Cobalt(II)-Azabis(oxazoline)-Catalyzed Conjugate Reduction of α,β-Unsaturated Carbonyl Compounds

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Received: September 17, 2004; Accepted: December 10, 2004

Abstract: Azabis(oxazolines) prove to be superior ligands for the enantioselective, cobalt(II)-catalyzed conjugate reduction of α,β-unsaturated carbonyl compounds with sodium borohydride. β-Trisubstituted α,β-unsaturated esters and amides as well as γ-butenolides are readily converted to their corresponding saturated counterparts with enantioselectivities up to 97% ee.

Keywords: azabis(oxazolines); cobalt; conjugate reduction; transition metals; α,β-unsaturated amides, α,β-unsaturated esters

Introduction

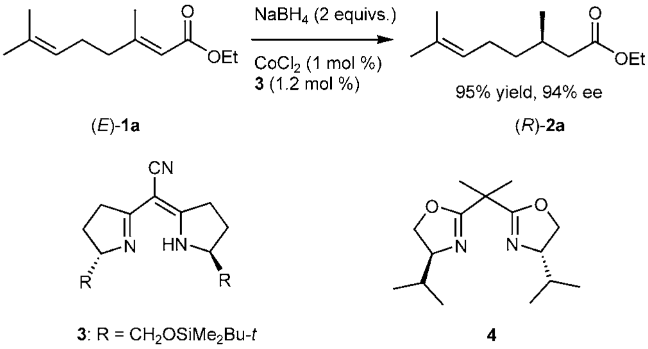
Enantioselective transfer of hydrogen to prochiral carbon-carbon double bonds belongs to the most important catalytic asymmetric processes to date. In this context, the conjugate reduction of α,β-unsaturated carbonyl compounds offers a valuable method for the construction of building blocks with a β-stereogenic center found in many natural products.[1] Recently, for this purpose a very efficient system based on polyhydroxymethylsilane (PMHS) as stoichiometric reducing agent using chiral Cu(I)/biarylphosphines[2] or Cu(I)/ferrocenyldiphosphines has been introduced.[3] Already in 1989 Pfaltz reported the use of semicorrin ligands such as **3** in combination with $CoCl_2$ to effect the conjugate reduction of α,β-unsaturated esters and amides by sodium borohydride with high enantioselectivities.[4] Despite the ease of use and the remarkable results obtained by the latter protocol, the limited availability of semicorrins from the chiral pool might have been prohibitive for its wider recognition. Subsequently, aldiminatocobalt(II) complexes[5] were examined in the 1,4-reduction of acrylamides, which gave generally lower selectivities as compared to the semicorrins, but did also allow the control of the α-stereocenter in this process.

Results and Discussion

Ligand Screening

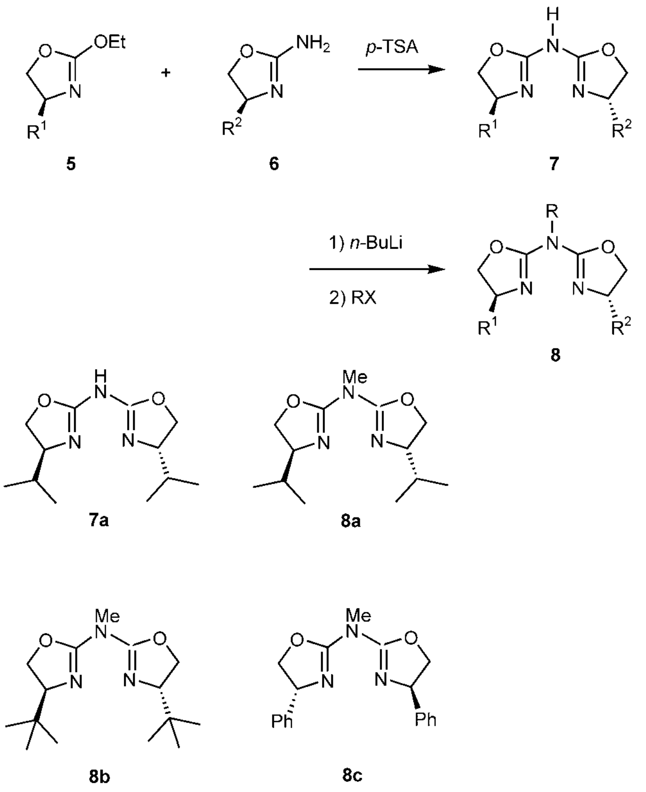
An obvious alternative might have been the substitution of the semicorrins **3** by the structurally related bis(oxazoline) ligands **4**, which have proved to be superior ligands for a wide range of catalytic asymmetric processes, and are readily accessible from amino acids in a broad variety regarding the substituent R.[6] However, when we tested **4** for the reduction of **1a** under the standard conditions being reported, no reaction at all was observed.[7] These results suggested that a more electron-rich ligand might be a prerequisite for the title reaction.

We recently introduced azabis(oxazolines) **7** (Scheme 2) as chiral ligands for asymmetric catalysis,[8] which are readily synthesized by condensation of **5** and **6**, both of which are conveniently available[9] from the chiral pool in either enantiomeric form. Although these ligands promote asymmetric reactions such as the Cu(I)-catalyzed cyclopropanation in a similar way like bis(oxazolines), they are nevertheless considerably more electron-rich as reflected in their inferior activity for Lewis acid-catalyzed reactions such as [4+2] cycloadditions, their superior properties in ionic liquids[10] or for immobilization by ion exchange on nafion-silica hybrid materials or synthetic laponite clay as catalyst supports.[11]



Scheme 1. Co(II)-catalyzed conjugate reduction of α,β-unsaturated esters.

DOI: 10.1002/adsc.200404295



Scheme 2. Synthesis of azabis(oxazoline) ligands.

Based on the hypothesis that an electron-rich ligand might be advantageous for the cobalt(II)-catalyzed conjugate reduction, we therefore wanted to investigate azabis(oxazolines) for this process. An initial screening using azabis(oxazoline) ligands **7a** and **8a–c** in the reduction of **1a** to **2a** was therefore conducted (Table 1).

Under the basic conditions applied the azabis(oxazoline) **7a** should serve as an anionic ligand in close analogy to semicorrin **3**. However, the reduction of **1a** proceeded sluggishly, resulting in the formation of **2a** in racemic form in very low yield (entry 1). In distinct contrast, with the *N*-methylated azabis(oxazoline) **8a** greatly improved yields (82%) and excellent enantioselectivity (96% ee) were achieved (entry 2), which compares well with the best catalysts described so far for this transformation. Increasing the steric bulk by *t*-butyl substitution in the azabis(oxazoline) framework, resulting often[12] in even more selective catalysts is not tolerated at all: no reaction was observed when **8b** was employed (entry 3). However, the phenyl-substituted ligand **8c** performs even slightly better than **8a** with respect to yield (entry 4), and was therefore used in subsequent reactions. Since **8a** and **8c** are pseudoenantiomeric to each other, it was not surprising that **2a** is obtained with opposite stereochemistry with respect to these ligands. The amount of catalyst could be reduced to 1 mol % with only a small reduction in yield and selectivity, however, further lowering the amount to 0.1 mol % was not tolerated well (entries 5 and 6).

Reduction of α,β-Unsaturated Esters and γ-Butyrolactones

Other esters were subsequently investigated in the conjugate reduction catalyzed by $CoCl_2$ and **8c** (Table 2).

Good yields and high enantioselectivities were obtained with a number of aromatic and aliphatic substrates. Especially, (*Z*)-**1b** gave rise to (*R*)-**2b** with 94% ee (entry 4), which has been a problematic substrate with the semicorrin ligand **3**.[13] Especially noteworthy is the smooth conversion of (*E*)-**1d** (entry 7), since the resulting (*S*)-**2d** can be converted after deprotection into the corresponding γ-butyrolactone **10a**,[14] thus providing an alternative route to this important class of compounds[15] with respect to the direct reduction of butenolides **9**. Indeed, **9** also proved to be suitable substrates for the conjugate reduction catalyzed by $CoCl_2$/**8c**, however, yields and selectivities were somewhat lower than for the acyclic substrates described above (Scheme 3).

Table 1. Co(II)-catalyzed conjugate reduction of **1a** in the presence of various azabis(oxazoline) ligands.[a]

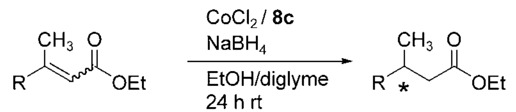
Entry	Ligand	Yield of **2a** [%]	Selectivity for **2a** % ee	Configuration of **2a**
1	**7a**	12	0	–
2	**8a**	82	96	*S*
3	**8b**	0	–	–
4	**8c**	86	96	*R*
5[b]	**8c**	81	94	*R*
6[c]	**8c**	22	49	*R*

[a] *Reagents and conditions:* 2.5 mol % $CoCl_2 \cdot 6\,H_2O$, 2.8 mol % ligand, 2.5 equivs. $NaBH_4$, EtOH/diglyme 1:1, 24 h, room temperature.

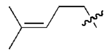
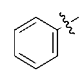
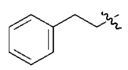
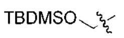
[b] 1 mol % $CoCl_2 \cdot 6\,H_2O$, 1.2 mol % **8c**.

[c] 0.1 mol % $CoCl_2 \cdot 6\,H_2O$, 0.12 mol % **8c**.

Table 2. Conjugate reduction of α,β-unsaturated esters with $NaBH_4$ catalyzed by $CoCl_2$/**8c**.[a]



1 **2**

Entry	R		Yield [%]	ee [%]	2
1		(*E*)-**1a**	88	96	(*R*)-**2a**
2		(*Z*)-**1a**	87	96	(*S*)-**2a**
3		(*E*)-**1b**	86	92	(*S*)-**2b**
4		(*Z*)-**1b**	89	94	(*R*)-**2b**
5		(*E*)-**1c**	86	93	(*R*)-**2c**
6		(*Z*)-**1c**	86	97	(*S*)-**2c**
7	 TBDMSO	(*E*)-**1d**	85	95	(*S*)-**2d**

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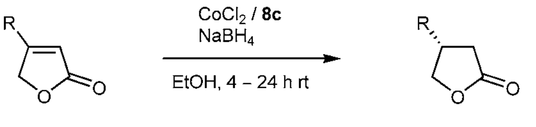
[a] *Reagents and Conditions:* 2.5 mol % $CoCl_2 \cdot 6\,H_2O$, 2.8 mol % **8c**, 2.5 equivs. $NaBH_4$, EtOH/diglyme 1:1, 24 h, room temperature.



9a: R = Me
9b: R = Bu

10a: R = Me 54% (86% ee)
10b: R = Bu 65% (86% ee)

Reagents and Conditions: 2.5 mol % $CoCl_2 \cdot 6\,H_2O$, 2.8 mol % **8c**, 1.0 equiv. $NaBH_4$, EtOH, 4 h, room temperature.

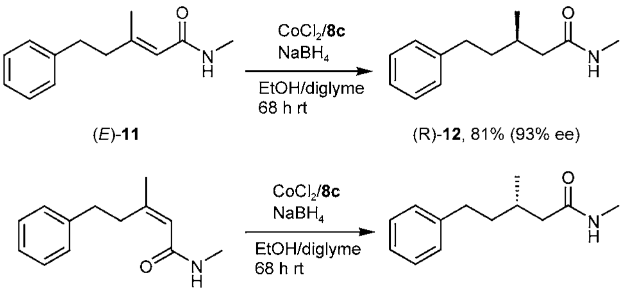
Scheme 3. Conjugate reduction of butenolides **9**

Reduction of α,β-Unsaturated Amides

Finally, *N*-methylamides instead of esters can be used in the conjugate reduction with very good results as demonstrated with **11** (Scheme 4). Under the same conditions the reaction times were found to be longer in comparison to the corresponding ethyl esters, nevertheless, both (*E*)- and (*Z*)-**11** could be converted to (*R*)- and (*S*)-**12**, respectively, in good yields with 93 and 95% ee, respectively.

Conclusion

We could demonstrate that appropriately functionalized aza(bisoxazolines) are highly efficient chiral promoters of the Co(II)-catalyzed conjugate reduction of α,β-unsaturated compounds, thus, providing a readily available and widely variable ligand system for this process.



Reagents and Conditions: 2.5 mol % $CoCl_2 \cdot 6\,H_2O$, 2.8 mol % ligand, 2.5 equivs. $NaBH_4$, EtOH/diglyme 1:1, 68 h, room temperature.

Scheme 4. Conjugate reduction of amides **11**.

Experimental Section

General Remarks

Infrared spectra were recorded on a Bio-Rad Excalibur Series spectrometer. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at ambient temperature. NMR spectra were recorded on a Bruker AC 250 or Avance 300 (^1H: 250 MHz or 300 MHz, ^{13}C: 75 MHz) spectrometer using TMS as internal standard ($\delta = 0$) unless otherwise noted. Mass spectra were measured on Varian MAT 311A and Finnigan MAT 95 spectrometers. Analytical thin layer chromatography was performed on Merck TLC aluminium sheets silica gel 60 F254. For liquid chromatography Merck silica gel 60 (230–400 mesh ASTM) was used. GC and HPLC analyses were performed as indicated. Racemic compounds analogous to the enantiomerically enriched compounds described below were prepared by reduction of the olefin substrates under a hydrogen atmosphere catalyzed by Pd/C. All reactions were carried out in oven-dried glassware under a nitrogen atmosphere. Benzene and diglyme were distilled from CaH_2, methanol and ethanol from Mg, diethyl ether from Na-alloy. Ethyl *trans*-β-methylcinnamate was purchased from Aldrich. Other reagents were used without purification unless otherwise noted.

General Procedure A (GP A): Asymmetric Conjugate Reduction of α,β-Unsaturated Esters

To $CoCl_2 \cdot 6\,H_2O$ (0.013 mmol, 2.5 mol %) was added a solution of **8c** (0.014 mmol, 4.5 mg) in ethanol (0.5 mL) and the mixture was stirred for 10 min until a deep blue solution resulted. A solution of the unsaturated ester (0.50 mmol) in ethanol (0.5 mL) and diglyme (1.0 mL) was added, and the reaction mixture was cooled to 0 °C. $NaBH_4$ (1.25 mmol, 47.3 mg) was added in small portions during which the solution turned pink. After complete addition the mixture was stirred 24 h at room temperature. The mixture was diluted with water (10 mL) and extracted with dichloromethane (3 × 15 mL). The combined organic layers were washed 3 times with water (10 mL) and finally dried over $MgSO_4$. The solvent was evaporated and the residue was purified by column chromatography.

Ethyl (*R*)-Citronellate [(*R*)-2a][2a]

Ethyl (*E*)-geranate [(*E*)-**1**] was reacted following GP A. Purification by column chromatography (hexanes/diethyl ether, 20:1) afforded (*R*)-**2a** as a clear oil; yield: 88 mg (0.44 mmol, 88%, 96% ee determined by chiral GC analysis [HP 5890 A, Restek Rt-β DEX cst, oven 60 °C, inj.: split 250 °C, det.: FID 300 °C, 150 kPa H_2]); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.13–5.04$ (m, 1H), 4.12 (q, $J = 7.1$ Hz, 2H), 2.30, (dd, $J = 14.5$, 5.9 Hz, 1H), 2.10 (dd, $J = 14.5$, 8.2 Hz, 1H), 2.04–1.88 (m, 3H), 1.68 (s, 3H), 1.60 (s, 3H), 1.42–1.14 (m, 5H), 0.94 (d, $J = 6.6$ Hz, 3H); t_R: 66.4 min (*R*), 69.3 min (*S*); $[\alpha]_D$: +4.9° (*c* 1.0, $CHCl_3$).

Ethyl (*S*)-Citronellate [(*S*)-2a]

Ethyl (*Z*)-geranate [(*Z*)-**1a**] was reacted following GP A. Purification by column chromatography (hexanes/diethyl ether, 20:1) afforded the product (*S*)-**2a** as a clear oil; yield: 86 mg (0.43 mmol, 87%, 96% ee); $[\alpha]_D$: −4.1° (*c* 1.0, $CHCl_3$). NMR and GC data were the same as reported in the previous example.

Ethyl (*S*)-3-Phenylbutyrate [(*S*)-2b][2a]

Ethyl *trans*-β-methylcinnamate [(*E*)-**1b**] was reacted following GP A. Purification by column chromatography (hexanes/diethyl ether, 20:1) afforded (*S*)-**2b** as a clear oil; yield: 83 mg (0.43 mmol, 86%, 92% ee determined by chiral GC analysis [HP 5890 A, Restek Rt-β DEX cst, oven 55 °C, inj.: split 260 °C, det.: FID 250 °C, 151 kPa H_2]); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.33–7.14$ (m, 5H), 4.07 (q, $J = 7.1$ Hz, 2H), 3.35–3.21 (m, 1H), 2.61 (dd, $J = 15.0$, 7.0 Hz, 1H), 2.53 (dd, $J = 15.0$, 8.2 Hz, 1H), 1.30 (d, $J = 7.0$ Hz, 3H), 1.18 (t, $J = 7.1$ Hz, 3H);[1] t_R: 182.6 min (*S*), 192.8 min (*R*); $[\alpha]_D$: +24.1° (*c* 1.0, $CHCl_3$).

Ethyl (*R*)-3-Phenylbutyrate [(*R*)-2b]

Ethyl *cis*-β-methylcinnamate [(*Z*)-**1b**] was reacted following GP A. Purification by column chromatography (hexanes/diethyl ether, 20:1) afforded (*R*)-**2b** as a clear oil; yield: 86 mg (0.45 mmol, 89%, 94% ee); $[\alpha]_D$: −25.2° (*c* 1.0, $CHCl_3$). NMR and GC data were the same as reported in the previous example.

Ethyl (*R*)-3-Methyl-5-phenylpentanoate [(*R*)-2c][2a]

Ethyl (*E*)-3-methyl-5-phenylpent-2-enoate [(*E*)-**1c**] was reacted following GP A. Purification by column chromatography (hexanes/ethyl acetate, 30:1) afforded (*R*)-**2c** as a clear oil; yield: 95 mg (0.43 mmol, 86%, 93% ee determined by chiral HPLC analysis [Hewlett Packard HP1090M, Daicel Chiralcel OB, ethanol/2-propanol, 99:1, 0.3 mL/min, UV 254 nm, 12 °C]; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.32–7.24$ (m, 2H), 7.21–7.14 (m, 3H), 4.13 (q, $J = 7.1$ Hz, 2H), 2.74–2.53 (m, 2H), 2.35 (dd, $J = 14.6$, 6.0 Hz, 1H), 2.16 (dd, $J = 14.6$, 6.6 Hz, 1H), 2.10–1.94 (m, 1H), 1.74–1.60 (m, 1H), 1.56–1.44 (m, 1H), 1.25 (t, $J = 7.1$ Hz, 3H), 1.01 (d, $J = 6.6$ Hz, 3H); t_R: 26.1 min (*S*), 28.9 min (*R*); $[\alpha]_D$: +15.0° (*c* 1.0, $CHCl_3$).

Ethyl (*S*)-3-Methyl-5-phenylpentanoate [(*S*)-2c]

Ethyl (*Z*)-3-methyl-5-phenylpent-2-enoate [(*Z*)-**1c**] was reacted following GP A. Purification by column chromatography (hexanes/ethyl acetate, 30:1) afforded (*S*)-**2c** as a clear oil; yield: 95 mg (0.43 mmol, 86%, 97% ee determined by chiral HPLC analysis); $[\alpha]_D$: −15.7° (*c* 1.0, $CHCl_3$). NMR and GC data were the same as reported in the previous example.

(*S*)-4-(*tert*-Butyldimethylsilanyloxy)-3-methylbutyric Acid Ethyl Ester [(*S*)-2d]

(*E*)-4-(*tert*-butyldimethylsilanyloxy)-3-methylbut-2-enoic acid ethyl ester [(*E*)-**1d**] was reacted following GP A. Purification by column chromatography (hexanes/ethyl acetate, 30:1) afforded (*S*)-**2d** as a clear oil; yield: 110 mg (0.42 mmol, 85%, 95% ee); ^{1}H NMR (300 MHz, $CDCl_3$ without TMS): $\delta = 4.12$ (q, $J = 7.1$ Hz, 2H), 3.49 (dd, $J = 9.8$, 5.4 Hz, 1H), 3.40 (dd, $J = 9.8$, 6.3 Hz, 1H), 2.54–2.39 (m, 1H), 2.21–2.01 (m, 2H), 1.25 (t, $J = 7.1$ Hz, 3H), 0.93 (t, $J = 6.6$ Hz, 3H), 0.89 (s, 9 H), 0.03 (s, 6H); ^{13}C NMR (75 Hz, $CDCl_3$): $\delta = 173.3$, 67.4, 60.1, 38.2, 33.1, 25.9, 18.3, 16.5, 14.3, −5.4; IR (KBr): $\nu = 2957$, 2930, 2858, 17.37, 1470 cm^{-1}; HRMS: *m/z* calcd. for $[C_{13}H_{28}O_3Si + H^+]$: 261.1886; found: 261.1889; $[\alpha]_D$: −5.2° (*c* 1.0, $CHCl_3$).

The enantioselectivity was determined by deprotection of the alcohol followed by cyclization to the corresponding lactone with *p*-TSA in MeOH. Chiral GC analysis (HP 5890 A, Restek Rt-β DEX cst, oven 120 °C, inj.: split 250 °C, det.: FID 300 °C, 150 kPa H_2: t_R: 14.2 min (*R*), 14.5 min (*S*); $[\alpha]_D$: −22.2° (*c* 1.0, $CHCl_3$).

General Procedure B (GP B): Asymmetric Conjugate Reduction of Lactones

To $CoCl_2 \cdot 6\,H_2O$ (2.5 mol %, 0.013 mmol) was added a solution of **8c** (0.014 mmol, 4.5 mg) in ethanol (0.5 mL), and the mixture was stirred for 10 min during which the solution turned to a deep blue color. A solution of the unsaturated lactone (0.50 mmol) in ethanol (0.5 mL) was added, and the reaction mixture was cooled to 0 °C. $NaBH_4$ (0.5 mmol, 18.9 mg) was added and the reaction mixture was stirred at room temperature for the indicated time. The solution was quenched with 2 mL of 2 N HCl followed by addition of 5 mL of water. The mixture was washed with dichloromethane (3 × 20 mL) and the combined organic layers were dried over $MgSO_4$. After removing of the solvent the residue was purified by column chromatography.

(*R*)-4-Methyldihydrofuran-2(3*H*)-one [(*R*)-10a][16]

4-Methyl-2(5*H*)-furan-2-one (**9a**) was reacted for 24 h according to GP B. Purification by column chromatography (hexanes/ethyl acetate, 80:20) afforded (*R*)-**10a** as a clear oil; yield: 27 mg (0.27 mmol, 54%, 86% ee determined by chiral GC analysis [HP 5890 A, Restek Rt-β DEX cst, oven 120 °C, inj.: split 250 °C, det.: FID 300 °C, 70 kPa H_2]); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 4.39$ (dd, $J = 8.8$, 7.4 Hz, 1H), 3.85 (dd, $J = 8.8$, 6.4 Hz, 1H), 2.73–2.55 (m, 2H), 2.20–2.05 (m, 1H), 1.14 (d, $J = 6.6$ Hz, 3H); t_R: 14.4 min (*R*), 15.7 min (*S*); $[\alpha]_D$: +18.9° (*c* 0.6, $CHCl_3$).

(*R*)-4-Butyldihydrofuran-2(3*H*)-one [(*R*)-10b][17]

4-Butyl-2(5*H*)-furan-2-one (**9b**) was reacted for 4 h according to GP B. Purification by column chromatography (hexanes/ethyl acetate, 80:20) afforded (*R*)-**10b** as a clear oil; yield: 46 mg (0.32 mmol, 65%, 86% ee determined by chiral GC analysis [HP 5890 II, Restek Rt-β DEX cst, oven 140 °C, inj.: split 250 °C, det.: FID 350 °C, 150 kPa H_2,]; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 4.46$–4.37 (m, 1H), 3.92, (dd, $J = 9.0$, 7.1 Hz, 1H), 2.68–2.45 (m, 2H), 2.27–2.10 (m, 1H), 1.53–1.42 (m, 2H), 1.38–1.21 (m, 4H), 0.90 (t, $J = 6.8$ Hz, 3H); t_R: 25.7 (*R*), 27.5 (*S*); $[\alpha]_D$: +5.6° (*c* 1.0, $CHCl_3$).

General Procedure C (GP C): Asymmetric Conjugate Reduction of α,β-Unsaturated Amides

To $CoCl_2 \cdot 6\,H_2O$ (2.5 mol %, 0.013 mmol) was added a solution of **8c** (0.014 mmol, 4.5 mg) in 0.5 mL of ethanol and the mixture was stirred for 10 min during which the solution turned to a deep blue color. A solution of unsaturated amide (103 mg, 0.50 mmol) in 0.5 mL of ethanol and 1.0 mL of diglyme was added, and the reaction mixture was cooled to 0 °C. $NaBH_4$ (1.25 mmol, 47.3 mg) was added in small portions, and the mixture was stirred 72 h at room temperature. Water (10 mL) was added and the mixture was extracted with dichloromethane (3 × 15 mL). The combined organic layers were washed with ice water (10 mL), brine (3 × 10 mL) and dried over $MgSO_4$. After concentration the residue was purified by column chromatography to afford the product as a white solid.

(*R*)-*N*,3-Dimethyl-5-phenylpentanamide [(*R*)-12][4b]

(*E*)-*N*,3-Dimethyl-5-phenylpent-2-enamide [(*E*)-**11**] was reacted according to GP C. Purification by column chromatography (hexanes/ethyl acetate, 1:5) afforded (*R*)-**12** as a white solid; yield: 83 mg (0.40 mmol, 81%, 93% ee); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.31$–7.23 (m, 2H), 7.21–7.13 (m, 3H), 5.6–5.2 (bs, 1H), 2.79 (d, $J = 4.8$ Hz, 3H), 2.75–2.50 (m, 2H), 2.28–2.13 (m, 1H), 2.10–1.91 (m, 2H), 1.75–1.60 (m, 1H), 1.55–1.40, (m, 1H), 1.00 (d, $J = 6.4$ Hz, 3H); $[\alpha]_D$: +17.3° (*c* 1.0, $CHCl_3$); mp 68–70 °C.

The enantioselectivity was determined as follows. To the reduced amide (0.197 mmol, 40.4 mg) in a pressure vessel with nitrogen inlet were added 2 mL of 25% aqueous sulfuric acid. The mixture was degassed at 0.1 Torr and then heated to 140 °C for 36 h. The cooled reaction mixture was diluted with 2 N NaOH (pH 14), washed with diethyl ether (3 × 50 ml), acidified with 2 N HCl (pH 2) and extracted with diethyl ether (3 × 100 ml). The combined organic layers were washed with brine (3 × 50 ml) and dried over $MgSO_4$. The resulting 3-methyl-5-phenylpentanoic acid (0.189 mmol, 36.4 mg, 96%) was dissolved in benzene (1 mL), then oxalyl chloride (0.56 mmol, 71.2 mg), was added and the mixture was heated to 80 °C for 2 h. The solvent was evaporated and diethyl ether (1 mL) was added. (*S*)-Phenylethylamine (0.56 mmol, 67.9 mg), was added and the reaction mixture was stirred 2 h at room temperature. The mixture was diluted with diethyl ether (100 mL), washed with 2 N HCl (3 × 50 mL) and dried over $MgSO_4$. The organic layer was concentrated to yield (*R*)-3-methyl-5-phenyl-*N*-[(*S*)-1-phenylethyl]pentanamide; yield: 58 mg (quant.); chiral GC analysis (HP 5890 A, Phenomenex ZB-1a, oven 125–130 °C, inj.: split 250 °C, det.: FID 300 °C, 150 kPa H_2): t_R: 81.3 (*R*), 83.7 min (*S*).

(*S*)-*N*,3-Dimethyl-5-phenylpentanamide [(*S*)-12][4b]

(*Z*)-*N*,3-Dimethyl-5-phenylpent-2-enamide [(*S*)-**11**] was reacted according GP C. Purification by column chromatography (hexanes/ethyl acetate, 1:5) afforded (*S*)-**12** as a white solid; yield: 90 mg (0.44 mmol, 88%, 95% ee); $[\alpha]_D$: −17.9° (*c* 1.0, $CHCl_3$). NMR data and melting point were the same as reported in the previous example.

Acknowledgements

This work was supported by the Fonds der Chemischen Industrie and through generous chemical gifts by Degussa AG.

References and Notes

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