Organic LETTERS

Letter

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Enantioselective α-Benzoyloxylation of Malonic Diesters by Phase-Transfer Catalysis

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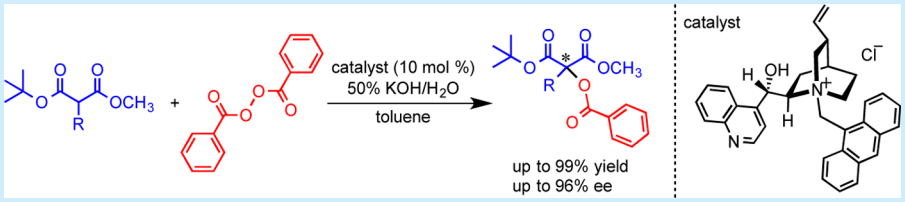
Supporting Information



ABSTRACT: A highly enantioselective α-benzoyloxylation of malonic diester has been achieved by phase-transfer catalysis. The reaction of α-monosubstituted *tert*-butyl methyl malonate with benzoyl peroxide in the presence of aqueous KOH and *N*-(9-anthracenylmethyl)cinchoninium chloride afforded the corresponding α,α-disubstituted products in generally excellent chemical yields (up to 99% yield) with high enantioselectivities (up to 96% ee). In addition, the utility of this methodology was exhibited by the synthesis of a mineralocorticoid receptor antagonist.

Asymmetric construction of a chiral center at the α-carbon of malonic diesters is an important synthetic strategy because chiral malonates are attractive synthetic building blocks due to their readiness to undergo chemoselective transformations.[1] However, there have been few reports of enantioselective catalytic additions at the α-position of malonyl derivatives.[2] In particular, enantioselective synthesis of the quaternary substituted carbon chiral center is difficult and quite challenging due to steric repulsion between the substituents. In this context, Park and co-workers have developed enantioselective catalytic additions at the α-position of malonyl derivatives.[3] Our laboratory has also been interested in the asymmetric construction of α,α-dialkyl malonic diesters, and we previously reported a highly enantioselective alkylation of malonic diester under phase-transfer catalytic conditions.[4]

Similarly, there have been few reports of the enantioselective synthesis of α-alkyl α-hydroxy malonyl derivatives, and these syntheses are even more challenging than the synthesis of chiral malonates. α-Alkyl α-hydroxy malonyl derivatives are among the most important classes of compounds for the formation of tertiary alcohols and versatile intermediates for the synthesis of natural products and biologically active compounds.[5] To our knowledge, there is only one report of an enantioselective direct C−O bond-forming reaction at the α-position of malonates, by Shibata and co-workers,[6] who described the highly enantioselective direct α-hydroxylation of malonate using oxaziridine as an oxidant and (*R*,*R*)-DBFOX/Ni^{II} complex as a transition metal catalyst. Maruoka and co-workers obtained α-alkyl α-hydroxy β-keto esters with high enantioselectivities by employing the phase-transfer catalyzed asymmetric alkylation of α-benzoyloxy β-keto esters as a key asymmetric C−C bond forming step. However, an attempt to extend this method in the reaction with *tert*-butyl methyl α-benzoyloxy malonate led to the formation of the α-alkyl α-benzoyloxy malonate with low enantioselectivity.[7] More recently, Shibatomi and co-workers reported the enantioselective synthesis of α-aryloxy-β-keto ester through asymmetric α-chlorination of β-keto esters and S_N2 reaction with phenols and ultimately achieved the enantioselective synthesis of α-aryloxy malonate through the α-choromalonate.[8]

In order to develop a new and convenient method for synthesizing chiral α-hydroxy malonates, we investigated the asymmetric α-benzoyloxylation of *tert*-butyl methyl α-monoalkylated malonate under phase-transfer conditions using cinchona alkaloid derivatives.[9] *tert*-Butyl and methyl ester are simple protecting groups that are readily cleaved chemoselectively under acidic or alkaline conditions. Phase-transfer catalytic reactions are among the most efficient synthetic methods, both from the viewpoints of low cost and being environmentally benign.[10] α-Benzoyloxylation is a useful synthetic strategy for introducing an oxygen atom at the α-position of ketone or ester groups. Although catalytic α-benzoyloxylation reactions have been accomplished by metal,[11] enamine,[12] and Bu_4NI catalysis,[13] there has been no report of this reaction using phase-transfer catalysis. In this paper, we report the highly efficient enantioselective α-benzoyloxylation of *tert*-butyl methyl α-monoalkylated malonate using cinchona alkaloid derivatives as inexpensive phase-transfer catalysts (PTCs). The present reaction is the first example of an organocatalyzed asymmetric direct α-benzoyloxylation of malonic diesters. In addition, the utility of this method is

Received: September 7, 2016

DOI: 10.1021/acs.orglett.6b02682
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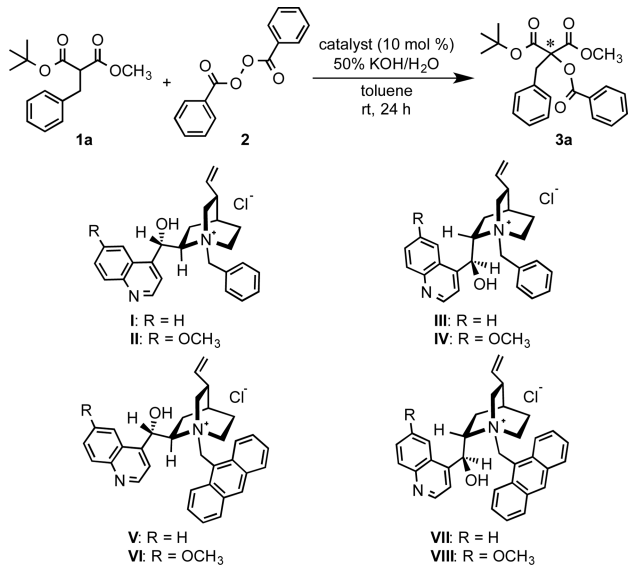
demonstrated by the synthesis of a mineralocorticoid receptor antagonist being developed by a group at Merck.[14]

To initiate our study, we screened various cinchona alkaloid derivatives as PTCs for the benzoyloxylation reaction. α-Benzyl *tert*-butyl methyl malonate (**1a**) was adopted as the substrate for benzoyloxylation with benzoyl peroxide (BPO, **2**) in the presence of a PTC. Addition of PTCs **I**–**VIII** to the reaction mixture accelerated the reaction rate considerably in each case. The enantiomeric excess of the purified α-benzoyloxy malonate **3a** was measured by chiral HPLC, and the absolute configuration was determined by comparison with specific rotation values reported in the literature.[7] The results are summarized in Table 1.

Table 1. Catalyst Screening for the α-Benzoyloxylation of *tert*-Butyl Methyl Malonate 1a



entry[a]	PTC	yield[b] (%)	ee[c] (%)	config
1	**I**	37	56	(*S*)
2	**II**	36	52	(*S*)
3	**III**	44	5	(*R*)
4	**IV**	45	11	(*R*)
5	**V**	63	81	(*S*)
6	**VI**	47	36	(*S*)
7	**VII**	39	7	(*R*)
8	**VIII**	64	2	(*R*)

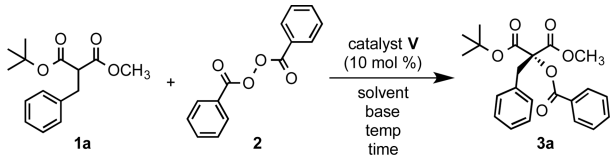
[a]The reactions were performed with **1a** (0.1 mmol), **2** (0.1 mmol), catalyst (0.01 mmol), and 50% KOH/H_2O (100 μL) in toluene (1 mL) at room temperature for 24 h. [b]Determined by ^1H NMR analysis using 1,3,5-trimethylbenzene as an internal standard. [c]Determined by chiral HPLC.

We first attempted to use cinchoninium derivatives **I**-**IV** containing an *N*-benzyl group as a catalyst for benzoyloxylation. Treatment of malonate **1a** with BPO (**2**) in the presence of 50% (w/w) KOH/H_2O and 10 mol % of PTC **I** in toluene at room temperature gave the corresponding α-benzoyloxy malonate **3a** in low yield with moderate enantioselectivity (Table 1, entry 1). The reaction with *N*-benzylquinidinium chloride (**II**) also afforded malonate **3a** in low yield with moderate enantioselectivity (Table 1, entry 2). In contrast, *N*-benzylcinchonidinium **III** and *N*-benzylquininium **IV** provided poor enantioselectivities (Table 1, entries 3 and 4).

The effects of an *N*-anthracenylmethyl group on the catalysts were examined next. *N*-(9-Anthracenylmethyl)cinchoninium catalyst **V** afforded the product **3a** in moderate yield (63%) with good enantioselectivity (81% ee, Table 1, entry 5). *N*-Anthracenylmethylquinine catalyst **VI** gave both a low yield and low enantioselectivity (Table 1, entry 6). *N*-Anthracenylmethylcinchonidinium **VII** and *N*-anthracenylmethylquininium **VIII** gave poor enantioselectivities (Table 1, entries 7 and 8). Consequently, catalyst **V**, which provided the highest enantioselectivity, was selected for further studies.

To further improve the enantioselectivity, we focused our attention on reaction conditions using *N*-(9-anthracenylmethyl)cinchoninium chloride (**V**) as the catalyst. The results of the optimization studies are summarized in Table 2. We first

Table 2. Optimization Studies of the α-Benzoyloxylation



entry[a]	solvent	base	temp (°C)	time (h)	yield[b] (%)	ee[c] (%)
1	CH_2Cl_2	50% KOH	rt	24	59	7
2	Et_2O	50% KOH	rt	24	91	49
3	hexane	50% KOH	rt	24	44	18
4	toluene	50% KOH	rt	24	73	81
5	toluene	50% NaOH	rt	24	99	36
6	toluene	50% CsOH	rt	24	4	65
7	toluene	75% CsOH	rt	24	49	84
8	toluene	LiOH	rt	24	98	13
9	toluene	NaOH	rt	24	98	32
10	toluene	KOH	rt	24	>99	38
11	toluene	CsOH	rt	24	>99	42
12	toluene	Na_2CO_3	rt	24	NR[d]	ND[e]
13	toluene	K_2CO_3	rt	24	18	83
14	toluene	$CaCO_3$	rt	24	NR[d]	ND[e]
15	toluene	Cs_2CO_3	rt	24	94	83
16	toluene	50% KOH	0	24	>99	89
17	toluene	75% CsOH	0	48	62	91
18	toluene	Cs_2CO_3	0	48	73	91
19	toluene	50% KOH	−20	48	>99	93
20	toluene	Cs_2CO_3	−20	96	6	90
21	toluene	50% KOH	−40	48	>99	95
22	toluene	50% KOH	−50	48	81	91
23	toluene	50% KOH	−60	48	68	92

[a]The reactions were performed with **1a** (0.1 mmol), **2** (0.2 mmol), catalyst (0.01 mmol), and base in toluene (1 mL). [b]Determined by ^1H NMR analysis using 1,3,5-trimethylbenzene as an internal standard. [c]Determined by chiral HPLC. [d]No reaction. [e]Not detected.

investigated the α-benzoyloxylation of malonate **1a** in various solvents. A survey of solvents revealed that the reaction medium had a significant effect on the α-benzoyloxylation reaction rate. Using CH_2Cl_2 as the solvent resulted in moderate yields and poor enantioselectivity (Table 2, entry 1). Reactions carried out in Et_2O gave a high yield but low enantioselectivity (Table 2, entry 2), whereas hexane as a solvent resulted in a moderate yield and poor enantioselectivity (Table 2, entry 3). However, performing the reaction in toluene provided the highest enantioselectivity (81% ee) (Table 2, entry 4).

DOI: 10.1021/acs.orglett.6b02682
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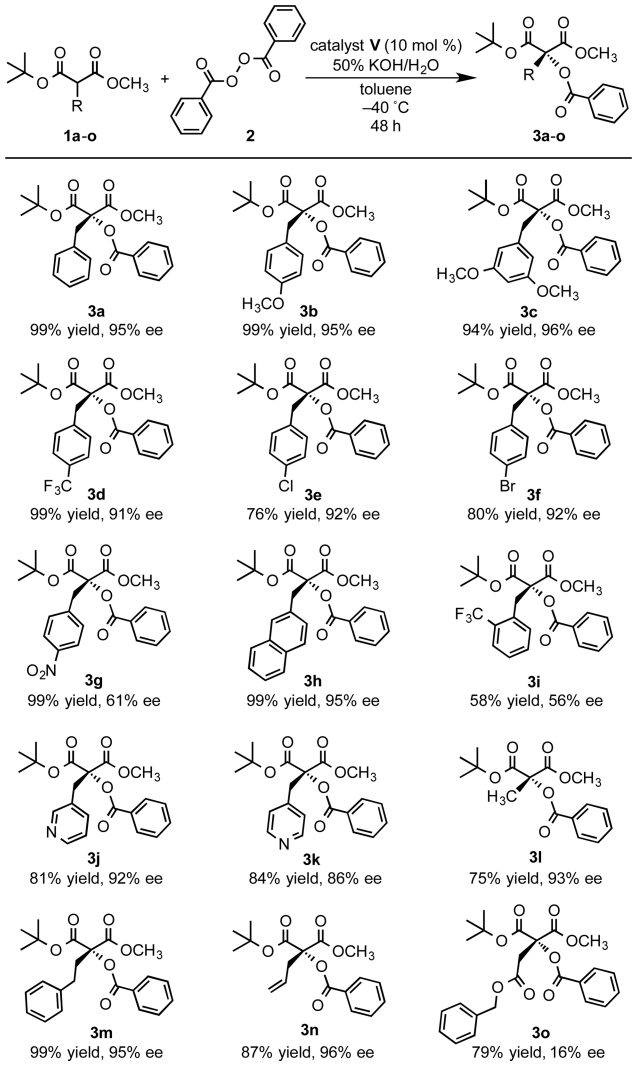
We next screened several bases in toluene in the presence of catalyst **V** (Table 2, entries 5−15). Although the use of 50% NaOH aqueous solution provided a higher yield, the enantioselectivity was low (Table 2, entry 5). The use of 50% CsOH aq provided a poor yield and moderate enantioselectivity, but 75% CsOH aq provided both a higher yield and high enantioselectivity (Table 2, entries 6 and 7). The solid bases LiOH, NaOH, KOH, and CsOH all resulted in excellent yields of α-benzoyloxy product **3a**, but the enantioselectivities were unsatisfactory (Table 2, entries 8−11). Solid Na_2CO_3 and $CaCO_3$ were completely ineffective (Table 2, entries 12 and 14), whereas K_2CO_3 provided a low yield and high selectivity (Table 2, entry 13) and Cs_2CO_3 provided both a high yield and high selectivity (Table 2, entry 15).

We next investigated the reaction temperature, using 50% KOH aq, 75% CsOH aq, or Cs_2CO_3 as the base; with all bases, enantioselectivity increased when the reaction temperature was decreased to 0 °C (Table 2, entries 16−18). With Cs_2CO_3, a further decrease in the reaction temperature led to a decrease in yield without a decrease in enantioselectivity (Table 2, entries 18 and 20). In contrast, 50% KOH aq resulted in an increase in enantioselectivity as the reaction temperature was gradually decreased to −40 °C (Table 2, entries 16, 19, and 21), although further cooling to −50 °C and −60 °C decreased significantly both the chemical yield and enantioselectivity (Table 2, entries 22 and 23). Accordingly, conducting the reaction in toluene and 50% KOH at −40 °C using PTC **V** was considered optimal with respect to ee and chemical yield of the product.

With the optimal reaction conditions in hand, we then examined malonates **1a−o** to demonstrate the general utility of the cinchona catalyst **V** in asymmetric α-benzoyloxylation reactions. The results are summarized in Scheme 1. The α-benzoyloxylation of malonate **1** (0.2 mmol) with BPO (**2**, 0.4 mmol) was carried out in toluene (2.0 mL) using PTC **V** (0.02 mmol) at −40 °C for 48 h. Significantly, the majority of the reactions using malonates **1** afforded the corresponding α-benzoyl products **3** with excellent yields and enantioselectivities. Benzyl-type substituted substrates **1a−i** yielded enantioenriched α-benzoyl products **3a−i** containing a quaternary stereocenter in good to excellent yields and enantiopurities. 4-Nitrobenzyl substrate **1g** provided moderate enantioselectivity. The reason is not clear, but presumably, hydrogen bond, which formed between the nitro group and the catalyst **V**, affected the enantioselectivity. Ortho-substituted benzyl substrate **1i** provided moderate yield and enantioselectivity. In the case of pyridin-3-ylmethy **1j**, and pyridin-4-ylmethyl substituted malonates **1k**, both reactions afforded good yields and enantioselectivities. Similarly, substitution of the benzyl group with other groups such as methyl **1l**, homobenzyl **1m**, and allyl **1n** provided the corresponding α-adducts **3l−n** in excellent yields and enantiopurities. However, use of the α-acetate group substrate **1o** afforded **3o** in good yield but with unsatisfactory enantioselectivity.

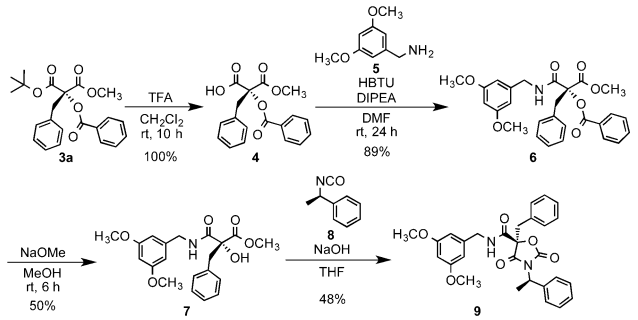
The synthesis of a biologically active compound was investigated to demonstrate the utility of the present methodology for α-benzoylation reactions. The synthesis of mineralocorticoid receptor antagonist **9** from α,α-disubstituted malonate **3a** is depicted in Scheme 2. Removal of the *tert*-butyl group from **3a** with TFA afforded the carboxylic acid **4** in quantitative yield. The acid **4** was coupled with 3,5-dimethoxybenzylamine (**5**) to afford amide **6** in 89% yield. Removal of the benzoyl group of α,α-disubstituted malonate **6** by treatment with NaOMe in MeOH furnished tertiary alcohol **7**.

Scheme 1. Substrate Scope of the α-Benzoyloxylation[a]



[a]The reactions were performed with **1** (0.2 mmol), **2** (0.4 mmol), catalyst **V** (0.02 mmol), and 50% KOH/H_2O (0.2 mL) in toluene (2 mL). Yields of isolated product. The enantiomeric excess values were determined by chiral HPLC.

Scheme 2. Synthesis of Mineralocorticoid Receptor Antagonist 9



Subsequent conversion to the final target oxazolidinedione **9** was achieved by condensation with commercially available isocyanate **8** in the presence of sodium hydroxide. The stereochemistry of **9** was confirmed by comparison of the measured spectra data with the literature value.[14a]

DOI: 10.1021/acs.orglett.6b02682
Org. Lett. XXXX, XXX, XXX−XXX

In conclusion, we have described the first enantioselective α-benzoyloxylation of malonic diesters promoted by a phase-transfer catalyst. The reaction of the α-monosubstituted malonate with benzoyl peroxide in the presence of *N*-(9-anthracenylmethyl)cinchoninium chloride afforded the corresponding α,α-disubstituted products in excellent yields with high enantioselectivities. The utility of this method was demonstrated by the successful synthesis of a mineralocorticoid receptor antagonist. We are currently investigating the synthesis of other useful compounds via the enantioselective α-benzoyloxylation of other malonic diesters in addition to *tert*-butyl methyl malonate. The results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02682.

Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra and HPLC traces (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by a "High-Tech Research Center" Project for Private Universities: matching fund subsidy from MEXT (Ministry of Education, Culture, Sports, Science and Technology), and a Grant-in-Aid for Scientific Research (C) from the Japan Society for the Promotion of Science.

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DOI: 10.1021/acs.orglett.6b02682
Org. Lett. XXXX, XXX, XXX−XXX