藥 學 碩 士 學 位 論 文

Part I : Reoptimized Phase-transfer Catalytic Alkylation of α-acetylthiomalonate

Part II : Application and Confirm the Absolute Configuration of α-benzoxy-α-alkylmalonate

Part I : α–acetylthiomalonate의 상전이 촉매 **Alkylation**의 최적화 연구

Part II : α-benzoxy-α-alkylmalonate의 응용 및 절대배열 확인

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Reoptimized Phase-transfer Catalytic Alkylation of α-acetylthiomalonte

α-acetylthiomalonte의 상전이 촉매 Alkylation의 최적화 연구

ABSTRACT

Organosulfur compounds are widely present in bioactive natural products and pharmaceuticals. The C-S bond formation is basic approach to synthesize the organosulfur compound. Among the C-S bond formation, construction of sulfur-bearing chiral quaternary carbon center is the most challenging target. There have been many synthetic methods for construction of sulfur-bearing chiral quaternary carbon center, but most of them were reactions through the sulfa nucleophile attack. However, these conventional methods have limitations in preparing sulfa nucleophiles and modifying its substrates.

In 2011, our research team reported novel synthetic method for chiral α,α-dialkylmalonates in high chemical yield and optical yield by asymmetric phase-transfer catalyzed alkylation of modified malonates in the presence of chiral quaternary ammonium salts, and successfully proved its value by application of the natural product total synthesis and bioactive chemical block synthesis. To expand the research scope, we designed new substrate bearing heteroatoms to malonate's α–position especially sulfur. Into this new sulfur bearing substrate, we tried to insert the various electrophiles via asymmetric phase transfer catalytic alkylation.

As a result, enantioselective alkylation of *tert*-butyl diphenylmethyl α-acetylthiomalonate was accomplished through asymmetric phase-transfer catalysis in the presence of (*S,S*)-3,4,5-trifluorophenyl-NAS bromide as chiral catalyst and 50% KOH (aq) as base solution, toluene as organic solvent at -20 °C reaction temperature to afford the corresponding α-acetylthio-α-alkylmalonates in high chemical (up to 99%) and optical yields (up to 98% ee).

Keywords: enantioselective synthesis, α-acetylthio-α-alkylmalonate, asymmetric phase-transfer catalysis, quaternary carbon center

Student Number: 2015-21891

INTRODUCTION

1. Synthesis of organosulfur compounds

1.1. Organosulfur compounds

The organosulfur compounds are structures that are easily found in amino acids and peptides that are basic biological components.[1] Also, it is present in biologically active natural products and pharmaceuticals (**Figure 1**).[1]

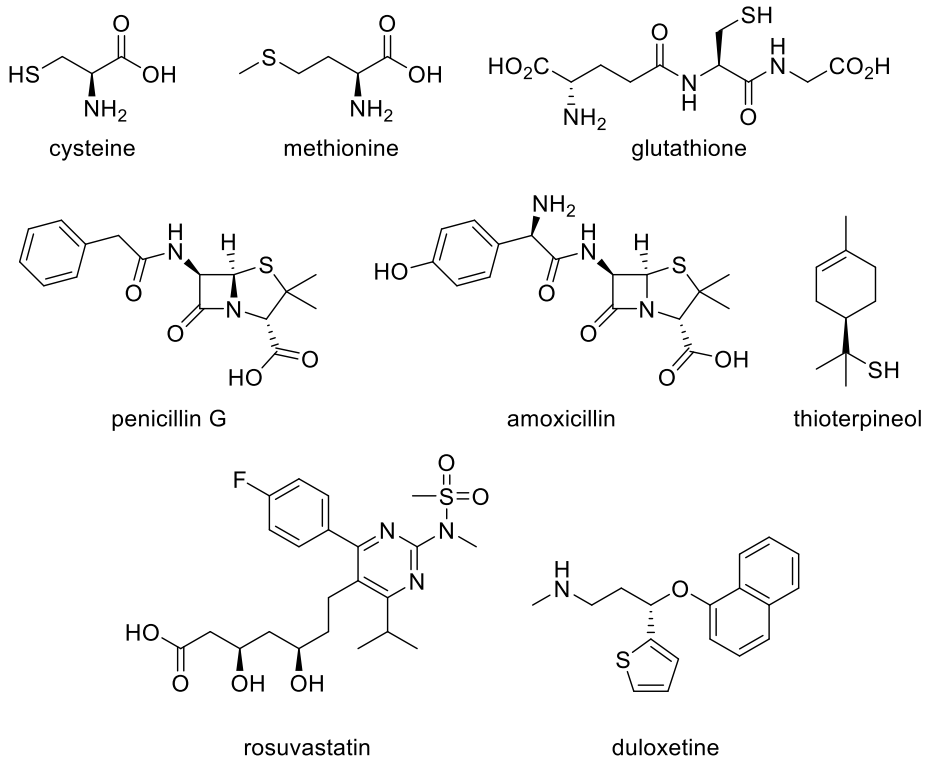


Figure 1. Various organosulfur compounds present in nature and pharmaceuticals [1]

It is no surprise that 7 of the top 10 most sold drugs in the US in 2009 were organosulfur

compounds, considering their biological importance (**Figure 2**).[2]

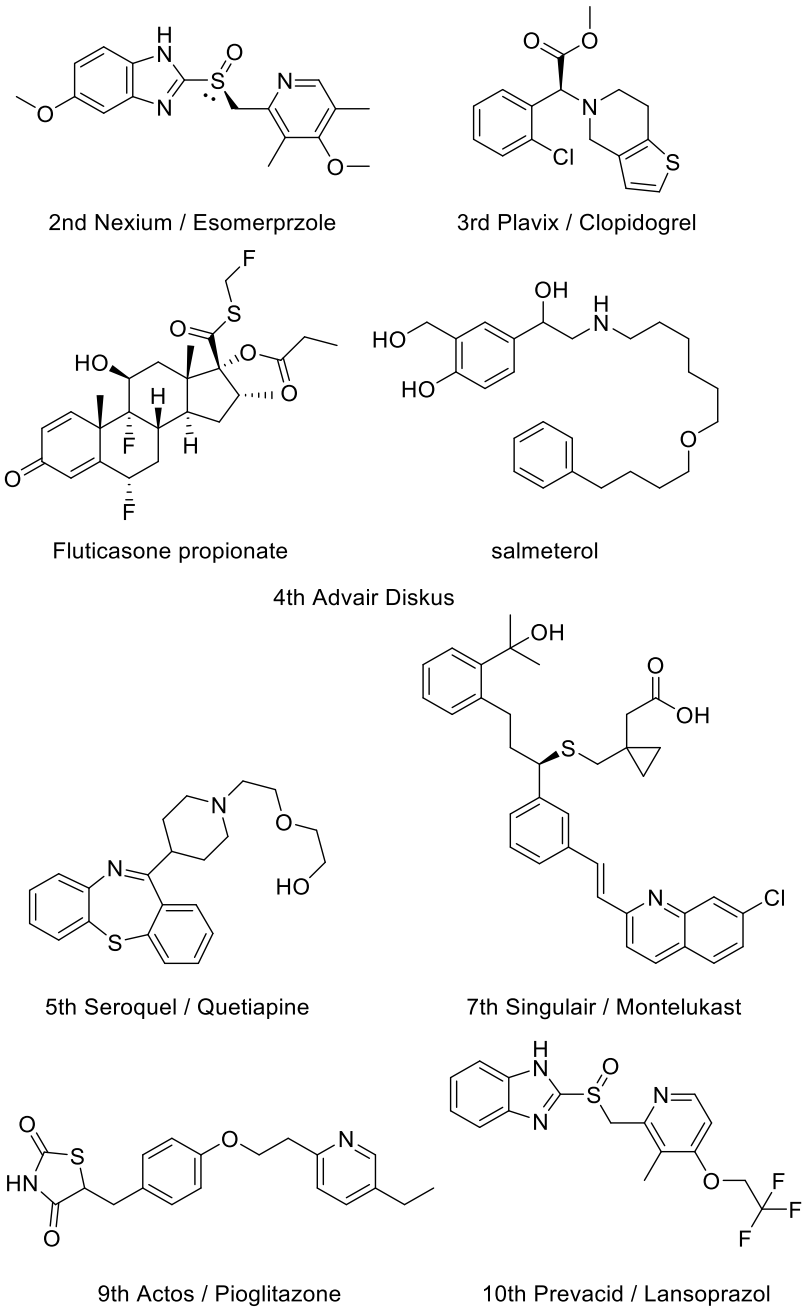


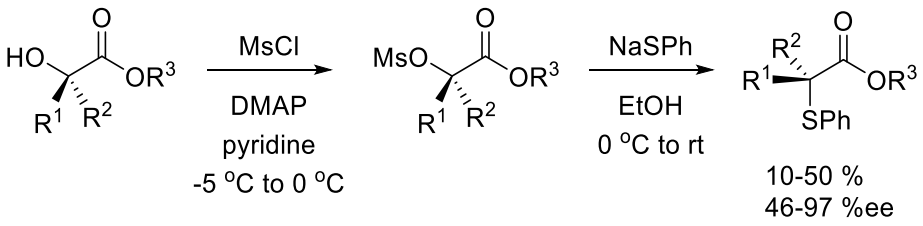
Figure 2. 7 of the top 10 bestselling organosulfur pharmaceuticals in the USA in 2009

and its ranks and brand names [2]

The potential of the organosulfur compound as drug attracted the attention of many organic chemists, which led to the development of new methodologies.

1.2. Previous approaches to synthesize the sulfur-bearing chiral quaternary carbon center

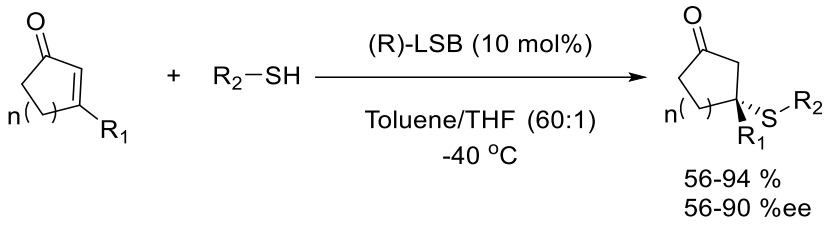
In spite of many researches and studies, construction of sulfur-bearing chiral quaternary carbon center remains major synthetic challenge.[3] There are few useful methods for the construction of sulfur-bearing chiral quaternary carbon center. Mostly these methods are enantioselective attack of sulfur nucleophile on tertiary carbon center or disubstituted alkene.[3] In other word, these synthetic approaches are C-S bond formation. For example, in 2009, Jon A. Tunge and coworkers have been successfully construct sulfur-bearing chiral quaternary carbon center undergoes S_N2 displacement of mesylate leaving group by thiophenol using substrate as α-hydroxy esters (**Scheme 1**).[4]



Scheme 1. Jon A. Tunge and coworkers Work (S_N2 displacement of mesylate group) [4]

The substrate α-hydroxy ester promotes S_N2 reaction because electron-withdrawing substituent ester inhibits S_N1 reaction, also the planar nature of the ester group would better embrace the steric hindrance toward approach of the nucleophile.[4]

The other way to synthesize sulfur-bearing chiral quaternary carbon center is asymmetric sulfa-Michael addition. Asymmetric sulfa-Micahel addition is proceeded by enantioselective addition of a sulfur nucleophile to disubstituted terminal of conjugated alkene.[3] Example of asymmetric sulfa-Michael addition, in 1998, Shibasaki group introduced (*R*)-LaNa$_3$tris(binaphthoxide) (LSB) catalyzed asymmetric addition to cyclic enones (**Scheme 2**).[5] And they have been successfully synthesize the sulfur-bearing chiral quaternary carbon center with modest chemical and optical yield.



Scheme 2. Shibasaki group's Work (Sulfa-Michael addition) [5]

However, these traditional methodologies which proceed by attack of sulfa nucleophile have significant limitations. These limitations are irregular chemical yield and optical yield, difficulty of modifying the substrate and limited sulfur nucleophiles. Irregular chemical yield and optical yield are presumed the steric hinderance of substrate which result from tertiary carbon center and low activity of disubstituted alkenes.[3] Also, difficulty in modifying the substrate and absence of various nucleophiles leads to the difficulty of synthesizing various chiral compounds.

1.3. Reverse strategy to synthesize the sulfur-bearing chiral quaternary carbon center

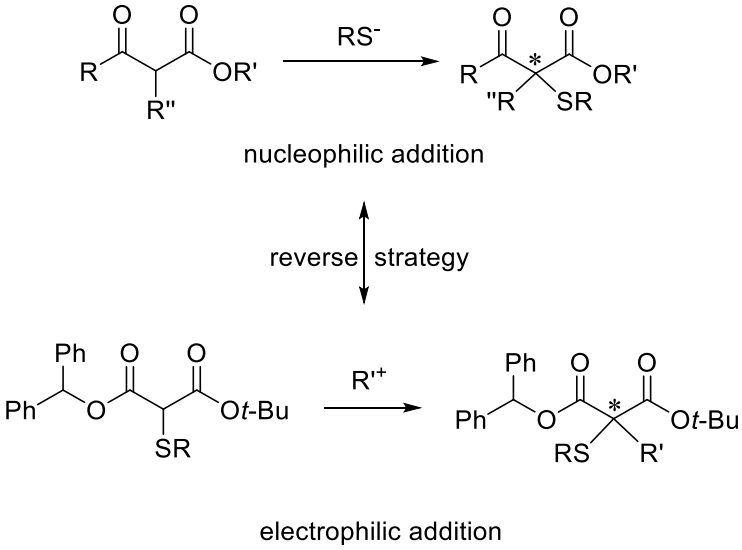


Figure 3. Reverse strategy to synthesize sulfur-bearing chiral quaternary carbon center

As mentioned above, there were various limitations to conventional methods, so we have to change the synthetic strategy. Our new strategy is to obtain many sulfur-bearing chiral compound by introducing various electrophiles to a substrate which can be modified in various ways (**Figure 3**). In other words, we changed our strategy to C-C bond formation rather than C-S bond formation. To accomplish this challenge, we set up a new substrate bearing sulfur at malonate substrate's α-position and try to obtain various chiral compounds by asymmetric phase-transfer catalytic alkylation with numerous electrophiles.

2. Phase-transfer Catalysis

2.1. Asymmetric phase-transfer catalysis

Phase-transfer catalysis, the reaction that we used to construct the sulfur-bearing chiral quaternary carbon center, is well known reaction in academia and industry. Phase-transfer catalysis is heterogeneous reaction which proceeds in two different phase such as water layer and organic layer. In theory, when chemical substances are separated from each other in the water layer and the organic layer, interaction between those two substances is difficult and the reaction is hardly proceeded. But if, a particular molecule crosses two phases and allows the chemical substance on each phase to meet and react, the reaction will proceed well. Here, the term particular molecule means "phase-transfer catalyst" and the reaction that happens between water phase and organic phase is called “phase-transfer catalysis”. In this case, since the catalyst moving between the two phases is the core of the reaction, the reaction rate may be significantly reduced or the reaction may not be possible in the absence of the catalyst.

The reaction system of phase-transfer catalysis consists of the following materials. First, the substrate as nucleophile, quaternary ammonium salts as phase-transfer catalyst and electrophile which reacts with substrate, organic solvent and aqueous base solution for trigger the reaction. In phase-transfer catalysis, the reaction proceeds simply by dissolving the substrate, catalyst and electrophile in organic solvent, and finally adding an aqueous base solution.

As you can see the reaction process, phase-transfer catalysis features simple experimental operations, mild and safe reaction conditions. Also, its virtue is using inexpensive reagents and solvents, environmentally friendly procedure, possibility of large scale preparation. Most importantly, this reaction is asymmetric synthesis and brings high chemical and

optical yields. Finally, it is very useful reaction in the pharmaceutical industry because metal is not involved in the reaction process.

2.2. Mechanism of phase-transfer catalysis

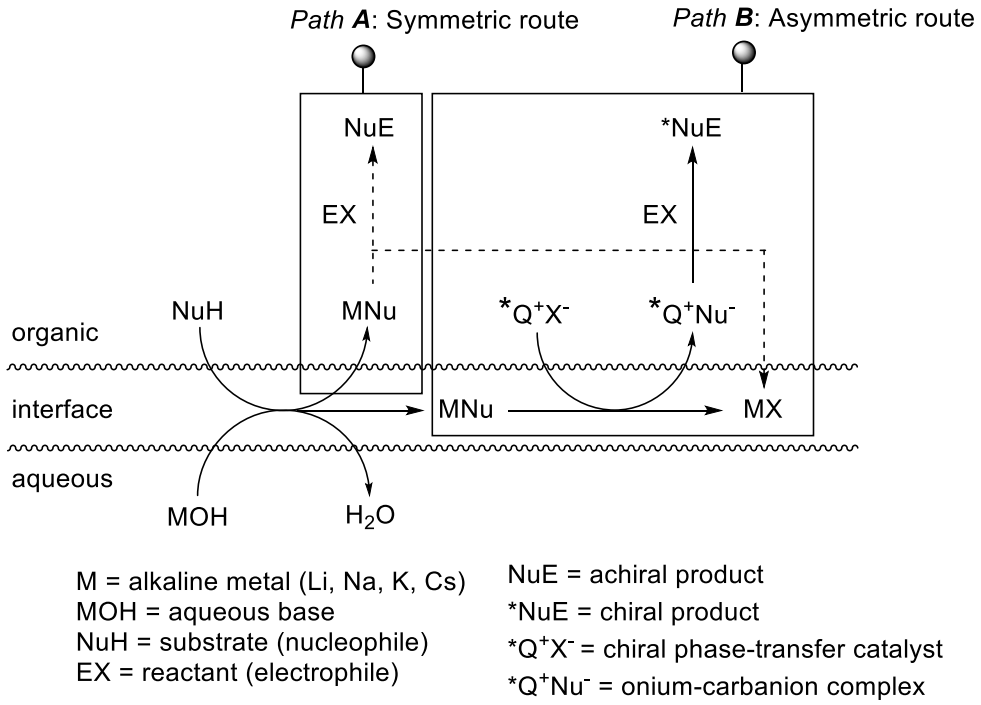


Figure 4. Most convincing mechanism of phase-transfer catalysis [6]

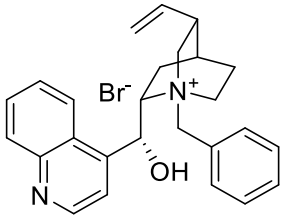
There are many hypotheses about the mechanism of phase-transfer catalysis, but we will introduce the most convincing hypothesis. **Figure 4** shows that reaction system is divided into water phase, organic phase and interface. This hypothesis emphasizes that phase-transfer catalysis occurs at the interface. The reaction path is divided into two paths, Path A and Path B. The difference between Path A and Path B is dependent on whether or not the chiral catalyst is involved in the reaction. Our major concern is Path B which is asymmetric route.

First, at the interface, the aqueous base (MOH) and the nucleophile (Nu) meet to form a substrate-alkali metal (MNu) and the remainder form H_2O immediately go to the water layer. Second, at the interface, the substrate-alkali metal (MNu) meets the chiral phase-transfer catalyst ($*Q^+X^-$) and form the onium-carbanion salts ($*Q^+Nu^-$). Finally, the onium-carbanion salt ($*Q^+Nu^-$) and electrophile (EX) meet and react in the organic layer to form a chiral product (*NuE).

2.3. Chiral Phase-transfer Catalysts

The role of chiral phase-transfer catalyst in asymmetric phase-transfer catalysis is very important. Not only does it mediate the reaction across the two phases, but also greatly affects the rate of the reaction and the chirality of the product. The effect of the catalyst on the product's chirality is due to the phase-transfer catalyst ($*Q^+X^-$) reacting with the substrate-alkali metal salt (MNu) to form the onium-carbanion complex ($*Q^+Nu^-$). The stronger the binding of the onium-carbanion complex, the higher the enantiomeric excess of the chiral product. To improve enantiomeric excess, many synthetic organic chemists have been developed chiral phase-transfer catalysts. There are various chiral phase-transfer catalyst which derived from natural products or non-natural products.[12]

First of all, we introduce the most well-known natural product derived phase-transfer catalyst, cinchona alkaloid derived phase-transfer catalyst. Not only are there catalysts designed by eminent scholars like O'Donnell and Corey, but there are also catalysts designed by our research team (**Figure 5**). The advantage of the cinchona alkaloid derived phase-transfer catalyst is that easy to make phase-transfer catalysts from inexpensive natural products such as cinchonine, cinchonidine, quinine and quinidine through simple reactions.[7]



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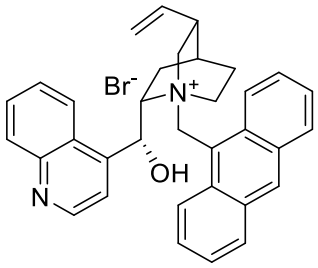

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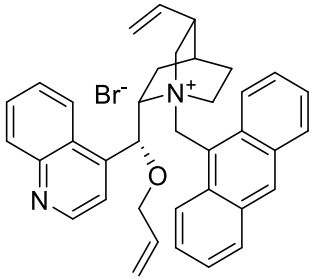

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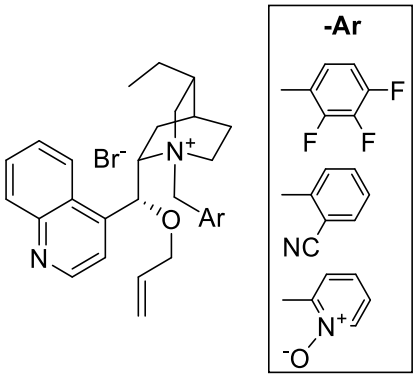

Jew, S.-s. et al. *Org. Lett.* **2002**, *4*, 4245.
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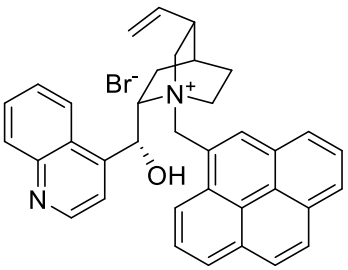

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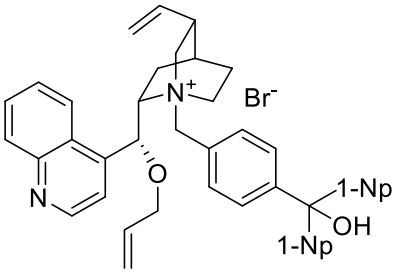
Tetrahedron **2005**, *61*, 1443.



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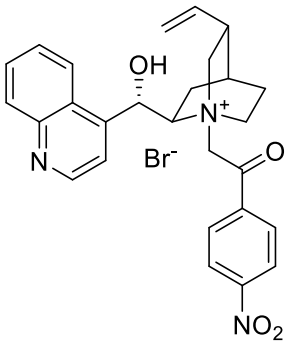

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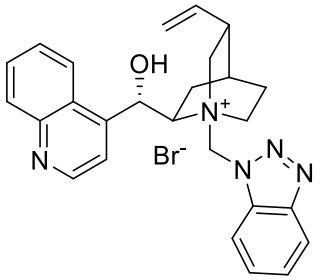
J. Mol. Catal. **2007**, 276, 102.



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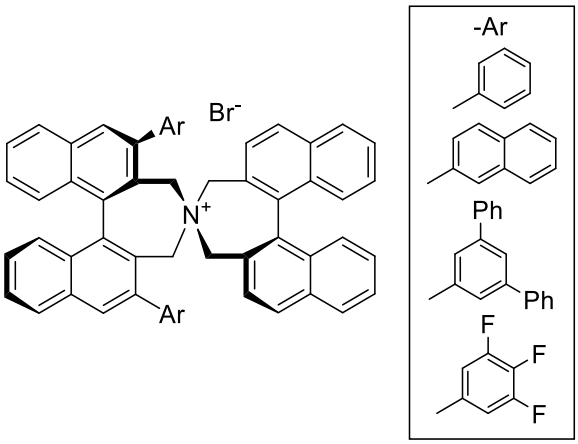
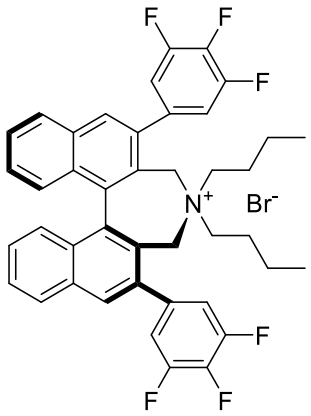
Syn. Lett. **2009**, 1311.

Figure 5. Cinchona alkaloid-derived phase-transfer catalysts

However, since the cinchona-alkaloid derived phase-transfer catalyst has β-hydrogen, there is a disadvantage that degradation by hofmann elimination could occur.[7]





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J. Am. Chem. Soc. **1999**, *121*, 6519.
J. Am. Chem. Soc. **2003**, *125*, 5139.

Maruoka, K. et al.
Angew. Chem., Int. Ed. **2005**, *44*, 154917.

Figure 6. Binaphthyl-modified phase-transfer catalysts [8]

On the other hand, binaphthyl-modified phase-transfer catalyst developed by the Maruoka

group[8] does not have β-hydrogen, so it is stable under basic conditions and has a good chemical yield and optical yield with small amount (**Figure 6**).[7]

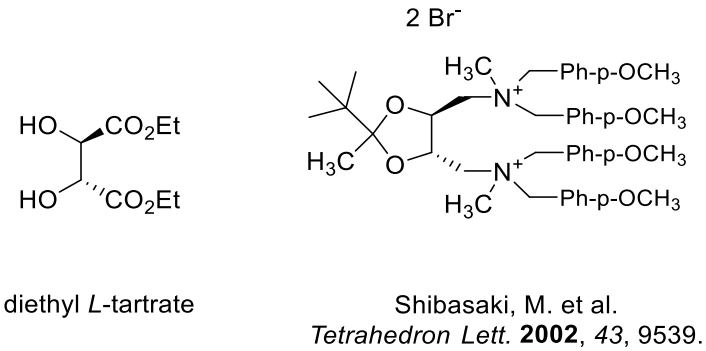


Figure 7. Tartrate-derived phase-transfer catalysts [9]

The tartrate-derived phase-transfer catalyst introduced by the Shibasaki group[9] has an unusual form with two active quaternary ammonium salts (**Figure 7**).

2.4. Design of Substrates for Phase-transfer Catalytic Alkylation

Our research team have been studying phase-transfer catalytic alkylation and have designed variety of substrates accordingly. From the 1,3-diketo system, the following substrates were designed and phase-transfer alkylation proceeded to obtain good optical yield and the results were published in various journals (**Figure 8**).

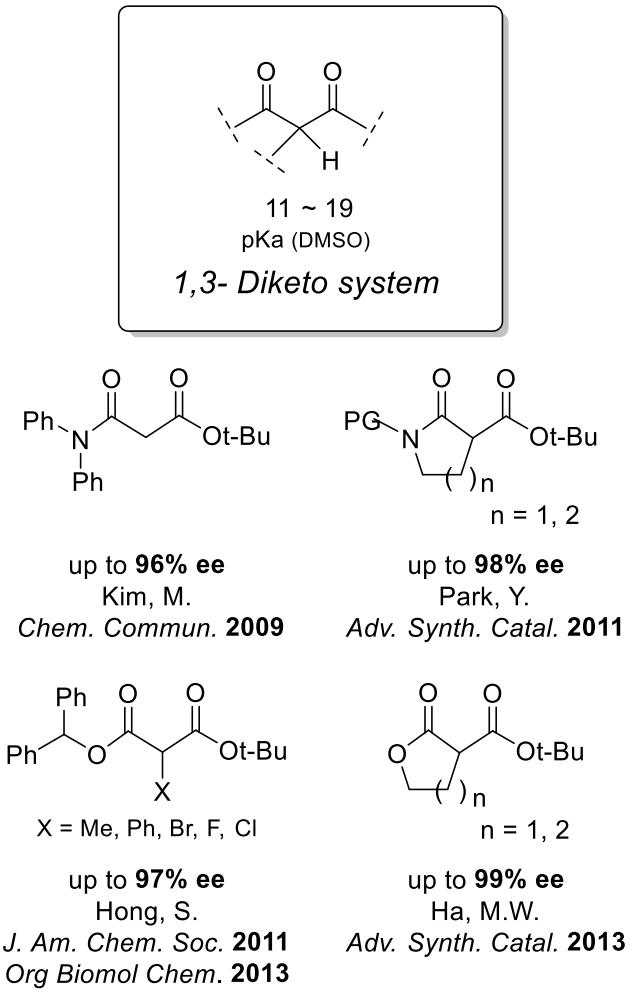
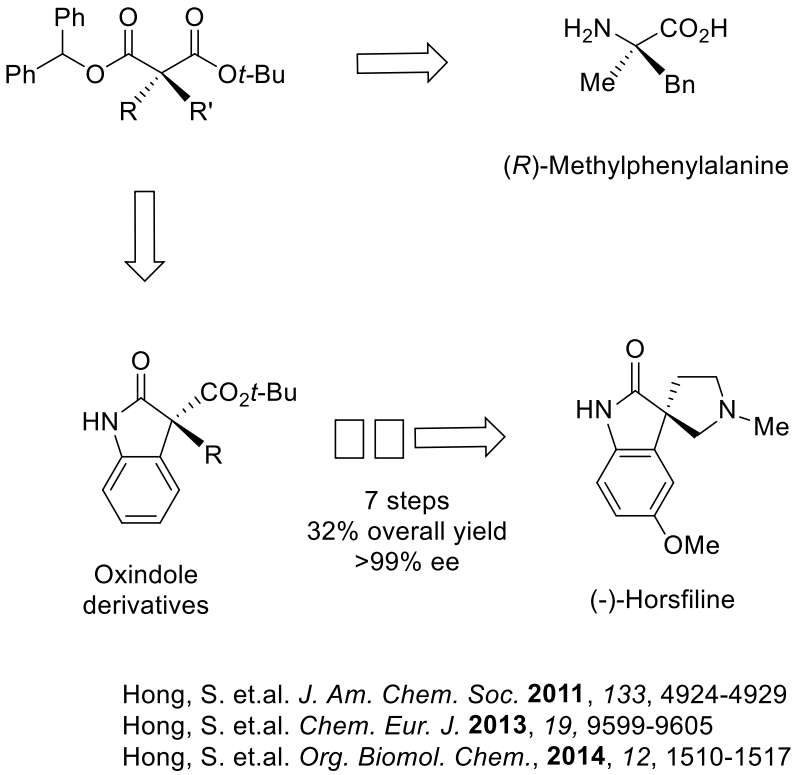


Figure 8. Design of the substrate from the 1,3-diketo system

In particular, the recently designed benzhydryl *tert*-butyl malonate structure was able to synthesis of chiral quaternary center with high optical yield as well as synthesize the (*R*)-Methylphenylalanine by simple hydrolysis.[10] We also successfully synthesized horsifiline, a natural product, using this substrate (**Figure 9**).[10]



Hong, S. et.al. *J. Am. Chem. Soc.* **2011**, *133*, 4924-4929
Hong, S. et.al. *Chem. Eur. J.* **2013**, *19,* 9599-9605
Hong, S. et.al. *Org. Biomol. Chem.*, **2014**, *12*, 1510-1517

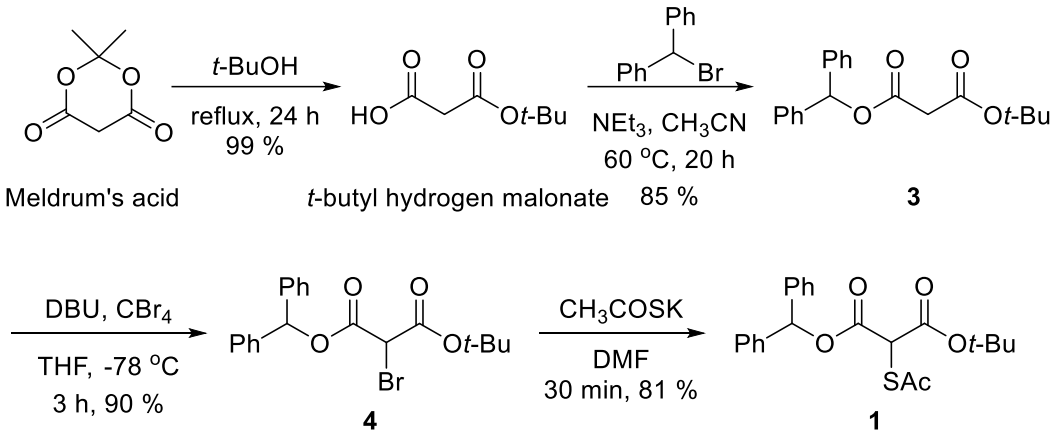
Figure 9. Application of benzhydryl tert-butyl malonate substrate [10]

To make a sulfur-bearing chiral quaternary carbon center, we synthesized a new substrate by sulfur-bearing at the α-position of the benzhydryl *tert*-butyl malonate substrate. Details about synthesis of substrates is on the result and discussion below.

RESULTS AND DISCUSSION

1. Synthesis of α-acetylthiomalonate substrate

As mentioned in the introduction, a suitable substrate was designed to make sulfur-bearing chiral quaternary carbon center. The synthesis of the α-acetylthiomalonate substrate proceeds in 4 steps with Meldrum's acid as the starting material as follows (**Scheme 3**).



Scheme 3. Synthesis of α-acetylthiomalonate substrate

First, *tert*-butanol was added to meldrum's acid, and the temperature was increased by 90 °C to reflux for 24 hours to obtain *tert*-butyl hydrogen malonate. Although *tert*-butyl hydrogen malonate was commercially available reagent, it was better to obtain it in this way because it is difficult to store and easily decomposed. Then, *tert*-butyl hydrogen malonate was dissolved in acetonitrile, and α-bromodiphenylmethane, triethylamine were added to the reaction at 60 °C to synthesize benzhydryl *tert*-butyl malonate (**3**). After that, to perform the monobromination at α-position, benzhydryl *tert*-butyl malonate (**3**) was dissolved in THF, and tetrabromomethane and DBU were added at -78 °C to proceed the reaction. The important fact in the reaction was that it should maintain a temperature of -

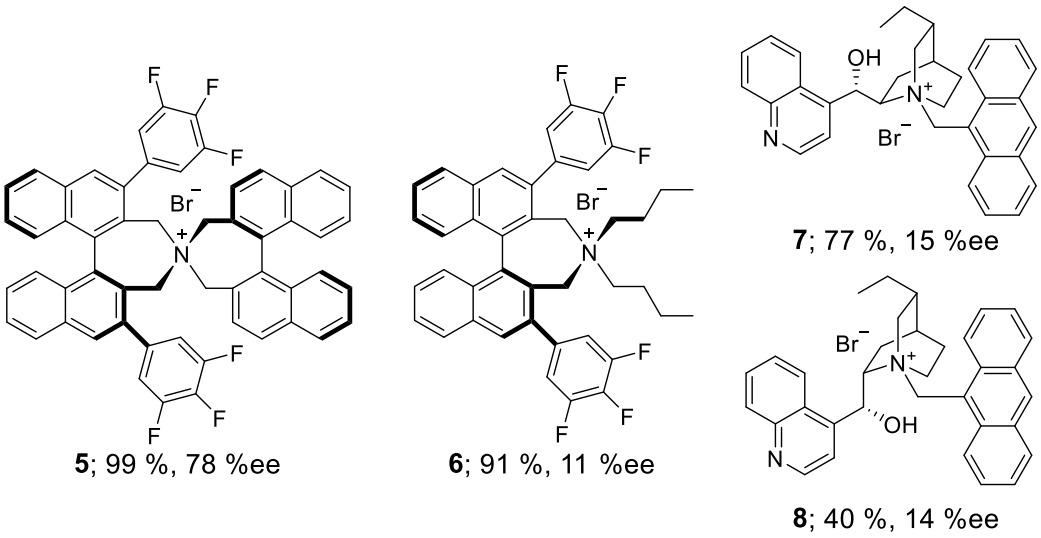
78 °C. If the temperature could not be kept constant, the dibromination might proceed and ruins the reaction. Finally, we synthesized the desired substrate through S_N2 reaction. After dissolving α-bromomalonate substrate (**4**) in DMF and adding potassium thioacetate at room temperature, we could construct the desired substrate, α-acetylthiomalonate (**1**).

2. Reoptimization of phase-transfer catalytic alkylation

In 2013, our team synthesized several chiral compounds by asymmetric phase-transfer catalytic alkylation with α-acetylthiomalonate, but the optical yield was not constant and the yield was very low.[11] Therefore, we performed reoptimization to obtain better chemical and optical yields. The results were as followed.

2.1. Reoptimization of phase-transfer catalyst

First, we reoptimized the phase-transfer catalyst. Reoptimization of the catalyst was carried out under room temperature using the 50% KOH (5 eq), benzyl bromide (5 eq), and toluene. The results are shown in **Figure 10**.



5; 99 %, 78 %ee

6; 91 %, 11 %ee

7; 77 %, 15 %ee

8; 40 %, 14 %ee

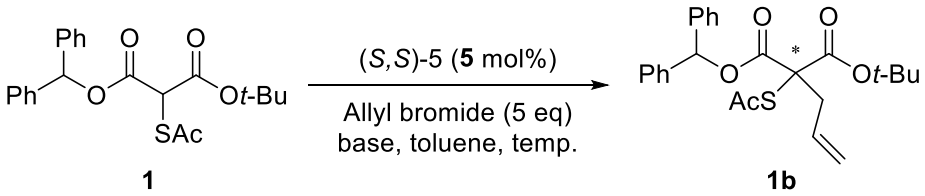
Figure 10. Reoptimization of chiral phase-transfer catalyst

The catalyst with the highest chemical and optical yields were achieved by (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide **5** which produced by the Maruoka group. Another catalyst **6** also produced by Maruoka group, presented high chemical yield but very low optical yield. The others, cinchonine derived catalyst **7** and cinchonidine derived catalyst **8**

presented very low chemical and optical yields. So, we concluded that the (*S,S*)-3,4,5-trifluorophenyl-NAS bromide **5** was the most suitable catalyst.

2.2. Reoptimization of base and temperature for asymmetric phase-transfer catalytic alkylation

Based on the result of previous studies, we conclude that toluene was the most suitable solvent for asymmetric phase-transfer catalytic alkylation. However, the temperature and the base were important factors for asymmetric phase-transfer catalytic alkylation so we proceeded the reoptimization.



1 **1b**

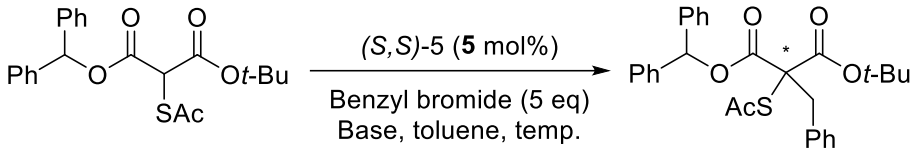
entry	base	T (^{o}C)	time (h)	yield (%)	ee (%)
1	50% CsOH (aq)	rt	1	87	71
2	50% KOH (aq)	rt	1	99	78
3	50% KOH (aq)	0	20	95	84
4	50% KOH (aq)	-20	40	95	89
5	50% KOH (aq)	-40	144	33	90

Table 1. Asymmetric phase-transfer catalytic allylation

Asymmetric phase-tranfer catalysis was performed using allylbromide to find optimized

reaction conditions. The result were shown in **Table 1.** As a result it was confirmed that 50% KOH (aq) had better chemical yield and optical yield than 50% CsOH (aq), and the optical yield was higher as the temperature was lowered gradually. However, when the temperature was lowered to -40 °C, it was found that the reaction rate was very slow and also affected the chemical yield.

We also reacted with benzyl bromide at varying temperatures to determine if the change in optical yield with temperature was equally applicable to the arylation (**Table 2**).



1 **1e**

entry	base	T (°C)	time (h)	yield (%)	ee (%)
1	50% KOH (aq)	rt	1	99	90
2	50% KOH (aq)	0	20	95	92
3	50% KOH (aq)	-20	40	95	95

Table 2. Asymmetric phase-transfer catalytic arylation

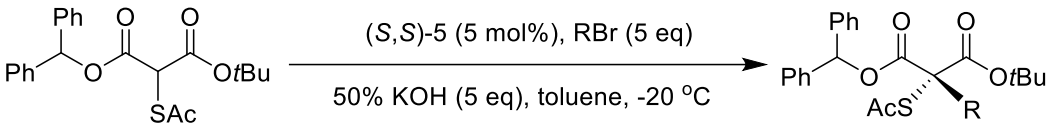
As a result, it was confirmed that lowering the reaction temperature had an adverse effect on the chemical yield due to the longer reaction time, but the optical yield was improved. By comparing the change of the chemical yield and optical yield according to the low temperature, the optimum temperature was found and it was concluded that -20 °C is the most suitable temperature.

3. Asymmetric phase-transfer catalytic alkylation of α-acetylthiomalonates with various electrophile

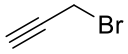
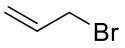
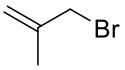
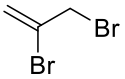
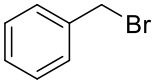
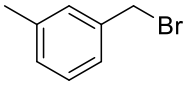
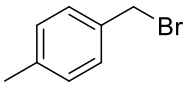
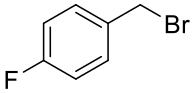
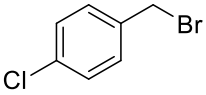
As we mentioned in the introduction, our research goal was through the strategy of C-C bond formation to react with various electrophiles and a substrate to obtain many chiral compounds. From the experiments, we found that the optimum conditions for phase-transfer catalysis were toluene as organic solvent, (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide as a catalyst, 50% KOH as aqueous base were used and the reaction was carried out at -20 °C. Under optimized condition, 18 electrophiles were performed phase-transfer catalysis.

As a result, we synthesized 18 chiral products, which contains chiral sulfur-bearing quaternary carbon center with high chemical and optical yields (**Table 3**). Most of the chemical yields were more than 90 %. Also, the optical yields were more than 90 %ee.

However, entry 1, propargyl bromide exhibited a relatively low chemical yield of 81 % and an optical yield of 61 %ee. We presumably assumes that propargyl would have been difficult to substitute because it had a structurally linear. The electrophile with the highest chemical yield and optical yield showed 99 % and 98 %ee with entry 9, 4-chlorobenzyl bromide.



1 **1a-r**

Entry	R-Br		Time (h)	Yield (%)	ee%
1		(a)	23	81	61
2		(b)	40	95	89
3		(c)	23	86	94
4		(d)	24	91	92
5		(e)	40	99	95
6		(f)	8	95	94
7		(g)	4	96	96
8		(h)	4.5	99	97
9		(i)	7	99	98

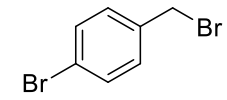
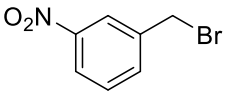
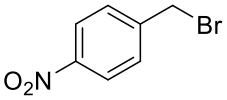
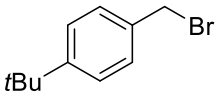
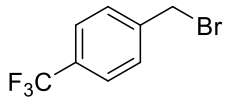
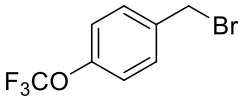
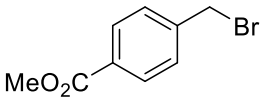
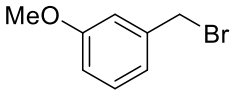
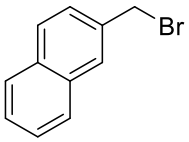
Entry	R-Br		Time (h)	Yield (%)	ee%
10		(j)	5	99	97
11		(k)	7.5	99	86
12		(l)	4.5	98	95
13		(m)	7	99	96
14		(n)	6	99	96
15		(o)	5	86	96
16		(p)	6.5	99	96
17		(q)	8.5	96	96
18		(r)	30	91	91

Table 3. Asymmetric phase-transfer catalytic alkylation of α-acetylthiomalonate with various electrophiles

4. Absolute configuration of α-acetylthio- α-alkylmalonate

To confirm the absolute configuration of α-acetylthio-α-alkylmalonates, we crystallized 4-trifluoromethoxybenzylated product **1o** and perform the X-ray crystallography analysis. X-ray crystallography structure of **1o** is displayed in **Figure 11**. We found that the absolute configuration of **1o** was (*R*)-form.

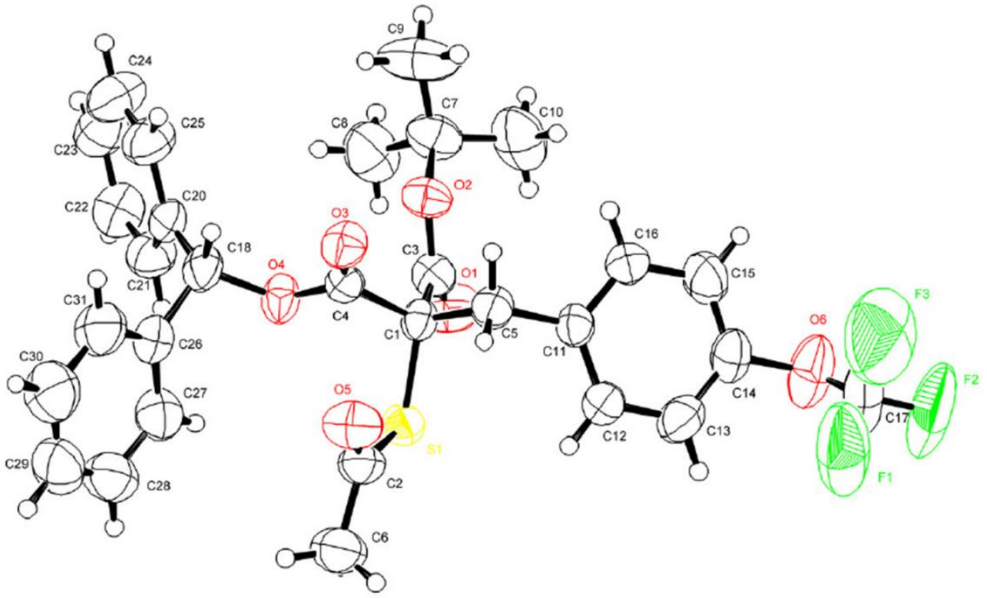
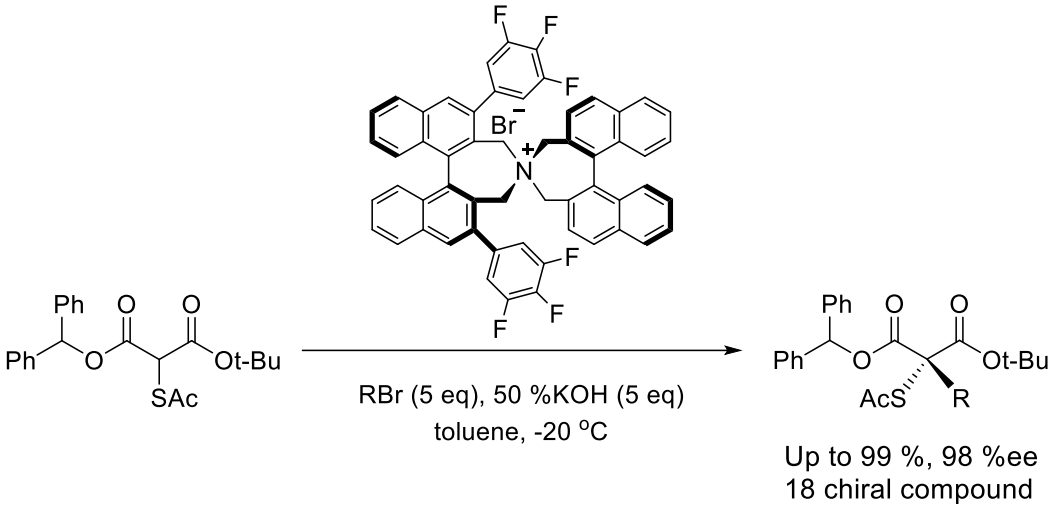


Figure 11. X-ray Crystallography Structure of **1o** (*Acknowledgement : Dr. Jae Kyun Lee / Neuro-Medicine Center, Korea Institute of Science and Technology*)

CONCLUSION

A novel asymmetric phase-transfer catalytic alkylation for synthesize the α-acetylthio-α-alkylmalonates, which contains the sulfur-bearing chiral quaternary carbon center has been developed. This new method differs from the conventional approach in that it involves the alkylation of various electrophiles onto a sulfur-bearing substrate. We made new substrate by substituting acetylthio at the α-position of the benzhydryl tert-butyl malonate structure.



Scheme 4. Enantioselective synthesis of α-acetylthio-α-alkylmalonate via novel phase-transfer catalytic alkylation

Then, chiral α-acetylthio-α-alkylmalonate were synthesized by adding (*S,S)*-3,4,5-trifluoropheynyl-NAS bromide, 50% KOH(aq) and various electrophiles under toluene at -20 ° C. We obtained total of 18 chiral α-acetylthio-α-alkylmalonates in 99 % and 98 %ee yields, respectively. Finally, chiral α-acetylthio-α-alkylmalonate's absolute configuration was confirmed (*R*)-form by X-ray crystallography. The new asymmetric phase-transfer catalysis is expected to be very useful method for making bioactive natural products or pharmaceuticals, which has sulfur-bearing chiral quaternary carbon center.

EXPERIMENTAL SECTION

1. General Methods

1.1. Solvents and reagents

All reagents bought from commercial sources were used without further purification. Organic solvents were concentrated under reduced pressure using a Büchi rotary evaporator. 50% w/v aqueous KOH and 50% w/v aqueous CsOH was used as stock solution. Phase-transfer catalysts **(5, 6,** and **8)** were purchased from the commercial source (Wako and Sigma Aldrich). Phase-transfer catalyst **(7)** was prepared according to the reported procedure.[S1]

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 analysis. The enantiomeric excess (ee) of the chiral products was determined by HPLC using 4.6 mm × 250 mm Daicel Chiralpak AD-H.

1.3. Spectral data

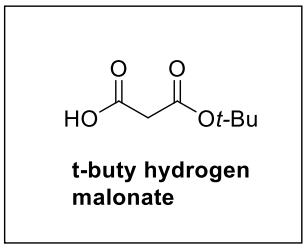
Infrared (IR) spectra were recorded on a JASCO FT/IR-4200 spectrometer. Nuclear magnetic resonance (^{1}H-NMR and ^{13}C-NMR) spectra were measured on JEOL JNM-LA

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 [500 MHz (^{1}H), 125 MHz (^{13}C)] spectrometer, using $CHCl_3$-*d* as solvents, and were reported in ppm relative to $CHCl_3$ (δ 7.24) for ^{1}H-NMR and relative to the central $CDCl_3$ (δ 77.23) resonance for ^{13}C-NMR. Coupling constants (*J*) in ^{1}H-NMR are in Hz. Low-resolution mass spectra (LRMS) and high-resolution mass spectra (HRMS) were measured on a JEOL JMS 700, JEOL JMS 600-W spectrometer, or Agilent 6530 Q-TOF (ESI) spectrometer. 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.

2. α-acetylthio-α-alkylmalonates

2.1. Preparation of α-acetylthiomalonate substrate

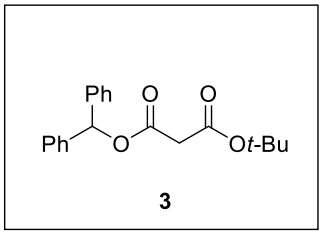
Synthesis of *tert*-Butyl hydrogen malonate



t-buty hydrogen malonate

Meldrum's acid (3 g, 26 mmol) was added to *tert*-Butyl alcohol (30 ml). Then the reaction mixture was refluxed for 24 hours, evaporated and concentrated *in vacuo* to afford *tert*-butyl hydrogen malonate as colorless oil (4.18 g, 98% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.35 (s, 2H), 1.49 (s, 9H) ppm. *tert*-Butyl hydrogen malonate is known compound and commercially available.

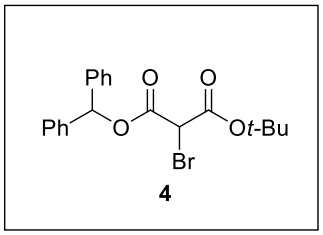
Synthesis of benzhydryl *tert*-butyl malonate (3)



3

tert-Butyl hydrogen malonate (3 ml, 19.5 mmol)was dissolved in acetonitrile (50 ml) and heated to reflux. To this solution were added α-bromodiphenylmethane (5.3 g, 21.4 mmol) and trimethylamine (3 ml, 21.4 mmol) in sequence. The reaction was stirred for 24 hours. After the completion of reaction, the acetonitrile was evaporated under reduced pressure and dissolved in dichloromethane. Then, washing with brine (150 mL × 2), drying over anhydrous $MgSO_4$, filtration, and purifying by column chromatography (silica gel, hexane : EtOAc = 30 : 1) afforded benzhydryl *tert*-butyl malonate **3** (5.4 g, 85% yield) as a yellow oil. ^{1}H NMR (300 MHz, CDCl3) δ 7.34 ~ 7.18 (m, 10H), 6.89 (s, 1H), 3.33 (s, 2H), 1.36 (s, 9H) ppm; ^{13}C NMR (100 MHz, CDCl3) δ 165.8, 165.3, 139.6, 128.4, 127.9, 127.1, 82.0, 77.6, 43.2, 27.7 ppm; IR (KBr) 2960, 2924, 2853, 1732, 1680, 1462, 1377, 1021, 773 cm^{-1}; HRMS (ESI) calcd for $[C_{20}H_{22}O_4Na]^+$ ($[M^+ Na]^+$) 349.1410, found: 349.1422.

Synthesis of α-bromomalonate substrate (4)

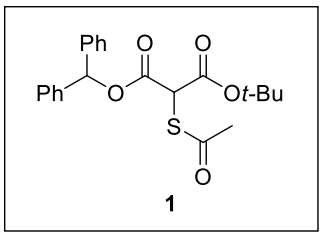


4

A solution of **3** (1.86 g, 5.7 mmol) in dry THF (34 ml) was added to the DBU (852 μl, 5.7mmol) and dropwise the CBr_4 (2.3g, 6.84mmol) in THF (0.2 M) at -78 ^{o}C. The reaction mixture was stirred at -78 ^{o}C for 3 hours. After completion of reaction, the mixture was quenched with NH_4Cl and diluted with hexane (100 ml), washed with brine (50 ml). The aqueous layer was extracted by dichloromethane (100 ml). The organic layer dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane : EtOAc = 25 : 1) to afford α-bromomalonate substrate **4** (2.07 g, 90% yield) as colorless oil. ^{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, CDCl3) δ 163.8, 162.9, 138.9, 138.89, 128.5, 128.48, 128.3, 128.2, 127.3, 127.04, 84.4, 79.3, 44.2, 27.5 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.

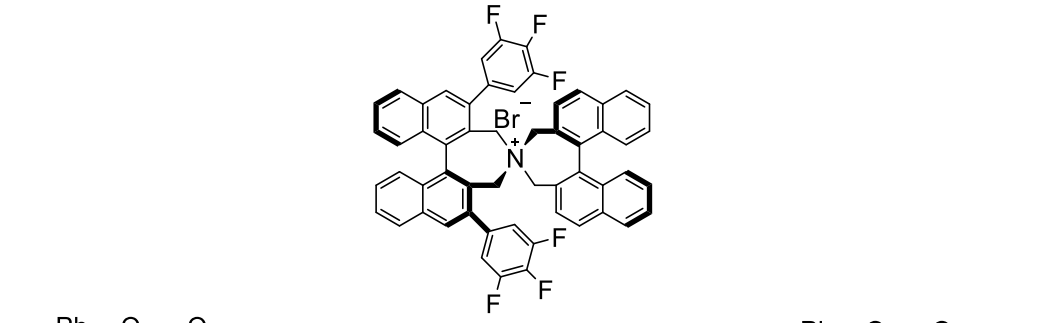
Synthesis of α-acetylthiomalonate substrate (1)



1

Potassium acetylthioate (427 mg, 3.73 mmol) was added to a stirred solution of α-bromomalonate substrate (**4**, 1.01 g, 3.73 mmol) in dry dimethylformamide (25 ml) at room temperature under argon atmosphere. The reaction was stirred at same temperature for 30 minutes. The reaction solvent was evaporated and diluted with EtOAc (200 ml), extracted with brine (100 ml x 2 times), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane : EtOAc = 15 : 1) to afford α–acetylthiomalonate substrate **1** (802 mg, 81% yield) as a white solid. mp 70 °C ; ^1H-NMR (300 MHz, $CDCl_3$) δ 7.32 ~ 7.24 (m, 10H), 6.90 (s, 1H), 5.07 (s, 1H), 2.37 (s, 3H), 1.33 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 192.2, 165.2, 164.3, 139.2, 139.1, 128.48, 128.45, 128.13, 128.09, 127.2, 127.1, 83.9, 78.8, 51.6, 29.9, 27.6 ppm; IR (KBr) 3033, 2981, 1738, 1545, 1446, 1220, 1139, 948, 767, 686, 674 cm^{-1}; HRMS (FAB) calcd for $[C_{22}H_{24}O_5]^+$ ($[M+Na]^+$): 423.1242, found: 423.1247.

2.2. General Procedure of Phase-transfer Catalytic alkylation



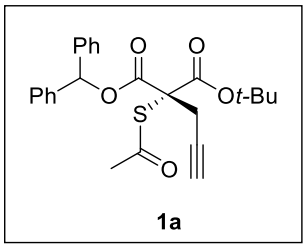
1 **1a-r**

1a R= CH_2CCH
1b R= CH_2CHCH_2
1c R= $CH_2C(CH_3)CH_2$
1d R= $CH_2C(Br)CH_2$
1e R= $C_6H_5CH_2$
1f R= 3-Me-$C_6H_4CH_2$
1g R= 4-Me-$C_6H_4CH_2$
1h R= 4-F-$C_6H_4CH_2$
1i R= 4-Cl-$C_6H_4CH_2$
1j R= 4-Br-$C_6H_4CH_2$
1k R= 3-NO_2-$C_6H_4CH_2$
1l R= 4-NO_2-$C_6H_4CH_2$
1m R= 4-*t*Bu-$C_6H_4CH_2$
1n R= 4-CF_3-$C_6H_4CH_2$
1o R= 4-OCF_3-$C_6H_4CH_2$
1p R= 4-MeO_2C-$C_6H_4CH_2$
1q R= 3-MeO-$C_6H_4CH_2$
1r R= β-naphtyl-CH_2

Scheme 5. General Procedure of asymmetric phase-transfer catalytic alkylation

Alkyl bromide (42.1 μl, 0.49 mmol) was added to a solution of α-acetylthiomalonate substrate **1** (30 mg, 0.10 mmol) and (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide **5** (4.5 mg, 0.005 mmol) in toluene (324 μL) at room temperature. At the designated low temperature, aqueous 50% w/v aqueous KOH (42.1 μl, 0.49 mmol) was added to the reaction mixture and stirred until the starting material disappeared. After completion of the reaction, the reaction mixture was diluted with ethyl acetate (20ml), washed with brine (10mL x 2), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel eluting with hexane-EtOAc solution (10:1) to afford **1a** (33.4 mg, 99% yield) as a colorless oil.

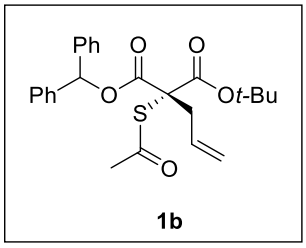
1-benzhydryl 3-(*tert*-butyl) (*R*)-2-(acetylthio)-2-(prop-2-yn-1-yl)malonate (1a)



1a

Following the general procedure from the substrate **1** using propargyl bromide, the title molecule **1a** was obtained as a yellow oil (81% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.32 ~ 7.26 (m, 10H), 6.94 (s, 1H), 3.32 (ddd, J_1 = 23.66 Hz, J_2 = 17.45 Hz, J_3 = 2.60 Hz, 2H), 2.23 (s, 3H), 2.01 ~ 2.00 (m, 1H), 1.30 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 194.2, 165.2, 164.1, 139.2, 139.1, 128.39, 128.35, 128.2, 128.09, 128.08, 127.4, 127.3, 84.5, 79.0, 78.7, 71.8, 65.3, 29.9, 27.4, 26.6 ppm; IR (KBr) 2979, 2930, 1738, 1705, 1370, 1258, 1143, 954, 756, 700, 621 cm^{-1}; HRMS (FAB): calcd for $[C_{25}H_{26}O_5SNa]^+$ ($[M+Na]^+$): 461.1399, found: 461.1395; The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane : 2-propanol = 80 : 20, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time: major isomer 12.06 min, minor isomer 18.71 min, 61% ee, $[\alpha]^{20}_D$ = - 3.47 (*c* 1.0, $CHCl_3$).

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

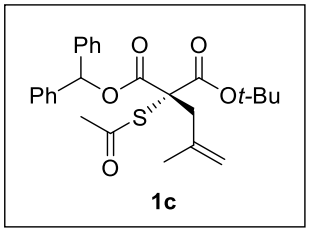


1b

Following the general procedure from the substrate **1** using allyl bromide, the title molecule **1b** was obtained as a colorless oil (95% yield). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.34 ~ 7.25 (m, 10H), 6.92 (s, 1H), 5.76 ~ 5.68 (m, 1H), 5.04 (s, 1H) 5.02 (d, *J* = 5.20 Hz, 1H), 3.10 ~ 3.02 (m, 2H), 2.18 (s, 3H), 1.26 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 193.6, 166.2, 165.3, 139.4, 139.3, 132.0, 128.4, 128.3, 128.1, 128.0, 127.5, 127.2, 119.6, 83.9, 78.6, 65.7, 39.0, 30.0, 27.5 ppm; IR (KBr) 2927, 1732, 1695, 1451, 1370, 1220, 1153, 953, 768, 674 cm^{-1}; HRMS (FAB): calcd for $[C_{25}H_{28}O_5SNa]^+$ ($[M+Na]^+$): 463.1555, found: 463.1557; The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane : 2-propanol = 80 : 20, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time: minor isomer 10.51 min,

major isomer 15.96 min, 89% ee, $[\alpha]^{20}_{D}$ = - 14.47 (*c* 1.0, $CHCl_3$).

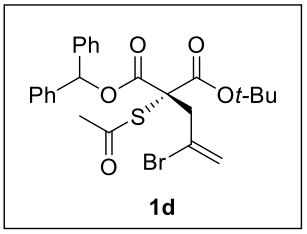
1-benzhydryl 3-(*tert*-butyl) (*R*)-2-(acetylthio)-2-(2-methylallyl)malonate (1c)



1c

Following the general procedure from the substrate **1** using 3-bromo-2-methylpropene, the title molecule **1c** was obtained as a pale yellow oil (86% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.37 ~ 7.26 (m, 10H), 6.94 (s, 1H), 4.81 (s, 1H), 4.67 (s, 1H), 3.14 (s, 2H), 2.20 (s, 3H), 1.64 (s, 3H), 1.27 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 193.9, 166.6, 165.7, 140.4, 139.32, 139.30, 128.4, 128.3, 128.1, 128.0, 127.6, 127.3, 116.1, 83.9, 78.7, 65.7, 41.4, 29.9, 27.4, 23.4 ppm; IR (KBr) 2925, 2853, 1732, 1693, 1455, 1370, 1255, 1200, 1148, 950, 761, 699 cm^{-1}; HRMS (FAB): calcd for $[C_{26}H_{30}O_5SNa]^+$ ($[M+Na]^+$): 477.1712, found: 477.1726; The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane : 2-propanol = 80 : 20, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time: minor isomer 8.44 min, major isomer 12.60 min, 94% ee, $[\alpha]^{20}_{D}$ = - 23.78 (*c* 1.0, $CHCl_3$).

1-benzhydryl 3-(*tert*-butyl) (*R*)-2-(acetylthio)-2-(2-bromoallyl)malonate (1d)

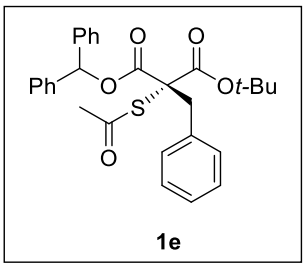


1d

Following the general procedure from the substrate **1** using 2,3-bromopropene, the title molecule **1d** was obtained as a yellow oil (91% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.37 ~ 7.27 (s, 10H), 6.94 (s, 1H), 5.53 (s, 1H), 5.50 (d, J = 1.83 Hz, 1H), 3.63 (dd, J_1 = 22.40 Hz, J_2 = 15.83 Hz, 2H), 2.22 (s, 3H), 1.28 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 194.3, 165.7, 164.6, 139.1, 128.44, 128.36, 128.2, 128.1, 127.5, 127.3, 127.2, 121.9, 84.5, 79.1, 65.5, 44.0, 29.9, 27.4 ppm; IR (KBr) 2928, 1735, 1692, 1626, 1370, 1245, 1205, 1146, 1003, 953, 761, 699 cm^{-1}; HRMS (FAB): calcd for $[C_{25}H_{27}O_5BrSNa]^+$ ($[M+Na]^+$): 541.0660, found: 541.0655; The

enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane : 2-propanol = 80 : 20, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time: minor isomer 10.58 min, major isomer 15.07 min, 92% ee, $[\alpha]^{20}_{D}$ = - 1.29 (*c* 1.0, $CHCl_3$).

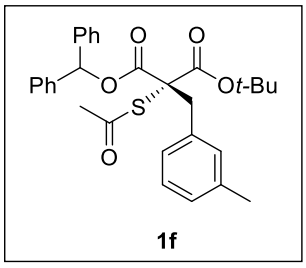
1-benzhydryl 3-(*tert*-butyl) (*R*)-2-(acetylthio)-2-benzylmalonate (1e)



1e

Following the general procedure from the substrate **1** using benzyl bromide, the title molecule **1e** was obtained as a colorless oil (99% yield). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.36 ~ 7.31 (m, 4H), 7.30 ~ 7.25 (m, 6H), 7.20 ~ 7.13 (m, 3H), 7.02 (d, J = 6.90 Hz, 2H), 6.94 (s, 1H), 3.67 (dd, J_1 = 25.78 Hz, J_2 = 14.43 Hz, 2H), 2.17 (s, 3H), 1.25 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 194.0, 166.3, 165.2, 139.24, 139.23, 135.4, 130.6, 128.5, 128.3, 128.2, 127.95, 127.91, 127.7, 127.2, 127.1, 84.0, 78.8, 67.3, 39.5, 30.0, 27.5 ppm; IR (KBr) 3033, 2979, 1732, 1691, 1455, 1370, 1220, 1147, 951, 773, 699 cm^{-1}; HRMS (FAB): calcd for $[C_{29}H_{30}O_5SNa]^+$ ($[M+Na]^+$): 513.1712, found: 513.1722; The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane : 2-propanol = 80 : 20, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time: minor isomer 11.94 min, major isomer 16.44 min, 95% ee, $[\alpha]^{20}_{D}$ = + 74.53 (*c* 1.0, $CHCl_3$).

1-benzhydryl 3-(*tert*-butyl) (*R*)-2-(acetylthio)-2-(3-methylbenzyl)malonate (1f)

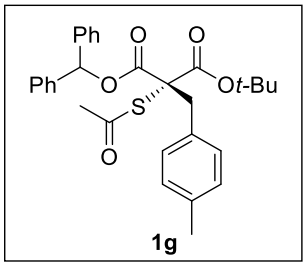


1f

Following the general procedure from the substrate **1** using 3-methylbenzyl bromide, the title molecule **1f** was obtained as a pale yellow oil (95% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.39 ~ 7.29 (m, 10H), 7.09 ~ 6.92 (m, 3H), 6.86 ~ 6.83 (m, 2H), 3.64 (dd, J_1 = 20.97 Hz, J_2 = 14.37 Hz, 2H), 2.22 (s, 3H), 2.20 (s, 3H), 1.26 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ

194.0, 166.4, 165.3, 139.3, 137.4, 135.3, 131.3, 128.5, 128.3, 128.1, 127.93, 127.90, 127.8, 127.7, 127.6, 127.2, 84.0, 78.7, 67.3, 39.4, 30.0, 27.5, 21.3 ppm; IR (KBr) 2952, 2930, 1728, 1683, 1445, 1366, 1249, 1090, 947, 892, 699 cm^{-1}; HRMS (FAB): calcd for $[C_{30}H_{33}O_5S]^+$ ($[M+H]^+$): 505.2049, found: 505.2058; The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane : 2-propanol = 80 : 20, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time: minor isomer 8.11 min, major isomer 10.51 min, 94% ee, $[\alpha]^{20}_D$ = + 80.42 (*c* 1.0, $CHCl_3$).

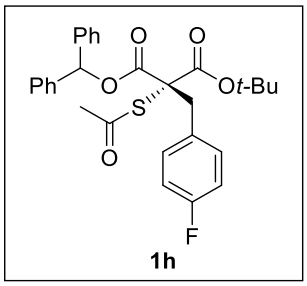
1-benzhydryl 3-(*tert*-butyl) (*R*)-2-(acetylthio)-2-(4-methylbenzyl)malonate (1g)



1g

Following the general procedure from the substrate **1**, using 4-methylbenzyl bromide, the title molecule **1g** was obtained as a pale yellow oil (96% yield). ^{1}H-NMR (500 MHz, CDCl3) δ 7.37 ~ 7.31 (m, 4H), 7.30 ~ 7.28 (m, 6H), 6.96 ~ 6.94 (m, 3H), 6.89 (d, *J* = 7.80 Hz, 2H), 3.62 (d, *J* = 3.70 Hz, 2H), 2.26 (s, 3H), 2.21 (s, 3H), 1.26 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 194.0, 166.4, 165.3, 139.3, 136.7, 132.2, 130.4, 128.6, 128.4, 128.3, 128.1, 127.9, 127.7, 127.2, 83.9, 78.7, 67.5, 39.1, 30.0, 27.5, 21.1 ppm; IR (KBr) 2979, 2927, 1733, 1692, 1455, 1370, 1257, 1182, 1148, 952, 746, 700 cm^{-1}; HRMS (FAB): calcd for $[C_{30}H_{32}O_5SNa]^+$ ($[M+Na]^+$): 527.1868, found: 527.1861; The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane : 2-propanol = 80 : 20, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time: minor isomer 13.99 min, major isomer 16.66 min, 96% ee, $[\alpha]^{20}_D$ = + 93.26 (*c* 1.0, $CHCl_3$).

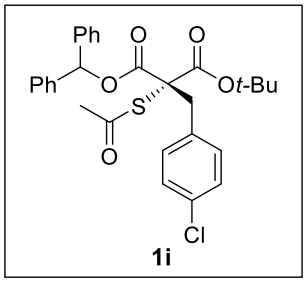
1-benzhydryl 3-(*tert*-butyl) (*R*)-2-(acetylthio)-2-(4-fluorobenzyl)malonate (1h)



1h

Following the general procedure from the substrate **1** using 4-fluorobenzyl bromide, the title molecule **1h** was obtained as a pale yellow oil (99% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.38 ~ 7.26 (m, 10H), 7.00 ~ 6.95 (m, 3H), 6.86 ~ 6.80 (m, 2H), 3.64 (dd, J_1 =16.11 Hz, J_2 =14.67 Hz, 2H), 2.23 (s, 3H), 1.26 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 193.9, 166.18, 165.17, 162.1 (d, J = 244.0Hz), 139.14, 139.1, 132.1 (d, J = 7.80 Hz), 131.0 (d, J = 3.20 Hz), 128.5, 128.3, 128.2, 128.0, 127.6, 127.2, 114.7 (d, J = 21.10 Hz), 84.1, 78.8, 67.2, 38.8, 30.0, 27.5 ppm; IR (KBr) 2930, 1732, 1692, 1509, 1370, 1257, 1221, 1148, 842, 772, 700, 648 cm^{-1}; HRMS (FAB): calcd for $[C_{29}H_{29}O_5FSNa]^+$ ($[M+Na]^+$): 531.1617, found: 531.1599; The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane : 2-propanol = 80 : 20, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time: minor isomer 12.45 min, major isomer 14.55 min, 97% ee, $[\alpha]^{20}_D$ = + 56.50 (*c* 1.0, $CHCl_3$).

1-benzhydryl 3-(*tert*-butyl) (*R*)-2-(acetylthio)-2-(4-chlorobenzyl)malonate (1i)

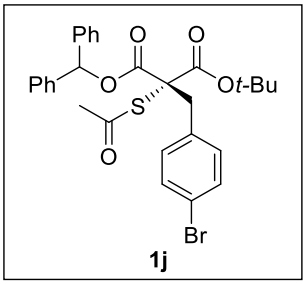


1i

Following the general procedure from the substrate **1**, using 4-chlorobenzyl bromide, the title molecule **1i** was obtained as a pale yellow oil (99% yield). ^{1}H-NMR (300 MHz, CDCl3) δ 7.34 ~ 7.24 (m, 10H), 7.09 ~ 7.08 (m, 2H), 6.93 ~ 6.91 (m, 3H), 3.26 (s, 2H), 2.21 (s, 3H), 1.25 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 193.9, 166.1, 165.1, 139.1, 139.0, 133.8, 133.1, 131.9, 128.5, 128.3, 128.2, 128.1, 127.6, 127.2, 84.2, 78.9, 67.0, 38.9, 30.0, 27.5 ppm; IR (KBr) 2926, 1733, 1692, 1493, 1370, 1256, 1181, 1148, 951, 772, 699 cm^{-1}; HRMS (FAB): calcd for $[C_{29}H_{29}O_5ClSNa]^+$ ($[M+Na]^+$): 547.1322, found: 547.1331; The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane : 2-propanol

= 80 : 20, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time: minor isomer 15.51 min, major isomer 18.61 min, 98% ee, $[\alpha]^{20}_{D}$ = + 96.64 (*c* 1.0, $CHCl_3$).

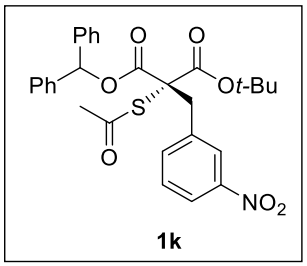
1-benzhydryl 3-(*tert*-butyl) (*R*)-2-(acetylthio)-2-(4-bromobenzyl)malonate (1j)



1j

Following the general procedure from the substrate **1** using 4-bromobenzyl bromide, the title molecule **1j** was obtained as a pale yellow oil (99% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.36 ~ 7.25 (m, 12H), 6.94 (s, 1H), 6.87 (d, *J* = 8.43 Hz, 2H), 3.62 (s, 2H), 2.23 (s, 3H), 1.27 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 193.9, 166.1, 165.1, 139.1, 139.0, 134.4, 132.3, 131.0, 128.5, 128.4, 128.3, 128.1, 127.6, 127.2, 121.3, 84.2, 78.9, 67.0, 38.9, 30.0, 27.5 ppm; IR (KBr) 2979, 2929, 1733, 1693, 1489, 1455, 1370, 1256, 1148, 1012, 951, 759, 699, 634 cm^{-1}; HRMS (FAB): calcd for $[C_{29}H_{29}O_5BrSNa]^+$ ($[M+Na]^+$): 591.0817, found: 591.0828; The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane : 2-propanol = 80 : 20, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time: minor isomer 18.44 min, major isomer 21.40 min, 97% ee, $[\alpha]^{20}_{D}$ = + 111.17 (*c* 1.0, $CHCl_3$).

1-benzhydryl 3-(*tert*-butyl) (*R*)-2-(acetylthio)-2-(3-nitrobenzyl)malonate (1k)

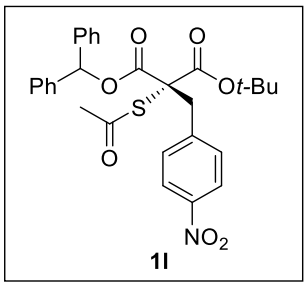


1k

Following the general procedure from the substrate **1** using 3-nitrobenzyl bromide, the title molecule **1k** was obtained as a pale yellow oil (99% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.07 ~ 8.03 (m, 1H), 7.98 (s, 1H), 7.36 ~ 7.26 (m, 12H), 6.96 (s, 1H), 3.77 (d, J_1 = 16.56 Hz, J_2 = 14.37 Hz, 2H), 2.25 (s, 3H), 1.28 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 193.9, 165.8, 164.8, 147.8, 139.0, 137.4, 136.8, 128.8, 128.5, 128.4, 128.3, 128.1, 127.5, 127.1,

125.5, 122.3, 84.8, 79.0, 66.8, 39.0, 30.0, 27.5 ppm; IR (KBr) 2979, 1731, 1694, 1530, 1352, 1258, 1147, 952, 771, 700, 647 cm^{-1}; HRMS (FAB): calcd for $[C_{29}H_{29}O_7NSNa]^+$ ($[M+Na]^+$): 558.1562, found: 558.1551; The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane : 2-propanol = 80 : 20, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time: minor isomer 16.41 min, major isomer 19.23 min, 86% ee, $[\alpha]^{20}_D$ = + 69.93 (*c* 1.0, $CHCl_3$).

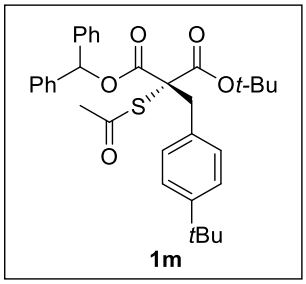
1-benzhydryl 3-(*tert*-butyl) (*R*)-2-(acetylthio)-2-(4-nitrobenzyl)malonate (1l)



1l

Following the general procedure from the substrate **1** using 4-nitrobenzyl bromide, the title molecule **1l** was obtained as a pale yellow oil (98% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.43 Hz, 2H), 7.34 ~ 7.25 (m, 10H), 7.15 (d, *J* = 8.43 Hz, 2H), 6.94 (s, 1H), 3.76 (dd, J_1 = 16.65 Hz, J_2 = 14.28 Hz, 2H), 2.25 (s, 3H), 1.29 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 193.8, 165.8, 164.9, 147.1, 143.1, 138.9, 138.8, 131.4, 128.5, 128.4, 128.2, 127.5, 127.2, 123.0, 84.5, 79.1, 66.5, 39.3, 30.1, 27.5 ppm; IR (KBr) 2926, 2854, 1732, 1694, 1522, 1348, 1258, 1147, 951, 764, 699, 646 cm^{-1}; HRMS (FAB): calcd for $[C_{29}H_{29}O_7NSNa]^+$ ($[M+Na]^+$): 558.1562, found: 558.1591; The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane : 2-propanol = 80 : 20, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time: minor isomer 24.01 min, major isomer 26.66 min, 95% ee, $[\alpha]^{20}_D$ = + 79.89 (*c* 1.0, $CHCl_3$).

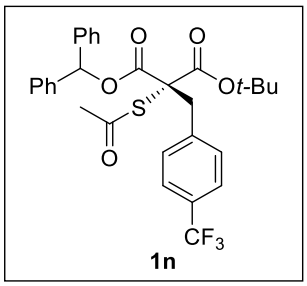
1-benzhydryl 3-(*tert*-butyl) (*R*)-2-(acetylthio)-2-(4-(*tert*-butyl)benzyl)malonate (1m)



1m

Following the general procedure from the substrate **1** using 4-(*tert*-butyl)benzyl bromide, the title molecule **1m** was obtained as a pale yellow oil (99% yield). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.36 ~ 7.25 (m, 10H), 7.15 (d, *J* = 8.20 Hz, 2H), 6.97 (d, *J* = 8.15 Hz, 2H), 6.94 (s, 1H), 3.63 (dd, J_1 = 31.40 Hz, J_2 = 14.45 Hz, 2H), 2.21 (s, 3H), 1.25 (s, 9H), 1.23 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 194.0, 166.4, 165.3, 149.9, 139.3, 132.2, 130.3, 128.4, 128.3, 128.1, 127.9, 127.6, 127.3, 124.8, 83.9, 78.7, 67.3, 39.1, 34.4, 31.3, 30.0, 27.5 ppm; IR (KBr) 2963, 1733, 1692, 1456, 1369, 1257, 1182, 1148, 952, 759, 699, 647 cm^{-1}; HRMS (FAB): calcd for $[C_{33}H_{38}O_5SNa]^+$ ($[M+Na]^+$): 569.2338, found: 569.2325; The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane : 2-propanol = 90 : 10, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time: minor isomer 14.78 min, major isomer 16.53 min, 96% ee, $[\alpha]^{20}_D$ = + 53.64 (*c* 1.0, $CHCl_3$).

1-benzhydryl 3-(*tert*-butyl) (*R*)-2-(acetylthio)-2-(4-trifluoromethyl)benzyl) malonate (1n)

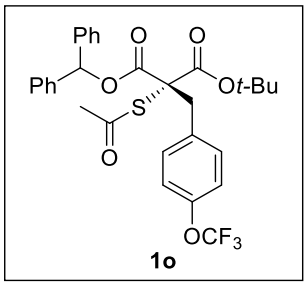


1n

Following the general procedure from the substrate **1** using 4-(trifluoromethyl)benzyl bromide, the title molecule **1n** was obtained as a pale yellow oil (99% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.40 ~ 7.25 (m, 12H), 7.11 (d, *J* = 7.86 Hz, 2H), 6.95 (s, 1H), 3.72 (s, 2H), 2.24 (s, 3H), 1.27 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 193.9, 166.0, 165.0, 139.5, 139.04, 138.99, 130.9, 129.4 (d, *J* = 32.10 Hz), 128.5, 128.3, 128.2, 128.1, 127.6, 127.2, 124.8 (d, *J* = 3.00 Hz), 124.1 (d, *J* = 270.50 Hz), 84.3, 78.9, 66.8, 39.3, 30.0, 27.5 ppm; IR (KBr) 2926, 1733, 1694, 1371, 1326, 1148, 1113, 1067, 761, 699, 632 cm^{-1}; HRMS (FAB): calcd for $[C_{30}H_{29}O_5F_3SNa]^+$ ($[M+Na]^+$): 581.1586, found: 581.1575; The enantioselectivity was

determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane : 2-propanol = 99 : 1, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time: minor isomer 78.77 min, major isomer 87.07 min, 96% ee, $[\alpha]^{20}_{D}$ = + 36.16 (*c* 1.0, $CHCl_3$).

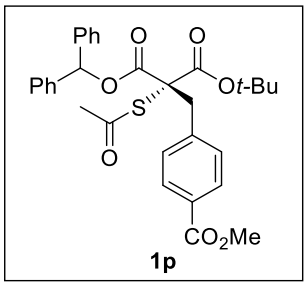
1-benzhydryl 3-(*tert*-butyl) (*R*)-2-(acetylthio)-2-(4-(trifluoromethoxy)benzyl) malonate (1o)



1o

Following the general procedure from the substrate **1** using 4-(trifluoromethoxy)benzyl bromide, the title molecule **1o** was obtained as a white solid (86% yield). mp 68 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.37 ~ 7.26 (m, 9H), 7.06 ~ 6.95 (m, 6H), 3.67 (dd, J_1 = 20.16 Hz, J_2 = 14.46 Hz, 2H), 2.23 (s, 3H), 1.25 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 193.9, 166.1, 165.1, 148.4, 139.10, 139.06, 134.1, 132.0, 128.5, 128.3, 128.2, 128.1, 127.6, 127.2, 120.3, 84.3, 78.9, 66.9, 38.9, 30.0, 27.4 ppm; IR (KBr) 2981, 1733, 1693, 1508, 1371, 1259, 1149, 1109, 951, 743, 699, 646 cm^{-1}; HRMS (FAB): calcd for $[C_{30}H_{29}O_6F_3SNa]^+$ ($[M+Na^+]$): 597.1535, found: 597.1545; The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane : 2-propanol = 99 : 1, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time: minor isomer 54.51 min, major isomer 56.66 min, 96% ee, $[\alpha]^{20}_{D}$ = + 52.02 (*c* 1.0, $CHCl_3$).

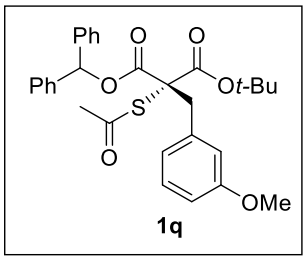
1-benzhydryl 3-(*tert*-butyl) (*R*)-2-(acetylthio)-2-(4-(methoxycarbonyl)benzyl) malonate (1p)



1p

Following the general procedure from the substrate **1** using methyl 4-(bromomethyl)benzoate, the title molecule **1p** was obtained as a pale yellow oil (99% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.82 (d, J = 8.22 Hz, 2H), 7.36 ~ 7.26 (m, 10H), 7.09 (d, J = 8.25 Hz, 2H), 6.95 (s, 1H), 3.88 (s, 3H), 3.71 (d, J_1 = 16.02 Hz, J_2 = 14.37 Hz, 2H), 2.23 (s, 3H), 1.27 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 193.9, 166.8, 166.0, 165.0, 140.8, 139.1, 139.0, 130.6, 129.2, 129.0, 128.5, 128.3, 128.2, 128.0, 127.6, 127.2, 84.3, 78.9, 66.9, 52.0, 39.4, 30.0, 27.5 ppm; IR (KBr) 2925, 2853, 1725, 1693, 1436, 1370, 1281, 1147, 1021, 952, 760, 700, 647 cm^{-1}; HRMS (FAB): calcd for $[C_{31}H_{32}O_7SNa]^+$ ($[M+Na]^+$): 571.1766, found: 571.1755; The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane : 2-propanol = 80 : 20, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time: minor isomer 16.98 min, major isomer 21.67 min, 96% ee, $[\alpha]^{20}_{D}$ = + 110.02 (*c* 1.0, $CHCl_3$).

1-benzhydryl 3-(*tert*-butyl) (*R*)-2-(acetylthio)-2-(3-methoxybenzyl)malonate (1q)

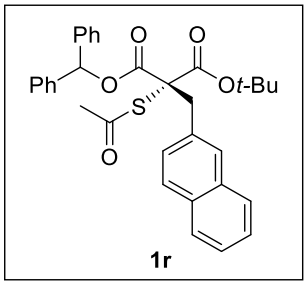


1q

Following the general procedure from the substrate **1** using 3-methoxybenzyl bromide, the title molecule **1q** was obtained as a pale yellow oil (96% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.39 ~ 7.23 (m, 10H), 7.11 ~ 7.05 (m, 1H), 6.96 (s, 1H), 6.76 ~ 6.72 (m, 1H), 6.64 ~ 6.61 (m, 2H), 3.66 (dd, J_1 = 18.03 Hz, J_2 = 14.58 Hz. 2H), 3.66 (s, 3H), 2.22 (s, 3H), 1.25 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 194.0, 166.3, 165.2, 159.1, 139.2, 136.9, 128.8, 128.5, 128.3, 128.1, 128.0, 127.5, 127.3, 122.9, 116.3, 112.6, 84.0, 78.7, 67.2, 55.0, 39.5, 30.0, 27.4 ppm; IR (KBr) 2931, 1733, 1692, 1455, 1370, 1263, 1148, 1052, 953, 771, 699, 645

cm^{-1}; HRMS (FAB): calcd for $[C_{30}H_{32}O_6SNa]^+$ ($[M+Na]^+$): 543.1817, found: 543.1308; The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane : 2-propanol = 80 : 20, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time: minor isomer 11.29 min, major isomer 14.08 min, 96% ee, $[\alpha]^{20}_D$ = + 35.86 (*c* 1.0, $CHCl_3$).

1-benzhydryl 3-(*tert*-butyl) (*R*)-2-(acetylthio)-2-(naphthalen-2-ylmethyl) malonate (1r)



1r

Following the general procedure from the substrate **1** using 2-(bromomethyl) naphthalene, the title molecule **1r** was obtained as a pale yellow oil (91% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.78 ~ 7.75 (m, 1H), 7.66 ~ 7.59 (m, 2H), 7.49 (s, 1H), 7.44 ~ 7.26 (m, 12H), 7.18 (d, J = 8.40 Hz, 1H), 6.97 (s, 1H), 3.90 ~ 3.80 (dd, J_1 = 17.10 Hz, J_2 = 14.37 Hz, 2H), 2.24 (s, 3H), 1.26 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 194.1, 166.3, 165.3, 139.22, 139.18, 133.04, 133.00, 132.5, 129.4, 128.6, 128.5, 128.3, 128.2, 128.0, 127.7, 127.6, 127.5, 127.4, 127.2, 125.8, 125.7, 84.1, 78.8, 67.5, 39.6, 30.0, 27.5 ppm; IR (KBr) 2928, 1732, 1691, 1370, 1254, 1216, 1147, 771, 700, 645 cm^{-1}; HRMS (FAB): calcd for $[C_{33}H_{32}O_5SNa]^+$ ($[M+Na]^+$): 563.1868, found: 563.1887; The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane : 2-propanol = 80 : 20, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time: minor isomer 13.96 min, major isomer 19.34 min, 91% ee, $[\alpha]^{20}_D$ = + 188.19 (*c* 1.0, $CHCl_3$).

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국 문 초 록

유기황화합물은 자연과 생물학적 시스템에 널리 존재하는 물질로 천연물 및 의약품에서 그 구조를 쉽게 발견할 수 있다. 유기황화합물의 생물학적 중요성 때문에 비대칭의 탄소-황 결합을 만들기 위한 시도가 있어왔다. 그 중 가장 널리 쓰이는 방법은 황-마이클 첨가반응으로 직접적으로 설페닐레이션 하는 방법이다. 그러나 설페닐레이션은 기질준비의 어려움과 작용기의 변형이 어렵다는 단점이 있었다.

지난 2011년, 본 연구실에서는 알파,알파-다이알킬말로네이트에 광학활성이 있는 사차암모늄 염을 촉매로 하여 상전이촉매반응을 통해 높은 화학적 수율과 입체선택성을 갖는 알킬레이션의 새로운 합성법을 보고한 바 있다. 또한 이 합성법을 이용하여 천연물의 전합성과 유용한 유도체를 합성함으로써 유용성을 입증하였다. 이 기질의 영역을 확장하고자 알파-아세틸싸이오말로네이트에 상전이 촉매 알킬화 반응으로 황 원소를 포함하는 비대칭 4차 탄소 골격의 합성법을 시도하였다.

그 결과 터트-부틸 다이페닐메틸 알파-아세틸싸이오말로네이트에 상전이 촉매인 (*S,S*)-3,4,5-트라이플로로페닐-NAS 브로마이드와 염기수용액인 50% 포타슘하이드록사이드와 유기용매인 톨루엔을 사용하여 -20°C의 온도에서 입체선택적 알킬레이션 하여 알파-아세틸싸이오-알파-알킬말로네이트를 최대 99 %의 높은 화학적 수율과 98 %ee의 높은 광학적 수율로 합성하였다.

주요어: 입체선택적합성, 상전이 촉매 반응, 알파-아세틸싸이오-알파-알킬말로네이트

학번: 2015-21891

Part II

Application and Confirm the Absolute Configuration of chiral α-benzoxy-α-alkylmalonate

α-benzoxy-α-alkylmalonate의 응용 및 절대배열 확인

ABSTRACT

In 2013, our research team developed enantioselective synthetic method for α-benzoyloxy-α-alkylmalonates via PTC alkylation. The asymmetric PTC α-alkylation of α-benzoxymalonate produced the corresponding α-benzoxy-α-alkylmalonates with high chemical (up to 99 %) and optical (up to 93 %ee) yields. However, we didn't try the derivatization of α-benzoxy-α-alkylmalonates and we couldn't get the absolute configuration by X-ray crystallography.

Accordingly, we have been proceeded the derivatization of α-benzoxy-α-alkylmalonates. We could synthesize the chiral β-hydroxydiester, α,β-dihydroxyester, α,β-epoxyester, and 1,2-diol via multiple steps of reaction. From this applications we could confirm the absolute configuration of chiral α-benzoxy-α-alkylmalonate. The absolute configuration of α-benzoxy-α-alkylmalonate was assigned as *R* by the chemical conversion to a known compound 1,2-diol.

Keywords: enantioselective synthesis, α-benzoxy-α-alkylmalonate, asymmetric phase-transfer catalysis, quaternary carbon center, derivatization

Student Number: 2015-21891

INTRODUCTION

1. The organic compounds with chiral tertiary alcohols

Chiral tertiary alcohol is very important structure in medicinal chemistry. The structure is widely present in bioactive natural products, pharmaceuticals and derivatives (**Figure 12**).[1] Many organic synthetic chemists have been developed various methodologies to make chiral tertiary alcohol structures. Among them, the modification of α-hydroxymalonate could be useful because it has the advantage of obtaining various derivatives.[2] So, our research team have been studied the construction of chiral quaternary carbon center on α-hydroxymalonate.

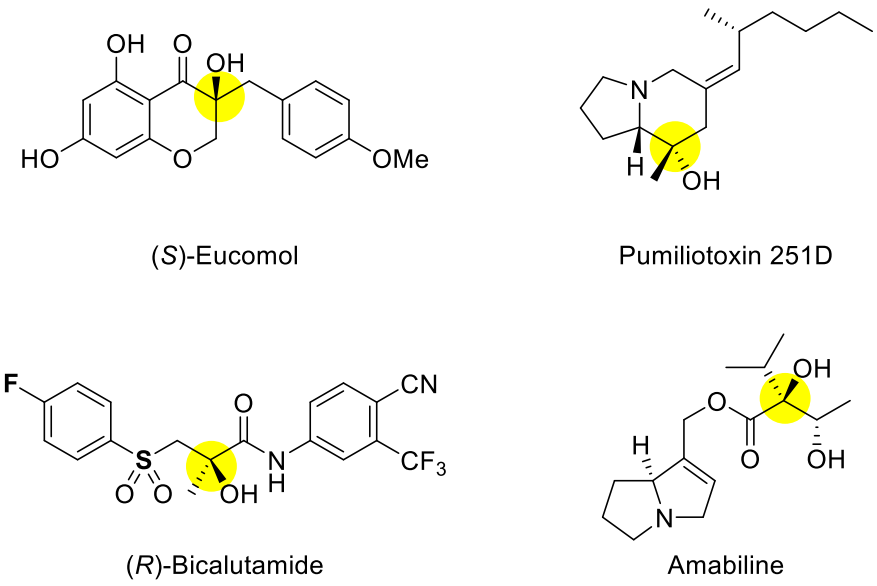
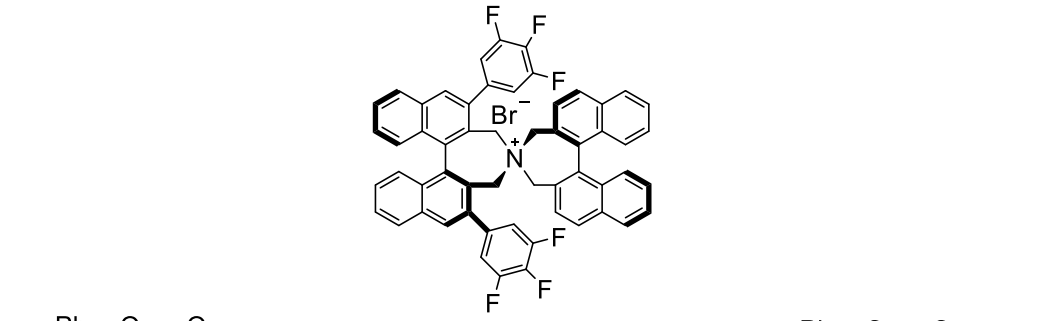


Figure 12. The bioactive natural products and pharmaceuticals containing chiral tertiary alcohol [1]

2. Asymmetric phase-transfer catalyzed alkylation of α-benzoxymalonate



2 **2a-n**

2a R= $CH_3(CH_2)_4CH_2$
2b R= CH_2CHCH_2
2c R= $CH_2C(CH_3)CH_2$
2d R= $CH_2C(Br)CH_2$
2e R= $C_6H_5CH_2$
2f R= 4-Me-$C_6H_4CH_2$
2g R= 4-*t*Bu-$C_6H_4CH_2$
2h R= 3-MeO-$C_6H_4CH_2$
2i R= 3,5-$(MeO)_2$-$C_6H_4CH_2$
2j R= 4-F-$C_6H_4CH_2$
2k R= 4-Cl-$C_6H_4CH_2$
2l R= 4-Br-$C_6H_4CH_2$
2m R= 4-NO_2-$C_6H_4CH_2$
2n R= β-naphtyl-CH_2

Scheme 6. Asymmetric phase-transfer catalytic alkylation of α-benzoxymalonate with various electrophiles [1]

In 2013, our research team (Kim, S. and coworkers) have been achieved chiral products by phase-transfer catalytic alkylation of various electrophiles to α-benzoxymalonate.[2] The reaction was carried out using (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide as the catalyst, 50% CsOH (aq) as the base solution and Toluene as the organic solvent at -20 °C.[2] Using this newly developed reaction, we have been created total 14 chiral products with up to 99 % chemical yield and 93 %ee optical yield.[2]

However, we have not been able to proceed the additional application of our chiral product,

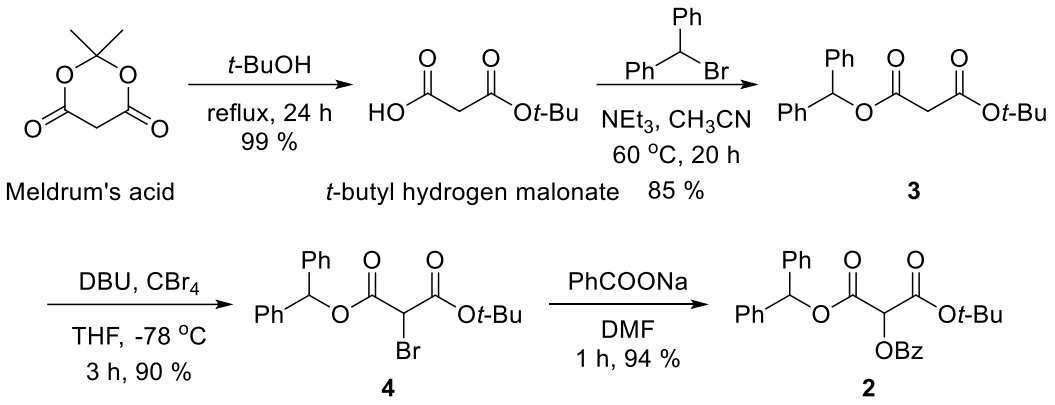
α-benzoxy-α-alkylmalonate. In addition, X-ray crystallography was performed to confirm the absolute configuration of α-benzoxy-α-alkylmalonates, but failed to obtain correct form.

We have predicted that the synthesized α-benzoxy-α-alkylmalonates have potential to make useful chemical blocks through simple modification. So, our research team have been studied to obtain the valuable chemical blocks by performing α-benzoxy-α-alkylmalonates derivatization, also we tried to find the absolute configuration in the process.

RESULTS AND DISCUSSION

1. Derivatization of α-benzoxy-α-alkylmalonate

As mentioned in the introduction, our research goal was to synthesize derivatives that are available in medicinal chemistry by proceeding the application of α-benzoxy-α-alkylmaonate. Prior to the derivatization, the substrate α-benzoxymalonate was synthesized. The synthesis of α-benzoxymalonate was similar to the synthesis of α-acetylthiomalonate.

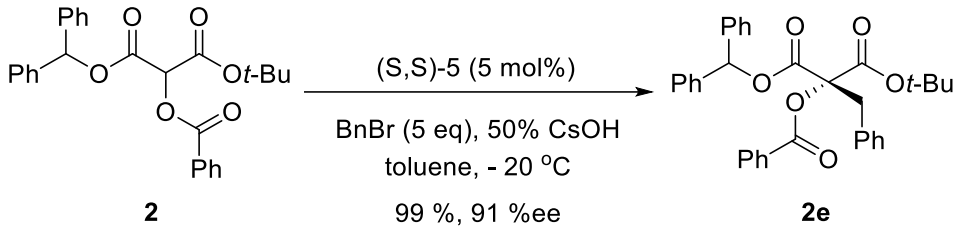


Scheme 7. Synthesis of α-benzoxymalonate substrate

First, *tert*-butanol was added to meldrum's acid, and the temperature was increased by 90 °C to reflux for 24 hours to obtain *tert*-butyl hydrogen malonate. Then, *tert*-butyl hydrogen malonate was dissolved in acetonitrile, and α-bromodiphenylmethane, triethylamine were added to the reaction at 60 °C to synthesize benzhydryl *tert*-butyl malonate **3**. After that, to perform the monobromination at α-position, benzhydryl *tert*-butyl malonate **3** was dissolved in THF, and tetrabromomethane and DBU were added at -78 °C to proceed the reaction. Finally, dissolving α-bromomalonate substrate **4** in DMF and adding sodium benzoate at room temperature, we could construct the desired substrate, α-

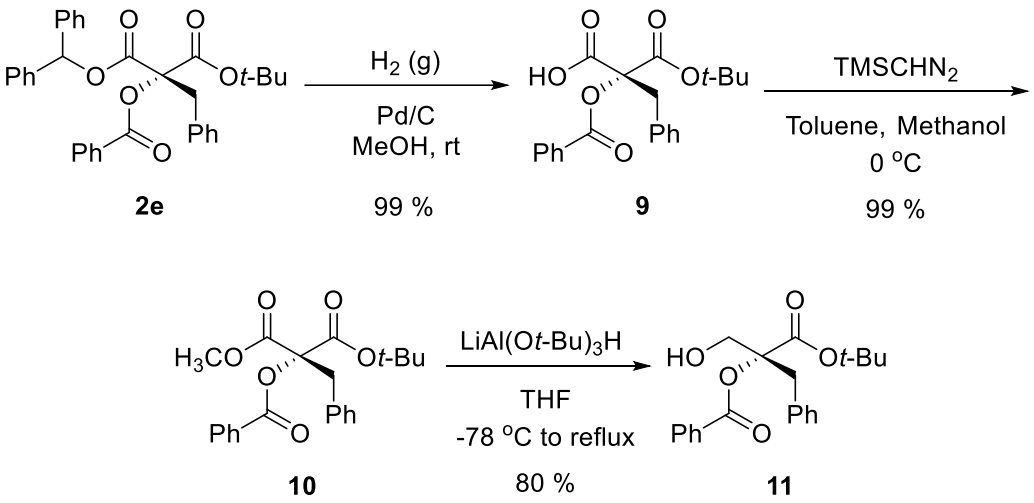
benzoxymalonate **2** (**Scheme 7**).

After completion of the substrate, enantioselective phase-transfer catalysis was performed to synthesize α-benzoxy-α-alkymalonate in 99 % and 91 %ee yield (**Scheme 8**).



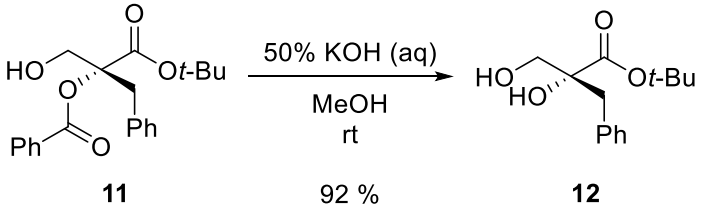
Scheme 8. Phase-transfer catalysis of α-benzoxymalonate with benzylbromide

Then, the derivatization proceeded to synthesized β-hydroxydiester **11** via multiple steps. First, diphenylmethane was removed by hydrogenation using Pd/C and hydrogen gas. Then, we synthesize the methyl ester using trimethylsilydiazomethane. Finally, partial reduction with *tert*-butoxide-substituted LAH and β-hydroxydiaester **11** were obtained (**Scheme 9**).



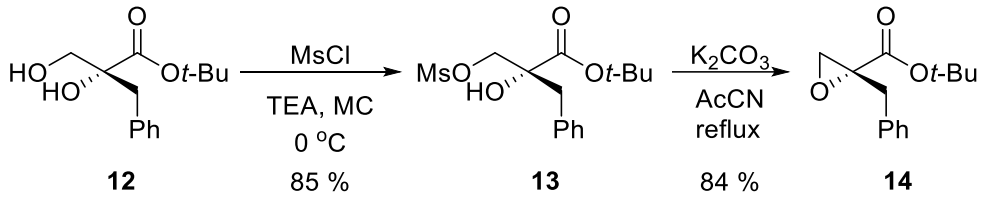
Scheme 9. Synthesis of β-hydroxydiester

The reason for the partial reduction after making the methyl ester was that it was difficult to handle the compound **9** which was acid form. In fact, the use of a strong reducing agent to achieve partial reduction of only carboxylic acid resulted in the reduction of both esters.



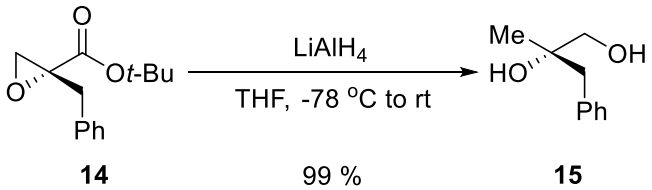
Scheme 10. Synthesis of α,β-dihydroxyester

β-Hydroxydiester **11** was hydrolyzed with 50 % KOH (aq) to obtain α,β-dihydroxyester **12** (**Scheme 10**). Derivatization was continued to obtain more derivatives.



Scheme 11. Synthesis of α,β-epoxyester

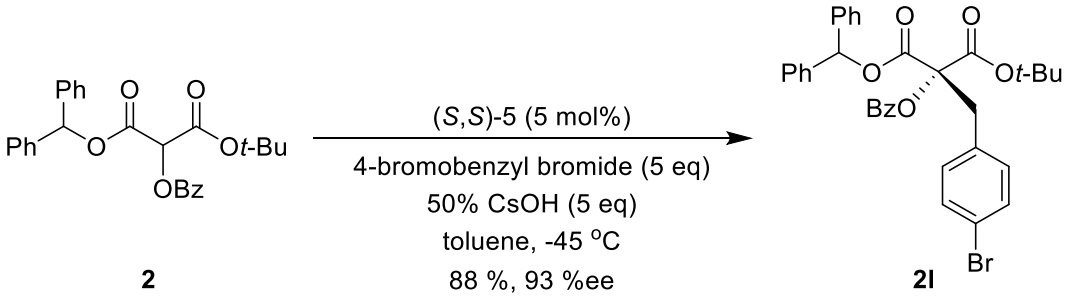
α,β-epoxyester **14** could be obtained by ring closure reaction using potassium carbonate after mesylation of α,β-dihydroxyester **12** (**Schem 11**). Finally, 1,2-diol could be synthesized by reducing epoxide and t-butylester with LAH. (**Scheme 12**)



Scheme 12. Synthesis of 1,2-diol

2. Confirm the absolute configuration of α-benzoxy-α-alkylmalonate

Our other research goal was the confirmation of the absolute configuration of α-benzoxy-α-alkylmalonate. To achieve this goal, we tried to lower the reaction temperature and increase the optical yield of the chiral compound and crystallize it for X-ray crystallography (**Scheme 13**).

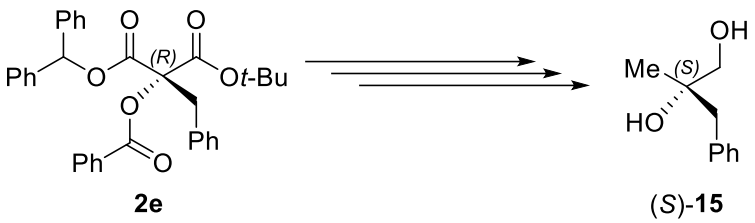


Scheme 13. Synthesis of 4-bromobenzylate product at -45 °C

We synthesized 4-bromobenzylated product **2l** for easy measurement of x-ray crystallography and obtained it with 93 %ee yield. However, despite increasing the purity of the material by increasing the optical yield, the results of x-ray crystallography were measured as racemate. This was probably because the remaining 7 % racemate formed crystals. This hypothesis was supported by the fact that we actually used various solvents to make the crystal, but it was extremely difficult to make them.

Fortunately, we could confirm the absolute configuration by comparing the polarimeter because the 1,2-diol, a derivative we synthesized, was a known compound[3]. The specific rotation of the 1,2-diol synthesized by us was +9.6 ° and the specific rotation of the known compound[3] was -11.6 °. Since the absolute configuration of the known compound has the (*R*)-form[3], we conclude that the synthesized 1,2-diol has a (*S*)-form. Accordingly, it was

confirmed that α-benzoxy-α-alkylmalonates had a (*R*)-form (**Figure 13**).



$[\alpha]_D^{20}$ = -9.6° (c 1.0, EtOH 95 %), 91 %ee

(R)-15: $[\alpha]_D^{20}$ = +11.4° (c 1.0, EtOH 95 %), 94 %ee,

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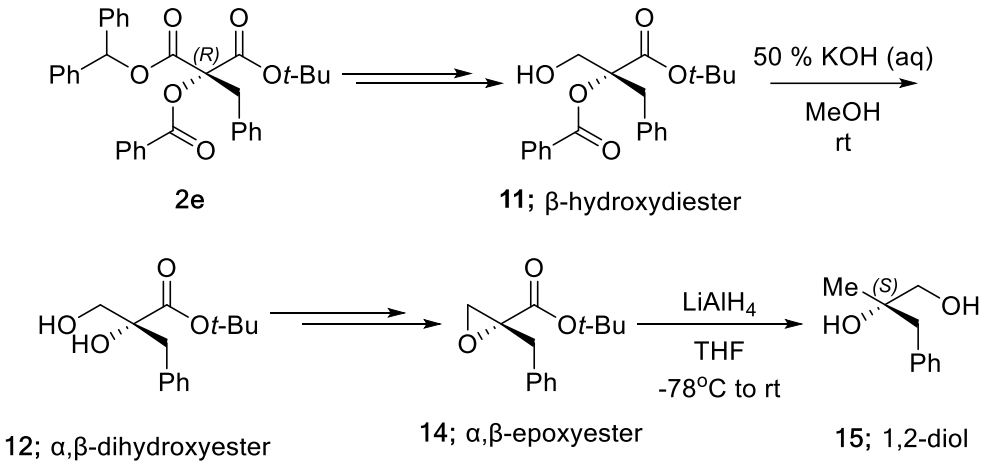
Figure 13. Confirm the absolute configuration by comparing polarimeters

CONCLUSION

As a follow-up study of enantioselective synthesis of α-benzoxy-α-alkylmalonate via phase-transfer catalytic alkylation, derivatization of α-benzoxy-α-alkylmalonate proceeded and absolute configuration was confirmed. As a result of derivatization, important derivatives in medicinal chemistry such as chiral β-hydroxydiester, α,β-dihydroxyester, α,β-epoxyester, and 1,2-diol were synthesized.



Scheme 14. Derivatization of α-benzoxy-α-alkylmalonate

Also, we have been successfully confirmed the absolute configuration by comparing the polarimeter of 1,2-diol. The polarimeter of 1,2-diol was -9.6°, confirmed to have (*S*)-form. Accordingly, the α-benzoxy-α-alkylmalonate has a logical conclusion that it has (*R*)-form. These subsequent studies have demonstrated the usefulness of enantioselective synthesis of α-benzoxy-α-alkylmalonate via phase-transfer catalytic alkylation. The result of this study was published in RSC Advances as communication (*RSC Adv.*, **2016**, *6*, 77427).

EXPERIMENTAL SECTION

1. General Methods

1.1. Solvents and reagents

All reagents bought from commercial sources were used without further purification. Organic solvents were concentrated under reduced pressure using a Büchi rotary evaporator. 50% w/v aqueous KOH and 50% w/v aqueous CsOH was used as stock solution. Phase-transfer catalysts **(5)** were purchased from the commercial source (Wako and Sigma Aldrich).

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 analysis. The values of enantiomeric excess (ee) of chiral products were 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-4200 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 [500 MHz (^{1}H), 125 MHz (^{13}C)] spectrometer, using $CHCl_3$-*d* as solvents, and were reported

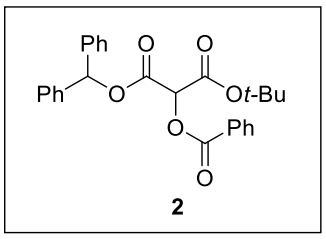
in ppm relative to $CHCl_3$ (δ 7.24) for ^{1}H-NMR and relative to the central $CDCl_3$ (δ 77.23) resonance for ^{13}C-NMR. Coupling constants (*J*) in ^{1}H-NMR are in Hz. Low-resolution mass spectra (LRMS) and high-resolution mass spectra (HRMS) were measured on a JEOL JMS 700, JEOL JMS 600-W spectrometer, or Agilent 6530 Q-TOF (ESI) spectrometer. 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.

2. Derivatization of α-benzoxy-α-alkylmalonate

2.1. Preparation of α-benzoxy-α-alkylmalonate

Synthesize the α-benzoxymalonate substrate **2** proceeds same as the synthesis of α-acetylthiomalonate substrate. The difference is last step, which undergoes S_N2 reaction via Sodium benzoate. The procedure and spectral data of α-benzoxymalonate substrate **2** and its alkylated products are described below.

Synthesis of α-benzoxymalonate substrate (2)

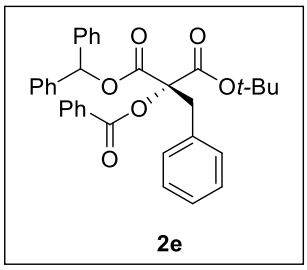


2

Sodium benzoate (1.06 g, 7.33 mmol) was added to a stirred solution of α-bromomalonate substrate **4** (1.98 g, 4.89 mmol) in dry dimethylformamide (49 ml) at room temperature under argon atmosphere. The reaction was stirred until the TLC analysis showed that the reaction was complete (1 hour). The reaction solvent was evaporated and diluted with EtOAc (200 ml), extracted with brine (100 ml x 2 times), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes : EtOAc = 25 : 1) to

afford α-benzoxymalonate substrate **2** was obtained as a white solid (94% yield). mp 98 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.14 ~ 8.11 (m, 2H), 7.60 ~ 7.55 (m, 1H), 7.46 ~ 7.41 (m, 2H), 7.36 ~ 7.23 (m, 10H), 7.01 (s, 1H), 5.78 (s, 1H), 1.40 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.1, 163.8, 163.0, 139.1, 133.7, 130.2, 128.55, 128.49, 128.46, 128.2, 127.3, 127.1, 84.05, 78.7, 72.7, 27.7 ppm; IR (KBr) 2980, 1768, 1734, 1602, 1496, 1453, 1369, 1235, 1119, 1002, 838, 744, 700 cm^{-1}; HRMS (FAB): calcd for $[C_{27}H_{27}O_6]^+$: 447.1808, found: 447.1815.

1-Benzhydryl 3-(*tert*-butyl) (*R*)-2-(benzoyloxy)-2-benzylmalonate (2e)

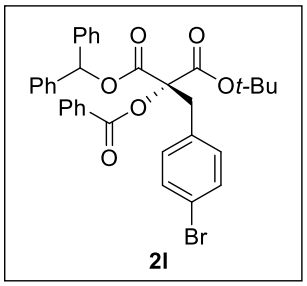


2e

Benzyl bromide (134 μl, 1.12 mmol) was added to a solution of α-benzoxymalonate substrate **2** (100 mg, 0.22 mmol) and (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide **5** (10 mg, 0.0112 mmol) in toluene (747 μl) at room temperature. At the designated low temperature, aqueous 50% w/v aqueous CsOH (196 μl, 1.12 mmol) was added to the reaction mixture and stirred until the starting material disappeared. After completion of the reaction, the reaction mixture was diluted with ethyl acetate (25ml), washed with brine (10ml x 2), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel eluting with hexane-EtOAc solution (25:1) to afford **2e** (33.4 mg, 98% yield) as a white oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.01 ~ 7.98 (d, *J* = 7.68 Hz, 2H), 7.59 ~ 7.55 (m, 1H), 7.44 ~ 7.39 (m, 2H), 7.34 ~ 7.19 (m, 10H), 7.17 ~ 7.10 (m, 3H). 7.04 ~ 7.02 (m, 2H), 6.99 (s, 1H), 3.72 (s, 2H), 1.30 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 165.6, 165.0, 164.4, 139.3, 139.1, 134.0, 133.4, 130.2, 130.0, 129.4, 128.5, 128.4, 128.3, 128.1, 127.9, 127.7, 127.1, 83.8, 83.6, 78.5, 39.3, 27.6 ppm; IR (KBr) 3064, 3032, 1752, 1727, 1601, 1495, 1453, 1370, 1284, 1108, 1033, 954, 742 cm^{-1}; HRMS (FAB): calcd for $[C_{34}H_{32}O_6Na]^+$ ($[M+Na]^+$): 559.2097, found: 559.2098; The enantioselectivity was determined by

chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane : 2-propanol = 85 : 15, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time: major isomer 8.78 min, minor isomer 11.32 min, 91% ee, $[\alpha]^{20}_{D}$ = + 7.24 (*c* 1.0, $CHCl_3$).

1-Benzhydryl 3-(*tert*-butyl)(*R*)-2-(benzoyloxy)-2-(4-bromobenzyl)malonate (2l)



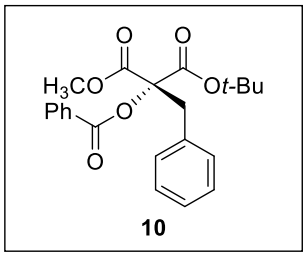
2l

4-Bromobenzyl bromide (123 mg, 0.5 mmol) was added to a solution of α-benzoxymalonate substrate **2** (44 mg, 0.1 mmol) and (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide **5** (4.5 mg, 0.005 mmol) in toluene (330 μl) at room temperature. At the designated low temperature (-45 °C), aqueous 50% w/v aqueous CsOH (86 μl, 0.5 mmol) was added to the reaction mixture and stirred until the starting material disappeared. After completion of the reaction, the reaction mixture was diluted with ethyl acetate (25ml), washed with brine (10ml x 2), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel eluting with hexane-EtOAc solution (25:1) to afford **2l** (46 mg, 88 % yield) as a colorless crystal. mp 64 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.01 ~ 7.98 (m, 2H), 7.62 ~ 7.56 (m, 1H), 7.50 ~ 7.41 (m, 2H), 7.38 ~ 7.18 (m, 12H), 6.97 (s, 1H), 6.87 ~ 6.82 (m, 2H), 3.66 (s, 2H), 1.32 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.3, 164.9, 164.4, 139.2, 139.0, 133.6, 133.1, 131.8, 131.3, 129.9, 129.2, 128.5, 128.3, 128.2, 128.0, 127.6, 127.1, 121.3, 83.8, 83.6, 78.6, 38.7, 27.6 ppm; IR (KBr) 2930, 2310, 1750, 1730, 1602, 1489, 1452, 1395, 1316, 1176, 1070, 1012, 954, 712, 648 cm^{-1}; HRMS (FAB): calcd for $[C_{34}H_{32}BrO_6]^+$ ($[M+H]^+$): 615.1382, found: 615.1364; The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane : 2-propanol = 85 : 15, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time: major isomer 10.83 min, minor isomer 14.23 min, 93% ee, $[\alpha]^{20}_{D}$ = + 7.79 (*c* 1.0,

$CHCl_3$).

2.2. Synthesis of α-benzoxy-α-alkylmalonate derivatives

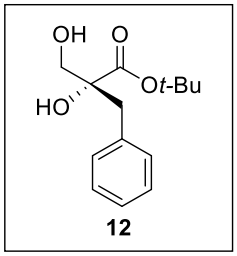
(*R*)-1-Methyl 3-*tert*-butyl 2-(benzoyloxy)-2-benzylmalonate (10)



10

Pd/C (100 mg) was added to a methanolic solution (50 ml) of **2e** (2.6 g, 4.85 mmol) and the reaction mixture was stirred for 1 hr under 1 atm of H_2. The reaction mixture was filtered over a pad of celite to remove Pd/C and the methanol solvent was evaporated *in vacuo* to afford mono-acid (**9**). Without further purification, 2 equiv. of TMS diazomethane (10 mmol) was added to a toluene-CH_3OH (4:1) solution of **9** and the reaction mixture was stirred for 1 hr at 0 °C. After completion of reaction, the mixture was quenched with acetic acid and followed by evaporation. The residue was diluted with EtOAc (100 ml), washed with brine (50 ml), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane : EtOAc = 20 : 1) to afford **10** (1.86 g, 99% yield) as pale yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.05 ~ 8.03 (d, *J* = 7.14 Hz, 2H), 7.59 ~ 7.54 (t, *J* = 7.2 Hz, 1H), 7.45 ~ 7.40 (t, *J* = 7.6 Hz, 2H), 7.25 ~ 7.23 (m, 5H), 3.78 (s, 3H), 3.66 (s, 2H), 1.42 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 167.2, 165.0, 164.7, 134.2, 133.4, 130.3, 130.0, 129.3, 128.4, 128.2, 127.3, 83.6, 83.5, 52.9, 39.9, 27.7 ppm; IR (KBr) 3064, 3033, 2979, 1755, 1731, 1602, 1584, 1496, 1453, 1438, 1394, 1370, 1285, 1250, 1208, 1155, 1109, 1057, 958, 843, 713 cm^{-1}; HRMS (FAB): calcd for $[C_{22}H_{25}O_6]^+$ ($[M+H]^+$): 385.1651, found: 385.1652; $[\alpha]^{20}_D$ = + 3.46 (*c* 1.0, $CHCl_3$).

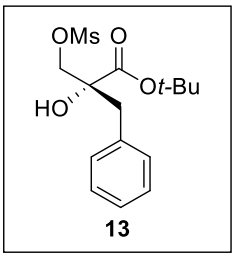
(*R*)-*tert*-Butyl 2-benzyl-2,3-dihydroxypropanoate (12)



12

To a THF solution (20 ml) of **10** (1.02 g, 2.66 mmol) was added a THF solution (3.4 ml) of $LiAl(O\textit{t}\text{-}Bu)_3H$ (13.31 mmol) at −78 °C. The reaction solution was warmed to room temperature and stirred for 5 hours at 60 °C. The reaction was quenched by Rochelle solution (10 ml), diluted with EtOAc (100 ml), washed with brine (50 ml x 2), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane : EtOAc = 4 : 1) to afford **12** (0.62 g, 92% yield) as color less oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.30 ~ 7.19 (m, 5H), 3.85 (d, *J* = 10.98 Hz, 1H), 3.65 (d, *J* = 10.98 Hz, 1H), 2.94 (d, *J* = 13.73 Hz, 1H), 2.88 (d, *J* = 13.73 Hz, 1H), 1.42 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 173.5, 135.5, 130.4, 128.3, 127.2, 83.6, 78.8, 68.3, 41.2, 28.2 ppm; IR (KBr) 3470, 3032, 2978, 2930, 1728, 1496, 1456, 1395, 1370, 1281, 1220, 1160, 1121, 1035, 938, 845, 773, 701, 673 cm^{-1}; HRMS (FAB): calcd for $[C_{14}H_{21}O_4]^+$ ($[M+H]^+$): 253.1440, found: 253.1444; $[\alpha]^{20}_D = -4.92$ (*c* 1.0, $CHCl_3$).

(*R*)-*tert*-Butyl 2-benzyl-2-hydroxy-3-[(methylsulfonyl)oxy]propanoate (13)

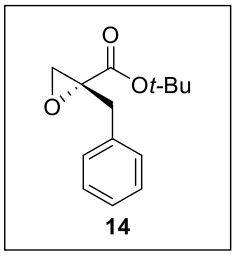


13

To a CH_2Cl_2 solution (6 ml) of **12** (150 mg, 0.59 mmol) was added MsCl (56 μl, 0.72 mmol) and Et_3N (100 μl, 0.72 mmol) at −10 °C. After stirring for 1 hour at −10 °C, reaction mixture was evaporated and the residue was diluted with EtOAc (30 ml), washed with brine (10 ml), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane : EtOAc = 4 : 1) to afford **13** (166 mg, 85% yield) as colorless oil. ^{1}H-NMR (300 MHz, CD_3OD) δ

7.29 ~ 7.21 (m, 5H), 4.45 (d, *J* = 9.98 Hz, 1H), 4.18 (d, *J* = 9.98 Hz, 1H), 3.08 (s, 3H), 3.00 (d, *J* = 13.74 Hz, 1H), 2.93 (d, *J* = 13.74 Hz, 1H), 1.41 (s, 9H) ppm; ^{13}C-NMR (125 MHz, CD_3OD) MHz, 74, 136.3, 131.6, 129.1, 128.0, 84.1, 78.1, 75.3, 42.3, 37.4, 28.1 ppm; IR (KBr) 3501, 3032, 2978, 2939, 1733, 1496, 1457, 1395, 1359, 1254, 1177, 1134, 993, 967, 837, 793, 741, 702 cm^{-1}; HRMS (FAB): calcd for $[C_{15}H_{23}O_6S]^+$ ($[M+H]^+$): 331.1215, found: 331.1212; $[\alpha]^{20}_D$ = − 3.18 (*c* 1.0, $CHCl_3$).

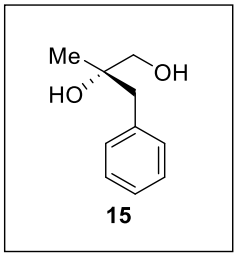
(*R*)-*tert*-Butyl 2-benzyloxirane-2-carboxylate (14)



14

To a CH_3CN solution (6 ml) of **13** (118 mg, 0.36 mmol) was added K_2CO_3 (500 mg, 3.6 mmol). The reaction mixture was refluxed for 6 hours. The reaction mixture was diluted with EtOAc (50 ml), washed with brine (10 ml x 2), 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 **14** (69 mg, 84% yield) as colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.32 ~ 7.19 (m, 5H), 3.33 (d, *J* = 14.85 Hz, 1H), 3.05 (d, *J* = 14.85 Hz, 1H), 3.00 (d, *J* = 5.87 Hz, 1H), 2.67 (d, *J* = 5.87 Hz, 1H), 1.38 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 169.0, 136.2, 129.8, 128.4, 126.9, 82.5, 57.5, 37.2, 31.1, 27.9 ppm; IR (KBr) 2979, 2932, 1738, 1496, 1456, 1393, 1369, 1304, 1257, 1215, 1157, 1122, 1076, 1032, 939, 846, 771, 736, 700 cm^{-1}; HRMS (FAB): calcd for $[C_{14}H_{19}O_3]^+$ ($[M+H]^+$): 235.1334, found: 235.1330; $[\alpha]^{20}_D$ = + 13.92 (*c* 1.0, $CHCl_3$).

(*S*)-2-methyl-3-phenylpropane-1,2-diol (15)



15

To a THF solution (0.5 ml) of epoxide **14** (9.5 mg, 0.041 mmol) was added a THF solution (0.2 ml) of $LiAlH_4$ (8 mg, 0.2 mmol) at −78 °C. The reaction solution was stirred for 1 hour and gradually raised the temperature to room temperature. The reaction was quenched by Rochelle solution (1 ml), diluted with EtOAc (10 ml), washed with brine (5 ml), dried over anhydrous $MgSO_4$, filtered, and concenturated in *vacuo*. The residue was purified by column chromatography (silica gel, hexane : EtOAc = 1 : 1) to afford **15** (6.8 mg, 99% yield) as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.35 ~ 7.22 (m, 5H), 3.51 (d, *J* = 10.8 Hz, 1H), 3.44 (d, *J* = 10.8 Hz, 1H), 2.86 (dd, *J* = 13.29 Hz, 1H), 2.79 (dd, *J* = 13.29 Hz, 1H), 1.86 (brs, OH, 1H), 1.61 (brs, OH, 1H), 1.15 (s, 3H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 137.1, 130.6, 128.6, 126.9, 73.1, 69.5, 44.9, 23.9 ppm; The spectral data were exactly same as previously reported data; $[\alpha]_D^{20}$ = –9.6 (*c* 1.0, EtOH 95%); lit[S4](*R*)-**15**, $[\alpha]_D^{20}$ = +11.4 (*c* 1.0, EtOH 95%), 94% ee.

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국 문 초 록

지난 2013년, 본 연구실은 상전이 촉매 반응을 통하여 알파-벤족시-알파-알킬말로네이트를 입체선택적으로 합성하여, 최대 99 %의 높은 화학적 수율과 93 %ee의 높은 광학적 수율을 얻은 바 있다. 그러나 본 합성법을 이용한 응용에 관한 연구는 진행이 된 바 없었으며, 입체선택적으로 합성한 알파-벤족시-알파-알킬말로네이트의 엑스레이크리스탈로그래피를 측정하여 절대배열을 알아보려 하였으나 실패하였다.

이에 본 합성법의 응용으로 다단계 반응에 걸쳐서 베타-하이드록시다이이스터, 알파,베타-다이하이드록시 이스터와 알파,베타-에폭시이스터 그리고 1,2-다이올과 같은 의약합성에 유용한 유도체를 얻을 수 있었다. 또한 1,2-다이올은 알려져 있는 화합물로서 우리가 합성한 물질의 선광도를 비교하여 알파-벤족시-알파-알킬말로네이트가 R의 절대배열을 가졌음을 확인할 수 있었다.

주요어: 입체선택적합성, 상전이 촉매 반응, 알파-벤족시-알파-알킬말로네이트

학번: 2015-21891