Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 169–176

TETRAHEDRON: *ASYMMETRY*

New 1-amino-1,2-diphenylethanols as ligands for the enantioselective addition of alkyllithiums to benzaldehyde

Michael Schön and Reto Naef *

Novartis Pharma AG, CH-4002, Basel, Switzerland

Received 9 November 1998; accepted 23 November 1998

Abstract

In the presence of equimolar amounts of lithium alkoxides derived from *N*-substituted 2-amino-1,2-diphenylethanols, alkyllithium reagents add to benzaldehyde to furnish optically active secondary alcohols with enantiomeric excesses of up to 86%. The best results were obtained using the *N*-isopropyl-*N*-methyl substituted aminoalcohol.

1. Introduction

Without any doubt, the enantioselective addition of organometallic reagents to aldehydes and ketones are among the most powerful reactions in organic synthesis and consequently have been extensively studied in the past 20 years.[1–3] Despite spectacular successes, the methods developed often display some major disadvantages. In almost every case substantial excesses of the ligand and temperatures below −100°C[1,2] are required in order to obtain good selectivities, or the reagent has to be prepared independently.[3] Two notable exceptions are the TADDOL-mediated addition of Grignard reagents developed by Seebach[4] and the addition of diorganozincs to aldehydes[5] and ketones[6] under aminoalcohol catalysis; although the scope of the former reaction is strictly limited to the availability of the organozinc reagents.

We therefore set ourselves the goal of developing new ligands which could be easily used by adding an equimolar amount of the ligand to the solution of the organolithium reagent followed by addition of the appropriate aldehyde or ketone at −78°C. We report herein our preliminary studies concerning the asymmetric addition of butyllithium to benzaldehyde in THF† at −78°C as a standard reaction.

* Corresponding author. E-mail: reto.naef@pharma.novartis.com

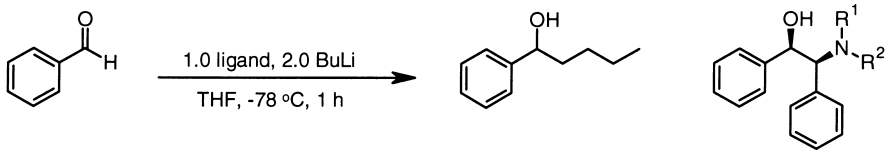
† In accordance with Jackman[2e] and coworkers THF turned out to be the solvent of choice.

0957-4166/99/$ - see front matter
PII: S0957-4166(98)00473-X

2. Results and discussion

We have surveyed various readily available amino-alcohols in order to investigate their structure–selectivity relationships. 2-Dimethylamino-1,2-diphenylethanol **1**[7] (entry 1 in Table 1) provided encouraging results and represents (to the best of our knowledge) the best literature ligand under the reaction conditions applied {71% ee favouring the (*S*)-enantiomer, see entry 1 in Table 1}.[2e] It is noteworthy that other known ligands for the enantioselective addition of organolithium reagents to aldehydes, e.g. Mukaiyama's prolinol,[2a] gave disappointing results using our standard reaction conditions {17% ee favouring the (*S*)-enantiomer}.

Table 1
Reaction of benzaldehyde with butyllithium in the presence of ligands **1–9**[7–9]



1-9

Entry	Ligand	R^1	R^2	Yield[a]	ee (%)[b]	Configuration[c]
1	**1**[7]	Me	Me	91	71	*S*
2	**2**[8]		$-(CH_2)_2-$	78	57	*S*
3	**3**[9]	^{n}Bu	^{n}Bu	91	25	*S*
4	**4**	Me	^{n}Bu	90	68	*S*
5	**5**	Me	^{i}Pr	85	78	*S*
6	**6**	Me	3-pentyl	89	64	*S*
7	**7**	Me	cyclohexyl	89	47	*S*
8	**8**	Me	cyclopentyl	83	62	*S*
9	**9**	Me	2-morpholinoethyl	77	50	*S*

a: Yield of isolated chromatographed material. **b:** Determined by HPLC on a chiral column. **c:** Established by comparison of the specific rotation with literature values.

Since the work of Mukaiyama,[2a] Soai[10] and Thompson[11] clearly demonstrated that changing the steric and electronic nature of the amino group can have a significant influence on the enantioselectivity of the addition reaction, we chose ligand **1** as the lead structure. The derivatives, prepared according to standard alkylation and reductive amination procedures,[‡] are summarised in Table 1.

We considered that the introduction of two different substituents on the nitrogen could improve the enantioselectivity of the addition reaction by the formation of an additional stereocentre during the chelation process. Although it is at present not clear whether the coordination is stereoselective, the effect of the additional stereocentre is apparent (Table 1, entries 4–9 compared with 1–3). On the one hand, branched alkyl substituents were shown to improve the (*S*)-selectivity (entries 1 and 5); whilst on

[‡] For further details refer to the experimental section.

the other hand, the introduction of an additional chelating group (entry 9) reduces the (*S*)-selectivity.[§] *N*-Isopropylamine **5** turned out to be the most effective ligand and was chosen for further investigations.

It should be noted that in the case of the *N*-isopropyl substituted ligand **5**, a change in the molar ratio of ligand alkoxide Li-**5**:BuLi:PhCHO from 1:1:1 to 4:1:1 has no significant influence on the enantioselectivity (Table 2, entries 3–5). These results are in strong contrast to those reported for the addition of methyllithium to benzaldehyde in the presence of ligand **1**.[2e] Further investigations are in progress, but it should be stressed that these ratios do not necessarily define the stoichiometry of the reactant since alkyllithium, lithium alkoxide and several mixed aggregates may co-exist in equilibrium. The enantioselectivities obtained using a catalytic amount of the ligand alkoxide Li-**5** indicate that there is no significant enhancement in the reactivity.

Table 2
Effect of the concentration of lithium alkoxide Li-**5** on the enantioselectivity of butyllithium addition to benzaldehyde in THF at −78°C

Entry	**Li-5**	:	BuLi	:	PhCHO	ee (%)[a,b]
1	0.1	:	1.0	:	1.0	11
2	0.5	:	1.0	:	1.0	50
3	1.0	:	1.0	:	1.0	78
4	4.0	:	2.0	:	1.0	79
5	4.0	:	1.0	:	1.0	82

a: Determined by HPLC on a chiral column. **b:** All alcohols had (*S*)-configuration.

To elucidate the potential of the 2-amino-1,2-diphenylethanol mediated enantioselective addition to benzaldehyde we also surveyed a series of organolithium reagents. The results observed are summarised in Table 3.

The results presented in Table 3 clearly demonstrate the potential of the known ligand **1**[2e] in the enantioselective addition of a variety of different organolithium reagents (except ^{t}BuLi[¶]) to aldehydes using convenient reaction conditions. However, the facial selectivity can be improved significantly by using the corresponding *N*-isopropylamine **5**. Although small in terms of energy — a change from 76:24 to 93:7 (Table 3, entries 1 and 2) corresponds to a difference of only 0.5 kcal/mol in free activation energy $\Delta\Delta G^{\neq}_{195}$ — this effect might be of great practical significance.

The stereochemical outcome of the addition reaction may be rationalised by the transition state model shown in Fig. 1. Lithium alkoxide Li-**5** and the organolithium reagent form a rigid, mixed dimer[||] whose conformation is fixed by the additional stereocentre at the chelating nitrogen atom.[††] Benzaldehyde is coordinated via an LiX-bridge and its phenyl moiety is placed in a pseudo-equatorial position

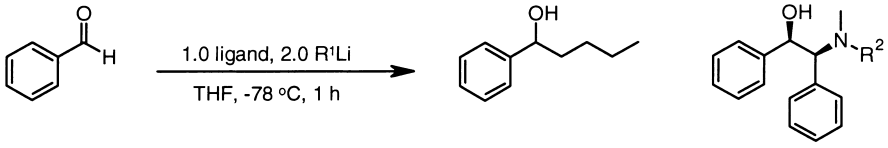
[§] In the case of α,α-diphenylprolinol-derived ligands, the 2-morpholinoethyl substituent was shown to significantly improve the enantioselectivity of the addition of butyllithium to benzaldehyde, compared with the results obtained for DPMPM[12] {24% (*R*) obtained for the *N*-methyl compound vs 55% ee (*R*) for the diamine}. These results will be described elsewhere.

[¶] As a result of steric crowding, the formation of a chiral mixed dimer (see Fig. 1) seems to be impossible. It is also known from the literature that ^{t}BuLi forms no dimers or higher aggregates in ethereal solvents.[13]

[||] Garrity et al. were able to show by rapid-injection NMR studies that dimers are more reactive than the corresponding tetramers.[14]

[††] For a review on chelation of β-amino-lithoxides see Nichols et al.[15]

Table 3
Reaction of benzaldehyde with organolithium reagents in the presence of ligands **1** and **5**



1 R^2 = Me
5 R^2 = ^{i}Pr

	R^1Li	ligand **1**	ligand **5**
1	MeLi	52 % ee	86 % ee
2	BuLi	72 % ee	78 % ee
3	HexLi	55 % ee	75 % ee
4	^{t}BuLi	1 % ee	2 % ee
5	$TMSCH_2Li$[a]	58 % ee	85 % ee
6	TMS-C≡C-Li[b]	39 % ee	75 % ee

ee values determined by HPLC on a chiral column. All alcohols had (*S*)-configuration. Yields were in a range from 80 % to 93 %, except for entry 4 (61-62 %). **a:** Configuration unknown. **b:** Prepared *in situ* from (trimethylsilyl)acetylene and butyllihium.

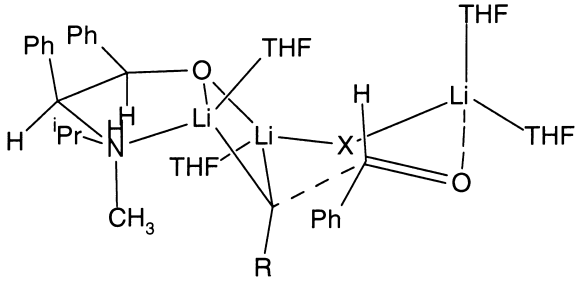


Figure 1.

avoiding steric interaction with the coordinated tetrahydrofuran molecule. The nucleophilic addition to benzaldehyde occurs from the *Si*-face.

In conclusion, we have demonstrated that 2-*N*,*N*-dialkylamino-1,2-diphenylethanols are effective ligands for the enantioselective addition of organolithium reagents to aldehydes. In addition, we have developed an operationally simple procedure for the synthesis of optically active secondary alcohols using commercially available organolithium reagents. Considering the high reactivity[14] of the reaction partners involved in this reaction, the observed enantioselectivity using these simple ligands is unexpected and quite remarkable. Our current efforts focus on further improvement of the ligands and elucidation of the scope and the limitation of this method, especially with regard to other electrophiles.

3. Experimental

3.1. General

Solvents and reagents were purified and dried according to standard procedures. TLC analyses were done on Si60 F_{254}-coated plates (E. Merck); detection was by UV at 254 nm or phosphomolybdic acid (10% in EtOH). Silica 0.040–0.063 mm (E. Merck) was used for flash chromatography. Melting points were determined on a Büchi 512 apparatus and are uncorrected. IR spectra were recorded on a Bruker IFS 66 spectrometer. NMR spectra were obtained from a Bruker AMX 400 spectrometer. Specific rotation was measured on a Perkin–Elmer polarimeter 241 MC.

3.2. Preparation of ligands **4**–**9**

3.2.1. (1R,2S)-N-Butyl-N-methyl-2-amino-1,2-diphenylethanol **4**

A suspension of commercially available (1*R*,2*S*)-2-amino-1,2-diphenylethanol (1.77 g, 8.30 mmol) and K_2CO_3 (1.15 g, 8.30 mmol) in butyl bromide (2.27 g, 16.6 mmol) and EtOH (16 ml) was heated under reflux for 1 day. The mixture was filtered and concentrated in vacuo to leave a white solid (2.1 g). Column chromatography (hexane:EtOAc, 1:2) furnished the pure *N*-butylamine (1.32 g, 59%) and *N*,*N*-dibutylamine (0.64 g, 27%) with spectroscopic data identical to those reported,[9] both as colourless crystals: mp 135–136°C (*N*-butylamine), 141–142°C (*N*,*N*-dibutylamine).

To a solution of the *N*-butylamine in $HCOOH/H_2O$ (1.4 ml+0.33 ml) was added formaldehyde at 100°C (37% aqueous solution, 1.05 ml) and stirring was continued for an additional 4 h. The mixture was cooled and made alkaline with 2 N NaOH followed by extraction with EtOAc (3×10 ml). The combined organic layers were dried over Na_2SO_4 and evaporated. Purification of the crude product by column chromatography (hexane:EtOAc, 1:1) afforded ligand **4** (1.35 g, 57%) as a colourless oil. $[\alpha]_D^{20}$ −58.0 (*c*=0.39, $CHCl_3$). HRMS (EI) calcd for $C_{19}H_{25}NO$ 284.2016 (MH^+), found 284.2009 (MH^+). IR (neat) 3200–3600, 3062, 3028, 2957, 2931, 2861, 2796, 1495, 1453, 1198, 1090, 1059, 1029, 775, 750, 702 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.88 (t, *J*=7 Hz), 1.15–1.35 (m, 2H), 1.4–1.6 (m, 2H), 2.36 (s, 3H), 2.4–2.6 (m, 2H), 3.53 (d, *J*=6 Hz, 1H), 5.34 (d, *J*=6 Hz, 1H), 7.0–7.3 (m, 10H). ^{13}C NMR ($CDCl_3$) δ 14.4, 20.7, 29.1, 40.0, 55.1, 72.9, 75.8, 126.6, 127.2, 127.6, 127.9, 130.0, 137.0, 141.8.

3.2.2. (1R,2S)-N-Isopropyl-N-methyl-2-amino-1,2-diphenylethanol **5**

Typical procedure: According to the procedure of Shioiri,[16] acetone (2.96 g, 50.9 mmol) and sodium cyanoborohydride (998 mg, 12.7 mmol) were added to a solution of commercially available (1*R*,2*S*)-2-amino-1,2-diphenylethanol (1.81 g, 8.49 mmol) in MeOH (34 ml). The pH of the solution was adjusted to ca. 4 by adding acetic acid and the resulting mixture was stirred for 5 h. The mixture was made alkaline by adding 2 N NaOH and extracted with EtOAc (3×50 ml). The combined organic layers were dried over Na_2SO_4 and evaporated to leave 2.08 g (96%) of the crude *N*-isopropylamine which was used for the next step without further purification.

To a solution of the crude product in $HCOOH/H_2O$ (2.4 ml+0.6 ml) was added formaldehyde at 100°C (37% aqueous solution, 1.8 ml) and stirring was continued for an additional 4 h. The mixture was cooled and made alkaline with 2 N NaOH followed by extraction with EtOAc (3×10 ml). The combined organic layers were dried over Na_2SO_4 and evaporated. Purification of the crude product by column chromatography (hexane:EtOAc, 2:1) afforded ligand **5** (1.99 g, 87%) as colourless crystals: mp 67–68°C. $[\alpha]_D^{20}$ −105 (*c*=0.52, $CHCl_3$). Anal. calcd for $C_{18}H_{23}NO$: C, 80.26; H, 8.61; N, 5.20. Found: C, 80.16; H, 8.65; N, 5.26. IR (KBr) 3200–3700, 2971, 2882, 2783, 1453, 1388, 1367, 1200, 1184, 1060,

1047, 791, 764, 706, 696, 589 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.89, 1.00 (2d, *J*=6 Hz, 6H), 2.36 (s, 3H), 3.10 (h, *J*=6 Hz, 1H), 3.57 (d, *J*=4 Hz, 1H), 5.24 (d, *J*=4 Hz, 1H), 6.9–7.2 (m, 10H). ^{13}C NMR ($CDCl_3$) δ 15.5, 20.1, 32.3, 49.5, 72.6, 74.4, 126.5, 127.0, 17.4, 127.8, 129.9, 137.5, 141.6.

*3.2.3. (1*R,*2*S*)*-N-*(3-Pentyl)*-N-*methyl-2-amino-1,2-diphenylethanol* ***6***

According to the typical procedure given for **5**; 1.18 g (5.53 mmol) (1*R*,2*S*)-2-amino-1,2-diphenylethanol; 651 mg (8.30 mmol) sodium cyanoborohydride; 476 mg (5.53 mmol) 3-pentanone; 22 ml MeOH; reaction time 3 days at r.t.; column chromatography (hexane:EtOAc, 1:1) of the crude product afforded the pure secondary amine (1.14 g, 73%) as a colourless oil; 0.75 ml HCOOH, 0.19 ml H_2O, 0.56 ml 37% aq. H_2CO; reaction time 6 h at 100°C; column chromatography (hexane:EtOAc, 9:1) of crude product afforded ligand **6** (1.02 g, 85%) as a colourless oil. $[\alpha]_D^{20}$ −83.0 (*c*=1.71, $CHCl_3$). Anal. calcd for $C_{20}H_{27}NO$: C, 80.76; H, 9.15; N, 4.71. Found: C, 80.64; H, 9.28; N, 4.73. IR (neat) 3200–3700, 2962, 2932, 2873, 1495, 1453, 1200, 1089, 1054, 1030, 999, 922, 777, 754, 701 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.69, 0.99 (2t, *J*=7 Hz, 6H), 1.2–1.6 (m, 4H), 2.36 (s, 3H), 2.45–2.55 (m, 1H), 3.74 (d, *J*=4 Hz, 1H), 5.33 (d, *J*=4 Hz, 1H), 6.9–7.2 (m, 10H). ^{13}C NMR ($CDCl_3$) δ 11.9, 12.0, 21.8, 23.6, 32.5, 61.8, 72.7, 74.3, 126.4, 126.9, 127.4, 127.8, 130.2, 132.3, 137.3, 141.5.

*3.2.4. (1*R,*2*S*)*-N-*Cyclohexyl*-N-*methyl-2-amino-1,2-diphenylethanol* ***7***

According to the typical procedure given for **5**; 1.18 g (5.53 mmol) (1*R*,2*S*)-2-amino-1,2-diphenylethanol; 651 mg (8.30 mmol) sodium cyanoborohydride; 815 mg (8.30 mmol) cyclohexanone; 22 ml MeOH; reaction time 3 days at r.t.; column chromatography (hexane:EtOAc, 1:1) of the crude product afforded the pure secondary amine (860 mg, 52%) as a colourless oil; 1.4 ml HCOOH, 0.35 ml H_2O, 1.0 ml 37% aq. H_2CO; reaction time 6 h at 100°C; column chromatography (hexane:EtOAc, 2:1) of crude product afforded ligand **7** (770 mg, 45%) as colourless crystals: mp 87–88°C. $[\alpha]_D^{20}$ −74.3 (*c*=0.44, $CHCl_3$). Anal. calcd for $C_{21}H_{27}NO$: C, 81.51; H, 8.79; N, 4.53. Found: C, 81.43; H, 8.80; N, 4.68. IR (KBr) 3200–3700, 2937, 2857, 2783, 1451, 1339, 1198, 1088, 1061, 1052, 1030, 1020, 771, 751, 705 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.9–1.8 (m, 10H), 2.40 (s, 3H), 2,65 (tt, *J*=12 Hz, 3 Hz, 1H), 2.74 (d, *J*=5 Hz, 1H), 5.29 (d, *J*=5 Hz, 1H), 6.9–7.2 (m, 10H). ^{13}C NMR ($CDCl_3$) δ 26.3, 26.6, 26.7, 27.4, 34.2, 59.0, 72.6, 73.7, 126.5, 126.9, 127.4, 127.8, 129.9, 137.6, 141.8.

*3.2.5. (1*R,*2*S*)*-N-*Cyclopentyl*-N-*methyl-2-amino-1,2-diphenylethanol* ***8***

According to the typical procedure given for **5**; 1.18 g (5.53 mmol) (1*R*,2*S*)-2-amino-1,2-diphenylethanol; 651 mg (8.30 mmol) sodium cyanoborohydride; 698 mg (8.30 mmol) cyclopentanone; 22 ml MeOH; reaction time 3 days at r.t.; column chromatography (hexane:EtOAc, 1:1) of the crude product afforded the pure secondary amine (1.02 g, 62%) as a colourless oil; 0.8 ml HCOOH, 0.2 ml H_2O, 0.6 ml 37% aq. H_2CO; reaction time 6 h at 100°C; column chromatography (hexane:EtOAc, 2:1) of crude product afforded ligand **8** (652 mg, 40%) as colourless crystals: mp 84–85°C. $[\alpha]_D^{20}$ −36.1 (*c*=1.46, $CHCl_3$). Anal. calcd for $C_{20}H_{25}NO$: C, 81.31; H, 8.53; N, 4.74. Found: C, 81.02; H, 8.84; N, 4.85. IR (KBr) 3000–3600, 3029, 3088, 2964, 2866, 2804, 1492, 1453, 1088, 1060, 1019, 781, 753, 710, 699, 608 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.3–1.8 (m, 8H), 2.28 (s, 3H), 3.1–3.2 (m, 1H), 3.69 (d, *J*=6 Hz, 1H), 5.33 (d, *J*=6 Hz, 1H), 7.0–7.2 (m, 10H). ^{13}C NMR ($CDCl_3$) δ 24.6, 24.7, 26.7, 34.4, 62.6, 73.1, 74.2, 126.8, 127.2, 127.6, 127.9, 128.0, 128.2, 130.0, 137.0, 142.3.

*3.2.6. (1*R,*2*S*)*-N-*(2-Morpholinoethyl)*-N-*methyl-2-amino-1,2-diphenylethanol* ***9***

A suspension of commercially available (1*R*,2*S*)-2-amino-1,2-diphenylethanol (799 mg, 3.75 mmol), *N*-(2-chloroethyl)-morpholine hydrochloride (837 mg, 4.50 mmol) and K_2CO_3 (1.04 g, 7.50 mmol) in

EtOH (10 ml) was heated under reflux for 18 h. The mixture was filtered and concentrated in vacuo to leave 2.33 g of a colourless oil which was purified by column chromatography (EtOAc+5% NEt_3). The pure secondary amine (1.01 g, 83%) was dissolved in 98% HCOOH (8.0 ml) and H_2O (1.8 ml). The reaction mixture was heated under reflux, 37% aq. H_2CO was added (6.0 ml) and stirring was continued for 18 h. The mixture was cooled and made alkaline with 2 N NaOH followed by extraction with EtOAc (3×10 ml). The combined organic layers were dried over Na_2SO_4 and evaporated. Purification of the crude product by column chromatography (EtOAc+5% NEt_3) afforded ligand **9** (676 mg, 54%) as a colourless oil. $[\alpha]_D^{20}$ −20.6 (*c*=0.33, $CHCl_3$). Anal. calcd for $C_{21}H_{28}N_2O_2$: C, 74.08; H, 8.29; N, 8.23. Found: C, 73.80; H, 8.12; N, 8.21. IR (KBr) 3200–3400, 2967, 2948, 2852, 2812, 1448, 1385, 1118, 1032, 1010, 867, 766, 749, 707, 700, 652 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.34 (s, 3H), 2.4–2.9 (m, 8H), 3.56 (d, *J*=5 Hz, 1H), 3.65–3.75 (m, 4H), 5.36 (d, *J*=5 Hz, 1H), 7.0–7.2 (m, 10H). ^{13}C NMR ($CDCl_3$) δ 35.6, 53.6, 54.1, 58.1 67.5, 73.3, 74.5, 126.9, 127.5, 127.6, 127.9, 128.1, 128.3, 130.4, 136.8, 144.0.

3.3. General procedure for the enantioselective addition of organolithium reagents to aldehydes

A 25 ml flask, purged with Ar, was charged with a solution of the ligand (0.5 mmol) in dry THF (10 ml). At 0°C a solution of the organolithium reagent (1.0 mmol) was added and the resulting solution was cooled down to −78°C. Afterwards, the aldehyde (0.5 mmol) was added via syringe and stirring was continued for 1 h. The reaction mixture was quenched by addition of 1 M HCl (5 ml) and EtOAc (10 ml). Afterwards the organic layer was separated and the aqueous layer was extracted with EtOAc (3×10 ml). The extracts were dried over Na_2SO_4 and concentrated under reduced pressure. Preparative TLC (hexane:EtOAc, 9:1) of the residue afforded the *sec*-alcohol as chromatographically homogenous material. The enantiomeric composition was determined on a chiral HPLC column (Chiracel OD).[8]

Acknowledgements

We are grateful to Dr. N. Djordjevic and Mr. F. Houdière for carrying out the HPLC analysis.

References

1. (a) Tomioka, K. *Synthesis* **1990**, 541–549. (b) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49–70. (c) Devant, R. M.; Radunz, H.-E. In *Houben-Weyl — Methods of Organic Chemistry*; Helmchen, G.; Hoffmann, R. W.; Mulzer, J.; Schaumann, E., Eds; Thieme: Stuttgart, 1995; Vol. E21b, pp. 1151–1334. (d) Huryn, D. M. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds; Pergamon: New York, 1991; Vol. 1, pp. 70–75.
2. Important contributions in the field of enantioselective addition reactions of organolithium reagents: (a) Mukaiyama, T.; Soai, K.; Sato, T.; Shimizu, H.; Suzuki, K. *J. Am. Chem. Soc*. **1979**, *101*, 1455–1460. (b) Mazaeyrat, J. P.; Cram, D. J. *J. Am. Chem. Soc.* **1981**, *103*, 4585–4586. (c) Eleved, M. B.; Hogeveen, H. *Tetrahedron Lett*. **1984**, *25*, 5187–5190. (d) Kanoh, S.; Muramoto, H.; Maeda, K.; Kawaguchi, N.; Motoi, M.; Suda, H. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2244–2246. (e) Ye, M.; Lagaraj, S.; Jackman, L. M.; Hillegrass, K.; Hirsh, K. A.; Bollinger, A. M.; Grosz, A. L. *Tetrahedron* **1994**, *50*, 6109–6116. (f) Huffman, M. A.; Yasuda, N.; DeCamp, A. E.; Grabowski, E. J. J. *J. Org. Chem.* **1995**, *60*, 1590–1594. (f) Basu, A.; Beak, P. *J. Am. Chem. Soc*. **1996**, *118*, 1575–1576. (g) Scharpwinkel, K.; Tull, S.; Schäfer, H. J. *Tetrahedron: Asymmetry* **1996**, *7*, 2497–2500. (h) Thompson, A.; Corley, E. G.; Huntington, M. F.; Grabowski, E. J. J.; Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1998**, *120*, 2028–2038.
3. (a) Noyori, R.; Suga, S.; Kawai, K.; Okada, S.; Kitamura, M. *Pure Appl. Chem.* **1988**, *60*, 1597–1606. (b) Seebach, D.; Beck, A. K.; Roggo, S.; Wonnacott, A. *Chem. Ber.* **1985**, *118*, 3673–3682. (c) Reetz, M. T.; Kükenhöhner, T.; Weinig, P. *Tetrahedron Lett*. **1986**, *27*, 5711–5714. (d) Wang, J.-T.; Fan, X.; Feng, X.; Quian, Y.-M. *Synthesis* **1989**, 291–292.
4. (a) Weber, B.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 84–86. (b) Weber, B.; Seebach, D. *Tetrahedron* **1994**, 1341–1344.

5. (a) Oguni, N.; Omi, T.; Yamamoto, Y.; Nakamura, A. *Chem. Lett.* **1983**, 841–842. (b) Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071–6072. (c) Soai, K.; Niwa S. *Chem. Rev.* **1992**, *92*, 833–856. (d) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York; Chapter 5.
6. (a) Dosa, P. I.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 445–446. (b) Ramon, J. D.; Yus, M. *Tetrahedron Lett.* **1998**, *39*, 1239–1242.
7. Noyori, R.; Suga, S.; Kwai, K.; Okada, S.; Kitamura, M.; Oguni, N.; Hayashi, M.; Kaneko, T.; Matsuda, Y. *J. Organomet. Chem.* **1990**, *382*, 19–37.
8. Jiang, Y.-Z.; Qin, Y.; Mi, A.-Q.; Wu, L.-J. *Chin. J. Chem.* **1996**, *14*, 74–79.
9. Soai, K.; Yokoyama, S.; Ebihara, K.; Hayasaka, T. *J. Chem. Soc., Chem. Commun.* **1987**, *22*, 1690–1691.
10. (a) Soai, K.; Yokoyama, S.; Hayasaka, T. *J. Org. Chem.* **1991**, 4264–4268. (b) Niwa, S.; Soai, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 937–943.
11. Thompson, A. S.; Corley, E. G.; Huntington, M. F.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 8937–8940.
12. Soai, K.; Ookawa, A.; Kaba, T.; Ogawa, K. *J. Am. Chem. Soc.* **1987**, *109*, 7111–7115.
13. Lewis, H. L.; Brown, T. L. *J. Am. Chem. Soc.* **1970**, *92*, 4664–4670.
14. (a) McGarrity, J. F.; Ogle, C. A. *J. Am. Chem Soc.* **1985**, *107*, 1805–1810. (b) McGarrity, J. F.; Ogle, C. A.; Brich, Z.; Loosli, H.-R. *J. Am. Chem Soc.* **1985**, *107*, 1810–1815.
15. Nichols, M. A.; McPhail, A. T.; Arnett, E. M. *J. Am. Chem. Soc.* **1991**, *113*, 6222–6233.
16. Ando, A.; Tatematsu, T.; Shioiri, T. *Chem. Pharm. Bull.* **1991**, *39*, 1967–1971.