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Enantioselective synthesis of α,α-disubstituted α-amino acids by Rh-catalyzed [2+2+2] cycloaddition of 1,6-diynes with protected dehydroamino acid

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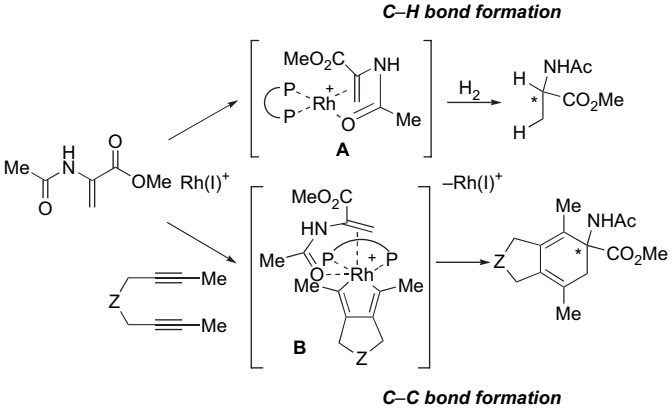
ABSTRACT

We have determined that a cationic rhodium(I)/BINAP complex catalyzes a [2+2+2] cycloaddition of 1,6-diynes with a protected dehydroamino acid, leading to protected α-amino acids bearing a quaternary carbon center in high yield with high enantioselectivity.

1. Introduction

The cationic rhodium(I)/bisphosphine complex-catalyzed enantioselective hydrogenation of a protected dehydroamino acid (formation of two C–H bonds) is an efficient and reliable method for the synthesis of an α-amino acid possessing a tertiary carbon center.[1] Bidentate coordination through the alkene moiety and the amide carbonyl group to rhodium furnishes intermediate **A**, which induces high enantioselectivity (Scheme 1).[2] Although α,α-disubstituted α-amino acids possessing a stereochemically stable quaternary carbon center are useful compounds for controlling secondary structures of peptides,[3] they cannot be synthesized by enantioselective hydrogenation.[4] On the other hand, cationic rhodium(I)/modified-BINAP complexes have been used in enantioselective [2+2+2] cycloadditions[5–7] involving monoalkenes.[8,9] For example, 1,1- and 1,2-disubstituted monoalkenes bearing an alkoxycarbonyl group reacted with 1,6-diynes to give the corresponding chiral cyclohexadienes in high yields with high enantiomeric excesses, although a large excess of monoalkenes and/or slow addition of 1,6-diynes were necessary.[8] We anticipated that a protected dehydroamino acid would be a suitable substrate for a rhodium-catalyzed enantioselective [2+2+2] cycloaddition with 1,6-diynes (formation of three C–C bonds) because of the strong bidentate coordination through the alkene moiety and the amide carbonyl group furnishing intermediate **B**, which would provide α,α-disubstituted α-amino acid derivatives in high yield with high enantioselectivity (Scheme 1).[10,11]



Scheme 1. Rh-catalyzed enantioselective hydrogenation and [2+2+2] cycloaddition of a protected dehydroamino acid.

2. Results and discussion

We first investigated the reaction of tosylamide linked 1,6-diyne **1a** with only a slight excess (1.1 equiv) of protected dehydroamino acid **2a** at room temperature using 10 mol % of a cationic rhodium(I)/BINAP-type bisphosphine complex as a catalyst (Table 1). We were pleased to find that the reaction smoothly proceeded by using BINAP as a ligand to give the desired α-amino acid derivative **3aa** in high yield with high ee without slow addition of 1,6-diyne **1a** (entry 1). A comparable result was obtained by using H_8-BINAP as a ligand (entry 2), while both yield and ee were decreased when Segphos was used as a ligand (entry 3). The use of sterically demanding xyl-BINAP significantly decreased the yield of **3aa** (entry 4). The catalytic activity of the cationic rhodium catalyst

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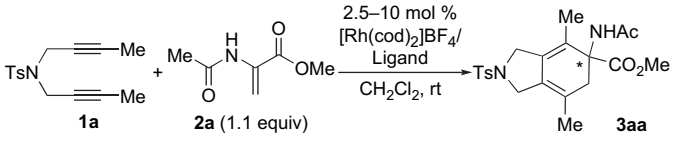
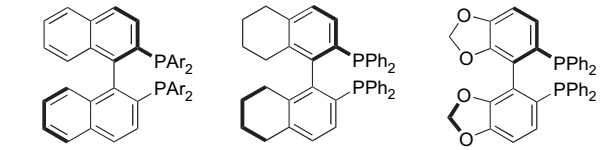
Table 1
Screening of ligands for Rh-catalyzed enantioselective [2+2+2] cycloaddition of **1a** with **2a**[a]





Entry	Ligand	Catalyst (mol %)	Time (h)	Yield[b] (%)	ee (%)
1	(*R*)-BINAP	10	1	96	97 (*S*)
2	(*R*)-H_8-BINAP	10	1	97	98 (*S*)
3	(*R*)-Segphos	10	1	91	91 (*S*)
4	(*S*)-xyl-BINAP	10	3	68	97 (*R*)
5	(*R*)-BINAP	5	1	95	96 (*S*)
6	(*R*)-BINAP	2.5	1	91	97 (*S*)

[a] $[Rh(cod)_2]BF_4$ (0.0038–0.015 mmol, 2.5–10 mol %), ligand (0.0038–0.015 mmol, 2.5–10 mol %), **1a** (0.15 mmol), **2a** (0.165 mmol, 1.1 equiv), and CH_2Cl_2 (1.5 mL) were used.
[b] Isolated yield.

with BINAP ligand is very high so that the reaction could be carried out with 5 mol % (entry 5) and 2.5 mol % (entry 6) of the catalyst without appreciable erosion of both yield and ee.

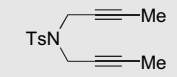
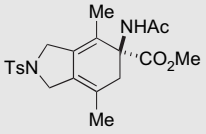
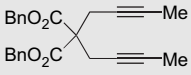
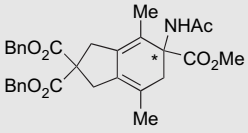
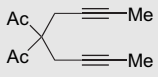
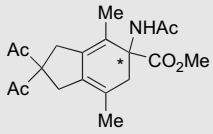
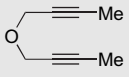
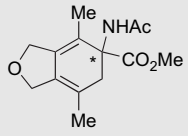
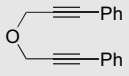
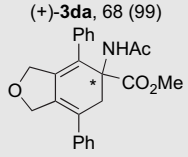
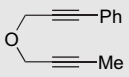
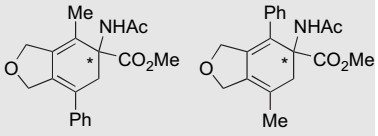
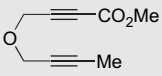
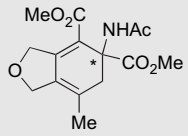
Thus, we explored the scope of this process with respect to 1,6-diynes as shown in Table 2. Not only tosylamide (**1a**, entry 1) but also malonate (**1b**, entry 2), acetyl acetone (**1c**, entry 3), and oxygen (**1d**, entry 4) linked 1,6-diynes could be employed for this reaction. With respect to the substituents at the alkyne terminus, not only methyl (**1a**–**d**, entries 1–4) but also phenyl (**1e** and **1f**, entries 5 and 6) and methoxycarbonyl (**1g**, entry 7) substituted 1,6-diynes could participate in this reaction. In the case of unsymmetrical 1,6-diynes, perfect regioselectivity was observed in the reaction of 1,6-diyne **1g** with **2a** furnishing the corresponding protected acidic amino acid (−)-**3ga** in good yield with excellent ee (entry 7), while moderate regioselectivity was observed in the reaction of 1,6-diyne **1f** with **2a** (entry 6). The absolute configuration of (−)-**3aa**, which was prepared by using (*S*)-xyl-BINAP as a ligand (Table 1, entry 4), was determined to be *R* configuration by the anomalous dispersion method (Fig. 1).

Although $Rh(I)^+$/BINAP-catalyzed [2+2+2] cycloadditions of 1,6-diyne **1a** with protected 1,2-disubstituted dehydro-β-amino acids **2b**–**d** were also investigated, the desired protected β-amino acids **3ab**–**3ad** were not obtained at all (Scheme 2).

Scheme 3 depicts a possible mechanism for the highly selective formation of (*S*)-(+)-**3aa** by using the cationic rhodium(I)/(*R*)-BINAP complex as a catalyst. The reaction of 1,6-diyne **1a** with rhodium followed by coordination of **2a** to rhodium through the alkene moiety and the amide carbonyl furnishes intermediate **C** due to the steric repulsion between the methoxycarbonyl group of **2a** and the axial phenyl group of (*R*)-BINAP. Insertion and reductive elimination of rhodium furnishes (*S*)-**3aa**.

The reactions of various enamides with 1,6-diyne **1a** were also examined as shown in Scheme 4. Enamide **2e** bearing a methyl group instead of a methoxycarbonyl group reacted with **1a** to furnish the corresponding cyclohexadiene (+)-**3ae** with high ee along with aromatized product **5**. The reaction of **1a** with enamide **2f** bearing a hydrogen instead of a methoxycarbonyl group furnished

Table 2
$Rh(I)^+$/(*R*)-BINAP-catalyzed enantioselective [2+2+2] cycloaddition of **1a**–**g** with **2a**[a]

Entry	Diyne **1**	Time (h)	Product **3**/**4**, % yield[b] (% ee)
1	 **1a**	1	 (*S*)-(+)-**3aa**, 95 (96)
2	 **1b**	3	 (+)-**3ba**, 90 (93)
3	 **1c**	16	 (+)-**3ca**, 91 (98)
4	 **1d**	1	 (+)-**3da**, 68 (99)
5	 **1e**	16	 (+)-**3ea**, 84 (99)
6	 **1f**	1	 (+)-**3fa**, 53 (99) (+)-**4fa**, 20 (99)
7	 **1g**	3	 (−)-**3ga**, 67 (99)

[a] Reactions were conducted using $[Rh(cod)_2]BF_4$/(*R*)-BINAP (0.0075 mmol, 5 mol %), **1a**–**g** (0.15 mmol), **2a** (0.165 mmol, 1.1 equiv), and CH_2Cl_2 (1.5 mL) at room temperature.
[b] Isolated yield.

a complex mixture of dienes. Accordingly, the methoxycarbonyl group of **2a** is not necessary to induce high enantioselectivity, but it stabilizes the cyclohexadiene structure and avoids the aromatization.

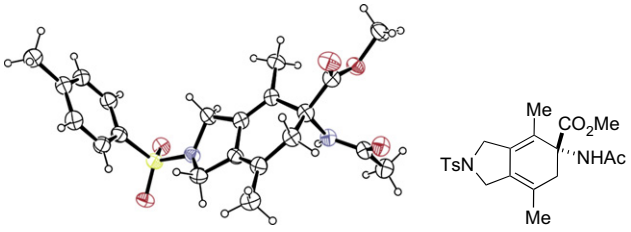
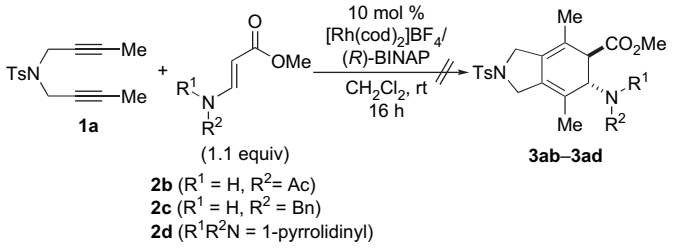
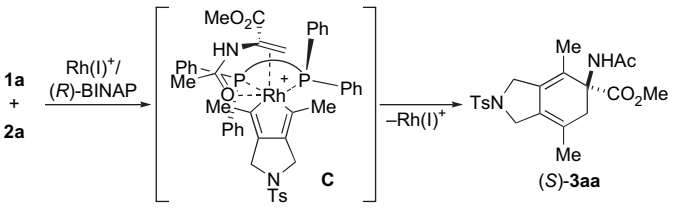


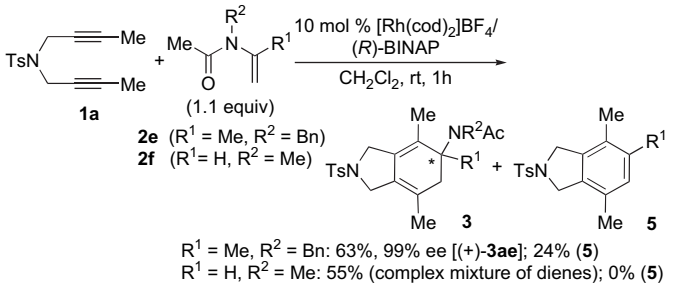
Figure 1. X-ray crystal structure of (*R*)-(−)-**3aa**, prepared by using (*S*)-xyl-BINAP as a ligand.



Scheme 2. Rh-catalyzed reactions of 1,6-diyne **1a** with protected dehydroamino acids **2b–d**.

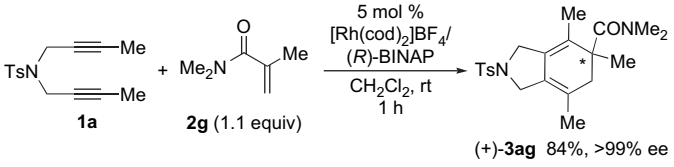


Scheme 3. Possible mechanism for the selective formation of (*S*)-(+)-**3aa** by using a $Rh(I)^+$/(*R*)-BINAP complex as a catalyst.



Scheme 4. Rh-catalyzed reactions of 1,6-diyne **1a** with enamides **2e** and **2f**.

As electron-deficient enamide **2a** showed high reactivity and selectivity toward the reaction with 1,6-diyne **1a**, *N*,*N*-dimethylmethacrylamide (**2g**) possessing an electron-deficient and coordinating carbamoyl group would show higher reactivity and selectivity toward the reaction with 1,6-diyne **1a** than do methacrylates.[8a] Indeed, the reaction of **1a** with **2g** proceeded in high yield with perfect ee without employment of excess **2g** and slow addition of **1a** (Scheme 5).



Scheme 5. Rh-catalyzed reaction of 1,6-diyne **1a** with *N*,*N*-dimethylmethacrylamide (**2g**).

3. Conclusion

In conclusion, we have determined that a cationic rhodium(I)/BINAP complex catalyzes a [2+2+2] cycloaddition of 1,6-diynes with a protected dehydroamino acid leading to protected α,α-disubstituted α-amino acids in high yield with high enantioselectivity. Future studies will focus on the utilization of new α,α-disubstituted α-amino acids as chiral reagents or building blocks in organic synthesis.

4. Experimental

4.1. General

^1H NMR spectra were recorded at 300 MHz using JEOL AL 300 spectrometer. ^{13}C NMR spectra were obtained with complete proton decoupling at 75 MHz using JEOL AL 300 spectrometer. HRMS data were obtained on JEOL JMS-700. Infrared spectra were obtained on a Jasco FT/IR-4100. Optical rotation was measured with Jasco DIP-1000 polarimeter. Anhydrous CH_2Cl_2 (No. 27,099-7) was obtained from Aldrich and used as received. H_8-BINAP, Segphos, and xyl-BINAP were obtained from Takasago International Corporation. 1,6-Diynes **1a**,[12] **1b**,[8a] **1c**,[13] **1d**,[12] **1e**,[14] **1f**,[12] and **1g**,[15] and enamides **2b**[16] and **2c**[17] were reported in the literatures. Enamides **2a**, **2d**, and **2f** were commercially available. All other reagents were obtained from commercial sources and used as received. All reactions were carried out under an atmosphere of argon or nitrogen in oven-dried glassware with magnetic stirring.

4.2. Representative procedure for Rh-catalyzed [2+2+2] cycloadditions of 1,6-diynes 1 with protected dehydroamino acid 2a (Table 2, entry 1)

(*R*)-BINAP (4.7 mg, 0.0075 mmol) and $[Rh(cod)_2]BF_4$ (3.1 mg, 0.0075 mmol) were dissolved in CH_2Cl_2 (1.0 mL) and the mixture was stirred at room temperature for 5 min. H_2 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 dissolved in CH_2Cl_2 (0.3 mL). To this solution was added a solution of **1a** (41.3 mg, 0.15 mmol) and **2a** (23.6 mg, 0.165 mmol) in CH_2Cl_2 (1.2 mL). The mixture was stirred at room temperature for 1 h. The resulting solution was concentrated and purified by preparative TLC (hexane/EtOAc/Et_3N=1:4:1), which furnished (*S*)-(+)-**3aa** (59.8 mg, 0.143 mmol, 95% yield, 96% ee) as a colorless solid.

*4.2.1. (S)-(+)-5-Acetylamino-4,7-dimethyl-2-(toluene-4-sulfonyl)-2,3,5,6-tetrahydro-1H-isoindole-5-carboxylic acid methyl ester [(S)-(+)-**3aa**]*

Mp 178.0–178.8 °C; $[\alpha]_D^{25}$ +176.3 (*c* 1.23, $CHCl_3$, 96% ee); IR (neat) 3366, 2951, 1735, 1654, 1163 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.72 (d, *J*=8.1 Hz, 2H), 7.35 (d, *J*=8.1 Hz, 2H), 6.24 (s, 1H), 4.03–3.89 (m, 4H), 3.72 (s, 3H), 2.87 (d, *J*=18.6 Hz, 1H), 2.78 (d, *J*=18.6 Hz, 1H), 2.44 (s, 3H), 1.95 (s, 3H), 1.66 (s, 3H), 1.61 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.3, 169.5, 143.8, 133.4, 132.6, 129.8, 127.7, 125.0, 124.9, 118.0, 62.7, 53.0, 51.0, 50.3, 38.3, 23.5, 21.5, 19.1, 14.4; HRMS (ESI) calcd for $C_{21}H_{26}N_2O_5SNa$ $[M+Na]^+$ 441.1460, found 441.1450; CHIRALPAK AD–H, hexane/2-PrOH=90:10, 1.0 mL/min, retention times: 31.1 min (minor isomer) and 41.2 min (major isomer).

*4.2.2. (+)-5-Acetylamino-4,7-dimethyl-1,3,5,6-tetrahydro-indene-2,2,5-tricarboxylic acid dibenzyl ester methyl ester [(+)-**3ba**]*

Colorless oil; $[\alpha]_D^{25}$ +85.7 (*c* 2.16, $CHCl_3$, 93% ee); IR (neat) 2951, 2371, 1734, 1653, 1239 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.32–7.24 (m, 10H), 5.65 (s, 1H), 5.13 (s, 4H), 3.70 (s, 3H), 3.05 (d, *J*=16.5 Hz, 2H), 2.97 (d, *J*=16.5 Hz, 2H), 2.88 (s, 2H), 1.90 (s, 3H), 1.69 (s, 3H), 1.66 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.4, 171.2, 170.8, 169.6, 137.0, 135.39, 135.36, 128.51, 128.49, 128.3, 128.2, 127.81, 127.76, 125.3, 118.4, 67.18, 67.15, 63.0, 58.7, 52.6, 38.0, 37.8, 36.7, 23.5, 19.2, 14.6; HRMS (ESI) calcd for $C_{31}H_{33}NO_7Na$ $[M+Na]^+$ 554.2155, found 554.2149; CHIRALCEL OD–H, hexane/2-PrOH=90:10, 1.0 mL/min, retention times: 26.9 min (major isomer) and 35.9 min (minor isomer).

*4.2.3. (+)-2,2-Diacetyl-5-acetylamino-4,7-dimethyl-2,3,5,6-tetrahydro-1H-indene-5-carboxylic acid methyl ester [(+)-**3ca**]*

Pale yellow oil; $[\alpha]_D^{25}$ +100.4 (*c* 0.95 $CHCl_3$, 98% ee); IR (neat) 3384, 2952, 1698, 1658, 735 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.96

(s, 1H), 3.73 (s, 3H), 2.94 (d, J=16.2 Hz, 2H), 2.88 (d, J=18.0 Hz, 1H), 2.86 (d, J=16.2 Hz, 2H), 2.80 (d, J=18.0 Hz, 1H), 2.16 (s, 3H), 2.13 (s, 3H), 1.97 (s, 3H), 1.74 (s, 3H), 1.69 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 205.6, 205.5, 172.7, 169.4, 136.7, 127.8, 125.2, 118.6, 72.3, 63.0, 52.8, 38.5, 35.6, 34.5, 26.7, 26.6, 23.6, 19.1, 14.5; HRMS (ESI) calcd for $C_{19}H_{25}NO_5Na$ $[M+Na]^+$ 370.1630, found 370.1618; CHIRALCEL OD–H, hexane/2-PrOH=90:10, 1.0 mL/min, retention times: 20.7 min (major isomer) and 27.6 min (minor isomer).

*4.2.4. (+)-5-Acetylamino-4,7-dimethyl-1,3,5,6-tetrahydro-isobenzofuran-5-carboxylic acid methyl ester [(+)-**3da**]*

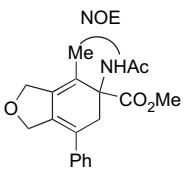
Colorless oil; $[\alpha]_D^{25}$ +198.8 (*c* 1.20, $CHCl_3$, 99% ee); IR (neat) 3410, 2952, 1734, 1653, 1235 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.05 (s, 1H), 4.55–4.44 (m, 4H), 3.77 (s, 3H), 2.93 (s, 2H), 1.99 (s, 3H), 1.70 (s, 3H), 1.64 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.5, 169.5, 136.9, 128.0, 122.6, 115.3, 70.5, 70.2, 63.1, 52.9, 38.6, 23.5, 19.2, 14.6; HRMS (ESI) calcd for $C_{14}H_{19}NO_4Na$ $[M+Na]^+$ 288.1212, found 288.1194; CHIRALPAK AD–H, hexane/2-PrOH=97:3, 1.0 mL/min, retention times: 36.7 min (minor isomer) and 38.2 min (major isomer).

*4.2.5. (+)-5-Acetylamino-4,7-diphenyl-1,3,5,6-tetrahydro-isobenzofuran-5-carboxylic acid methyl ester [(+)-**3ea**]*

Colorless solid; mp 94.1–95.0 °C; $[\alpha]_D^{25}$ +161.2 (*c* 0.57, $CHCl_3$, 99% ee); IR (neat) 3420, 2366, 1734, 1652, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40–7.26 (m, 8H), 7.16 (d, J=7.8 Hz, 2H), 6.23 (s, 1H), 4.78 (s, 2H), 4.47 (d, J=13.5 Hz, 1H), 4.38 (d, J=13.5 Hz, 1H), 3.82 (d, J=17.7 Hz, 1H), 3.61 (s, 3H), 3.42 (d, J=17.7 Hz, 1H), 1.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.5, 169.4, 140.4, 139.2, 136.5, 131.2, 128.5, 128.3, 128.2, 127.9, 127.6, 127.4, 126.7, 124.1, 71.1, 70.7, 63.6, 52.9, 37.6, 23.7; HRMS (ESI) calcd for $C_{24}H_{23}NO_4Na$ $[M+Na]^+$ 412.1525, found 412.1515; CHIRALPAK AD–H, hexane/2-PrOH=90:10, 1.0 mL/min, retention times: 18.1 min (major isomer) and 33.8 min (minor isomer).

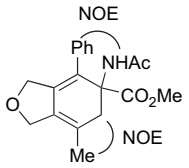
*4.2.6. (+)-5-Acetylamino-4-methyl-7-phenyl-1,3,5,6-tetrahydro-isobenzofuran-5-carboxylic acid methyl ester [(+)-**3fa**]*

Colorless oil; $[\alpha]_D^{25}$ +165.3 (*c* 0.61, $CHCl_3$, 99% ee); IR (neat) 3289, 3018, 1732, 1653, 1518, 758 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.33–7.26 (m, 3H), 7.09–7.06 (m, 2H), 6.26 (s, 1H), 4.62–4.53 (m, 2H), 4.41 (d, J=13.5 Hz, 1H), 4.31 (d, J=13.5 Hz, 1H), 3.63 (s, 3H), 3.22 (d, J=18.3 Hz, 1H), 2.94 (d, J=18.3 Hz, 1H), 1.88 (s, 3H), 1.77 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.9, 169.1, 139.3, 136.7, 128.7, 128.3, 128.2, 127.6, 124.5, 121.2, 71.1, 70.0, 63.1, 52.9, 39.8, 23.8, 19.3; HRMS (ESI) calcd for $C_{19}H_{21}NO_4Na$ $[M+Na]^+$ 350.1368, found 350.1345; CHIRALPAK AD–H, hexane/2-PrOH=90:10, 1.0 mL/min, retention times: 8.7 min (major isomer) and 14.6 min (minor isomer). The regioisomer structure was determined by NOE experiment.



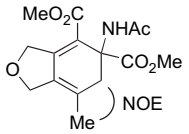
*4.2.7. (+)-5-Acetylamino-7-methyl-4-phenyl-1,3,5,6-tetrahydro-isobenzofuran-5-carboxylic acid methyl ester [(+)-**4fa**]*

Pale yellow oil; $[\alpha]_D^{25}$ +253.6 (*c* 1.29, $CHCl_3$, 99% ee); IR (neat) 3293, 3014, 1736, 1653, 1521, 1230, 761 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36–7.18 (m, 5H), 6.06 (s, 1H), 4.75 (d, J=14.7 Hz, 1H), 4.70 (d, J=14.7 Hz, 1H), 4.60–4.49 (m, 2H), 3.79 (s, 3H), 3.52 (d, J=17.4 Hz, 1H), 3.36 (d, J=17.4 Hz, 1H), 1.98 (s, 3H), 1.74 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.2, 169.7, 139.4, 138.0, 130.7, 128.4, 127.3, 126.4, 125.5, 118.7, 71.3, 70.0, 63.4, 53.0, 36.4, 23.5, 15.0; HRMS (ESI) calcd for $C_{19}H_{21}NO_4Na$ $[M+Na]^+$ 350.1368, found 350.1365; CHIRALPAK AD–H, hexane/2-PrOH=90:10, 1.0 mL/min, retention times: 13.0 min (major isomer) and 17.8 min (minor isomer). The regioisomer structure was determined by NOE experiment.



*4.2.8. (−)-5-Acetylamino-7-methyl-1,3,5,6-tetrahydro-isobenzofuran-4,5-dicarboxylic acid dimethyl ester [(−)-**3ga**]*

Colorless oil; $[\alpha]_D^{25}$ −87.6 (*c* 1.03, $CHCl_3$, 99% ee); IR (neat) 3364, 2952, 1746, 1710, 1685, 1281 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.06 (s, 1H), 4.97 (d, J=16.8 Hz, 1H), 4.87 (d, J=16.8 Hz, 1H), 4.65 (d, J=12.9 Hz, 1H), 4.60 (d, J=12.9 Hz, 1H), 3.78 (s, 3H), 3.72 (s, 3H), 2.84 (d, J=18.9 Hz, 1H), 2.73 (d, J=18.9 Hz, 1H), 1.97 (s, 3H), 1.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.7, 168.7, 166.5, 152.7, 131.6, 128.6, 111.0, 73.4, 69.7, 59.3, 53.4, 51.6, 42.0, 24.0, 19.4; HRMS (ESI) calcd for $C_{15}H_{19}NO_6Na$ $[M+Na]^+$ 332.1110, found 332.1075; CHIRALPAK AD–H, hexane/2-PrOH=90:10, 1.0 mL/min, retention times: 13.6 min (major isomer) and 20.2 min (minor isomer). The regioisomer structure was determined by NOE experiment.



*4.2.9. (+)-N-Benzyl-N-[4,5,7-trimethyl-2-(toluene-4-sulfonyl)-2,3,5,6-tetrahydro-1H-isoindol-5-yl]-acetamide [(+)-**3ae**]*

Yellow oil; $[\alpha]_D^{25}$ +25.5 (*c* 0.68, $CHCl_3$, 99% ee); IR (neat) 3063, 1645, 1342, 1163, 668 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.71 (d, J=8.1 Hz, 2H), 7.37–7.24 (m, 5H), 7.19 (d, J=8.1 Hz, 2H), 4.89–4.45 (m, 2H), 4.13–3.90 (m, 2H), 3.90–3.61 (m, 2H), 3.35–3.00 (m, 1H), 2.43 (s, 3H), 2.12 (s, 3H), 1.84–1.68 (m, 1H), 1.55 (s, 6H), 1.15 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.6, 143.6, 138.7, 132.8, 129.7, 128.81, 128.78, 128.7, 127.7, 127.2, 125.8, 123.5, 63.4, 50.8, 50.5, 49.7, 42.8, 24.1, 23.7, 21.5, 19.3, 14.0; HRMS (ESI) calcd for $C_{27}H_{32}N_2O_3SNa$ $[M+Na]^+$ 487.2031, found 487.2025; CHIRALPAK AD–H, hexane/2-PrOH=80:20, 1.0 mL/min, retention times: 15.9 min (minor isomer) and 19.2 min (major isomer).

*4.2.10. 4,5,7-Trimethyl-2-(toluene-4-sulfonyl)-2,3-dihydro-1H-isoindole (**5**)*

Colorless solid; mp 179.4–180.3 °C; IR (KBr) 3089, 2918, 2853, 2734, 1937, 1596, 1463, 1302, 1096, 822 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.78 (d, J=8.1 Hz, 2H), 7.31 (d, J=8.1 Hz, 2H), 6.83 (s, 1H), 4.57 (s, 2H), 4.55 (s, 2H), 2.40 (s, 3H), 2.19 (s, 3H), 2.12 (s, 3H), 2.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.5, 136.1, 135.0, 133.8, 132.2, 130.3, 129.7, 129.2, 128.0, 127.5, 53.7, 53.4, 21.4, 19.1, 18.1, 15.3; HRMS (EI) calcd for $C_{18}H_{21}NO_2S$ $[M]^+$ 315.1293, found 315.1280.

*4.2.11. (+)-4,5,7-Trimethyl-2-(toluene-4-sulfonyl)-2,3,5,6-tetrahydro-1H-isoindole-5-carboxylic acid dimethylamide [(+)-**3ag**]*

Pale yellow oil; $[\alpha]_D^{25}$ +30.3 (*c* 2.44, $CHCl_3$, >99% ee); IR (neat) 2925, 1634, 1344, 1162, 753 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.74 (d, J=8.1 Hz, 2H), 7.35 (d, J=8.1 Hz, 2H), 4.10–3.82 (m, 4H), 2.94 (s, 6H), 2.58 (d, J=18.3 Hz, 1H), 2.44 (s, 3H), 1.95 (d, J=18.3 Hz, 1H), 1.65 (s, 3H), 1.55 (s, 3H), 1.13 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.4, 143.6, 132.9, 129.7, 127.7, 126.2, 125.7, 125.5, 121.4, 50.6, 50.5, 47.6, 40.3, 38.1, 36.7, 24.3, 21.5, 19.2, 14.7; HRMS (ESI) calcd for $C_{21}H_{28}N_2O_3SNa$ $[M+Na]^+$ 411.1718, found 411.1683; CHIRALPAK AD–H, hexane/2-PrOH=90:10, 1.0 mL/min, retention times: 25.0 min (minor isomer) and 32.9 min (major isomer).

4.3. *N*-Benzyl-*N*-isopropenylacetamide (2e)

A mixture of benzylamine (1.1 g, 10.0 mmol) and acetone (2.0 mL) in a sealed tube was stirred at 120 °C for 1 h using microwave reactor. The resulting mixture was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (15 mL). After cooling to 0 °C, Et_3N (2.1 mL, 15 mmol) and acetyl chloride (0.79 g, 10 mmol) were added in this order. After stirring at room temperature for 0.5 h, the reaction was quenched with water and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by a silica gel column chromatography (eluent: hexane/EtOAc) to give **2e** (0.48 g, 0.25 mmol, 25% yield) as a yellow oil. IR (neat) 3330, 2979, 2936, 1645, 1391 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.31–7.18 (m, 5H), 4.97 (s, 1H), 4.66 (s, 1H), 4.63 (s, 2H), 2.11 (s, 3H), 1.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.4, 144.3, 137.8, 128.5, 128.3, 127.2, 115.8, 48.8, 21.7, 20.9; HRMS (ESI) calcd for $C_{12}H_{15}NONa$ $[M+Na]^+$ 212.1051, found 212.1051.

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Supplementary data

^1H NMR spectra of all new compounds (PDF) and X-ray crystallographic files for (*R*)-(−)-**3aa** (CIF) are provided. This material is available free of charge via the internet. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.04.107.

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