Advantage of Anaerobic Conditions in the Highly Enantioselective Synthesis of α,α-Dialkyl-α-Amino Acids by Chiral Phase-Transfer Catalysis

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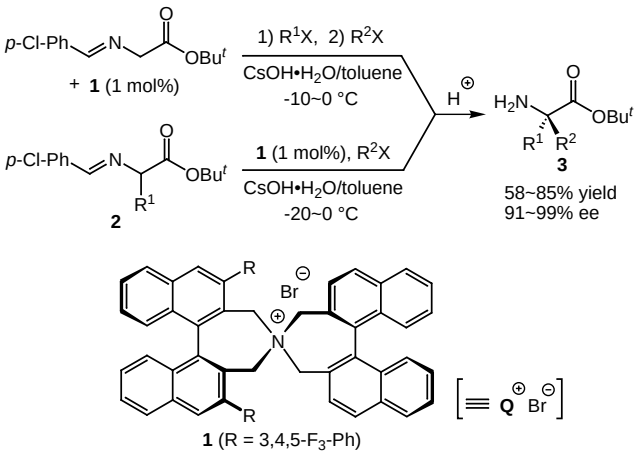
Abstract: Intervention of the enolate oxidation in the catalytic asymmetric phase-transfer alkylation of protected α-amino acid derivatives under aerobic conditions has been addressed, and anaerobic conditions have been introduced to obtain synthetically satisfactory chemical yields as well as a high level of enantioselectivity.

Key words: alkylation, anaerobic conditions, chiral phase-transfer catalysis, protected α-amino acid derivatives, oxidation

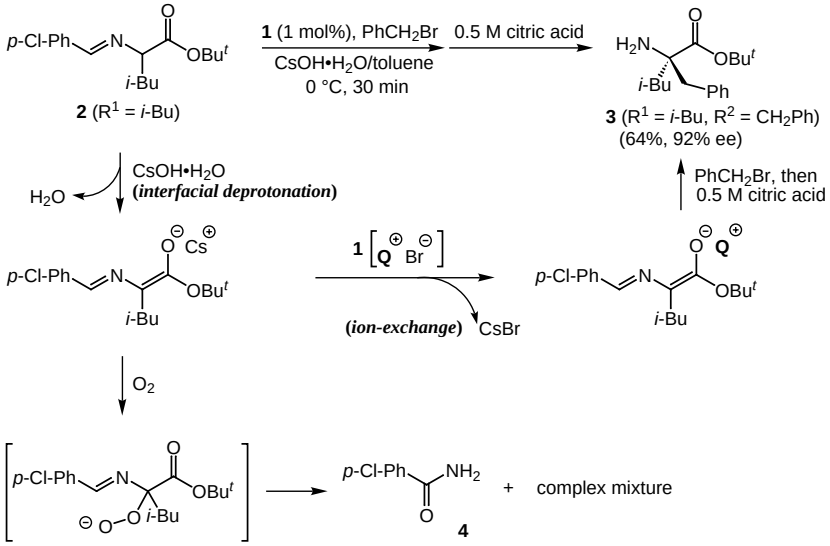
Recently, we disclosed a broadly useful and practical procedure for the enantioselective synthesis of nonproteinogenic α,α-dialkyl-α-amino acids under solid-liquid phase-transfer conditions using rationally designed C_2-symmetric chiral quaternary ammonium salts of type **1** as catalysts [(*S*,*S*)-3,4,5-trifluorophenyl-NAS-bromide [54,838-3] and (*S*,*S*)-β-naphthyl-NAS-bromide [54,839-1] from Aldrich Chemical Co. Ltd.].[1,2] A wide variety of α,α-dialkyl-α-amino acids can be efficiently prepared with enantioselectivities as high as 99% ee either by the one-pot, double alkylation of aldimine Schiff base of glycine *tert*-butyl ester or by the simple alkylation of aldimine Schiff base **2** derived from the corresponding α-amino acids.[3] Although excellent enantioselectivity was constantly observed, the chemical yields of the products were varied and generally modest, which prompted us to investigate the fundamental reason for this in relation to the mechanistic aspect of this asymmetric phase-transfer catalytic alkylation. Since we performed the reaction under aerobic conditions, it seemed conceivable that rapid oxidation of the in situ generated enolate with molecular oxygen could occur concurrently with the desired alkylation step, thereby resulting in a certain decrease of the chemical yield. In this letter, we address this problem and report the anaerobic conditions for the highly enantioselective alkylation of protected α-amino acid derivatives by chiral phase-transfer catalysis.

Alkylation of aldimine Schiff base derived from leucine *tert*-butyl ester (**2**, R^1 = *i*-Bu) with benzyl bromide (1.2 equiv) in the presence of the catalyst **1** (1 mol%) and CsOH•H_2O (5 equiv) in toluene proceeded smoothly at 0 °C under aerobic conditions to give the corresponding benzylation product **3** (R^1 = *i*-Bu, R^2 = CH_2Ph) in 64% isolated yield with 92% ee.[1] The observed asymmetric induction can be interpreted for by the generally proposed interfacial mechanism: the cesium enolate of **2** (R^1 = *i*-Bu) produced through interfacial deprotonation with

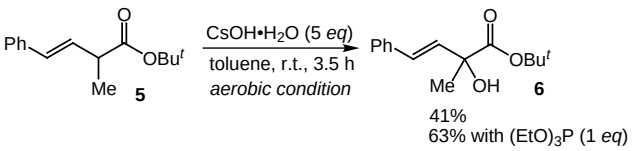


CsOH•H_2O experiences the extremely fast ion-exchange with **1** to give the corresponding chiral enolate that reacts with benzyl bromide in an asymmetric fashion as illustrated in Scheme 1.[4] This is consistent with the fact that attempted benzylation of **2** (R^1 = *i*-Bu) in the absence of catalyst under otherwise similar conditions afforded the racemic product **3** (R^1 = *i*-Bu, R^2 = CH_2Ph) in 51% yield. Based on the plausible mechanistic profile, we assumed that the initially formed cesium enolate could be rapidly oxidized by molecular oxygen under aerobic conditions as also shown in Scheme 1, and this pathway would compete with the desired alkylation, lowering the chemical yield. Actually, upon mixing **2** (R^1 = *i*-Bu) and CsOH•H_2O (5 equiv) in toluene at 0 °C, instantaneous consumption of the starting Schiff base was observed to furnish a deteriorated mixture from which *p*-chlorobenzamide (**4**) was isolated (23%),[5,6] while almost complete preservation of **2** (R^1 = *i*-Bu) was confirmed after similar treatment under argon atmosphere.

To obtain more direct and compelling evidence for the intervention of the enolate oxidation with molecular oxygen, we prepared ester **5** as a carbon analogue of alanine-derived Schiff base and examined its oxidation under aerobic conditions. Interestingly, simple treatment of **5** with 5 equiv of CsOH•H_2O in toluene at room temperature for 3.5 h resulted in formation of the corresponding α-hydroxy ester **6** in 41% yield, and the yield was improved to 63% by employing triethyl phosphite (1 equiv) as an additive (Scheme 2).[7]



Scheme 1



Scheme 2

With this information in hand, we set out to optimize the reaction with rigorous exclusion of air, and eventually found that treatment of **2** (R^1 = *i*-Bu) with benzyl bromide (1.2 equiv) and CsOH•H_2O (5 equiv) under the influence of **1** (1 mol%) in reagent grade toluene at -25 °C for 20 h under argon atmosphere gave rise to **3** (R^1 = *i*-Bu, R^2 = CH_2Ph) in 90% yield after acidic hydrolysis; the enantiomeric excess was determined to be 97% ee (Scheme 3). A synthetically satisfactory chemical yield as well as a high level of enantioselectivity were also attained in the reaction with allyl bromide. Particularly emphasized is the fact that catalytic asymmetric alkylation of phenylglycine-derived aldimine Schiff base was found to be feasible with various alkyl halides, producing the corresponding fully protected α,α-dialkyl-α-amino acids in excellent yields and enantioselectivities as also included in Scheme 3.[8] This represents an attractive feature of our procedure in light of the formidable difficulty encountered in the direct arylation of α-amino acid-derived substrate in an asymmetric fashion. It should be noted that the benzylation of **2** (R^1 = Ph) under aerobic conditions showed gradual decomposition of **2** (R^1 = Ph) at -40 °C for 25 h and the desired alkylation product **3** (R^1 = Ph, R^2 = CH_2Ph) was obtained in only 10% yield with 82% ee.

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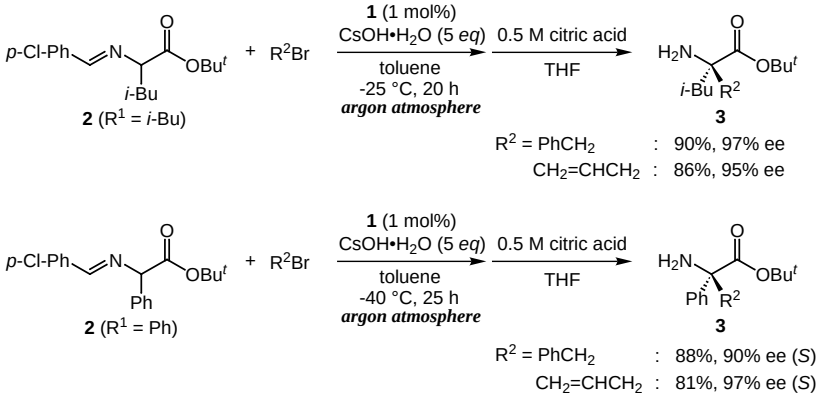

Scheme 3

References and Notes

(1) Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122*, 5228. See also: Ooi, T.; Kameda, M.; Tannai, H.; Maruoka, K. *Tetrahedron Lett.* **2000**, *41*, 8339; Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **1999**, *121*, 6519.

(2) The catalyst **1** as well as the one with β-naphthyl group on 3,3'-position are going to be commercially available from Aldrich Chemical Co. Ltd. as (*S*,*S*)-3,4,5-Trifluorophenyl-NAS-Bromide (**1**) [54,838-3] and (*S*,*S*)-β-Naphthyl-NAS-Bromide [54,839-1].

(3) For other recent examples of the asymmetric synthesis of α,α-dialkyl-α-amino acids under PTC conditions, see: (a) Belokon, Y. N.; Davies, R. G.; North, M. *Tetrahedron Lett.* **2000**, *41*, 7245. (b) Lygo, B.; Crosby, J.; Peterson, J. A. *Tetrahedron Lett.* **1999**, *40*, 8671. (c) Belokon, Y. N.; North, M.; Kublitski, V. S.; Ikonnikov, N. S.; Krasik, P. E.; Maleev, V. I. *Tetrahedron Lett.* **1999**, *40*, 6105. (d) Belokon, Y. N.; Kochetkov, K. A.; Churkina, T. D.; Ikonnikov, N. S.; Chesnokov, A. A.; Larionov, O. V.; Parmar, V. S.; Kumar, R.; Kagan, H. B. *Tetrahedron: Asymmetry* **1998**, *9*, 851. (e) O'Donnell, J. M.; Wu, S. *Tetrahedron: Asymmetry* **1992**, *3*, 591.

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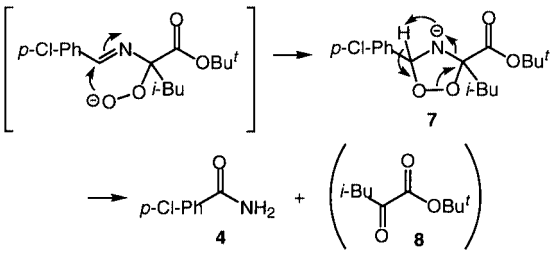
(5) The isolated *p*-chlorobenzamide (**4**) was fully characterized: 400 MHz ^{1}H NMR ($CDCl_3$) δ 7.76 (2H, d, *J* = 8.6 Hz, *p*-Cl-Ph), 7.43 (2H, d, *J* = 8.6 Hz, *p*-Cl-Ph), 5.95 (2H, br s, NH_2); IR (KBr) 3369, 3179, 3055, 1659, 1620, 1408, 1090, 791 cm^{-1}. MS: m/z 155 (M^+), 139 (100%), 111.

(6) Although the exact mechanism of generating **4** is unclear at present, one explanation includes the intramolecular attack of the peroxy anion on the imine moiety and subsequent degradation of **7** as shown below, though we were able to isolate only a trace amount of α-keto ester **8**.



(7) Masui, M.; Ando, A.; Shioiri, T. *Tetrahedron Lett.* **1988**, *29*, 2835.

(8) Enantiopurity was determined by HPLC analysis of the amino ester using a chiral column (DAICEL Chiralpak AD for benzylation and Chiralcel OD for allylation products) with hexane-isopropanol as solvent. Absolute configuration was determined by cleavage of the *tert*-butyl ester (6 N HCl) and comparison of the optical rotation of the free amino acid with the literature value. See: Hartwig, W.; Schollkopt, U. *Liebigs Ann. Chem.* **1982**, 1952.

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