Second-Generation Paracyclophane Imine Ligands for the Dialkylzinc Addition to Aldehydes. Optimization of the Branched Side Chain leads to Improvement for Aliphatic Aldehydes

Sebastian Höfener, Frank Lauterwasser, Stefan Bräse*

Institut für Organische Chemie, Universität Karlsruhe (TH), Fritz-Haber-Weg 6, 76131 Karlsruhe, Germany
Fax: (+49)-721-608-8581, e-mail: braese@ioc.uka.de

Received: March 7, 2004; Accepted: May 20, 2004

Dedicated to Dr. Joe P. Richmond on the occasion of his 60th birthday.

Abstract: Two novel diastereomeric [2.2]paracyclophane ketimine ligands (S_pS)-**2** and (R_pS)-**2**, which unite a planar chiral element and a central chiral element, were used towards the enantioselective diethylzinc addition onto aliphatic aldehydes. These improved second-generation ligands, which are stable in air and water and are easy to obtain, showed significant improvements with respect to the ligands that were previously used.

Keywords: asymmetric catalysis; dialkylzinc; natural products; paracyclophanes; secondary alcohols

Introduction

The asymmetric alkylzinc addition to aldehydes is an enantioselective C–C-bond forming reaction and thus an important alternative to the Grignard reaction.[1] The high ligand dependence of this reaction is illustrated by the fact that aliphatic and aromatic aldehydes do not significantly react with dialkylzinc reagents in the absence of an appropriate ligand. Another advantage of the alkylzinc addition is its tolerance of other functional groups such as esters or ketones.

As a result, the addition of dialkylzinc onto aromatic aldehydes is one of the most studied enantioselective catalytic reactions and presents a useful tool for ligand screening. Despite the hundreds of ligands that have been reported,[2] very few of them have been successful in catalyzing the diethylzinc addition to aliphatic, and in particular, α-unbranched aldehydes. One such example is a modified norephedrine derivative used by Nugent et al.[3] It produced excellent ee values for the 1,2-addition products of various substrates, except for hexanal, in which a diminished enantiomeric excess of 87% ee was reported.

The synthesis of simple aliphatic secondary alcohols is still a challenge for asymmetric catalysis. However, the asymmetric addition of alkylmetal species to aliphatic aldehydes may, in selected cases, be the method of choice. For example, the asymmetric reaction of diethylzinc with hexanal and subsequent aqueous work-up leads directly to scalemic 3-octanol which, in the (*R*)-configuration, is the sex attractant pheromone of *Myrmica scabrinodis*. The (*S*)-enantiomer is an alarm pheromone found in the ants *Crematogaster castanea* and *C. liengmei*.[4]

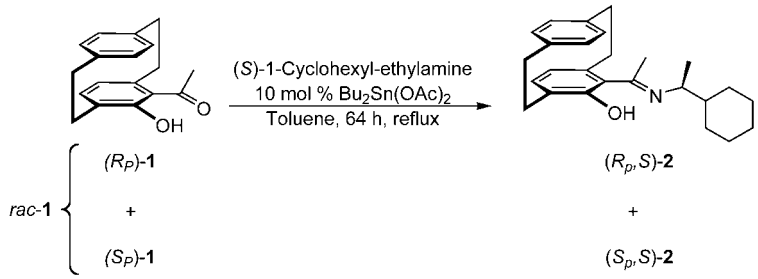
Recently, we introduced ketimines derived from [2.2]paracyclophane as powerful ligands in the alkylzinc addition onto aromatic and α-branched aldehydes. Rozenberg and Belokon,[5] who synthesized the first generation of this ligand class, used them for resolution of the corresponding racemic hydroxyl ketones. These ligands were employed in diethylzinc and alkenylzinc addition to aldehydes.[6] A further application is the addition of dialkyl- or diphenylzinc to imines.[7] A substantial advantage of these ligands is that they are stable in air and water and can be prepared in large quantities.

Within this article we describe the addition of diethylzinc catalyzed by a [2.2]paracyclophane-based ketimine ligand of the second generation. This type of ligand unites a central chiral element with a planar chiral element, while the latter is the dominating one.[8] Herein, we report the diethylzinc addition catalyzed by the new diastereomeric ligands (R_pS)-**2** and (S_pS)-**2** which were tested for an enlarged substrate spectrum.

Results and Discussion

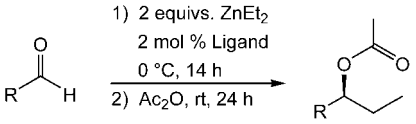
The novel ligands (R_pS)-**2** and (S_pS)-**2** were synthesized starting from AHPC (*rac*-**1**), in turn prepared according to Rozenberg, Belokon and coworkers.[5] The ligands

 DOI: 10.1002/adsc.200404068



Scheme 1. Synthesis of $(R_\beta S)$-**2** and $(S_\beta S)$-**2**.

Table 1. Diethylzinc addition to aliphatic aldehydes.[a]



Entry	Substrate	Ligand	Product	Conversion [%][b]	ee [%][b]
1	2-Ethylbutyraldehyde (**3a**)	$(S_\beta S)$-**2**	(+)-**4a**	quant.	97
2	2-Ethylbutyraldehyde (**3a**)	$(R_\beta S)$-**2**	(−)-**4a**	quant.	89
3	3-Thiophenecarboxaldehyde (**3b**)	$(S_\beta S)$-**2**	(+)-**4b**	quant.	91
4	3-Thiophenecarboxaldehyde (**3b**)	$(R_\beta S)$-**2**	(−)-**4b**	quant.	80
5	Cyclohexanecarboxaldehyde (**3c**)	$(S_\beta S)$-**2**	(+)-**4c**	quant.	95
6	Cyclohexanecarboxaldehyde (**3c**)	$(R_\beta S)$-**2**	(−)-**4c**	quant.	95
7	Decanal (**3d**)	$(S_\beta S)$-**2**	(+)-**4d**	quant.	84
8	Decanal (**3d**)	$(R_\beta S)$-**2**	(−)-**4d**	quant.	86
9	Hexanal (**3e**)	$(S_\beta S)$-**2**	(+)-**4e**	quant.	86
10	Hexanal (**3e**)	$(R_\beta S)$-**2**	(−)-**4e**	quant.	85
11	Isobutyraldehyde (**3f**)	$(S_\beta S)$-**2**	**4f**[c]	quant.	96
12	Isobutyraldehyde (**3f**)	$(R_\beta S)$-**2**	**4f**[c]	quant.	96

[a] 1) 0.5 mmol aldehyde, 1.0 mmol diethylzinc (1 m in hexane), 2 mol % Ligand, 0 °C, 14 h ; 2) Ac_2O, room temperature, 24 h; 3) half saturated NH_4Cl solution.
[b] Conversion was measured by GC on an achiral stationary phase (HP 1), enantiomeric excess was determined by GC on chiral stationary phase (CP-Chirasil-Dex).
[c] Optical rotation was not determined.

were separated after the final step by column chromatography and differ only in the configuration of the planar chiral element.

The ligands are used in the asymmetric 1,2-addition of diethylzinc with different aldehydes **3a–f** as depicted in Table 1.

Inspired by the publication of Nugent et al.,[3] we decided to quench the zinc alkoxide species with acetic anhydride. As a result, the appropriate esters **4a–f** were obtained instead of the secondary alcohols, which would usually result from quenching with a proton source. The advantage is a lower volatility of the products and a far better separation on a chiral stationary phase (CP-Chirasil-Dex). For each substrate, the two diastereomeric species $(S_\beta S)$-**2** and $(R_\beta S)$-**2** (Scheme 1) were applied. The application of these diastereomeric ligands in the diethylzinc addition towards aliphatic and aromatic aldehydes demonstrated that the two ligands $(S_\beta S)$-**2** and $(R_\beta S)$-**2** always yield the appropriate esters with opposite configurations (Table 1).

The conversions were excellent in all cases, but the ee values varied from moderate to good. 2-Ethylbutanal as substrate with (S_P,S)-**2** as catalyst yielded the product with 97% ee (entry 1), while using $(R_\beta S)$-**2** gave the enantiomer with 89% ee (entry 2). Here, one can see the high influence of planar chirality on the stereoselection of the catalysis. Changing the configuration (from S_P to R_P) led to the appropriate enantiomer with a small loss in enantiomeric excess. In the first case, using (S_P,S)-**2**, the two chiral elements, S_P and S, worked together in a mutual manner. In the second case, however using $(R_\beta S)$-**2**, R_P and S worked against each other. A comparable case is observable using 3-thiophenecarboxaldehyde as the substrate. The ligand $(S_\beta S)$-**2** furnishes the

product (+)-**4b** with 91% ee (entry 3), while the enantiomer (−)-**4b** resulting from ($R_{\beta}S$)-**2** showed an 80% ee (entry 4). For the remaining substrates, the ee values obtained were nearly the same for both ligands applied while the products had the opposite configuration as observed in the previous examples. It appears that the central chiral element here has neither an influence on the configuration nor an influence on the ee value. However, previous examinations in our group showed that ee values on a high level are only possible by cooperative effects between the planar chiral and central chiral elements. Compared to our first generation ligands where the cyclohexyl ring was substituted by a phenyl ring,[6] our new second generation ligands exhibited excellent results. For the substrates decanal, cyclohexanecarboxaldehyde and isobutyl aldehyde, a remarkable improvement in enantiomeric excess (increase by 10% ee) was observed.

Conclusion

Within this article we described the enantioselective diethylzinc additions of the two diastereomeric [2.2]paracyclophane ketimine ligands, ($S_{\beta}S$)-**2** and ($R_{\beta}S$)-**2**, onto aliphatic aldehydes that still presents itself as a high benchmark for many ligands. With our improved second-generation ligands, we were able to raise the enantiomeric excess for several aliphatic substrates by 10% ee with respect to the ligand system that we used previously.

Experimental Section

General Remarks

All catalysis reactions were performed in 10-mL vials under an argon atmosphere. Substrates were purchased from commercial sources and were used without further purification. Diethylzinc was purchased as a 1 M solution in hexane from Fluka. Conversions were measured by GC on an achiral stationary phase (HP 1). Enantiomeric excesses were determined by GC on a chiral stationary phase (CP-Chirasil-Dex). ^{1}H and ^{13}C NMR spectra were recorded on Bruker DP300 (300 MHz/75 MHz) and Bruker DP400 (400 MHz/100 MHz) spectrometers using $CDCl_3$ as the solvent and shift reference (7.26 ppm/77.00 ppm). Optical rotations were determined on a Perkin Elmer 241 polarimeter (Na, 589 nm).

(R_p,S)-5-(1′-Cyclohexylethyliminoethyl)-4-hydroxy[2.2]paracyclophane

A solution of 100 mg (0.38 mmol) of (R_p)-5-acetyl-4-hydroxy-[2.2]paracyclophane and 146 μL (1.0 mmol) of (*S*)-cyclohexylethylamine, with a catalytic amount of dibutyltin diacetate (10 mol %) in 40 mL of toluene, was refluxed for 40 h with a Dean–Stark trap (filled with mol sieves MS 4 Å). A 1 M solution of HCl was then added. The organic layer was separated, extracted with dichloromethane, and dried with magnesium sulfate. The solvent was removed at reduced pressure, and the obtained residue was then purified by column chromatography (dichloromethane). The product was obtained as an orange oil; yield: 100 mg (70%); R_f = 0.73 (cyclohexane/ethyl acetate, 5/1); $[\alpha]_D^{20}$: +659 (*c* 1.0; $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94–1.35 (m_c, 8H), 1.45–1.60 (m, 1H), 1.63–1.88 (m_c, 5H), 2.27 [s, 3H, NC(C*H*$_3$)PC], 2.45–2.55 (m, 2H), 2.80–3.20 (m_c, 4H), 3.36–3.44 (m_c, 2H), 3.58 [p, *J* = 6.1 Hz, NC*H*(CH_3)], 6.15 (d, *J* = 7.3 Hz, 1H), 6.30 (dd, *J* = 7.6 Hz, 1.8 Hz, 1H), 6.39 (d, *J* = 7.6 Hz, 1H), 6.45 (dd, *J* = 7.9 Hz, 1.8 Hz, 1H), 6.59 (dd, *J* = 7.6 Hz, 1.8 Hz, 1H), 6.95 (dd, *J* = 7.9 Hz, 2.1 Hz, 1H), 16.19 (s, 1H, O*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.18 (p), 19.44 (p), 26.28 (s), 26.40 (s), 29.48 (s), 29.63 (s), 30.36 (s), 33.86 (s), 35.45 (s), 37.66 (s), 43.91 (t), 58.47 (t), 121.65 (q), 125.27 (t), 126.98 (t), 129.61 (t), 129.73 (q), 131.14 (t), 132.75 (t), 135.78 (t), 137.50 (q), 139.94 (q), 140.60 (q), 164.28 (q, C-4), 168.92 (q, PC*C*(CH_3)N); IR (KBr): ν = 2925 (s), 2850 (s), 1738 (m), 1594 (s), 1446 (s), 1240 (s) cm^{-1}; MS (70 eV, EI): *m/z* (%) = 375 (90) [M$^+$], 271 (100), 188 (53), 162 (53); HRMS: calcd. for $C_{26}H_{33}NO$: 375.2562; found: 375.2564.

(S_p,S)-5-(1′-Cyclohexylethyliminoethyl)-4-hydroxy[2.2]paracyclophane

As above, 100 mg (0.38 mmol) of (S_p)-5-acetyl-4-hydroxy[2.2]-paracyclophane and 146 μL (1.0 mmol) of (*S*)-cyclohexylethylamine afforded a yellow-orange solid; yield: 120 mg (84%); R_f = 0.55 (cyclohexane/ethyl acetate, 5/1); $[\alpha]_D^{20}$: −645 (*c* 1.0; $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.20 [d, *J* = 6.4 Hz, 3H, NCH(C*H*$_3$)], 1.16–1.40 (m_c, 5H), 1.56–1.65 (m, 1H), 1.71–1.78 (m, 1H), 1.82–1.92 (m_c, 3H), 1.99–2.05 (m, 1H), 2.27 [s, 3H, NC(C*H*$_3$)PC], 2.45–2.52 (m, 1H), 2.61–2.68 (m, 1H), 2.85–3.20 (m_c, 4H), 3.30–3.44 (m_c, 2H), 3.58 [p, *J* = 6.1 Hz, NC*H*(CH_3)], 6.14 (d, *J* = 7.3 Hz, 1H), 6.32 (dd, *J* = 7.6 Hz, 1.8 Hz, 1H), 6.38 (d, *J* = 7.6 Hz, 1H), 6.48 (dd, *J* = 7.9 Hz, 1.8 Hz, 1H), 6.62 (dd, *J* = 7.6 Hz, 1.8 Hz, 1H), 6.95 (dd, *J* = 7.9 Hz, 2.1 Hz, 1H), 16.39 (s, 1 H, O*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.60 (p), 19.49 (p), 26.35 (s), 26.40 (s), 26.64 (s), 29.13 (s), 30.10 (s), 33.88 (s), 35.54 (s), 37.43 (s), 44.35 (t), 58.05 (t), 121.61 (q), 124.92 (t), 127.05 (t), 129.85 (q), 130.23 (t), 131.42 (t), 132.66 (t), 136.19 (t), 137.59 (q), 140.10 (q), 140.69 (q), 165.35 (q, C-4), 168.78 [q, PC*C*(CH_3)N]; IR (KBr): ν = 2925 (s), 2850 (s), 1738 (m), 1594 (s), 1446 (s), 1240 (s) cm^{-1}; MS (70 eV, EI): *m/z* (%) = 375 (100) [M$^+$], 271 (97), 188 (52), 162 (50); HRMS: calcd. for $C_{26}H_{33}NO$: 375.2562; found: 375.2564.

General Procedure for Diethylzinc Addition to Aldehydes

To a vial containing 3.7 mg (0.01 mmol) of ketimine alcohol ($S_{\beta}S$)-**2** or ($R_{\beta}S$)-**2**, 1 mL (1 mmol) of a 1 M solution of diethylzinc in hexane was added. After stirring for 10 min, the solution was cooled to 0 °C and 0.5 mmol of aldehyde was then added. The reaction mixture was stirred for 14 h before it was quenched with 0.19 mL (2.0 mmol) of acetic anhydride. The

solution was allowed to stir for 24 h at room temperature. Then, 4 mL of half-saturated ammonium chloride solution were added carefully. The mixture was then diluted with 4 mL of diethyl ether. The aqueous phase was separated and the organic phase was washed 3 times with water before it was dried with magnesium sulfate. The solvents were removed at reduced pressure and the residue was then purified by column chromatography.

4-Ethyl-3-hexyl Acetate[9]

Following the general procedure, 62 μL (0.5 mmol) of 2-ethylbutanal were reacted with diethyl zinc (1 M in hexanes), either with ($S_\beta S$)-**2** or ($R_\beta S$)-**2**, and purified by column chromatography (pentane/diethyl ether, 5/1); ^{1}H NMR ($CDCl_3$): $\delta = 0.86$ (tr, 3H, $J = 7.39$ Hz), 0.88 (t, 3H, $J = 7.39$ Hz), 0.89 (t, 3H, $J =$ 7.35), 1.23–1.44 (m, 5H), 1.55 (dq, 2H, $J = 5.75$, 7.35 Hz), 2.03 (s, 3H), 4.87 (ddd, 1H, $J = 4.27$, 5.75, 6.99 Hz); ^{13}C NMR ($CDCl_3$): $\delta = 10.08$, 11.53, 11.63, 21.12, 21.72, 21.99, 23.92, 43.94, 77.05, 170.95. The products derived from ($S_\beta S$)-**1** or ($R_\beta S$)-**2** possess opposite configurations. ($S_\beta S$)-**2** yielded the product with 97% ee (GC analysis: CP-Chirasil-Dex), with ($R_\beta S$)-**2**: 89% ee (GC analysis: CP-Chirasil-Dex).

3-Dodecyl Acetate[10]

Following the general procedure, 94 μL (0.5 mmol) of decanal were reacted with diethylzinc (1 M in hexanes), either with ($S_\beta S$)-**2** or ($R_\beta S$)-**2**, and purified by column chromatography (cyclohexane/ethyl acetate, 5/1, or cyclohexane/ethyl acetate, 9/1); ^{1}H NMR ($CDCl_3$): $\delta = 0.86$ (t, 6H, $J = 7.39$ Hz), 1.21–1.61 (m, 18H), 2.02 (s, 3H), 4.79 (tt, 1H, $J = 6.22$, 6.22 Hz); ^{13}C NMR ($CDCl_3$): $\delta = 9.51$, 14.03, 21.16, 22.63, 25.30, 26.92, 29.26, 29.50, 31.85, 33.58, 75.51, 170.86 ppm. The products possess opposite configurations. Catalysis with ($S_\beta S$)-**2** yielded the product with $[\alpha]_D^{20}$: +5.90 (c 1.14; $CHCl_3$); GC analysis (CP-Chirasil-Dex) 84% ee; with ($R_\beta S$)-**2**: $[\alpha]_D^{19}$: −5.86 (c 0.99; $CHCl_3$); (GC analysis: CP-Chirasil-Dex) 86% ee.

3-Octyl Acetate[11]

Following the general procedure, 60 μL (0.5 mmol) of hexanal were reacted with diethylzinc (1 M in hexanes) either with ($S_\beta S$)-**2** or ($R_\beta S$)-**2**, and purified by column chromatography (cyclohexane/ethyl acetate, 5/1, or pentane/diethyl ether, 29/1). NMR data were in accordance with the values in the literature. The products possess opposite configurations. With ($S_\beta S$)-**2** $[\alpha]_D^{20}$: +6.64 (c 1.09; $CHCl_3$); (GC analysis: CP-Chirasil-Dex) 86% ee; with ($R_\beta S$)-**2** $[\alpha]_D^{20}$: −6.67 (c 0.55; $CHCl_3$); (GC analysis: CP-Chirasil-Dex) 85% ee.

1-Cyclohexyl-2-propyl Acetate

Following the general procedure, 61 μL (0.5 mmol) of cyclohexanecarboxaldehyde were reacted with diethylzinc (1 M in hexanes), either with ($S_\beta S$)-**1** or ($R_\beta S$)-**2**, and purified by column chromatography (cyclohexane/ethyl acetate, 5/1). NMR data were in accordance to the values in the literature. The products possess opposite configurations. With ($S_\beta S$)-**2** $[\alpha]_D^{21}$: +29.11 (c 1.07; $CHCl_3$); (GC analysis: CP-Chirasil-Dex) 95% ee; with ($R_\beta S$)-**2** $[\alpha]_D^{21}$: −26.6 (c 0.17; $CHCl_3$); (GC analysis: CP-Chirasil-Dex) 95% ee.

1-(3-Thienyl)-1-propyl Acetate

Following the general procedure, 44 μL (0.5 mmol) of 3-thiophenecarboxaldehyde were reacted with diethylzinc (1 M in hexanes), either with ($S_\beta S$)-**2** or ($R_\beta S$)-**2**, and purified by column chromatography (pentane/diethyl ether, 5/1, or cyclohexane/ethyl acetate, 9/1). NMR data were in accordance to the values in the literature. The products possess opposite configurations. With ($S_\beta S$)-**2** $[\alpha]_D^{20}$: +111.5 (c 1.00; $CHCl_3$); (GC analysis: CP-Chirasil-Dex) 91% ee; with ($R_\beta S$)-**2**: $[\alpha]_D^{21}$: −108.2 (c 0.43; $CHCl_3$); (GC analysis: CP-Chirasil-Dex) 80% ee.

2-Methyl-3-pentyl Acetate[12]

Following the general procedure, 46 μL (0.5 mmol) of isobutyl aldehyde was reacted with diethyl zinc (1 M in hexanes), either with ($S_\beta S$)-**2** or ($R_\beta S$)-**2**. Due to its high volatility, the organic layers were not concentrated under vacuum. The products have opposite configurations. With ($S_\beta S$)-**2** (GC analysis: CP-Chirasil-Dex) 97% ee; with ($R_\beta S$)-**2** (GC analysis: CP-Chirasil-Dex) 96% ee.

Acknowledgements

We thank the DFG (SFB 380) for financial support and Dr. Stefan Dahmen (Cynora GmbH) for some preliminary results in this area. Cyclohexylethylamine (Chipros) was a generous gift from the BASF AG (Dr. Ditrich).

References and Notes

[1] V. Grignard, *C. R. Hebd. Sceances Acad. Sci.* **1900**, *130*, 2823.
[2] K. Soai, S. Niwa, *Chem. Rev.* **1992**, *92*, 833–856; L. Pu, H.-B. Yu, *Chem. Rev.* **2001**, *101*, 757.
[3] W. A. Nugent, *Org. Lett.* **2002**, *13*, 2133–2136.
[4] B. T. Cho, D. J. Kim, *Tetrahedron* **2003**, *59*, 2457–2462 and references cited therein.
[5] V. Rozenberg, T. Danilova, E. Sergeeva, E. Vorontsov, Z. Starikova, K. Lysenko, Y. Belokon, *Eur. J. Chem.* **2000**, 3295.
[6] S. Dahmen, S. Bräse, *Chem. Commun.* **2002**, 26–27; S. Dahmen, S. Bräse, *Org. Lett.* **2001**, *3*, 4119–4122; S. Dahmen, *Ph. D. Thesis*, RWTH Aachen, **2002**; S. Dahmen, *Org. Lett.* **2004**, *6*, asap.
[7] N. Hermanns, S. Dahmen, C. Bolm, S. Bräse, *Angew. Chem.* **2002**, *114*, 3844–3846; *Angew. Chem. Int. Ed.* **2002**, *41*, 3692–3694; S. Dahmen, S. Bräse, *J. Am. Chem. Soc.* **2002**, *124*, 5940–5941.
[8] For a discussion of central *vs.* planar cirality in the context of ferrocenylamine ligands, see: S. D. Pastor, A. Togni, *J. Am. Chem. Soc.* **1989**, *111*, 2333–2334.

[9] K. Subba Reddy, L. Sola, A. Moyano, M. A. Pericas, A. Riera, *Synthesis* **2000**, 165–176.
[10] P. ten Holte, J.-P. Wijgergangs, L.Thijs, B. Zwanenburg, *Org. Lett.* **1999**, *1*, 1095–1097; P. J. Hermsen, J. G. O. Cremers, L. Thijs, B. Zwanenburg, *Tetrahedron Lett.* **2001**, *42*, 4243–4245.
[11] M. L. Richmond, C. T. Seto, *J. Org. Chem.* **2003**, *68*, 7505–7508; S. Chattopadhyay, V. R. Mamdapur, M. S. Chadha, *J. Chem. Res. Synopses* **1990**, *8*, 235.
[12] N. Arroyo, U. Haslinger, K. Mereiter, M. Widhalm, *Tetrahedron: Asymmetry* **2000**, *11*, 4207–4219; G. Palmieri, *Tetrahedron: Asymmetry* **2000**, *11*, 3361–3373.

