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藥學碩士學位論文

Enantioselective synthesis of α-acetythio-α-alkylmalonate via Phase-transfer Catalytic alkylation

상전이 촉매 알킬화 반응을 통한

α-acetylthio-α-alkylmalonate 의 입체선택적 합성

2015 年 **2** 月

서울대학교 대학원

약학과 약품제조화학전공

이 민 준

ABSTRACT

Chiral α-thioacyl malonates and their equivalents are potentially valuable intermediates for the synthesis of natural products and pharmaceuticals. α-Thioacyl malonate itself can be easily modified to chiral mercaptoglycerol(3-mercaptopropane-1,2-diol) or α-thioacyl esters according to the chemical conversion of two esters. There have been many synthetic approaches to construct sulfur-bearing quaternary chiral carbon center, mostly by direct sulfa-Michael addition. However, sulfenylation has shortages in preparing substrates and modifying functional groups.

Recently, our research team reported a new synthetic method for chiral α,α-dialkylmalonates in high chemical yield and enantioselectivity by phase-transfer catalytic (PTC) desymmetrization of malonates in the presence of chiral quaternary ammonium salts, and successfully proved its usefulness by applications to the synthesis of various chiral building blocks bearing quaternary carbon center. To expand the research scope, we designed a novel synthetic method for constructing sulfur-bearing chiral carbon center by asymmetric alkylation of α-acylthiomalonate via PTC reaction.

Enantioselective alkylation of *tert*-butyl diphenylmethyl α-acetylthiomalonate was accomplished under phase-transfer catalysis in the presence of (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide as PTC catalyst to afford the corresponding α-acetylthio-α-alkylmalonates in high chemical (up to 99%) and optical yields (up to 95% ee) which could be readily converted to versatile chiral intermediates.

Key words : Enantioselective synthesis, α-acetylthio-α-alkylmalonate, phase-transfer catalysis

Student ID: 2013-21603

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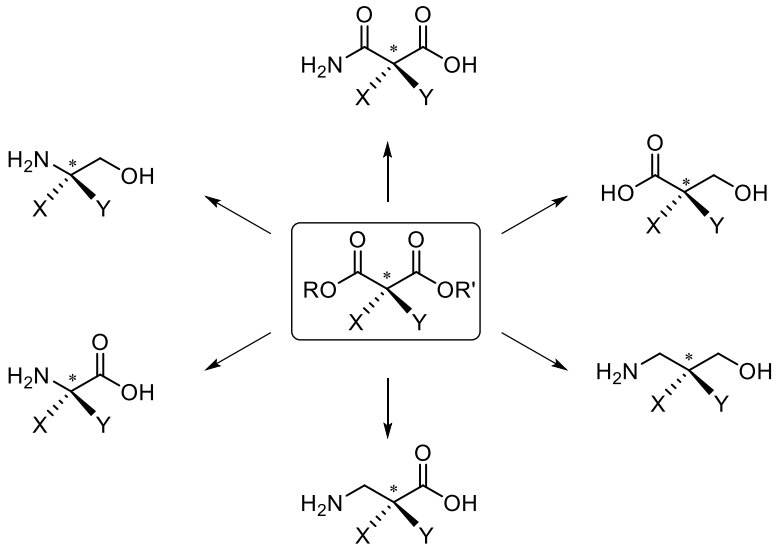
INTRODUCTION

1. General characteristics of malonate compounds

Malonates are one of the most fundamental starting materials in organic synthesis for C-C bond formation.[1] These contain adjacent dicarbonyl group with two esters located in the β-positions. Malonates which have two ester substituents at the β-positions are able to have chiral α carbon. Malonic ester's α hydrogens are adjacent to two carbonyls, therefore the acidity of α-proton (pK_a value = 13) is appropriate to be deprotonated by weak base. This means the α-proton of malonates can be easily substituted to other functional groups including C-C bond formation. Also, the dicarbonyl compounds have considerable synthetic value, because the ester groups can be modified to various other functional groups. Enolate of malolonic ester is readily formed and converted to various chemical moieties via several modifications. (Figure **1**).



1. Representative modification of chiral malonates

These optically active derivatives of chiral malonates can be important building blocks in the synthesis of biologically active pharmaceuticals and natural products. Since chiral α,α-dialkylmalonates are especially resistant to racemization under normal reaction conditions, it can be used in the synthesis of chiral compounds without loss or miss of chirality of quaternary carbon centers. Therefore, achieving chiral α,α-dialkylmalonates has been regarded as quite challenging in asymmetric synthetic fields.

2. Phase-transfer catalysis

2-1. Phase-transfer catalysis

Phase-transfer catalysis(PTC) is a synthetic method that escalates reaction rate under heterogeneous condition by using a chemical substance(catalyst) that utilizes molecular or ionic transfer from a phase to another phase. Commonly, the reaction system is composed of two phases; organic phase containing an acidic compound and an electrophile, and an aqueous of solid phase of inorganic base such as alkaline metal (Na, K, Cs) hydroxide or carbonate. The key reactive intermediate in this type of reaction is the onium-carbanion species, mostly onium-enolate complex or onium-nitronate complex, which reacts with the electrophile in the organic phase to afford the desired compound. Without this catalyst-substrate complex, the reaction does not proceed. Phase-transfer catalysts that are mostly used are onium (ammonium, phoshonium, and sometimes arsonium) salts or complexing agents (crown ethers, polyethers, polyols, etc) that may mask and solulilize inorganic cations, and replacing the location.

There are many advantages that phase-transfer catalysis a very useful tool for many organic syntheses:

- Mild reaction conditions
- Inexpensive reagents and solvents
- Simple experimental procedures
- Environmentally friendly reagents and solvents
- Large-scale preparation
- High-yield processes

The use of chiral phase-transfer catalysis to introduce chirality is significantly different from ordinary chiral transition metal complexes; for example, metal-free asymmetric organocatalysis is extremely valuable for pharmaceutical processes because it eliminates the need to remove toxic trace metals.

2-2. Mechanism of chiral phase-transfer catalysis

The mechanism of asymmetric phase-transfer catalysis consists of 3 steps as follows: (Figure 2) [2]

step 1) interfacial deprotonation of nucleophile(NuH) by hydroxide base(MOH)

step 2) subsequent ion-exchange of the anion with the catalyst generates a lipophilic chiral ammonium enolate, which goes into organic phase

step 3) chiral enolate salt reacts with electrophile(alkyl halide) to afford the asymmetric monoalkylation product with regeneration of the catalyst.

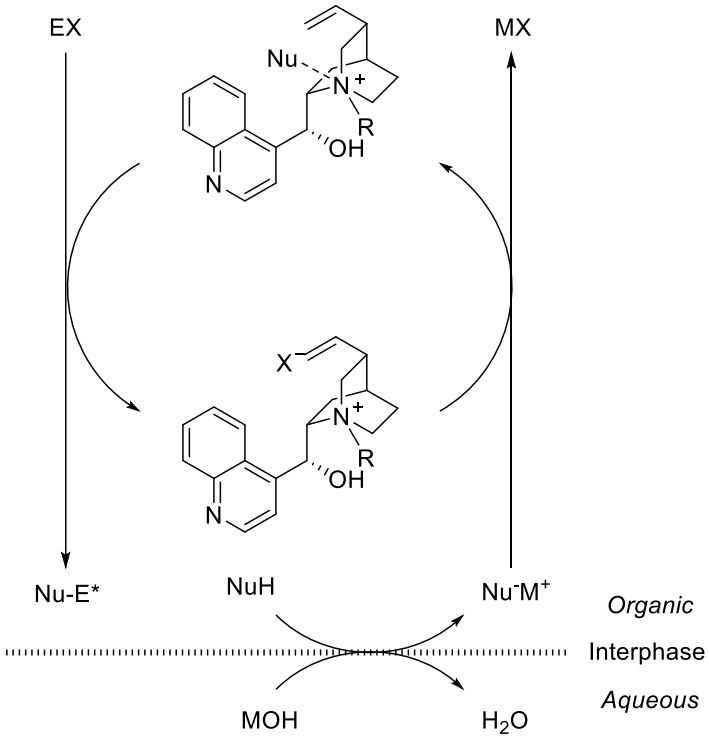
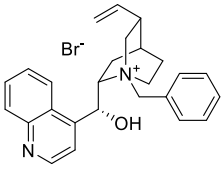


Figure 2. General mechanism of asymmetric phase-transfer catalysis

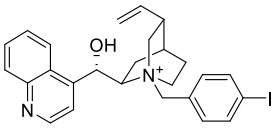
2-3. Phase-transfer catalyst

Chiral phase-transfer catalysts are divided into two types: *Cinchona*-derived catalysts and non *Cinchona*-derived catalysts (Figure **3**).[3] *Cinchona* alkaloid in inexpensive chiral source that used for parent body of chiral catalyst frequently. Alkylation of amine moiety delivers quaternary ammonium center that can coordinate with enolate of substrate.

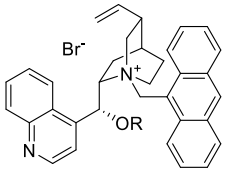
Cinchona-derived catalysts



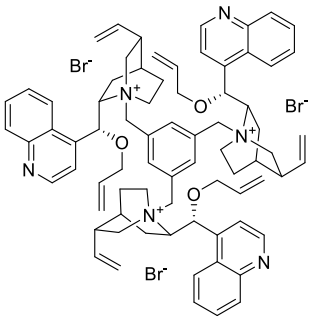
O'Donnell, M. J. *JACS* **1989**, 111, 2353



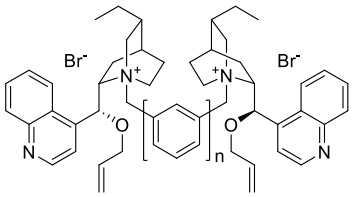
Shioiri, T. *TL* **2001**, 42, 4645



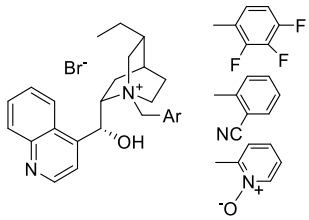
Lygo, B. *TL* **1997**, 38, 8595 (R = H)
Corey, E. J. *JACS* **1997**, 114, 12424 (R = allyl)



Park, H. -g. *TL* **2001**, 42, 4645

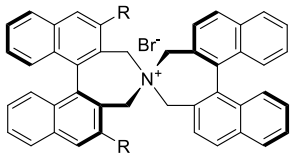


Jew, S. S. *C C*. **2001**, 1244 (n = 1)
Park, H. G. *Angew. Chem. Int. Ed.* **2002**, 41, 3036 (n = 2)

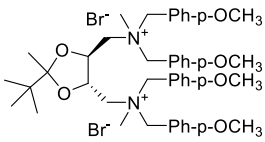


Jew, S. -s. *OL*. **2002**, 4, 4245
Park, H. -g. *OL*. **2005**, 7, 1129.

Non C*inchona*-derived catalysts



Maruoka, K
JACS **1999**, 121, 6519 (R = β-napthyl)
JACS **2003**, 125, 5139 (R = 3,4,5-F_3-Ph))



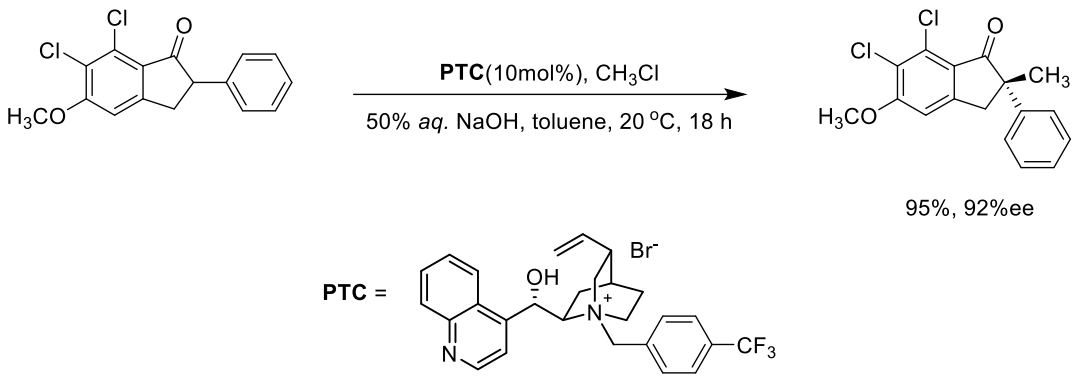
Shibasaki, M. *TL* **2002**, 43, 9539

Figure 3. *Cinchona*-derived and non *Cinchona*-derived phase-transfer catalysts

3. Asymmetric alkylation via phase-transfer catalysis

3-1. The first efficient chiral phase-transfer catalysis

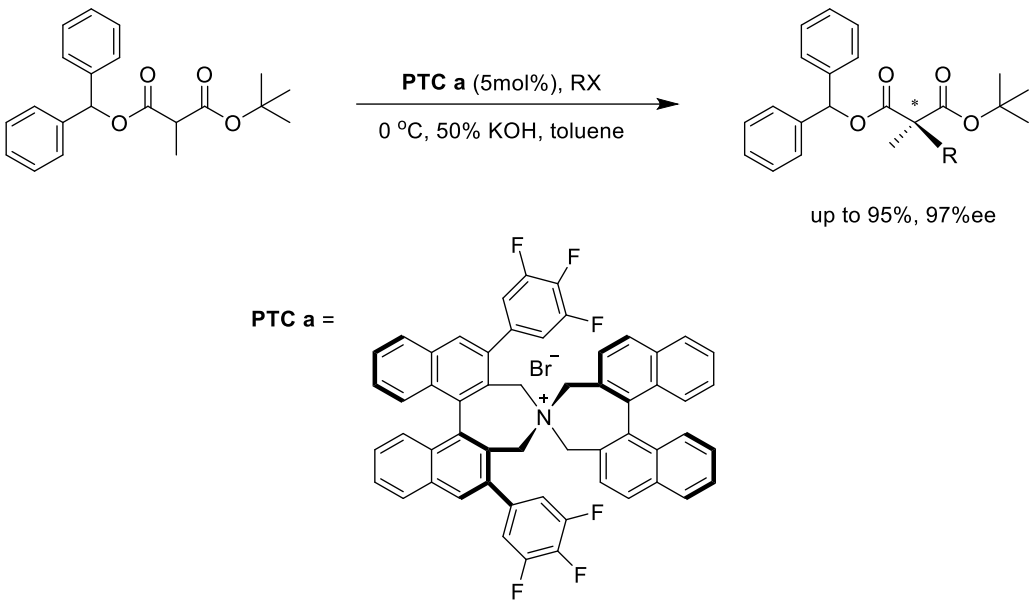
In 1984, Merck group reported first enantioselective alkylation under cinchona-derived phase-transfer catalytic conditions.[4] In this report, methylation of 6,7-dichloro-5-methoxy-2-phenyl-1-indanone is performed in high yield and enantioselectivity (95%,92% ee) (scheme **1**).



Scheme 1. The first asymmetric phase-transfer catalytic alkylation

3-2. The first chiral phase-transfer catalysis of malonate

Our laboratory successfully applied enantioselective phase-transfer catalytic alkylation to malonate substrate, 1-diphenyl 3-*tert*-butyl 2-methylmalonate, and successfully obtained alkylated product **2** in excellent yield and high enantioselectivity (Scheme **2**). [5]

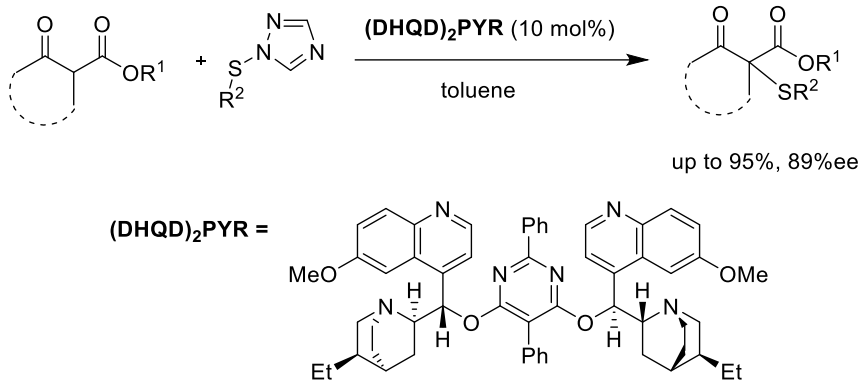


Scheme 2. The first phase-transfer catalytic alkylation of malonate

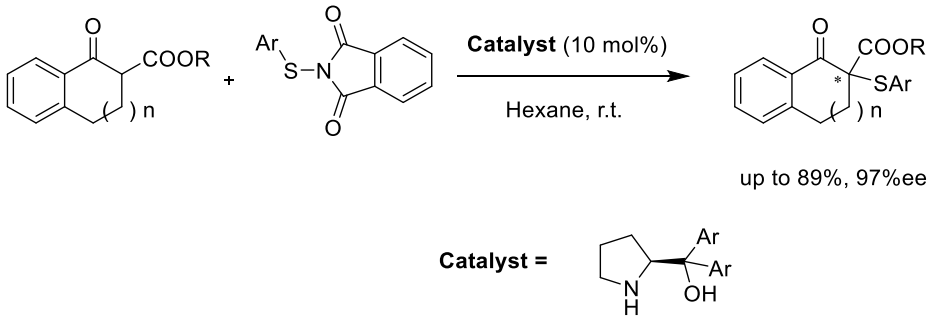
3-3. Previous approaches to construct S-bearing chiral carbon center

In many pharmaceutical and natural products, the sulfur-bearing moieties can be privileged structures. Chiral sulfur-bearing compounds have a variety of utilities in numerous areas, such as efficient ligands, organocatalysts, and chiral auxiliaries and reagents.

To attain these challenging chiral sulfur-containing compounds, many protocols have been addressed.[6] In 2005, Jørgensen and co-workers introduced a highly enantioselective organocatalytic α-sulfenylation (Scheme **3**). [7] To expand the substrate scope, in 2009, Zhu group introduced prolinol derivative catalyst and used *N*-(arylthio)phthalimides as sulfenylating reagents (Scheme **4**). [8]



Scheme 3. Enantioselective sulfenylation of cyclic β-keto esters (1)



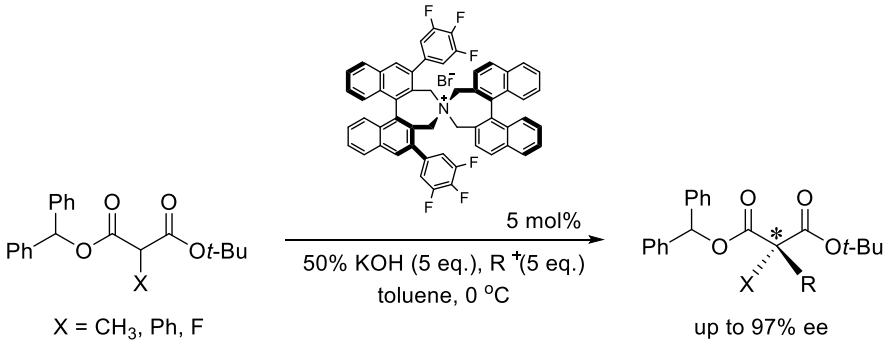
Scheme 4. Enantioselective sulfenylation of cyclic β-keto esters (2)

However, those approach are inefficient for expanding a scope of substrate. Unlikely to malonate substrate, the substrate used in those approach cannot be modified to another functional group because of the cyclic moiety. In methodological aspect, restriction to small-scale process by the catalyst makes inappropriate for applying to industrial process. Inspired by recent studies of our research team on direct α-alkylation of malonates via phase-transfer catalytic (PTC) reaction, I decided to attempt a new synthetic method of synthesizing chiral α-acylthio-α-alkylmalonate.

RESULTS AND DISCUSSION

1. Substrate design and preparation for PTC alkylation

As mentioned in the introduction, our research team reported the first enantioselective synthetic method for the construction of a quaternary carbon center of malonates via phase-transfer catalytic α-alkylation. As descripted, malonates are one of the most fundamental chiral building blocks. Over several preliminary search for the best substrate, high enantioselectivities (up to 97% e.e) were obtained with malonates that having a *tert*-butyl and a diphenyl methyl group in the each ester group. [5] To synthesize diverse α,α-dialkylmalonates, α-position of substrate malonates was substituted with alkyl, aryl, halogen groups, and underwent PTC substitution with various alkyl halides (Scheme **5**).



Scheme 5. Enantioselective PTC α-alkylation of malonate substrates

As mentioned in Scheme **3** and **4**, direct sulfenylation of β-ketoesters was reported by Jørgensen and Zhu group. This synthetic method showed high stereoselectivity and chemical yield. However, this method is difficult to apply because each of various substrates for sulfenylation should be synthesized respectively.

Given that phase-transfer catalysis makes it easier to synthesize a variety of chiral malonate products proved by our previous research on α,α-dialkylmalonates, a new synthetic approach using α-acylthio-α-alkylmalonate via phase-transfer catalysis was designed. For the promising result, *tert*-butyl group and diphenyl methyl group at each ester group were adopted. The essential part of this substrate, α-position of malonate needed to be substituted with acylthio group as a protection of thiol group (Figure **4**). With this α-acyloxymalonate, α-alkylation via phase-transfer catalysis was supposed to be performed to furnish α-acyloxy-α-alkylmalonate with a quaternary carbon center.

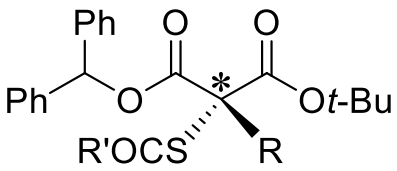
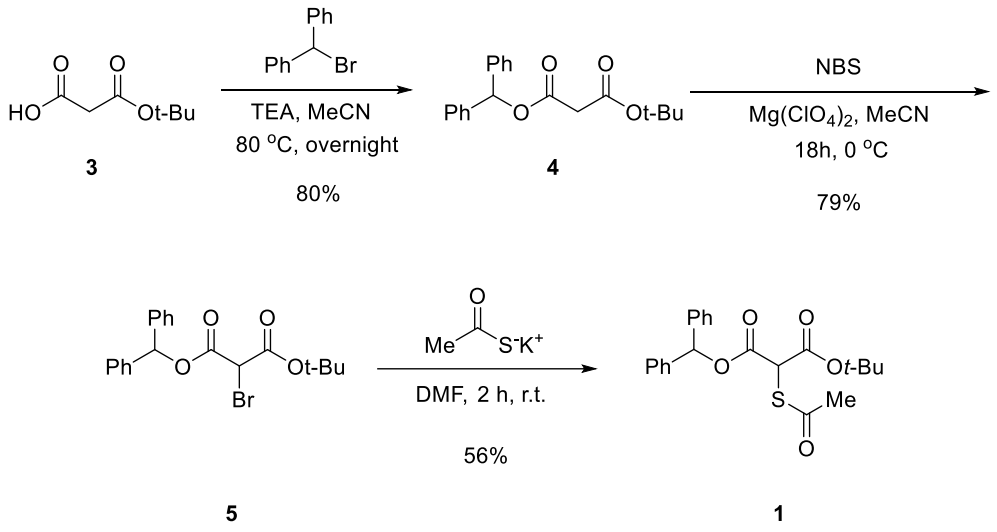


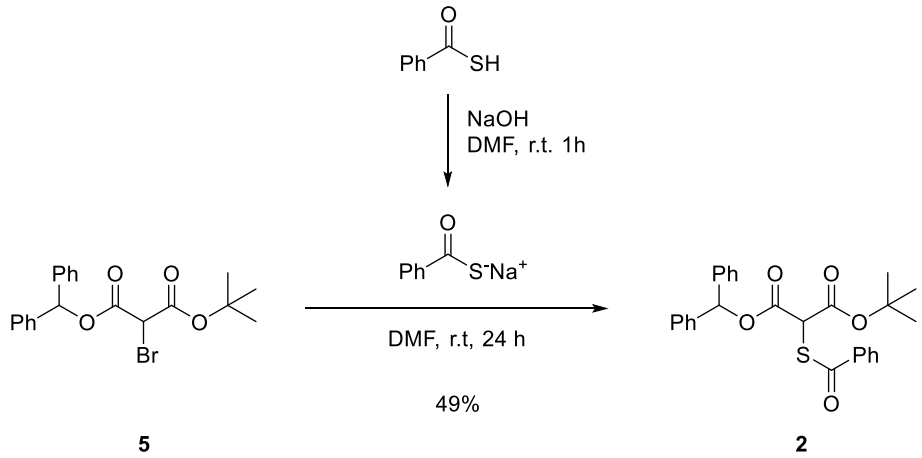
Figure 4. Design of novel acetylthiomalonate as substrate for PTC alkylation

α-Acylthiomalonate substrate was prepared from commercially available *tert*-butyl hydrogen malonates **3** in several steps described in Scheme **6** and **7**. First, carboxylate of *tert*-butyl hydrogen malonates underwent substitution with diphenyl methyl group in basic and warm condition. N-bromosuccinimide and Magnesium perchlorate was used to provide mono-substituted α-bromomalonate **5** at low temperature. In the last step, substitution was performed with potassium acetylthioate and sodium benzothioate to

furnish the PTC substrates, α-acetylthomalonate and α-benzoylthiomalonate, respectively (Scheme **5**). In case of α-benzoylthiomalonate, Benzothioate reagent was non-commercially available, so benzothioate was prepared in-situ by salt exchange of benzoic thio acid. To select the optimal substrate between these two substrates, PTC alkylation of them was conducted subsequently.



Scheme 6. Synthesis of α-acetylthiomalonate

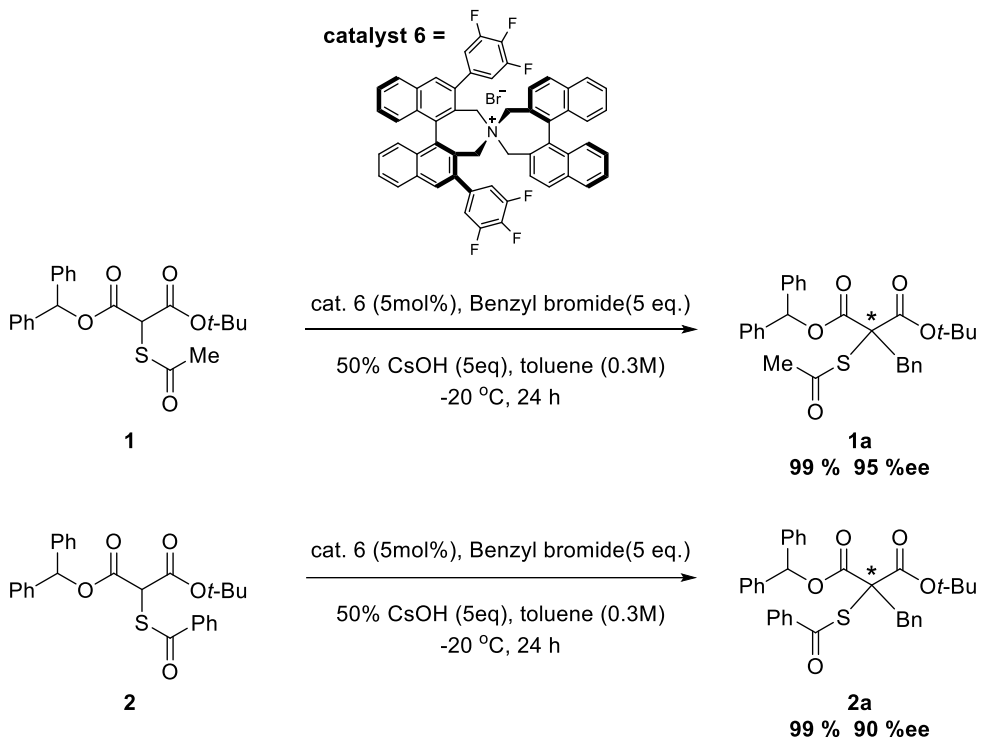


Scheme 7. Synthesis of α-benzoylthiomalonate

2. Enantioselective phase-transfer catalyst reaction of α-acetylthiomalonate

2-1. Optimization of PTC reaction of α-acetylthiomalonate

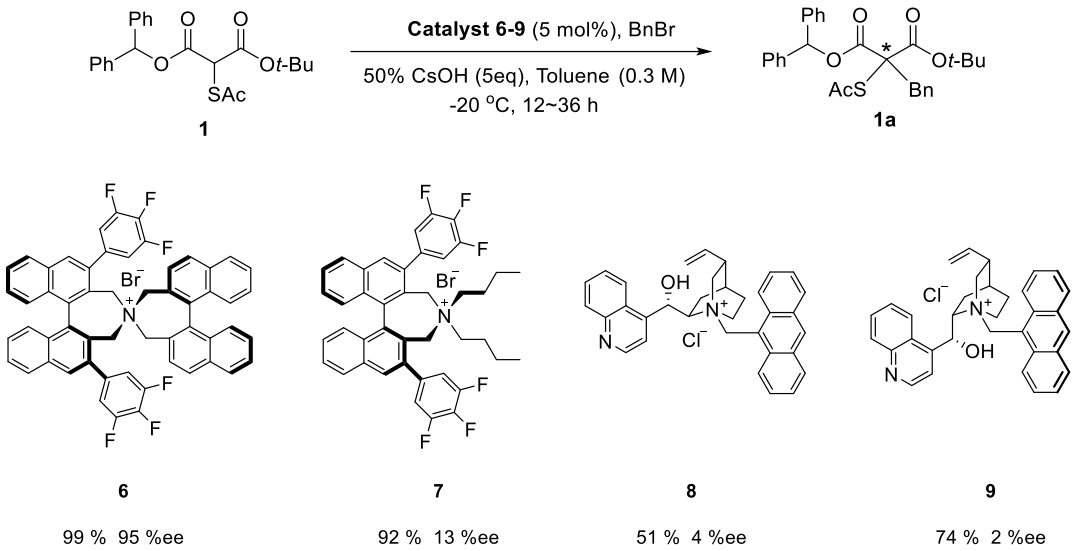
Before searching for the best condition for PTC alkylation, two prepared α-acylthiomalonates were compared under the same circumstance to determine which compound is better substrate for PTC alkylation.



Scheme 8. Comparison of acylthiomalonates for PTC alkylation

Phase-transfer catalyst, base and solvent condition was referred from our research team's previous studies; (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide as a catalyst (0.5mol%), 50% CsOH as a base (5eq), toluene (0.3M) is the optimized reaction condition. Substrate seems vulnerable under room temperature, so the screening is conducted under -20°C. After PTC benzylation at -20°C temperature, α-acylthiomalonate **1** showed a higher enantioselectivity (Scheme **7**), and determined to a proper PTC substrate.

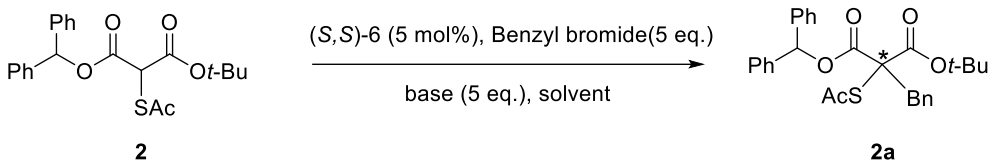
Optimization of phase-transfer catalyst proceeded on the next step. Reaction condition except for the catalyst was set up as the former one, and four catalysts were employed respectively with substrate **1** for comparison.



Scheme 9. Catalyst comparison for PTC alkylation

Likely to the previous research, both the highest enantioselectivity and chemical yield were obtained while using catalyst **6**, and other three catalysts; n-butyl substituted (S,S)-maruoka **7**, *Cinchonine* derived catalyst **7**, C*inchonidine* derived **8** showed significantly lower yields and enantioselectivity (Scheme **8**).

Table 1. Optimization of base, solvent, reaction temperature



entry	base	T (°C)	solvent	Time (h)	Yield (%)	ee (%)
1	50% KOH	0	toluene	18	97	89
2	50% CsOH	0	toluene	18	95	92
3	KOH(s)	-20	toluene	24	90	89
4	CsOH(s)	-20	toluene	18	91	91
5	K_2CO_3	-20	toluene	No reaction		
6	50% CsOH	-20	CH_2Cl_2	Decomposition		
7	50% CsOH	0	cyclopentyl methyl ether	12	88	87
8	50% CsOH	-20	toluene	24	99	95
9	50% CsOH	-40	toluene	24	93	92

As shown in Table **1**, optimization experiment of the rest conditions (base, solvent, reaction temperature) succeeded. Five kinds of base were chosen according to our past research result; 50% Potassium hydroxide, 50% Cesium hydroxide as an aqueous base (entry 1,2) and their solid form base (entry 3,4) and Potassium bicarbonate (entry 5). With solid form base, substrate was likely to be decomposed, which resulted in much lower chemical yield and enantioselectivity than PTC benzylation with aqueous base. With potassium bicarbonate, no reaction occurred. 50% Cesium hydroxide showed the best result and was selected as optimized base.

It turned out that solvents for PTC benzylation have influence on chemical yield and enantioselectivity after solvent screening (entry 2, 6-7). Under dichloromethane solvent, substrate was decomposed, Cyclopentyl methyl ether showed poor yield and enantioselectivity. Preferable chemical and optical yields were observed with toluene.

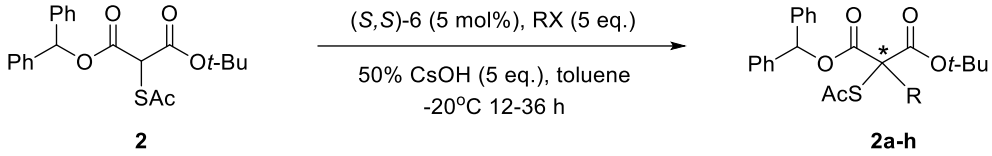
As substrate is vulnerable under room temperature, the reaction above -20 ^{o}C has many byproducts, and result in poor enantioselectivity. Regarding reaction temperature screening (entry 2, 8-9), both chemical yield and enantioselectivity has improved as the temperature decreased until -20°C, but lowered back under -40°C.

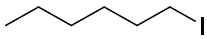
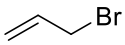
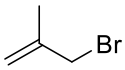
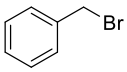
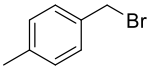
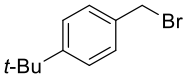
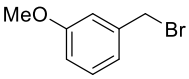
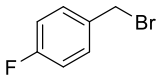
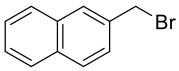
The screening data under varied reaction conditions put together, the optimized reaction condition was determined. It turned out that 50% Cesium hydroxide as base, toluene as solvent, (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide as catalyst and -20°C reaction temperature is the best environment for PTC alkylation of α-acetylthiomalonates.

2-2. Enantioselective PTC alkylation with various alkyl halides

To investigate its scope, PTC alkylation to substrate **1** with various electrophiles performed under the optimized condition. As shown in Table **2**, 9 kinds of electrophiles were examined. The best chemical yield and enantioselectivity was observed while benzylating the α-proton of substrate (99% yield, 95% ee, entry 4), allylation (95% yield, 89% ee, entry 2) followed. PTC alkylation with chain aliphatic electrophile such as iodohexane was likely to be decomposed that resulted in poor yield. Alkylation with allyl bromide and 3-bromo 2-methyl propene showed moderate enantioselectivity (entry 2-3). PTC alkylation of electrophiles that possess aromatic rings were expected to show better enantioselectivity, but the result was not much satisfactory to our expectation. Electrophiles with aromatic rings having *para*-substituted electron donating group showed less optical yields than the benzylated product (entry 5-6). Also, it seems that electron withdrawing group (Fluorine) in aromatic ring has insignificant influence on enantioselectivity (entry 8). Alkylation with 2-(bromomethyl)Naphthalene showed low enantioselectivity (entry 9).

Table 2. Enantioselective PTC alkylation of α-acetylthiomalonate



entry	RX	Time (h)	Yield (%)	ee (%)
1		12	60	80
2		36	90	89
3		12	93	87
4		18	99	95
5		24	89	87
6		36	99	86
7		24	95	79
8		24	98	81
9		36	97	73

3. Application of α-acetylthio-α-alkylmalonates

Under the optimized condition, PTC alkylation with various electrophiles performed successfully. In case of these α-alkylated α-acetylthiomalonates, its functional groups are readily hydrolysable without loss of chirality in carbon center. Once hydrolyzed, various functional groups can be substituted or added. Acetylthio group can be easily converted to thiol group, and by consecutive process, it can be oxidized to sulfide, sulfoxide, sulfone and so on (Figure **5**).

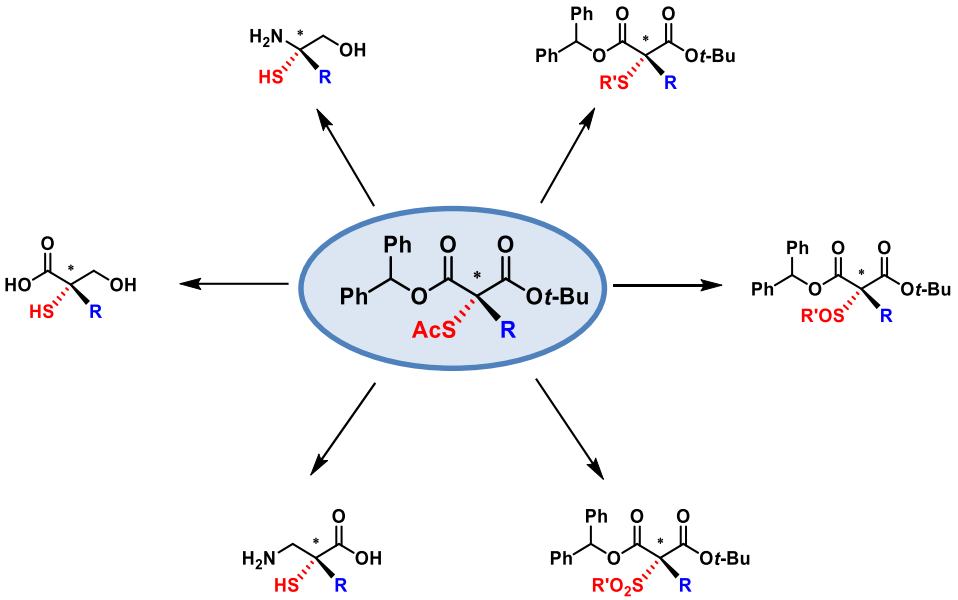
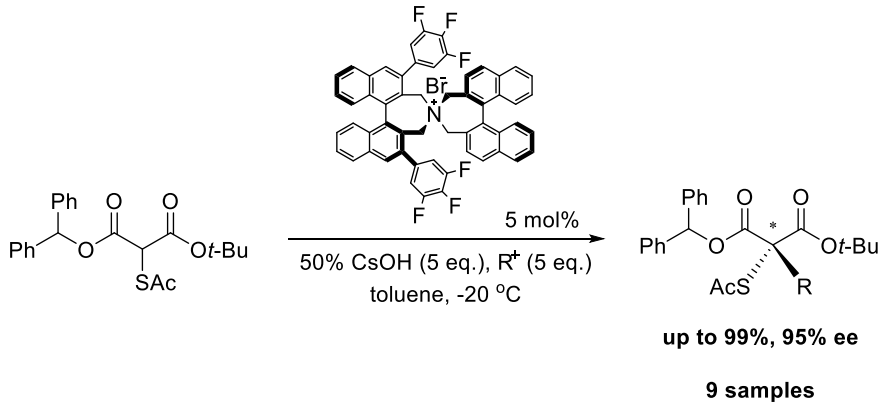


Figure 5. Modification of chiral α-acetylthio-α-alkylmalonates

Therefore, as α-alkylated α-acetylthiomalonates are convenient sulfur-bearing chiral moieties, it can be useful building blocks in the synthesis of biologically active pharmaceuticals and natural products. Study on conversion and application of α-acetylthio-α-alkylmalonates is in process.

CONCLUSION

A new asymmetric synthetic method to prepare α-alkylated α-acetylthiomalonates for the construction of a sulfur-bearing quaternary carbon center via phase-transfer catalytic alkylation has been developed. 9 hydrolysable substrates was designed and utilized on the optimization precess for obtaining more stereoselective results. Finally we figured out enantioselective α-alkylation of diphenylmethyl *tert*-butyl α-acetylthiomalonates under phase-transfer catalytic conditions in the presence of (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide ((*S*,*S*)-**6**) afforded the corresponding α-acetylthio-α-alkylmalonates in high chemical (up to 99%) and optical yields (up to 95% ee), which are readily modified to versatile chiral intermediates.



Scheme 10. Enantioselective PTC alkylation of novel α-acetylthiomalonate substrate

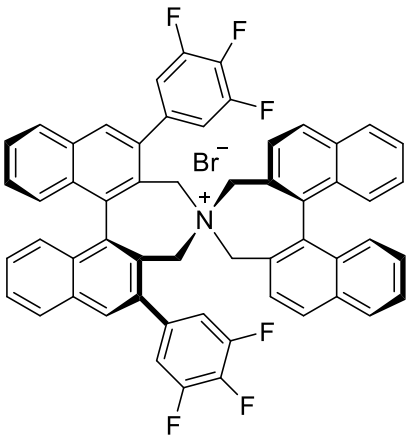
Our new developed catalytic system provides an attractive synthetic method for versatile chiral building blocks, which could be readily converted to chiral target molecules involving sulfur-bearing quaternary carbon centers.

EXPERIMENTAL SECTION

General Methods

1.1. Solvents and Reagents

All reagents bought from commercial sources were unpurified. Organic solvents were concentrated under reduced pressure using a Büchi rotary evaporator. As the commercially available KOH was a pellet type, solid KOH should be grinded to the powder form for successful reaction and high enantiopurity. 50% v/w aqueous CsOH was used as a stock solution. Phase-transfer catalyst **6** (Wako) was purchased from the commercial source.



6

1.2. Chromatography and HPLC

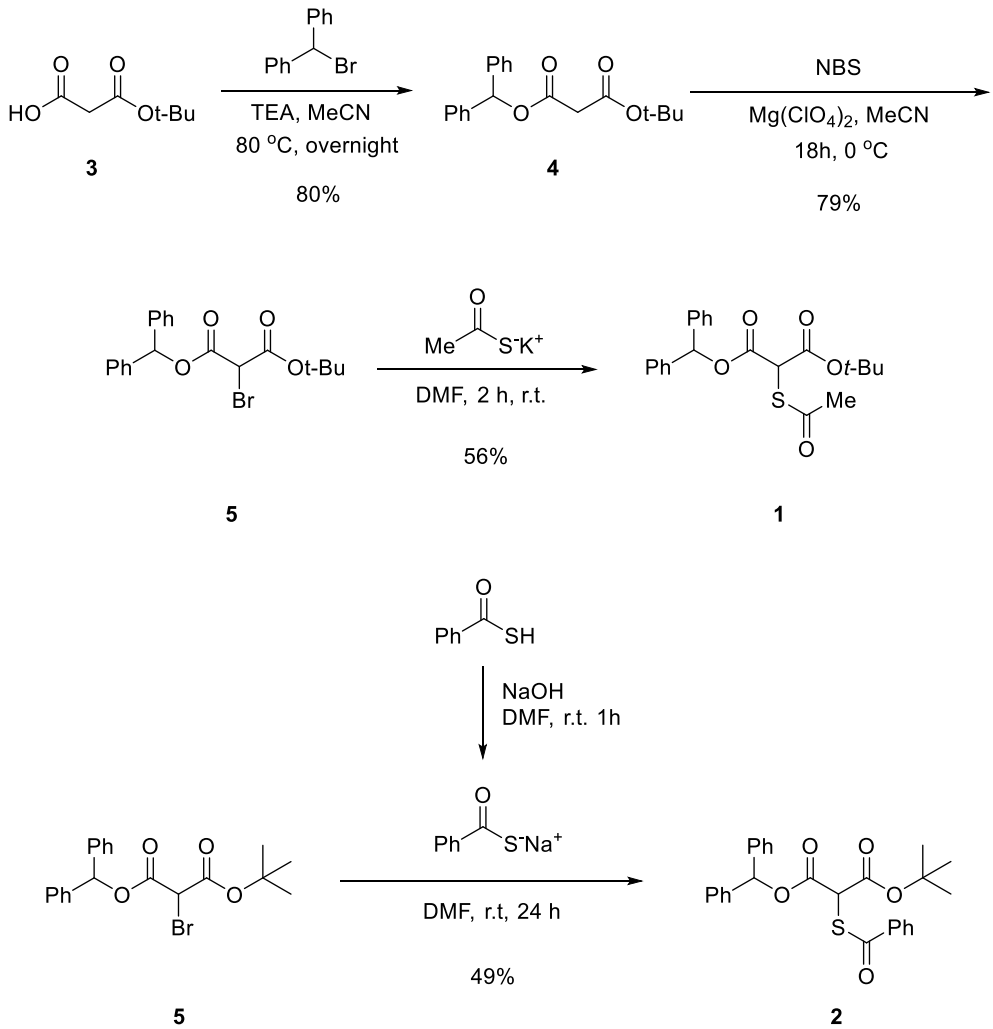
TLC analyses were performed using Merck precoated TLC plate (silica gel 60 GF_{254}, 0.25 mm). Flash column chromatography was carried out using E. Merck Kieselgel 60 (230~400 mesh). Instrument (Hitachi, L-2130) and software (Hitachi, Version LaChrom 8908800-07) were used as HPLC. The enantiomeric excess (ee) of the products was determined by HPLC using 4.6 mm × 250 mm Daicel Chiralpak AD-H.

1.3. Spectral data

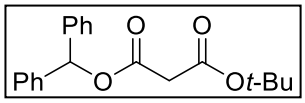
Infrared (IR) spectra were recorded on a JASCO FT/IR-300E and Perkin-Elmer 1710 FT spectrometer. Nuclear magnetic resonance (^{1}H-NMR and ^{13}C-NMR) spectra were measured on JEOL JNM-LA 300 [300 MHz (^{1}H) , 75 MHz (^{13}C)] spectrometer, JEOL JNM-GSX 400 [400 MHz (^{1}H), 100 MHz (^{13}C)] spectrometer, and Bruker AMX 500 [125 MHz (^{13}C)] using $CHCl_3$-*d* or CH_3OH-*d* as solvents, and were reported in ppm relative to $CHCl_3$ (δ 7.24), CH_3OH (δ 3.3) for ^{1}H-NMR and relative to the central $CHCl_3$ (δ 77.23), CH_3OH (δ 49.15) resonance for ^{13}C-NMR. Coupling constants (*J*) in ^{1}H-NMR, ^{13}C-NMR are in Hz. High-resolution mass spectra (HRMS) were measured on a JEOL JMS 700 or JEOL JMS 600-W. Melting points were measured on a Büchi B-540 melting point apparatus and were not corrected. Optical rotations were measured on a JASCO polarimeter P-2000 series or a JASCO DIP-1000 digital polarimeter.

2. α-acylthio-α-alkylmalonates

2.1. Preparation of α-acylthiomalonate substrate

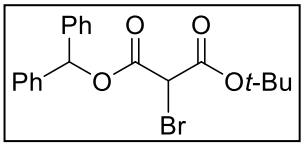


Synthesis of benzhydryl tert-butyl malonate (4)



Triethylamine (5.44 mL, 39 mmol) was added to a solution of *tert*-butyl hydrogen malonate (4.62 mL, 30 mmol) and α-Bromodiphenyl methane (9.64 g, 39 mmol) in acetonitrile (60 mL). At 80 ℃, reaction mixture was stirred for 22 h. Then reaction mixture was evaporated and diluted with ethyl acetate (600 mL). Organic layer was washed with saturated aqueous solution of ammonium chloride (200 mL) and brine (200 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane:EtOAc = 40:1~10:1) to afford **7** (7.83 g, 80% yield) as pale yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.36~7.19 (m, 10H), 6.96 (s, 1H), 3.33 (s, 2H), 1.40 (s, 9H) ppm ; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 165.32, 164.88, 139.41, 128.07, 127.60, 126.80, 81.40, 77.24, 42.77, 27.41 ppm ; IR (KBr) 3033, 2979, 1730, 1496, 1454, 1393, 1369, 1329, 1259, 1144, 1081, 992, 836, 748, 699, 647 cm^{-1} ; HRMS (ESI) : calcd for $[C_{20}H_{22}O_4Na]^+$: 349.1410, found : 349.1422.

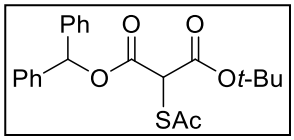
Synthesis of α-bromomalonate substrates (5)



A solution of **4** (750 mg, 2.298 mmol) in dry MeCN (23 mL) was added to the *N*-bromosuccinimide (2.757 mmol) and Magnesium perchlorate (154 mg, 0.689 mmol) at 0 ℃. The reaction mixture was stirred for 23 hours. After solvent was removed on a rotary evaporator, the mixture was diluted with EtOAc (400 mL) and washed with brine (100 mL). The organic layers were dried with $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane:EtOAc = 40:1~20:1), **5** was obtained as colorless oil (736 mg, 79% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.35~7.27

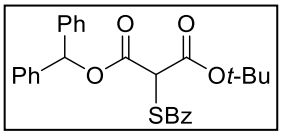
(m, 10H), 6.94 (s, 1H), 4.48 (s, 1H), 1.36 (s, 9H) ppm ; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 163.77, 162.90, 138.91, 138.89, 128.52, 128.48, 128.28, 128.17, 127.29, 127.04, 84.40, 79.26, 44.24, 27.47 ppm ; IR (KBr) 2981, 1740, 1496, 1455, 1370, 1294, 1256, 1139, 989, 848, 748, 699 cm^{-1} ; HRMS (CI) : calcd for $[C_{20}H_{20}FO_4]^+$: 403.0545, found : 403.0545.

Synthesis of α-acetylthiomalonate substrate (1)



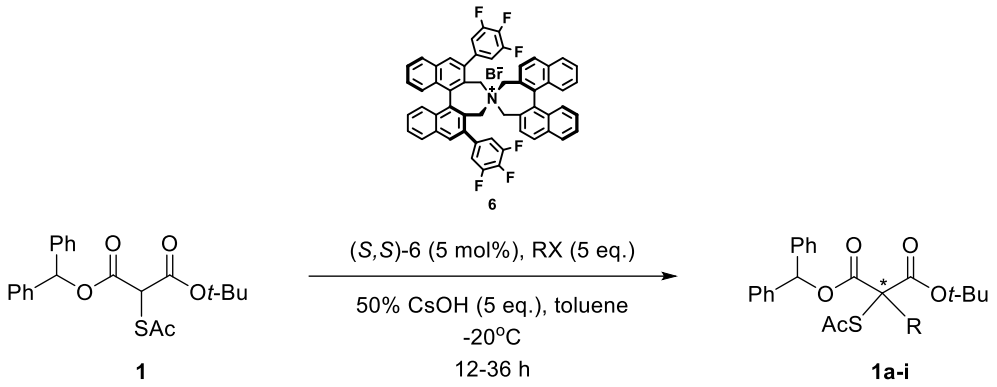
Potassium acetylthioate (127 mg, 1.11 mmol) was added to a stirred solution of **5** (300 mg, 0.740 mmol) in dry DMF (10mL), and Argon gas was substituted. The reaction mixture was stirred for 2 hours. After solvent was removed on a rotary evaporator, the mixture was diluted with EtOAc (300 mL) and washed with brine (80 mL). The organic layers were dried with $MgSO_4$, and concentrated *in vacuo*. After purification by column chromatography (silica gel, hexane:EtOAc = 15:1), **1** was obtained as brown oil (186 mg, 56% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.32-7.24 (m, 10H), 6.9 (s, 1H), 5.07 (s, 1H), 2.37 (s, 3H), 1.33 (s, 9H) ppm ; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 165.16, 164.25, 139.16, 128.46, 128.10, 127.13, 82.13, 77.71, 77.31, 77.00, 76.68, 51.60, 29.85, 27.82 ppm ; IR (KBr) 2979.48, 1729.83, 1495.53, 1455.03, 1393.32, 1369.21, 1259.29, 1142.62, 991.23, 835.99, 771.39, 699.07, 647.00 cm^{-1}.

Synthesis of α-benzoylthiomalonate substrate (2)



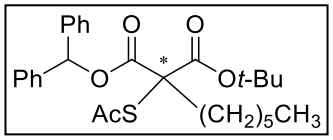
Sodium hydroxide was added to stirred solution of Benzoic thio acid (72 μL, 0.62 mmol) in dry DMF (1ml), and Argon gas was substituted. After stirring for an hour, the mixture was added to a stirred solution of **5** (200 mg, 0.49 mmol) in dry DMF (5mL). The reaction mixture was stirred for 2 hours. After solvent was removed on a rotary evaporator, the mixture was diluted with EtOAc (300 mL) and washed with brine (80 mL). The organic layers were dried with $MgSO_4$, and concentrated *in vacuo*. After purification by column chromatography (silica gel, hexane:EtOAc = 10:1), **2** was obtained as brown oil (112.3 mg, 49.5% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.96~7.89 (m, 2H), 7.61-7.56 (m, 1H), 7.47-7.42 (m, 2H), 7.36-7.21 (m, 10H), 6.96 (s, 1H), 5.31 (s, 1H), 1.35 (s, 9H) ppm ; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 188.56, 165.26, 164.35, 139.64, 135.68, 128.73, 128.45, 128.08, 127.49, 127.14, 83.86, 78.85, 77.71, 77.31, 77.00, 76.68, 51.60, 27.59 ppm ; IR (KBr) 2979, 1729, 1495, 1455, 1393, 1369, 1259, 1143, 992, 835, 771, 699, 647 cm^{-1}.

2.2. General procedure for asymmetric phase-transfer catalytic alkylation



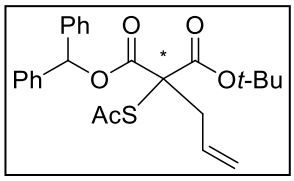
Alkyl halides (0.25 mmol) was added to a solution of α-acetylthiomalonate substrates (0.05 mmol) and (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide (**6**, 2.3 mg, 0.0025 mmol) in toluene (0.166 mL). At the designated temperature, 50% CsOH (43.5 μL, 0.25 mmol) was added to the reaction mixtures and stirred for designated time. EYELA PSL-1400 was used for low temperature stirring and the stirring rate was 7. The reaction mixtures was diluted with EtOAc (10 mL), washed with brine (2×3 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane:EtOAc = 10:1) to afford alkylated malonates.

1-Benzhydryl 3-*tert*-butyl 2-acetylthio-2-hexylmalonate (**1a**)



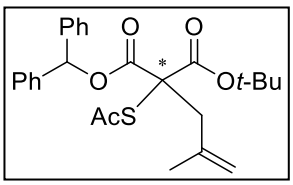
Following the general procedure, reaction was started from **1** (20 mg, 0.05 mmol) using iodohexane (37 μL, 0.25 mmol). After 12 hours, **1a** was obtained as colorless oil (14.5 mg, 60% yield). HPLC analysis (Chiralpak AD-H, hexane:2-propanol = 85:15, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time = major 5.707 min, minor 7.160 min, 67% ee ; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.26-7.19 (m, 10H), 6.94 (s, 1H), 3.28-3.23 (t, 3H *J*=7.25 Hz), 2.1 (s, 3H), 1.28 (s, 9H), 1.24-1.15 (m, 8H), 0.80-0.75 (m, 3H) ppm ; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 194.90, 166.77, 139.24, 128.00, 126.17, 82.13, 77.91, 77.31, 63.27, 31.81, 30.51, 28.77, 27.82, 23.13, 14.16 ppm ; IR (KBr) 2929, 1730, 1455, 1369, 1219, 1149, 772, 699cm^{-1} ; $[\alpha]^{20}_{D}$ = +7.81 (*c* 1, $CHCl_3$).

1-Benzhydryl 3-*tert*-butyl 2-acetylthio-2-allylmalonate (**1b**)



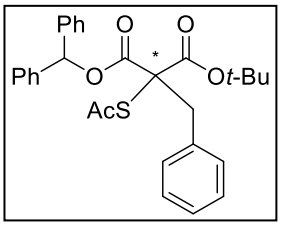
Following the general procedure, reaction was started from **1** (20 mg, 0.05 mmol) using allyl bromide (21.6 μL, 0.25 mmol). After 36 hours, **1b** was obtained as colorless oil (19.8 mg, 90% yield). HPLC analysis (Chiralpak AD-H, hexane:2-propanol = 85:15, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time = major 6.233 min, minor 8.567 min, 51% ee ; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.32-7.24 (m, 10H), 6.9(s, 1H), 5.78-5.64(m, 1H), 5.05-4.99 (m, 2H), 3.07-3.04 (m, 2H), 2.18 (m, 3H), 1.25 (s, 9H) ppm ; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 166.23, 165.29, 139.37, 131.97, 128.39, 127.95, 127.25, 119.59, 83.9., 78.56, 77.23, 76.99, 65.73, 33.99, 29.97, 27.51 ppm ; IR (KBr) 2976, 1730, 1496, 1455, 1393, 1368, 1240, 1145, 1001, 919, 844, 759, 699, 647 cm^{-1} ; $[\alpha]^{20}_{D}$ = -3.81 (*c* 1, $CHCl_3$).

1-Benzhydryl 3-*tert*-butyl 2-acetylthio-2-(2-methylallyl)malonate (**1c**)



Following the general procedure, reaction was started from **1** (20 mg, 0.05 mmol) using 3-bromo-2-methyl propene (25 μL, 0.25 mmol). After 12 hours, **1c** was obtained as colorless oil (21 mg, 92.5% yield). HPLC analysis (Chiralpak AD-H, hexane:2-propanol = 85:15, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time = major 5.703 min, minor 7.610 min, 57% ee ; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.27-7.21 (m, 10H), 6.89(s, 1H), 4.67-4.61(d, 2H), 3.57-3.51 (m, 2H), 2.56-2.54 (m, 3H), 1.66(s, 3H), 1.30 (s, 9H) ppm ; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 168.37, 167.77, 141.55, 139.71, 128.45, 127.96, 127.23, 112.32, 81.92, 77.55, 77.32, 77.00, 76.68, 51.56, 36.47, 27.76, 22.24 ppm ; IR (KBr) 2978, 1731, 1496, 1455, 1393, 1369, 1248, 1145, 999, 897, 844, 759, 699, 647 cm^{-1} ; $[\alpha]^{20}_{D}$ = -2.44 (*c* 1, $CHCl_3$).

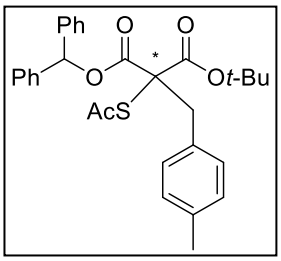
1-Benzhydryl 3-*tert*-butyl 2-acetylthio-2-benzylmalonate (**1d**)



Following the general procedure, reaction was started from **1** (20 mg, 0.05 mmol) using benzyl bromide (29 μL, 0.25 mmol). After 18 hours, **1d** was obtained as white solid (24.3 mg, 99% yield). HPLC analysis (Chiralpak AD-H, hexane:2-propanol = 85:15, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time = major 8.253 min, minor 12.763 min, 80% ee ; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.37-7.28 (m, 10H), 7.21-7.11 (m, 3H), 7.03-7.00 (m, 2H), 6.94 (s, 1H), 3.72-3.61 (m, 2H), 2.21 (s, 3H), 1.24 (s, 9H) ppm ; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 166.32, 166.23, 139.24, 135.38, 128.46, 128.30, 128.15, 127.91, 127.65, 127.23, 127.14, 84.04, 78.75, 77.25, 77.00, 76.74, 67.30, 39.52,

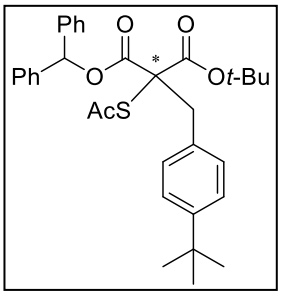
29.98, 27.47 ppm ; IR (KBr) 2978, 1730, 1496, 1455, 1369, 1219, 1142, 1001, 772, 698 cm^{-1} ; $[\alpha]^{20}_{D}$ = -17.98 (*c* 1, $CHCl_3$) ; m.p. = 73 ℃.

1-Benzhydryl 3-*tert*-butyl 2-acetylthio-2-(4-methylbenzyl)malonate (**1e**)



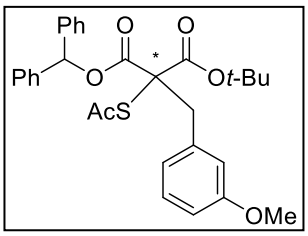
Following the general procedure, reaction was started from **1** (20 mg, 0.05 mmol) using 4-methylbenzyl bromide (46.2 mg, 0.25 mmol). After 24 hours, **1e** was obtained as white solid (22.4 mg, 89% yield). HPLC analysis (Chiralpak AD-H, hexane:2-propanol = 90:10, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time = major 12.380 min, minor 14.540 min, 49.6% ee ; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.32-7.01 (m, 14H), 6.85 (s, 1H), 3.67-3.62 (t, 2H *J*=7.68 Hz), 3.20-3.12 (m, 3H), 2.28 (s, 3H), 1.29 (s, 9H) ppm ; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 168.30, 167.62, 139.66, 136.04, 134.72, 129.10, 128.72, 128.39, 128.33, 127.95, 127.83, 127.32, 127.14, 82.01, 77.54, 77.32, 77.20, 77.00, 76.68, 54.99, 34.22, 27.74, 21.02 ppm ; IR (KBr) 2928, 2356, 1742, 1448, 1340, 1219, 1154, 948, 856, 772, 694, 647 cm^{-1} ; $[\alpha]^{20}_{D}$ = -65.71 (*c* 1, $CHCl_3$) ; m.p. = 120 ℃.

1-Benzhydryl 3-*tert*-butyl 2-acetylthio-2-(4-*tert*-butylbenzyl)malonate (**1f**)



Following the general procedure, reaction was started from **1** (20 mg, 0.05 mmol) using 4-*tert*-buthylbenzyl bromide (56.71 μL, 0.25 mmol). After 36 hours, **1f** was obtained as pale yellow oil (27.04 mg, 99% yield). HPLC analysis (Chiralpak AD-H, hexane:2-propanol = 90:10, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time = major 6.373 min, minor 9.217 min, 46% ee ; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.78-6.36 (m, 15H), 3.19-3.14 (t, 2H *J*=7.89 Hz), 2.74-2.64 (m, 3H), 0.77-0.74 (m, 18H) ppm ; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 168.33, 149.36, 139.66, 130.01, 128.51, 128.38, 127.92, 127.63, 127.28, 127.18, 125.27, 124.92, 81.98, 77.88, 77.59, 77.20, 77.00, 76.68, 60.35, 54.78, 38.47, 34.08, 31.32, 27.71 ppm ; IR (KBr) 2964, 1730, 1514, 1496, 1455, 1393, 1367, 1231, 1143, 1002, 843, 771, 699 cm^{-1} ; $[\alpha]^{20}_{D}$ = -56.72 (*c* 1, $CHCl_3$).

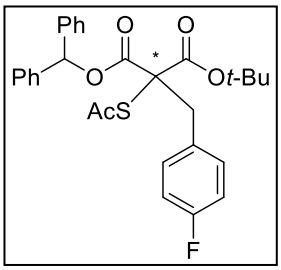
1-Benzhydryl 3-*tert*-butyl 2-acetylthio-2-(3-methoxybenzyl)malonate (**1g**)



Following the general procedure, reaction was started from **1** (20 mg, 0.05 mmol) using 3-methoxybenzyl bromide (35 μL, 0.25 mmol). After 24 hours, **1g** was obtained as colorless oil/ (24.7 mg, 95% yield). HPLC analysis (Chiralpak AD-H, hexane:2-propanol = 90:10, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time = major 10.587 min, minor 17.463 min, 79% ee ; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.33-7.10 (m, 13H), 6.93-6.69 (m, 2H), 3.80-3.64 (m, 3H), 3.38-3.37 (m, 3H), 3.18-3.15 (m, 2H), 1.39 (s, 9H) ppm ; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 168.22, 165.92, 139.67, 128.47, 128.41,

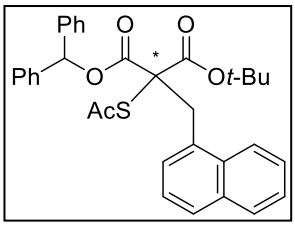
128.02, 127.88, 127.20, 77.32, 77.21, 76.68, 54.79, 43.30, 34.67, 27.84 ppm ; IR (KBr) 2934, 2321, 1726, 1601, 1490, 1455, 1369, 1263, 1218, 1154, 1044, 840, 772, 698, 649 cm^{-1} ; $[\alpha]^{20}_{D}$ = -77.94 (*c* 1, $CHCl_3$).

1-Benzhydryl 3-*tert*-butyl 2-acetylthio-2-(4-fluorobenzyl)malonate (**1h**)



Following the general procedure, reaction was started from **1** (20 mg, 0.05 mmol) using 4-fluorobenzyl bromide (30.6 μL, 0.25 mmol). After 24 hours, **1h** was obtained as white solid (24.9 mg, 98% yield). HPLC analysis (Chiralpak AD-H, hexane:2-propanol = 90:10, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time = major 14.463 min, minor 17.923 min, 50% ee ; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.28-7.0 (m, 12H), 6.85-6.77 (m, 3H), 3.61-3.55 (t, 2H *J*= 7.86Hz), 3.12-3.04 (m, 3H), 1.26 (s, 9H) ppm ; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 168.08, 167.40, 133.47, 130.42, 130.34, 128.45, 128.01, 127.95, 127.30, 127.11, 115.32, 115.11, 82.22, 77.65, 77.32, 77.20, 77.00, 76.68, 54.94, 33.82, 27.74 ppm ; IR (KBr) 2978, 2310, 1730, 1602, 1509, 1455, 1369, 1221, 1142, 1002, 844, 772, 699 cm^{-1} ; $[\alpha]^{20}_{D}$ = -69.94 (*c* 1, $CHCl_3$) ; m.p. = 90.8 ℃.

1-Benzhydryl 3-*tert*-butyl 2-acetylthio-2-(naphthalene-1-ylmethyl)malonate (**1i**)



Following the general procedure, reaction was started from **1** (20 mg, 0.05 mmol) using 2-(bromomethyl) naphthalene (55.2 mg, 0.25 mmol). After 36 hours, **1i** was obtained as colorless oil (26.2 mg, 97% yield). HPLC analysis (Chiralpak AD-H, hexane:2-propanol = 90:10, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time = major 15.170 min, minor 24.443 min, 20% ee ; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.84-7.07 (m, 17H), 6.86 (s, 1H), 3.83-3.77 (t, 2H *J*= 7.68Hz), 3.45-3.33 (m, 3H), 1.30 (s, 9H) ppm ; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 168.23, 167.56, 139.57, 139.44, 135.33, 133.46, 132.32, 128.39, 128.26, 128.12, 127.97, 127.81, 127.63, 127.56, 127.48, 127.43, 127.30, 127.13, 127.01, 126.75, 126.55, 126.46, 125.94, 125.49, 82.16, 77.65, 77.32, 77.20, 77.00, 76.68, 54.82, 34.80, 34.01, 27.83 ppm ; IR (KBr) 2978, 2364, 1729, 1600, 1495, 1455, 1368, 1340, 1219, 1142, 1002, 844, 817, 772, 699 cm^{-1} ; $[\alpha]^{20}_{D}$ = -27.21 (*c* 1, $CHCl_3$).

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국 문 초 록

비대칭적인 α-thio malonate는 유기합성에서 높은 합성적 가치를 지니는 출발 물질이며, 양쪽의 ester group을 변환시킴에 따라 생물학적 활성이 있는 천연물이나 의약품을 합성 하는데 이용될 수 있다. 황 원소를 포함하는 비대칭적인 4차 탄소 골격을 만들기 위한 많은 시도가 있었으나, 기질의 준비와 작용기의 변형이 어려운 단점이 있었다.

이에 앞서 본 연구실에서는 최초로 상 전이 촉매 반응을 통한 malonate 의 입체 선택적인 α-alkylation을 성공적으로 수행한 바 있다. 앞서 수행한 α-acetoxymalonate와 α-benzoxymalonate를 이용한 1,3-dicarbonyl 화합물의 입체 선택적인 α-hydroxylation 연구를 확장하기 위하여, 본 연구자는 황 원소를 포함하는 비대칭적 4차 탄소 골격을 만들기 위해 촉매로 (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide를 사용하고 *tert*-butyl diphenylmethyl α-acetylthiomalonate를 기질로 하여 입체선택적인 alkylation을 수행하였고, 상 전이 촉매 반응 (Phase-Transfer Catalysis)을 통해 높은 화학 수율 (99%)과 광학 수율(95% ee)을 보이며 다양한 chiral 중간체로 변환될 수 있는 α-acetylthio-α-alkylmalonate를 성공적으로 합성하였다.

Key word: 입체선택적 합성, α-acetylthio-α-alkylmalonate, 상전이 촉매 반응 (Phase - Transfer Catalysis)

학번: 2013-21603