Stereoselective Alkylation

Highly Enantioselective Construction of Quaternary Stereocenters on β-Keto Esters by Phase-Transfer Catalytic Asymmetric Alkylation and Michael Reaction**

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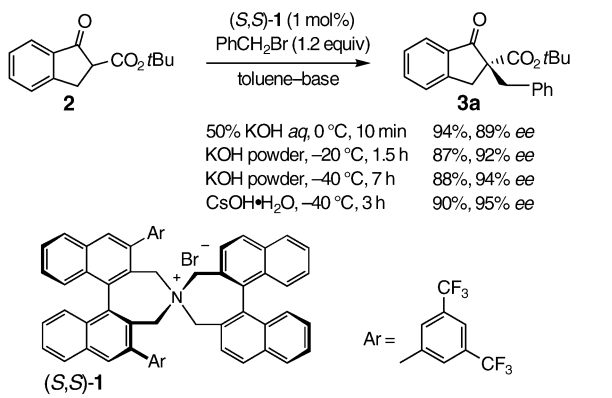
The construction of organic molecules containing chiral quaternary carbon centers by catalytic enantioselective reactions represents a very challenging and demanding area in organic synthesis,[1] because in addition to the inherent difficulty of developing an appropriate catalyst system, chiral fully substituted carbon centers are often essential for the biological activity of natural products and pharmaceuticals. Among the various transformations suitable for this purpose, the catalytic asymmetric alkylation of β-keto esters facilitates the direct stereocontrolled formation of quaternary stereocenters with structurally diverse substituents, which offers ample opportunity for further structural elaboration. However, few examples have been demonstrated to date, and only palladium-catalyzed asymmetric allylic alkylation has proved to be promising as an alternative strategy.[2] Although a method for asymmetric alkylation under phase-transfer catalysis should provide a simple yet potential solution to this problem, it is far being a synthetically useful method.[3,4] Herein we wish to report highly enantioselective phase-transfer alkylation of β-keto esters catalyzed by *N*-spiro C_2-symmetric chiral quaternary ammonium salt **1**,[5] which results in the catalytic asymmetric establishment of a quaternary stereogenic center (Scheme 1). We also describe further utilization of our approach to establishing chirality by asymmetric Michael addition to α,β-unsaturated carbonyl compounds.

As expected based on the relatively low reactivity of metal enolates of 1,3-dicarbonyl compounds, attempted treatment of 2-*tert*-butoxycarbonyl-1-indanone (**2**) with benzyl bromide (1.2 equiv) in toluene/50% KOH aqueous solution at 0°C for several hours led to gradual formation of the alkylation product **3a** (13% yield after 6 h). In marked contrast, however, the benzylation in the presence of 1 mol% of chiral ammonium bromide **1** under otherwise similar conditions proceeded instantaneously to give **3a** in 94% yield and, fortunately, the selectivity was determined to be 89% *ee* (Scheme 1). To improve the enantioselectivity, we examined the effect of temperature on the reaction with solid inorganic bases and found that vigorous stirring of the mixture of **2**, benzyl bromide (1.2 equiv), **1** (1 mol%), and powdered KOH (5 equiv) in toluene at −20°C for 1.5 h afforded **3a** in 87% yield with 92% *ee*.[6] Even higher selectivity (94% *ee*) was achieved by conducting the reaction at −40°C, though the reaction was slower. The reactivity was improved when $CsOH{\cdot}H_2O$ was used as a base, leading to the production of **3a** in 90% yield with 95% *ee* after a reaction time of 3 h.[7]



Scheme 1. Optimization of the reaction conditions for the phase-transfer enantioselective benzylation of β-keto ester **2** in the presence of the catalyst (*S*,*S*)-**1**.

With these optimized conditions in hand, we explored the general applicability of the present phase-transfer catalytic asymmetric alkylation system; the results are summarized in Table 1. The catalytic asymmetric creation of quaternary carbon centers by introduction of methyl and allylic substituents to substrate **2** has been demonstrated with appropriate electrophiles. Excellent chemical yields as well as enantioselectivities were attained (entries 2–4). Introduction of a functionalized benzylic side chain was also successfully realized, and the desired product was obtained in 86% yield with 97% *ee* (entry 5). Not only cyclopentanone derivatives but also 2-alkoxycarbonylcyclohexanones appeared to be good candidates for this alkylation, and a high level of enantioselectivity was observed (entry 8). Moreover, enantiofacial differentiation of the enolate derived from an acyclic β-keto ester was feasible with our approach (entry 9).

Optically active α,α-dialkyl-β-keto esters can be readily converted to the corresponding β-hydroxy acid and β-amino acid derivatives without loss of chirality as exemplified in Scheme 2. Reduction of **4** (97% *ee*) with L-Selectride in THF at −78°C gave rise to the β-hydroxy ester **5** (97% *ee*) with a diastereomeric ratio of 86:14.[8] Further, reductive amination of **4** with benzyl amine and sodium cyanoborohydride in the presence of 4 Å molecular sieves in MeOH afforded the N-protected β-amino ester **6** almost quantitatively.[9]

Furthermore, our approach was found to be applicable to catalytic asymmetric Michael addition of β-keto esters to α,β-unsaturated carbonyl compounds, which is also a very

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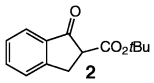
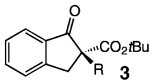
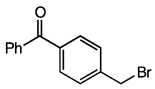
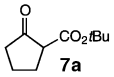
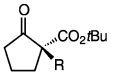
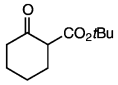
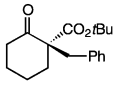
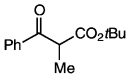
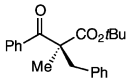
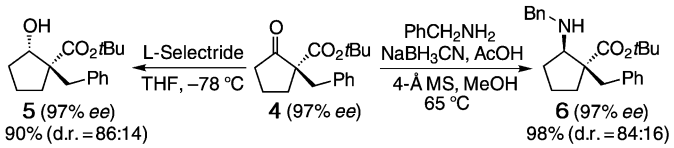
Table 1: Catalytic enantioselective phase-transfer alkylation of β-keto esters.[a]

Entry	β-Keto ester	RX	Conditions [°C, h]	Product	Yield [%][b]	Sel. [% *ee*][c] (config)
1	 **2**	$PhCH_2Br$	−40, 3	 **3**	90	95 (*R*)[d]
2		Me_2SO_4	−30, 7		99	87 (*R*)[d,e]
3		$CH_2{=}CHCH_2Br$	−50, 12		94	91
4		$PhCH{=}CHCH_2Br$	−40, 5		93	96
5			−40, 7		86	97
6	 **7a**	$PhCH_2Br$	−40, 2.5		94	97 (*S*)[f]
7		$PhCH{=}CHCH_2Br$	−60, 9	80	92	
8		$PhCH_2Br$	−40, 4		88	92 (*S*)[f]
9		$PhCH_2Br$	−30, 9		96	85

[a] Unless otherwise specified, the reaction was carried out with 1.2 equiv RX and 5 equiv $CsOH{\cdot}H_2O$ in the presence of 1 mol% **1** in toluene under the given reaction conditions. [b] Yield of isolated product. [c] Enantiopurity was determined by HPLC analysis of the alkylated product with a chiral column: DAICEL Chiralcel OD-H (entries 1, 6–9), Chiralpak AS (entry 2), and Chiralpak AD (entries 3–5) with hexane/2-propanol or hexane/ethanol as eluent. [d] Absolute configuration was determined by comparison of the optical rotation of the corresponding methyl ester with the literature value.[15] [e] With 3 equiv Me_2SO_4. [f] Assigned by comparison of the HPLC retention time with that reported.[3b]



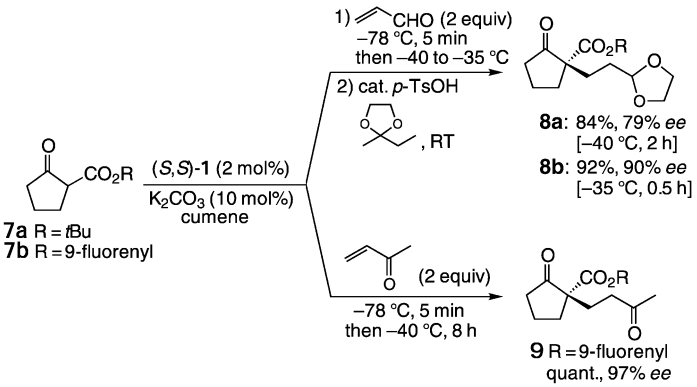
Scheme 2. Facile derivatization of optically active **4** to give the corresponding β-hydroxy ester **5** and β-amino ester **6**. MS = molecular sieves.

attractive tool for the synthesis of compounds with chiral quaternary carbon centers.[10] Particularly, in contrast to the previous methods elaborated for the reaction with α,β-unsaturated ketones and esters,[11] our system enabled the use of α,β-unsaturated aldehydes as a Michael acceptors, leading to the construction of quaternary stereocenter having three different functionalities of carbonyl origin. For instance, treatment of 2-*tert*-butoxycarbonylcyclopentanone (**7a**) with acrolein in the presence of **1** (2 mol%) and K_2CO_3 (10 mol%) in cumene at −78 °C followed by stirring at −40 °C for 2 h resulted in clean formation of the corresponding Michael adduct, which was isolated as its acetal **8a** in 84% yield with 79% *ee*.[12] Interestingly, use of fluorenyl ester **7b** as a substrate dramatically improved the enantioselectivity to 90% *ee* (92% yield) (Scheme 3). The reaction of **7b** with α,β-unsaturated ketones such as methyl vinyl ketone also proceeded smoothly under similar conditions, and the desired **9** was obtained quantitatively with 97% *ee*.[13]

In conclusion, we have accomplished the highly enantioselective phase-transfer catalytic alkylation and Michael reaction of β-keto esters by using a designer chiral quaternary ammonium salt as the catalyst, which allows efficient construction of fully substituted stereogenic centers. This provides a reliable route for the asymmetric synthesis of not only α,α-dialkyl-β-hydroxy acid and β-amino acid derivatives but also other useful building blocks with chiral quaternary carbon atoms.

Experimental Section

A representative procedure for enantioselective alkylation of β-keto ester **2** under solid–liquid phase-transfer conditions (entry 1 in Table 1): To a mixture of **2** (69.7 mg, 0.30 mmol) and (*S*,*S*)-**1** (3.2 mg, 0.003 mmol, 1 mol%) in toluene (2 mL) was added benzyl bromide (42.8 μL, 0.36 mmol) and $CsOH{\cdot}H_2O$ (252 mg, 1.5 mmol) at −40 °C under argon atmosphere, and the mixture was stirred for 4 h at the same temperature. The reaction mixture was diluted with water and extracted with Et_2O (three times). The combined extracts were washed with water and brine, and then dried over Na_2SO_4. Evaporation of solvent and purification of the residual crude products by column chromatography on silica gel (hexane/Et_2O = 5:1 as eluent) gave (*R*)-**3a** (86.0 mg, 0.27 mmol, 90% yield, 95% *ee*) as a colorless oil. $[\alpha]_D^{26} = +134.3°$ ($c = 1.2$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.72$ (1H, d, $J = 7.2$ Hz, Ar-H), 7.51 (1H, t, $J = 7.2$ Hz, Ar-H), 7.33 (1H, d, $J = 7.2$ Hz, Ar-H), 7.31 (1H, t, $J = 7.2$ Hz, Ar-H), 7.20–7.06 (5H, m, Ph), 3.56 (1H, d, $J = 17.2$ Hz, CH_2), 3.43 (1H, d, $J = 17.6$ Hz, CH_2), 3.26 (1H, d, $J = 17.6$ Hz, CH_2), 3.12 (1H, d, $J = 17.2$ Hz, CH_2), 1.38 ppm (9H, s, *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 202.4$, 169.5, 153.2, 136.7, 135.3, 134.9, 129.8, 128.0, 127.3, 126.5, 126.0, 124.4, 82.0, 62.4, 39.4, 35.7, 27.8 ppm; IR (liquid film): $\tilde{\nu} = 2978$, 2930, 1740, 1709, 1607,



Scheme 3. Catalytic asymmetric Michael addition of β-keto ester **7** to α,β-unsaturated carbonyl compounds under phase-transfer conditions. RT = room temperature.

1456, 1369, 1254, 1215, 1151, 1026, 932, 847, 762, 739, 702 cm^{-1}. HRMS (ESI-TOF) calcd for $C_{21}H_{22}O_3Na$ ($[M+Na]^+$): 345.1461, found: 345.1470. HPLC conditions: DAICEL Chiralcel OD-H, hexane/*i*PrOH = 100:1, flow rate = 0.5 mL min^{-1}, retention times = 14.2 min (*R*), 17.1 min (*S*).

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Keywords: alkylation · asymmetric synthesis · Michael addition · phase-transfer catalysis

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[6] The results of the benzylation of **2** with other alkaline metal hydroxides under similar conditions are as follows: 2% yield, 45% *ee* with LiOH; 40% yield, 83% *ee* with NaOH.

[7] Although a chiral ammonium bromide of type **1** having a 3,4,5-trifluorophenyl group (Ar = 3,4,5-F_3-Ph), a promising catalyst for the synthesis of α,α-dialkyl-α-amino acids,[5b] was also found to be effective, it lacked generality in the present system. A typical example is the benzylation of *tert*-butyl 2-benzoylpropanoate (43%, 70% *ee* with **1** (Ar = 3,4,5-F_3-Ph); see entry 9 in Table 1 for comparison).

[8] Absolute configuration of the hydroxy-bearing carbon center of **5** was determined to be *S* by ^{1}H NMR analysis of the corresponding (*R*) and (*S*) Mosher esters.[14]

[9] The stereochemistry of **6** was assigned by an NOE experiment.

[10] For recent reviews on catalytic asymmetric Michael reactions, see: a) N. Krause, A. Hoffman-Röder, *Synthesis* **2001**, 171; b) M. Sibi, S. Manyem, *Tetrahedron* **2000**, *56*, 8033; c) M. Kanai, M. Shibasaki in *Catalytic Asymmetric Synthesis*, 2nd ed. (Ed.: I. Ojima), Wiley, New York, **2000**, p. 569; d) K. Tomioka, Y. Nagaoka in *Comprehensive Asymmetric Catalysis, Vol. 3* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, Chap. 31.1.

[11] For a recent successful example, see: a) Y. Hamashima, D. Hotta, M. Sodeoka, *J. Am. Chem. Soc.* **2002**, *124*, 11240 and related references cited therein. This type of reaction by chiral phase-transfer catalysis has so far been unsuccessful; see: b) G. Szöllösi, M. Bartók, *Chirality* **2001**, *13*, 614.

[12] With toluene as solvent, the enantioselectivity was slightly decreased (97% yield, 73% *ee* with **7a**).

[13] The absolute configuration of **9** was determined by comparison of the optical rotation with the reported value after conversion to the corresponding methyl ester.[10a]

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