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Phase-Transfer-Catalyzed Asymmetric Glycolate Alkylation

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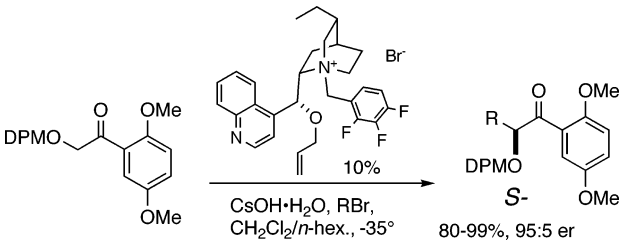
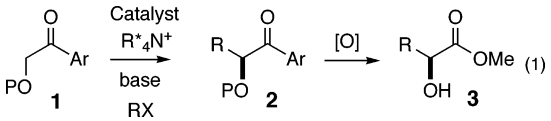
ABSTRACT



Asymmetric surrogate glycolate alkylation has been performed under phase-transfer conditions. Diphenylmethyloxy-2,5-dimethoxyacetophenone with trifluorobenzyl cinchonidinium catalyst and cesium hydroxide provided alkylation products at −35 °C in high yield (80−99%) and with excellent enantioselectivities (90:10 to 95:5). Useful α-hydroxy products were obtained using bis-TMS peroxide Baeyer−Villiger conditions and selective transesterification. The intermediate aryl ester can be obtained with >99% ee after a single recrystallization. A tight ion-pair model for the observed (*S*)-stereoinduction is proposed.

Phase-transfer catalysis (PTC), through ion pairing of a reactive anion with an enantiopure ammonium ion, has been developed for asymmetric glycine alkylations, enone epoxidation, conjugate additions, and other transformations.[1] Advantages of this approach include use of inexpensive cinchona alkaloid-derived catalysts, readily available in both enantiomeric antipodes, simple hydroxide bases, and mild conditions that can be run in either liquid−liquid or liquid−solid mode. Benzophenone imine *tert*-butyl glycine, with its extended enolate conjugation and low pK_a value (18.7, DMSO),[1c] continues to be a popular substrate for amino acid synthesis and catalyst development.[2] As a first step toward development of PTC reactions with oxygenated substrates, we now report a novel alkoxyacetophenone **1** that undergoes highly selective catalytic glycolate alkylation with various electrophiles (eq 1).[3] The resultant product undergoes Baeyer−Villiger-type oxidation to give the aryl ester, which is readily transesterified to produce the useful α-hydroxy ester **3**.



Using an alkoxyester substrate (pK_a ∼28), which would provide direct access to glycolate esters, did not give alkylation products under various PTC conditions. The more acidic benzyloxy acetophenones (pK_a ∼22) were then screened for reactivity using the Park−Jew trifluorobenzyl cinchonidinium (CD) bromide catalyst **4**[2f] (10 mol %) with

(1) (a) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013−3028. (b) Kacprzak, K.; Gawronski, J. *Synthesis* **2001**, 961−998. (c) O'Donnell, M. J. *Aldrichimica Acta* **2001**, *3*, 3−15.

(2) (a) O'Donnell, M. J.; Bennett, W. D.; Wu, S. *J. Am. Chem. Soc.* **1989**, *111*, 2353−2354. (b) O'Donnell, M. J.; Delgado, F.; Hostettler, C.; Schwesinger, R. *Tetrahedron Lett.* **1998**, *39*, 8775−8778. (c) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414−12415. (d) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1997**, *38*, 8595−8598. For a related unsaturated ester, see: (e) Corey, E. J.; Bo, Y.; Busch-Petersen, J. *J. Am. Chem. Soc.* **1998**, *120*, 13000−13001. (f) Ooi, T.; Kameda, K.; Maruoka, K. *J. Am. Chem. Soc.* **1999**, *121*, 6519−6520. (g) Jew, S.; Yoo, M.; Jeong, B.; Park, I. Y.; Park, H. *Org. Lett.* **2002**, *4*, 4245−4248. (h) Park, H.; Jeong, B.; Yoo, M.; Lee, J.; Park, M.; Lee, Y.; Kim, M.; Jew, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 3036−3038.

(3) Previous asymmetric glycolate alkylations are limited to chiral auxiliaries: Crimmins, M. T.; Emmitte, K. A.; Katz, J. D. *Org. Lett.* **2000**, *2*, 2165−2167. and references therein.

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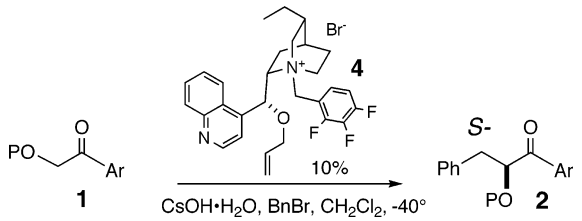
Table 1. Asymmetric Glycolate PTC Alkylation



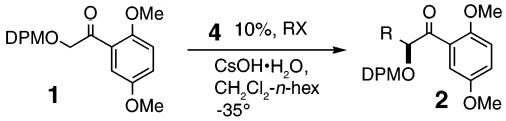
entry	P	Ar	time (h)	% yield[a]	er[b]
1[c]	Bn	Ph	26	74	63:37
2	Bn	*p*-anisyl	6	82	77:23
3	Bn	*o*-anisyl	8	78	83:17
4	Bn	*o*-toluyl	12	72	81:19
5	Bn	2,4-diMeOPh	13	90	76:24
6	Bn	2,5-diMeOPh	7	83	86:14
7	PMB	2,5-diMeOPh	9	83	84:16
8	2-NapCH$_2$−	2,5-diMeOPh	13	80	87:13
9	DPM	2,5-diMeOPh	7	80	90:10
10[d]	DPM	2,5-diMeOPh	13	96	93:7

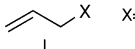
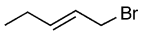
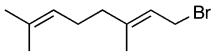
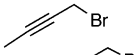
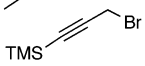
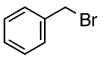
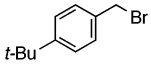
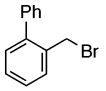
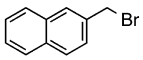
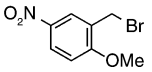
[a] Yields are for isolated, chromatographed materials. [b] Determined by chiral HPLC with comparison to racemic materials. [c] Performed with aq KOH in toluene. [d] Performed with a mixture of CH_2Cl_2:*n*-hex 1:1 as the solvent.

cesium hydroxide (5 equiv) as a base (Table 1). In the presence of excess benzyl bromide (5 equiv) with aryl ketone **1**, the alkylation product **2** was obtained (entry 1). It was envisioned that more electron-rich aryl ketones would give higher reactivity and selectivity consistent with the tight ion-pair model.[2c] This turned out to be the case in that the 2,5-dimethoxy ketone (entry 6) gave an 83% yield after 7 h at −40 °C with an 86:14 er (enantiomeric ratio, 72% ee). Other ketones, including naphthyl and xylyl substrates, were less effective. The 2,5-dimethoxy functionality was maintained, and various protecting groups at C-2 were explored. Methyl ether-protected ketone and others, including monoarylmethyl (entries 7, 8) and aryl ethers, gave lower selectivity. Finally, the benzhydryl (diphenylmethyl, DPM) ether substrate **1** was found to be superior, providing product in 7 h with 90:10 enantioselectivity (entry 9). Changing the solvent to 1:1 methylene chloride/*n*-hexane provided further improvement in yield and selectivity to 93:7 er (entry 10). With toluene as a solvent, the selectivity was also high; however, the reaction rate was greatly slowed, requiring 28 h for completion. Other solvents and combinations investigated were less effective. The reactions with RbOH or aqueous KOH as a base were slow, while $Ba(OH)_2$ and BTPP gave only trace product formation. Use of the Corey−Lygo 9-anthracenyl methyl-CD[2c,d] catalyst in place of **4** gave 70:30 er selectivity for **2** (P = DPM, Ar = 2,5-diMeOPh) and the Maruoka 2,2′-dinaphthyl-bis-binaphthylammonium PTC catalyst[2e] gave still lower selectivity under these conditions. At −60 °C, the reaction selectivity was not improved (92:8, 52 h, 69%). Variations of catalyst **4** and further modifications of the reaction conditions did not lead to improved selectivity.

Using these optimized conditions with aryl ketone **1**, asymmetric glycolate PTC alkylations with catalyst **4** and various allyl, propargyl, and benzyl halides (5 equiv) were performed (Table 2). Allyl bromides (entries 1−3) reacted

Table 2. PTC Alkylation with Allyl, Propargyl, and Benzyl Halides



entry	RX	time (hr)	% yield[a]	er[b]
1	 X=Br I	5 3	83 81	92:8 85:15
2		5	78	94:6
3		4	85	91:9
4		8	80	92:8
5		4	89	90:10
6		4	88	91:9
7		13	94	93:7
8		5	96	92:8
9		9	99	95:5
10		12	91	92:8
11		24	91	94:6

[a] Chromatographed, isolated yields. [b] Determined by chiral HPLC with comparison to racemic materials.

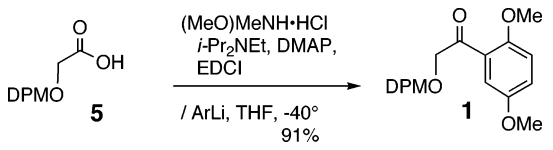
with high isolated yields and selectivities in 4−5 h. Allyl iodide reacted at a faster rate; however, the selectivity was reduced. Methallyl bromide gave the highest selectivity at 94:6 er. Geranyl bromide was somewhat slower at 8 h. Propargyl bromides substituted at the γ-position (entries 5, 6) were also effective with high selectivity in 4 h. Yields and selectivities were uniformly high with benzyl bromides (entries 7−11), and the reaction times varied depending on the substitution pattern. Benzyl bromide required 13 h for completion, while *p*-*tert*-butyl BnBr terminated in 5 h with high selectivity (92:8). *o*-Phenyl BnBr (entry 9) gave a quantitative yield after 9 h with 95:5 selectivity (90% ee). Entries 1 and 7 have been repeated many times, including on a gram scale with reproducible results. Catalyst **4** can be recovered in pure form as the chloride salt during the workup step (71%)[4] and excess 2-naphthylmethyl bromide (entry 10) was easily recovered (75%) upon purification.

The requisite aryl ketones **1**, including the optimal electron-rich substrate (P = DPM, Ar = 2,5-dimethoxyphenyl, mp 82 °C), were readily made from protected glycolic

(4) See Supporting Information for experimental details.

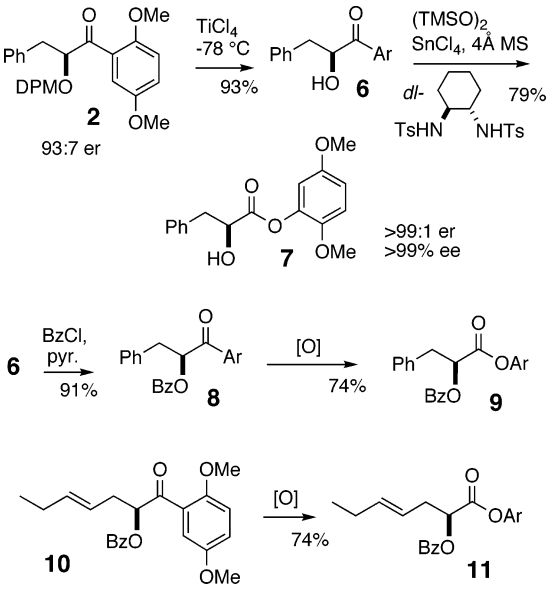
acid **5** via the Weinreb amide followed by displacement with the corresponding aryllithium reagent (Scheme 1). This one-pot operation conveniently converts glycolic acid **5** to **1** in excellent yield (91%).

Scheme 1



Baeyer−Villiger conversion of the aryl ketone PTC product to the corresponding aryl ester was then addressed. PTC product **2** was deprotected using $TiCl_4$ to give alcohol **6** (Scheme 2). Aryl ester **7** (Ar = 2,5-dimethoxyphenyl) was

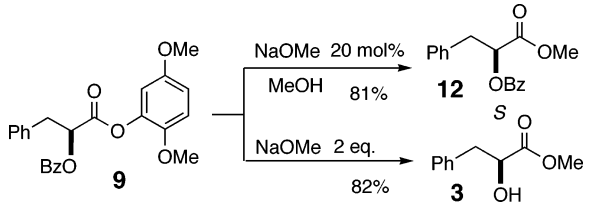
Scheme 2



then formed in 79% yield under Baeyer−Villiger-type oxidation conditions using a modification of the reported conditions with bis-TMS peroxide (2.0 equiv) and $SnCl_4$•bis-sulfonamide complex (±1 equiv).[5] MCPBA was not effective for this step. We were pleased to find that a single recrystallization of hydroxyester **7** (mp 128−130 °C) from warm Et_2O gave further enantioenrichment to an er of >99:1 (>99% ee).[4] Alcohol **6** was also protected as the benzoate ester **8**, and oxidation gave **9** in 72% yield. A key benefit of these peroxide conditions is that, unlike peracids, these conditions do not effect alkene epoxidation and thus allow for expansion of the scope of the process to include unsaturated substrates.[6] Benzoate **10**, obtained in high selectivity (entry 3, Table 2), was readily formed and converted to the aryl ester **11** using the same oxidation conditions in 74% yield. No trace of epoxide product was seen.

Selective transesterification conditions were also developed for the aryl ester intermediate **9** to establish the stereochemistry and to demonstrate multistep utility (Scheme 3).

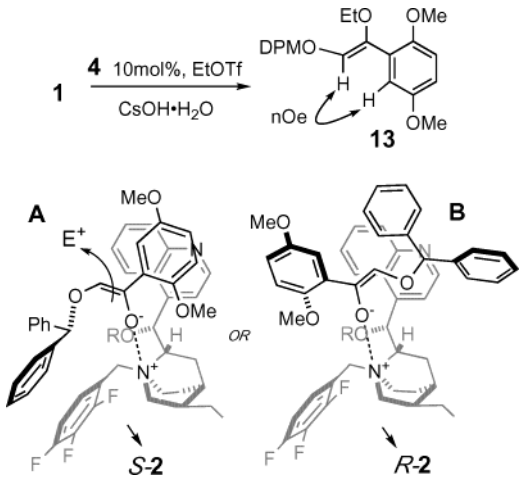
Scheme 3



Catalytic NaOMe (20 mol %) gave (*S*)-methyl ester **12** with the benzoate ester intact without racemization. In complementary fashion, excess NaOMe (2 equiv) generated (*S*)-2-hydroxy methyl ester **3** ($[\alpha]_D$ −8.8°).[7] A combination of attenuated lone-pair *n*-π carbonyl resonance by the *O*-aryl oxygen and greater stability of the aryloxy leaving group appears to be the origin of this useful chemoselectivity leading to **12**.[8] A single-crystal X-ray structure was solved for benzoate **8** that also established the proposed stereochemistry.[4]

The stereoinduction of the process can be rationalized using a modification of the tight-ion pair model proposed by Corey for asymmetric glycine PTC (Scheme 4).[2c] The

Scheme 4



Z-enolate from **1** was trapped with EtOTf to give vinyl ether **13** under the PTC conditions and confirmed by NMR.[4] With

(5) Göttlich, R.; Yamakoshi, K.; Sasai, H.; Shibasaki, M. *Synlett* **1997**, 971−974.

(6) (a) Sawada, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 10521−10532. (b) Yoshikawa, N.; Suzuki, T.; Shibasaki, M. *J. Org. Chem.* **2002**, *67*, 2556−2565.

(7) *c* 2.0, $CHCl_3$. Lit. −7.6° (*c* 2.0, $CHCl_3$): Davis, F. A.; Haque, M. S.; Ulatowski, T. G.; Towson, J. C. *J. Org. Chem.* **1986**, *51*, 2402−2404.

the oxygen of the *Z*-enolate of **1** pointing directly at the least hindered face of the CD nitrogen of **4**, two orientations can be envisioned, **A** and **B**. The catalyst is shaded for clarity, and the enolate oxygen−quinuclidine nitrogen interaction is highlighted. The extended portion of the enolate in **A**, made up of the 2,5-dimethoxyphenyl portion of the substrate, maximizes van der Waals contact with the isoquinoline of the catalyst, and the DPM group interacts with the trifluorobenzyl group. This arrangement leads to the major product, (*S*)-**2**, as a result of *re*-face attack. Arrangement **B** places the DPM group over the isoquinoline with the 2,5-dimethoxyphenyl group twisted out of resonance, giving (*R*)-**2**.

Asymmetric, catalytic glycolate alkylation has been achieved with high reactivity and selectivity with various alkylating agents through a surrogate DPM-protected acetophenone under asymmetric PTC conditions. Applications with other electrophiles will now open new approaches to a variety of enantiomerically enriched oxygenated products applicable to multistep synthesis.

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Supporting Information Available: Experimental and spectral data for all compounds, including X-ray data for ketone **8** and HPLC chromatograms for selected alkylation products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) For a discussion of base-mediated ester hydrolysis, $B_{AC}2$, see: Lowry, T. H.; Richardson, K. S. In *Mechanism and Theory in Organic Chemistry*, 2nd ed.; Harper and Row; New York, 1981; p 651.