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Facile synthesis of L-Dopa *tert*-butyl ester by catalytic enantioselective phase-transfer alkylation

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Abstract

Facile asymmetric synthesis of L-Dopa and related amino acid esters has been achieved by phase-transfer catalysis of the rationally designed C_2-symmetric chiral quaternary ammonium salts **1**. The 'scale-up' experiment performed with 5.00 g of *tert*-butyl glycinate-benzophenone Schiff base (**2**) represents the practical aspect of our approach. © 2000 Elsevier Science Ltd. All rights reserved.

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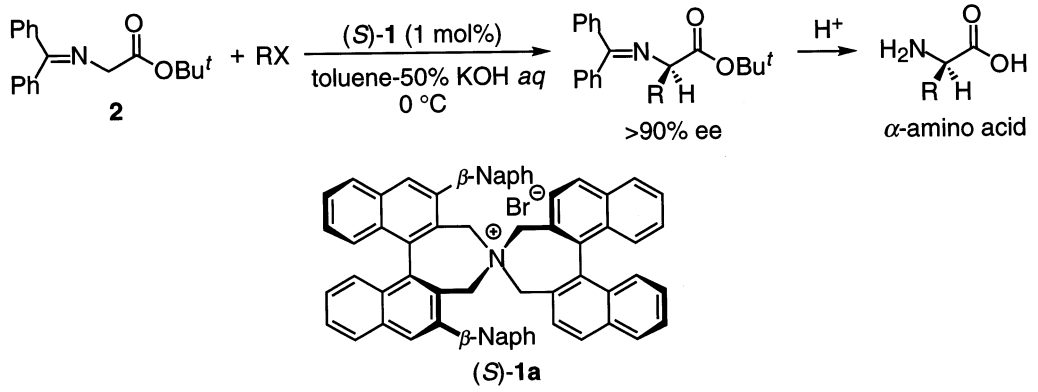
Recently, we reported the rational molecular design of C_2-symmetric chiral quaternary ammonium salt (*S*)-**1a** as a new chiral phase-transfer catalyst and demonstrated its remarkable efficiency in the catalytic enantioselective alkylation of *tert*-butyl glycinate-benzophenone Schiff base (**2**) under mild phase-transfer conditions (Scheme 1).[1] Since both enantiomers of the



Scheme 1.

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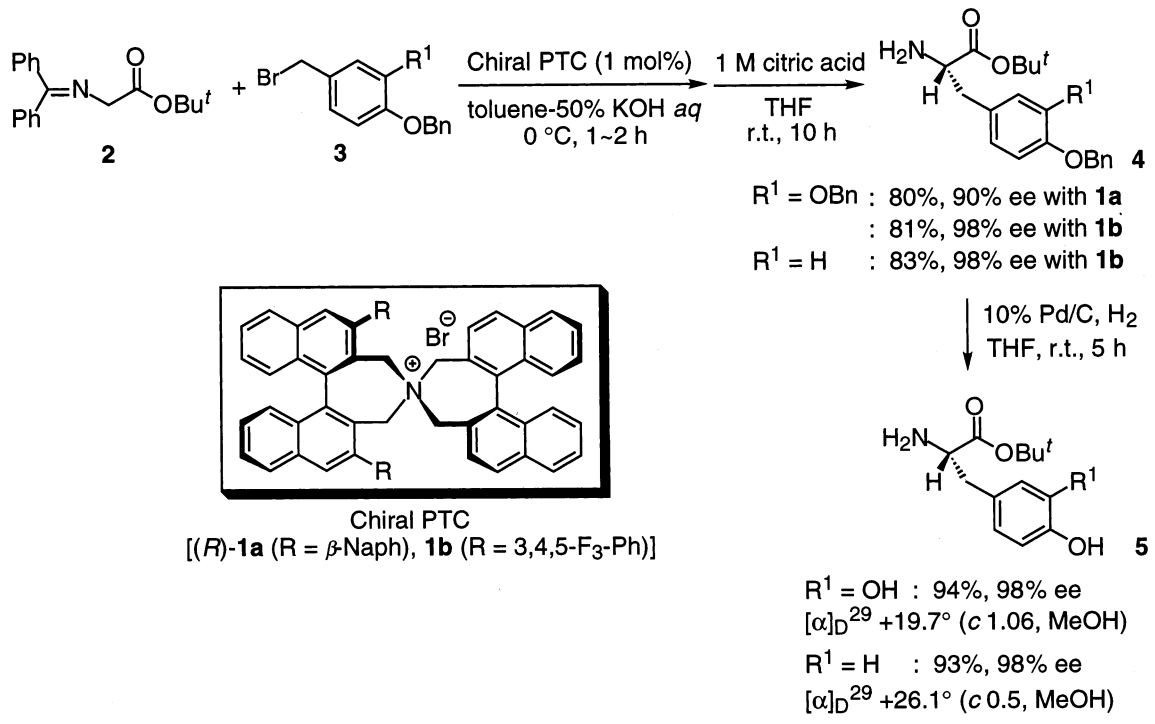
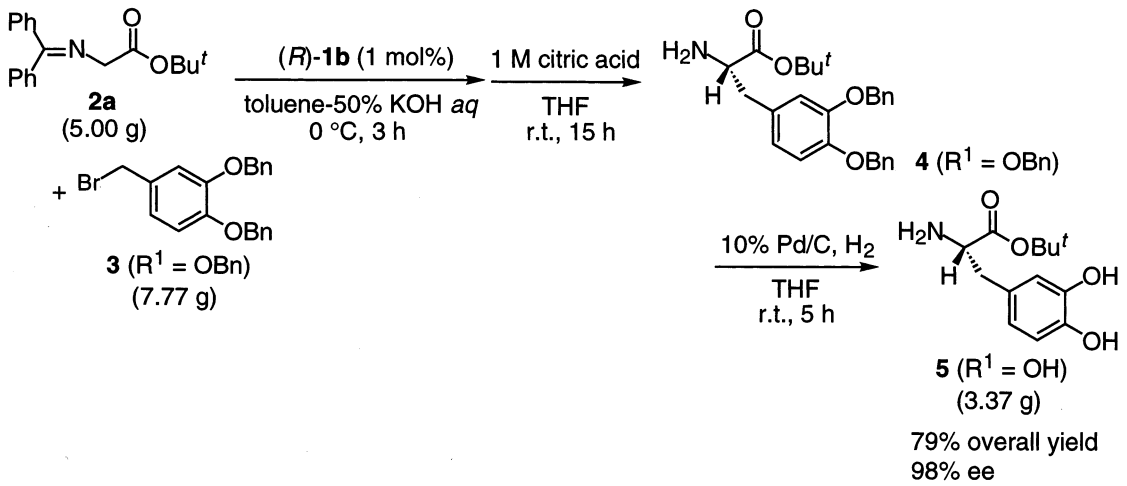
catalyst of type **1** can be readily assembled in exactly the same manner starting from either (*R*)- or (*S*)-binaphthol, a wide variety of natural and unnatural α-amino acids can be synthesized in an enantiomerically pure form by the phase-transfer catalytic alkylation of substrate **2**. In this letter, we wish to describe the successful utilization of this advantage for the facile synthesis of L-Dopa (L-3,4-dihydroxyphenylalanine) esters, which have usually been prepared in an enzymatic way and tested as potential drugs for the treatment of Parkinson's disease.[2]

The simple synthetic route to L-Dopa esters is illustrated in Scheme 2. Catalytic phase-transfer alkylation of **2** with benzyl bromide **3** (R^1 = OBn) (1.2 equiv.)[3] in toluene–50% KOH aqueous solution (volume ratio = 3:1) proceeded smoothly at 0°C in the presence of (*R*)-**1a** (1 mol%) to furnish fully protected L-Dopa *tert*-butyl ester, which was subsequently treated with a 1 M citric acid in THF at room temperature for 10 h to afford the corresponding amino ester **4** (R^1 = OBn) in 80% isolated yield. Although the enantiomeric excess was determined to be 90% ee by chiral HPLC analysis, it did not seem fully satisfactory because further purification such as recrystallization would be required to increase the enantiomeric purity. Therefore, we employed (*R*)-**1b** as a catalyst[4] and found that the alkylation of **2** with (*R*)-**1b** (1 mol%) and **3** (R^1 = OBn; 1.2 equiv.) under otherwise identical conditions gave rise to the amino ester **4** (R^1 = OBn) with excellent enantioselectivity (98% ee). Debenzylation of **4** (R^1 = OBn) under catalytic hydrogenation conditions produced the desired L-Dopa *tert*-butyl ester (**5**; R^1 = OH) in 93% yield. Being exemplified by the feasibility of asymmetric synthesis of natural tyrosine *tert*-butyl ester (**5**; R^1 = H), as also shown in Scheme 2, the present concise and practical procedures should enable highly enantioselective synthesis of various L-Dopa analogues and related α-amino acids.



Scheme 2.

With this information at hand, we performed a 'scale-up' experiment with 5.00 g of **2** and 7.77 g of **3** (R^1=OBn), providing 3.37 g of the desired L-Dopa *tert*-butyl ester (**5**; R^1=OH) as illustrated in Scheme 3. The attractive feature of this method is that, in addition to its operational simplicity, the catalyst (*R*)-**1b** can be recovered and reused in the present enantioselective phase-transfer alkylation.[5]



Scheme 3.

The following typical procedures provide supporting experimental detail in a large-scale preparation of L-Dopa *tert*-butyl ester: a 300 mL round-bottom flask containing a magnetic stirring bar and a solution of glycine *tert*-butyl ester benzophenone Schiff base (**2**; 5.00 g, 16.9 mmol), 3,4-dibenzyloxybenzyl bromide (7.77 g, 20.3 mmol) and (*R*)-**1b** (155 mg, 0.169 mmol) in toluene (100 mL) was immersed in an ice-water bath. After 10 min of gentle stirring, cold 50% KOH aqueous solution (33.3 mL) was added by a pipette and the reaction mixture was stirred vigorously (1365 rpm) for 3 h.[6] The resulting mixture was then poured into water (100 mL) and extracted with CH_2Cl_2 (2×60 mL). The organic layer was dried over Na_2SO_4 and concentrated. The residue was dissolved in THF (60 mL) and a 1.0 M citric acid aqueous solution (150 mL) was added. This solution was stirred at room temperature for 15 h. After removal of THF in vacuo, the aqueous solution was neutralized with $NaHCO_3$ and extracted with CH_2Cl_2 (3×60 mL). The organic extracts were dried over Na_2SO_4 and concentrated. Purification of the residual oil by column chromatography on silica gel (ethyl acetate/hexane=3:2, then ethyl acetate only as eluants) gave the amino ester **4** (R^1=OBn) (6.20 g, 14.2 mmol; 84% yield, 98% ee) as a colorless oil. The enantiomeric excess was determined by chiral HPLC analysis (DAICEL CHIRALCEL OD, hexane/2-propanol=4:1, flow rate=0.5 mL/min, retention time; 24.3 min (*S*) and 28.4 min (*R*)). 400 MHz ^{1}H NMR ($CDCl_3$) δ 7.44 (4H, d, J=7.6 Hz, Ph), 7.26–7.37 (6H, m, Ph), 6.87 (1H, d, J=8.0 Hz, Ar–H), 6.82 (1H, s, Ar–H), 6.72 (1H, d, J=8.0 Hz, Ar–H), 5.13 (4H, s, 2(OCH_2Ph)), 3.52 (1H, dd, J=5.6, 7.6 Hz, CHC=O), 2.93 (1H, dd, J=5.6, 13.6 Hz, CHAr), 2.72 (1H, dd, J=7.6, 13.6 Hz, CHAr), 1.48 (2H, br s, NH_2), 1.42 (9H, s, *t*-Bu).

To a THF (45 mL) solution of the amino ester **4** (R^1=OBn) (6.20 g, 14.2 mmol) in a 100 mL round-bottom flask was added 10% palladium on activated carbon (350 mg) at 0°C under argon. Then, argon was replaced by H_2 and the reaction mixture was stirred for 5 h at room temperature. The mixture was filtered to remove the catalyst and the filtrate was concentrated.

Purification of the residual oil by column chromatography on silica gel (ethyl acetate as eluant) gave L-Dopa *tert*-butyl ester (**5**; $R^1=OH$) [3.37 g, 13.3 mmol, 94% yield, $[\alpha]_D^{29}$ +19.7° (*c* 1.06, MeOH)] as a white solid. 400 MHz ^1H NMR ($CDCl_3$) δ 6.74 (1H, d, $J=8.4$ Hz, Ar–H), 6.57 (1H, s, Ar–H), 6.56 (1H, d, $J=8.4$ Hz, Ar–H), 4.04 (4H, br, 2OH and NH_2), 3.63 (1H, dd, $J=4.8$, 8.4 Hz, CHC=O), 3.02 (1H, dd, $J=4.8$, 13.6 Hz, CHAr), 2.68 (1H, dd, $J=8.4$, 13.6 Hz, CHAr), 1.42 (9H, s, *t*-Bu); IR (KBr) 3462, 3337, 3288, 2977, 2939, 2625, 1734, 1609, 1533, 1472, 1367, 1308, 1283, 1159, 1111, 1043, 854, 799 cm^{-1}. MS: *m*/*z* 254 ($[M+H]^+$), 238, 198 (100%), 181, 152, 123, 57. HRMS calcd for $C_{13}H_{20}O_4N$: 254.1393 ($[M+H]^+$). Found: 254.1384 ($[M+H]^+$).

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5. After neutralization with 1N HBr, the catalyst (*R*)-**1b** can be recovered by short silica gel column chromatography with dichloromethane/methanol = 30:1 to 10:1 as eluant (72% recovery yield) before the acidic hydrolysis. The recovered catalyst (*R*)-**1b** was reused several times without losing activity and enantioselectivity (second cycle: 80%, 98% ee; third cycle: 79%, 98% ee).
6. Use of a mechanical stirrer or a homogenizer would be required for further scale-up.