Synthesis of Enantioenriched 2-Substituted 4-Phenylbutylamines by Hydrogenolysis of Optically Pure 6-Alkoxy-5,6-dihydro-4*H*-1,2-oxazines

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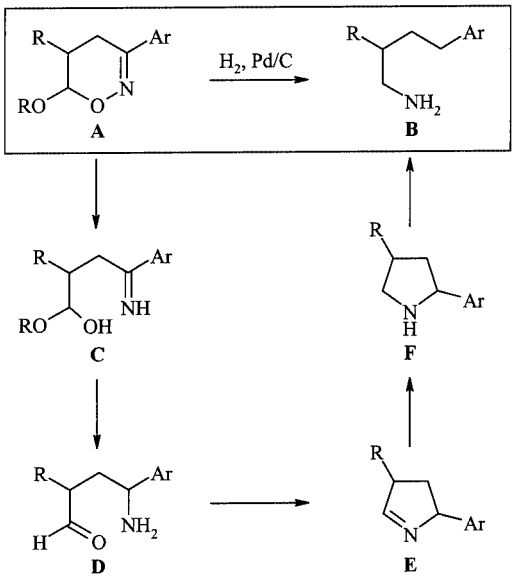
Lewis acid promoted exchange of the 6-ethoxy group of 6*H*-1,2-oxazines **1**–**3** with (–)-menthol furnished the optically active heterocycles **4**–**6**. Diastereomers **4a** and **4b**, which could be separated efficiently by chromatography, were excellent substrates for highly diastereoselective conjugate additions of phenyllithium and *n*-butyllithium, thus providing the enantiopure *trans*-substituted 1,2-oxazines **7a**, **7b**, **8a**, and **8b** in good yields. Exhaustive hydrogenolysis of **7a** afforded the primary amine **9** with an enantiomeric excess of 80%, whereas hydrogenolysis of **8a** and **8b** gave the corresponding amines (*R*)-**11** and (*S*)-**11**, respectively, with an *ee* of more than 90%.

Introduction

We have demonstrated in earlier investigations that exhaustive hydrogenolysis of 3-phenyl-substituted 6-alkoxy-5,6-dihydro-4*H*-1,2-oxazines **A** in the presence of palladium transforms these heterocycles into the 4-phenylbutylamines **B** (Scheme 1).[1–5] The mechanism of this cascade reaction is illustrated in Scheme 1 and involves a reductive cleavage of the N–O bond, fragmentation of the resulting semiacetal **C** and reduction of the C=N bond. Recyclization of **D** furnishes the cyclic imine **E**, which is then reduced to pyrrolidine **F**. Compounds **F** can be isolated as products if the substituent at C-2 of **F** is not an aryl group[6] or if a substituent at C-3 hampers the last reduction step sterically or electronically.[5] However, for starting materials such as **A** the reaction proceeds to completion and hydrogenolysis of the benzylic C–N bond affords the primary amine **B** as the final product usually in good yield.[1–5]



Scheme 1

Results and Discussion

In previous publications we reported the synthesis of enantioenriched 2-methyl-4-phenylbutylamine (*ee* up to > 90%) from this reductive cleavage sequence employing 6-alkoxy-6*H*-1,2-oxazine precursors synthesised by an asymmetric hetero-Diels–Alder reaction with enantiopure enol ether auxiliaries.[2] We now want to present our first results with enantiopure 1,2-oxazines **A** synthesised by an alternative route (Scheme 2). This method employs a highly diastereoselective conjugate addition of organolithium compounds to enantiopure 6*H*-1,2-oxazines such as **4a** and **4b**. These precursor compounds were prepared by a Lewis acid catalysed exchange of the 6-ethoxy group of racemic 1,2-oxazine **1**[7] employing (–)-menthol as auxiliary. This reaction involves an azapyrylium ion[8] and provides a 45:55 mixture of the two diastereomers **4a**,**b** in 89% yield, which can be separated either by column chromatography or — more efficiently — by HPLC, furnishing the diastereomerically pure precursor compounds **4a** and **4b** in 28% and 52% yield, respectively. Use of methyl mandelate as the auxiliary was less efficient.[9] The conversion of 6-ethoxy-substituted

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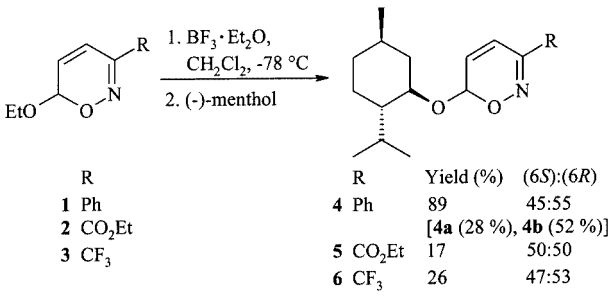
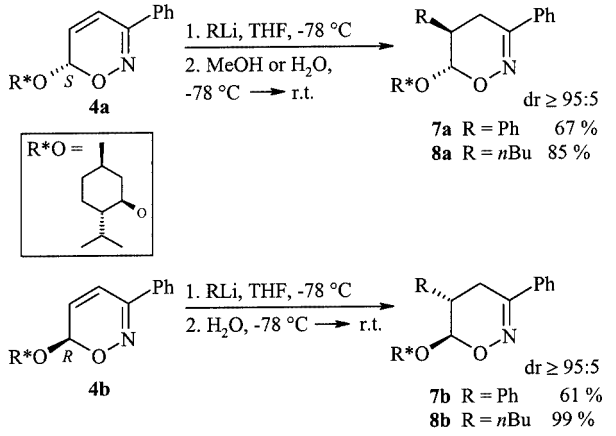


Scheme 2

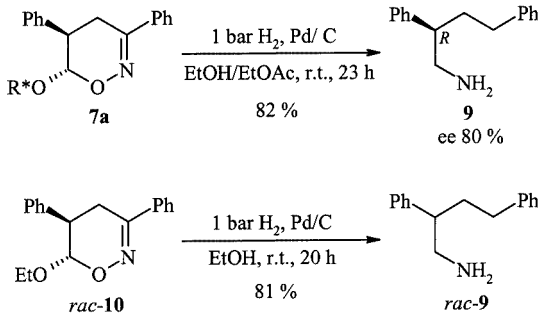
1,2-oxazines was also examined with compounds **2** and **3**. The exchanges were less efficient in these cases (although not optimized) and resulted in isomers **5a**,**b** and **6a**,**b**. Again, the diastereomers are separable by chromatography.[9] The ratios of **a**:**b** in all three examples seem to reflect the thermodynamic equilibria which are, as expected, not far from 50:50. The absolute configuration of **4a** at C-6 is *S* as unambiguously determined by an X-ray analysis.[10]

With the two enantiopure diastereomers **4a** and **4b** in hand we investigated the conjugate addition of organolithium compounds and the hydrogenolysis of the resulting adducts. Reactions with phenyllithium and *n*-butyllithium were executed as described for racemic 6*H*-1,2-oxazines,[11,12] and for **4a** they furnished products **7a** and **8a** in good yields (Scheme 3). As expected, the bulky 6-menthyloxy group of **4a** leads to highly selective *trans*-additions furnishing diastereomerically pure compounds (*dr* ≥ 95:5). Similarly, reactions of diastereomer **4b** with the two organolithium compounds furnished adducts **7b** and **8b**, again with excellent *trans* selectivity. The chirality of the menthyl group seems to have no dramatic influence on the yields and diastereoselectivities in these addition reactions. However, we observed a clear effect on the efficiency of the conjugate addition when a sterically more demanding aryllithium compound was added to 3-(*p*-methoxyphenyl)-substituted 6*H*-1,2-oxazines corresponding to **4a** and **4b**, thus revealing an interesting matched/mismatched situation.[5]



Scheme 3

When compound **7a** was exhaustively hydrogenated under standard conditions it provided **9** in good yield and with a specific optical rotation of −5.85 (*c* = 0.99, $CHCl_3$; Scheme 4). Since **9** was not known in an enantiopure form we prepared a racemic sample of *rac*-**9** from *rac*-**10**[12] and compared the Mosher amides of enantioenriched **9** by HPLC with those of the diastereomers obtained from *rac*-**9**. Thus, an enantiomeric excess of 80% could be determined for optically active **9**. Since the absolute configuration at C-5 of **7a** is *R* the predominant enantiomer of **9** should also have an *R* configuration at C-2. It is obvious that the corresponding *S* enantiomer is available in an analogous fashion with **7b** as the starting material.

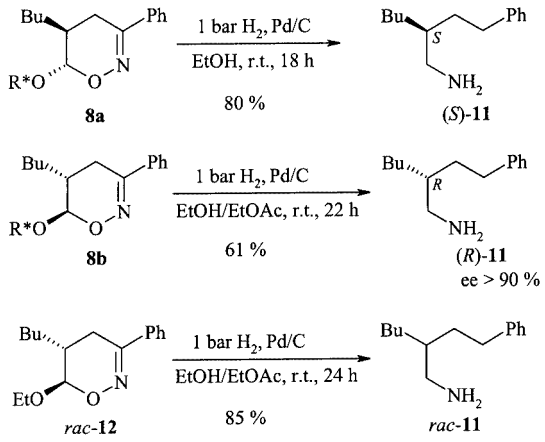


Scheme 4

Hydrogenolysis of the 5-butyl-substituted 1,2-oxazines **8a** and **8b** afforded the expected primary amine **11** with a negligible optical rotation (−0.37 starting from **8b**). Since we did not expect almost complete racemization in these experiments, we prepared a sample of *rac*-**11** by conjugate addition of *n*-butyllithium to *rac*-**12** followed by hydrogenolysis.[12] The corresponding diastereomeric Mosher amides of *rac*-**11** did not show two HPLC signals. However, a splitting of signals of two carbon atoms was observed in the ^{13}C NMR spectrum. In contrast, the Mosher amide derived from the primary amine **11** obtained from **8b** did not show this splitting. Since the signals were relatively broad an error of approximately 5% must be allowed for this method of analysis. Nevertheless, these experiments reveal that (*R*)-**11** was formed with an enantiomeric excess of ≥90%. It is likely that (*S*)-**11** has a similar enantiopurity. The preferential absolute configurations at the stereogenic centres as depicted in Scheme 5 are derived from the configurations of the precursor heterocycles **8a** and **8b**.

Conclusion

The experiments disclosed here demonstrate that enantiopure 6*H*-1,2-oxazines such as **4a** and **4b** are available with reasonable efficiency by separation of the diastereomers obtained after 6-alkoxy group exchange with (−)-menthol as auxiliary. We have demonstrated again[11,12] that the conjugate addition of phenyllithium or *n*-butyllithium



Scheme 5

occurs with a very high *trans* selectivity. Since the stereogenic centre generated in this addition step is not directly involved during hydrogenolysis the slight loss of enantiopurity on going from **7a** to **9** is probably caused at the stage of the intermediate γ-amino aldehyde (**D** in Scheme 1). The phenyl group enhances the C-H acidity in the α-position and partial racemization by deprotonation/protonation or via the enol tautomer may lower the optical purity of the final product. An isomerization at the stage of the cyclic imine (**E** in Scheme 1) to an enamine as intermediate is also possible but seems less probable. The reaction sequence as illustrated here for the model substrates **7a**, **8a**, and **8b** leads to 2-substituted 4-phenylbutylamines with good to high enantiopurity. It should also be applicable to other substitution patterns since many organolithium compounds can be used in the first step of the sequence. In the racemic series we have already combined the conjugate addition of organolithium compounds with trapping of the intermediate with a large variety of electrophiles.[11,12] This method introduces an additional substituent at C-4 with high *trans* selectivity (with respect to the group at C-5). Thus, the method described here should be extendable to enantioenriched primary amines with two stereogenic centres at C-2 and C-3.

Experimental Section

General: Unless otherwise stated all reactions were performed under an argon atmosphere in flame-dried flasks by adding the components with a syringe. All solvents were dried using standard procedures. IR spectra were measured with a Perkin−Elmer FT-IR spectrometer Nicolet 5 SXC or Nicolet 205. ^{1}H and ^{13}C NMR spectra were recorded on Bruker instruments (AC 300, WH 270, AC 250, AC 200) in $CDCl_3$ solution. The chemical shifts are given relative to TMS or to the $CDCl_3$ signal (δ_H = 7.27, δ_C = 77.0). Higher order NMR spectra were approximately interpreted as first-order spectra if possible. Neutral aluminium oxide (activity III, Fluka/Merck) or silica gel (0.040−0.063 mm, Fluka) were used for column chromatography. Nucleosil 50−5 (Macherey & Nagel) was used for HPLC. Melting points are uncorrected. Optical rotations were determined with Perkin−Elmer 141 or Perkin−Elmer 241 polarimeter at 20 °C. The starting materials **1**,[7] **2**,[7] **3**,[7] **10**[12] and **12**[12] were prepared by literature procedures. All other chemicals are commercially available and were used as received.

General Procedure for the Preparation of 6-Menthyloxy-6*H*-1,2-oxazines 4−6: $BF_3{\cdot}OEt_2$ (2 equiv.) was added at −78 °C to a solution of the 1,2-oxazine **1**, **2** or **3** in CH_2Cl_2 (20 mL/mmol). After stirring for 30 min the optically active alcohol (3 equiv.) was added and the solution was allowed to warm to room temp. The reaction mixture was stirred for 24 h, then water (5 mL/mmol) was added, the phases separated, the organic layer dried (Na_2SO_4) and the solvent evaporated. The crude products were purified by chromatography (neutral aluminium oxide). The diastereomers were separated by HPLC or flash chromatography.

6-[(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyloxy]-3-phenyl-6*H*-1,2-oxazine (4): According to the general procedure, $BF_3{\cdot}OEt_2$ (0.75 mL, 5.97 mmol) and (−)-menthol (1.41 g, 9.00 mmol) were added to a solution of 1,2-oxazine **1** (0.610 g, 3.00 mmol) in CH_2Cl_2. Purification of the crude product [(6*R*):(6*S*) = 55:45] by chromatography (*n*-hexane/ethyl acetate, 8:1) led to 1,2-oxazine **4** (0.836 g, 89%). The separation of the diastereomers by HPLC (*n*-hexane + 5% ethyl acetate) yielded **4a** (0.261 g, 28%) as colourless crystals (m.p. 132−136 °C) and **4b** (0.492 g, 52%) as colourless crystals (m.p. 98−103 °C).

(6*S*)-[(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyloxy]-3-phenyl-6*H*-1,2-oxazine (4a): $[\alpha]_D^{20}$ = +54.7 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (200 MHz): δ = 7.76−7.66, 7.47−7.37 (2 m, 2 H, 3 H, Ph), 6.60 (d, *J* = 10.0 Hz, 1 H, 4-H), 6.42 (dd, *J* = 4.5, 10 Hz, 1 H, 5-H), 5.64 (d, *J* = 4.5 Hz, 1 H, 6-H), 3.62 (dt, *J* = 4.5, 10.5 Hz, 1 H, 1′-H), 2.36−2.21 (m, 1 H, 2′-H), 2.10 [m_c, 1 H, C*H*$(CH_3)_2$], 1.70−0.74 (m*, 7 H, 3′-H, 4′-H, 5′-H, 6′-H), *contains 0.92, 0.83 [2 d, *J* = 7.0 Hz, 3 H each, CH(C*H*$_3)_2$], 0.90 (d, *J* = 6.5 Hz, 3 H, 5′-CH_3) ppm. ^{13}C NMR (50.3 MHz): δ = 153.9 (s, C-3), 134.2, 129.7, 128.6, 126.1, 126.0 (s, 4 d, C-5, Ph), 116.2 (d, C-4), 93.1 (d, C-6), 79.9 (d, C-1′), 48.5 (d, C-2′), 42.3 (t, C-6′), 34.3 (t, C-4′), 31.8 (d, C-5′), 25.7 [d, *C*H$(CH_3)_2$], 23.3 (t, C-3′), 22.1, 21.1, 16.3 (3 q, CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3100−2750 cm^{-1} (C−H), 1640 (C=C), 1525 (C=N). $C_{20}H_{27}NO_2$ (313.4) calcd. C 76.65, H 8.68, N 4.47; found C 76.84, H 8.78, N 4.50.

(6*R*)-[(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyloxy]-3-phenyl-6*H*-1,2-oxazine (4b): $[\alpha]_D^{20}$ = −104.8 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (200 MHz): δ = 7.75−7.61, 7.47−7.37 (2 m, 2 H, 3 H, Ph), 6.61 (d, *J* = 10.0 Hz, 1 H, 4-H), 6.37 (dd, *J* = 4.5, 10 Hz, 1 H, 5-H), 5.76 (d, *J* = 4.5 Hz, 1 H, 6-H), 3.84 (dt, *J* = 4, 10.5 Hz, 1 H, 1′-H), 2.23−2.08 (m, 1 H, 2′-H), 1.99 [m_c, 1 H, C*H*$(CH_3)_2$], 1.74−0.77 (m*, 7 H, 3′-H, 4′-H, 5′-H, 6′-H), *contains 0.94 (d, *J* = 6.5 Hz, 3 H, 5′-CH_3), 0.83, 0.81 [2 d, *J* = 7.0 Hz, 3 H each, CH(C*H*$_3)_2$] ppm. ^{13}C NMR (50.3 MHz): δ = 154.1 (s, C-3), 134.2, 129.6, 128.7, 126.5, 125.9 (s, 4 d, C-5, Ph), 116.1 (d, C-4), 88.2 (d, C-6), 75.0 (d, C-1′), 48.2 (d, C-2′), 40.3 (t, C-6′), 34.5 (t, C-4′), 31.5 (d, C-5′), 25.3 [d, *C*H$(CH_3)_2$], 23.5 (t, C-3′), 23.3, 20.8, 16.0 (3 q, CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3150−2825 cm^{-1} (C−H), 1640 (C=C), 1550 (C=N). $C_{20}H_{27}NO_2$ (313.4) calcd. C 76.65, H 8.68, N 4.47; found C 76.82, H 8.91, N 4.48.

Ethyl 6-[(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyloxy]-6*H*-1,2-oxazine-3-carboxylate (5): According to the general procedure, $BF_3{\cdot}OEt_2$ (0.13 mL, 1.04 mmol) and (−)-menthol (0.235 g, 1.50 mmol) were added to a solution of 1,2-oxazine **2** (0.100 g, 0.500 mmol) in CH_2Cl_2 (20 mL/mmol). The access of menthol was removed by distillation. Chromatography (*n*-hexane/ethyl acetate, 8:1) of the crude product yielded **5** [26 mg, 17%, (6*R*):(6*S*) 50:50] as a colourless solid. ^{1}H NMR (300 MHz): δ = 6.70, 6.68 (2 d, *J* = 10.0 Hz, 0.5 H each, 4-H), 6.27, 6.24 (2 dd, *J* = 4.5, 10 Hz,

0.5 H each, 5-H), 5.80, 5.70 (2 d, J = 4.5 Hz, 0.5 H each, 6-H), 4.49−4.30 (m, 4 H, OCH_2), 3.80, 3.60 (dt, J = 4, 10 Hz, 1 H, 1′-H), 2.33−2.22 (m, 1 H, 2′-H), 2.15−1.85 [m, 3 H, 2′-H, CH(CH_3)$_2$], 1.72−0.72 (m, 7 H, 3′-H, 4′-H, 5′-H, 6′-H), 1.38, 1.37 (t, J = 7.0 Hz, 1.5 H each, CH_3), 0.94, 0.91 (2 d, J = 6.5 Hz, 1.5 H each, 5′-CH_3), 0.90, 0.83, 0.80, 0.79 [4 d, J = 7.0 Hz, 1.5 H each, CH(CH_3)$_2$] ppm. ^{13}C NMR (75.5 MHz): δ = 162.4, 162.2 (2 s, C=O), 148.3, 148.0 (s, C-3), 125.1, 124.4 (2 d, C-5), 114.7 (d, C-4), 94.2, 89.3 (2 d, C-6), 81.4, 75.9 (2 d, C-1′), 62.2, 62.1 (2 t, OCH_2), 48.3, 47.9 (2 d, C-2′), 42.5, 40.3 (2 t, C-6′), 34.4, 34.2 (2 t, C-4′), 31.7, 31.4 (2 d, C-5′), 25.7, 25.2 [2 d, CH(CH_3)$_2$], 23.30, 23.27 (2 t, C-3′), 22.2, 22.1, 21.0, 20.9, 16.3, 15.8, 14.14, 14.11 (8 q, CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 2960−2870 cm^{-1} (C−H), 1725 (C=O), 1635 (C=C), 1530 (C=N). $C_{17}H_{27}NO_4$ (309.4): calcd. C 65.99, H 8.80, N 4.53; found C 65.92, H 8.85, N 4.32.

6-[(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyloxy]-3-trifluoromethyl-6*H*-1,2-oxazine (6): According to the general procedure, BF_3·OEt_2 (0.13 mL, 1.04 mmol) and (−)-menthol (0.235 g, 1.50 mmol) were added to a solution of 1,2-oxazine **3** (0.098 g, 0.500 mmol) in CH_2Cl_2. The access of menthol was removed by distillation. Chromatography (*n*-hexane/ethyl acetate, 4:1) of the crude product yielded **6** [31 mg, 26%, (6*R*):(6*S*) 53:47]. $C_{15}H_{22}F_3NO_2$ (305.3): calcd. C 59.00, H 7.26, N 4.59; found C 58.93, H 7.29, N 4.95.

A sample of **6** obtained by asymmetric cycloaddition was separated by flash-chromatography (*n*-hexane/ethyl acetate 15:1).[9]

(6*S*)-[(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyloxy]-3-trifluoromethyl-6*H*-1,2-oxazine (6a): Colourless crystals, m.p. 64−71 °C. $[\alpha]_D^{20}$ = +128 (c = 0.47, $CHCl_3$). ^{1}H NMR (200 MHz): δ = 6.38 (dd, J = 4, 10 Hz, 1 H, 5-H), 6.29 (d, J = 10.0 Hz, 1 H, 4-H), 5.70 (d, J = 4.0 Hz, 1 H, 6-H), 3.60 (dt, J = 4.5, 10.5 Hz, 1 H, 1′-H), 2.27−1.95 [m, 2 H, 2′-H, CH(CH_3)$_2$], 1.72−0.75 (m*, 7 H, 3′-H, 4′-H, 5′-H, 6′-H), *contains 0.92 (d, J = 6.5 Hz, 3 H, 5′-CH_3), 0.91, 0.81 [2 d, J = 7.0 Hz, 3 H each, CH(CH_3)$_2$] ppm. ^{13}C NMR (50.3 MHz): δ = 147.1 (q, $^2J_{C,F}$ = 35 Hz, C-3), 126.2 (d, C-5), 120.3 (q, $^1J_{C,F}$ = 274 Hz, CF_3), 111.9 (d, C-4), 94.0 (d, C-6), 81.2 (d, C-1′), 48.3 (d, C-2′), 42.2 (t, C-6′), 34.2 (t, C-4′), 31.7 (d, C-5′), 25.7 [d, CH(CH_3)$_2$], 23.2 (t, C-3′), 22.1, 21.0, 16.3 (3 q, CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 2980−2820 cm^{-1} (C−H), 1630 (C=C), 1570 (C=N).

(6*R*)-[(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyloxy]-3-trifluoromethyl-6*H*-1,2-oxazine (6b): Colourless oil. $[\alpha]_D^{20}$ = −174 (c = 0.43, $CHCl_3$). ^{1}H NMR (200 MHz): δ = 6.35 (dd, J = 3.5, 9.5 Hz, 1 H, 5-H), 6.25 (d, J = 9.5 Hz, 1 H, 4-H), 5.81 (d, J = 3.5 Hz, 1 H, 6-H), 3.81 (dt, J = 4, 10.5 Hz, 1 H, 1′-H), 2.20−2.08, 1.89 [m, m_c, 1 H each, 2′-H, CH(CH_3)$_2$], 1.72−0.74 (m*, 7 H, 3′-H, 4′-H, 5′-H, 6′-H), *contains 0.94 (d, J = 6.5 Hz, 3 H, 5′-CH_3), 0.84, 0.77 [2 d, J = 7.0 Hz, 3 H each, CH(CH_3)$_2$] ppm. ^{13}C NMR (50.3 MHz): δ = 147.6 (q, $^2J_{C,F}$ = 35 Hz, C-3), 126.9 (d, C-5), 120.4 (q, $^1J_{C,F}$ = 274 Hz, CF_3), 112.0 (d, C-4), 89.2 (d, C-6), 75.7 (d, C-1′), 48.0 (d, C-2′), 40.1 (t, C-6′), 34.3 (t, C-4′), 31.4 (d, C-5′), 25.3 [d, CH(CH_3)$_2$], 23.3 (t, C-3′), 22.2, 20.7, 15.7 (3 q, CH_3).

General Procedure for the Addition of Organolithium Compounds to 4: A solution of 6*H*-1,2-oxazine **4** (1 equiv.) in THF (10 mL/mmol of 1,2-oxazine) at −78 °C was added over a period of 15 min to a solution of the corresponding organolithium compound (2.2 equiv.) in THF (10 mL/mmol of 1,2-oxazine). Methanol or water was then added and the mixture was allowed to warm to room temp. After addition of a sat. aqueous ammonium chloride solution (10 mL/mmol of 1,2-oxazine) the mixture was extracted with diethyl ether (2 × 20 mL/mmol of 1,2-oxazine), the combined extracts were dried (Na_2SO_4) and the solvent removed in vacuo. The crude product was purified by column chromatography (neutral aluminium oxide).

(5*R*,6*S*)-6-[(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyloxy]-3,5-diphenyl-5,6-dihydro-4*H*-1,2-oxazine (7a): According to the general procedure, a solution of 1,2-oxazine **4a** (223 mg, 0.707 mmol) in THF (7 mL) was added to a solution of phenyllithium (0.80 mL, 1.60 mmol, 2 M solution in cyclohexane/diethyl ether). After addition of H_2O (0.5 mL) the mixture was allowed to warm to room temp. Chromatography (*n*-hexane/ethyl acetate 25:1) and HPLC (*n*-hexane + 2% ethyl acetate) yielded **7a** (184 mg, 67%) as a colourless solid, m.p. 139 °C, and **4a** (20 mg, 9%). $[\alpha]_D^{20}$ = +7.7 (c = 1.01, $CHCl_3$). ^{1}H NMR (270 MHz): δ = 7.76−7.70 (m, 2 H, Ph), 7.42−7.22 (m, 8 H, Ph), 5.06 (d, J = 4.4 Hz, 1 H, 6-H), 3.47 (dt, J = 4.4, 10.7 Hz, 1 H, 1′-H), 3.36−3.29 (m, 1 H, 5-H), 3.08 (dd, J = 7.4, 18.4 Hz, 1 H, 4-H_{ax}), 2.74 (dd, J = 5.2, 18.4 Hz, 1 H, 4-H_{eq}), 2.31−2.23 (m, 1 H, 2′-H), 1.84−1.72 [m, 1 H, CH(CH_3)$_2$], 1.63−0.60 (m*, 7 H, 3′-H, 4′-H, 5′-H, 6′-H), *contains 0.87 (q, J = 6.6 Hz, 3 H, CH_3), 0.79, 0.61 (2 d, J = 7.4 Hz, 3 H each, CH_3) ppm. ^{13}C NMR (62.9 MHz): δ = 155.9 (s, C-3), 140.4, 135.7, 129.7, 128.7, 128.5, 127.7, 127.2, 125.6 (2 s, 6 d, Ph), 101.2 (d, C-6), 80.5 (d, C-1′), 48.8 (d, C-2′), 42.8 (t, C-6′), 40.0 (d, C-5), 34.3 (t, C-4′), 31.7 (d, C-5′), 26.0 [d, CH(CH_3)$_2$], 25.4 (t, C-4), 23.1 (t, C-3′), 22.2 (q, 5′-CH_3), 21.1, 16.1 [2 q, CH(CH$_3$)] ppm. IR (KBr): $\tilde{\nu}$ = 3095−2840 cm^{-1} (C−H), 1605 (C=N), 1090, 890, 690. $C_{26}H_{33}NO_2$ (391.6): calcd. C 79.76, H 8.49, N 3.58; found C 79.71, H 8.31, N 3.74.

(5*S*,6*R*)-6-[(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyloxy]-3,5-diphenyl-5,6-dihydro-4*H*-1,2-oxazine (7b): According to the general procedure, a solution of 1,2-oxazine **4b** (115 mg, 0.365 mmol) in THF (4 mL) was added to a solution of phenyllithium (0.45 mL, 0.90 mmol, 2 M solution in cyclohexane/diethyl ether). After addition of H_2O (0.3 mL) the mixture was allowed to warm to room temp. Chromatography (*n*-hexane/ethyl acetate 25:1) yielded **7b** (57 mg, 40%) as a colourless solid, m.p. 170−171 °C, and a mixture of **7b** and **4b** (36 mg, **7b**:**4b** = 85:15, calculated yield of **7b**: 31 mg, 21%). $[\alpha]_D^{20}$ = −46.7 (c = 1.02, $CHCl_3$). ^{1}H NMR (270 MHz): δ = 7.74−7.70 (m, 2 H, Ph), 7.40−7.24 (m, 8 H, Ph), 5.27 (d, J = 2.2 Hz, 1 H, 6-H), 3.72 (dt, J = 3.9, 10.7 Hz, 1 H, 1′-H), 3.35−3.30 (m, 1 H, 5-H), 3.05 (dd, J = 8.1, 18.4 Hz, 1 H, 4-H_{ax}), 2.71 (dd, J = 1.5, 18.4 Hz, 1 H, 4-H_{eq}), 2.18−2.14 (m, 1 H, 2′-H), 2.09−1.98 [m, 1 H, CH(CH_3)$_2$], 1.67−0.69 (m*, 7 H, 3′-H, 4′-H, 5′-H, 6′-H), *contains 0.90, 0.80, 0.70 (3 d, J = 6.6 Hz, 3 H each, CH_3) ppm. ^{13}C NMR (62.9 MHz): δ = 156.2 (s, C-3), 140.8, 135.9, 129.6, 128.7, 128.5, 127.6, 127.2, 125.5 (2 s, 6 d, Ph), 94.0 (d, C-6), 74.4 (d, C-1′), 48.1 (d, C-2′), 39.5 (d, C-5), 39.2 (t, C-6′), 34.5 (t, C-4′), 31.3 (d, C-5′), 25.5 [d, CH(CH_3)$_2$], 23.9 (t, C-4), 23.2 (t, C-3′), 22.3 (q, 5′-CH_3), 21.0, 15.8 [2 q, CH(CH$_3$)$_2$] ppm. IR (KBr): $\tilde{\nu}$ = 2960−2865 cm^{-1} (C−H), 1600 (C=N), 1090, 1015, 885, 700. $C_{26}H_{33}NO_2$ (391.6): calcd. C 79.76, H 8.49, N 3.58; found C 79.50, H 8.29, N 3.35.

(5*R*,6*S*)-5-*n*-Butyl-6-[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyloxy]-3-phenyl-5,6-dihydro-4*H*-1,2-oxazine (8a): According to the general procedure, a solution of 1,2-oxazine **4a** (470 mg, 1.50 mmol) in THF (15 mL) was added to a solution of *n*-butyllithium (1.32 mL, 3.30 mmol, 2.5 M solution in *n*-hexane). After addition of methanol (1.00 mL) the mixture was allowed to warm to room temp. After work-up no further purification was necessary. 1,2-Oxazine **8a** (471 mg, 85%) was isolated as colourless solid (m.p. 109−113 °C, *de* ≥ 94%). $[\alpha]_D^{20}$ = +40.9 (c = 0.80, $CHCl_3$). ^{1}H NMR (300 MHz): δ = 7.74−7.65, 7.41−7.35 (2 m, 2 H, 3 H, Ph), 4.90 (d, J = 3.0 Hz, 1 H, 6-H), 3.54 (dt, J = 4.5, 10.5 Hz, 1 H, 1′-

H), 2.79 (dd, J = 7, 18 Hz, 1 H, 4-H_{ax}), 2.29 (dd, J = 2.5, 18 Hz, 1 H, 4-H_{eq}), 2.24−2.00 [m, 3 H, 2′-H, C*H*$(CH_3)_2$, 5-H], 1.69−0.70 (m*, 13 H, 3′-H, 4′-H, 5′-H, 6′-H, CH_2), *contains 0.92, 0.82 [2 d, J = 7.0 Hz, 3 H each, CH(CH_3)$_2$], 0.90 (t, J = 7.0 Hz, 3 H, CH_3), 0.87 (d, J = 6.5 Hz, 3 H, 5′-H) ppm. ^{13}C NMR (75.5 MHz): δ = 155.0 (s, C-3), 136.5, 129.4, 128.4, 125.5 (s, 3 d, Ph), 100.3 (d, C-6), 79.6 (d, C-1′), 48.9 (d, C-2′), 42.7 (t, C-6′), 34.4 (t, C-4′), 32.9, 31.7 (2 d, C-5, C-5′), 30.7, 29.0 (2 t, CH_2), 25.7 [d, C*H*$(CH_3)_2$], 23.7, 23.3, 22.7 (3 t, CH_2, C-4, C-3′), 22.2, 21.2, 16.3, 14.0 (4 q, CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3100−2850 cm^{-1} (C−H), 1625, 1620 (C=C, C=N). $C_{24}H_{37}NO_2$ (371.6): calcd. C 77.58, H 10.04, N 3.77; found C 77.45, H 10.42, N 3.49.

(5*R*,6*R*)-5-*n*-Butyl-6-[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyloxy]-3-phenyl-5,6-dihydro-4*H*-1,2-oxazine (8b): According to the general procedure, a solution of 1,2-oxazine **4b** (313 mg, 1.00 mmol) in THF (10 mL) was added to a solution of *n*-butyllithium (0.91 mL, 2.20 mmol, 2.42 M solution in *n*-hexane). After addition of H_2O (0.6 mL) the mixture was allowed to warm to room temp. After work-up no further purification was necessary. 1,2-Oxazine **8b** (368 mg, 99%) was isolated as colourless crystals (m.p. 78−80 °C, *de* ≥ 98% by HPLC). $[\alpha]_D^{20}$ = −102 (c = 1.13, $CHCl_3$). ^{1}H NMR (300 MHz): δ = 7.70−7.61, 7.41−7.34 (2 m, 2 H, 3 H, Ph), 5.12 (d, J = 3.0 Hz, 1 H, 6-H), 3.70 (dt, J = 4.5, 10.5 Hz, 1 H, 1′-H), 2.75 (dd, J = 7, 18 Hz, 1 H, 4-H_{ax}), 2.32 (dd, J = 2, 18 Hz, 1 H, 4-H_{eq}), 2.25−2.15 (m, 1 H, 2′-H), 1.99 [m_c, 2 H, C*H*$(CH_3)_2$, 5-H], 1.71−0.63 (m*, 13 H, 3′-H, 4′-H, 5′-H, 6′-H, CH_2), *contains 0.94 (d, J = 6.5 Hz, 3 H, 5′-CH_3), 0.93 (t, J = 6.5 Hz, 3 H, CH_3), 0.78, 0.68 (2 d, J = 7.0 Hz, 3 H each, CH(CH_3)$_2$] ppm. ^{13}C NMR (75.5 MHz): δ = 155.3 (s, C-3), 136.5, 129.3, 128.4, 125.5 (s, 3 d, Ph), 94.1 (d, C-6), 74.0 (d, C-1′), 48.1 (d, C-2′), 39.6 (t, C-6′), 34.6 (t, C-4′), 32.8, 31.3 (2 d, C-5, C-5′), 30.9, 29.1 (2 t, CH_2), 25.4 [d, $CH(CH_3)_2$], 23.2, 23.1, 22.7 (3 t, CH_2, C-4, C-3′), 22.4, 21.0, 15.7, 14.0 (4 q, CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3100−2850 cm^{-1} (C−H), 1625, 1620 (C=C, C=N). $C_{24}H_{37}NO_2$ (371.6): calcd. C 77.58, H 10.04, N 3.77; found C 77.67, H 10.24, N 3.76.

General Procedure for the Hydrogenolysis of 1,2-Oxazines 7a, 8a, 8b, 10 and 12: Ethanol or ethanol/ethyl acetate and Pd (10%)/C were saturated with hydrogen. Then, the corresponding 1,2-oxazine was added and the mixture stirred under hydrogen at atmospheric pressure and room temp for the time indicated below. The suspension was then filtered through a sintered glass plug which contained a pad of Celite, eluting with ethyl acetate. The filtrate was concentrated in vacuo and the crude product was purified by kugelrohr distillation.

2,4-Diphenylbutylamine (*rac*-9):[13] According to the general procedure, 1,2-oxazine **10** (300 mg, 1.07 mmol) and Pd/C (110 mg) in ethanol (10 mL) and ethyl acetate (3 mL) were stirred under hydrogen atmosphere for 20 h. Kugelrohr distillation (0.015 mbar, 110 °C) yielded *rac*-**9** (195 mg, 81%) as a colourless oil. ^{1}H NMR (270 MHz): δ = 7.42−7.02 (m, 10 H, Ph), 3.00−2.76 (m, 2 H, 1-H), 2.62−2.52 (m, 1 H, 2-H), 2.51−2.43 (m, 2 H, 4-H), 2.05−1.85 (m, 2 H, 3-H), 1.31 (br. s, 2 H, NH_2) ppm. ^{13}C NMR (62.9 MHz): δ = 142.9, 142.1, 128.5, 128.2, 128.2, 128.0, 126.5, 125.6 (2 s, 6 d, Ph), 49.0 (d, C-2), 48.1 (t, C-4), 35.4, 33.5 (2 t, C-3, C-1) ppm. IR (film): $\tilde{\nu}$ = 3375 cm^{-1} (N−H), 3085−2860 (C−H), 1600, 1495, 1455, 760, 700. MS (EI, 80 eV): m/z (%) = 225 (100) [M^+], 194 (25) [$M^+ - CH_3NH_2$], 121 (24), 104 (41), 91 (66), 30 (86). HRMS (EI, 80 eV) $C_{16}H_{19}NO$: calcd. 225.1518; found 225.1543.

A Mosher amide of **9** was prepared according to ref.[14] The diastereomers show two HPLC peaks (*n*-hexane + 2% ethyl acetate, 4 × 244 mm, flow 1 mL/min, 52 bar; ret. time 42 min/44 min).

(*S*)-2,4-Diphenylbutylamine [(*S*)-9]: According to the general procedure, 1,2-oxazine **7a** (136 mg, 0.347 mmol) and Pd/C (36 mg) in ethanol (5 mL) and ethyl acetate (3 mL) were stirred under hydrogen atmosphere for 23 h. Kugelrohr distillation (0.015 mbar, 100 °C) yielded **9** (64 mg, 82%, *ee* 80%) as a colourless oil. $[\alpha]_D^{20}$ = −5.85 (c = 0.99, $CHCl_3$).

(*S*)-1-Hexyl-2-(2-phenylethyl)amine [(*S*)-11]: According to the general procedure, 1,2-oxazine **8a** (186 mg, 0.500 mmol) and Pd/C (50 mg) in ethanol (5 mL) were stirred under hydrogen atmosphere for 22 h. kugelrohr distillation (0.015 mbar, 100 °C) yielded (*S*)-**11** (80 mg, 80%) as a colourless oil. $[\alpha]_D^{20}$ = 0.00 (c = 0.87, $CHCl_3$). ^{1}H NMR (300 MHz): δ = 7.29−7.05 (m, 5 H, Ph), 2.59 (d, J = 5.0 Hz, 2 H, 1-H), 2.58 (t, J = 8.0 Hz, 2 H, 2′-H), 1.65−1.10 (m, 11 H, NH_2, 1′-H, 2-H, 3-H, 4-H, 5-H), 0.91−0.75 (m, 3 H, CH_3) ppm. ^{13}C NMR (75.5 MHz): δ = 142.8, 128.3*, 125.6 (s, 2 d, Ph), 45.1 (t, C-1), 40.6 (d, C-2), 33.5, 33.2, 31.1, 28.9, 23.1 (5 t, C-1′, C-2′, C-3, C-4, C-5), 14.1 (q, CH_3) ppm, *higher intensity. IR (film): $\tilde{\nu}$ = 3500−3100 cm^{-1} (N−H), 3100−2860 (C−H), 1600 (C=C). $C_{14}H_{23}N$ (205.3): calcd. C 81.89, H 11.29, N 6.82; found C 81.44, H 11.77, N 6.56.

(*R*)-1-Hexyl-2-(2-phenylethyl)amine [(*R*)-11]: According to the general procedure, 1,2-oxazine **8b** (168 mg, 0.452 mmol) and Pd/C (50 mg) in ethanol (5 mL) and ethyl acetate (5 mL) were stirred under hydrogen atmosphere for 18 h. Kugelrohr distillation (0.015 mbar, 100 °C) yielded (*R*)-**11** (57 mg, 61%) as a colourless oil. $[\alpha]_D^{20}$ = −0.37 (c = 1.09, $CHCl_3$).

1-Hexyl-2-(2-phenylethyl)amine (*rac*-11): According to the general procedure 1,2-oxazine **12** (219 mg, 0.833 mmol) and Pd/C (85 mg) in ethanol (10 mL) and ethyl acetate (5 mL) were stirred under hydrogen atmosphere for 24 h. Kugelrohr distillation (0.015 mbar, 100 °C) yielded *rac*-**11** (145 mg, 85%) as a colourless oil. A Mosher amide of **11** was prepared according to ref.[14] The diastereomers show two signals for two of the carbon atoms in the ^{13}C NMR spectrum: ^{13}C NMR (62.9 MHz, C_6D_6): δ = 165.9 (s, C=O), 142.7, 133.7 (2 s, Ph), 129.5, 128.7, 128.6, 128.4, 127.6, 126.1 (6 d, Ph), 122.3 (s, CF_3), 54.8 (q, OCH_3), 42.4 (t, CH_2), 37.9 (d, CH), 33.9, 33.8*, 33.1, 33.0*, 31.6, 28.9, 23.2 (7 t, CH_2), 14.2 (q, CH_3). (*signal of the second diastereomer).

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[1] C. Hippeli, R. Zimmer, H.-U. Reißig, *Liebigs Ann. Chem.* **1990**, 469−474.
[2] T. Arnold, B. Orschel, H.-U. Reißig, *Angew. Chem.* **1992**, *104*, 1084−1086; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1033−1035.
[3] K. Paulini, A. Gerold, H.-U. Reißig, *Liebigs Ann.* **1995**, 667−671.
[4] R. Zimmer, J. Angermann, U. Hain, F. Hiller, H.-U. Reißig, *Synthesis* **1997**, 1467−1474.

[5] M. Buchholz, *Dissertation*, Freie Universität Berlin, **2002**.
[6] [6a] E. J. T. Chrystal, T. L. Gilchrist, W. Stretch, *J. Chem. Res. (S)* **1987**, 180−181; *J. Chem. Res. (M)* **1987**, 1563−1575. [6b] R. Henning, U. Lerch, H. Urbach, *Synthesis* **1989**, 265−268. [6c] J. Angermann, K. Homann, H.-U. Reißig, R. Zimmer, *Synlett* **1995**, 1014−1016.
[7] K. Homann, J. Angermann, M. Collas, R. Zimmer, H.-U. Reißig, *J. Prakt. Chem.* **1998**, *340*, 649−655.
[8] K. Homann, R. Zimmer, H.-U. Reißig, *J. Prakt. Chem.* **1995**, *337*, 521−528.
[9] F. Hiller, *Dissertation*, Technische Universität Dresden, **1997**.
[10] U. Jänicke-Rössler, G. Zahn, F. Hiller, H.-U. Reißig, *Z. Kristallogr. NCS* **1998**, *213*, 261−262.
[11] R. Zimmer, F. Hiller, H.-U. Reißig, *Heterocycles* **1999**, *50*, 393−401.
[12] M. Buchholz, H.-U. Reißig, *Synthesis* **2002**, 1412−1422.
[13] H. Adkins, G. M. Whitman, *J. Am. Chem. Soc.* **1942**, *64*, 150−154.
[14] J. A. Dale, D. L. Dull, H. S. Mosher, *J. Org. Chem.* **1969**, *34*, 2543−2549.

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