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Tetrahedron
Tetrahedron 63 (2007) 12853–12859

Rhodium-catalyzed enantioselective [2+2+2] cycloaddition of diynes with unfunctionalized alkenes

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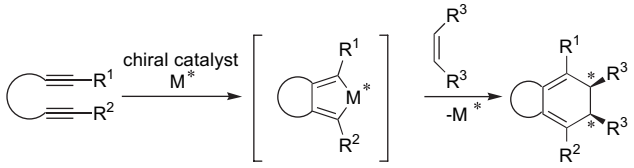
Received 19 September 2007; revised 12 October 2007; accepted 13 October 2007
Available online 16 October 2007

Abstract—A chiral rhodium complex catalyzed an enantioselective [2+2+2] cycloaddition of unsymmetrical diynes with norbornene, and tetracyclic products were obtained in good to excellent ee. The cycloaddition of a symmetrical diyne with styrene derivatives as coupling partners gave bicyclic products in good ee.

1. Introduction

Transition metal-catalyzed [2+2+2] cycloaddition of C2 motifs, such as alkynes and alkenes, is a well established protocol for the synthesis of six-membered ring systems.[1] In 2004, three independent reports of enantioselective cyclotrimerization along with the generation of axial chirality made a fresh development in [2+2+2] cycloaddition as a synthetic tool.[2,3] Various types of enantioselective [2+2+2] cycloaddition of three alkyne moieties were successively published using iridium,[4] rhodium,[5] and cobalt complexes.[6] In contrast, the reaction of two alkyne and an alkene moieties is another pattern of [2+2+2] cycloaddition, which gives cyclohexa-1,3-dienes, and several transition metal complexes have been reported as efficient catalysts.[7,8] Evans and we independently realized the first asymmetric version of the [2+2+2] cycloaddition of enynes with monoalkynes using chiral Rh catalysts.[9] We further published the enantioselective [2+2+2] cycloaddition of symmetrical diynes with 1,1-disubstituted alkenes as a new strategy for the construction of quaternary carbon stereocenters, where we used enoates and enones as alkene motifs.[10]

We here report an enantioselective [2+2+2] cycloaddition of unsymmetrical diynes with symmetrical 1,2-disubstituted alkenes, which gives multicyclic products with two adjacent asymmetric carbon stereocenters (Scheme 1).



Scheme 1. [2+2+2] Cycloaddition of unsymmetrical diynes with symmetrical alkenes.

In particular, we focused on unfunctionalized alkenes and chose norbornene as a coupling partner.[11] The reaction of symmetrical diynes with 1,1-disubstituted alkenes without functional group is also discussed.

2. Results and discussion

2.1. Enantioselective [2+2+2] cycloaddition of unsymmetrical diynes with norbornene derivatives

We examined the reaction of norbornene with nitrogen-tethered diyne **1a** with an ester functionality on its alkyne terminus because methoxycarbonyl group induced high enantioselectivity in the Rh-catalyzed enantioselective [2+2] cycloaddition of alkyne and norbornene.[12] Various phosphorus bidentate ligands were investigated and selected examples are listed in Table 1. In the case of conventional BINAP, tetracyclic cycloadduct **2a** was obtained in moderate yield with good ee (entry 1). SYNPHOS, which has 1,4-dioxane structures, apparently gave better results (entry 2). When 1,4-dioxane was replaced with 1,3-dioxolane (SEGPHOS), the reaction was facilitated: the diyne was completely consumed within 1 h and higher ee was achieved;

Keywords: Cycloaddition; Enantioselective; Norbornene; Rhodium; Styrene.
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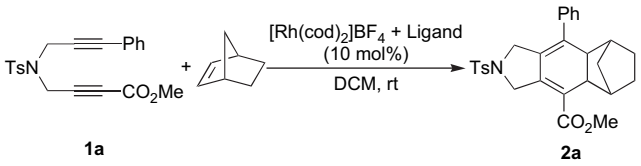
0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.10.053

Table 1. Investigation of appropriate chiral ligands for Rh complex in the [2+2+2] cycloaddition of diyne **1a** with norbornene



1a **2a**

Entry[a]	Ligand[b]	Time (h)	Yield of **2a** (%)	ee (%)
1	BINAP	3	52	75
2	SYNPHOS	10	78	78
3	SEGPHOS	1	31	85
4	DIFLUORPHOS	6	83	96
5	MeDUPHOS	48	21	87
6	BDPP	48	Trace	—

[a] Diyne **1a**/norbornene=1/2.

[b] (*S*)- and (*S*,*S*) isomers were used. BINAP: 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl; SYNPHOS: 6,6′-bis(diphenylphosphino)-2,2′,3,3′-tetrahydro-5,5′-bi-1,4-benzodioxin; SEGPHOS: 5,5′-bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole; DIFLUORPHOS: 5,5′-bis(diphenylphosphino)-2,2,2′,2′-tetrafluoro-4,4′-bi-1,3-benzodixole; MeDUPHOS: 1,2-bis(2,5-diisopropylphospholano)benzene; BDPP: 2,4-bis(diphenylphosphino)pentane.

however, the yield was low because of the formation of various unidentified by-products (entry 3). DIFLUORPHOS with 2,2-difluoro-1,3-dioxolane structures gave the best results in both yield and ee and the absolute configuration of compound **2a** was ascertained by X-ray measurements (entry 4 and Fig. 1). MeDUPHOS also induced high enantioselectivity but diyne **1a** remained after 48 h and yield was low (entry 5). The Rh–BDPP complex showed almost no catalytic activity (entry 6).

We next examined the influence of the substituent of the alkyne terminus on the enantioselectivity (Table 2). When acetyl group was introduced in place of methoxycarbonyl group, the enantiomeric excess of the corresponding product **2b** remained high, but various by-products were formed (entry 1). On the contrary, methoxymethyl and methyl groups gave obviously low enantioselectivity (entries 2 and 3). These results imply that oxygen atom of carbonyl group

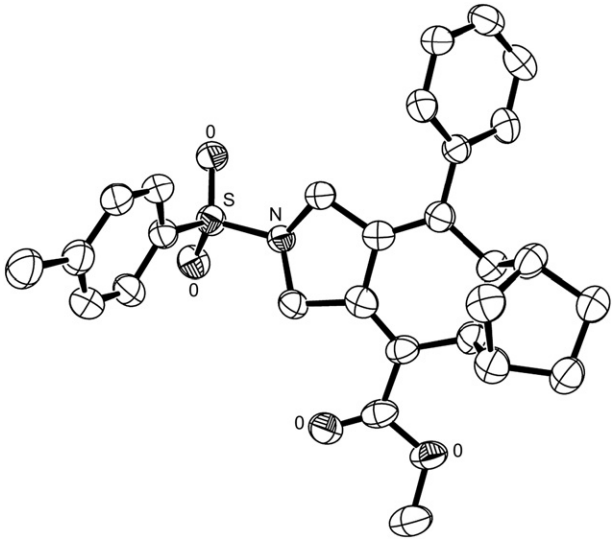
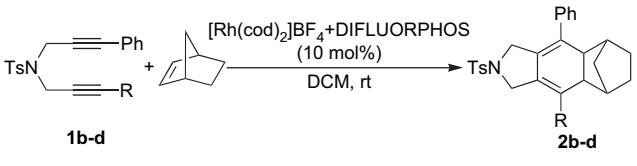


Figure 1. ORTEP diagram of compound **2a**.

Table 2. The reaction of diynes with a few substituents on their alkyne termini



1b-d **2b-d**

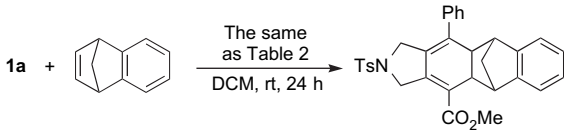
Entry[a]	R	Diyne	Time (h)	Yield (%)	ee (%)
1	C(=O)Me	**1b**	0.5	56 (**2b**)	95
2	CH_2OMe	**1c**	1	70 (**2c**)	69
3	Me	**1d**	1	34 (**2d**)	69

[a] Diyne/norbornene=1/2.

plays an important role in high enantioselectivity and that ester functionality controls the reactivity of the alkyne moiety for selective cross-coupling of metallacyclopentadiene intermediate and norbornene.

Various diynes, possessing methoxycarbonyl on their termini, were submitted to the [2+2+2] cycloaddition with norbornene using in situ-prepared Rh–DIFLUORPHOS catalyst (Table 3). Electron-donating and -withdrawing groups on aryl group were tolerable, and the corresponding tetracyclic products **2e**, **2f** were obtained in high yield and ee (entries 1 and 2). Carbon- and oxygen-tethered diynes **1g**, **1h** were also appropriate substrates (entries 3 and 4). In place of aryl groups, methyl group could be introduced as a substituent on the alkyne terminus, and almost perfect enantioselectivity was achieved (entry 5).

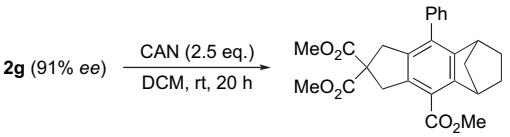
As a norbornene derivative, we examined the reaction of benzonorbornadiene with diyne **1a** under the same reaction conditions: pentacyclic product **2j** was obtained in acceptable yield with high ee (Eq. 1).



(1)

2j 67%, 92% *ee*

Further transformation of tetracyclic adduct **2g** using CAN (cerium ammonium nitrate) gave aromatized product **3g** in high yield (Eq. 2).[13] Therefore, the present protocol could be used for the synthesis of chiral benzonorbornenes.



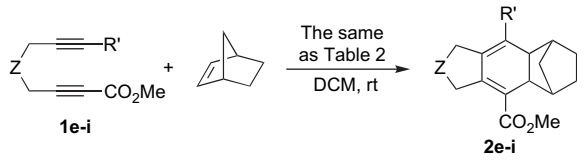
(2)

3g 96%, 90% *ee*

2.2. Enantioselective [2+2+2] cycloaddition of a symmetrical diyne with styrene derivatives

In our previous communication, we used enoates and enones as alkene motifs in the enantioselective [2+2+2] cycloaddition

Table 3. Enantioselective [2+2+2] cycloaddition of various diynes with norbornene

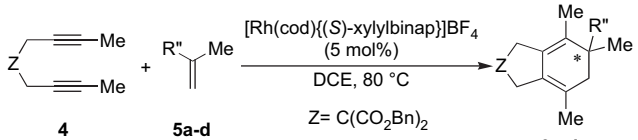


Entry[a]	Z	R′	Diyne	Time (h)	Yield (%)	ee (%)
1	NTs	4-(MeO)C_6H_4	**1e**	1	90 (**2e**)	95
2	NTs	4-(EtO_2C)C_6H_4	**1f**	4	93 (**2f**)	96
3	$C(CO_2Me)_2$	C_6H_5	**1g**	1	71 (**2g**)	91
4	O	C_6H_5	**1h**	3	51 (**2h**)	95
5	$C(CO_2Me)_2$	Me	**1i**	1	82 (**2i**)	99

[a] Diyne/norbornene=1/2.

with symmetrical diynes.[10] We have considered that coordination of oxygen atom of carbonyl moiety to metal center of the chiral catalyst realized high enantioselectivity. As a control experiment, we chose α-methylstyrene (**5a**) and submitted to the reaction using isolated Rh–xylylBINAP catalyst (Table 4, entry 1): the ee of cycloadduct **6a** was almost 90%,[14,15] however, which was lower than that in the reaction of methyl methacrylate (98% ee).[16] These results imply that high enantioselectivity could be achieved even using unfunctionalized alkene but that oxygen atom of carbonyl moiety plays a pivotal role for the further improvement of enantioselectivity. Styrene derivatives **5b**, **5c** with electron-donating and -withdrawing group, respectively, also gave the corresponding products **6b**, **6c** yet in lower ee (entries 2 and 3). 2,3-Dimethylbuta-1,3-diene (**5d**) could also react with diyne **4** and moderate ee was achieved (entry 4).

Table 4. Enantioselective [2+2+2] cycloaddition of diyne **4** with styrene derivatives and a diene



Entry	R″	Alkene	Time (h)	Yield (%)	ee (%)
1[a]	C_6H_5	**5a**	0.2	78 (**6a**)	88
2[a]	4-(MeO)C_6H_4	**5b**	0.2	78 (**6b**)	72
3[a]	4-FC_6H_4	**5c**	0.2	75 (**6c**)	73
4[b]	CH_2=CMe	**5d**	14	37 (**6d**)	55

[a] Diyne **4**/alkene=1/10 and the diyne was added dropwise over 30 min.
[b] Diyne **4**/alkene=1/20 and the reaction was examined at 60 °C.

3. Conclusion

In summary, we have developed highly enantioselective intramolecular [2+2+2] cycloaddition of diynes with unfunctionalized alkenes using chiral Rh catalysts. The reaction of unsymmetrical diynes with norbornene gave chiral tetracyclic cyclohexa-1,3-dienes in high to excellent ee and that of a symmetrical diyne with styrene derivatives gave bicyclic cyclohexa-1,3-dienes in good ee.

4. Experimental

4.1. General

Anhydrous dichloromethane and dichloroethane are commercially available. They were dried over molecular sieves 4Å (MS 4Å) and degassed by argon bubbling before use. All reactions were examined under an argon atmosphere. IR spectra were recorded with Horiba FT730 spectrophotometer. NMR spectra were measured with JEOL AL-400 and Lambda500 spectrometers using tetramethylsilane as an internal standard and $CDCl_3$ as a solvent except ^{13}C NMR of diyne **1a**. Mass spectra were measured with JEOL JMS-SX102A. Optical rotation was measured with Jasco DIP-1000 polarimeter.

4.2. Typical experimental procedure for enantioselective [2+2+2] cycloaddition of diyne 1 with norbornene (entry 4 in Tables 1–3)

Under an atmosphere of argon, DIFLUORPHOS (6.8 mg, 0.010 mmol) and $[Rh(cod)_2]BF_4$ (4.1 mg, 0.010 mmol) were stirred in dichloromethane (1.0 mL) at room temperature for 5 min. After the reaction vessel was purged with hydrogen gas, the solution was stirred for further 30 min. Both the solvent and hydrogen gas were removed under reduced pressure; then the reaction vessel was filled with argon gas. After the addition of dichloromethane (0.40 mL), diyne (0.10 mmol) in dichloromethane (0.80 mL) and norbornene (0.20 mmol) in dichloromethane (0.80 mL) were subsequently added, and the reaction mixture was stirred at room temperature. After the completion of reaction, the volatiles were removed under reduced pressure, and the obtained crude products were purified by thin-layer chromatography to give a pure cycloadduct.

4.2.1. Methyl 4-*N*-(3-phenylprop-2-ynyl)-*N*-tosylamino-but-2-ynoate (1a). Yellow solid; mp 65 °C; IR (CH_2Cl_2) 2243, 1718, 1354, 1259, 1165 cm^{-1}; ^1H NMR δ 2.37 (s, 3H), 3.72 (s, 3H), 4.35 (s, 2H), 4.39 (s, 2H), 7.16–7.21 (m, 2H), 7.23–7.34 (m, 5H), 7.76 (d, J=6.6 Hz, 2H); ^{13}C NMR (C_6D_6) δ 21.1, 36.7, 37.9, 52.0, 77.6, 80.8, 81.9, 86.5, 122.6, 128.2, 128.3, 128.3, 128.6, 130.0, 132.0, 143.7, 153.0. Anal. Calcd for $C_{21}H_{19}NO_4S$: C, 66.12; H, 5.02; N, 3.67. Found: C, 66.12; H, 4.95; N, 3.61. HRMS (FAB, positive) m/z calcd for $C_{21}H_{20}NO_4S$, 382.1113 ($[M+H]^+$); found, 382.1106 ($[M+H]^+$).

4.2.2. 3-Acetyl-*N*-(3-phenylprop-2-ynyl)-*N*-tosylprop-2-yn-1-amine (1b). Yellow oil; IR (CH_2Cl_2) 2214, 1682, 1354, 1165 cm^{-1}; ^1H NMR δ 2.17 (s, 3H), 2.37 (s, 3H), 4.38 (s, 2H), 4.39 (s, 2H), 7.18–7.36 (m, 7H), 7.76 (d, J=8.3 Hz, 2H); ^{13}C NMR δ 21.4, 32.3, 36.7, 37.7, 80.8, 84.0, 84.6, 86.3, 121.8, 127.9, 128.2, 128.7, 129.7, 131.6, 134.9, 144.2, 183.4. HRMS (FAB, positive) m/z calcd for $C_{21}H_{20}NO_3S$, 366.1164 ($[M+H]^+$); found, 366.1185 ($[M+H]^+$).

4.2.3. 3-Methoxy-*N*-(3-phenylprop-2-ynyl)-*N*-tosylbut-2-yn-1-amine (1c). Pale yellow oil; IR (CH_2Cl_2) 2241, 1350, 1163, 1093 cm^{-1}; ^1H NMR δ 2.34 (s, 3H), 3.27 (s, 3H), 3.96 (s, 2H), 4.25 (s, 2H), 4.39 (s, 2H), 7.13–7.19 (m, 2H), 7.21–7.31 (m, 5H), 7.75 (d, J=8.3 Hz, 2H); ^{13}C NMR

δ 21.3, 36.7, 37.2, 57.4, 59.6, 79.0, 81.3, 81.5, 85.7, 122.0, 127.8, 128.0, 128.4, 129.4, 131.5, 135.2, 143.7. HRMS (FAB, positive) *m/z* calcd for $C_{21}H_{22}NO_3S$, 368.1320 ($[M+H]^+$); found, 368.1335 ($[M+H]^+$).

4.2.4. *N*-(3-Phenylprop-2-ynyl)-*N*-tosylbut-2-yn-1-amine (1d). Dark yellow oil; IR (CH_2Cl_2) 2920, 2241, 1352, 1163 cm^{-1}; ^1H NMR δ 1.68 (t, *J*=2.4 Hz, 3H), 2.35 (s, 3H), 4.13 (q, *J*=2.4 Hz, 2H), 4.38 (s, 2H), 7.14–7.19 (m, 2H), 7.22–7.32 (m, 5H), 7.75 (d, *J*=8.3 Hz, 2H); ^{13}C NMR δ 3.4, 21.4, 37.0, 37.0, 71.6, 81.6, 81.8, 85.5, 122.2, 127.9, 128.1, 128.4, 129.4, 131.5, 135.4, 143.6. HRMS (FAB, positive) *m/z* calcd for $C_{20}H_{20}NO_3S$, 338.1214 ($[M+H]^+$); found, 338.1217 ($[M+H]^+$).

4.2.5. Methyl 4-*N*-(3-(4-methoxyphenyl)prop-2-ynyl)-*N*-tosylaminobut-2-ynoate (1e). Yellow solid; mp 79 °C; IR (CH_2Cl_2) 2243, 1716, 1354, 1250, 1163, 1093 cm^{-1}; ^1H NMR δ 2.38 (s, 3H), 3.72 (s, 3H), 3.79 (s, 3H), 4.34 (s, 2H), 4.36 (s, 2H), 6.78 (d, *J*=8.7 Hz, 2H), 7.13 (d, *J*=8.7 Hz, 2H), 7.29 (d, *J*=8.2 Hz, 2H), 7.75 (d, *J*=8.2 Hz, 2H); ^{13}C NMR δ 21.5, 36.4, 37.8, 52.7, 55.2, 76.9, 79.3, 80.5, 86.3, 113.8, 113.9, 127.8, 129.7, 133.1, 134.8, 144.2, 153.1, 159.8. Anal. Calcd for $C_{22}H_{21}NO_5S$: C, 64.22; H, 5.14; N, 3.40. Found: C, 63.97; H, 4.97; N, 3.38. HRMS (FAB, positive) *m/z* calcd for $C_{22}H_{22}NO_5S$, 412.1218 ($[M+H]^+$); found, 412.1182 ($[M+H]^+$).

4.2.6. Methyl 4-*N*-(3-(4-ethoxycarbonylphenyl)prop-2-ynyl)-*N*-tosylaminobut-2-ynoate (1f). Yellow solid; mp 69 °C; IR (CH_2Cl_2) 2243, 1716, 1356, 1273, 1165 cm^{-1}; ^1H NMR δ 1.39 (t, *J*=7.1 Hz, 3H), 2.37 (s, 3H), 3.72 (s, 3H), 4.35 (s, 2H), 4.38 (q, *J*=7.1 Hz, 2H), 4.41 (s, 2H), 7.24 (d, *J*=8.6 Hz, 2H), 7.30 (d, *J*=8.1 Hz, 2H), 7.76 (d, *J*=8.1 Hz, 2H), 7.94 (d, *J*=8.6 Hz, 2H); ^{13}C NMR δ 14.3, 21.5, 36.7, 37.7, 52.8, 61.2, 77.1, 80.2, 83.8, 85.6, 126.3, 127.9, 129.3, 130.0, 130.3, 131.5, 134.8, 144.4, 153.0, 165.8. Anal. Calcd for $C_{24}H_{23}NO_6S$: C, 63.56; H, 5.11; N, 3.09. Found: C, 63.25; H, 5.06; N, 2.86. HRMS (FAB, positive) *m/z* calcd for $C_{24}H_{24}NO_6S$, 454.1324 ($[M+H]^+$); found, 454.1310 ($[M+H]^+$).

4.2.7. Trimethyl 7-phenyl hepta-1,6-diyne-1,4,4-tricarboxylate (1g). Pale yellow oil; IR (CH_2Cl_2) 2243, 1755, 1747, 1327, 1259 cm^{-1}; ^1H NMR δ 3.21 (s, 4H), 3.75 (s, 3H), 3.80 (s, 6H), 7.25–7.31 (m, 3H), 7.33–7.39 (m, 2H); ^{13}C NMR δ 23.1, 24.0, 52.7, 53.3, 56.5, 75.4, 83.0, 83.2, 84.2, 122.7, 128.2, 131.6, 153.6, 168.7 (a signal in the aromatic region was overlapped). HRMS (FAB, positive) *m/z* calcd for $C_{19}H_{19}O_6$, 343.1181 ($[M+H]^+$); found, 343.1179 ($[M+H]^+$).

4.2.8. (3-Methxoxycarbonyl)prop-2-ynyl 3-phenylprop-2-ynyl ether (1h). Pale yellow oil; IR (CH_2Cl_2) 2239, 1720, 1255 cm^{-1}; ^1H NMR δ 3.74 (s, 3H), 4.42 (s, 2H), 4.46 (s, 2H), 7.27–7.34 (m, 3H), 7.42–7.46 (m, 2H); ^{13}C NMR δ 52.5, 55.8, 57.6, 76.7, 82.7, 83.4, 87.1, 121.9, 128.1, 128.4, 131.5, 153.1. HRMS (FAB, positive) *m/z* calcd for $C_{14}H_{11}O_3$, 227.0708 ($[M-1]^+$); found, 227.0695 ($[M-1]^+$).

4.2.9. Trimethyl octa-1,6-diyne-1,4,4-tricarboxylate (1i). Pale yellow oil; IR (CH_2Cl_2) 2243, 1747, 1728, 1265, 1217 cm^{-1}; ^1H NMR δ 1.76 (s, 3H), 2.92 (s, 2H), 3.13 (s, 2H), 3.75 (s, 3H), 3.78 (s, 6H); ^{13}C NMR δ 3.4, 22.8, 23.2, 52.6, 53.1, 56.4, 72.3, 75.2, 79.7, 83.3, 153.5, 168.8. HRMS (FAB, positive) *m/z* calcd for $C_{14}H_{17}O_6$, 281.1025 ($[M+H]^+$); found, 281.1041 ($[M+H]^+$).

4.2.10. 3-Methylcarbonyl-9-phenyl-6-tosyl-6-azatetracyclo[9.2.1.0^{2,10}.0^{4,8}]tetradeca-3,8-diene (2a). Pale yellow oil; IR (CH_2Cl_2) 1703, 1350, 1248, 1165 cm^{-1}; ^1H NMR δ 1.08 (d, *J*=9.8 Hz, 1H), 1.23–1.37 (m, 1H), 1.42–1.55 (m, 4H), 1.92 (br s, 1H), 2.20 (br s, 1H), 2.43 (s, 3H), 2.90 (d, *J*=12.1 Hz, 1H), 2.98 (d, *J*=12.1 Hz, 1H), 3.74–3.81 (m, 1H), 3.78 (s, 3H), 4.02 (dd, *J*=2.3, 14.3 Hz, 1H), 4.26 (dd, *J*=1.8, 17.1 Hz, 1H), 4.45 (d, *J*=17.1 Hz, 1H), 7.11 (d, *J*=7.1 Hz, 2H), 7.28–7.41 (m, 5H), 7.67 (d, *J*=8.1 Hz, 2H); ^{13}C NMR δ 21.5, 30.0, 30.3, 34.2, 43.7, 43.8, 47.0, 49.3, 50.7, 51.6, 53.5, 119.3, 126.8, 127.8, 127.9, 128.7, 129.1, 129.7, 133.0, 137.4, 139.5, 143.7, 143.9, 167.6. HRMS (FAB, positive) *m/z* calcd for $C_{28}H_{30}NO_4S$, 476.1895 ($[M+H]^+$); found, 476.1873 ($[M+H]^+$); $[\alpha]_D^{24}$ 130.0 (*c* 1.29, $CHCl_3$, 95% ee). The enantiomeric excess was determined by chiral HPLC analysis using a chiral column (Daicel Chiralpak IA×2: 4×250 mm, 254 nm UV detector, rt, eluent: 30% dichloromethane in hexane, flow rate: 1.0 mL/min, retention time: 22 min for major isomer and 24 min for minor isomer). Crystal data: $C_{28}H_{29}O_4NS$, *M*=475.60, monoclinic, space group $P2_1/C$ (#14), *a*=12.8725(8) Å, *b*=8.9895(6) Å, *c*=21.1398(12) Å, β=100.016(3)°, *V*=2409.0(3) Å^3, *T*=123 K, *Z*=4, μ(Cu Kα)=14.777 cm^{-1}, number of reflections measured: total 41,666, unique: 4411 (R_{int}=0.095), *R*1=0.0693, *wR*2=0.1854 (CCDC 660625).

4.2.11. 3-Acetyl-9-phenyl-6-tosyl-6-azatetracyclo-[9.2.1.0^{2,10}.0^{4,8}]tetradeca-3,8-diene (2b). Pale yellow oil; IR (CH_2Cl_2) 1680, 1348, 1163 cm^{-1}; ^1H NMR δ 1.15 (d, *J*=10.0 Hz, 1H), 1.24–1.77 (m, 5H), 1.94 (br s, 1H), 2.09 (br s, 1H), 2.25 (s, 3H), 2.44 (s, 3H), 2.94 (d, *J*=11.7 Hz, 1H), 3.10 (d, *J*=11.7 Hz, 1H), 3.82 (dd, *J*=1.7, 14.1 Hz, 1H), 3.96 (dd, *J*=2.7, 14.1 Hz, 1H), 4.20 (dd, *J*=2.2, 17.6 Hz, 1H), 4.37 (dd, *J*=1.2, 17.6 Hz, 1H), 7.10–7.15 (m, 2H), 7.28–7.35 (m, 3H), 7.36–7.41 (m, 2H), 7.68 (d, *J*=8.3 Hz, 2H); ^{13}C NMR δ 21.5, 28.0, 30.3, 30.4, 34.3, 43.3, 44.6, 47.6, 49.8, 50.6, 53.9, 126.4, 126.7, 127.9, 128.0, 128.7, 129.6, 129.7, 132.8, 137.0, 139.3, 142.1, 143.7, 199.8. HRMS (FAB, positive) *m/z* calcd for $C_{28}H_{29}NO_3S$, 459.1868; found, 459.1866; $[\alpha]_D^{24}$ 108.2 (*c* 1.26, $CHCl_3$, 95% ee). The enantiomeric excess was determined by chiral HPLC analysis using a chiral column (Daicel Chiralpak AD-H: 4×250 mm, 254 nm UV detector, rt, eluent: 10% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 22 min for major isomer and 24 min for minor isomer).

4.2.12. 3-Methoxymethyl-9-phenyl-6-tosyl-6-azatetracyclo[9.2.1.0^{2,10}.0^{4,8}]tetradeca-3,8-diene (2c). Pale yellow oil; IR (CH_2Cl_2) 1348, 1163, 1095 cm^{-1}, ^1H NMR δ 1.07 (d, *J*=9.5 Hz, 1H), 1.18–1.69 (m, 5H), 1.93 (br s, 1H), 2.32 (br s, 1H), 2.43 (s, 3H), 2.56 (d, *J*=11.7 Hz, 1H), 2.91 (d, *J*=11.7 Hz, 1H), 3.32 (s, 3H), 3.72 (d, *J*=13.9 Hz, 1H), 3.81 (d, *J*=12.1 Hz, 1H), 3.87–4.00 (m, 3H), 4.11 (d, *J*=13.9 Hz, 1H), 7.10 (d, *J*=7.6 Hz, 2H), 7.21–7.39 (m, 5H), 7.66 (d, *J*=7.8 Hz, 2H); ^{13}C NMR δ 21.5, 29.8, 30.4, 34.4, 43.9, 44.2, 46.4, 48.6, 50.5, 51.2, 58.3, 72.1, 125.3, 127.0, 127.1, 127.8, 128.3, 128.5, 129.6, 130.4, 130.8,

132.8, 140.4, 143.6. HRMS (FAB, positive) *m/z* calcd for $C_{28}H_{31}NO_3S$, 461.2025; found, 461.2026; $[\alpha]_D^{29}$ 79.6 (*c* 0.30, $CHCl_3$, 69% ee). The enantiomeric excess was determined by chiral HPLC analysis using a chiral column (Daicel Chiralpak AD-H: 4×250 mm, 254 nm UV detector, rt, eluent: 10% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 13 min for minor isomer and 35 min for major isomer).

4.2.13. 3-Methyl-9-phenyl-6-tosyl-6-azatetracyclo-[9.2.1.0^{2,10}.0^{4,8}]tetradeca-3,8-diene (2d). Yellow oil; IR (CH_2Cl_2) 2954, 1348, 1163 cm^{-1}; ^1H NMR δ 1.04 (d, *J*=9.8 Hz, 1H), 1.19–1.71 (m, 5H), 1.65 (s, 3H), 1.94 (br s, 1H), 2.29 (br s, 1H), 2.37 (d, *J*=11.3 Hz, 1H), 2.43 (s, 3H), 2.88 (d, *J*=11.3 Hz, 1H), 3.75 (dd, *J*=2.0, 14.1 Hz, 1H), 3.83 (d, *J*=13.4 Hz, 1H), 3.97 (d, *J*=13.4 Hz, 1H), 4.03 (dd, *J*=2.4, 14.1 Hz, 1H), 7.09–7.12 (m, 2H), 7.20–7.27 (m, 1H), 7.28–7.37 (m, 4H), 7.66–7.68 (m, 2H); ^{13}C NMR δ 18.4, 21.5, 29.7, 30.4, 34.2, 43.8, 44.1, 48.6, 50.4, 50.7, 51.7, 100.6, 125.6, 126.8, 127.1, 127.8, 128.2, 128.5, 129.6, 133.0, 140.7, 143.5 (a signal in the aromatic region was overlapped). HRMS (FAB, positive) *m/z* calcd for $C_{27}H_{29}NO_2S$, 431.1919; found, 431.1875; $[\alpha]_D^{24}$ 41.7 (*c* 1.30, $CHCl_3$, 69% ee). The enantiomeric excess was determined by chiral HPLC analysis using a chiral column (Daicel Chiralpak IA: 4×250 mm, 254 nm UV detector, rt, eluent: 5% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 13 min for minor isomer and 20 min for major isomer).

4.2.14. 3-Methoxycarbonyl-9-(4-methoxyphenyl)-6-tosyl-6-azatetracyclo[9.2.1.0^{2,10}.0^{4,8}]tetradeca-3,8-diene (2e). Pale yellow oil; IR (CH_2Cl_2) 1701, 1348, 1244, 1163 cm^{-1}; ^1H NMR δ 1.06 (d, *J*=9.5 Hz, 1H), 1.26–1.38 (m, 1H), 1.46–1.48 (m, 4H), 1.92 (br s, 1H), 2.19 (br s, 1H), 2.43 (s, 3H), 2.88 (d, *J*=11.9 Hz, 1H), 2.97 (d, *J*=11.9 Hz, 1H), 3.73–3.88 (m, 1H), 3.77 (s, 3H), 3.84 (s, 3H), 4.03 (d, *J*=14.1 Hz, 1H), 4.23 (d, *J*=17.2 Hz, 1H), 4.46 (d, *J*=17.2 Hz, 1H), 6.90 (d, *J*=8.3 Hz, 2H), 7.07 (d, *J*=8.3 Hz, 2H), 7.31 (d, *J*=7.8 Hz, 2H), 7.67 (d, *J*=7.8 Hz, 2H); ^{13}C NMR δ 21.5, 30.0, 30.3, 34.2, 43.6, 44.0, 47.0, 49.0, 51.0, 51.6, 53.5, 55.3, 114.0, 118.8, 127.8, 128.1, 128.3, 129.7, 131.7, 133.0, 137.2, 143.7, 144.2, 159.2, 167.6. HRMS (FAB, positive) *m/z* calcd for $C_{29}H_{31}NO_5S$, 505.1923; found, 505.1921; $[\alpha]_D^{25}$ 162.7 (*c* 1.15, $CHCl_3$, 95% ee). The enantiomeric excess was determined by chiral HPLC analysis using a chiral column (Daicel Chiralpak IA: 4×250 mm, 254 nm UV detector, rt, eluent: 30% dichloromethane in hexane, flow rate: 1.0 mL/min, retention time: 12 min for minor isomer and 14 min for major isomer).

4.2.15. 3-Methoxycarbonyl-9-(4-ethoxycarbonylphenyl)-6-tosyl-6-azatetracyclo[9.2.1.0^{2,10}.0^{4,8}]tetradeca-3,8-diene (2f). Pale yellow oil; IR (CH_2Cl_2) 1709, 1350, 1261, 1165 cm^{-1}; ^1H NMR δ 1.10 (d, *J*=9.9 Hz, 1H), 1.24–1.35 (m, 1H), 1.41 (t, *J*=7.1 Hz, 3H), 1.45–1.53 (m, 4H), 1.87 (br s, 1H), 2.22 (br s, 1H), 2.44 (s, 3H), 2.92 (d, *J*=12.1 Hz, 1H), 2.99 (d, *J*=12.1 Hz, 1H), 3.73 (dd, *J*=2.0, 14.5 Hz, 1H), 3.78 (s, 3H), 4.00 (dd, *J*=2.6, 14.5 Hz, 1H), 4.27 (dd, *J*=2.4, 17.3 Hz, 1H), 4.40 (dq, J_d=1.6 Hz, J_q=7.1 Hz, 2H), 4.45 (dd, *J*=1.9, 17.3 Hz, 1H), 7.19 (d, *J*=8.6 Hz, 2H), 7.31 (d, *J*=8.1 Hz, 2H), 7.66 (d, *J*=8.1 Hz, 2H), 8.05 (d, *J*=8.6 Hz, 2H); ^{13}C NMR δ 14.3, 21.5, 30.0, 30.4, 34.2, 43.7, 43.8, 46.9, 49.1, 50.6, 51.7, 53.4, 61.1, 120.1, 126.8, 127.8, 129.7, 130.0, 130.1, 132.9, 136.3, 143.5, 143.8, 144.1, 166.0, 167.4. HRMS (FAB, positive) *m/z* calcd for $C_{31}H_{34}NO_6S$, 548.2107 ($[M+H]^+$); found, 458.2109 ($[M+H]^+$); $[\alpha]_D^{40}$ 100.7 (*c* 1.60, $CHCl_3$, 95% ee). The enantiomeric excess was determined by chiral HPLC analysis using a chiral column (Daicel Chiralpak IA: 4×250 mm, 254 nm UV detector, rt, eluent: 30% 2-propanol in hexane, flow rate: 1.5 mL/min, retention time: 31 min for minor isomer and 33 min for major isomer).

4.2.16. Trimethyl 9-phenyltetracyclo[9.2.1.0^{2,10}.0^{4,8}]-tetradeca-3,8-diene-3,6,6-tricarboxylate (2g). Yellow oil; IR (CH_2Cl_2) 1736, 1705, 1244, 1203 cm^{-1}; ^1H NMR δ 1.10 (d, *J*=9.7 Hz, 1H), 1.28–1.37 (m, 1H), 1.43–1.53 (m, 3H), 1.60 (d, *J*=9.7 Hz, 1H), 1.95 (br s, 1H), 2.21 (br s, 1H), 2.74 (d, *J*=16.7 Hz, 1H), 2.99 (d, *J*=12.1 Hz, 1H), 3.03 (d, *J*=12.1 Hz, 1H), 3.13 (dd, *J*=2.6, 16.7 Hz, 1H), 3.32 (dd, *J*=2.3, 18.8 Hz, 1H), 3.58 (d, *J*=18.8 Hz, 1H), 3.63 (s, 3H), 3.75 (s, 3H), 3.77 (s, 3H), 7.21–7.29 (m, 3H), 7.33–7.38 (m, 2H); ^{13}C NMR δ 30.1, 30.3, 34.1, 38.3, 41.0, 43.8, 44.0, 47.0, 49.3, 51.3, 52.8, 52.8, 58.0, 119.9, 127.2, 127.4, 128.3, 132.0, 137.0, 140.6, 147.2, 168.5, 171.6, 171.9. HRMS (FAB, positive) *m/z* calcd for $C_{26}H_{28}O_6$, 436.1886; found, 436.1882; $[\alpha]_D^{29}$ 164.3 (*c* 1.16, $CHCl_3$, 91% ee). The enantiomeric excess was determined by chiral HPLC analysis using a chiral column (Daicel Chiralpak IA: 4×250 mm, 254 nm UV detector, rt, eluent: 5% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 10 min for major isomer and 11 min for minor isomer).

4.2.17. 3-Methoxycarbonyl-9-phenyl-6-tosyl-6-oxatetracyclo[9.2.1.0^{2,10}.0^{4,8}]tetradeca-3,8-diene (2h). Colorless oil; IR (CH_2Cl_2) 1705, 1248, 1128 cm^{-1}; ^1H NMR δ 1.15 (d, *J*=10.0 Hz, 1H), 1.35–1.46 (m, 1H), 1.49–1.60 (m, 3H), 1.66 (d, *J*=10.0 Hz, 1H), 2.01 (br s, 1H), 2.30 (br s, 1H), 3.02 (d, *J*=11.8 Hz, 1H), 3.19 (d, *J*=11.8 Hz, 1H), 3.78 (s, 3H), 4.29 (dd, *J*=1.3, 13.2 Hz, 1H), 4.66 (dd, *J*=2.0, 13.2 Hz, 1H), 4.75 (dd, *J*=1.7, 16.3 Hz, 1H), 4.89 (dd, *J*=1.2, 16.3 Hz, 1H), 7.17–7.40 (m, 5H); ^{13}C NMR δ 30.2, 30.4, 34.3, 44.0, 44.1, 47.0, 48.9, 51.4, 70.5, 72.9, 117.4, 126.8, 127.7, 128.5, 132.4, 134.9, 139.9, 148.1, 168.0. HRMS (FAB, positive) *m/z* calcd for $C_{21}H_{22}O_3$, 322.1569; found, 322.1577; $[\alpha]_D^{25}$ 111.2 (*c* 1.06, $CHCl_3$, 95% ee). The enantiomeric excess was determined by chiral HPLC analysis using a chiral column (Daicel Chiralpak IA: 4×250 mm, 254 nm UV detector, rt, eluent: 5% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 6 min for minor isomer and 8 min for major isomer).

4.2.18. Trimethyl 9-methyltetracyclo[9.2.1.0^{2,10}.0^{4,8}]-tetradeca-3,8-diene-3,6,6-tricarboxylate (2i). Colorless oil; IR (CH_2Cl_2) 2952, 1738, 1701, 1244, 1203 cm^{-1}; ^1H NMR δ 1.09 (d, *J*=9.5 Hz, 1H), 1.36–1.58 (m, 4H), 1.60–1.68 (m, 1H), 1.73 (s, 3H), 2.19 (br s, 1H), 2.28 (br s, 1H), 2.45 (d, *J*=11.8 Hz, 1H), 2.84 (d, *J*=11.8 Hz, 1H), 2.90 (br s, 2H), 3.35 (dd, *J*=1.6, 19.0 Hz, 1H), 3.46 (dd, *J*=2.0, 19.0 Hz, 1H), 3.73 (s, 3H), 3.73 (s, 3H), 3.74 (s, 3H); ^{13}C NMR δ 18.9, 29.9, 30.4, 34.0, 37.0, 41.2, 43.2, 44.0, 46.7, 50.9, 51.1, 52.8, 58.0, 118.2, 130.5, 133.8, 147.6, 168.6, 172.0, 172.1 (a signal in the aliphatic region is overlapped). HRMS (FAB, positive) *m/z* calcd for $C_{21}H_{26}O_6$, 374.1729; found, 374.1726; $[\alpha]_D^{24}$ 59.0 (*c* 1.50, $CHCl_3$, 99% ee). The

enantiomeric excess was determined by chiral HPLC analysis using a chiral column (Daicel Chiralcel OD-H: 4× 250 mm, 254 nm UV detector, rt, eluent: 5% 2-propanol in hexane, flow rate: 0.5 mL/min, retention time: 12 min for major isomer and 13 min for minor isomer).

4.2.19. 12,13-Benzo-3-methoxycarbonyl-9-phenyl-6-tosyl-6-azatetracyclo[9.2.1.0^{2,10}.0^{4,8}]tetradeca-3,8-diene (2j). Colorless oil; IR (CH_2Cl_2) 1705, 1350, 1244, 1163 cm^{-1}; ^{1}H NMR δ 1.59 (d, J=9.3 Hz, 1H), 1.81 (d, J=9.3 Hz, 1H), 2.41 (s, 3H), 2.91 (d, J=11.8 Hz, 1H), 3.03 (d, J=11.8 Hz, 1H), 3.06 (br s, 1H), 3.40 (br s, 1H), 3.86 (s, 3H), 3.86–3.90 (m, 1H), 4.14 (dd, J=2.3, 14.5 Hz, 1H), 4.34 (dd, J=2.2, 17.3 Hz, 1H), 4.55 (dd, J=1.5, 17.3 Hz, 1H), 6.96–7.50 (m, 11H), 7.69 (d, J=8.3 Hz, 2H); ^{13}C NMR δ 21.5, 42.3, 44.2, 47.1, 50.8, 51.6, 51.8, 53.5, 54.1, 119.4, 120.8, 120.8, 126.0, 126.2, 126.8, 127.8, 128.3, 128.9, 129.7, 130.1, 132.9, 137.6, 139.2, 143.8, 145.1, 147.6, 148.3, 167.3. HRMS (FAB, positive) m/z calcd for $C_{32}H_{30}NO_4S$, 524.1895 ([M+H]$^+$); found, 524.1928 ([M+H]$^+$); $[\alpha]_D^{24}$ 84.1 (c 1.76, $CHCl_3$, 92% ee). The enantiomeric excess was determined by chiral HPLC analysis using a chiral column (Daicel Chiralpak IB: 4×250 mm, 254 nm UV detector, rt, eluent: 5% 2-propanol in hexane, flow rate: 0.5 mL/min, retention time: 22 min for minor isomer and 24 min for major isomer).

4.2.20. 3-Methylcarbonyl-9-phenyl-6-tosyl-6-azatetracyclo[9.2.1.0^{2,10}.0^{4,8}]tetradeca-2(10), 3,8-triene (3g). Colorless oil; IR (CH_2Cl_2) 1736, 1716, 1248, 1209 cm^{-1}; ^{1}H NMR δ 1.16–1.34 (m, 2H), 1.41–1.48 (m, 1H), 1.65–1.72 (m, 1H), 1.82–1.91(m, 1H), 1.92–2.01 (m, 1H), 3.24 (br s, 1H), 3.37 (d, J=16.7 Hz, 1H), 3.49 (d, J=16.7 Hz, 1H), 3.69 (s, 3H), 3.73 (s, 3H), 3.91 (s, 2H), 3.93 (s, 3H), 4.08 (br s, 1H), 7.25–7.40 (m, 3H), 7.42–7.48 (m, 2H); ^{13}C NMR δ 26.2, 27.0, 39.7, 41.7, 42.0, 44.2, 48.5, 51.6, 52.9, 52.9, 59.6, 119.6, 127.3, 128.3, 128.9, 135.1, 136.3, 138.1, 138.4, 147.1, 149.8, 167.7, 172.3 (a signal in the aromatic region was overlapped). HRMS (FAB, positive) m/z calcd for $C_{26}H_{26}O_6$, 434.1729; found, 434.1732; $[\alpha]_D^{26}$ 26.5 (c 0.85, $CHCl_3$, 90% ee). The enantiomeric excess was determined by chiral HPLC analysis using a chiral column (Daicel Chiralpak IA: 4×250 mm, 254 nm UV detector, rt, eluent: 5% 2-propanol in hexane, flow rate: 0.5 mL/min, retention time: 16 min for major isomer and 17 min for minor isomer).

4.3. Typical experimental procedure for enantioselective [2+2+2] cycloaddition of diyne 4 with styrene derivatives (Table 4)

The reaction was examined by the same procedure as that in the literature except styrene derivatives were used in place of methyl methacrylate.[10]

4.3.1. Dibenzyl 3-phenyl-2,3,5-trimethylbicyclo[4.3.0]-nona-1,5-diene-8,8-dicarboxylate (6a). Yellow oil; IR (CH_2Cl_2) 1734, 1238, 1184, 698 cm^{-1}; ^{1}H NMR δ 1.32 (s, 3H), 1.43 (s, 3H), 1.60 (s, 3H), 2.14 (d, J=17.1 Hz, 1H), 2.42 (d, J=17.1 Hz, 1H), 3.01–3.12 (m, 4H), 5.11–5.19 (m, 4H), 7.13–7.30 (m, 15H); ^{13}C NMR δ 15.7, 19.4, 23.9, 37.0, 37.8, 44.1, 48.4, 59.1, 67.1, 67.1, 122.5, 125.6, 126.7, 127.9, 128.2, 128.5, 129.0, 129.2, 132.0, 135.6, 148.6, 171.4, 171.5 (5 signals were overlapped at aromatic region). HRMS (FAB, positive) m/z calcd for $C_{34}H_{35}O_4$, 507.2535 ([M+H]$^+$); found, 507.2536 ([M+H]$^+$); $[\alpha]_D^{27}$ 5.74 (c 0.87, $CHCl_3$, 88% ee). The enantiomeric excess was determined by HPLC analysis using a chiral column (Daicel Chiralpak AD-H: 4×250 mm, 254 nm UV detector, rt, eluent: 10% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 5.5 min for major isomer and 6.0 min for minor isomer).

4.3.2. Dibenzyl 3-(4-fluorophenyl)-2,3,5-trimethylbicyclo[4.3.0]nona-1,5-diene-8,8-dicarboxylate (6b). Yellow oil; IR (CH_2Cl_2) 1734, 1261, 1236, 698 cm^{-1}; ^{1}H NMR δ 1.31 (s, 3H), 1.42 (s, 3H), 1.60 (s, 3H), 2.15 (d, J=16.9 Hz, 1H), 2.33 (d, J=16.9 Hz, 1H), 2.98–3.12 (m, 4H), 5.11–5.18 (m, 4H), 6.88–6.93 (m, 2H), 7.19–7.36 (m, 12H); ^{13}C NMR δ 15.6, 19.4, 24.4, 37.0, 37.8, 43.5, 48.5, 59.1, 67.1, 114.4, 114.6, 122.5, 127.8, 127.9, 128.1, 128.2, 128.2, 128.5, 128.9, 129.2, 132.3, 135.6, 144.0, 144.0, 161.0 (d, J=243.8 Hz), 171.4, 171.4 (a signal in aliphatic region was overlapped). HRMS (FAB, positive) m/z calcd for $C_{34}H_{33}FO_4$, 524.2363; found, 524.2364; $[\alpha]_D^{24}$ 3.99 (c 1.95, $CHCl_3$, 73% ee). The enantiomeric excess was determined by HPLC analysis using a chiral column (Daicel Chiralpak AD-H: 4×250 mm, 254 nm UV detector, rt, eluent: 5% 2-propanol in hexane, flow rate: 0.5 mL/min, retention time: 17 min for major isomer and 20 min for minor isomer).

4.3.3. Dibenzyl 3-(4-methoxyphenyl)-2,3,5-trimethylbicyclo[4.3.0]nona-1,5-diene-8,8-dicarboxylate (6c). Yellow oil; IR (CH_2Cl_2) 1734, 1250, 1182, 698 cm^{-1}; ^{1}H NMR δ 1.30 (s, 3H), 1.43 (s, 3H), 1.60 (s, 3H), 2.13 (d, J=16.9 Hz, 1H), 2.37 (d, J=16.9 Hz, 1H), 2.98–3.11 (m, 4H), 3.76 (s, 3H), 5.14–5.16 (m, 4H), 6.77–6.79 (m, 2H), 7.17–7.30 (m, 12H); ^{13}C NMR δ 15.6, 19.4, 24.3, 37.0, 37.8, 43.3, 48.4, 55.1, 59.2, 67.0, 113.2, 122.5, 127.6, 127.8, 127.8, 128.1, 128.5, 129.0, 129.5, 131.8, 135.6, 140.6, 157.5, 171.4, 171.5 (a signal in the aliphatic region and 3 signals in the aromatic region were overlapped). HRMS (FAB, positive) m/z calcd for $C_{35}H_{36}O_5$, 536.2563; found, 536.2558; $[\alpha]_D^{20}$ 8.93 (c 1.34, $CHCl_3$, 72% ee). The enantiomeric excess was determined by HPLC analysis using a chiral column (Daicel Chiralpak AD-H: 4×250 mm, 254 nm UV detector, rt, eluent: 5% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 12 min for major isomer and 14 min for minor isomer).

4.3.4. Dibenzyl 3-isopropenyl-2,3,5-trimethylbicyclo[4.3.0]nona-1,5-diene-8,8-dicarboxylate (6d). Yellow oil; IR (CH_2Cl_2) 1736, 1236, 696 cm^{-1}; ^{1}H NMR δ 1.05 (s, 3H), 1.51 (s, 3H), 1.65 (s, 3H), 1.65 (s, 3H), 1.79 (d, J=17.0 Hz, 1H), 2.34 (d, J=17.0 Hz, 1H), 2.93–3.02 (m, 4H), 4.72 (d, J=1.3 Hz, 1H), 4.77 (d, J=1.3 Hz, 1H), 5.09–5.15 (m, 4H), 7.23–7.33 (m, 10H); ^{13}C NMR δ 14.6, 19.4, 20.2, 23.5, 37.0, 37.8, 42.9, 45.3, 59.1, 67.0, 67.0, 110.4, 122.4, 127.8, 128.1, 128.1, 128.5, 128.6, 131.5, 135.6, 150.0, 171.5 (4 signals at aromatic region and 1 signal at carbonyl region were overlapped). HRMS (FAB, positive) m/z calcd for $C_{31}H_{34}O_4$, 470.2457; found, 470.2419; $[\alpha]_D^{32}$ 6.81 (c 0.56, $CHCl_3$, 54% ee). The enantiomeric excess was determined by HPLC analysis using a chiral column (Daicel Chiralpak AD-H: 4×250 mm, 254 nm UV detector, rt, eluent: 1% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 14 min for major isomer and 15 min for minor isomer).

Acknowledgements

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

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