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Asymmetric Synthesis of α-Acyl-γ-butyrolactones Possessing All-Carbon Quaternary Stereocenters by Phase-Transfer-Catalyzed Alkylation

Takashi Ooi,[a] Takashi Miki,[a] Kazuhiro Fukumoto,[a] and Keiji Maruoka[a,*]

[a] Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo, Kyoto 606-8502, Japan
Fax: (+81)-75-753-4041; e-mail: maruoka@kuchem.kyoto-u.ac.jp

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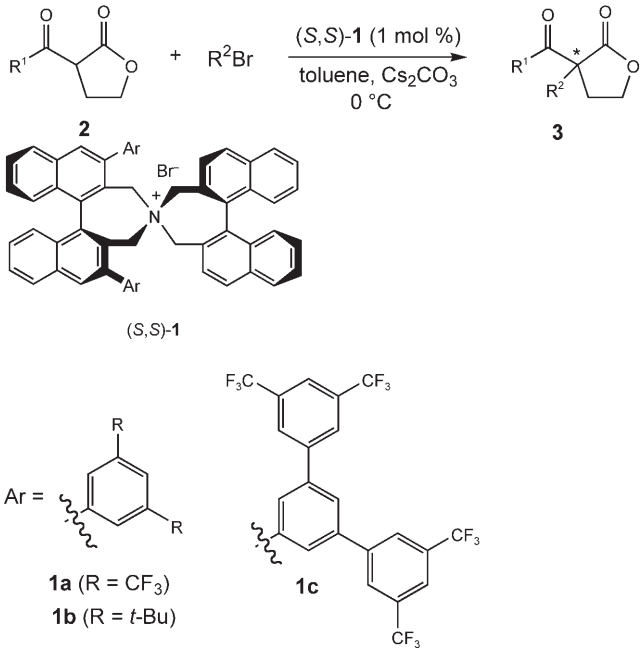
Abstract: The enantioselective construction of all-carbon quaternary stereocenters on α-acyl-γ-butyrolactones has been achieved by the *N*-spiro chiral quaternary ammonium bromide **1**-catalyzed alkylation under mild phase-transfer conditions. The resulting α-alkylated keto lactones serve as valuable chiral building blocks in organic synthesis as clearly demonstrated by the facile conversion to optically active α,α-dialkyl-α-amino acid derivatives *via* Schmidt rearrangement.

Keywords: α-acyl-γ-butyrolactones; chiral quaternary ammonium bromide; organic catalysis; phase-transfer alkylation; quaternary carbon centers

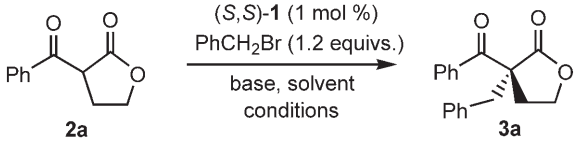
The asymmetric construction of all-carbon quaternary stereocenters on highly functionalized organic molecules, particularly in a catalytic manner, represents a very challenging yet important task in current organic synthesis.[1] We recently contributed to this rapidly growing area by achieving phase-transfer-catalyzed asymmetric alkylation and Michael reaction of β-keto esters with *N*-spiro C_2-symmetric chiral quaternary ammonium salt **1a** as catalyst.[2] During our continuous efforts for expanding the synthetic utility of our approach, we sought to extend the substrate range to heterocyclic donors such as lactones in view of their potential usefulness as chiral building blocks.[3] Herein we report the highly enantioselective alkylation of α-acyl-γ-butyrolactones catalyzed by **1** under mild phase-transfer conditions, providing a direct access to enantiomerically enriched α-alkylated keto lactones **3** (Scheme 1).

Attempted reaction of α-benzoyl-γ-butyrolactone (**2a**) with benzyl bromide in the presence of K_2CO_3 (5 equivs.) and (*S*,*S*)-**1a**[2,4a] (1 mol%) in toluene proceeded sluggishly at 0°C and the desired alkylation product **3a** was obtained in only 12% yield after 24 h of stirring (entry 1 in Table 1). However, the enantiomeric excess of **3a** was revealed to be quite promising (89% *ee*), and thus different bases were examined for rate enhancement without sacrificing the stereoselectivity. Fortunately, the benzylation was completed in 9 h when Cs_2CO_3 was employed, giving rise to **3a** in 85% with 88% *ee* (entry 2). Here, use of other solvents such as mesitylene, *o*-xylene and more polar *tert*-butyl methyl ether (TBME) did not lead to an improvement of the enantioselectivity (entries 3–5). We also evaluated the steric effect of the 3,3′-aromatic substituents (Ar) of the catalyst using **1b**[4d] and **1c**,[4b,c] which showed the superiority of **1a** in terms of both reactivity and selectivity (entries 6 and 7). Finally, the highest enantioselectivity (91% *ee*) was found to be attainable by performing the alkylation at −20°C, although a prolonged reaction time was required (entry 8).[5]



Scheme 1. Asymmetric alkylation of α-acyl-γ-butyrolactones **2** under phase-transfer conditions using (*S*,*S*)-**1** as catalyst.

Table 1. Screening of the reaction parameters in the phase-transfer-catalyzed benzylation of α-benzoyl-γ-butyrolactone (**2a**) using (*S*,*S*)-**1** as catalyst.[a]



Entry	Catalyst	Base	Solvent	Temperature [°C]	Reaction time [h]	Yield [%][b]	% *ee*[c]
1	**1a**	K_2CO_3	toluene	0	24	12	89
2	**1a**	Cs_2CO_3		0	9	85	88
3	**1a**		mesitylene	0	18	80	80
4	**1a**		*o*-xylene	0	12	83	83
5	**1a**		TBME	0	36	89	88
6	**1b**		toluene	0	9	80	61
7	**1c**			0	20	90	66
8	**1a**			−20	84	91	91

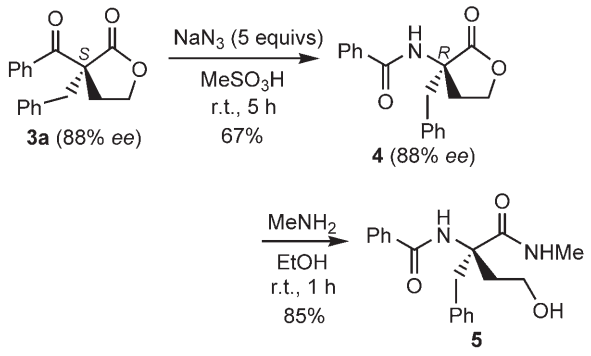
[a] The reaction was carried out with 1.2 equivs. of benzyl bromide in the presence of 5 equivs. of base and 1 mol % of (*S*,*S*)-**1** in an appropriate solvent under the given reaction conditions.
[b] Isolated yield.
[c] Enantiopurity of **3a** was determined by HPLC analysis using a chiral column (DAICEL Chiralpak AD-H) with hexane-2-propanol as solvent. Absolute configuration of the major enantiomer of **3a** was assigned to be *S*.[5]

On the basis of the results, the catalysis of (*S*,*S*)-**1a** in toluene at 0 °C was applied to further investigations on the substrate scope.[6] As summarized in Table 2, the alkylation was relatively less sensitive to the character of the benzylic bromide aromatic moiety in terms of both enantioselectivity and reaction efficiency. Electron-withdrawing and -donating substituents at the *para* position afforded a marginal effect on the selectivity (entries 1 and 2). In addition, 2-naphthyl- and 2-pyridylmethyl bromides were tolerated for the reaction (entries 3 and 4). Unfortunately, however, the use of allylic bromides and propargyl bromide as an elecrophilic partner led to an erosion of the stereoselectivity (entries 5–7).

Structural variation in the α-acyl-γ-butyrolactone component was also possible without loss of enantioselectivity as evident from the results of the benzylation of the substrates bearing *para*-substituted benzoyl groups (entries 8–10). It is noteworthy that the butyrolactone possessing an alkylcarbonyl moiety appeared to be a good candidate for this phase-transfer-catalyzed asymmetric quaternization, and the corresponding α-alkylated keto lactone was obtained with good enantiomeric excess (entry 11).

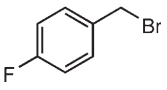
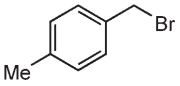
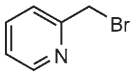
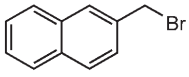
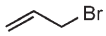
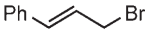
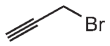
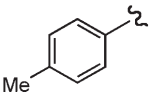
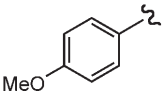
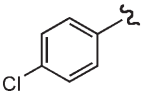
The α-alkylated keto lactones of high enantiomeric purity can be readily transformed to the protected α-alkyl-α-amino lactones by Schmidt rearrangement with complete retention of the configuration of the α-quaternary stereocenters.[7] For instance, treatment of **3a** [88 % *ee* (*S*)] with sodium azide in methanesulfonic acid at room temperature for 5 h resulted in the formation of α-(*N*-benzoylamino)-α-benzyl-γ-butyrolactone (**4**) in 67 % yield without loss of the enantiomeric excess [88 % *ee* (*R*)] (Scheme 2). The usefulness of the resulting **4** as a synthetic intermediate was also highlighted by the subsequent facile aminolysis with methylamine,[8] affording the optically active, functionalized α,α-dialkyl-α-amino amide **5** in high yield as indicated in Scheme 2.

In summary, we have successfully demonstrated that the present phase-transfer-catalyzed alkylation strategy for the asymmetric construction of all-carbon quaternary stereocenters on 1,3-dicarbonyl compounds can nicely accommodate α-acyl-γ-butyrolactones. This finding certainly expands the synthetic utility of our approach based on the use of *N*-spiro chiral quaternary ammonium bromide **1a** as an efficient phase-transfer catalyst, and provides a practical access to a variety of optically active α-alkylated keto lactones as well as α,α-dialkyl-α-amino acid derivatives.



Scheme 2. Facile conversion of of **3a** to α,α-dialkyl-α-amino acid derivatives **4** and **5**.

Table 2. Phase-transfer-catalyzed asymmetric quaternization of **2**.[a]

Entry	**2** (R^1)	R^2Br	Reaction time [h]	Yield [%][b]	% *ee*[c]
1	Ph		6	80	87
2	Ph		9	85	83
3	Ph		15	87	80
4	Ph		12	83	83
5	Ph		10	82	56
6[d]	Ph		72	89	61
7	Ph		48	40	29
8		$PhCH_2Br$	24	97	88
9		$PhCH_2Br$	24	94	90
10		$PhCH_2Br$	24	79	88
11	*i*-Pr	$PhCH_2Br$	24	82	78

[a] The reaction was carried out with 1.2 equivs. of R^2Br in the presence of 1 mol% of (*S*,*S*)-**1a** and 5 equivs. of Cs_2CO_3 in toluene at 0°C for the given reaction time.
[b] Isolated yield.
[c] Enantiopurity of **3** was determined by HPLC analysis using a chiral column (DAICEL Chiralpak AD-H or Chiralcel OD-H) with hexane-2-propanol as solvent.
[d] Performed at −10°C.

Experimental Section

Preparation of α-Benzoyl-γ-butyrolactone (2a)[9]

To a solution of lithium diisopropylamide (12.5 mmol) in THF (20 mL) was added γ-butyrolactone (384 μL, 5.0 mmol) at −78°C under an argon atmosphere and the mixture was stirred for 1 h at the same temperature. Then, benzoyl chloride (640 μL, 5.5 mmol) was added at −78°C and stirring was continued for 15 min. The reaction mixture was diluted with 1 N HCl and extracted with AcOEt (3 times). The combined organic extracts were washed with brine and dried over Na_2SO_4. Evaporation of solvents and purification of the residual crude products by column chromatography on silica gel (hexane/AcOEt = 4:1 as eluent) gave α-benzoyl-γ-butyrolactone (**2a**); yield: 808 mg (4.25 mmol, 85%).

Representative Procedure for the Phase-Transfer-Catalyzed Alkylation of 2 (Entry 2 in Table 1)

To a mixture of α-benzoyl-γ-butyrolactone (**2a**; 57.2 mg, 0.30 mmol) and (*S*,*S*)-**1a** (3.2 mg, 0.003 mmol, 1 mol%) in toluene (3 mL) was added benzyl bromide (43 μL, 0.36 mmol) and Cs_2CO_3 (488 mg, 1.5 mmol) sequentially at 0°C under an argon atmosphere, and the mixture was stirred for 9 h at the same temperature. The resulting mixture was diluted with water and extracted with AcOEt (3 times). The combined organic extracts were washed with brine and then dried over Na_2SO_4. Evaporation of solvents and purification of the residual crude products by column chromatography on silica gel (hexane/AcOEt = 6:1 as eluent) gave the corresponding alkylation product **3a**;[10] yield: 72.1 mg (0.257 mmol, 85%); $[\alpha]_D^{29}$: +5.8° (*c* 0.96, $CHCl_3$) [88% *ee* (*S*)]; ^1H NMR (400 MHz, $CDCl_3$, room temperature): δ = 8.03 (2H, d, *J* = 7.6 Hz, Ph), 7.57 (1H, t, *J* = 7.6 Hz, Ph), 7.47 (2H, dd, *J* = 7.6, 7.6 Hz, Ph), 7.29–7.22 (3H, m, Ph), 7.17–7.11 (2H, m, Ph), 4.23 (1H, ddd, *J* = 8.8, 8.0, 6.8 Hz, CH_2O), 3.68 (1H, ddd, *J* = 8.8, 8.8, 5.6 Hz, CH_2O), 3.50 (1H, d, *J* = 13.6 Hz, CH_2Ph), 3.45 (1H, d, *J* = 13.6 Hz, CH_2Ph), 2.88 (1H, ddd, *J* = 13.6, 8.0, 5.6 Hz, CH_2CH_2O), 2.34 (1H, ddd, *J* = 13.6, 8.8, 6.8 Hz, CH_2CH_2O); ^{13}C NMR (100 MHz, $CDCl_3$, room temperature): δ = 195.1, 176.1, 135.1, 132.9, 129.8, 129.0, 128.5, 128.5, 127.2, 66.3, 60.5, 40.8, 31.6; HPLC conditions: DAICEL Chiralpak AD-H, hexane/*i*-PrOH = 10:1, flow rate = 0.5 mL min^{-1}, retention times: 21.3 min (*S*), 23.4 min (*R*).

Acknowledgements

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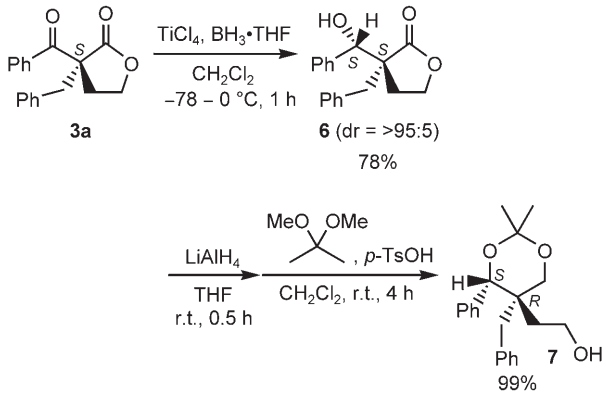
[5] For the assignment of the absolute configuration, **3a** was first reduced to the corresponding β-hydroxy lactone **6** diastereoselectively by $TiCl_4$-BH_3·THF system,[11] and the relative stereochemistry of **6** was verified by NOE measurement after derivatization to cyclic ketal **7** as shown below.[12] Then, the absolute configuration of the hydroxy-bearing carbon of **6** was determined to be *S* by ^{1}H NMR analysis of the corresponding (*R*)- and (*S*)-MTPA esters,[13] eventually confirming the absolute configuration of the adjacent α-quaternary stereocenter of **6** to be *S*.



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