Synthesis P. Roszkowski et al. Paper

Novel (+)-3-Carene Derivatives and Their Application in Asymmetric Synthesis

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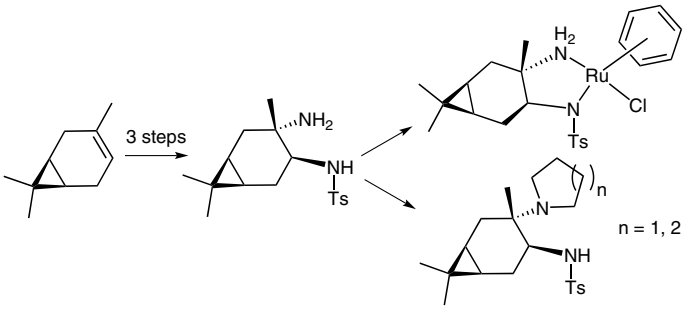


Received: 05.08.2014
Accepted after revision: 06.11.2014
Published online: 03.12.2014
DOI: 10.1055/s-0034-1378942; Art ID: ss-2014-n0492-op

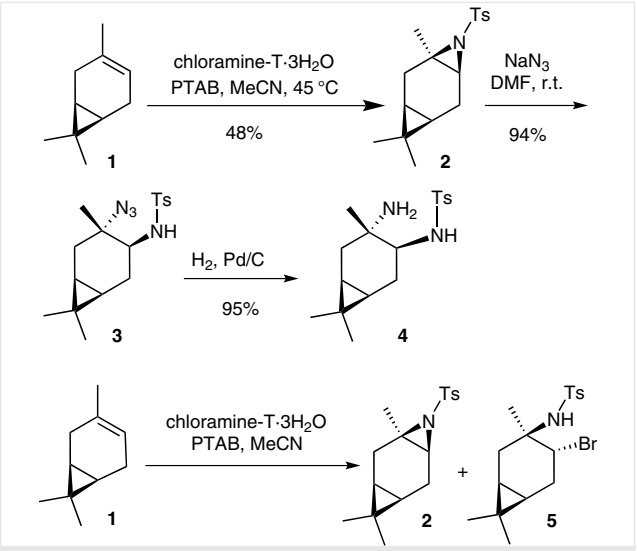
Abstract A simple synthetic procedure for the preparation of mono-N-tosylated-1,2-diamines derived from (+)-3-carene is described. (+)-3-Carene is transformed into the corresponding *N*-tosylaziridine derivative using chloramine-T trihydrate. Subsequent ring opening with sodium azide followed by reduction of the azide function gives the optically pure mono-N-tosylated-1,2-diamine. This ligand is effective in asymmetric transfer hydrogenations of aromatic ketones. It can also be transformed into other chiral ligands by alkylation of the amino group for application in the addition of diethylzinc to benzaldehydes.

Key words asymmetric catalysis, chiral auxiliaries, hydrogen transfer, ligands, natural products

Naturally occurring terpenes such as (+)-3-carene, (–)-α- and (–)-β-pinene and (*R*)-(+)-limonene are readily available chiral reagents that are widely used in organic synthesis. They may serve as the chiral core of auxiliaries or ligands in different stereoselective catalytic transformations,[1] and as substrates for the construction of complex chiral molecules.[2] Several amino alcohols and diamines, the structures of which are based on monoterpenes, have been developed and employed as chiral ligands for asymmetric transfer hydrogenations to ketones and for the enantioselective addition of dialkylzinc reagents to aldehydes. Singaram et al. have prepared several β-amino alcohols from limonene oxide and have evaluated them as efficient catalysts for the asymmetric addition of organometallic reagents to aldehydes,[3a,b] and for the asymmetric hydrogenation of ketones.[3] Moreover, Palmieri et al. have developed convenient methods for the synthesis of new diamines and amino alcohols based on limonene and (+)-3-carene epoxides.[4] The procedures reported by Fülöp et al. have enabled the preparation of amino diols[5a] from (+)-3-carene, and sulfonated diamines[5b] from (–)-apopinene, with these terpenes serving as chiral catalysts in the addition of diethylzinc to aldehydes. In the same type of reaction Wills successfully used monotosylated 1,2-diphenylethylene diamine derivatives.[6] Suisse and co-workers synthesized β-amino alcohol ligands based on α-pinene and used them in asymmetric transfer hydrogenations of acetophenones.[7] Recently, we described a simple procedure for the transformation of limonene into *trans*-1,2-diamine derivatives and demonstrated their effectiveness as ligands in asymmetric transfer hydrogenations of aromatic ketones and imines.[8]

In continuation of our interest in monoterpenes as a source of chiral ligands, herein we present the synthesis of new (+)-3-carene-based monotosylated diamines and their application in asymmetric hydrogenations of acetophenones and enantioselective additions of diethylzinc to benzaldehydes.

The synthetic route to obtain mono-N-tosylated *trans*-1,2-diamine **4** is shown in Scheme 1. The starting material, (+)-3-carene (**1**) was converted into *cis*-aziridine **2** via a direct N-tosylaziridination reaction.[9] Thus, treatment of carene **1** with chloramine-T trihydrate in the presence of phenyltrimethylammonium tribromide (PTAB) at 25 °C resulted in the formation of *cis*-aziridine **2** in 34% yield (Table 1, entry 2). Additionally, the bromine-containing by-product **5** was isolated in 12% yield. Increasing the reaction temperature to 45 °C gave a higher 48% yield of product **2** (Table 1, entry 3), but the yield was still lower than that reported by Sureshkumar[9a] (64%). Under these conditions, the bromine derivative **5** was not detected. When the reaction was carried out at 0 °C, the brominated compound **5** was isolated as the major product in 23% yield, and the aziridine was formed in only 20% yield (Table 1, entry 1).



Scheme 1 Synthetic pathway toward monotosylated diamine **4**

Table 1 Investigation of the N-Tosylaziridination Reaction

Entry	Temp (°C)	Time (h)	**2** (%)	**5** (%)
1	0	4	20	23
2	25	4	34	12
3	45	4	48	0

The absolute stereochemistry of compound **5** was determined on the basis of X-ray crystal analysis, as shown in Figure 1.

The subsequent nucleophilic ring opening of carene *N*-tosylaziridine **2** by the azide anion is a regio- and diastereoselective process. The reaction of **2** with sodium azide (NaN_3) occurred at the more sterically hindered tertiary carbon atom and led to formation of the azido amine **3** (94% yield), with inversion of the configuration at this stereogenic center. The absolute configuration of compound **3** was determined by single crystal X-ray analysis, as shown in Figure 2. Finally, compound **3** was hydrogenated over 10% palladium on charcoal to afford the desired monotosylated diamine **4**, almost quantitatively.

In order to evaluate diamine **4** as a potential ligand, we chose to study a ruthenium-catalyzed asymmetric hydrogen transfer (ATH) protocol on a series of ketones. Two typical reduction procedures were examined. In the first method, the catalyst **6** was prepared in situ by mixing benzeneruthenium(II) chloride dimer {[$RuCl_2$(benzene)]$_2$}with amine **4** and triethylamine (Ru:**4**:Et_3N molar ratio = 1:2.5:2) in acetonitrile under argon. After stirring for 20 minutes at

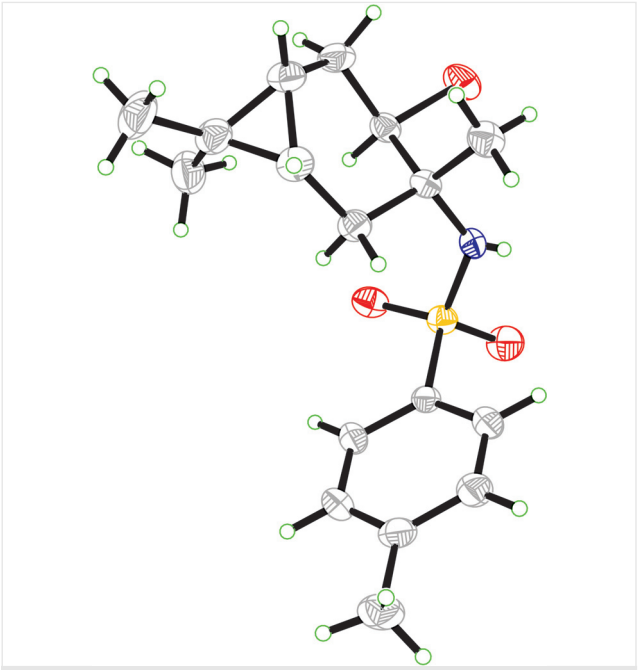


Figure 1 The X-ray crystal structure (ORTEP) of compound **5**

room temperature (24–25 °C), a solution of the catalyst and a mixture of formic acid and triethylamine were added to the ketone.

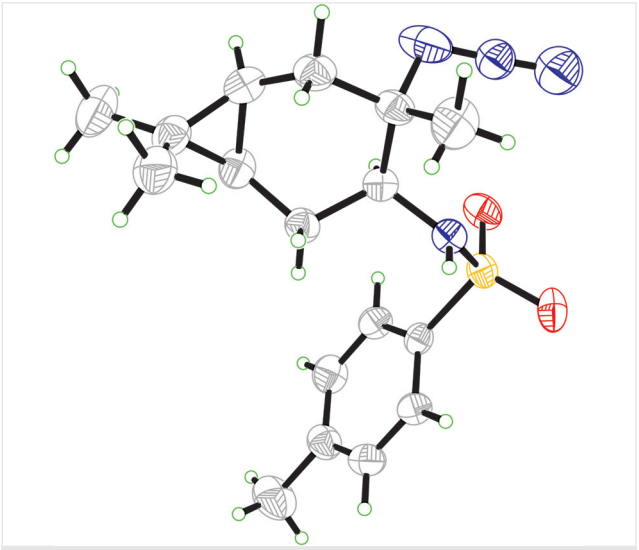
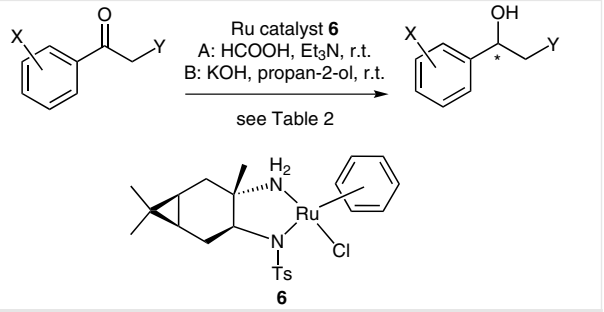


Figure 2 The crystal structure (ORTEP) of compound **3**

The reduction of the acetophenones was carried out at 24–25 °C and the reaction progress was monitored by TLC (Scheme 2). Unfortunately, hydrogenation of ketones under these conditions gave the corresponding products in low yields and low optical purities.



Scheme 2 Asymmetric transfer hydrogenation of acetophenones using catalyst **6**

Taking into account the unsatisfactory results, we next conducted the reductions under alkaline conditions. In this version, the catalyst was prepared in situ by heating $[RuCl_2(benzene)]_2$ in the presence of amine **4** and KOH (Ru:**4**:KOH molar ratio = 1:2.5:8), at 70 °C, in propan-2-ol under argon. After stirring for 20 minutes, the catalyst solution was cooled to room temperature (24–25 °C) and the ketone was added to the mixture. The reduction of the acetophenones was carried out 24–25 °C and once again, the reaction progress was monitored by TLC. Under these conditions the reduction was much faster and gave the expected alcohols in high yields after 24 hours, however, the optical purities remained at moderate levels (Table 2). The best results for the asymmetric hydrogenation with **6** were obtained with *meta*-substituted acetophenones, with the yields and enantiomeric excesses ranging from 60–76% and 45–73%, respectively. The lowest enantioselectivities were observed for ketones containing *ortho*-substituents, but the yields were higher in these cases (see Scheme 2 and Table 2).

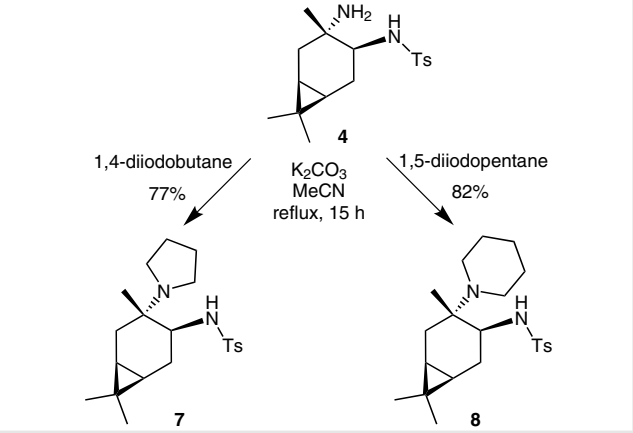
It has already been shown that derivatives containing a combination of a monosulfonylated amine and a tertiary amine group can be used as efficient ligands in diethylzinc addition reactions.[5b,6] Therefore, we transformed amine **4** into compounds **7** and **8**. Ligands **7** and **8** were prepared according to the procedure described by Wills.[6] As shown in Scheme 3, reactions of amine **4** with the appropriate diiodoalkanes gave new chiral N-alkylated derivatives in good yields.

Amines **7** and **8** were subsequently used as catalysts in ethylation reactions with substituted benzaldehydes (Scheme 4). These ligands containing tertiary amino groups gave the expected products in high yields but with moderate enantiomeric excesses. Slightly better enantioselectivities were obtained using derivative **8**, which contained a piperidine ring (Table 3).

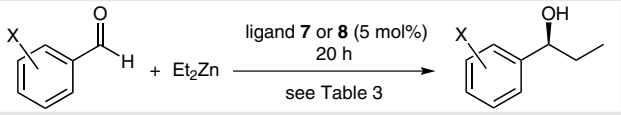
Table 2 The Asymmetric Transfer Hydrogenation of Acetophenones Using Catalyst **6**

Entry	X	Y	Time	Yield (%)	ee (%)[c,d]
1[a]	H	H	6 d	22	32 (*S*)
2[a]	H	Me	6 d	5	36 (*S*)
3[a]	*o*-Cl	H	6 d	9	12 (*R*)
4[a]	*p*-Cl	H	6 d	16	23 (*S*)
5[a]	*o*-Br	H	6 d	25	9 (*R*)
6[a]	*p*-Br	H	6 d	27	16 (*S*)
7[a]	*p*-Me	H	6 d	32	36 (*S*)
8[a]	*p*-MeO	H	6 d	29	34 (*S*)
9[b]	H	H	24 h	62	64 (*S*)
10[b]	H	Me	24 h	77	56 (*S*)
11[b]	*o*-Cl	H	24 h	83	22 (*R*)
12[b]	*m*-Cl	H	24 h	75	48 (*S*)
13[b]	*p*-Cl	H	24 h	62	42 (*S*)
14[b]	*o*-Br	H	24 h	85	20 (*R*)
15[b]	*m*-Br	H	24 h	76	45 (*S*)
16[b]	*p*-Br	H	24 h	75	36 (*S*)
17[b]	*o*-Me	H	24 h	65	24 (*R*)
18[b]	*m*-Me	H	24 h	60	73 (*S*)
19[b]	*p*-Me	H	24 h	68	52 (*S*)
20[b]	*p*-MeO	H	24 h	74	71 (*S*)

[a] The reaction was carried out at room temperature using the ketone (2.40 mmol) in MeCN (1 mL) and a formic acid/triethylamine mixture (5:2, 1 mL); S/C = 100.
[b] The reaction was carried out at room temperature using the ketone (2.40 mmol) in propan-2-ol (1 mL) and 0.1 M KOH solution in propan-2-ol (1 mL); S/C = 100.
[c] Determined by GC analysis using a Supelco cyclodextrin β-DEX 120 capillary column (20 × 0.25 mm I.D., 0.25 μm film thickness).
[d] Configuration determined by the sign of the specific rotation of the isolated product.



Scheme 3 Synthesis of N-alkylated catalysts **7** and **8**



Scheme 4 The ethylation reaction of substituted benzaldehydes with catalysts **7** and **8**

Table 3 Ethylation Reactions of Benzaldehydes with Catalysts **7** and **8**

Entry	Cat.	X	Yield (%)	ee (%)[a,b]
1	**7**	H	82	38 (*R*)
2	**8**	H	93	56 (*R*)
3	**7**	*p*-Cl	85	27 (*R*)
4	**8**	*p*-Cl	92	48 (*R*)
5	**7**	*p*-MeO	87	41 (*R*)
6	**8**	*p*-MeO	90	54 (*R*)

[a] Determined by GC analysis using a Supelco cyclodextrin β-DEX 120 capillary column (20 m × 0.25 mm I.D., 0.25 μm film thickness).
[b] Configuration determined by the sign of the specific rotation of the isolated product.

In summary, we have presented a simple synthesis of new monotosylated diamine derivatives **4**, **7** and **8** starting from the inexpensive, enantiomerically pure natural product, (+)-3-carene. We have shown that these diamines can be used as ligands for the asymmetric reduction of aromatic ketones and addition reactions of diethylzinc to benzaldehydes.

All solvents used in the reactions were anhydrous. TLC analyses were performed on silica gel plates (Merck Kieselgel GF_{254}) and were made visual using UV light or iodine vapor. Column chromatography was carried out at atmospheric pressure using Silica Gel 60 (Merck, 230–400 mesh) and mixtures of $CHCl_3$–MeOH or hexane–EtOAc as eluents. Melting points were determined on a Boetius hot-plate microscope and are uncorrected. Optical rotations were measured on a Perkin-Elmer 247 MC polarimeter. IR spectra were recorded using a Shimadzu FTIR-8400S spectrometer. Optical purities were determined by HPLC analysis using a Chiralcel OD-H column or by GC analysis using a β-DEX 120 capillary column. NMR spectra were obtained on Varian Unity Plus spectrometers operating at 500 MHz or 200 MHz (^{1}H NMR) and at 125 MHz or 50 MHz (^{13}C NMR). The spectra were recorded in $CDCl_3$ and the chemical shifts are given as δ values (in ppm) relative to TMS. Mass spectrometry was performed on Quatro LC Micromass and LCT Micromass TOF HiRes apparatus. Single crystal X-ray measurements were run on an Oxford Diffraction Excalibur R CCD κ-axis diffractometer using monochromatic CuKα radiation. After initial corrections and data reduction, intensities of reflections were used to solve and consecutively refine the structures using the SHELXS97 and SHELXL97 programs.[10]

(1*S*,3*R*,5*S*,7*R*)-3,8,8-Trimethyl-4-(toluene-4-sulfonyl)-4-azatricyclo[5.1.0.0^{3,5}]octane (2)

To a stirred suspension of (+)-3-carene (4.32 g, 31.71 mmol) and chloramine-T trihydrate (TsNClNa·$3H_2O$) (9.82 g, 34.88 mmol) in MeCN (120 mL) was added phenyltrimethylammonium tribromide (PTAB) (1.19 g, 3.17 mmol). After 4 h of vigorous stirring at 45 °C, the mixture was concentrated. To the oily residue were added EtOAc (150 mL) and H_2O (60 mL), and after separation of the layers, the aq layer was extracted with EtOAc (60 mL). The combined organic layers were washed with brine (60 mL), dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography on silica gel (hexane–EtOAc, 0–4% of EtOAc) to afford aziridine **2** (48%, 4.65 g) as a colorless oil.

$[\alpha]_D^{23}$ +4.4 (*c* 1.0, $CHCl_3$); the optical purity (>98% ee) was determined by HPLC (Chiralcel OD-H, hexane–*i*-PrOH, 95:5, 1 mL/min); t_R = 7.2 min.

IR (CH_2Cl_2): 3373, 3276, 2967, 2868, 1646, 1599, 1447, 1337, 1160, 1093, 912, 815 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.56–0.67 (m, 2 H), 0.77 (s, 3 H), 0.84–0.87 (m, 1 H), 0.98 (s, 3 H), 1.12–1.23 (m, 1 H), 1.76 (s, 3 H), 2.04–2.32 (m, 2 H), 2.42 (s, 3 H), 3.02 (dd, *J* = 7.8, 3.8 Hz, 1 H), 7.29 (d, *J* = 8.2 Hz, 2 H), 7.77 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.8, 19.07, 19.09, 19.3, 19.4, 20.8, 21.8, 27.9, 28.6, 47.2, 51.5, 127.2, 129.6, 138.6, 143.6.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{23}NO_2SNa$: 328.1347; found: 328.1363.

(1*R*,3*S*,4*S*,6*S*)-*N*-(4-Azido-4,7,7-trimethylbicyclo[4.1.0]heptan-3-yl)-4-methylbenzenesulfonamide (3)

To a stirred solution of aziridine **2** (3.1 g, 10.15 mmol) in DMF (150 mL) was added NaN_3 (2.52 g, 40.60 mmol). The resulting suspension was stirred at 24–25 °C for 20 h and then the solvent was evaporated in vacuo. To the residue were added Et_2O (50 mL) and H_2O (25 mL), the layers were separated and the aq layer was extracted with Et_2O (2 × 40 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and the solvent was evaporated in vacuo. The oily residue was purified by column chromatography on silica gel (hexane–EtOAc, 0–20% of EtOAc) to afford azide **3** (94%, 3.32 g) as colorless crystals.

Mp 111–113 °C; $[\alpha]_D^{23}$ +11.9 (*c* 1.0, $CHCl_3$); the optical purity (>98% ee) was determined by HPLC (Chiralcel OD-H, hexane–*i*-PrOH, 90:10, 1 mL/min); t_R = 12.9 min.

IR (CH_2Cl_2): 3377, 3283, 3064, 2948, 2867, 2106, 1652, 1340, 1163, 1083, 914, 815 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.60–0.67 (m, 2 H), 0.77–0.84 (m, 1 H), 0.90 (s, 3 H), 0.97 (m, 3 H), 1.02–1.07 (m, 1 H), 1.17 (s, 3 H), 1.78–1.83 (m, 1 H), 1.99–2.04 (m, 1 H), 2.44 (s, 3 H), 3.21–3.26 (m, 1 H), 4.85 (d, *J* = 9.0 Hz, 1 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 7.78 (d, *J* = 8.5 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.0, 17.5, 18.4, 21.1, 21.6, 22.6, 25.6, 28.0, 31.1, 56.7, 63.6, 127.1, 129.7, 137.4, 143.6.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{24}N_4O_2SNa$: 371.1518; found: 371.1506.

Monocrystals of **3** suitable for crystallographic measurements were obtained by slow evaporation from hexane–EtOAc solution. The absolute structure of the studied crystal, and hence the absolute configuration of the compound was determined based on the value of the Flack parameter.[11] Since its value for the structure shown in Figure 2 was approximately 0, the molecular structure has the depicted configuration. These data have been deposited with the Cambridge Crystallographic Data Centre, CCDC 990398.

(1*S*,3*R*,4*R*,6*R*)-*N*-(4-Bromo-3,7,7-trimethylbicyclo[4.1.0]heptan-3-yl)-4-methylbenzenesulfonamide (5)

To a stirred suspension of (+)-3-carene (3.16 g, 23.20 mmol) and chloramine-T trihydrate (TsNClNa·$3H_2O$) (4.91 g, 25.52 mmol) in MeCN (90 mL) was added phenyltrimethylammonium tribromide (PTAB)

(0.87 g, 2.32 mmol). After 4 h of vigorous stirring at 0 °C, the mixture was concentrated. To the oily residue were added EtOAc (115 mL) and H_2O (45 mL), and after separation of the layers, the aq layer was extracted with EtOAc (45 mL). The combined organic layers were washed with brine (45 mL), dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography on silica gel (hexane–EtOAc, 0–10% of EtOAc) to afford brominated amide **5** (23%, 2.06 g) as colorless crystals.

Mp 161.5–162.5 °C; $[\alpha]_D^{23}$ –94.0 (*c* 1.0, $CHCl_3$); the optical purity (>98% ee) was determined by HPLC (Chiralcel OD-H, hexane–*i*-PrOH, 95:5, 1 mL/min); t_R = 10.1 min.

IR (CH_2Cl_2): 3356, 2944, 2867, 1652, 1316, 1155, 1091, 990, 815 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.63–0.72 (m, 2 H), 0.89 (s, 3 H), 0.93 (s, 3 H), 1.31 (s, 3 H), 1.54–1.62 (m, 2 H), 2.33–2.39 (m, 2 H), 2.43 (s, 3 H), 4.10 (t, *J* = 9.2 Hz, 1 H), 4.98 (s, 1 H), 7.29 (d, *J* = 9.0 Hz, 2 H), 7.79 (d, *J* = 8.2 Hz, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.7, 18.1, 18.6, 20.4, 21.7, 21.9, 28.5, 30.6, 31.1, 59.0, 63.2, 127.2, 129.8, 140.5, 143.4.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{24}{}^{79}BrNO_2SNa$: 408.0609; found: 408.0619; *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{24}{}^{81}BrNO_2SNa$: 410.0588; found: 410.0597.

Monocrystals of **5** suitable for crystallographic measurements were obtained by slow evaporation from dichloromethane solution. The absolute structure of the studied crystal, and hence the absolute configuration of the compound was determined based on the value of the Flack parameter.[11] Since its value for the structure shown in Figure 1 was approximately 0, the molecular structure has the depicted configuration. These data have been deposited with the Cambridge Crystallographic Data Centre, CCDC 990399.

(1*R*,3*S*,4*S*,6*S*)-*N*-(4-Amino-4,7,7-trimethylbicyclo[4.1.0]heptan-3-yl)-4-methylbenzenesulfonamide (4)

To a stirred solution of azide **3** (2.51 g, 7.20 mmol) in anhydrous EtOH (120 mL) was added 10% Pd/C (500 mg), and the resulting suspension was shaken for 4 h at 24–25 °C under an atm of H_2 (balloon). The ethanolic solution was filtered through Celite® and the solvent was evaporated in vacuo. The oily residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH, 0–3% of MeOH) to afford compound **4** (95%, 2.21 g) as a colorless oil.

$[\alpha]_D^{23}$ –22.1 (*c* 1.0, $CHCl_3$); the optical purity (>98% ee) was determined by HPLC (Chiralcel OD-H, hexane–*i*-PrOH, 80:20, 1 mL/min); t_R = 6.9 min.

IR (CH_2Cl_2): 3373, 2946, 1652, 1340, 1161, 1092, 815 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.57 (q, *J* = 8.0 Hz, 1 H), 0.66 (q, *J* = 8.0 Hz, 1 H), 0.82–0.88 (m, 1 H), 0.90 (s, 3 H), 0.94 (s, 3 H), 1.06 (s, 3 H), 1.06–1.10 (m, 1 H), 1.56–1.62 (m, 1 H), 1.83 (dd, *J* = 15.0, 8.5 Hz, 1 H), 2.43 (s, 3 H), 3.06 (dd, *J* = 15.0, 5.0 Hz, 1 H), 7.31 (d, *J* = 8.5 Hz, 2 H), 7.79 (d, *J* = 8.5 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.1, 17.4, 18.3, 21.5, 21.8, 24.9, 26.6, 28.1, 32.9, 52.2, 59.8, 127.1, 129.7, 137.5, 143.4.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{27}N_2O_2S$: 323.1793; found: 323.1780.

(1*R*,3*S*,4*S*,6*S*)-4-Methyl-*N*-{4,7,7-trimethyl-4-(pyrrolidin-1-yl)bicyclo[4.1.0]heptan-3-yl}-benzenesulfonamide (7)

To a vigorously stirred suspension of amine **4** (0.40 g, 1.24 mmol) and K_2CO_3 (0.45 g, 3.23 mmol) in MeCN (8 mL) was added 1,4-diiodobutane (0.44 g, 1.43 mmol). The resulting mixture was stirred at reflux temperature for 15 h, after which the solvent was evaporated in vacuo. To the residue were added CH_2Cl_2 (50 mL) and H_2O (50 mL). The organic phase was separated, washed with brine (15 mL) and dried over $MgSO_4$. After evaporation of the solvent, the oily residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH, 0–2% of MeOH) to give compound **7** (77%, 0.36 g) as a colorless oil.

$[\alpha]_D^{23}$ +55.7 (*c* 1.0, $CHCl_3$); the enantiomeric purity (>98% ee) was determined by HPLC (Chiralcel OD-H, hexane–*i*-PrOH, 80:20, 1 mL/min); t_R = 7.1 min.

IR (CH_2Cl_2): 3361, 3254, 2949, 1652, 1599, 1340, 1162, 1093, 815 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.39–0.44 (m, 1 H), 0.66–0.71 (m, 1 H), 0.75–0.85 (m, 2 H), 0.88 (s, 3 H), 0.94 (s, 3 H), 1.03 (s, 3 H), 1.61 (br s, 4 H), 2.05 (br s, 2 H), 2.35 (br s, 2 H), 2.43 (s, 3 H), 2.53 (br s, 2 H), 3.22 (dd, *J* = 10.0, 2.0 Hz, 1 H), 7.31 (d, *J* = 8.0 Hz, 2 H), 7.79 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.1, 18.4, 18.7, 21.5, 22.4, 23.0, 23.6, 25.0, 25.8, 28.1, 45.6, 55.6, 127.2, 129.5, 137.4, 143.2.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{32}N_2O_2SNa$: 399.2082; found: 399.2098.

(1*R*,3*S*,4*S*,6*S*)-4-Methyl-*N*-{4,7,7-trimethyl-4-(piperidin-1-yl)bicyclo[4.1.0]heptan-3-yl}-benzenesulfonamide (8)

To a vigorously stirred suspension of amine **4** (0.70 g, 2.17 mmol) and K_2CO_3 (0.75 g, 5.43 mmol) in MeCN (15 mL) was added 1,5-diiodopentane (0.84 g, 2.60 mmol). The resulting mixture was stirred at reflux temperature for 15 h, after which the solvent was evaporated under reduced pressure. To the residue were added CH_2Cl_2 (100 mL) and H_2O (100 mL). The organic phase was separated, washed with brine (30 mL) and dried over $MgSO_4$. After evaporation of the solvent, the oily residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH, 0–1.5% of MeOH) to give compound **8** (82%, 1.06 g) as a colorless oil.

$[\alpha]_D^{23}$ +43.0 (*c* 1.0, $CHCl_3$); the enantiomeric purity (>98% ee) was determined by HPLC (Chiralcel OD-H, hexane–*i*-PrOH, 80:20, 1 mL/min); t_R = 5.0 min.

IR (CH_2Cl_2): 3386, 3264, 2938, 1652, 1599, 1457, 1340, 1167, 1092, 902, 815 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.34–0.39 (m, 1 H), 0.64–0.73 (m, 2 H), 0.77–0.83 (m, 1 H), 0.89 (s, 3 H), 0.91 (s, 3 H), 0.94 (s, 3 H), 1.33 (br s, 6 H), 2.03 (dd, *J* = 16.5, 9.0 Hz, 1 H), 2.14–2.19 (m, 1 H), 2.22–2.36 (m, 4 H), 2.43 (s, 3 H), 3.22 (dd, *J* = 12.0, 4.0 Hz, 1 H), 7.31 (d, *J* = 8.0 Hz, 2 H), 7.79 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.1, 18.4, 19.0, 21.5, 22.2, 22.9, 23.4, 24.9, 25.4, 26.7, 28.2, 46.7, 54.3, 127.3, 129.5, 137.2, 143.1.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{34}N_2O_2SNa$: 413.2239; found: 413.2251.

Preparation of Catalyst 6 for the Reductions with HCOOH–Et_3N as the Hydrogen Source

A mixture of $[RuCl_2(benzene)]_2$ (6 mg, 12 μmol), ligand **4** (9.7 mg, 30 μmol) and Et_3N (24 μmol) in MeCN (1 mL) was stirred at 24–25 °C for 30 min. After this time, the resulting pale brown solution of the catalyst was used immediately for the reduction of the ketones.

Reductions of Ketones Using Catalyst 6 and HCOOH–Et_3N; General Procedure

A solution of the preformed ruthenium catalyst **6** in MeCN (1 mL, 24 μmol) and an azeotropic mixture of HCOOH–Et_3N (1 mL) were added to a vial containing the ketone (2.4 mmol). The mixture was stirred at 24–25 °C for 6 d (monitored by TLC). After evaporation of the sol-

vents, CH_2Cl_2 (4 mL) and 10% aq HCl (1.5 mL) were added to the residue. The layers were separated and the aq layer was extracted with CH_2Cl_2 (2 × 2 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The product[12,13] was isolated by filtration through a short-path silica gel column using $CHCl_3$ (dried over $CaCl_2$) as the eluent. The enantiomeric excess was determined by GC analysis using a Supelco cyclodextrin β-DEX 120 capillary column (20 m × 0.25 mm I.D., 0.25 µm film thickness). The results obtained from the reduction reactions are summarized in Table 2.

Preparation of Catalyst 6 for the Reductions with Propan-2-ol as the Hydrogen Source

A mixture of $[RuCl_2(benzene)]_2$ (6 mg, 12 µmol), ligand **4** (9.7 mg, 30 µmol) and propan-2-ol (2 mL) was heated at 80 °C for 20 min under an Ar atm. After cooling to room temperature (24–25 °C), the resulting orange solution was used immediately for the reduction of the ketones.

Reductions of Ketones Using Catalyst 6 and Propan-2-ol; General Procedure

A solution of preformed ruthenium catalyst **6** (24 µmol) in propan-2-ol (2 mL) and 0.1 M KOH solution (1 mL) was added to a vial containing a solution of the ketone (2.4 mmol) in propan-2-ol (1 mL). The mixture was stirred at 24–25 °C for 24 h (monitored by TLC). The reaction mixture was neutralized with dilute HCl and then concentrated in vacuo. The residue was diluted with CH_2Cl_2 (8 mL), washed with brine (2 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The product[12,13] was isolated by filtration through a short-path silica gel column using $CHCl_3$ (dried over $CaCl_2$) as the eluent. The enantiomeric excess was determined by GC analysis using a Supelco cyclodextrin β-DEX 120 capillary column (20 m × 0.25 mm I.D., 0.25 µm film thickness). The results obtained from the reduction reactions are summarized in Table 2.

Catalytic Asymmetric Addition of Diethylzinc to Aldehydes; General Procedure

To a stirred solution of ligand **7** (9 mg, 0.024 mmol) in anhydrous hexane (2 mL) under an Ar atm was added dropwise a solution of Et_2Zn (1.0 mL, 1.0 M in hexane) at 0 °C. After being stirred for an additional 1 h, freshly distilled aldehyde (53 mg, 0.5 mmol) was added via a syringe. The resulting mixture was stirred at 0 °C for another 20 h and then quenched with aq HCl (2 M). The aq phase was extracted with EtOAc (3 × 5 mL) and the combined organic phase dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the product[12,14] was isolated by filtration through a short-path silica gel column using $CHCl_3$ (dried over $CaCl_2$) as the eluent. The enantiomeric excess was determined by GC analysis using a Supelco cyclodextrin β-DEX 120 capillary column (20 m x 0.25 mm I.D. and 0.25 µm film thickness). The results obtained from the reduction reactions are summarized in Table 3.

Acknowledgment

We acknowledge the financial support from the Polish Ministry of Science and Higher Education in the form of grant N N204 117939. We cordially thank Dr. Dariusz Błachut (Internal Security Agency) for the determination of ee values by GC and Dr Stefan Czarnocki for valuable experimental assistance.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1378942.

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