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Highly enantioselective monoalkylation of *p*-chlorobenzaldehyde imine of glycine *tert*-butyl ester under mild phase-transfer conditions

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Abstract—The selective monoalkylation of glycine *tert*-butyl ester aldimine Schiff base **3** has been realized in high chemical yield with excellent enantioselectivity under mild liquid–liquid phase-transfer conditions by the use of binaphthyl-derived chiral quaternary ammonium bromides **7** and **8** as catalysts. This achievement demonstrates that **3** can be used as a cost-effective substrate for the preparation of optically active α-alkyl-α-amino acid derivatives by chiral phase-transfer catalysis.

1. Introduction

The enantioselective alkylation of the benzophenone imine of glycine *tert*-butyl ester **1** using chiral phase-transfer catalysts has been developed into a powerful method for the synthesis of optically active α-amino acid derivatives.[1] A key feature of this extremely useful asymmetric transformation is the selective monoalkylation of **1** due to the considerable difference in acidity of the α-proton between the starting substrate **1** and the corresponding monoalkylation product **4**. This property, imparted by the presence of the benzophenone imine moiety, is essential for securing the configurational stability of the newly created stereogenic center in **4** under the basic reaction conditions. On the other hand, the *p*-chlorobenzaldehyde imine of α-alkyl-α-amino acid *tert*-butyl ester **2** has been employed for the preparation of optically active α,α-dialkyl-α-amino acid derivatives by phase-transfer-catalyzed alkylation.[1,2] This is certainly because the α-proton of **2** is acidic enough to be deprotonated under typical conditions in contrast to its benzophenone imine counterpart **4**, and hence aldimine Schiff base **3**[3a] derived from glycine *tert*-butyl ester has long been regarded as an unsuitable substrate for the stereoselective monoalkylation. Over the course of our recent studies in this area of research, we became intrigued with the possibility of the enantioselective monoalkylation of **3** under appropriate phase-transfer conditions in view of its practical advantages such as low cost. Herein, we report that the selective monoalkylation of **3** is indeed feasible under mild liquid–liquid phase-transfer conditions, and our binaphthyl-derived chiral quaternary ammonium bromides **7**[3] and **8**[4] act as an efficient catalyst to achieve rigorous stereochemical control (Scheme 1).

2. Results and discussion

The requisite aldimine Schiff base **3** can be readily prepared by simple imine formation between glycine *tert*-butyl ester and *p*-chlorobenzaldehyde in MeOH at room temperature with the aid of $MgSO_4$. Monoalkylation of **3** was then performed by introducing a 50% KOH aqueous solution into a mixture of **3**, benzyl bromide (1.2 equiv), and (*R*,*R*)-**7** in toluene at 0 °C under an argon atmosphere followed by vigorous stirring at that temperature. The reaction was found to go to completion within 2 h and the corresponding α-benzyl-α-amino ester **6a** was obtained almost quantitatively without detectable production of the double benzylation product. Interestingly, the enantiomeric excess of **6a** was revealed to be 98% ee by HPLC analysis using a chiral column

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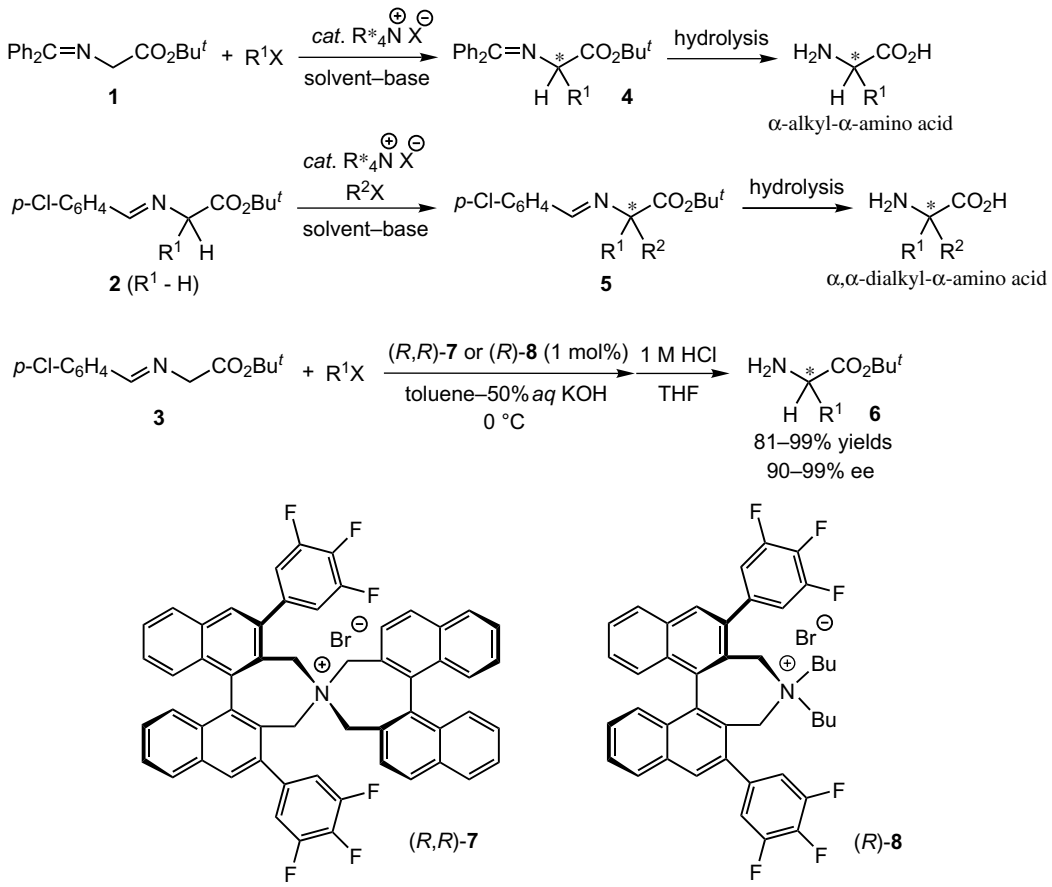


Scheme 1.

(entry 1 in Table 1). Moreover, the structurally simplified catalyst (*R*)-**8** exhibited comparable catalytic and chiral efficiency, giving **6a** in 95% yield with 98% ee (entry 2).

These promising results prompted us to conduct further experiments to probe the scope of common alkyl halides; and the selected examples listed in Table 1 demonstrate a rather surprising utility of this method. Generally, 1 mol % of **7** or **8** with 1.2 equiv of alkyl halide was sufficient enough for a smooth reaction. In addition to the representative *p*-substituted benzylic bromides, 1-bromomethyl naphthalene was well accommodated, offering practical access to a wide range of enantiomerically pure phenylalanine analogues (entries 3–8). For the simple allylation, **8** appeared to be a suitable catalyst (entries 9 and 10), while higher asymmetric induction was attained with **7** when cinnamyl bromide was a reacting partner (entries 13 and 14). Although significant rate retardation seemed inevitable in the reaction with less reactive alkyl halides, such as ethyl iodide under the present conditions (entry 15), it was overcome by using an excess amount of the electrophile (entries 16 and 17).

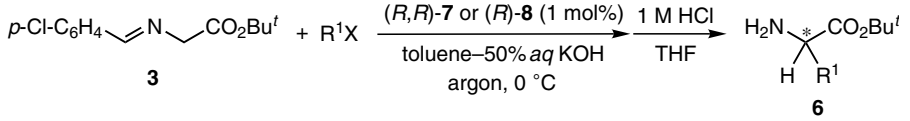
3. Conclusion

In conclusion, a highly enantioselective monoalkylation of *p*-chlorobenzaldehyde imine of glycine *tert*-butyl ester **3** has been accomplished by the utilization of either **7** or **8** as catalysts. The reaction proceeds smoothly at 0 °C in toluene with 50% KOH aqueous solution as a base, and a variety of alkyl halides are employable without fear of substantial racemization. *p*-Chlorobenzaldehyde, although inexpensive, can be recovered after acidic hydrolysis of the alkylation product, and directly reused for the condensation with glycine *tert*-butyl ester to prepare Schiff base **3**; this strengthens the practical aspect of the present methodology for application in the industrial production of various natural and unnatural α-amino acids.

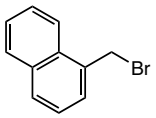
4. Experimental

A typical experimental procedure for the asymmetric alkylation of **3** under phase-transfer conditions is as follows (entry 7 in Table 1). A long reaction tube equipped with a cross shaped magnetic stir bar was charged with (*R*,*R*)-**7** (2.7 mg, 0.003 mmol), *p*-chlorobenzaldehyde imine of glycine *tert*-butyl ester **3** (76.1 mg, 0.30 mmol), 1-bromomethyl naphthalene (79.6 mg, 0.36 mmol), and toluene (2.0 mL). The flask was evacuated and filled with argon (three times, balloon), and the mixture was cooled to 0 °C in an ice bath. A solution of KOH (50 wt % in water, 0.6 mL) was added via syringe and the reaction mixture stirred vigorously under an argon atmosphere for 2 h at 0 °C. The reaction was quenched

Table 1. Asymmetric monoalkylation of **3** under phase-transfer conditions catalyzed by chiral quaternary ammonium bromide **7** or **8**[a]



3 **6**

Entry	Alkyl halide (R^1X)	Catalyst	Time (h)	Yield[b] (%)	ee[c] (%) (config)[d]	Product
1	$PhCH_2Br$	**7**	2	99	98 (*S*)	**6a**
2		**8**	2	95	98 (*S*)	**6a**
3	*p*-Me–$C_6H_4CH_2Br$	**7**	2	97	99	**6b**
4		**8**	4.5	96	98	**6b**
5	*p*-F–$C_6H_4CH_2Br$	**7**	2	99	95	**6c**
6		**8**	1.5	97	99	**6c**
7		**7**	2	96	99 (*S*)	**6d**
8		**8**	2	96	98 (*S*)	**6d**
9[e]	$CH_2{=}CHCH_2Br$	**7**	2	84	92	**6e**
10[e]		**8**	2	92	98	**6e**
11[e]	$CH_2{=}C(Me)CH_2Br$	**7**	2	99	98	**6f**
12[e]		**8**	2	95	96	**6f**
13	*trans*-PhCH=$CHCH_2Br$	**7**	3	82	94	**6g**
14		**8**	6	90	90	**6g**
15[e]	EtI	**7**	10	43	97 (*S*)	**6h**
16[e,f]		**7**	5	93	99 (*S*)	**6h**
17[e,f]		**8**	6	81	90 (*S*)	**6h**

[a] Unless otherwise noted, the reaction was carried out with 1.2 equiv of alkyl halide in the presence of 1 mol % of either (*R*,*R*)-**7** or (*R*)-**8** in toluene–50% KOH aqueous solution at 0 °C under argon atmosphere for the given reaction time.
[b] Isolated yield.
[c] Enantiomeric excess of the amino ester **6** was determined by HPLC analysis using a chiral column. See the typical procedure.
[d] The absolute configuration of **6a** was assigned by comparison of the specific rotation with the reported value.[5] For **6d** and the *N*-benzoate of **6h** the HPLC retention time was compared with that of the authentic sample independently synthesised via the alkylation of **1** using **7** as the catalyst.[3d]
[e] Isolated as its *N*-benzoate.
[f] With 10 equiv of EtI.

with H_2O (10 mL) at 0 °C and allowed to warm to room temperature. The mixture was separated and the aqueous phase extracted with Et_2O. The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was diluted with THF (10 mL) and the mixture was treated with 1 M HCl (10 mL) at 0 °C. After being stirred for 30 min, the reaction was allowed to warm to room temperature and extracted with Et_2O. The ethereal phase was back-extracted with 1 M HCl. The combined acidic aqueous layer was neutralized with solid $NaHCO_3$ at 0 °C and extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (1:3 hexane/EtOAc eluent) afforded **6d** as a clear oil (78.1 mg; 96% yield); $R_f = 0.29$ in 1:2 hexane/EtOAc; $[\alpha]_D^{26} = +33.6$ (*c* 1.04, $CHCl_3$, 99% ee); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.10 (1H, d, $J = 8.4$ Hz), 7.86 (1H, d, $J = 7.6$ Hz), 7.76 (1H, d, $J = 8.0$ Hz), 7.55–7.48 (2H, m), 7.42–7.35 (2H, m), 3.78 (1H, dd, $J = 5.2$, 8.8 Hz), 3.62 (1H, dd, $J = 5.2$, 14.0 Hz), 3.11 (1H, dd, $J = 8.8$, 14.0 Hz), 1.58 (2H, br), 1.40 (9H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.1, 133.7, 133.7, 131.8, 128.6, 127.4, 127.3, 125.9, 125.4, 125.1, 123.5, 81.1, 55.8, 39.0, 28.0; IR (neat) 3377, 1726, 1597, 1393, 1368, 1250, 1152, 793, 775; HRMS (ESI) calcd for $C_{17}H_{22}NO_2$: 272.1645 ($[M+H]^+$), found: 272.1649 ($[M+H]^+$); HPLC analysis: Daicel Chiralcel OD-H, hexane/2-propanol = 100:1, flow rate = 0.5 mL/min, $\lambda = 254$ nm, retention time; 53.2 min (*R*) and 81.1 min (*S*).

The volatile amino esters were isolated as their *N*-benzoates and subjected to HPLC analysis. The additional procedure required for the ethylation of **3** is representative. The alkylation experiment was conducted as described above. After its completion, H_2O (10 mL) was added at 0 °C and the whole mixture allowed to warm to room temperature. Then, the aqueous phase was separated and extracted with Et_2O. The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was diluted with THF (10 mL) and treated with 1 M HCl (10 mL) at 0 °C. After stirring for 30 min, the mixture was allowed to warm to room temperature and extracted with Et_2O. The ethereal phase was back-extracted with 1 M HCl. The combined acidic aqueous layer was neutralized with solid $NaHCO_3$ at 0 °C and extracted with $CHCl_3$. The combined organic layer was dried over Na_2SO_4 and filtrated without aspiration. The filtrate was cooled to 0 °C, and Et_3N (84.0 μL, 0.6 mmol) and benzoyl chloride (70.0 μL, 0.6 mmol) added sequentially. The reaction mixture was stirred for 1 h at 0 °C and evaporated in vacuo. The residue was purified by flash column chromatography

on silica gel (9:1 hexane/EtOAc eluent) to give **6h** as a white solid (73.2 mg; 93% yield); $R_f = 0.53$ in 4:1 hexane/EtOAc; $[\alpha]_D^{29} = +42.9$ (*c* 1.00, $CHCl_3$, 99% ee); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.81 (2H, m), 7.50 (1H, m), 7.43 (2H, m), 6.76 (1H, br), 4.69 (1H, m), 2.02 (1H, m), 1.83 (1H, m), 1.50 (9H, s), 0.96 (3H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.6, 166.6, 134.2, 131.4, 128.4, 126.9, 82.2, 54.0, 28.1, 25.9, 9.3; IR (neat) 3335, 3062, 1732, 1641, 1365, 1253, 1152, 777, 711; HRMS (ESI) calcd for $C_{15}H_{21}NNaO_3$: 286.1414 ($[M+Na]^+$), found: 286.1412 ($[M+Na]^+$); HPLC analysis: Daicel Chiralpak AD-H, hexane/2-propanol = 20:1, flow rate = 0.5 mL/min, $\lambda = 254$ nm, retention time; 16.9 min (minor) and 47.5 min (major).

Acknowledgments

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