl_2 (0.75 mL). While stirring the solution at r.t., hydrogen gas was introduced to the flask, and the solution was further stirred for 30 min at r.t. After removal of the solvent and hydrogen under reduced pressure, argon gas was introduced. DCE (0.25 mL) was added to the flask, and the solution was stirred at r.t. to give a mars yellow solution. Then, a dienyne (0.10 mmol) in DCE (0.75 mL) were added to the solution, and the mixture was stirred at the appropriate temperature. After completion of the reaction, the solvent was removed under reduced pressure, and the crude products were purified by TLC to give a chiral cycloadduct. The ee was determined by HPLC analysis using a chiral column.

4-Methyl-2,7-bis(*p*-toluenesulfonyl)-1,3,5,6,8,8a,8b,-heptahydro-2,7-diaza-*as*-indacene (2a)

White solid (mp 191 °C). IR (KBr): 1337, 1155, 820, 663 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.49 (s, 3 H), 1.53–1.66 (m, 2 H), 1.81 (d, *J* = 18.6 Hz, 1 H), 2.04 (dd, *J* = 6.4, 18.6 Hz, 1 H), 2.24–2.32 (m, 1 H), 2.35 (dd, *J* = 8.1, 8.8 Hz, 1 H), 2.43 (s, 3 H), 2.48 (s, 3 H), 2.74 (dd, *J* = 9.1, 10.4 Hz, 1 H), 3.20 (d, *J* = 10.4 Hz, 1 H), 3.31 (dd, *J* = 4.6, 10.4 Hz, 1 H), 3.46 (dd, *J* = 9.1, 10.4 Hz, 1 H), 3.54 (dd, *J* = 8.1, 8.8 Hz, 1 H), 3.55 (d, *J* = 13.2 Hz, 1 H), 3.83 (d, *J* = 13.2 Hz, 1 H), 7.30–7.38 (m, 4 H), 7.65–7.72 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.0, 21.5, 21.5, 29.9, 35.8, 37.8, 38.6, 49.7, 51.2, 52.8, 53.5, 123.9, 127.1, 127.3, 127.6, 129.7, 129.8, 132.9, 133.5, 143.6, 144.0. HRMS–FAB (positive): *m/z* calcd for $C_{25}H_{31}N_2O_4S_2$: 487.1725 $[M + 1]^+$; found: 487.1724 $[M + 1]^+$; $[\alpha]_D^{18}$ 17.4 (*c* 1.02, $CHCl_3$, 87% ee). The ee was determined by HPLC analysis using a chiral column [Daicel Chiralpak IA-H: 4 × 250 mm, 254 nm UV detector, r.t., eluent: 50% CH_2Cl_2 in hexane, flow rate: 1.0 mL/min; t_R (minor isomer) = 10 min; t_R (major isomer) = 12 min].

2,2-Bis(methoxycarbonyl)-4-methyl-7-(*p*-toluenesulfonyl)-1,3,5,6,8,8a,8b-heptahydro-7-aza-*as*-indacene (2b)

Colorless oil. IR (neat) 1734, 1344, 1161, 665, 594, 550 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.23 (s, 3 H), 1.64–1.85 (m, 3 H), 1.85–1.97 (m, 1 H), 2.07 (dd, *J* = 7.6, 15.4 Hz, 1 H), 2.16–2.29 (m, 1 H), 2.44 (s, 3 H), 2.52 (dd, *J* = 7.6, 15.4 Hz, 1 H), 2.75–2.90 (m, 2 H), 2.97 (d, *J* = 17.2 Hz, 1 H), 3.25–3.37 (m, 2 H), 3.44 (dd, *J* = 8.8, 9.0 Hz, 1 H), 3.71 (s, 3 H), 3.74 (s, 3 H), 7.32 (d, *J* = 8.2 Hz, 2 H), 7.71 (d, *J* = 8.2 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.1, 21.5, 30.5, 36.3, 37.2, 38.5, 40.3, 41.8, 51.7, 52.8, 52.8, 52.9, 58.0, 123.5, 127.3, 129.7, 131.2, 134.2, 143.3, 172.1, 172.4. HRMS–FAB (positive): *m/z* calcd for $C_{23}H_{30}NO_6S$: 448.1794 $[M + 1]^+$; found: 448.1792 $[M + 1]^+$; $[\alpha]_D^{27}$ 40.1 (*c* 1.60, $CHCl_3$, 95% ee). The ee was determined by HPLC analysis using a chiral column [Daicel Chiralpak AD-H: 4 × 250 mm, 254 nm UV detector, r.t., eluent: 20% 2-PrOH in hexane, flow rate: 1.0 mL/min; t_R (minor isomer) = 12 min; t_R (major isomer) = 18 min].

4-Methyl-7-(*p*-toluenesulfonyl)-1,3,5,6,8,8a,8b-heptahydro-7-aza-2-oxa-*as*-indacene (2c)

Colorless oil. IR (neat): 1342, 1165, 661, 594, 550 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.55 (s, 3 H), 1.72–1.81 (m, 1 H), 1.83–1.90 (m, 2 H), 2.08–2.20 (m, 1 H), 2.29–2.40 (m, 1 H), 2.44 (s, 3 H), 2.85 (dd, *J* = 9.1, 10.4 Hz, 1 H), 3.14 (dd, *J* = 7.8, 8.8 Hz, 1 H), 3.24 (d, *J* = 9.8 Hz, 1 H), 3.37 (dd, *J* = 5.2, 9.8 Hz, 1 H), 3.50 (dd, *J* = 9.1, 10.4 Hz, 1 H), 4.04 (dd, *J* = 7.8, 8.8 Hz, 1 H), 4.27 (d, *J* = 1.2 Hz, 2 H), 7.33 (d, *J* = 8.4 Hz, 2 H), 7.72 (d, *J* = 8.4 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.1, 21.5, 30.4, 36.3, 38.4, 39.1, 51.5, 53.2, 69.2, 73.7, 121.6, 127.3, 129.7, 131.2, 134.1, 143.5. HRMS–FAB (positive): *m/z* calcd for $C_{18}H_{24}NO_3S$: 334.1477 $[M + 1]^+$; found: 334.1490 $[M + 1]^+$; $[\alpha]_D^{19}$ 7.22 (*c* 0.420, $CHCl_3$, 73% ee). The ee was determined by HPLC analysis using a chiral column [Daicel Chiralpak OD-H: 4 × 250 mm, 254 nm UV detector, r.t., eluent: 20% 2-PrOH in hexane, flow rate: 1.0 mL/min; t_R (minor isomer) = 14 min; t_R (major isomer) = 21 min].

4-Phenyl-2,7-bis(*p*-toluenesulfonyl)-1,3,5,6,8,8a,8b,-heptahydro-2,7-diaza-*as*-indacene (2d)

Colorless solid (mp 170 °C). IR (KBr): 1344, 1159, 665, 550 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.82–1.93 (m, 1 H), 1.98–2.16 (m, 2 H), 2.34–2.53 (m, 1 H), 2.43 (s, 3 H), 2.47 (s, 3 H), 2.55–2.70 (m, 2 H), 2.93 (dd, *J* = 9.0, 9.7 Hz, 1 H), 3.23 (dd, *J* = 3.4, 10.0 Hz, 1 H), 3.32 (dd, *J* = 3.4, 10.0 Hz, 1 H), 3.42 (dd, *J* = 9.0, 9.7 Hz, 1 H), 3.53–3.70 (m, 2 H), 3.98 (d, *J* = 15.6 Hz, 1 H), 7.00–7.07 (m, 2 H), 7.22–7.34 (m, 5 H), 7.37 (d, *J* = 8.2 Hz, 2 H), 7.63 (d, *J* = 8.2 Hz, 2 H), 7.72 (d, *J* = 8.2 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5, 21.6, 30.4, 36.3, 39.4, 50.6, 51.7, 52.8, 53.0, 126.9, 127.3, 127.4, 127.6, 128.5, 129.6, 129.7, 129.8, 131.2, 133.4, 140.0, 143.7, 144.0 (a pair of peaks at the aromatic region is overlapped). HRMS–FAB (positive): *m/z* calcd for $C_{30}H_{33}N_2O_4S_2$: 549.1881 $[M + 1]^+$; found: 549.1881 $[M + 1]^+$; $[\alpha]_D^{18}$ 5.95 (*c* 0.740, $CHCl_3$, 86% ee). The ee was determined by HPLC analysis using a chiral column [Daicel Chiralpak IA-H: 4 × 250 mm, 254 nm UV detector, r.t., eluent: 50% CH_2Cl_2 in hexane, flow rate: 1.0 mL/min; t_R (minor isomer) = 7.7 min; t_R (major isomer) = 8.2 min].

2,2-Bis(methoxycarbonyl)-4-phenyl-7-(*p*-toluenesulfonyl)-1,3,5,6,8,8a,8b-heptahydro-7-aza-*as*-indacene (2e)

Colorless oil. IR (neat): 1734, 1344, 1163, 665, 590, 550 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.87 (dd, *J* = 10.4, 12.8 Hz, 1 H), 1.92–2.02 (m, 1 H), 2.05–2.25 (m, 2 H), 2.30–2.42 (m, 1 H), 2.45 (s, 3 H), 2.53–2.62 (m, 2 H), 2.88 (d, *J* = 17.4 Hz, 1 H), 2.97 (dd, *J* = 8.6, 9.4 Hz, 1 H), 3.10 (d, *J* = 17.4 Hz, 1 H), 3.24 (dd, *J* = 4.5, 9.6 Hz, 1 H), 3.36 (dd, *J* = 4.5, 9.6 Hz, 1 H), 3.42 (dd, *J* = 8.6, 9.4 Hz, 1 H), 3.66 (s, 3 H), 3.72 (s, 3 H), 7.14–7.24 (m, 3 H), 7.27–7.38 (m, 4 H), 7.70–7.76 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5, 31.5, 37.1, 38.4, 39.7, 40.5, 42.3, 52.4, 52.8, 52.9, 53.1, 58.7, 126.7, 127.4, 127.6, 128.2, 129.4, 129.7, 133.4, 135.9, 141.4, 143.5, 171.9, 172.0. HRMS–FAB (positive): *m/z* calcd for $C_{28}H_{32}NO_6S$: 510.1950 $[M + 1]^+$; found: 510.1924 $[M + 1]^+$; $[\alpha]_D^{28}$ 41.1 (*c* 1.21, $CHCl_3$, 92% ee). The ee was determined by HPLC analysis using a chiral column [Daicel Chiralpak IB-H: 4 × 250 mm, 254 nm UV detector, r.t., eluent: 20% 2-PrOH in hexane, flow rate: 1.0 mL/min; t_R (minor isomer) = 15 min; t_R (major isomer) = 16 min].

5-Phenyl-2-(*p*-toluenesulfonyl)-1,3,3a,4,10,10a,10b-heptahydro-2-aza-cyclopenta[*a*]fluorene (2h)

Colorless crystals (mp 143 °C). IR (KBr): 1340, 1165, 667, 594, 546 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.10–2.25 (m, 1 H), 2.30–2.58 (m, 8 H), 2.63 (dd, *J* = 7.6, 16.0 Hz, 1 H), 3.01–3.12 (m, 2 H), 3.30–3.55 (m, 2 H), 6.53 (d, *J* = 8.0 Hz, 1 H), 6.83 (dd, *J* = 7.2, 7.2 Hz, 1 H), 7.06 (dd, *J* = 7.2, 7.2 Hz, 1 H), 7.13–7.25 (m, 3 H), 7.27–7.45 (m, 5 H), 7.75 (d, *J* = 8.4 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5, 34.3, 36.5, 36.9, 41.5, 42.8, 52.6, 53.0, 123.5, 124.8, 126.1, 127.1, 127.4, 127.5, 128.0, 128.2, 128.7, 129.6, 130.1, 137.8, 142.1, 143.5 (two pairs of peaks at the aromatic region are overlapped). HRMS–FAB (positive): *m/z* calcd for $C_{28}H_{28}NO_2S$: 442.1840 $[M + 1]^+$; found: 442.1848 $[M + 1]^+$; $[\alpha]_D^{29}$ 34.2 (*c* 0.655, $CHCl_3$, 99% ee). The ee was determined by HPLC analysis using a chiral column [Daicel Chiralpak OD-H: 4 × 250 mm, 254 nm UV detector, r.t., eluent: 20% 2-PrOH in hexane, flow rate: 1.0 mL/min; t_R (minor isomer) = 15 min; t_R (major isomer) = 17 min]. Crystal data for $C_{28}H_{27}NO_2S$, *M* = 441.59, orthorhombic, space group $P2_12_12_1$ (no. 19), *a* = 7.8895(8) Å, *b* = 15.3909(16) Å, *c* = 19.578(2) Å, *V* = 2377.3(4) $Å^3$, *T* = 193 K, *Z* = 4, μ(Cu-Kα) = 13.943 cm^{-1}; number of reflections measured: total 27727 and unique 4362 (R_{int} = 0.085), *R*1 = 0.0411, *wR*2 = 0.0946, Flack parameter (Friedel pairs = 1863) 0.03(2). CCDC 762243.

4-Methyl-2,9-bis(*p*-toluenesulfonyl)-1,3,5,5a,8,10,10a,10b-octahydro-2,9-diaza-cyclohepta[*g*]indene (2l)

Colorless oil. IR (neat): 1344, 1163, 665, 548 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.49 (s, 3 H), 2.09–2.19 (m, 1 H), 2.43 (s, 3 H), 2.46 (s, 3 H), 2.65–2.87 (m, 4 H), 2.90–2.97 (m, 1 H), 2.98–3.04 (m, 1 H), 3.15–3.24 (m, 2 H), 3.31–3.42 (m, 3 H), 3.91 (d, *J* = 13.6 Hz, 1 H), 5.01–5.12 (m, 1 H), 5.62–5.72 (m, 1 H), 7.29–7.38 (m, 4 H), 7.64–7.74 (m, 4 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.6, 21.9, 36.3, 39.5, 40.6, 44.6, 49.9, 51.5, 52.5, 53.1, 127.4, 128.0, 128.4, 129.8, 129.9, 130.4, 130.8, 131.9, 134.2, 143.7, 143.9 (a pair of peaks at the aliphatic region and a pair of peaks at the aromatic region are overlapped). HRMS–FAB (positive): *m/z* calcd for $C_{27}H_{33}N_2O_4S_2$: 513.1881 $[M + 1]^+$; found: 513.1885 $[M + 1]^+$; $[\alpha]_D^{17}$ –15.9 (*c* 1.00, $CHCl_3$, 98% ee). The ee was determined by HPLC analysis using a chiral column [Daicel Chiralpak Doubly-arrayed IC-H: 4 × 250 mm, 254nm UV detector, r.t., eluent: 80% CH_2Cl_2 in hexane, flow rate: 0.5 mL/min; t_R (minor isomer) = 48 min; t_R (major isomer) = 58 min].

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(14) The counter anion of the Rh catalyst did not affect the yield of **2a** and its ee (BF_4: 74%, 87% ee, OTf: 69%, 86% ee).

(15) The ene-type products and their isomerized products were also formed in each entry.

(16) The reaction of carbon-tethered dienyne **1f** did not proceeded even at 80 °C. Oxygen-tethered dienyne **1g** was promptly consumed at r.t. but ene-type products were formed and no cycloadduct could be detected.

(17) Based on Scheme 2, the absolute configuration of the tricyclic product would be determined at the formation of the bicyclic metallacyclopentene, which is the same intermediate as that of [2+2+2] cycloaddition of enediynes, see ref. 7a.