DOI: 10.1002/ejoc.200700261

Synthesis of (–)-(*S*)-Norlaudanosine, (+)-(*R*)-*O*,*O*-Dimethylcoclaurine, and (+)-(*R*)-Salsolidine by Alkylation of an α-Aminonitrile

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Keywords: Alkaloids / Heterocycles / Umpolung / Asymmetric catalysis / Aminonitriles

A short asymmetric synthesis of 1-substituted 1,2,3,4-tetrahydroisoquinoline alkaloids by deprotonation of an unprotected α-aminonitrile and alkylation of the resulting carbanion followed by spontaneous elimination of HCN and asymmetric reduction is described.

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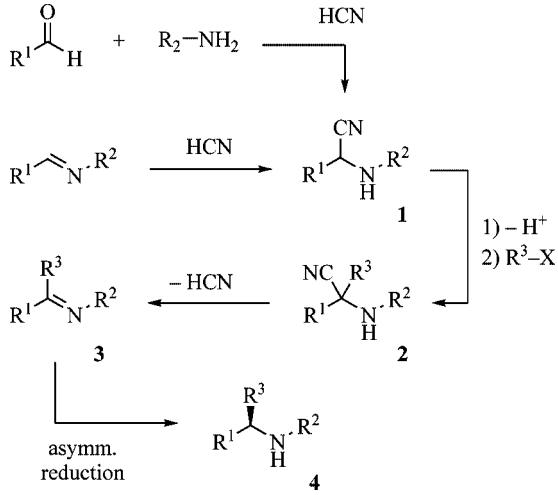
Introduction

Amines and nitrogen heterocycles are key structural elements found in an exceedingly large number of pharmaceuticals and agrochemicals.[1] Both synthetic compounds and natural products containing nitrogen frequently exhibit potent biological activities.[2] An example is the large group of tetrahydroisoquinoline alkaloids, several members of which have become classical targets for the development of new synthetic methodologies.[3–7] Here we report on a short asymmetric approach to α-branched secondary amines and its application to the synthesis of 1-substituted 1,2,3,4-tetrahydrosioquinoline alkaloids.

While investigating methods for the reversible Umpolung of the reactivity of the C=N bond,[8–10] we recently found that unprotected α-aminonitriles possessing a primary or secondary amino group can be deprotonated in the α-position without inducing elimination of HCN by means of a retro-Strecker reaction if a stabilizing α-substituent such as an aromatic or heteroaromatic ring is present. The resulting stabilized carbanions can be used as starting materials for the preparation of pyrrolidines, pyrroles, γ-amino acids, 1,2-diamines, or indoles in one-pot reaction procedures.[11–16] *C*-Alkylation of deprotonated unprotected aminonitriles **1** affords α-branched products **2**, from which HCN can be eliminated to form ketimines **3**.[17] Depending on the structure of the compound **3**, this elimination may occur spontaneously. Hydrolysis of imines **3** produces ketones, while their reduction furnishes α-branched amines **4**. In combination with methods for the enantioselective reduction of ketimines,[18] this reaction sequence can also be used for the asymmetric synthesis of compounds **4** (Scheme 1).



Scheme 1. Asymmetric synthesis of α-branched amines via α-aminonitriles.

Results and Discussion

The stable, crystalline 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (**6**; Scheme 2) is readily accessible by Bischler–Napieralski cyclization of *N*-formyl homoveratrylamine, to provide dihydroisoquinoline **5**, and subsequent addition of HCN.[19–21] Upon treatment with KHMDS in THF at –78 °C, the aminonitrile **6** is deprotonated in the α-position without induction of the elimination of HCN.[13] Addition of alkyl halides and warming to ambient temperature results directly in the formation of the 1-alkylated dihydroisoquinolines **8**. Apparently, the 1-substituted nitriles **7** are unstable and spontaneously eliminate HCN. Attempts to convert imines **8** into the aminonitriles **7** by treatment with HCN or TMSCN and various catalysts failed.

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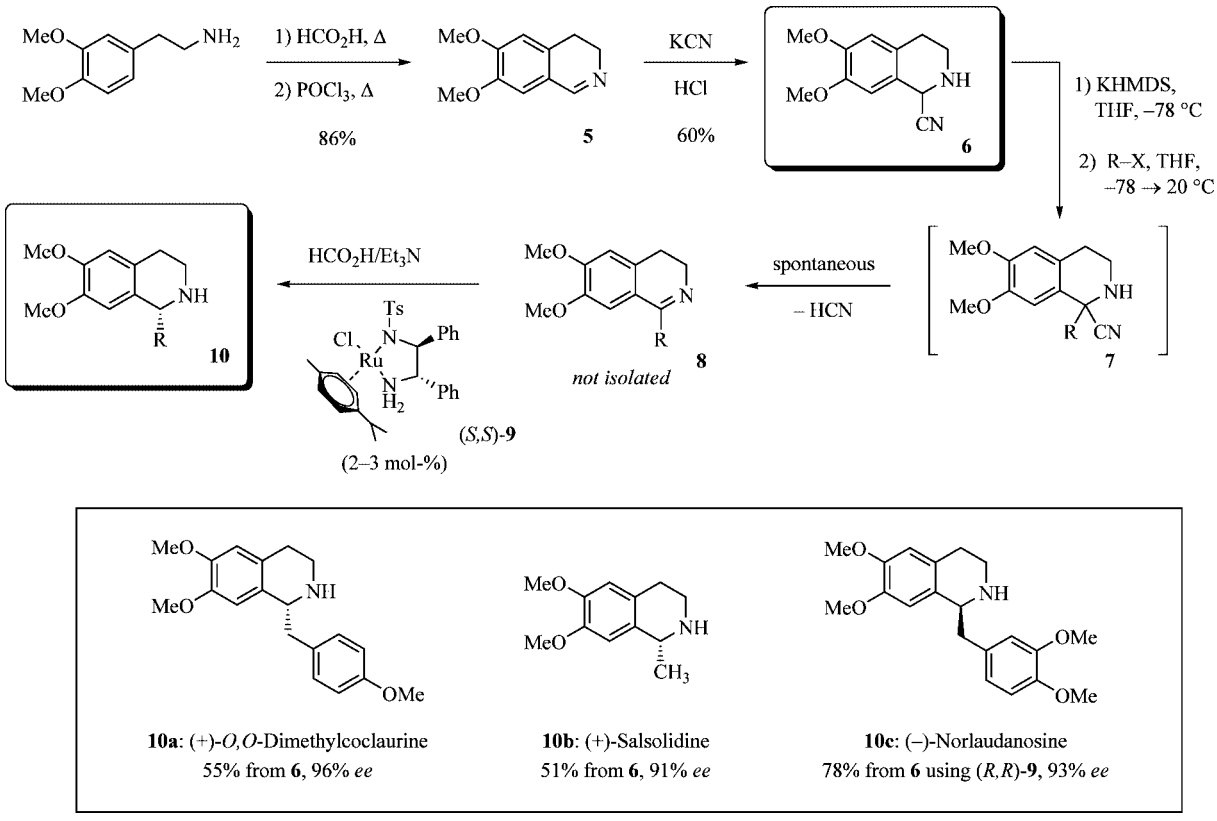

Scheme 2. Asymmetric synthesis of tetrahydroisoquinoline alkaloids from aminonitrile **6**.

The asymmetric reduction of dihydroisoquinolines with a chiral triacyloxyborohydride derived from *N*-benzyloxycarbonyl-L-proline described by Yamada and co-workers proved suitable for the in situ reduction of compounds **8** without prior workup.[22] The enantiomeric excess of the obtained (*S*)-*O*,*O*-dimethylcoclaurine (**10a**[23]) amounted to 69%, but the isolated yield was unsatisfactory. A similar reduction technique using a triacyloxyborohydride derived from *N*-phthaloyl-L-leucine has been described by Hajipour and Hantehzadeh.[24] While these authors report high yields and optically pure products obtained under solid-state conditions (grinding of the reagents with alumina in a mortar), we did not observe any reduction of crude or purified compounds **8** on using this procedure. On the other hand, the asymmetric transfer hydrogenation of **8** with Noyori's catalyst (**9**) and formic acid/triethylamine as the hydrogen source effected essentially quantitative reduction and was highly enantioselective for all synthesized compounds.[25] With the (*S*,*S*)-enantiomer of the catalyst, (*R*)-configured *O*,*O*-dimethylcoclaurine (**10a**) and salsolidine (**10b**) were obtained with 96% and 91% *ee*, respectively. The (*S*) enantiomer of norlaudanosine (**10c**) was obtained in 93% *ee* with the (*R*,*R*)-configured catalyst. Unfortunately, the Noyori system turned out to be more sensitive than the rugged Yamada reagent and both yield and optical purity of the products were severely affected by the presence of cyanide ions. Therefore, removal of the cyanide from the reaction mixture by extraction with a nickel chloride solution proved necessary (Scheme 2).

The alkylation of deprotonated aminonitriles and asymmetric reduction of the imines resulting from spontaneous or induced elimination of HCN from the reaction products provides a short path to chiral α-branched amines. The reaction sequence does not require the isolation or purification of the intermediates and, if cyanide-insensitive reducing agents are used, it can be performed as a one-pot procedure. Although compounds **10** have previously been directly synthesized by Bischler–Napieralski cyclization of amides from homoveratrylamine, our protocol permits the introduction of acid-sensitive side chains – which are incompatible with the harsh cyclization conditions – at C1.

Experimental Section

All reactions were carried out under argon unless stated otherwise. THF was dried by distillation from Na/benzophenone. 3,4-Dimethoxybenzyl bromide,[26,27] 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate,[28] and (1*R*,2*R*)- and (1*S*,2*S*)-*N*-(4-tolylsulfonyl)-1,2-diphenylethylenediamine[29,30] were prepared as described in the literature. Ethyl acetate was distilled from potassium carbonate, while petroleum ether (boiling range 40–70 °C) was distilled from calcium hydride. All other solvents and reagents were purchased from commercial suppliers and were used without further purification. TLC was performed on TLC aluminium sheets (silica gel 60 F_{254}, E. Merck). Flash chromatography was carried out on silica gel (32–63 μm, 60 Å, MP Biomedicals GmbH). Analytical RP-HPLC separations were performed on a Luna C18(2), 5 μm (Phenomenex) instrument using a Knauer MaxiStar K-1000 gradient pump and a Knauer Variable Wavelength Monitor. ^{1}H NMR and

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^{13}C NMR spectra were recorded on a Bruker AC 300 or Avance 400 instrument. Chemical shifts were referenced to the residual solvent signal ($CDCl_3$: δ_H = 7.24 ppm, δ_C = 77.0 ppm). FD-MS spectra were recorded on a Finnigan MAT 95 at a desorption voltage of 5 kV and with a heater current ramp of 10 mA min^{-1}. IR spectra were recorded on a Perkin–Elmer 1760X FTIR spectrometer. Melting points were measured on a Dr. Tottoli apparatus and are uncorrected. Determination of the enantiomeric excess was performed as described for each compound. The racemic products were prepared as reference compounds by one-pot reduction of the crude dihydroquinolines with $NaCNBH_3$.

6,7-Dimethoxy-3,4-dihydroisoquinoline (5): Formic acid (5.62 g, 122 mmol) was added with ice cooling to 3,4-dimethoxyphenethylamine (16.05 g, 88.6 mmol). The light yellow mass was heated to reflux (190 °C bath temperature) until TLC indicated complete conversion (2 h). After cooling, the yellow reaction mixture was diluted with toluene (75 mL). Phosphoryl chloride (27.4 g, 178 mmol) was added and the mixture was heated to reflux until TLC indicated complete conversion (1 h). After removal of toluene and excess phosphoryl chloride by distillation, the brown residue was washed with petroleum ether (100 mL) and taken up in 1,4-dioxane (30 mL).[31] The solution was poured onto ice (100 g) and the resulting homogeneous solution was washed with diethyl ether (2 × 50 mL). The organic extracts were discarded and the aqueous layer was basified to pH >12 by careful addition of solid NaOH (cooling). Extraction with diethyl ether (4 × 50 mL), drying over Na_2SO_4, and removal of the solvent in vacuo furnished **5** (14.48 g, 85.5%) as an amber-colored oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.64 (pseudo-t, J_{app} = 8.2 Hz, 2 H, 4-H_2), 3.65 (pseudo-t, J_{app} = 8.2 Hz, 2 H, 3-H_2), 3.86, 3.87 (2 s, 2 × 3 H, OCH_3), 6.63 (s, 1 H, 5-H), 6.74 (s, 1 H, 8-H), 8.18 (br. s, 1 H, 1-H) ppm. IR (film): $\tilde{\nu}$ = 2939, 2837, 1630, 1606, 1575, 1518, 1464, 1325, 1281, 1240, 1224, 1121 cm^{-1}.[32]

6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (6): A solution of KCN (7.88 g, 121 mmol) in water (40 mL) and a few crystals of bromophenol blue were added to a solution of **5** (7.33 g, 38.3 mmol) in MeOH (10 mL). The mixture was cooled to 0 °C, and concentrated hydrochloric acid (40 mL) was added slowly. The yellow reaction mixture turned green after 1 h and it was stirred at ambient temperature overnight. HCN vapors were removed by use of a slow stream of argon (caution!) and the mixture was poured into saturated aq. $NaHCO_3$ (200 mL). The mixture was made alkaline (blue color) by addition of solid $NaHCO_3$ and extracted with CH_2Cl_2 (7 × 70 mL). The combined organic layers were dried with Na_2SO_4 and the solvent was removed in vacuo to give **6** (4.99 g, 59.7%) as light yellow crystals. m.p. 106–107 °C, lit. 109–110 °C.[19] ^1H NMR (300 MHz, $CDCl_3$): δ = 2.12 (br. s, 1 H, NH), 2.67 (dt, ^2J_d = 16.2, ^3J_t = 3.6 Hz, 1 H, 4-H_a), 2.86 (m_c, 1 H, 4-H_b), 3.20–3.29 (m, 2 H, 3-H_2), 3.86, 3.87 (2 s, 2 × 3 H, OCH_3), 4.96 (s, 1 H, 1-H), 6.60, 6.66 (2 s, 2 × 1 H, 5-H, 8-H) ppm. IR (film): $\tilde{\nu}$ = 3334, 2936 (sh), 2836, 2220 (w), 1611, 1520, 1464, 1264, 1226, 1109, 1029 cm^{-1}.

(+)-(*R*)-*O*,*O*-Dimethylcoclaurine (10a): A solution of KHMDS (502.7 mg, 2.52 mmol) in dry THF (3.8 mL) was added at –78 °C to a solution of **6** (500 mg, 2.29 mmol) in dry THF (17.5 mL). After 4 min, a solution of 4-methoxybenzyl chloride (373 μL, 2.75 mmol) in dry THF (3.8 mL) was added. After stirring for 3 h at –78 °C, the mixture was gradually warmed to ambient temperature over the course of 7 h. After addition of NaOH solution (1 N, 60 mL), the mixture was extracted with CH_2Cl_2 (4 × 30 mL). The combined organic layers were dried with Na_2SO_4 and the solvent was removed in vacuo to yield a viscous reddish oil (704.5 mg). This material was dissolved in methanol (30 mL) and after addition of a solution of $NiCl_2 \cdot 6H_2O$ (300 mg) in water (30 mL), the mixture was extracted with CH_2Cl_2 (3 × 30 mL), the combined organic layers were washed with a solution of ammonia (10%, 30 mL) and brine (30 mL) and dried with Na_2SO_4, and the solvent was removed in vacuo to yield the cyanide-free crude imine **8a** (656.0 mg). Triethylamine (27.6 μL, 196 μmol) was added to a solution of dichloro(*p*-cymene)ruthenium(II) dimer (12.9 mg, 21 μmol) and (1*S*,2*S*)-*N*-(4-tolylsulfonyl)-1,2-diphenylethylenediamine (15.4 mg, 42 μmol) in dry DMF (0.44 mL). The solution was degassed by ultrasonication under a slow stream of argon and was subsequently heated to 80 °C for 1 h. The crude imine **8a**, dissolved in degassed dry DMF (4.2 mL), was added to the warm solution. After cooling to 0 °C, formic acid/triethylamine azeotrope (5:2, 1.0 mL) was added and the mixture was stirred for 3 h at ambient temperature. After addition of saturated aq. K_2CO_3 solution (30 mL) and water (20 mL), the reaction mixture was extracted with ethyl acetate (3 × 50 mL) and the combined organic layers were washed with brine and dried with Na_2SO_4. Removal of the solvent in vacuo gave the crude product (521.2 mg) as a brownish oil. A portion (81.1 mg) of this material was purified by column chromatography (silica, cyclohexane/$CHCl_3$/Et_2NH, 10:4:1) to give **10a** as a slightly brown oil (60.9 mg, 54.5%). $[\alpha]_D^{25}$ = +15.3 (*c* = 1, $CHCl_3$); ref.[33] +15.7 (*c* = 0.4, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.70 (br. s, 1 H, NH), 2.63–2.79 (m, 2 H, 4-H_2), 2.81–2.94 (m, 2 H, 3-H_2), 3.12–3.24 (m, 2 H, $ArCH_2$), 3.80, 3.82, 3.86 (3 s, 3 × 3 H, OCH_3), 4.10 (dd, *J* = 9.3, 4.4 Hz, 1 H, 1-H), 6.59, 6.63 (2 s, 2 × 1 H, 5-H, 8-H), 6.87 (AA′-part of AA′XX′ system, 2 H, 3′,5′-H), 7.17 (XX′-part of AA′XX′ system, 2 H, 2′,6′-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 29.5 (C-4), 40.7, 41.8 (C-3, $ArCH_2$), 55.2, 55.8, 55.9 (OCH_3), 56.9 (C-1), 109.4, 111.8 (C-5, C-8), 114.0 (2 C, C-3′,5′), 127.3, 130.6, 131.0 (C-1′, C-4a, C-8a), 130.3 (2 C, C-2′,6′), 146.9, 147.4 (C-5, C-7), 158.2 (C-4′) ppm. IR (film): $\tilde{\nu}$ = 3332, 2996, 2933 (sh), 2833, 1610, 1511, 1465 (sh), 1301, 1247 (sh), 1223, 1178, 1114, 1034 cm^{-1}. These data are in accordance with the values reported in the literature.[33]

Determination of the enantiomeric excess was carried out by derivatization with 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate and analytical HPLC. Eluent CH_3CN/H_2O 35:65, 1 mL min^{-1}, R_t(*S* derivative): 44.3 min, R_t(*R* derivative): 47.0 min. Enantiomeric ratio = 48.2:1, *ee* = 96%.

(+)-(*R*)-Salsolidine (10b): A solution of KHMDS (201.1 mg, 1.01 mmol) in dry THF (1.5 mL) was added at –78 °C to a solution of **6** (200 mg, 0.916 mmol) in dry THF (7 mL). After 4 min, a solution of iodomethane (68.5 μL, 1.01 mmol) in dry THF (1.5 mL) was added. After stirring for 3 h at –78 °C, the mixture was gradually warmed to ambient temperature over the course of 7 h. After addition of NaOH solution (1 N, 30 mL), the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried with Na_2SO_4 and the solvent was removed in vacuo to yield a reddish solid. This material was dissolved in methanol (20 mL) and, after addition of a solution of $NiCl_2 \cdot 6H_2O$ (160 mg) in water (20 mL), the mixture was extracted with CH_2Cl_2 (3 × 30 mL), the combined organic layers were washed with a 10% solution of ammonia (20 mL) and brine (20 mL) and dried with Na_2SO_4, and the solvent was removed in vacuo to yield the cyanide-free crude imine **8b** (177.5 mg) as a reddish solid. Triethylamine (11.4 μL, 82 μmol) was added to a solution of dichloro(*p*-cymene)ruthenium(II) dimer (5.3 mg, 8.6 μmol) and (1*S*,2*S*)-*N*-(4-tolylsulfonyl)-1,2-diphenylethylenediamine (6.3 mg, 17.2 μmol) in dry DMF (0.44 mL). The solution was degassed by ultrasonication under a slow stream of argon and was subsequently heated to 80 °C for 1 h. The crude imine **8b**, dissolved in degassed dry DMF (1.8 mL), was added to

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the warm solution. After cooling to 0 °C, formic acid/triethylamine azeotrope (5:2, 0.5 mL) was added and the mixture was stirred for 3 h at ambient temperature. After addition of saturated aq. K_2CO_3 solution (9 mL) and water (6 mL), the reaction mixture was extracted with ethyl acetate (3 × 15 mL) and the combined organic layers were washed with brine and dried with Na_2SO_4. Removal of the solvent in vacuo gave the crude product (156.3 mg) as a brownish oil. A portion (45.6 mg) of this material was purified by column chromatography (silica, petroleum ether/EtOAc/Et_2NH 8:3:1, R_f = 0.13) to give **10b** as a colorless oil (28.3 mg, 51.1%). $[\alpha]_D^{25}$ = +56.5 (*c* = 1, $CHCl_3$); ref.[24] –59.5 (*S* enantiomer, *c* = 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.42 (d, *J* = 6.6 Hz, 3 H, CH_3), 1.80 (br. s, 1 H, NH), 2.58–2.67, 2.72–2.82 (2 m, 2 × 1 H, 4-$H_{a,b}$), 2.93–3.02, 3.19–3.27 (2 m, 2 × 1 H, 3-$H_{a,b}$), 3.83, 3.84 (2 s, 2 × 3 H, OCH_3), 4.01 (q, *J* = 6.6 Hz, 1 H, 1-H), 6.55 (s, 1 H, 8-H), 6.61 (s, 1 H, 5-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 22.8 (CH_3), 29.5 (C-4), 41.8 (C-3), 51.2 (C-1), 55.8, 55.9 (OCH_3), 109.0, 111.7 (C-5, C-8), 126.8, 132.4 (C-4a, C-8a), 147.2, 147.3 (C-6, C-7) ppm. IR (film): $\tilde{\nu}$ = 3315, 2933 (sh), 2832, 1610, 1511, 1464 (sh), 1372, 1293, 1256, 1223, 1118 (sh), 1030, 858, 790 cm^{-1}.These data are in accordance with the values reported in the literature.[34]

Determination of the enantiomeric excess was carried out by derivatization with 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate and analytical HPLC. Eluent CH_3CN/H_2O 35:65, 1 mL min^{-1}, R_t ((*R*) derivative): 64.7 min, R_t ((*S*) derivative): 68.0 min. Enantiomeric ratio = 20.9:1, *ee* = 91%.

(–)-(*S*)-Norlaudanosine (10c): A solution of KHMDS (301.6 mg, 1.51 mmol) in dry THF (2.3 mL) was added at –78 °C to a solution of **6** (300 mg, 1.38 mmol) in dry THF (10.5 mL). After 4 min, a solution of 3,4-dimethoxybenzyl bromide (333.6 mg, 1.44 mmol) in dry THF (2.3 mL) was added. After stirring for 3 h at –78 °C, the mixture was warmed to ambient temperature. As TLC indicated incomplete conversion, another portion of KHMDS (274.2 mg, 1.38 mmol) in dry THF (2.3 mL) was added after 30 min and stirring was continued for further 20 min. The reaction mixture was poured into NaOH solution (1 N, 45 mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (4 × 25 mL) containing MeOH (10%).[35] The combined organic layers were washed with a solution of $NiCl_2 \cdot 6H_2O$ (300 mg) in water (30 mL), a solution of ammonia (10%, 30 mL), and brine (30 mL). After drying over Na_2SO_4, the solvent was removed in vacuo to yield the crude imine **8c** as an orange oil (557.6 mg). Triethylamine (28.2 μL, 206 μmol) was added to a solution of dichloro-*p*-cymene-ruthenium(II)-dimer (12.6 mg, 20.6 μmol) and (1*R*,2*R*)-*N*-(4-tolylsulfonyl)-1,2-diphenylethylenediamine (15.2 mg, 41.2 μmol) in dry DMF (1.1 mL). The solution was degassed by ultrasonication under a slow stream of argon and was subsequently heated to 80 °C for 1 h.[36] The crude imine **8c**, dissolved in degassed dry DMF (3.8 mL), was added to the warm solution. After cooling to 0 °C, formic acid/triethylamine azeotrope (5:2, 0.72 mL) was added and the mixture was stirred for 4.5 h at ambient temperature. Saturated aq. K_2CO_3 solution (9 mL) and water (6 mL) were added and the mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried with Na_2SO_4 and the solvent was removed in vacuo to furnish a slightly brown oil (514 mg), which was purified by column chromatography (silica, eluent petroleum ether/EtOAc/Et_2NH 8:2:1, R_f = 0.20) to give **10c** as a light yellow oil (368.1 mg, 77.9%). $[\alpha]_D^{25}$ = –21.9 (*c* = 1, $CHCl_3$); ref.[37] –21 (*c* = 1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.66 (br. s, 1 H, NH), 2.61–2.73, 2.77–2.92 (2 m, 2 × 2 H, $ArCH_2$, 4-H_2), 3.12–3.22 (m, 2 H, 3-H_2), 3.81, 3.83, 3.83, 3.85 (4 s, 4 × 3 H, OCH_3), 4.09 (m_c, 1 H, 1-H), 6.57, 6.64 (2 s, 2 × 1 H, 5-H, 8-H), 6.73–6.82 (m, 3 H, 2′-H, 5′-H, 6′-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 29.6 (C-4), 41.0, 42.3 ($ArCH_2$, C-3), 55.83, 55.85, 55.9, 56.0 (OCH_3), 56.9 (C-1), 109.3 (C-8), 111.3, 111.8, 112.4 (C-5, C-2′, C-5′), 121.4 (C-6′), 127.5 (C-4a), 130.5 (C-8a), 131.5 (C-1′), 147.0, 147.4, 147.6, 148.9 (C-6, C-7, C-3′, C-4′) ppm. IR (film): $\tilde{\nu}$ = 3327, 3010, 2935, 2833, 1609, 1590, 1515, 1464 (sh), 1262, 1235 (sh), 1112, 1028 cm^{-1}. FD-MS: *m/z* = 366.2 $[M + Na]^+$ (75%), 344.2 $[M + H]^+$ (100%). These data are in accordance with the values reported in the literature.[7]

Determination of the enantiomeric excess was carried out by ^1H NMR spectroscopy after derivatization with (*S*)-(*a*)-methylbenzyl isocyanate (*er* > 99.5:0.5). Enantiomeric ratio: 26.7:1, *ee* = 93%.

Supporting Information (see also the footnote on the first page of this article): ^1H and ^{13}C NMR spectra, as well as HPLC chromatograms.

Acknowledgments

This work was supported by the Deutsche Forschungsgemeinschaft (DFG) and the University of Mainz.

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Received: March 23, 2007
Published Online: June 19, 2007

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