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Highly Enantioselective Synthesis of α,α-Dialkylmalonates by Phase-Transfer Catalytic Desymmetrization

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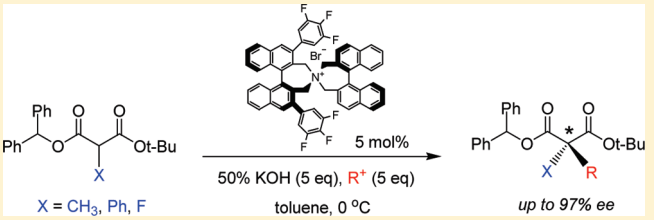
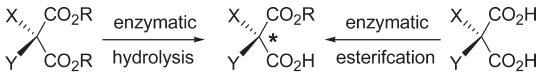
Supporting Information

ABSTRACT: A novel enantioselective synthetic method for the construction of a quaternary carbon center from malonates via phase-transfer catalytic (PTC) alkylation has been developed. The asymmetric α-alkylation of diphenylmethyl *tert*-butyl α-alkylmalonates with alkylating agents under phase-transfer catalysis conditions (aq 50% KOH, toluene, 0°C) in the presence of (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide (**8**) as PTC catalyst afforded the corresponding α,α-dialkylmalonates in high chemical (up to 99%) and optical yields (up to 97% ee) which could be readily converted to versatile chiral intermediates. Notably, the direct double α-alkylations of diphenylmethyl *tert*-butyl malonate also provided the corresponding α,α-dialkylmalonates without loss of enantioselectivity. The synthetic potential of this method has been demonstrated by the preparation of α,α-dialkylamino acid and oxindole systems.



INTRODUCTION

Malonates are one of the most fundamental synthetic starting materials in organic synthesis for C−C bond formation.[1] Notably, chiral α,α-dialkylmalonates (**1**) have been quite often employed for the construction of chiral quaternary carbon centers of biologically active natural products and pharmaceuticals. To date, chiral malonates could only be obtained by desymmetrization of (±)-α,α-dialkylmalonates or (±)-α,α-dialkylmalonic acids by enzymatic resolution via selective hydrolysis or selective esterification, respectively.[2] Although construction of chiral quaternary carbon centers by asymmetric α-alkylation of carbonyl systems,[3] β-ketoester systems,[4] and chiral induction of the β-position to malonate by asymmetric conjugate addition or palladium-catalyzed allylation of malonates[5] have been extensively studied, the enantioselective direct α-alkylation of malonates has not yet been reported.[6]



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Recently, we reported a new synthetic method for chiral α-monoalkylmalonamide esters by phase-transfer catalytic (PTC) mono-α-alkylation of *N*,*N*-diarylmalonamide esters and successfully proved its usefulness by applications to the synthesis of various chiral building blocks (Scheme 1).[7]

Although PTC alkylation of *N*,*N*-diarylmalonamide esters provided the corresponding monoalkylated products with high enantioselectivity, the dialkylation for the construction of the quaternary carbon center provided both low chemical yields (up to 65%) and poor enantioselectivities (up to 42%ee) due to the low acidity of the second α-proton by $A_{1,3}$-strain between the N-substitutents and α-substuents (Scheme 2).[8] In addition, there are some limitations in the derivatization of the chiral malonamide esters to various valuable chiral building blocks due to their relatively low chemical reactivity with respect to amide functionality and the limited chemoselectivity between amide and ester functional groups. In this article, we report a novel enantioselective synthesis of α,α-dialkylmalonates, one of the most fundamental chiral building blocks, via direct α-alkylation of malonates under phase-transfer catalytic conditions.[9]

RESULTS AND DISCUSSION

First, we needed to design enantiotopic unsymmetrical α-alkylmalonates as substrates for PTC α-alkylation. Since the *tert*-butyl ester group has historically been essential for high enantioselectivity in the previous enantioselective PTC α-alkylations, one of ester groups in the malonate substrate was employed with a *tert*-butyl group (Scheme 3).[10] For the preliminary study, benzyl *tert*-butyl α-methylmalonate (**10**) was prepared and examined by α-benzylation under typical PTC conditions based on previous reports. The enantioselective PTC benzylation of **10** was performed by the representative chiral phase-transfer catalysts (**4**−**9**, **5**−**10** mol %),[11] along with benzyl bromide (5.0 equiv) and 50% KOH (aq, 5.0 equiv) at 0 °C in toluene (entries 1−6 in Table 1). We thought at the beginning that the genera-

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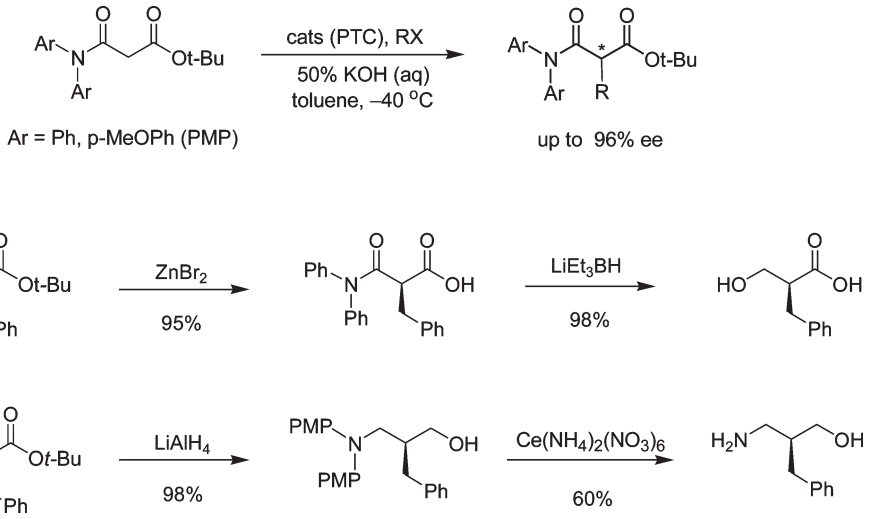
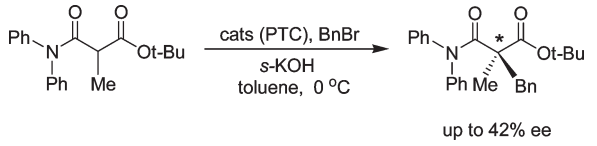
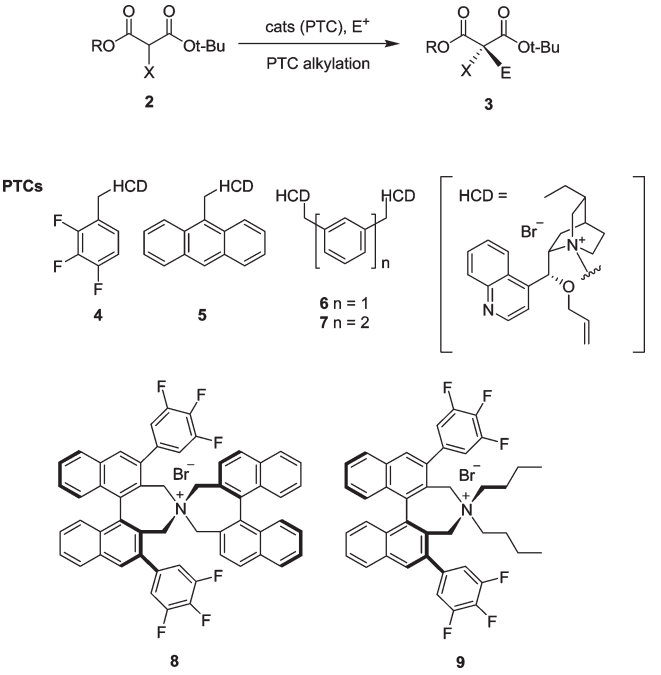
Scheme 1. Enantioselective Phase-Transfer Catalytic Mono-α-alkylation of Malonamide Esters and Their Applications



Scheme 2. Enantioselective Phase-Transfer Catalytic α,α-Dialkylation of Malonamide Esters



Scheme 3. Phase-Transfer Catalytic α-Alkylation of Malonates (2)



tion of chirality via the direct α-alkylation of α-methylmalonate would be quite challenging due to the variable conformations of the two ester groups. However, contrary to our expectation, catalyst **8** surprisingly afforded the α-benzylated product (**10c**) with 70% ee and 90% chemical yield (entry 5). Lower enantioselectivity was observed with **9** (entry 6, 61%, 49% ee), which previously showed excellent enantioselective efficiency compared with **8** in the PTC alkylation of glycinimine esters.[11f] All of the *cinchona*-derived catalysts (**4**−**7**) unfortunately afforded quite lower enantioselectivities with similar chemical yields compared to those of catalyst **8**.

The unexpected promising results prompted us to optimize the structure of malonate substrates to increase enantioselectivity. Five additional alkyl *tert*-butyl α-methylmalonates (**11**−**15**) were prepared by varying the ester alkyl groups, and their substrate efficiencies were evaluated by PTC benzylation in the presence of catalyst **8** (5 mol%).

As shown in Table 1 (entries 7−11), enantioselectivity values were dramatically dependent on the alkyl ester group. 2-Biphenyl groups (entry 7, **11**, 80% ee) gave slightly higher enantioselectivity compared to the benzyl group (entry 5, 70% ee), but comparable enantioselectivity was observed in nonaromatic cyclohexyl group (entry 8, **12**, 73% ee). The 9-anthracenylmethyl group (entry 9, **13**, 24% ee) exhibited quite low enantioselectivity. The best enantioselectivity was accomplished by the diphenylmethyl group (entry 10, **14**, 95% ee). It was notable that the fluorenyl group (entry 11, **15**, 10% ee), the cyclized form of the diphenylmethyl group (**14**), showed a loss of enantioselectivity. Its planar geometry might not be suitable for favorable binding to the PTC catalyst **8**. The variation of reaction temperature and solvent could not significantly increase both enantioselectivity and chemical yield, but a lower amount of catalyst **8** decreased the enantioselevtivity.

The substrate **14** was chosen for further investigation into the scope and limitations of enantioselective PTC alkylation with various electrophiles. The very high enantioselectivities (up to 97% ee) shown in Table 2 indicate that this reaction system is a very efficient enantioselective synthetic method for α,α-dialkylmalonates. Furthermore, α-phenyl- and α-fluoromalonate substrates (entry 7, **16**; entry 8, **17**) afforded very high enantioselectivities as well.

In addition, the successive double α-alkylations of malonate, **18**, also could afford the corresponding α,α-dialkylmalonates without loss of enantioselectivity with a high chemical yield (Scheme 4). To the best of our knowledge, this is the first report to accomplish enantioselective catalytic direct α-alkylation of malonates.

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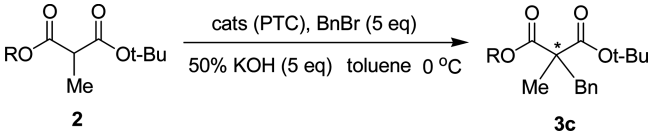
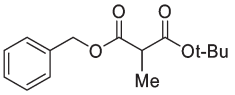
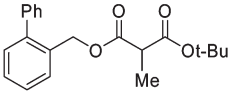
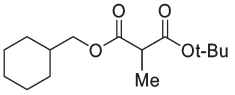
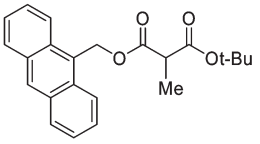
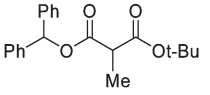
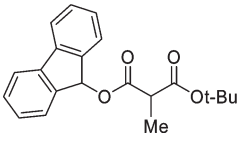
Table 1. Enantioselective PTC Alkylation of α-Methylmalonates[a]

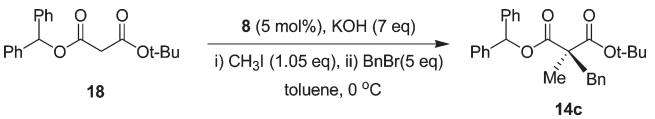


2 **3c**

entry	substrate (**2**)		catalyst (mol%)	time (h)	yield (%)[b]	ee (%)[c]
1		**10**	**4** (10)	15	92	15
2			**5** (10)	17	93	26
3			**6** (5)	24	84	7
4			**7** (5)	24	92	10
5			**8** (5)	16	90	70
6			**9** (5)	40	61	49
7		**11**	**8** (5)	13	90	80
8		**12**	**8** (5)	60	90	73[d]
9		**13**	**8** (5)	19	86	24
10		**14**	**8** (5)	13	95	95
11		**15**	**8** (5)	16	85	10

[a] Reactions were performed with 5.0 equiv of benzyl bromide and 5.0 equiv of 50% KOH (aq) under the given conditions. [b] Isolated yields. [c] Enantiopurity was determined by HPLC analysis using a chiral columns. [d] Enantiopurity was determined via **14c** transformed from **12c**.

Scheme 4. Double PTC α-Alkylations of Malonate 18



Optically active α,α-dialkylmalonates (**14c, 21, 23**) could be readily converted to non-natural α-amino acids and indole derivatives, respectively, as exemplified in Scheme 5. Catalytic hydrogenation of **14c** with Pd/C−H_2 followed by acid activation and ammonolysis gave *tert*-butyl malonamide ester (**19**). The Hofmann rearrangement of **19**[12] followed by acidic hydrolysis provided (*R*)-α-methylphenylalanine (90%).[13] PTC benzylations of **20** with benzyl bromide and 4-chlorobonzyl bromide afforded the corresponding α-benzylated product **21** (93%, 95% ee) and **23** (99%, 96% ee), respectively. The reduction of **21** and **23** by Raney Ni hydrogenation provided α,α-dialkyloxindole **22** (78%) and **24** (76%), respectively. This method can be applied to the synthesis of

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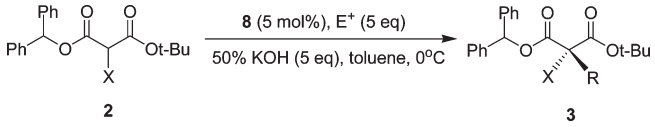
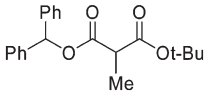
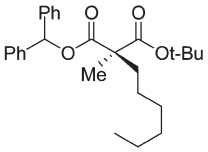
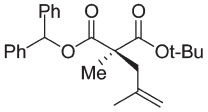
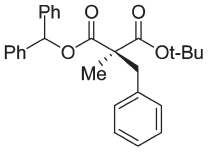
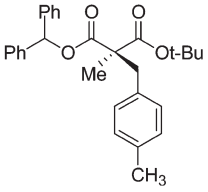
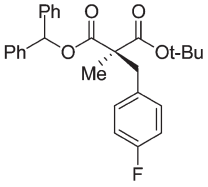
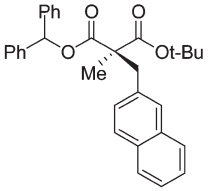
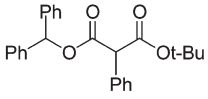
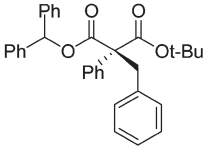
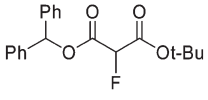
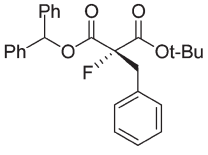
Table 2. Enantioselective Synthesis of α,α-Dialkylmalonates via PTC Alkylation[a]



2 3

entry	substrate (**2**)		E^+	product (**3**)		time (h)	yield (%)[b]	ee (%)[c]
1[d]		**14**	n-$C_6H_{13}I$ (**a**)		**14a**	24	80	92
2			CH_2=$C(CH_3)CH_2Br$ (**b**)		**14b**	13	87	94
3			BnBr (**c**)		**14c**	16	95	95(*S*)[e]
4			4-Me-BnBr (**d**)		**14d**	13	95	97
5			4-F-BnBr (**e**)		**14e**	14	92	95
6			β-Napthylmethyl Bromide (**f**)		**14f**	13	93	96
7		**16**	BnBr (**c**)		**16c**	5	99	96(*R*)[f]
8[g]		**17**	BnBr (**c**)		**17c**	90	99	93(*R*)[h]

[a] Reactions were performed with 5.0 equiv of benzyl bromide and 5.0 equiv of 50% KOH(aq) under the given conditions. [b] Isolated yields. [c] Enantiopurity was determined by HPLC analysis using a chiral column (DAICEL Chiralpak ADH). [d] Solid KOH(5.0 equiv) was used at −20 °C. [e] Absolute configuration was determined by comparison of the optical rotations of (*R*)-α-methylphenylalanine[13] prepared by acidic hydrolysis of the benzylated product, **14c**. [f] Absolute configuration was tentatively assigned *R* from the X-ray crystal structure of **24**. [g] Solid CsOH was used at −78 °C. [h] Absolute configuration was determined by comparison of the optical rotations of (*S*)-methyl *tert*-butyl α-fluoro-α-benzylmalonate[6b] prepared via the hydrogenation of the benzylated product, **17c**, followed by methyl esterification with excess of diazomethane.

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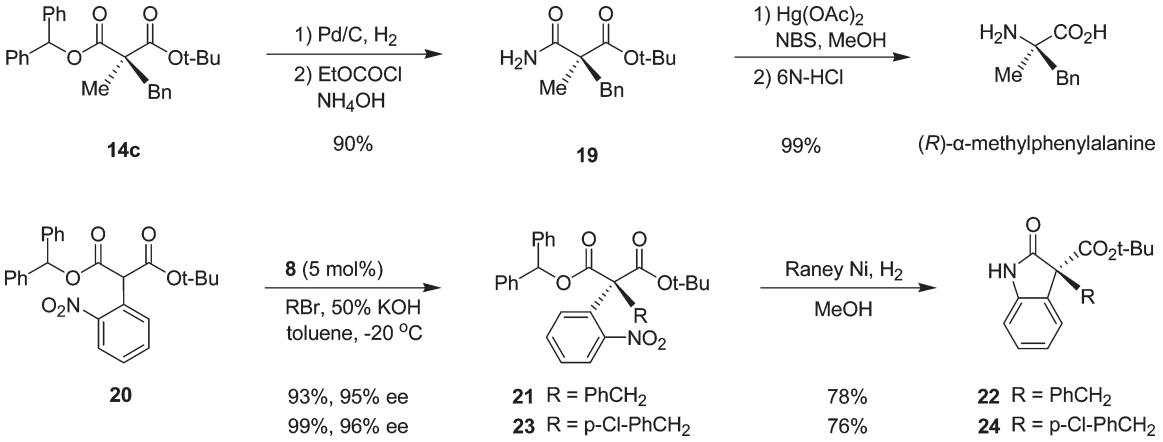
Scheme 5. Application of the Enantioselective PTC Alkylations of Malonates



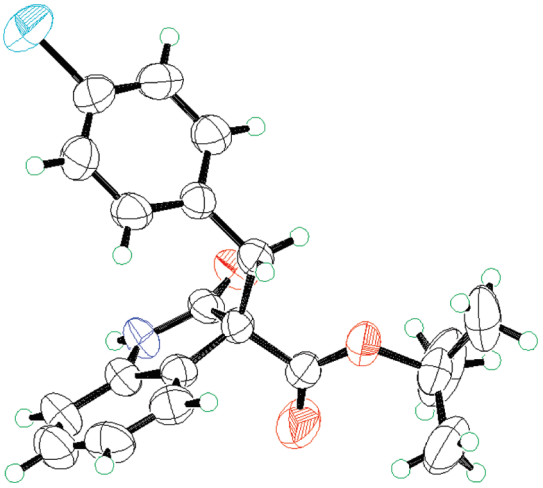


Figure 1. X-ray crystallographic structure of (*R*)-**24**.

oxindole based natural products, such as (+)-horsfiline, spirotryprostatin B, aspidospermidine, and mersicarpine.

CONCLUSIONS

A novel enantioselective synthetic method for α,α-dialkylmalonates via PTC alkylation has been developed. The asymmetric PTC α-alkylation of diphenylmethyl-*tert*-butyl α-alkylmalonates afforded the corresponding α,α-dialkylmalonates in high chemical (up to 99%) and optical yields (up to 97% ee). It is notable that the direct double α-alkylations of diphenylmethyl *tert*-butyl malonate (**18**) also provided the corresponding α,α-dialkylmalonates without loss of enantioselectivity. Our new catalytic system provides an attractive synthetic method for universal chiral building blocks that could be readily converted to versatile chiral target molecules involving quaternary carbon centers. Further applications are now under investigation.

ASSOCIATED CONTENT

Supporting Information. Representative experimental procedures and spectroscopic characterization of all new compounds as well as an X-ray crystallographic analysis of (*R*)-**24**. This information is available free of charge via the Internet at http://pubs.acs.org/.

AUTHOR INFORMATION

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