2-Amino-1,2,2-triphenylethanol: A Novel Chiral Reagent Containing the Diphenylaminomethyl Group. Enantioselective Addition of Diethylzinc to Benzaldehyde

Ralf Fleischer and Manfred Braun*

Institut für Organische und Makromolekulare Chemie, Universität Düsseldorf, Universitätsstraße 1, D-40225 Düsseldorf, Germany

Fax: +49 211 81 13085; E-mail: braunm@uni-duesseldorf.de

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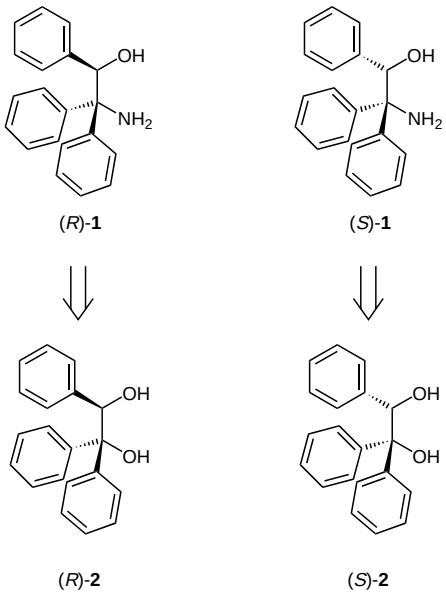
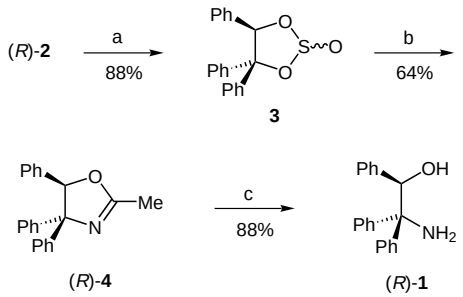
Abstract: The novel chiral amino alcohols (*R*)- and (*S*)-**1** are prepared from the corresponding enantiomer of ethanediol **2**. Alkoxytitanium complexes of the imines **8** derived from **1** are suitable to catalyze the addition of diethylzinc to benzaldehyde in up to 92% *e.e*.

In recent developments of asymmetric synthesis, the structural unit of the diarylhydroxymethyl group was frequently applied, not only in covalently bound chiral auxiliary reagents, but also in ligands and catalysts.[1] It led to an enhancement of stereoselectivity in many cases, although it is not a stereogenic group. After the application of the diarylhydroxymethyl motif in TADDOLs[2] and triphenylglycol-derived carboxylic esters,[3] it was also used in β-amino alcohols, most of which are based on valine and proline.[4] In this communication, we present a new chiral auxiliary reagent, (*R*)- and (*S*)-2-amino-1,2,2-triphenylethanol **1**, which contains the diphenyl*amino*methyl moiety, hitherto unexplored in asymmetric syntheses. The preparation and the first application of the novel reagent **1** in enantioselective additions of diethylzinc are reported.



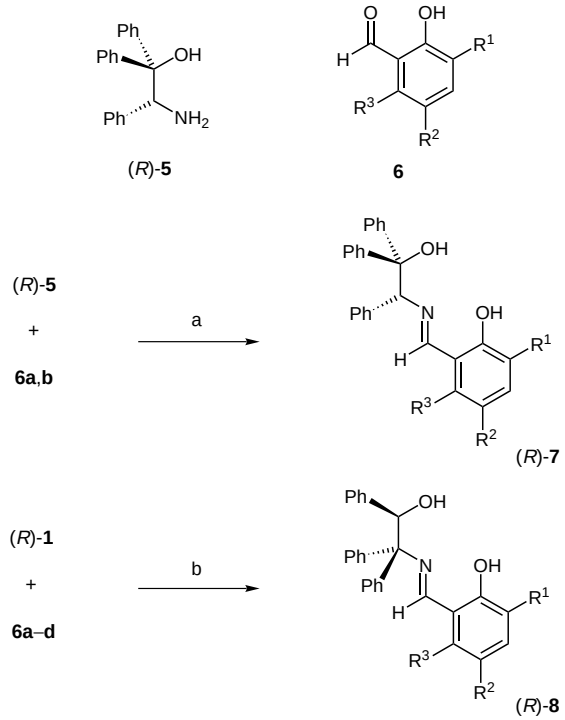
Scheme 1

(*R*)- and (*S*)-triphenylglycol **2**, readily available from the corresponding enantiomers of mandelic acid,[3,5] were chosen as starting materials for the amino alcohols (*R*)- and (*S*)-**1**, respectively. As described recently,[6] the cyclic sulfite **3** was generated from the diol (*R*)-**2** by treatment with thionyl chloride in the presence of triethylamine. Although the pure R_C,S_S stereoisomer can be readily isolated, the diastereomeric mixture of **3** was used in the following step: in an unprecedented variant of the Ritter reaction, the sulfite **3** delivered the oxazoline **4** upon treatment with triflic acid in acetonitrile.[7,8] Finally, the amino alcohol (*R*)-**1** was liberated from the oxazoline (*R*)-**4** by methanolysis in the presence of sulfuric acid, whereas (*S*)-**1** was prepared from (*S*)-oxazoline **4** by the same protocol (Scheme 2).[9]



Reagents and conditions: a) Ref. 6. b) CH_3CN (1.5 ml/mmol), TfOH (2.0 equiv.), –10°C → rt, 16 h. c) conc. H_2SO_4 (12% in MeOH), reflux, 10 d.

Scheme2



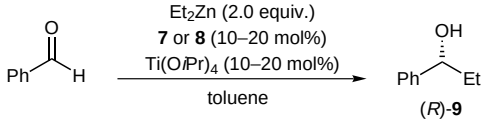
			R^1	R^2	R^3
6a	**7a**	**8a**	H	C_4H_4	
6b	**7b**	**8b**	*t*-Bu	H	H
6c		**8c**	*t*-Bu	*t*-Bu	H
6d		**8d**	*t*-Bu	OMe	H

Reagents and conditions: a) Ref. 14. b) Na_2SO_4, $MeOH/CH_2Cl_2$, 60°C, 12–20 h (**8a**–**c**); –20°C → rt, 48 h (**8d**).

Scheme 3

The phenylglycine-derived amino alcohol **5**,[10] obviously a regioisomer of reagent **1**, was used in enantioselective ketone reductions[11] and allylic oxidations[12] previously. When the regioisomers **1** and **5** were condensed with phenolic aldehydes **6**,[13] the imines **7** and **8** resulted.

Titanium complexes derived from ligands **7** were recently isolated and characterized.[14] In order to compare the efficiency of the regioisomeric chiral auxiliaries **1** and **5**, titanium complexes were generated from their imines **7** and **8** by treatment with titanium tetraisopropoxide followed by evaporation of 2-propanol. The catalysts formed thereby were used in the addition of diethylzinc to benzaldehyde,[15] a conversion previously not mediated by imine-alkoxytitanium complexes.[16] The enantiomeric excess of the alcohol **9** obtained thereby was determined by ^{1}H NMR analysis of the corresponding Mosher ester.[17] The titanium complexes derived from **7** and **8**, respectively, were used in amounts of 10 to 20 mole percent.



Scheme 4

Table 1. Addition of Diethylzinc to Benzaldehyde, Catalyzed by Imines **7**/**8** and Ti(O*i*-Pr)$_4$

Entry	Imine	**9**		
		Yield (%)	*e.e.* (%)	configuration
1	(*R*)-**7a**[a]	87	21	*R*
2	(*R*)-**7b**[a]	73	58	*R*
3	(*R*)-**8a**[a]	96	42	*R*
4	(*R*)-**8b**[a]	100	82	*R*
5	(*R*)-**8c**[b]	100	79	*R*
6	(*S*)-**8d**[b]	100	92	*S*

a) 20 mol% imine/Ti(O*i*-Pr)$_4$, 0°C, 16–24 h. b) 10 mol% imine/Ti(O*i*-Pr)$_4$, –20°C → –10°C, 12–15 h

As shown in Table 1, only moderate enantioselectivities were obtained with the phenylglycine-derived imines **7** (entries 1 and 2). A significant improvement was brought about when the chiral ligands **8** formed from the amino alcohol **1** were used (entries 3-5). Furthermore, a *t*-butyl group in *ortho* position to the phenol residue turned out to be crucial for enantioselectivity. A final improvement came from the introduction of a methoxy substituent in *para* position to the phenolic group in the imine **8d**. The electronic effect of that substituent[18] provided an *e.e.* of 92% in the diethylzinc addition (entry 6). Thus, the enantioselectivity relies mainly on the stereogenic center bearing a hydroxy rather than an amino group,[15e,19] so that the novel amino alcohol **1**[20] proved itself to be superior to the regioisomeric compound **5**. The role the diarylaminomethyl group may play in asymmetric synthesis remains to be determined by further investigations.

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(20) Selected data of (*S*)-**1**: white solid; m.p. 152–153.5°C; $[\alpha]_D^{20}$ = -219 (*c* = 1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ = 1.90 (br. s, 2 H, NH_2), 3.25 (br. s, 1 H, OH), 5.58 (s, 1 H, 1-H), 6.86–6.88 (m, 2 H, aromatic H), 7.06–7.32 (m, 11 H, aromatic H), 7.55–7.57 (m, 2 H, aromatic H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 65.6 (C-2), 77.4 (C-1), 126.4–128.2 (aromatic C), 139.7, 145.3, 145.8 (aromatic *ipso*-C); FAB-MS (NBA), *m*/z: 290 [M^+ + 1], 289 [M^+], 273 [$Ph_2C(OH)CHPh$], 272 [triphenyloxirane], 256 [Ph_2CCHPh], 183, 182 [$Ph_2C(NH_2)$], 167 [Ph_2CH], 165 [fluorenyl cation], 154, 107 [PhCH(OH)], 106, 105 [$PhC(NH_2)$ and/or PhCO], 104 [PhC(NH)], 77, 51; $C_{20}H_{19}NO$ (289.4): calcd. C 83.01, H 6.62, N 4.84; found C 83.16, H 6.73, N 4.69.