JOC*Note*

Enantioselective Alkylation of β-Keto Esters by Phase-Transfer Catalysis Using Chiral Quaternary Ammonium Salts

Eun Joo Park, Mi Hee Kim, and Dae Young Kim*

Department of Chemistry, Soonchunhyang University, Asan P.O. Box 97, Chungnam 336-600, Korea

dyoung@sch.ac.kr

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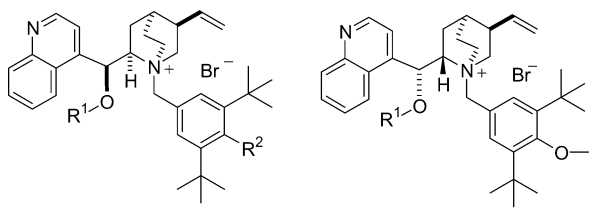
Abstract: Catalytic enantioselective alkylation promoted by a quaternary ammonium salt from cinchonine as a phase transfer catalyst is described. Treatment of cyclo β-keto esters with alkyl halide under mild reaction conditions afforded the corresponding α-alkylated β-keto esters in moderate to excellent yields with high enantiomeric excesses

The development of synthetic methods for enantioselective construction of quaternary carbon centers has received considerable attention in organic synthesis.[1] β-Keto esters become interesting substrates that permit ready and various opportunities for further structural manipulation.[2] Until now, there are a few reports for the enantioselective catalytic alkylation of β-keto esters, such as palladium-catalyzed asymmetric allylation[3] and phase-transfer alkylation of β-keto esters catalyzed by chiral ammonium salts.[4,5] Phase-transfer catalysis is an important and useful method in organic synthesis.[6] Recently, cinchona alkaloid-derived quaternary ammonium salts have been successfully applied to catalytic asymmetric synthesis.[7] The introduction of the bulky subunit at the bridgehead nitrogen of cinchona alkaloids leads to enhancement of the stereoselectivities in catalytic phase-transfer reactions.[8]



3a, R^1 = allyl, R^2 = OMe
3b, R^1 = benzyl, R^2 = OMe
3c, R^1 = propargyl, R^2 = OMe
3d, R^1 = allyl, R^2 = H

3e, R^1 = allyl

FIGURE 1.

As part of our research program toward the development of effective cinchona alkaloid-derived phase-transfer catalysts,[9] we report herein enantioselective alkylation of β-keto esters promoted by quaternary ammonium salts from cinchonine as phase-transfer catalysts.

To determine suitable reaction conditions for the catalytic enantioslective alkylation of β-keto esters, we initially investigated the reaction system by using 10 mol % of catalysts with tetralone carboxylate methyl ester **1a** as a model compound and allyl bromide as an alkylating agent (Table 1).

We first examined the alkylation of tetralone carboxylate **1a** with allyl bromide in the presence of various phase-transfer catalysts (10 mol %) in toluene at room temperature. Catalyst **3a** having an *O*-allyl group showed catalytic efficiency higher than that of other catalysts in

* To whom correspondence should be addressed. Tel: 82-41-530-1244. Fax: 82-41-530-1247.

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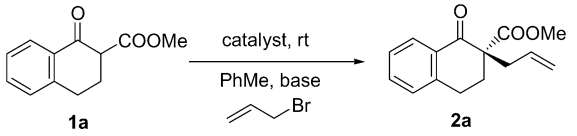
TABLE 1. Enantioselective Allylation of Tetralone Carboxylate 1a under Various Conditions



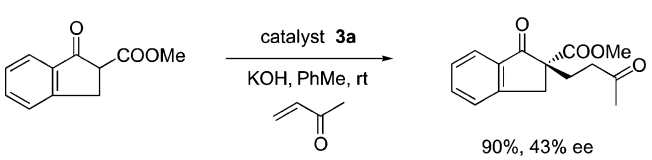
1a 2a

entry	catalyst	base	time (h)	temp (°C)	yield (%)	ee[a] (%)
1	**3a**	KOH	2	rt	94	68 (*S*)
2	**3a**	K_2CO_3	16	rt	85	59 (*S*)
3	**3a**	Cs_2CO_3	16	rt	87	55 (*S*)
4	**3a**	Rb_2CO_3	16	rt	85	57 (*S*)
5	**3a**	KOH	4	0	91	68 (*S*)
6	**3a**	KOH	8	−40	45	71 (*S*)
7[b]	**3a**	KOH	10	rt	65	36 (*S*)
8	**3b**	KOH	2	rt	93	1 (*S*)
9	**3c**	KOH	2	rt	91	60 (*S*)
10	**3d**	KOH	2	rt	87	57 (*S*)
11	**3e**	KOH	2	rt	89	15 (*R*)

[a] Enantiopurity of **2a** was determined by HPLC analysis with a Chiralcel OD-H column (2-propanol/hexane (1:9), 1.0 mL/min, λ_{max} = 254 nm). It was established by analysis of racemic **2a** that the enantiomers fully resolved. Absolute configuration was determined by comparison of the optical rotation of the corresponding methyl ester with the literature value.[10a] [b] This reaction was carried out in THF solvent.

terms of yields and enantioselectivity (Table 1). KOH, K_2CO_3, Cs_2CO_3, and Rb_2CO_3 were effective bases in this kind of reaction in the presence of catalyst **3a** (entries 1−4). Concerning the solvent, the use of toluene gave the best results, whereas the allylation in THF led to lower yield and enantioselectivity (enitres 1 and 7). Lowering the temperature to 0 and −40 °C with catalyst **3a** slightly increased the enantioselecticities (entries 5 and 6). As we expected, the reaction proceeded, but slowly and not completely in the absence of phase-transfer catalyst. Compound (*S*)-**2a** was formed as the excessive enantiomer, induced by cinchonine-derived catalysts (**3a**−**d**), which should be the case because all of these catalysts possesses the same chirality. The cinchonidine-derived catalyst (**3e**) led to the formation of (*R*)-**2a** in excess.

To examine the generality of the enantioselective alkylation of *β*-keto esters by using chiral phase-transfer catalyst **3a**, we studied the alkylation of cyclic *β*-keto esters **1** and **4** (Tables 2 and 3). As it can be seen by the results summarized in Tables 2 and 3, the corresponding α-alkylated *β*-keto esters **2** and **5** were obtained in good to excellent yields and enantioselectivities. Excellent enantioselectivities were obtained when the alkylating reagent was *p*-nitrobenzyl bromide (Table 2, entries 3, 8, and 12). Not only do 2-ethoxycarbonyl cyclopentanone and 2-ethoxycarbonyl cyclohexanone appear to be good candidates for this alkylation, moderate to high level of enantioselectivities of them were observed (Table 3).

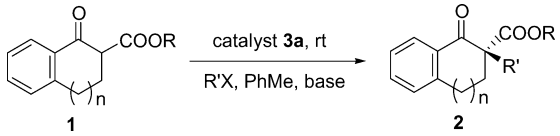


90%, 43% ee

Moreover, catalytic enantioselective Michael addition of *β*-keto ester to methyl vinyl ketone was achieved by using catalyst **3a**. The Michael adduct was obtained in high yield with moderate enantioselective excesses.[11]

In conclusion, we have accomplished the highly enantioselective alkylation of *β*-keto esters catalyzed by a

TABLE 2. Scope of the Enantioselective Alkylation of *β*-Keto Esters 1

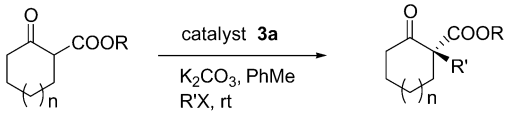


1 2

entry	*n*, R	R′X	base	time (h)	yield (%)	ee[a] (%)
1	1, Me	CH_2=$CHCH_2Br$	KOH	2	**2a,** 94	68 (*S*)[b]
2	1, Me	$PhCH_2Br$	KOH	26	**2b**, 85	66
3	1, Me	*p*-NO_2, $C_6H_4CH_2Br$	KOH	12	**2c**, 80	99
4	1, Me	PhCH=$CHCH_2Br$	KOH	3	**2d,** 98	59 (*S*)[b]
5	1, Et	$PhCH_2Br$	KOH	6	**2e**, 92	84
6	1, Et	EtBr	KOH	29	**2f**, 50	46
7	1, Et	CH_2=$CHCH_2Br$	KOH	16	**2g**, 75	60
8	1, Et	*p*-NO_2, $C_6H_4CH_2Br$	KOH	13	**2h**, 67	96
9	1, $PhCH_2$	$PhCH_2Br$	K_2CO_3	72	**2i**, 57	67
10	1, $PhCH_2$	CH_2=$CHCH_2Br$	KOH	6	**2j**, 61	47 (*S*)[b]
11	1, *t*-Bu	$PhCH_2Br$	K_2CO_3	48	**2k**, 70	75
12	1, *t*-Bu	*p*-NO_2, $C_6H_4CH_2Br$	KOH	6	**2l**, 74	99
13	0, Et	$PhCH_2Br$	K_2CO_3	72	**2m**, 71	63
14	0, Et	*p*-NO_2, $C_6H_4CH_2Br$	K_2CO_3	6	**2n**, 59	65
15	0, Et	CH_2=$CHCH_2Br$	K_2CO_3	45	**2o**, 70	57
16	0, Me	$PhCH_2Br$	K_2CO_3	15	**2p**, 85	63
17	0, $PhCH_2$	$PhCH_2Br$	K_2CO_3	72	**2q**, 30	44

[a] Enantiopurity of **2** was determined by HPLC analysis with Chiralcel OD-H (for **2a**, **2d**−**2f**, **2j**), OJ (for **2g**), AD (for **2b, 2c, 2h, 2i, 2k**−**2n, 2p, 2q**), and Whelk-O1 (for **2o**) columns, 2-propanol/hexane (1:9), 1.0 mL/min, λ_{max} = 254 nm. It was established by analysis of racemic **2** that the enantiomers fully resolved. [b] Absolute configuration was determined by comparison of the optical rotation and the HPLC retention time of the corresponding ester with literature value.[3b,10a]

TABLE 3. Scope of the Enantioselective Alkylation of *β*-Keto Esters 4



4 5

entry	*n*, R	R′X	time| (h)	yield (%)	ee[a] (%)
1	0, Et	$PhCH_2Br$	7	**5a**, 75	58
2	0, Et	*o*-NO_2, $C_6H_4CH_2Br$	15	**5b**, 68	50
3	0, Et	*p*-NO_2, $C_6H_4CH_2Br$	5	**5c**, 82	97
4	0, Et	*p*-Cl, $C_6H_4CH_2Cl$	15	**5d**, 70	57
5	1, Et	$PhCH_2Br$	15	**5e**, 52	61
6	1, Et	*p*-NO_2, $C_6H_4CH_2Br$	5	**5f**, 86	87
7	1, Et	*p*-Cl, $C_6H_4CH_2Cl$	15	**5g**, 72	77
8	1, Et	CH_2=$CHCH_2Br$	48	**5h**, 61	59 (*S*)[b]
9	1, Et	PhCH=$CHCH_2Br$	10	**5i**, 72	57 (*S*)[b]
10	1, Me	CH_2=$CHCH_2Br$	48	**5j**, 61	53 (*S*)[b]
11	1, Me	$PhCH_2Br$	40	**5k,** 82	53 (*S*)[b]
12	1, Me	*p*-Cl, $C_6H_4CH_2Cl$	15	**5l**, 65	57 (*S*)[b]
13	1, $PhCH_2$	CH_2=$CHCH_2Br$	45	**5m**, 57	53 (*S*)[b]

[a] Enantiopurity of **5** was determined by HPLC analysis with a Chiralpak AD (for **5a**), AS (for **5b**−**5d**), OD-H (for **5i**, **5m**), OJ (for **5g**), and Whelk-O1 (for **5e**, **5f**, **5h**, **5j**−**5l**) columns, 2-propanol/hexane (1:9), 1.0 mL/min, λ_{max} = 254 nm. It was established by analysis of racemic **5** that the enantiomers were fully resolved. [b] Absolute configuration was determined by comparison of the optical rotation and the HPLC retention time of the corresponding ester with literature value.[3b,4b,10]

phase-transfer catalyst derived from cinchonine, which allows efficient construction of fully substituted stereogenic centers. We are currently involved in the further development of these catalyst systems and investigating their applicability to other asymmetric phase-transfer processes.

Experimental Section

Typical Procedure for the Alkylation of *β*-Keto Esters. To a stirred solution of 2-(ethoxycarbonyl)-1-tetralone (65.47 mg, 0.3 mmol), KOH (101 mg, l.8 mmol), and cinchonium salt **3a** (l9 mg, 0.03 mmol) in toluene (3 mL) was added benzyl bromide (0.054 mL, 0.45 mmol) at room temperature. The reaction mixture was stirred for 6 h at room temperature. The mixture was diluted with saturated NH_4Cl solution (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated, and purified by flash chromatography to afford the α-alkylated *β*-keto ester **2e** (85.1 mg, 92%).

2-Benzyl-2-(ethoxycarbonyl)-1-tetralone (2e): R_f 0.30 (EtOAc/hexane = 1:9); $[\alpha]^{25}_D$ −7.9 (*c* 1.0, $CHCl_3$, 84% ee); ^1H NMR (200 MHz, $CDCl_3$) δ 8.07 (d, J = 9.1 Hz, 1H), 7.48−7.40 (m, 1H), 7.33−7.14 (m, 7H), 4.12 (q, J = 7.3 Hz, 2H), 3.47 (d, J = 13.5 Hz, 1H), 3.29 (d, J = 13.4 Hz, 1H), 3.11−3.00 (m, 1H), 2.91−2.78 (m, 1H), 2.54−2.43 (m, 1H), 2.05−1.90 (m, 1H), 1.14 (t, J = 7.3 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 194.6, 171.4, 143.1, 136.6, 133.4, 132.3, 130.8, 128.6, 128.1, 126.7, 61.5, 58.6, 39.9, 30.4, 26.0, 14.0; HRMS calcd for $C_{20}H_{20}O_3Na$ ($[M + Na]^+$) 331.1310, found 331.1319; HPLC (hexane/^{i}PrOH = 90:10, 254 nm, 0.5 mL/min) Chiralcel OD-H column, t_R = 11.95 min (minor), t_R = 12.54 min (major).

Supporting Information Available: General procedure and characterization of compounds **2a**−**q** and **5a**−**m**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Absolute configuration was determined by comparison of the optical rotation and the HPLC retention time of the corresponding ester with literature values; see: Nakajima, M.; Yamamoto, S.; Yamaguchi, Y.; Nakamura, S.; Hashimoto, S. *Tetrahedron* **2003**, *59*, 7307.