[27] The catalytic rate (R) of the oxidation of benzyl alcohol was expressed by $R = k_2[C]/\{1 + k_2/(k_1[A])\}$, where [C] and [A] are the amount of Ru/Al_2O_3 and the concentration of benzyl alcohol, respectively, and k_1 and k_2 are the rate constants for step 1 and step 2, respectively, and at 356 K these were 38 $h^{-1}g^{-1}$ and 42 M $h^{-1}g^{-1}$, respectively.
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Direct Asymmetric Aldol Reactions of Glycine Schiff Base with Aldehydes Catalyzed by Chiral Quaternary Ammonium Salts**

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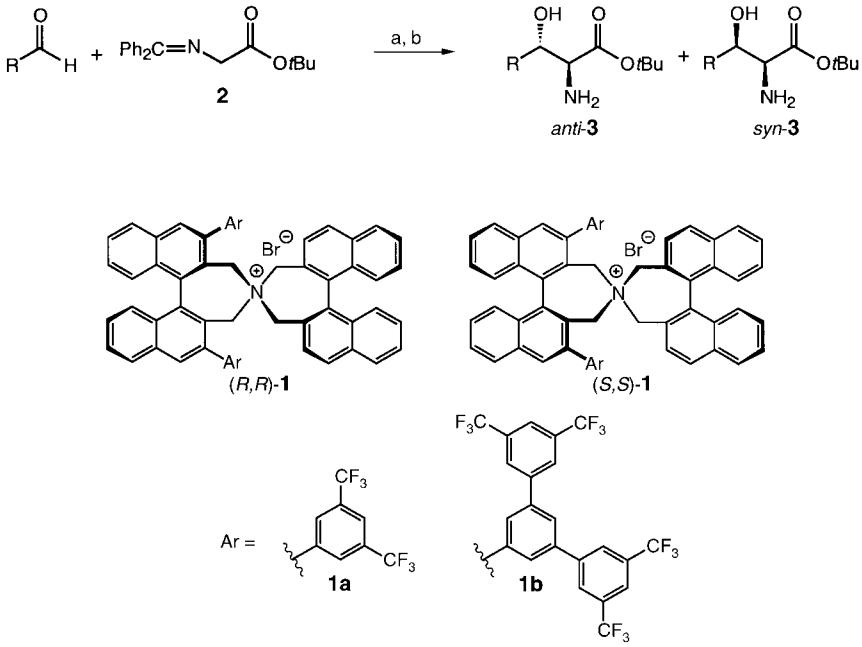
As naturally occurring α-amino acids as well as components of many complex biologically active cyclic peptides and enzyme inhibitors, optically active β-hydroxy-α-amino acids are extremely important chiral units, especially from the pharmaceutical viewpoint.[1] Furthermore, they are useful chiral building blocks in organic synthesis[2] as exemplified by their transformation into β-lactams,[3] β-halo-α-amino acids,[4] and aziridines.[5] Accordingly, numerous methods for the asymmetric synthesis of β-hydroxy-α-amino acids have been elaborated, most of which unfortunately involve multistep procedures and/or the inevitable use of a stoichiometric amount of chiral auxiliaries.[6–8] In this regard, the construction of their primary structure with the correct stereochemistry by the direct catalytic asymmetric aldol reaction of a glycine donor with aldehyde acceptors has been considered to be an ideal protocol.[9] However, there have been few successful examples to date,[10,11] except for the chemoenzymatic process with glycine-dependent aldolases.[9b,12] We report herein an efficient and direct asymmetric aldol reaction of glycine Schiff base **2**[13] with aldehydes under organic/aqueous biphasic conditions by using enantiomerically pure, C_2-symmetric chiral quaternary ammonium salt **1**[14] as a phase-transfer catalyst (Scheme 1). This approach provides a practical and environmentally benign chemical process for the synthesis of optically active β-hydroxy-α-amino acids.

Initially, we examined the direct asymmetric aldol reaction of prochiral glycine Schiff base **2** and 3-phenylpropanal as a representative acceptor under phase-transfer conditions. Thorough optimization of the catalyst structure and reaction conditions revealed that treatment of **2** with 3-phenylpropanal (2 equiv) in toluene/aqueous NaOH (1%) (*v*/*v* 1.25:1; 2 equiv of base for **2**) in the presence of chiral quaternary ammonium salt (*R*,*R*)-**1a** (2 mol%)[14d] at 0°C for 2 h and subsequent hydrolysis with HCl (1N) in THF resulted in the formation of the corresponding β-hydroxy-α-amino ester **3** (R = $PhCH_2CH_2$) in 76% yield with the *anti*/*syn* ratio of 3.3:1. The enantiomeric excess of the major *anti* isomer was determined to be 91% by chiral HPLC analysis (Table 1, entry 1). Significantly, use of (*R*,*R*)-**1b** (which contains a 3,5-bis(3,5-bis(trifluoromethyl)phenyl)phenyl substituent) as a catalyst enhanced both diastereo- and enantioselectivities in this system (*anti*/*syn* 12:1; 96% *ee* for *anti* isomer) (Table 1, entry 2).[15]



Scheme 1. Direct catalytic asymmetric aldol reaction of glycine Schiff base **2** with aldehydes in the presence of **1** under phase-transfer conditions. a) (*R*,*R*)-**1** (2 mol%), toluene/aqueous NaOH (1%), 0°C, 2 h; b) HCl (1N)/THF.

A variety of aldehydes were examined for this direct asymmetric aldol reaction with (*R*,*R*)-**1** and the results are listed in Table 1. Generally, the reaction proceeded smoothly at 0°C for 2 h to afford the *anti* isomer predominantly, with excellent enantioselectivity. Heptanal, an aliphatic aldehyde with a long hydrocarbon chain, was found to be a good candidate (Table 1, entry 3), thus indicating the feasibility of direct asymmetric synthesis of a variety of lipo β-hydroxy-α-amino acids, a useful component for the preparation of lipophilic peptides and glycopeptides with characteristic high

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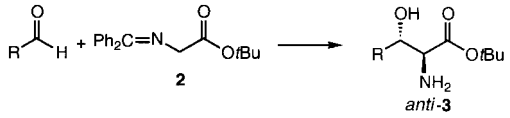
Table 1. Direct asymmetric aldol reactions of **2** with aldehydes by chiral phase-transfer catalysis of **1**.[a]



Entry	R	Catalyst	Yield [%][b]	*anti*/*syn*[c]	*ee* [%][d]
1	$PhCH_2CH_2$	**1a**	76	3.3:1	91
2	$PhCH_2CH_2$	**1b**	71	12:1	96
3	$CH_3(CH_2)_4CH_2$	**1b**	65	10:1	91
4	iPr_3SiOCH_2	**1b**	72	20:1	98
5	CH_2=$CHCH_2CH_2$	**1b**	62	6.3:1	80
6	CH_2=$CHCH_2CH_2$	**1a**	71	2.4:1	90
7	CH_3	**1a**	58	2.3:1	92[e]
8	*c*-C_6H_{11}	**1a**	40	2.8:1	95
9	*c*-C_6H_{11}	**1a**	78	1.2:1	93[f]

[a] Unless otherwise specified, the reaction was carried out with 2 equiv of aldehyde in the presence of (*R*,*R*)-**1** (2 mol%) in toluene/aqueous NaOH (1%) at 0°C for 2 h. [b] Yield of isolated product. [c] Determined by ^{1}H NMR analysis. [d] Enantiomeric excess of *anti*-**3**, which was determined by HPLC analysis of its *N*-benzoate by using a chiral column (DAICEL Chiralcel OD-H) with hexane/2-propanol or hexane/ethanol as solvent. [e] The reaction with (*S*,*S*)-**1a** as catalyst displayed similar reactivity and selectivity. [f] Use of dibutyl ether as solvent.

enzymatic stability and enhanced drug transport activity.[16] The reaction with α-triisopropylsiloxyacetaldehyde cleanly produced the desired β-hydroxy-α-amino ester **3** (R = iPr_3SiOCH_2) in 72% yield with virtually complete stereochemical control (*anti*/*syn* 20:1; 98% *ee*) (Table 1, entry 4), which parallels the L-threonine aldolase catalyzed aldol reaction used for the synthesis of the monobactam antibiotic carunoman and its analogues.[12b] Moreover, a key building block for the synthesis of the carbacephem antibiotic loracarbef, previously prepared by a chemoenzymatic process with serine hydroxymethyltransferase (SHMT),[12f] was readily assembled with 4-pentenal as acceptor; (*R*,*R*)-**1a** resulted in a higher enantioselectivity than did (*R*,*R*)-**1b** (Table 1, entries 5 and 6). We also found that L-*allo*-threonine *tert*-butyl ester can be obtained by the reaction of **2** with acetaldehyde in the presence of (*R*,*R*)-**1a**, which confirmed that the absolute configuration of the newly created α stereocenter is *S* (Table 1, entry 7).[17] This method allows a facile preparation of non-natural D-*allo*-threonine because of the ready availability of the enantiomerically pure catalyst (*S*,*S*)-**1a**. Interestingly, (*R*,*R*)-**1a** was also a suitable catalyst for the reaction with α-substituted aldehydes such as cyclohexanecarbaldehyde as acceptor; to attain sufficient reactivity, dibutyl ether was used as solvent (Table 1, entries 8 and 9).

In summary, the direct asymmetric aldol reaction of glycine Schiff base **2** with aldehyde acceptors proceeds under mild organic/aqueous biphasic conditions with excellent stereochemical control by using chiral quaternary ammonium salts as catalysts. This reaction offers a powerful chemical method for the synthesis of optically active β-hydroxy-α-amino acids, and complements the aldolase-based chemoenzymatic processes. Therefore, the present system can be regarded as an artificial glycine-dependent aldolase; its operational simplicity, environmentally friendly conditions, and suitability for large-scale reaction represent distinct advantages for practical industrial applications.

Experimental Section

Aqueous NaOH (1%; 2.4 mL) was added at 0°C under an argon atmosphere to a solution of *tert*-butyl glycinate benzophenone Schiff base **2** (88.6 mg, 0.3 mmol) and (*R*,*R*)-**1b** (9.9 mg, 2 mol%) in toluene (3.0 mL), and 3-phenylpropanal (79.0 μL, 0.6 mmol) was introduced dropwise. The whole mixture was stirred for 2 h at 0°C, and water and diethyl ether were then added. The ether phase was separated and washed with brine. The organic phase was dried over Na_2SO_4 and concentrated. The crude product was dissolved in THF (8.0 mL) and treated with HCl (1.0 N, 1.0 mL) at 0°C for 1 h. After removal of THF in vacuo, the aqueous solution was washed with diethyl ether three times and neutralized with $NaHCO_3$. The mixture was then extracted with CH_2Cl_2 three times. The combined extracts were dried over $MgSO_4$ and concentrated. Purification of the residue by column chromatography on silica gel with MeOH/CH_2Cl_2 (1:15) as eluent afforded the corresponding β-hydroxy-α-amino ester **3** (R = $PhCH_2CH_2$) (56.8 mg, 0.214 mmol, 71%, *anti*/*syn* 12:1). *anti*-**3** (R = $PhCH_2CH_2$): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.26 (m, 2H; Ph), 7.22–7.16 (m, 3H; Ph), 3.77 (ddd, *J* = 3.2, 4.4, 10.0 Hz, 1H; C*H*OH), 3.47 (d, *J* = 4.4 Hz, 1H; C*H*NH_2), 2.91–2.84 (ddd, *J* = 4.8, 9.2, 13.6 Hz, 1H; PhCH), 2.73–2.65 (ddd, *J* = 8.0, 8.0, 13.6 Hz, 1H; PhCH), 1.85 (br s, 3H; OH and NH_2), 1.75–1.65 (m, 1H; $PhCH_2CH$), 1.62–1.53 (m, 1H; $PhCH_2CH$), 1.41 ppm (s, 9H; *t*Bu). *syn*-**3** (R = $PhCH_2CH_2$): δ = 7.29–7.25 (m, 2H; Ph), 7.22–7.16 (m, 3H; Ph), 3.70 (ddd, *J* = 4.8, 5.2, 7.6 Hz, 1H; C*H*OH), 3.24 (d, *J* = 5.2 Hz, 1H; C*H*NH_2), 2.90–2.82 (ddd, *J* = 6.2, 9.0, 13.6 Hz, 1H; PhCH), 2.74–2.67 (ddd, *J* = 7.2, 8.8, 13.6 Hz, 1H; PhCH), 2.17 (br s, 3H; OH and NH_2), 1.85–1.78 (m, 2H; $PhCH_2CH_2$), 1.46 ppm (s, 9H; *t*Bu). The enantiomeric excess of the major *anti* isomer was determined to be 96% by HPLC analysis of its *N*-benzoate: chiral column, DAICEL Chiralcel OD-H, hexane/2-propanol (20:1), flow rate = 0.5 mL min^{-1}, retention times 23.06 min (minor) and 39.79 min (major).

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The Absolute Configuration of Bromochlorofluoromethane**

Prasad L. Polavarapu*

Bromochlorofluoromethane is the simplest chiral molecule that is used as an example to illustrate chirality or asymmetric carbon atoms, yet its absolute configuration remains uncertain. The synthesis of bromochlorofluoromethane in a pure form was achieved by Berry and Sturtevant in 1942.[1] They determined its boiling point, melting point, and refractive dispersion, but the individual enantiomers were not resolved. Despite the unavailability of enantiomers and their optical rotation values, Brewster hypothesized that (*S*)-bromochlorofluoromethane would have positive optical rotation, assuming that the polarizabilities decrease in the order Br > Cl > H > F.[2] Hargreaves and Modarai were able to resolve the enantiomers of 1-bromo-1-chloro-1-fluoroacetone and convert them into the corresponding bromochlorofluoromethane enantiomers.[3] They reported the specific rotations to be +0.20 and −0.13. In 1973 Applequist predicted, using an atom–dipole interaction model and assuming the polarizabilities to be in the order, Br > Cl > F > H, that (*S*)-bromochlorofluoromethane would have positive optical rotation.[4] However, the different polarizability orders chosen by Brewster and Applequist would yield opposite conclusions.[5] Collet and co-workers achieved optical resolution of bromochlorofluoromethane by enantioselective inclusion in cryptophan C.[6] Using the NMR resonance signals of (+) and (−) enantiomers encapsulated in cryptophan, they estimated the enantiomeric excess and maximum rotation values at five different wavelengths. In a different approach, Wilen et al. also resolved the enantiomers of bromochlorofluoromethane using brucine[5] and addressed the ambiguity remaining in the absolute configuration of bromochlorofluoromethane; Brewster and Applequist had arrived at the same assignment but using mutually conflicting polarizability trends. Wilen et al. concluded that "experimental determination of the absolute configuration of bromochlorofluoromethane is a challenge".[5] Using a quantum-mechanical static method, the specific rotation of (*R*)-bromochlorofluoromethane at the sodium D line was predicted (without the Lorentz factor) to be −6.[7,8] Comparison of this value with the experimental value of −1.78 reported by Collet et al. for enantiopure (−)-bromochlorofluoromethane, and based on the comparison of experimental and ab initio predicted Raman optical-activity (ROA) spectra, it was concluded that the absolute configuration of bromochlorofluoromethane is (*S*)-(+) and (*R*)-(−).[7]

Previous conclusions[7] on the absolute configuration were based on quantum-mechanical calculations of both ROA and specific rotation, carried out at the Hartree–Fock (HF) level using smaller basis sets. Since then, evidence has been collected[9] to indicate that the HF level calculations, because of lack of electron correlation, are not quantitatively accurate. DFT,[10] which includes electron correlation using density functionals, has now been widely accepted as the preferred approach for predicting molecular properties accurately. For reliable quantum mechanical predictions of specific rotations, those predicted at the HF level using small basis sets are not considered to be adequate and predictions with DFT and larger basis sets are necessary. Electron correlation and larger basis sets are also important for molecular polarizability derivatives, and hence Raman properties. Because the absolute configuration of bromochlorofluoromethane was suggested[7] based on HF calculations, the previously predicted specific rotation and ROA parameters of bromochlorofluoromethane must be verified using DFT and larger basis sets. The DFT method has been implemented recently for the prediction of specific rotation[11a] and of ROA[11b] in the quantum-mechanical program DALTON.[12] Thus it is important to reinvestigate the specific rotation and ROA of bromochlorofluoromethane. Recently Grimme[13] has reported DFT predictions of $[\alpha]_D$ for bromochlorofluoromethane. Because

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