Phase-Transfer-Catalyzed Enantioselective Alkylation of α-Benzoyloxy-β-Keto Ester

Takuya Hashimoto,[a] Keigo Sasaki,[a] Kazuhiro Fukumoto,[a] Yuichi Murase,[a] Takashi Ooi,[b] Keiji Maruoka*[a]

[a] Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo, Kyoto 606-8502, Japan
Fax +81(75)7534041; E-mail: maruoka@kuchem.kyoto-u.ac.jp

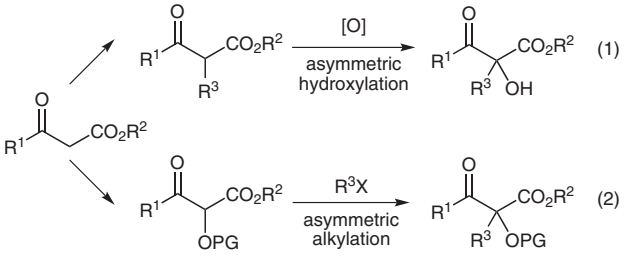
[b] Department of Applied Chemistry, Graduate School of Engineering, Nagoya University, Chikusa, Nagoya 464-8603, Japan

Received 10 October 2008

Abstract: Highly enantioselective alkylation of *tert*-butyl 2-benzoyloxy-3-oxobutanoate could be realized by the use of *N*-spiro chiral quaternary ammonium salt as phase-transfer catalyst, as a complementary approach to the asymmetric hydroxylation of α-alkyl-β-keto esters.

Key words: phase-transfer catalysis, alkylations, asymmetric catalysis, esters, alkyl halides

Asymmetric hydroxylation of α-alkyl-β-keto esters recently appeared as a unique tool to provide functionalized chiral *tert*-alcohol (Scheme 1, eq. 1).[1,2] Despite the attractiveness of this reaction, especially as a key intermediate for the preparation of 2,3-dihydroxycarboxylic acids containing a quaternary stereocenter, they generally suffer from the poor reactivity or enantioselectivity in the reaction of acyclic α-alkyl-β-keto esters irrespective of the catalyst employed. In this context, we planned to access these molecules in an optically enriched form relying on the well-established phase-transfer catalysis.[3] Thus, hydroxy group is initially incorporated into the α-position of the unfunctionalized β-keto ester as a prochiral molecule and the subsquent alkylation of this substrate under phase-transfer conditions is set as a crucial asymmetric induction step (Scheme 1, eq. 2).[4] The additional advantage of such a strategy is that a variety of chiral compounds are easily available just by changing the alkylating reagent (R^3 in Scheme 1), while anticipating the similar level of enantioselectity. Herein, we wish to report asymmetric alkylation of α-benzoyloxy-β-keto ester catalyzed by *N*-spiro chiral quaternary ammonium bromide **1** under liquid–solid phase-transfer conditions.



Scheme 1 Two distinctive approaches for the syntheses of α-alkyl-α-hydroxy-β-keto esters

SYNLETT 2009, No. 4, pp 0661–0663
Advanced online publication: 16.02.2009
DOI: 10.1055/s-0028-1087814; Art ID: Y01308ST

Asymmetric benzylation of *tert*-butyl 2-benzoyloxy-3-oxobutanoate (**2a**) catalyzed by 1 mol% *N*-spiro chiral quaternary ammonium bromide **1a** in the presence of 25% aqueous KOH was initially investigated in relation to our extensive researches on the use of **1** for various asymmetric phase-transfer catalysis.[5] Ester **2a** was chosen as a suitable substrate due to its ready availability and ease of deprotection after the reaction.[6] Gratifyingly, asymmetric benzylation proceeded smoothly at 0 °C to provide the alkylated compound **3a** in 72% yield with 79% ee (Table 1, entry 1). Further experiments using different catalysts revealed the efficiency of (*S*,*S*)-**1c**, with which the benzylated product was obtained in highest ee among the catalysts screened (entries 2–4). Anticipating the increase of the enantioselectivity, the reaction was then performed at lower temperature. When the reaction was performed under the influence of (*S*,*S*)-**1c** and 25% aqueous KOH at –20 °C, **3a** could be obtained with 90% ee (entry 5). We observed some amounts of hydrolyzed side products **4** and **5** (Figure 1) derived from **3a** in these reactions. To avoid such undesired processes, the reaction was then conducted under the influence of powdered KOH (1.5 equiv), while minimizing the amount of water present in the reaction mixture (entry 6). As a result, the benzylated compound was obtained in 91% yield without affecting the enantiomeric excess. Use of Cs_2CO_3 as base resulted in poor reactivity, leading to moderate conversion after prolonged reaction time (entry 7). Although further increase of the enantioselectivity could be achieved by conducting the reaction at –40 °C at the expense of the reaction time and the amount of base (entry 8), the reaction conditions employed in entry 6 was utilized for the further investigation, having the practical aspect in mind.

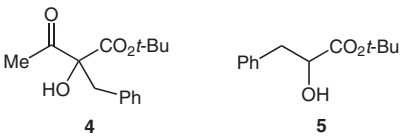
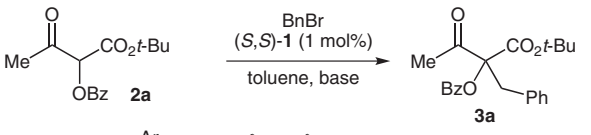
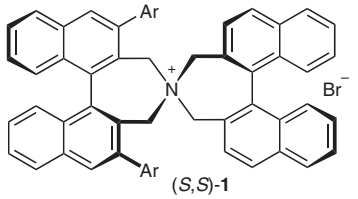


Figure 1

With the optimized conditions in hand, the scope and limitation of this asymmetric alkylation of α-benzoyloxy-β-keto ester was surveyed as shown in Table 2. Use of substituted benzyl bromides was initially evaluated. Irrespective of the electronic property of the aromatic rings,

Table 1 Asymmetric Alkylation of *tert*-Butyl 2-Benzoyloxy-3-Oxobutanoate[7] and Benzyl Bromide – Optimization of the Reaction Conditions[a]





1a Ar = 3,4,5-$F_3C_6H_2$
1b Ar = 2-naphthyl
1c Ar = 3,5-$(F_3C)_2C_6H_3$
1d Ar = 3,5-$Ph_2C_6H_3$

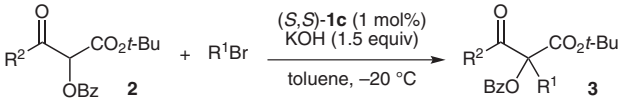
Entry	Catalyst	Base	Temp (°C)	Time (h)	Yield (%)[b]	ee (%)[c]
1	**1a**	25% KOH[d]	0	9	72	79
2	**1b**	25% KOH	0	9	72	60
3	**1c**	25% KOH	0	10	76	85
4	**1d**	25% KOH	0	9	83	62
5	**1c**	25% KOH	–20	12	79	90
6	**1c**	KOH[e]	–20	12	91	90
7	**1c**	Cs_2CO_3[f]	–20	96	49	89
8	**1c**	KOH[g]	–40	98	95	94

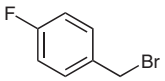
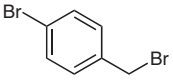
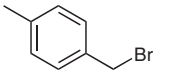
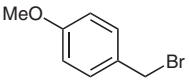
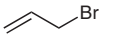
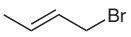
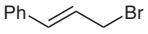
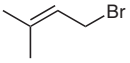
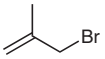
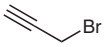
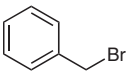
[a] Performed with *tert*-butyl 2-benzoyloxy-3-oxobutanoate (**2a**, 0.20 mmol) and benzyl bromide (0.24 mmol) in the presence of 1 mol% of catalyst (*S*,*S*)-**1** in toluene (2.0 mL) under the given reaction conditions.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] Aqueous KOH (0.50 mL).
[e] Powdered KOH (0.30 mmol).
[f] Powdered Cs_2CO_3 (1.0 mmol).
[g] Powdered KOH (1.0 mmol).

alkylated compounds were obtained in good yields with the selectivity ranging from 88% to 92% ee (entries 1–4). Allylic substrates were also suitable for this reaction furnishing the products in good yields and enantioselectivities (entries 5–9). Curiously, the reaction with propargyl bromide led to the significant drop of enantiomeric excess (entry 10). Our focus was then moved to the employment of other α-benzoyloxy-β-keto esters as nucleophiles. Asymmetric benzylation of 2-benzoyloxy-3-oxopentanoate **2b** furnished the alkylated compound in 88% yield with slightly diminished ee of 79%. Use of α-benzoyloxy-β-keto ester **2c** bearing propyl group as R^2 resulted in the further decrease of the enantioselectivity.

In conclusion, we succeeded in obtaining various α-alkyl-α-hydroxy-β-keto esters with uniformly high enantioselectivities by employing the phase-transfer catalyzed asymmetric alkylation of *tert*-butyl 2-benzoyloxy-3-oxobutanoate as a key asymmetric induction step.

Table 2 Asymmetric Alkylation of α-Benzoyloxy-β-Keto Esters and Alkyl Halides Catalyzed by (*S*,*S*)-**1c**[a]



Entry	R^1Br	R^2	Time (h)	Yield (%)[b]	ee (%)[c]
1		Me (**2a**)	10	**3b** 86	92
2		Me	10	**3c** 91	91
3		Me	4	**3d** 79	89
4		Me	7	**3e** 92	88
5		Me	20	**3f** 85	91
6[d]		Me	9	**3g** 90	91
7		Me	9	**3h** 88	90
8		Me	10	**3i** 89	87
9		Me	20	**3j** 41	83
10		Me	24	**3k** 29	61
11		Et (**2b**)	4	**3l** 88	79
12		Pr (**2c**)	12	**3m** 40	73

[a] Performed with **2** (0.2 mmol) and R^1Br (0.24 mmol) in the presence of 1 mol% of catalyst (*S*,*S*)-**1c** and powdered KOH (0.3 mmol) in toluene (2 mL) at –20 °C.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis or GC analysis.
[d] Crotyl bromide used as a 5:1 *E*/*Z* mixture.

Acknowledgment

This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

References and Notes

(1) For general reviews, see: (a) Christoffers, J.; Baro, A.; Werner, T. *Adv. Synth. Catal.* **2004**, *346*, 143. (b) Shibasaki, M.; Kanai, M. *Chem. Rev.* **2008**, *108*, 2853.
(2) (a) Toullec, P. Y.; Bonaccorsi, C.; Mezzetti, A.; Togni, A. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5810. (b) Bonaccorsi, C.; Althaus, M.; Becker, C.; Togni, A.; Mezzetti, A. *Pure Appl. Chem.* **2006**, *78*, 391. (c) Acocella, M. R.; Mancheno, O. G.; Bella, M.; Jørgensen, K. A. *J. Org.*

Chem. **2004**, *69*, 8165. (d) Ishimaru, T.; Shibata, N.; Nagai, J.; Nakamura, S.; Toru, T.; Kanemasa, S. *J. Am. Chem. Soc.* **2006**, *128*, 16488.

(3) For recent reviews, see: (a) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2007**, *107*, 5656. (b) Ooi, T.; Maruoka, K. *Angew. Chem. Int. Ed.* **2007**, *46*, 4222. (c) Ooi, T.; Maruoka, K. *Aldrichimica Acta* **2007**, *40*, 77. (d) Maruoka, K.; Ooi, T.; Kano, T. *Chem. Commun.* **2007**, 1487. (e) Maruoka, K. *Chimia* **2007**, *61*, 263. (f) Maruoka, K. *Org. Process Res. Dev.* **2008**, *12*, 679.

(4) For the phase-transfer-catalyzed asymmetric hydroxylation of oxindoles by molecular oxygen, see: Sano, D.; Nagata, K.; Itoh, T. *Org. Lett.* **2008**, *10*, 1593.

(5) (a) Ooi, T.; Miki, T.; Taniguchi, M.; Shiraishi, M.; Takeuchi, M.; Maruoka, K. *Angew. Chem. Int. Ed.* **2003**, *42*, 3796. (b) Ooi, T.; Miki, T.; Maruoka, K. *Org. Lett.* **2005**, *7*, 191. (c) Ooi, T.; Miki, T.; Fukumoto, K.; Maruoka, K. *Adv. Synth. Catal.* **2006**, *348*, 1539.

(6) Scheid, G.; Kuit, W.; Ruijter, E.; Orru, R. V. A.; Henke, E.; Bornsheuer, U.; Wessjohann, L. A. *Eur. J. Org. Chem.* **2004**, 1063.

(7) **Typical Procedure for the Catalytic Asymmetric Alkylation of *tert*-Butyl 2-Benzoyloxy-3-oxobutanoate under Phase-Transfer Conditions**

To a solution of phase-transfer catalyst (*S*,*S*)-**1c** (0.002 mmol, 2.2 mg) and **2a** (0.20 mmol, 55.7 mg) in toluene (2 mL) was added benzyl bromide (0.24 mmol, 28.5 μL) and the mixture was cooled to –20 °C. After adding freshly powdered KOH (0.3 mmol, 19.8 mg) to this mixture, the reaction mixture was vigorously stirred until the completion of the reaction. The mixture was then poured into sat. aq NH_4Cl and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 to give *tert*-butyl 2-benzoyloxy-2-benzyl-3-oxobutanoate as a colorless oil [91% (67.6 mg), 90% ee]. Enantiomeric purity was determined by HPLC analysis [(Daicel Chiralpak AD-H, hexane–2-PrOH (100:1), flow rate = 0.5 mL/min, t_R = 22.3 min(major) and 25.0 min(minor)].

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (2 H, d, *J* = 7.3 Hz, ArH), 7.61 (1 H, t, *J* = 7.6 Hz, ArH), 7.46 (2 H, app t, *J* = 7.8 Hz, ArH), 7.21–7.22 (3 H, m, ArH), 7.12 (2 H, m, ArH), 3.65 (2 H, s, $PhCH_2$), 2.25 (3 H, s, $COCH_3$), 1.40 (9 H, s, *t*-Bu). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.2, 165.3, 165.2, 134.4, 133.5, 130.2, 129.8, 129.3, 128.5, 128.3, 127.1, 89.0, 83.4, 38.8, 27.6, 27.4. IR (neat): 2978, 2932, 1755, 1721, 1279, 1152, 1107, 1094, 1069, 1026 912, 845, 733, 700 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_{22}H_{24}O_5$: 391.1516 $[M + Na]^+$; found: 391.1516 $[M + Na]^+$. $[\alpha]_D^{28}$ –46.5 (*c* 1.0, $CHCl_3$; 90% ee).