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Highly Enantioselective Synthesis of Cyclic and Functionalized α-Amino Acids By Means of a Chiral Phase Transfer Catalyst

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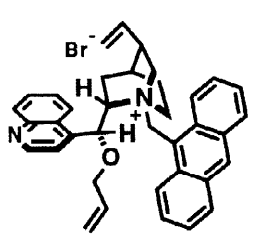
Dedicated to the memory of Professor Derek H. R. Barton.

Abstract: *The chiral quaternary ammonium salt* ***1*** *serves as phase transfer catalyst for the enantioselective conversion of the glycine derivative* ***2*** *to a variety of cyclic and acyclic chiral α-amino acids with enantioselectivities as high as 200 : 1 in alkylation and Michael addition reactions.*

We have described recently the design and application of the chiral phase transfer catalyst **1** to the highly enantioselective synthesis of a wide range of α-alkylated glycines by means of the reaction shown in equation (1).[1,2] The alkylation reaction proceeded with enantioselection between 400 : 1 and 60 : 1 for halides of the following types: (1) *n*-alkyl, (2) cyclopropylcarbinyl, (3) allyl, (4) benzyl, (5) propargyl and (6) Ar substituted benzyl, thus making available a very large number of chiral α-amino acids. One feature of our process is the use of solid $CsOH{\bullet}H_2O$ as the base in a solid-liquid phase transfer system with 5-10 mole % of the chiral quaternary ammonium salt **1** in methylene chloride as solvent. The alkylation product **3** is readily obtained in pure form after extractive workup, and the chiral quaternary ammonium salt **1** can be recovered efficiently for reuse.

The key to the success of this asymmetric synthesis of α-amino acids is the use of the cinchonidine salt **1** as catalyst. The design of this catalyst was based on previous experience in these laboratories on the rigidifying effect of the 9-anthracenylmethyl group on the conformation of quaternary ammonium salts of bis-cinchona alkaloids and especially NMR and X-ray crystallographic studies of such salts.[1,3] The bromide counter ion in crystalline **1** is situated as shown in the drawing about 4Å from the ammonium nitrogen with which it is paired. That location is the only one in the cinchonidinium salt which allows such close approach of the two counter ions since all the other faces of the N^+ unit are strongly sterically screened. As described earlier,[1] the high enantioselectivity and the absolute stereochemical sense of the alkylation shown in equation 1 can be understood in terms of a *tight, structured ion pair* of ammonium cation **1** and the enolate of **2** with the enolate oxygen at the location of the bromide ion in **1** and the remainder of the complex being arranged so as to allow maximum van der Waals contact.[1] That favored three-dimensional arrangement blocks one face of the nucleophilic carbon center of the enolate, but leaves the other (*si* face) free for attack by the alkylating agent.



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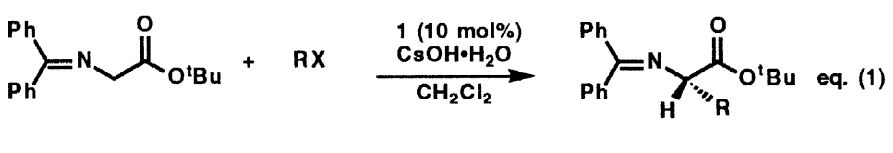


2 3

PII: S0040-4039(98)01067-3

This paper describes the application of catalyst **1** and substrate **2** to the synthesis of the cyclic amino acid (*S*)-pipecolic acid, (*S*)-glutamic acid and cyclic or acyclic α-keto-(*S*)-α-amino acids.

The synthetic route to (*S*)-pipecolic acid is outlined in Scheme 1. Catalytic phase transfer alkylation of *tert*-butyl ester **2** with 1-chloro-4-iodobutane using **1** as the chiral quaternary salt and solid $CsOH•H_2O$ as base afforded the (*S*)-4-chlorobutylated ester **4** of 99% ee (200 : 1 enantioselectivity as determined by HPLC analysis using a Chiralcel OD column with 0.5% isopropyl alcohol in hexane for elution at 23 °C, and 254 nm detection; retention times: *S*, 7.26 min; *R*, 11.16 min). The conversion of **4** to the *tert*-butyl ester of pipecolic acid (**7**) was accomplished in high yield by the sequence C=N reduction ($NaBH_4$) to **5**, cyclization to **6** and *N*-deprotection of **6**, according to Scheme 1.

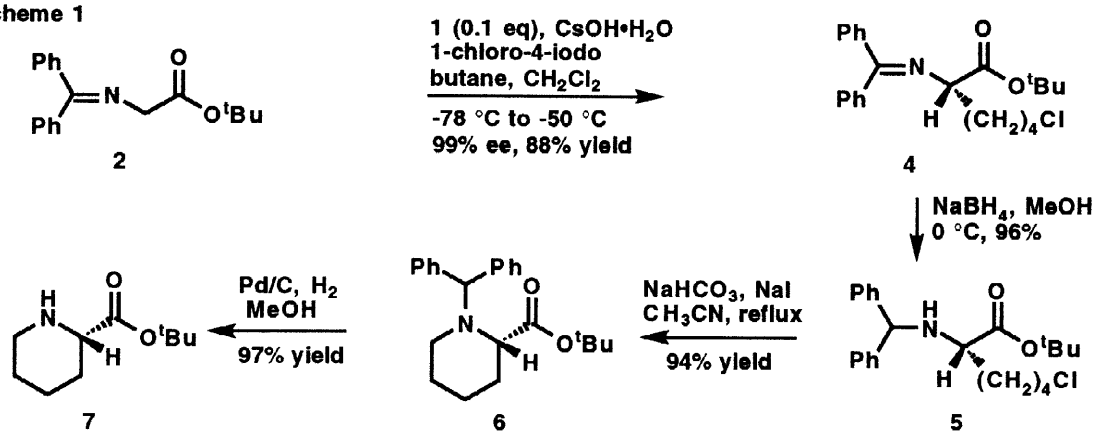
The synthetic route to glutamic acid, as outlined in Scheme 2, involved the enantioselective Michael addition of the tight ion pair of the enolate ion derived from **2** with the chiral ammonium ion **1** to methyl acrylate to produce the conjugate adduct **8** in 95% ee. Reduction of the C=N linkage of **8** ($NaBH_4$) and removal of the benzyhydryl protecting group from nitrogen (H_2, Pd on C) afforded the α-*tert*-butyl, γ-methyl ester of (*S*)-glutamic acid, an especially useful derivative for synthetic applications because the two carboxyl groups are differentiated. In addition (*S*)-glutamic acid was readily obtained from this diester by acid-catalyzed hydrolysis of both carboxyls. It is noteworthy that the absolute stereochemical course of the Michael addition to the ion pair of the enolate of **2** and **1** is the same as that for alkylation, i.e. attack by the electrophile on the *si*-face of the ion paired enolate.

2-Cyclohexenone also undergoes Michael addition with ester **2** under phase transfer conditions with catalyst **1** and $CsOH•H_2O$, the stereochemical course of the reaction being that shown in Scheme 3. The adduct **9** was formed with 200 : 1 enantioselectivity and 25 : 1 diastereoselectivity, as shown by HPLC analysis.[4] The relative stereochemistry of **9** was demonstrated by conversion to the crystalline acetate salt of **10** and X-ray diffraction analysis.[5] Similarly, ethyl vinyl ketone served as a highly selective Michael electrophile in the reaction with substrate **2**, quaternary ammonium catalyst **1** and $CsOH•H_2O$, to give the keto α-amino acid derivative **11** as shown in Scheme 4.

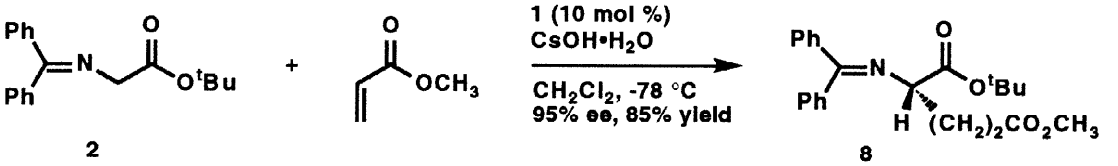
The catalytic enantioselective synthesis of a wide variety of α-amino acid derivatives, along the lines of the examples summarized in Schemes 1-4, is now both possible and practical through the use of the chiral phase transfer catalyst **1**. The following typical procedures provide supporting experimental detail.[6]

Formation of 4. To a mixture of *tert*-butylglycinate benzophenone imine (**2**) (50 mg, 0.17 mmol), *O*(9)-allyl-*N*-9-anthracenylmethylcinchonidinium bromide (**1**) (10 mg, 0.017 mmol,) and $CsOH•H_2O$ (250 mg, 1.67 mmol) in CH_2Cl_2 (0.5 mL) was added 1-chloro-4-iodobutane (0.1 mL, 0.82 mmol) dropwise at -78 °C. The mixture was stirred vigorously at -50 °C for 22 h. The suspension was diluted with ether (30 mL), washed with water (2x10 mL), brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the residue by silica chromatography (20:1 to 10:1 hexane-ethyl acetate) afforded the desired product as a colorless oil in 88% yield. The cinchona alkaloid catalyst **1** was recovered by extracting the aqueous layers with CH_2Cl_2 (2x20 mL). The combined organic phases were then washed with brine (3x10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford 80% (8 mg) of recovery yield of the catalyst **1** as the chloride (due to the brine wash); the change of the counterion does not effect the activity or selectivity of the catalyst. FTIR (film) 3000, 2977, 2954, 2932, 2866, 1732, 1623, 1455, 1446, 1367, 1315, 1287, 1254, 1220, 1148 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.0 Hz, 2H), 7.47-7.32 (m, 6H), 7.18-7.16 (m, 2H), 3.93 (t, *J* = 6.5 Hz, 1H), 3.51-3.48 (td, J = 7.0, 1.5 Hz, 2H), 1.93-1.88 (m, 2H), 1.74-1.68 (m, 2H), 1.44 (s, 9H), 1.48-1.36 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 170.2, 139.6, 136.6, 130.2, 128.7, 128.5, 128.4, 128.0, 127.7, 80.9, 65.8, 44.8, 32.8, 32.3, 28.0, 23.4 ppm; MS (CI^+): 386 $[M+H]^+$, 352, 330, 231, 186, 134, 110; HRMS (CI^+) calcd for $[C_{23}H_{28}NO_2Cl+H]^+$: 386.1887, found: 386.1873; $[\alpha]_D^{23}$ = -75.29 (*c* 0.9, CH_2Cl_2). The

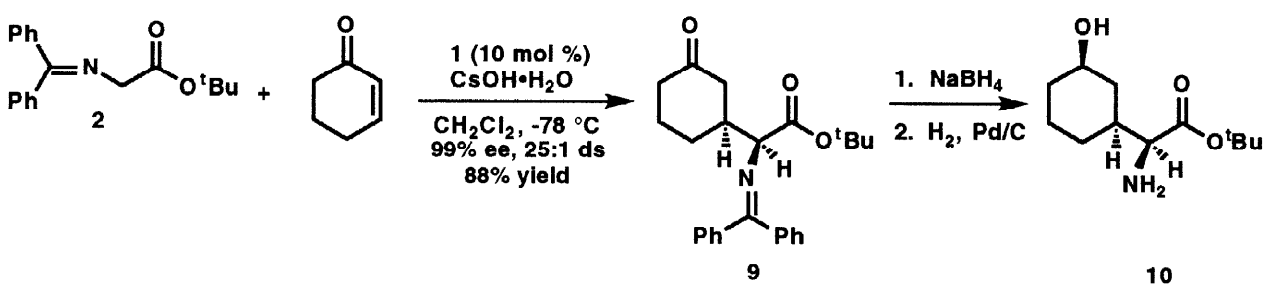
Scheme 1



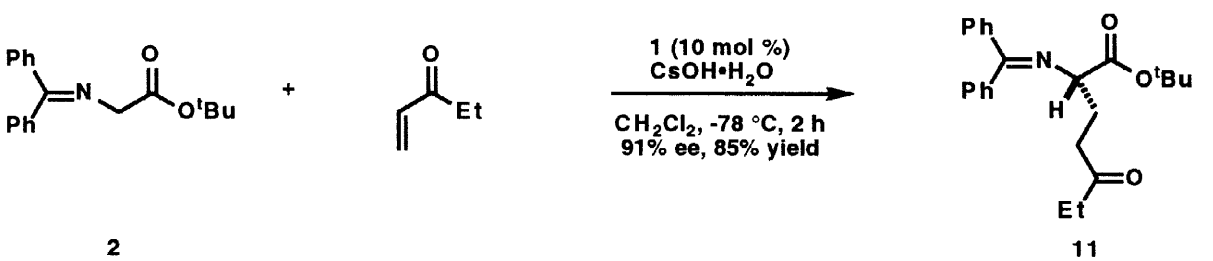
Scheme 2



Scheme 3



Scheme 4



enantioselectivity was determined by chiral HPLC analysis (Chiralcel OD column, 0.5% 2-propanol-hexane, 1 mL/min, 23 °C, λ = 254 nm, retention times: *S* (major) 7.26 min, *R* (minor) 11.16 min).

Formation of Michael Adduct 9. To a mixture of *tert*-butyl glycinate benzophenone imine (**2**) (50 mg, 0.17 mmol), *O*(9)-allyl-*N*-9-anthracenylmethylcinchonidinium bromide (**1**) (10 mg, 0.017 mmol) and $CsOH•H_2O$ (250 mg, 1.7 mmol) in 0.4 mL CH_2Cl_2 was added a solution of methyl acrylate (0.05 mL, 0.55 mmol) in 0.1 mL CH_2Cl_2 dropwise over 10 min at -78 °C. The resulting reaction mixture was stirred vigorously for 5 h at -78 °C and then diluted with Et_2O (30 mL). The organic phase was washed with H_2O (2x10 mL), brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by silica chromatography (20:1 to 5:1 hexane/ethyl acetate) afforded the desired product (55 mg, 85% yield) as a colorless oil. FTIR (film) 3061, 3056, 2977, 2950, 2933, 1735, 1624, 1446, 1368, 1316, 1277, 1254, 1195, 1150 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.2 Hz, 2H), 7.45-7.25 (m, 6H), 7.18-7.16 (m, 2H), 3.95 (dd, *J* = 7.2, 5.6 Hz, 1H), 3.59 (s, 3H), 2.39-2.35 (m, 2H), 2.24-2.18 (m, 2H), 1.43 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 170.6, 170.5, 139.3, 136.3, 130.2, 128.6, 128.4, 128.3, 127.8, 127.6, 80.9, 64.6, 51.3, 30.3, 28.4, 27.8 ppm; CIMS: 382 $[M+H]^+$ 280, 134; HRMS calcd for $[C_{23}H_{27}NO_4+H]^+$: 382.2018, found: 382.2017; $[\alpha]_D^{23}$ = -110.5 (*c* 2.4, CH_2Cl_2). The enantioselectivity was determined by chiral HPLC analysis (Regis Whelk-O1 column, 20% 2-propanol-hexane, 0.5 mL/min, 23 °C, λ = 254 nm, retention times: *R* (minor) 13.14 min, *S* (major) 15.35 min). The absolute configuration was determined by hydrolysis of the imine and ester groups (refluxing 6*N* HCl, 12 hr) followed by neutralization of the amine hydrochloride using propylene oxide in ethanol, to afford (*S*)-L-glutamic acid in 81% yield. $[\alpha]_D^{23}$ = +38.2 (*c* 0.46, 6*N* HCl), lit. $[\alpha]_D^{20}$ = +31.5 (*c* 2, 6*N* HCl).

References and Notes:

1. Corey, E. J.; Xu, F; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414.
2. For the early work on the application of substrate **2** to the enantioselective synthesis of α-amino acids see (a) O'Donnell, M. J.; Bennett, W. D.; Wu, S. *J. Am. Chem. Soc.* **1989**, *111*, 2353. (b) O'Donnell, M. J.; Wu, S.; Huffman, J. C. *Tetrahedron* **1994**, *50*, 4507. (c) Lipkowitz, K. B.; Cavanaugh, M. W.; Baker, B.; O'Donnell, M. J. *J. Org. Chem.* **1991**, *56*, 5181. (d) O'Donnell, M. J. *et al.* U.S. Patent 5,554,753, September 10, 1996. (e) O'Donnell, M. J.; Esikova, I. A.; Mi, A.; Shullenberger, D. F.; Wu, S. in *Phase-Transfer Catalysis*, M. E. Halpern, Ed., ACS Symposium Series 659, American Chemical Society, Washington, D.C., 1997, Chapter 10.
3. (a) Corey, E. J.; Noe, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 11038. (b) Corey, E. J.; Noe, M. C. *J. Am. Chem. Soc.* **1993**, *115*, 12579. (c) Corey, E. J.; Noe, M. C.; Sarshar, S. *Tetrahedron Lett.* **1994**, *35*, 2861. (d) Corey, E. J.; Noe, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 319. (e) Corey, E. J.; Noe, M. C.; Sarshar, S. *J. Am. Chem. Soc.* **1993**, *115*, 3828. (f) Corey, E. J.; Noe, M. C.; Ting, A. *Tetrahedron Lett.* **1996**, *37*, 1735.
4. The 25 : 1 diastereoselectivity in the formation of **9** is especially noteworthy. For a review of stereoselective Michael reactions, see Rossiter, B.; Swingle, N. *Chem. Rev.* **1992**, *92*, 771.
5. (a) Crystal structure data for the acetate salt of **10**: $C_{14}H_{27}NO_5$, FW 287.37, orthorhombic $P2_12_12_1$, a = 6.871(2) Å, b = 9.989(3) Å, c = 23.992(8) Å, α = β = γ = 90°, Z = 4, $R_1(I>2\sigma I)$ = 0.0461. (b) Detailed X-ray crystallographic data are available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.
6. This research was support by the National Science Foundation and the National Institutes of Health.