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Highly enantioselective diethylzinc addition to aldehydes catalyzed by D-glucosamine derivatives

Tomasz Bauer,* Joanna Tarasiuk and Konrad Paśniczek

Department of Chemistry, Warsaw University, Pasteura 1, PL-02-093 Warsaw, Poland

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Abstract—Synthesis of α-hydroxy sulfonamides derived from D-glucosamine and their application as ligands in the titanium tetraisopropoxide-promoted enantioselective addition of diethylzinc to benzaldehyde and selected aromatic and aliphatic aldehydes is presented. The reaction is highly enantioselective and enantiomeric excesses of up to 97% for benzaldehyde and 88% for *n*-hexanal were obtained. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

The enantioselective addition of organometallic reagents to aldehydes is a valuable method for the synthesis of optically active secondary alcohols. Although several efficient catalysts have been developed so far, full optimization of the asymmetric addition of diethylzinc to aldehydes still remains a challenge.

Various types of chiral amino alcohols were developed as chiral ligands for such additions. Since 1986, when DAIB was introduced by Noyori,[1] the number of very useful and efficient dialkylamino alcohols has grown dramatically,[2] and now includes not only dialkylamino alcohols but also amino thiols,[3] oxazolines[4–6] and even diols, such as TADDOLs[7,8] and BINOLs.[9–11] Further progress in enantioselective additions to aldehydes was achieved, when Ohno and co-workers reported diethylzinc additions in the presence of titanium tetraisopropoxide and chiral disulfonamide ligands.[12] Since then, extensive synthetic studies were conducted and α-hydroxy sulfonamides and disulfonamides were proven as very efficient ligands for additions of dialkylzinc reagents.[13–17] Among various amino alcohols used as ligands, derivatives of simple and easily available carbohydrates are only rarely reported,[18,19] and, in our opinion, remain underestimated. We are unaware of any carbohydrate-derived ligand possessing an α-hydroxy sulfonamide functionality.

Herein, we would like to present the application of *N*-tosylated derivatives of D-glucosamine as chiral ligands in the addition of diethylzinc to aldehydes. We have chosen D-glucosamine as an amino alcohol because it is relatively cheap and allows for stereochemical manipulations at stereogenic centers thus allowing the fine-tuning of its asymmetric induction capabilities.

2. Results and discussion

2.1. Synthesis of chiral ligands

Starting from the commercially available D-glucosamine **1**, methyl 2-deoxy-2-*p*-toluenesulfonamido-4,6-*O*-benzylidene-α-D-glucopyranoside **5** was synthesized using known procedures. Thus, D-glucosamine **1** was treated with methyl chloroformate in the presence of base, yielding the corresponding carbamate.[20] The product of this reaction was dissolved in 4% methanolic hydrogen chloride and heated under reflux to give almost exclusively **2** in 61% yield from D-glucosamine. The free hydroxyl groups at C(4) and C(6) (carbohydrate nomenclature) were protected as their benzylidene acetal by treatment with $C_6H_5CH(OMe)_2$ in the presence of a catalytic amount of *p*-toluenesulfonic acid.[21] After crystallization, compound **3** was obtained in 83% yield. Finally, the carbamate protecting group had to be converted to a *p*-toluenesulfonamide. The methyl carbamate appeared to be even more stable than expected and under standard conditions (reflux in 1.2 M aqueous NaOH in 1,4-dioxane) we were able

* Corresponding author. Tel.: (+48-22)-822-02-11, ext. 273; fax: (+48-22)-822-59-96; e-mail: tbauer@chem.uw.edu.pl

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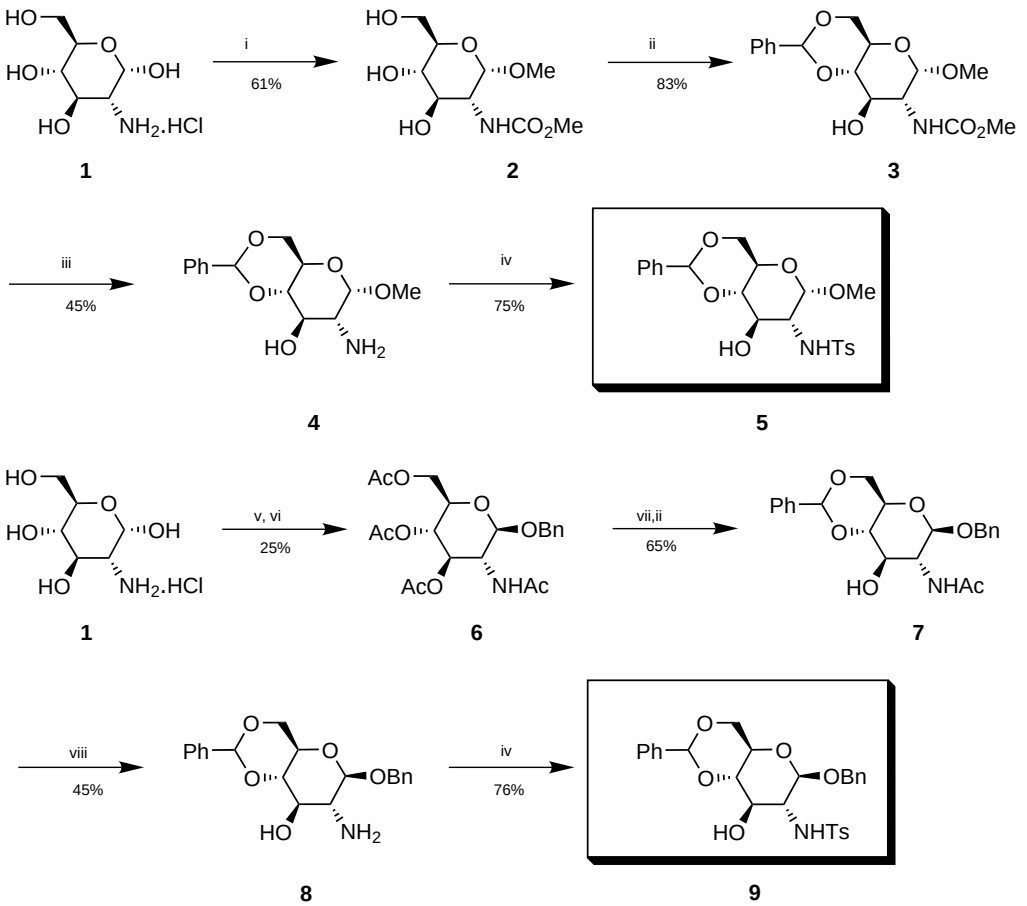
to obtain the free amine **4** only in a very low yield. We tested various reaction conditions and found that the best results can be achieved using 4 M ethanolic KOH in the presence of 2-methoxyethanol.[22,23] Compound **4** was obtained in 45% yield and selective *N*-tosylation gave methyl 2-deoxy-2-*p*-toluenesulfonamido-4,6-*O*-benzylidene-α-D-glucopyranoside **5** in 75% yield (Scheme 1).

The second ligand, the known compound **9** was synthesized in order to evaluate the influence of the configuration at the stereogenic center adjacent to the metal binding amino alcohol. Ligand **9** has β-configuration at the anomeric center, which is opposite to that of compound **5**. D-Glucosamine was peracetylated using acetic anhydride and pyridine and then treated with benzyl alcohol in the presence of tin tetrachloride and 4 Å molecular sieves to give β-benzyl glucopyranoside **6** in 25% yield.[24] The acetate protecting groups were selectively removed using sodium methoxide in methanol and the crude product of the reaction was subjected to benzylidenation as previously described, yielding derivative **7** (65%).[21] Hydrolysis of acetamide **7**, followed by selective *N*-tosylation gave ligand **9** in 76% yield (Scheme 1).[25]

2.2. Enantioselective addition of diethylzinc to benzaldehyde

With ligands **5** and **9** in hand, we studied the influence of the temperature and amount of the catalyst on the enantioselective ethylation of aromatic and aliphatic aldehydes. We started with the most popular model benzaldehyde. The first reaction of diethylzinc (3 equiv.) with benzaldehyde **10** was performed at −20°C in the presence of 0.2 equiv. of ligand **5** and titanium-(IV) isopropoxide (7 equiv.) in methylene chloride. (*R*)-1-Phenyl-1-propanol **11** was obtained in 89% isolated yield and 92% e.e. Repeating the reaction at room temperature afforded the product in 92% isolated yield with 94.7% e.e. Ligand **5** is equally or even more efficient when used in smaller amounts. The best results, as far as chemical yield and enantiomeric excess concerns were obtained when using 0.1 equiv. of **5**, which afforded **11** in 99% yield and with e.e. of 97.0%. Reactions conducted in the presence of 0.05 and 0.025 equiv. of ligand **5** are still highly enantioselective, although in the latter case the yield of the reaction drops significantly. These results place our ligand among the most active α-hydroxy- and disulfonamide catalysts,[13–17] but below the excellent Verdi disulfonamide catalyst, which can be effectively used at levels of



Scheme 1. Synthesis of methyl 2-deoxy-2-*p*-toluenesulfonamido-4,6-*O*-benzylidene-α-D-glucopyranoside **5** and benzyl 2-deoxy-2-*p*-toluenesulfonamido-4,6-*O*-benzylidene-β-D-glucopyranoside **9**. Reaction conditions: (i) Ref. 20; (ii) $PhCH(OMe)_2$, p-$TsOH_{cat}$, DMF; (iii) 4N KOH/EtOH, $MeOCH_2CH_2OH$; (iv) p-TsCl, Na_2CO_3, dioxan–H_2O; (v) Ac_2O/Py; (vi) BnOH, $SnCl_4$, 4 Å MS; (vii) 2N MeONa/MeOH; (viii) 4N KOH, EtOH.

only 0.01 mole equivalents.[15] The product, (*R*)-**11** appears not to be completely stable under the reaction conditions, and prolonged reaction times result in lower yields. We also observed slightly decreased enantioselectivity, which suggest that the (*R*)-enantiomer decomposes faster than the (*S*)-isomer. Finally, we have investigated influence of the configuration at the anomeric center. In the presence of 0.1 equiv. of ligand **9** (*R*)-1-phenyl-1-propanol was obtained in almost quantitative yield, but enantiomeric excess was very low—only 10%. Results of the addition of diethylzinc to benzaldehyde are presented in Table 1.

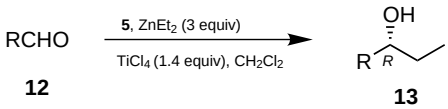
2.3. Enantioselective addition of diethylzinc to some aromatic and aliphatic aldehydes

Taking into account the results presented in Table 1, we carried out diethylzinc additions to some other representative aromatic and aliphatic aldehydes in the presence of ligand **5**. All reactions were performed at ambient temperature in the presence of 0.1 equiv. of chiral ligand using the standard procedure as described for benzaldehyde. As shown in Table 2 reaction of aromatic aldehydes proceeded with high enantioselectivity, (albeit slightly lower than in the case of benzaldehyde). Ethylation of cinnamaldehyde **12c** gave alcohol **13c** with good enantioselectivity (86%). The addition to cycloaliphatic aldehyde **12d** proceeded with much lower induction. Very good enantioselectivity (88% e.e.) was observed for a simple aliphatic aldehyde *n*-hexanal **12c**.

2.4. Mechanistic considerations

The contrasting induction abilities of ligands **5** and **9** call for an explanation. These two ligands differ from each other only by the configuration and substitution at the anomeric center, so this center has to be responsible for such dramatic changes in enantioselectivity. We believe that the type of substitution is less important than the configuration at C(1). Although the exact mechanism of the titanium-promoted addition of diethylzinc to aldehydes is so far unknown, recent structural and mechanistic investigations have shown that the active catalytic intermediate could be an ethyltitanium species derived from the transfer of an ethyl group from zinc to titanium. The catalytic species in our case can also be formed in the way proposed by Paquette et al., where, in the final step of the formation of the reacting species, coordination of aldehyde is concomitant with the migration of the ethyl substituent to an 'apical' position.[15] Thus, a plausible explanation

Table 2. Enantioselective addition of diethylzinc to selected aldehydes catalyzed by ligand **5**



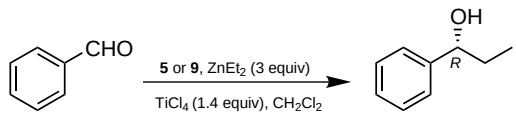
12 **13**

a R=3-ClPh
b R=4-MeOPh
c R=PhCH=CH
d R=*c*-C_6H_{11}
e R=$CH_3(CH_2)_5$

Entry	Aldehyde	Time (h)	Yield[a] (%)	E.e.[b,c] (%)
1	3-Chlorobenzaldehyde **12a**	2.5	85	90 (*R*)
2	4-Methoxybenzaldehyde **12b**	7	95	89 (*R*)
3	*trans*-Cinnamaldehyde **12c**	3	94	86 (*R*)
4	Cyclohexanecarboxaldehyde[d] **12d**	5	73	39 (*R*)
5	Hexanal[d] **12e**	1.5	80	88 (*R*)

[a] Isolated yield.
[b] Determined by HPLC analysis using a Daicel Chiracel OD column.
[c] Configuration of the major enantiomer in parentheses (based on the known elution order).
[d] HPLC analysis of the benzoate.

Table 1. Enantioselective addition of diethylzinc to benzaldehyde catalyzed by ligands **5** and **9**



10 **11**

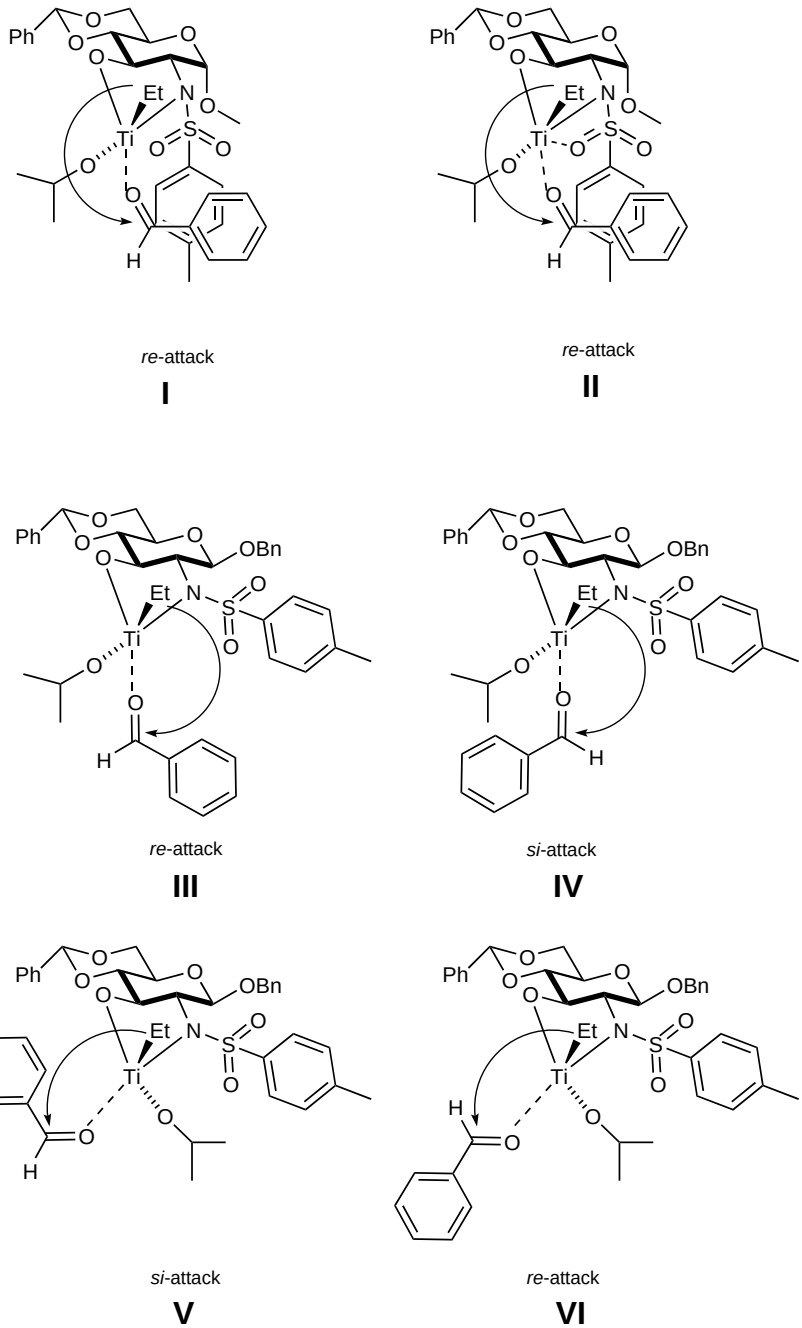
Entry	Ligand	Amount of ligand (equiv.)	Temp. (°C)	Time (h)	Yield[a] (%)	E.e.[b,c] (%)
1	**5**	0.2	−20	24	89	92 (*R*)
2	**5**	0.2	20	3	92	95 (*R*)
3	**5**	0.1	−20	24	81	94 (*R*)
4	**5**	0.1	20	3	99	97 (*R*)
5	**5**	0.1	20	20	97	95 (*R*)
6	**5**	0.05	−20	24	75	89 (*R*)
7	**5**	0.05	20	5	99	95 (*R*)
8	**5**	0.05	20	48	90	93 (*R*)
9	**5**	0.025	20	5	65	95 (*R*)
10	**9**	0.1	20	5	98	10 (*R*)

[a] Isolated yield.
[b] Determined by HPLC analysis using a Daicel Chiracel OD column.
[c] Configuration of the major enantiomer in parentheses.

of the stereochemical outcome of the reaction can be based on model transition states **I**–**VI** depicted at Scheme 2. In ligand **5** the axial methoxy substituent 'pushes' the tosyl group toward titanium. The isopropoxy group takes position in the least crowded environment and benzaldehyde coordinates in-between. Additionally, π-stacking effect of phenyl rings from benzaldehyde and tosyl group can further rigidify the transition state **I**. The low enantioselectivity observed for the cyclohexanecarboxaldehyde **12d** is in good agreement with this assumption. The coordination of titanium to one of the sulfonamide oxygens, as demonstrated by Walsh et al.[17] cannot also be excluded, as shown in model transition state **II**. Ligand **9** at the anomeric center has an equatorial benzyloxy substituent, which is located in a space remote from the reacting center. It allows for at least four possible transition states **III**–**VI** and seems to be the main cause of the low levels of asymmetric induction observed for ligand **9**.

3. Conclusions

We have presented synthesis of methyl 2-deoxy-2-*p*-toluenesulfonamido-4,6-*O*-benzylidene-α-D-glucopyran-



Scheme 2. Stereochemical models for an ethylation of benzaldehyde.

oside **5** and its application as chiral ligand in titanium promoted enantioselective diethylzinc addition to aromatic and aliphatic aldehydes. To the best of our knowledge, we have reported the first example of diethylzinc addition to aldehydes catalyzed by a carbohydrate derivative possessing an α-hydroxy sulfonamide functionality. We have shown that addition to both aromatic and aliphatic, but not cycloaliphatic aldehydes proceeds with high yield and enantioselectivity even with 0.1 equiv. of our ligand. Investigations aimed at defining the utility of this new ligand for other substrates and reactions are in progress.

4. Experimental

4.1. General

Melting points were determined using a Kofler hot stage apparatus and are uncorrected. Optical rotations were recorded using a Perkin–Elmer PE-241 polarimeter with a thermally jacketed 10-cm cell. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using a Varian 200 Unity Plus and Varian 500 Unity Plus spectrometers. All chemical shifts are quoted in parts per million relative to tetramethylsilane (δ, 0.00 ppm), and coupling constants (J) are measured in hertz. Reactions were carried using the Schlenk technique under argon when necessary. Flash column chromatography was completed using silica gel (Kieselgel-60, Merck, 230–400 mesh).

4.2. Preparation of methyl 2-deoxy-2-*p*-toluenesulfonamido-4,6-*O*-benzylidene-α-D-glucopyranoside 5

4.2.1. Methyl 4,6-*O*-benzylidene-2-deoxy-2-metoxycarbonylamido-α-D-glucopyranoside 3. To the methyl 2-deoxy-2-metoxycarbonylamido-α-D-glucopyranoside **2** (5.1 g, 20 mmol), dissolved in anhydrous DMF (100 mL) was added benzaldehyde dimethyl acetal (6 mL, 60 mmol) and catalytic amount of *p*-toluenesulfonic acid. Ethyl acetate (200 mL) was added and the solution was washed with water (3×100 mL), dried over anhydrous $MgSO_4$, filtered and evaporated. The residue was crystallized from MeOH–Et_2O to give **3** (5.6 g, 83%) Mp 214–216°C. ^{1}H NMR (200 MHz): 7.50–7.25 (m, 5H, Ph), 5.60 (s, 1H, C*H*Ph), 5.20 (d, 1H, N*H*), 4.75 (d, $J_{1,2}=2.6$, 1H, H-1), 4.30 (m, 1H, H-6$_e$), 4.95–4.85 (m, 4H, H-6$_a$, H-2, H-3, H-4), 4.85 (s, 3H, COOCH_3), 4.60–4.45 (m, 1H, H-5), 3.40 (s, 3H, OCH_3), 3.00 (d, 1H, O*H*). ^{13}C NMR (50 MHz): 161.8 (C=O) 136.9, 129.2, 129.2, 128.2, 126.29, 126.23, 101.9 (Ph*C*H), 99.1 (C1), 81.87, 81.82, 76.2 (*C*NH), 68.9 (*C*HOH), 62.3 (C6), 55.4 (anomeric OCH_3), 52.5 (ester OCH_3). $[\alpha]_D$ +41.5 (*c* 1.13, $CHCl_3$).

4.2.2. Methyl 4,6-*O*-benzylidene-2-deoxy-2-amino-α-D-glucopyranoside 4. Compound **3** (5.05 g, 15 mmol) was added to 4 M KOH solution in EtOH–$MeOCH_2CH_2OH$ 10:1 v/v and the mixture was heated under reflux for 14 h. The reaction mixture was cooled to room temperature and acidified to pH 8 using cold 1N HCl and the volatiles were removed using rotatory evaporator. Water (50 mL) was added to the residue and the solution was extracted with chloroform (5×20 mL). The combined organic extracts were washed with water, brine and dried over anhydrous $MgSO_4$. Crude product was purified by flash chromatography to afford **4** (yield 1.8 g, 45%) which was subjected to the next step. Mp 174–177°C. ^{1}H NMR (200 MHz): 7.60–7.25 (m, 5H, Ph), 5.50 (s, 1H, C*H*Ph), 4.70 (d, $J_{1,2}=3.6$, 1H, H-1), 4.20 (m, 1H, H-6$_e$), 3.80–3.60 (m, 3H, H-6$_a$, H-2, H-4), 3.50–3.40 (m, 2H, H-3, H-5), 3.40 (s, 3H, OCH_3), 2.80 (d, 1H, O*H*). ^{13}C NMR (50 MHz): 137.2, 129.2, 128.3, 126.2, 101.9 (Ph*C*H), 101.1 (C1), 82.1, 71.7, 69.1, 62.5 (C6), 56.6, 55.4 (anomeric O*C*H_3). $[\alpha]_D$ +105.2 (*c* 0.73, $CHCl_3$).

4.2.3. Methyl 4,6-*O*-benzylidene-2-deoxy-2-*p*-toluenesulfonamido-α-D-glucopyranoside 5. To a solution of **4** (3.0 g, 8.84 mmol) and Na_2CO_3 (1.28 g, 12.0 mmol) in 1:1 water–dioxan (60 mL) *p*-TsCl (2.3 g, 12.0 mmol) was added, and the mixture was stirred for 3.5 h at 5°C. Solvents were then evaporated in vacuo and the solid residue was extracted with chloroform, the organic phases were washed with water, brine and dried over anhydrous $MgSO_4$. After filtration and evaporation crude **5** was purified by flash chromatography (EtOAc–hexane 3:7 v/v) to give pure **5** (3.48 g, 8.8 mmol, 75%). Mp 187–189°C. ^{1}H NMR (200 MHz): 7.85–7.40 (dd, 4H, *Ph*CH_3), 7.40–7.20 (m, 5H, Ph), 5.50 (s, 1H, C*H*Ph), 5.10 (d, 1H, N*H*), 4.40 (d, $J_{1,2}=4$, 1H, H-1), 4.25 (m, 1H, H-6$_e$), 3.85–3.60 (m, 3H, H-6$_a$, H-2, H-4), 3.55–3.25 (m, 2H, H-3, H-5), 3.20 (s, 3H, OCH_3), 2.60 (d, 1H, O*H*), 2.40 (s, 3H, CH_3). ^{13}C NMR (50 MHz): 143.9, 137.5, 136.9, 129.8, 129.2, 128.2, 127.1, 126.2, 101.9 (PhCH), 98.7 (C1), 81.2, 69.4, 68.7, 62.1 (C6), 58.2, 55.5 (C2), 21.5 (CH_3). $[\alpha]_D$ +34.4 (*c* 0.77, $CHCl_3$). Elemental analysis found: C, 57.92; H, 5.79; N, 3.22; S, 7.36. $C_{21}H_{25}NO_7S$ requires C, 57.99; H, 6.13; N, 2.77; S, 7.43.

4.3. Typical procedure for diethylzinc addition reactions

To a solution of ligand **5** (43.5 mg, 0.1 mmol) in methylene chloride (5 mL) was added titanium tetraisopropoxide (0.42 mL, 1.4 mmol). The mixture was stirred for 1 h at room temperature, cooled to –78°C, and diethylzinc (1.1 M toluene solution, 0.27 mL, 3 mmol) was added. Stirring was continued at this temperature, and freshly distilled benzaldehyde (0.1 mL, 1 mmol) was added. The mixture was allowed to warm to room temperature and stirred for the time indicated in Table 1. The reaction was quenched with 1N HCl (10 mL), and insolubles were filtered off. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3×5 mL). The combined organic extracts were washed with brine, dried over $MgSO_{4anh}$ and purified by flash chromatography (hexane–ethyl acetate 5:1 v/v) to give (*R*)-1-phenylpropanol. Yield 135 mg; 99%. This product was subjected to HPLC analysis using a Chiracel OD column (3% 2-propanol in hexane).

Acknowledgements

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References

1. Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071–6072.
2. For reviews see: (a) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833–856; (b) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757–824.
3. Kang, J.; Kim, D. S.; Kim, J. I. *Synlett* **1994**, 842–844.
4. Falorni, M.; Collu, C.; Conti, S.; Giacomelli, G. *Tetrahedron: Asymmetry* **1996**, *7*, 293–299.
5. Aurich, H. G.; Biesemeier, F.; Geiger, M.; Harms, K. *Liebiegs Ann./Recl.* **1997**, 423.
6. Seebach, D.; Pichota, A.; Beck, A. K.; Pinkerton, A. B.; Litz, T.; Karjalainen, J.; Gramlich, V. *Org. Lett.* **1999**, *1*, 55–58.
7. Schmidt, B.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 99–101.
8. Ito, Y. N.; Ariza, X.; Beck, A. K.; Bohac, A.; Ganter, C.; Gawley, R. E.; Kuehnle, F. N.; Tuleja, J.; Wang, J. M.; Seebach, D. *Helv. Chim. Acta* **1994**, *77*, 2071–2210.
9. Mori, M.; Nakai, T. *Tetrahedron Lett.* **1997**, *38*, 6233–6236.
10. Zhang, F.-Y.; Yip, C.-W.; Cao, R.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1997**, *8*, 585–589.
11. Kitajima, H.; Aoki, Y.; Katsuki, T. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 207–217.
12. Takahashi, H.; Kawakita, T.; Ohno, M.; Yoshioka, M.; Kobayashi, S. *Tetrahedron* **1992**, *48*, 5691–5700.
13. Knochel, P.; Perea, J.; Almena, J.; Jones, P. *Tetrahedron* **1998**, *54*, 8275–8319.
14. Hwang, C.-D.; Uang, B.-J. *Tetrahedron: Asymmetry* **1998**, *9*, 3979–3984.
15. Paquette, L. A.; Zhou, R. *J. Org. Chem.* **1999**, *64*, 7929–7934.
16. Ito, K.; Kimura, Y.; Okamura, H.; Katsuki, T. *Synlett* **1992**, 573–574.
17. Royo, E.; Betancort, J. M.; Davis, T. J.; Caroll, P.; Walsh, P. J. *Organometallics* **2000**, *19*, 4840–4851 and references cited therein.
18. Cho, B. T.; Chun, Y. S.; Yang, W. K. *Tetrahedron: Asymmetry* **2000**, *11*, 2149–2157 and references cited therein.
19. Cho, B. T.; Kim, N. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2901–2907.
20. Ikeda, D.; Tsuchiya, T.; Umezawa, S. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 2529–2537.
21. Takahashi, S.; Terayama, H.; Kuzuhara, H. *Tetrahedron Lett.* **1991**, *32*, 5123–5126.
22. Miyake, T.; Tsuchiya, T.; Takahoshi, Y.; Umezawa, S. *Carbohydr. Res.* **1981**, *89*, 255–270.
23. Kobayashi, Y.; Tsuchiya, T.; Ohgi, T.; Taneichi, N.; Koyama, Y. *Carbohydr. Res.* **1992**, *230*, 89–106.
24. Aguilera, B.; Fernandes-Mayoralas, A.; Jaramillo, C. *Tetrahedron* **1997**, *53*, 5863–5876.
25. Gross, P. H.; Jeanloz, R. W. *J. Org. Chem.* **1967**, *32*, 2759–2763.