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Tetrahedron Letters 46 (2005) 8555–8558
Tetrahedron Letters

Convenient preparation of highly active phase-transfer catalyst for catalytic asymmetric synthesis of α-alkyl- and α,α-dialkyl-α-amino acids: application to the short asymmetric synthesis of BIRT-377

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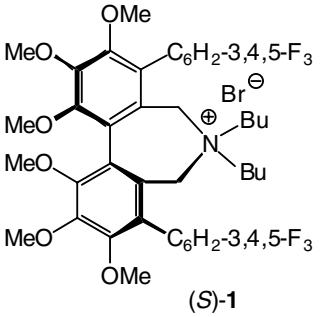
Received 1 September 2005; revised 28 September 2005; accepted 30 September 2005
Available online 21 October 2005

Abstract—A highly active phase-transfer catalyst was conveniently prepared from the known, easily available (*S*)-4,5,6,4′,5′,6′-hexamethoxybiphenyldicarboxylic acid. This catalyst exhibited the high catalytic performance (0.01–1 mol %) in the asymmetric alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester and *N*-(*p*-chlorophenylmethylene)alanine *tert*-butyl ester compared to the existing chiral phase-transfer catalysts, thereby allowing to realize a general and useful procedure for highly practical enantioselective synthesis of structurally diverse natural and unnatural α-alkyl-α-amino acids as well as α,α-dialkyl-α-amino acids.

Design of highly efficient catalysts to achieve both high reactivity and enantioselectivity is an ultimate goal in practical asymmetric synthesis.[1] However, despite numerous studies in asymmetric catalysis, truly efficient catalytic systems with high enantioselection at very low catalyst loading (e.g., <0.1 mol %) are still rare in asymmetric carbon–carbon bond formations, and major progress in terms of both enantioselection and catalyst loading is still most desirable for practical asymmetric synthesis. In consideration of the recent rapid development of organocatalytic reactions,[2] we are interested in the possibility of designing a new, yet efficient phase-transfer catalyst in an enantiomeric form as highly active organocatalyst.[3] Disclosed herein is the convenient preparation of new chiral phase-transfer catalyst **1** from a known chiral source and its application to the highly practical, enantioselective phase-transfer catalytic alkylation of protected glycine and α-alkyl-α-amino acid derivatives.[4,5]



(*S*)-**1**

The requisite catalyst (*S*)-**1** can be conveniently prepared from the known (*S*)-4,5,6,4′,5′,6′-hexamethoxybiphenyldicarboxylic acid (*S*)-**2** (Scheme 1) which is readily derived from commercially available gallic acid derivative or ellagic acid.[6] Reduction of diacid (*S*)-**2** with $BH_3{\cdot}SMe_2$ and subsequent addition of Br_2/Py gave rise to (*S*)-3,3′-dibromo-4,5,6,4′,5′,6′-hexamethoxybiphenyl-2,2′-dimethanol (*S*)-**3** in 95% yield.[7] Suzuki–Miyaura cross coupling of (*S*)-**3** with 3,4,5-trifluorophenylboronic acid in the presence of catalytic $Pd(OAc)_2$, P(*o*-Tol)$_3$, and K_3PO_4 in THF afforded (*S*)-3,3′-bis-(3,4,5-trifluorophenyl)-4,5,6,4′,5′,6′-hexamethoxy-biphenyl-2,2′-dimethanol (*S*)-**4** in 78% yield. Bromination of (*S*)-**4** with PBr_3 in THF and subsequent treatment with dibutylamine and K_2CO_3 in acetonitrile led to the formation of the catalyst (*S*)-**1** in 90% yield. The overall yield of (*S*)-**1** by five-step sequence from the known diacid (*S*)-**2** is 67%.

Keywords: Phase-transfer catalyst; Gallic acid; Glycine; Alkylation; α-Amino acids.
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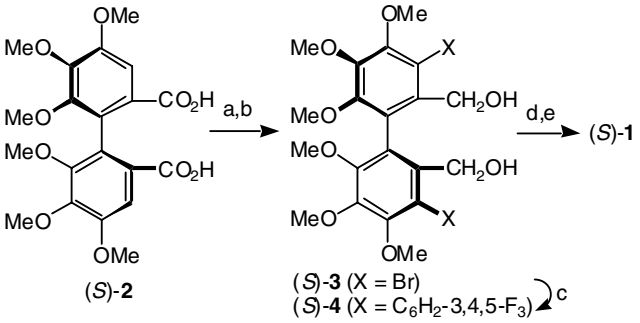
doi:10.1016/j.tetlet.2005.09.185

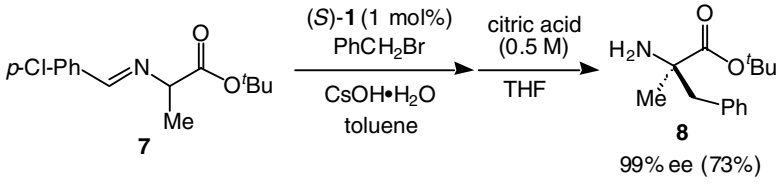


Scheme 1. Reagents and conditions: (a) $BH_3{\cdot}SMe_2$ (4 equiv), THF/$B(OMe)_3$ (2:1), 0 °C–rt; (b) Br_2/Py (7 equiv), THF, 0 °C (95% from **2**); (c) (3,4,5-F_3-C_6H_2)$B(OH)_2$ (5 equiv), $Pd(OAc)_2$ (20 mol %), P(*o*-Tol)$_3$ (80 mol %), $K_3PO_4{\cdot}nH_2O$ (10 equiv), THF, 88 °C (78%); (d) PBr_3 (1.5 equiv), THF, 0 °C; (e) Bu_2NH (1.1 equiv), K_2CO_3 (2 equiv), CH_3CN, reflux (90% from **4**).

The chiral efficiency of the phase-transfer catalyst (*S*)-**1** was examined by carrying out asymmetric alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester **5** (Table 1). Thus, reaction of **5** with benzyl bromide (1.5 eqiuv) and 50% aqueous KOH in toluene was effected in the presence of 1 mol % of catalyst (*S*)-**1** under argon atmosphere at 0–25 °C for several hours to furnish benzylation product **6** (R = CH_2Ph) in 95–97% yields with excellent enantioselectivity (97–98% ees) (entries 1 and 2). Quite surprisingly (*S*)-**1** was found to be a very active catalyst among existing chiral phase transfer catalysts, and the amount of the catalyst can be lowered to 0.1 and 0.05 mol % in the asymmetric benzylation of glycine derivative **5** without decreasing the enantioselectivity (entries 3 and 4).[8] Even 0.01 mol % of catalyst (*S*)-**1** still gave high enantioselectivity (96% ee at 25 °C for 24 h) (entry 5).

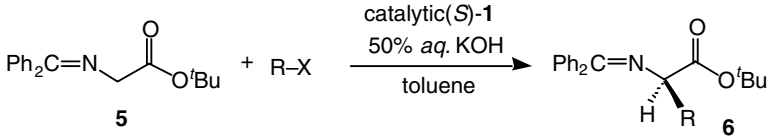
Other selected examples are also listed in Table 1. Several characteristic features of the present alkylations follow: (1) In contrast to the existing chiral phase-transfer catalysts, the catalyst (*S*)-**1** exhibited high catalytic performance (0.01–0.5 mol %), demonstrating the remarkable efficiency and practicability of the present approach for the enantioselective synthesis of α-alkyl-α-amino acids. (2) Not only benzylation and allylation, but also alkylation of **5** with a simple alkyl halide such as ethyl iodide proceeded smoothly under mild conditions to furnish the corresponding α-alkyl-α-amino acids in high yield and excellent enantioselectivity (entry 9).

The catalyst (*S*)-**1** is, of course, applicable to the asymmetric alkylation of aldimine Schiff base **7** derived from DL-alanine *tert*-butyl ester. Thus, reaction of **7** with benzyl bromide (1.5 eqiuv) and $CsOH{\cdot}H_2O$ (5 equiv) in toluene in the presence of 1 mol % of catalyst (*S*)-**1** under argon atmosphere at 0 °C for 10 h gave, after acidic work-up, rise to benzylation product **8** in 73% yield with 99% ee.



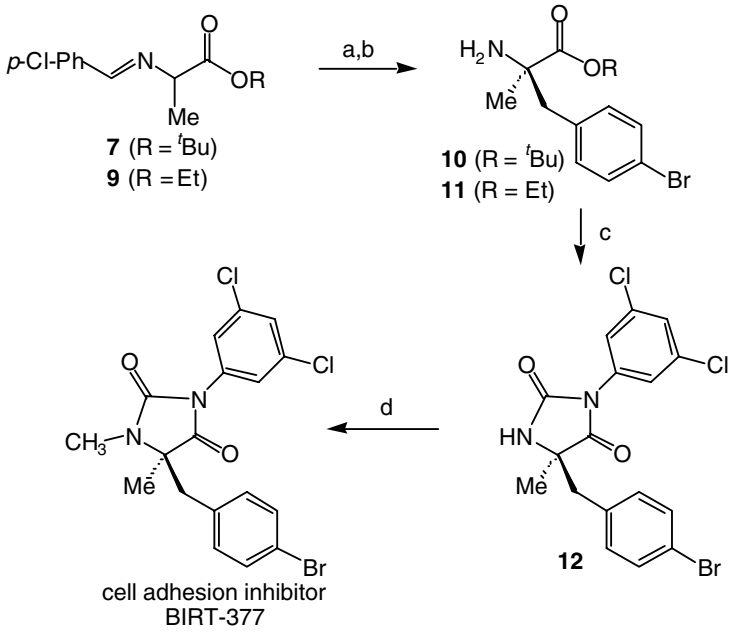
The present approach is highlighted by the short asymmetric synthesis of cell adhesion BIRT-377 (Scheme 2),

Table 1. Catalytic enantioselective phase-transfer alkylation of glycine derivative **5**[a]



Entry	Catalyst (mol %)	R–X	Condition (°C, h)	% Yield[b]	% ee[c] (config)
1	(*S*)-**1** (1)	$PhCH_2Br$	0, 6	95	98 (*R*)
2	(*S*)-**1** (1)		25, 4.5	97	97 (*R*)
3	(*S*)-**1** (0.1)		25, 11	96	97 (*R*)
4	(*S*)-**1** (0.05)		25, 20	94	97 (*R*)
5	(*S*)-**1** (0.01)		25, 24	95	96 (*R*)
6	(*S*)-**1** (0.05)	*p*-Br–C_6H_4–CH_2Br	25, 20	92	96 (*R*)
7	(*S*)-**1** (0.5)	$CH_2{=}CHCH_2Br$[d]	0, 5	99	96 (*R*)
8	(*S*)-**1** (0.5)	$HC{\equiv}CCH_2Br$[d]	0, 5	97	96 (*R*)
9	(*S*)-**1** (0.1)	CH_3CH_2I[e]	25, 36	80	94 (*R*)

[a] Unless otherwise specified, the reaction was carried out with 1.5 equiv of R–X in the presence of catalytic (*S*)-**1** in 50% aqueous KOH/toluene (volume ratio = 1:1.5) under the given reaction conditions.
[b] Isolated yield.
[c] Enantiopurity of **6** was determined by HPLC analysis using a chiral column [DAICEL Chiralcel OD] with hexane–isopropanol as solvent.
[d] Use of 3 equiv of R–X.
[e] Use of excess ethyl iodide (8 equiv).



Scheme 2. Reagents and conditions: (a) (*S*)-**1** (1 mol %), *p*-Br-$C_6H_4CH_2Br$ (1.5 equiv), $CsOH{\cdot}H_2O$ (5 equiv), toluene, 0 °C, 10 h; (b) citric acid (0.5 M), THF, room temp. (83% and 86% from **7** and **9**, respectively); (c) 3,5-Cl_2-C_6H_3NCO (1.1 equiv), Na_2CO_3, DMSO, 120 °C (86% and 90% from **10** and **11**, respectively); (d) $LiN(SiMe_3)_2$ (1.1 equiv), CH_3I (1.5 equiv), THF, 0 °C to room temp. (92%).

which is a potent inhibitor of the interaction between intercellular adhesion molecule-1 (ICAM-1) and lymphocyte function-associated antigen-1 (LFA-1).[9] Thus, the asymmetric *p*-bromobenzylation of alanine derivative **7** under similar phase transfer conditions as described above gave rise to *p*-bromobenzylalanine ester **10** in 97% ee (83% yield). A similar asymmetric *p*-bromobenzylation of alanine ethyl ester **9** gave the amino ester **11** in 90% ee (86% yield). The amino ester **10** or **11** was treated with 3,5-dichlorophenyl isocyanate in the presence of sodium carbonate in DMSO to furnish the hydantoin **12** in 86% or 90% yield, respectively. *N*-Methylation of **12** was effected with lithium bis(trimethylsilyl)amide and methyl iodide in THF to afford BIRT-377 in 92% yield.

In conclusion, we successfully prepared an efficient chiral phase-transfer catalyst of type **1** in a convenient way to realize a general and useful procedure for highly practical enantioselective synthesis of α-alkyl- and α,α-dialkyl-α-amino acids.

A typical experimental procedure of catalytic enantioselective benzylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester is as follows (entry 4 in Table 1): To a mixture of benzophenone imine glycine *tert*-butyl ester (**5**) (58.8 mg, 0.2 mmol) and chiral catalyst (*S*)-**1** (0.0828 mg, 0.0001 mmol) in toluene (1.5 mL)-50% KOH aqueous solution (1.0 mL) was added benzyl bromide (36.0 μL, 0.3 mmol) dropwise at 0 °C. The reaction mixture was stirred vigorously at room temperature for 20 h. The mixture was then poured into water and extracted with ether. The organic extracts were washed with brine and dried over Na_2SO_4. Evaporation of solvents and purification of the residual oil by column chromatography on silica gel (ether/hexane = 1:10 as eluant) gave the alkylation product **6** (R = CH_2Ph) (72.5 mg, 0.188 mmol, 94% yield) as a colorless oil. The enantiomeric excess was determined by chiral HPLC analysis (DAICEL CHIRALCEL OD, hexane/isopropanol = 100:1, flow rate = 0.5 mL/min, retention time; 14.8 min (*R*) and 28.2 min (*S*)).

Acknowledgements

This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan. Z.H. and M.K. are grateful to the Japan Society for the Promotion of Science for Young Scientists for a Research Fellowship.

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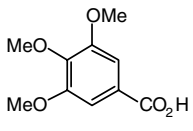

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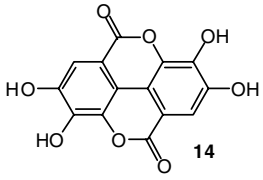

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