藥 學 碩 士 學 位 論 文

# Enantioselective synthesis of α-alkylthio-α-alkylmalonate via phase-transfer catalytic sulfenylation

# 상전이 촉매 sulfenylation 반응을 통한 α-alkylthio-α-alkylmalonate의 입체선택적 합성

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서울대학교 대학원

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# ABSTRACT

The chiral α-alkylthio-α-alkylmalonate derivative is one of the most potentially valuable intermediates to synthesize biologically active natural products and pharmaceuticals. There have been many synthetic approaches to construct sulfur-bearing quaternary chiral carbon centers, mostly by the direct sulfa-Michael addition. However, sulfenylation has many drawbacks in preparing substrates and modifying functional groups. To expand the scope of research, our research team designed a novel synthetic method for constructing sulfur-bearing chiral carbon centers by the asymmetric sulfenylation of α-alkylmalonates via phase-transfer catalysis.

Our research team recently reported the enantiomeric α-alkylation of malonates with high chemical yield and optical purity via phase-transfer catalysis for the first time and successfully proved its effectiveness through synthesizing various chiral building blocks bearing quaternary carbon centers using it. The phase-transfer catalysis occurs under relatively moderate conditions and its reagents and solvents are economical and environmentally sustainable.

The enantioselective phase-transfer catalytic sulfenylation of α-alkylmalonate was accomplished in the presence of the phase-transfer catalyst, (1*S*,2*S*,4*S*,5*R*)-2-((*R*)-(allyloxy)(6-methoxyquinolin-4-yl)methyl)-5-ethyl-1-(2,3,4-trifluorobenzyl)quinuclidin-1-ium bromide, to afford the corresponding α-alkylthio-α-alkylmalonates in high chemical (up to 97%) and optical (up to 90%) yields which can be readily converted to versatile chiral intermediates.

**Keywords:** enantioselective sulfenylation, α-alkylthio-α-alkylmalonate, asymmetric phase-transfer catalysis

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# INTRODUCTION

## 1. The characteristics of malonic esters

The malonic esters are 1,3-dicarbonyl compounds whose active methylene groups bearing relatively acidic α-protons adjacent to two electron-withdrawing carbonyl groups. Depending upon how we substitute two ester groups at both ends of the malonic ester, the chirality of α-carbon can be established and malonic ester itself can be converted to various chiral compounds. The conversion of malonic esters is not relatively hard, so they can be easily transformed into biologically active natural compounds and chiral pharmaceutical building blocks (**Figure 1**).

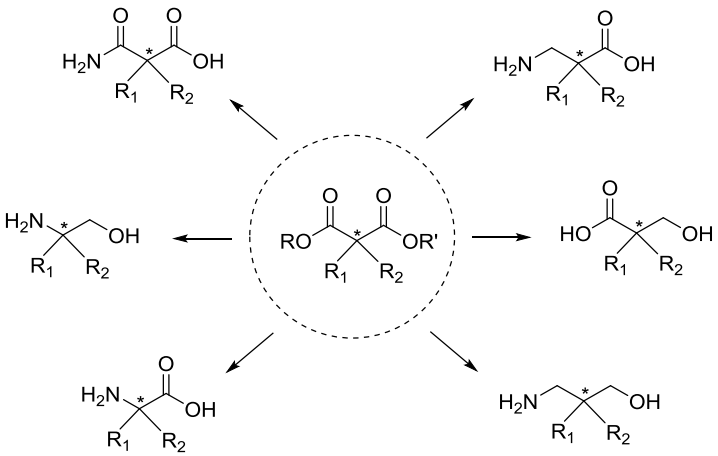



**Figure 1.** Various modification methods of malonic esters

# 2. Asymmetric phase-transfer catalysis

## 2.1. Nature of asymmetric phase-transfer catalysis

When chemical reactants are separated by two different liquid phases such as oil and water, they can't reach each other fast enough to react well. However, if we introduce the chiral phase-transfer catalyst (PTC) under appropriate conditions in this case, separated chemicals can reach each other much easier than before and react very well. The exact pathway for producing the reactive intermediate remains controversial, but it's obvious that there exists an interfacial region between two phases and chemicals in both phases can also exist in this region despite varying degrees. Once water-soluble alkaline metal base (MOH) existing in the interfacial region deprotonates the nucleophile (NuH), then water ($H_2O$) and metal enolate (MNu) are produced. There are two possible ways for the metal enolate to react (**Figure 2**[1]). First, it can generate undesired racemic product species (NuE) by directly moving to the organic phase and interacting with electrophile (EX) mainly existing there (Path A). Otherwise, the metal enolate can generate desired optically active chiral product species (*NuE) successfully when it interacts with the chiral PTC ($*Q^+X^-$) in the interfacial region right before moving to the organic phase and forms a highly reactive chiral onium enolate ($*Q^+Nu^-$) which restricts the approaching direction of electrophile and reacts with it coming from the appropriate direction (Path B). To obtain the highly enantiomerically pure chemicals (*NuE) from asymmetric phase-trasfer catalysis, the reaction speed of path B should be fast enough and the structure of chiral onium enolate ($*Q^+Nu^-$) should efficiently restrict the approaching direction of electrophile. The appropriate use of substrate, reagent, base, catalyst, solvent, and temperature can enhance the efficiency of phase-transfer catalysis. In conclusion, during phase-transfer catalysis, product compounds bearing new chiral centers can be produced and used PTCs can be reproduced continuously.

The asymmetric phase-transfer catalysis is easy-to-handle and produces good results under mild conditions. And it is safe and economical because it requires relatively inexpensive reagents and solvents. Moreover, it is environmentally sustainable because it requires no heavy-metal and less organic solvent. It is applicable to large-scale synthesis used in industrial chemistry.

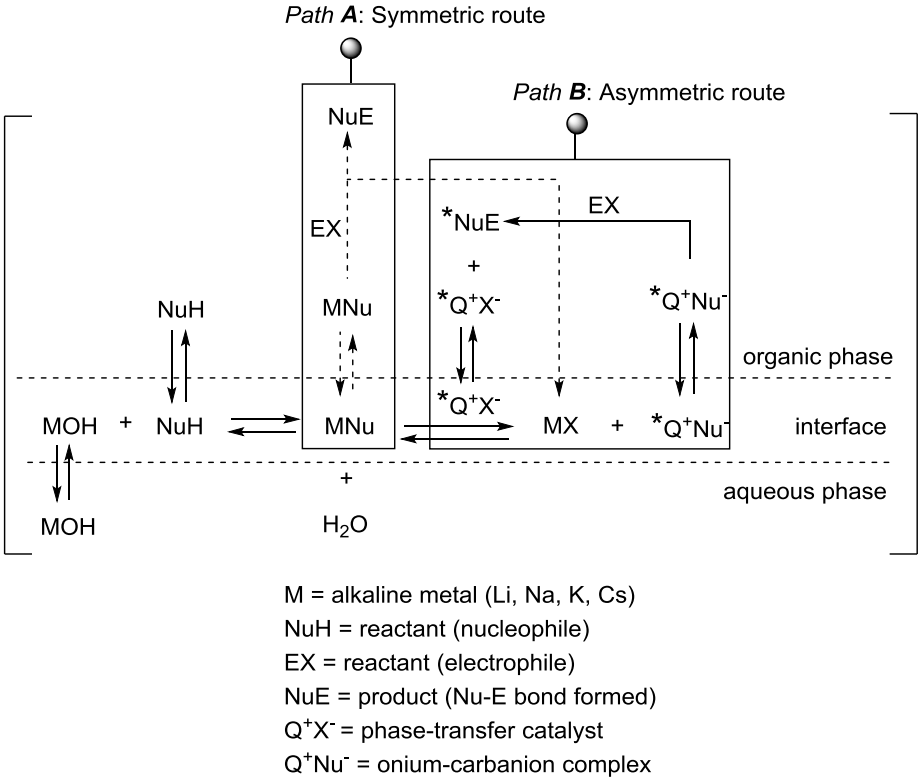
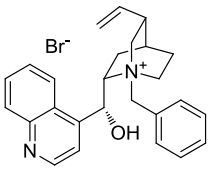



**Figure 2.** Interfacial mechanism of the asymmetric phase-transfer catalysis

## 2.2. Cinchona- and non-cinchona-class phase-transfer catalysts (PTCs)

During the phase-transfer catalysis, chiral phase-transfer catalysts (PTCs, $*Q^+X^-$) facilitate the reaction by forming ionic pairs ($*Q^+Nu^-$) with reactant salts (MNu) and PTCs make it easy for ionic pairs to migrate between organic and aqueous phase. Chiral PTCs induce the asymmetric reactions, so their roles are very important. Developed chiral PTCs until now can be divided into cinchona-(**Figure 3**) and non-cinchona-(**Figure 4**) class.

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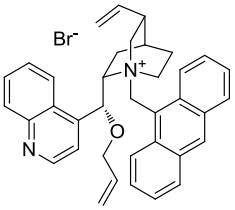


Corey, E. J. et al.,
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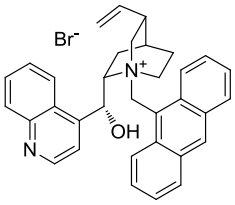


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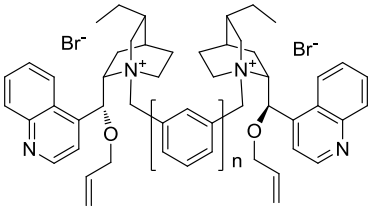


Jew, S.-s. et al., *Chem. Commun.* **2001**, 1244. (n=1)
Park, H.-g. *et al., Angew. Chem. Int. Ed*. **2002**, *41*, 3036. (n=2)

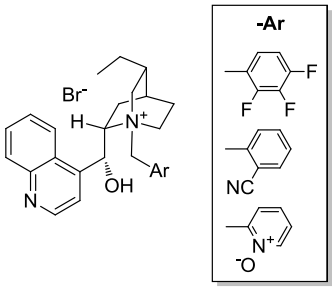


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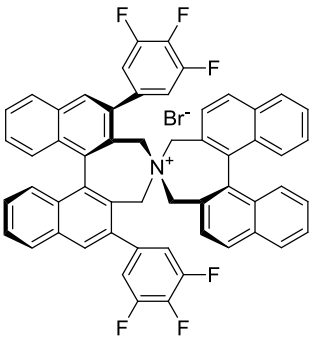
**Figure 3.** Cinchona-derived phase-transfer catalysts

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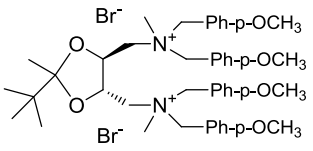


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**Figure 4.** Non-cinchona-derived phase-transfer catalysts

The well-known cinchona alkaloids, such as cinchonine, cinchonidine, quinine, and quinidine are important starting materials which can be used to develop a number of phase-transfer catalysts due to their various functional groups whose source materials are inexpensive and rather easy-to-convert. Our research team has developed several catalysts including dimers and trimers considering electronic effects and reported new PTC reactions which shows high chemical yield and optical yield using little amount of catalysts.

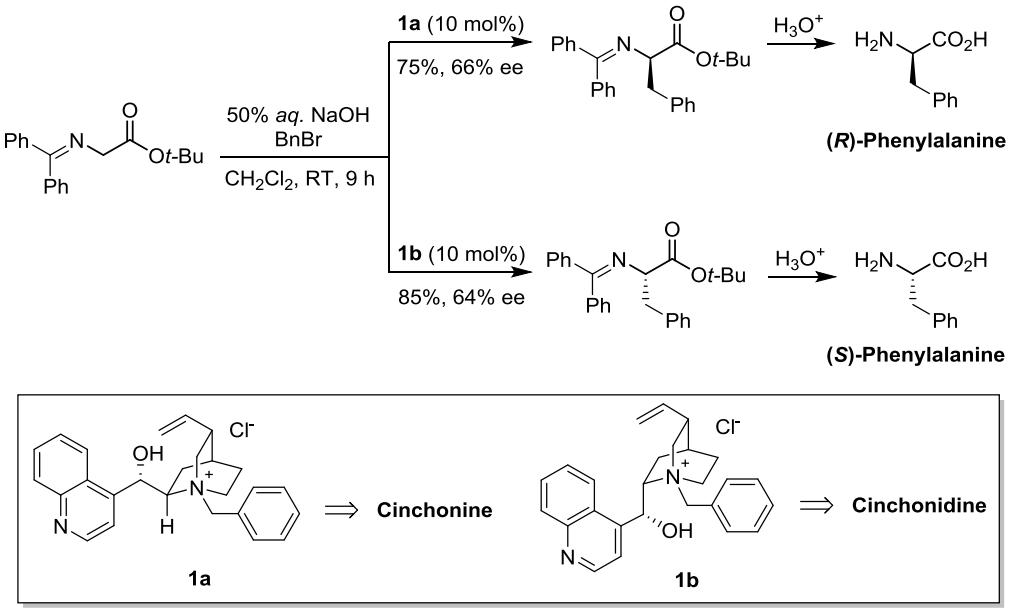
The Maruoka group[2] and the Shibasaki group[3] are well-known non-cinchona-class PTC developers. The Maruoka Group has developed them derived from binaphthols which are $C_2$-symmetric and chiral. These PTCs were applied to asymmetric alkylations, furnishing high chemical yield and optical yield.

Cinchona-class PTCs can be degraded by the Hoffmann elimination of the β-hydrogen. But non-cinchona-class PTCs are stable under basic conditions and furnish high chemical yield and optical yield. But these PTCs are rather difficult and expensive to be synthesized on a large scale

## 2.3. Asymmetric phase-transfer catalytic alkylations of the Schiff base

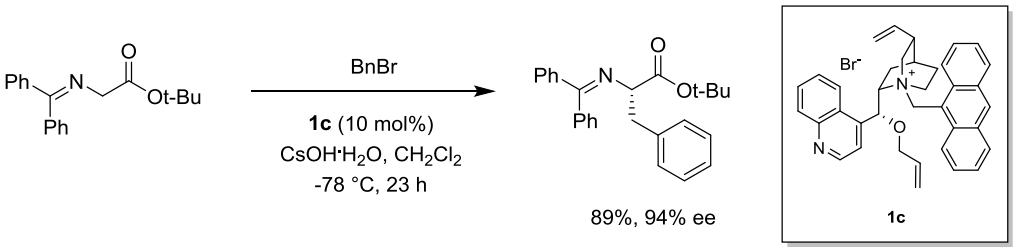
In 1978, the O'Donnell group suggested the Schiff base substrate, the *N*-(diphenylmethylene) glycine ethyl ester [4], to perform alkylation. The Schiff base showed an adequate acidity to perform reaction but involving incidental saponifications of the ethyl ester group became a problem. The diluted aqueous sodium hydroxide was used to prevent the hydrolysis.

In 1989, the O'Donnell group tested various ester groups on *N*-(diphenylmethylene) glycine ethyl ester and found the performance of *tert*-butyl ester group is excellent. So, the substrate of *N*-(diphenylmethylene) glycine *tert*-butyl ester[5] was suggested and subsequently tested on alkylations (**Scheme 1**). This substrate was stable under basic conditions, and able to use with the strong base such as BEMP, the Schwesineger base. The enatiomeric excess (ee) using this substrate was just up to 66%, but it facilitated the development of PTCs bearing cinchona alkaloid derivatives.



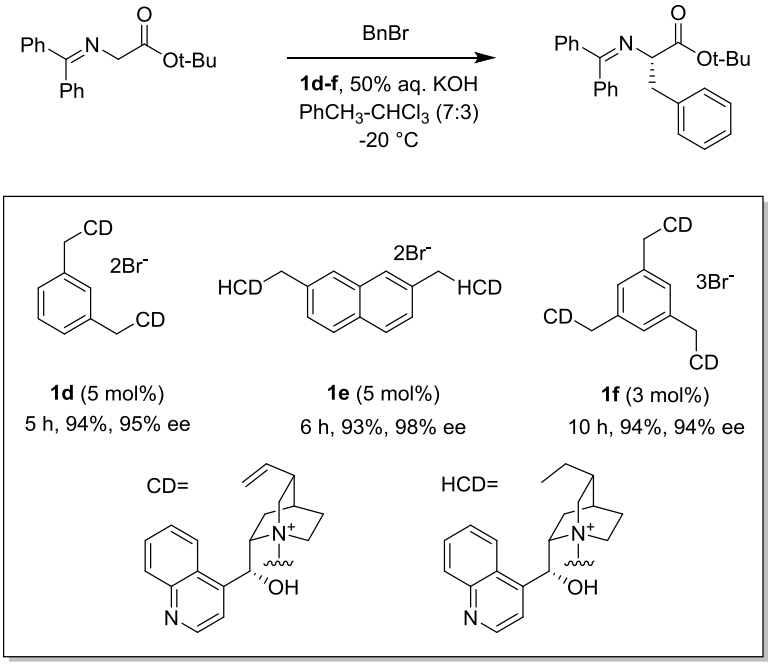

**Scheme 1.** O'Donnell's asymmetric alkylation of the glycine Schiff base

The Corey group[6] developed *O*-Allyl-*N*-anthracenylmethylcinchonidinium bromide as a new PTC, using it for the synthesis of the α-alkylglycine derivatives (**Scheme 2**).




**Scheme 2.** Corey's asymmetric alkylation of the glycine Schiff base

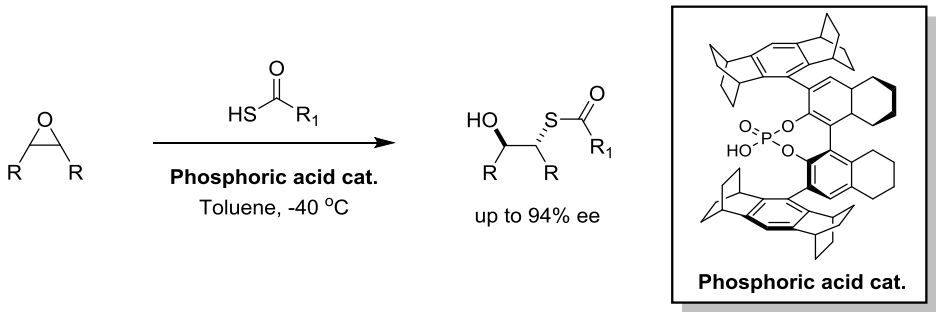
The Jew and Park[7] developed cinchona-class dimeric and trimeric PTCs attached to proper linkers and applied them to asymmetric alkylations of the glycine Schiff base substrate (**Scheme 3**).




**Scheme 3.** Jew and Park's asymmetric alkylation of the glycine Schiff base

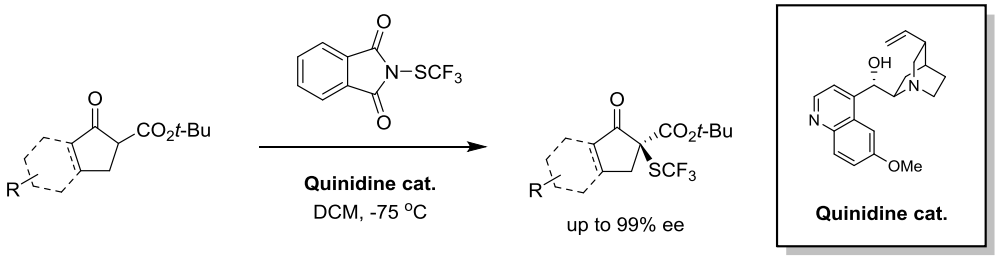
## 3. Asymmetric sulfenylations

The Benjamin group[8] developed a chiral, confined phosphoric acid catalyst and applied it to asymmetric thiocarboxylysis of the *meso*-epoxides. (**Scheme 4**).



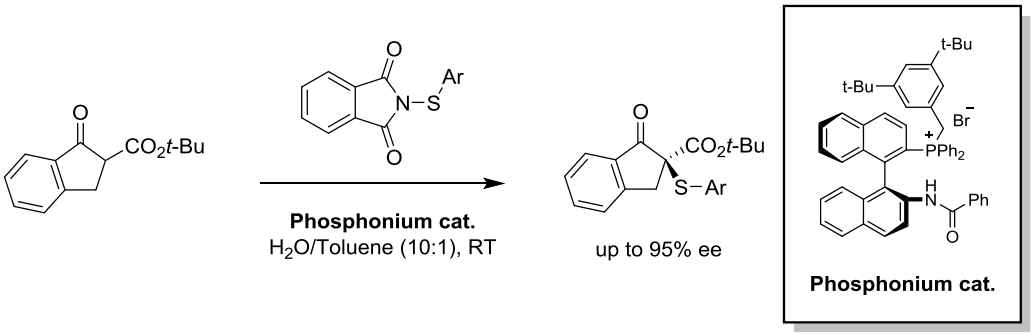

**Scheme 4.** Benjamin's asymmetric thiocarboxylysis of the *meso*-epoxides

The Magnus group[9] developed an enantioselective cinchona alkaloid catalyzed trifluoromethylsulfenylation of β-ketoesters with the *N*-(trifluoromethylthio)phthalimide as an electrophilic $SCF_3$ source. This enantioselective method enabled the construction of a quaternary chiral carbon center that bears a $SCF_3$ group. (**Scheme 5**).



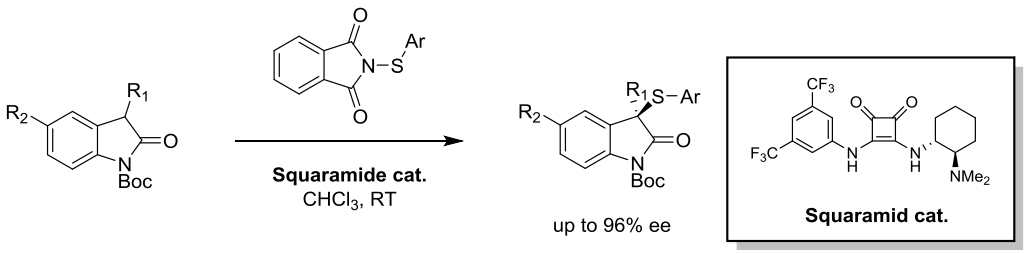

**Scheme 5.** Magnus' trifluoromethylthiolation of the β-keto esters

The Maruoka group[10] developed a novel bifunctional quaternary phophonium salt that possess amide moiety which functions as an effective chiral PTC and applied it to the enantioselective sulfenylation of the β-keto esters, using *N*-(arylthio)phthalimides (**Scheme 6**).




**Scheme 6.** Maruoka's phase-transfer arylthiolation of the β-keto esters

The Enders group[11] developed an organocatalytic, asymmetric sulfenylation of *N*-Boc-protected oxindoles by using *N*-(arylthio)phthalimides as the sulfenylating agents. This process was promoted by the use of a low catalyst loading of a squaramide, with a hydrogen-bonding activation mode furnishing the products. (**Scheme 7**).

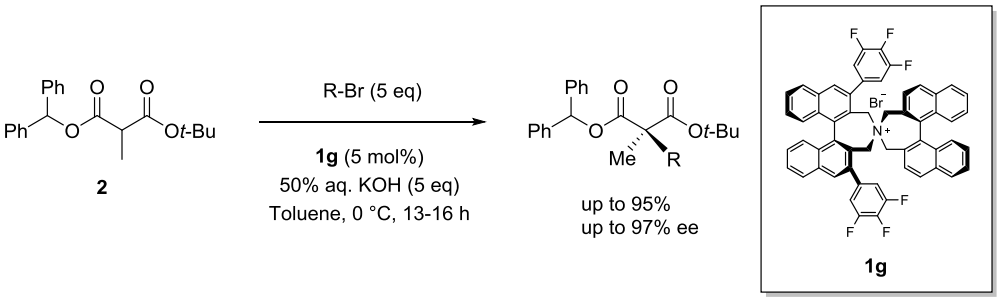



**Scheme 7.** Enders' arylthiolation of the *N*-Boc-protected oxindoles

# RESULTS AND DISCUSSION

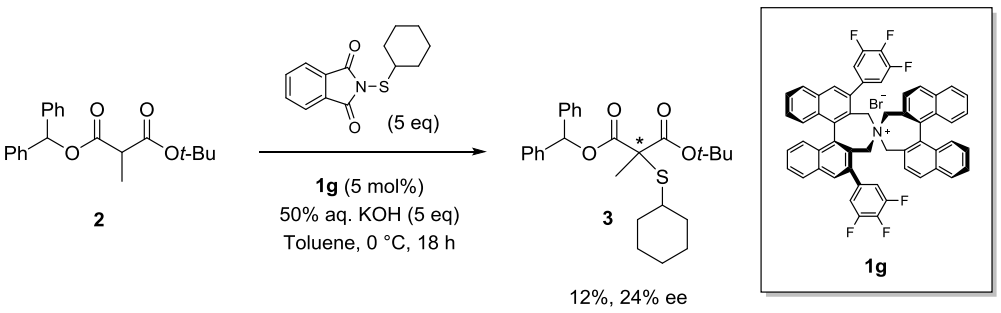
## 1. The design of a novel substrate for asymmetric sulfenylations

Our research team [12] developed the 1-benzhydryl 3-(*tert*-butyl) 2-methylmalonate **2** as a substrate for the asymmetric phase-transfer catalytic alkylation (**Scheme 8**).



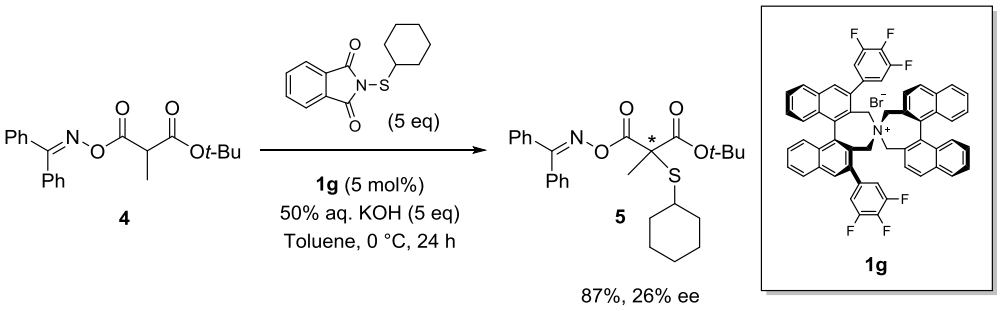

**Scheme 8.** A new asymmetric phase-transfer catalytic alkylation

We designed a model study of asymmetric phase-transfer catalytic sulfenylation, only trying another commercially available electrophile, *N*-(cyclohexylthio)phthalimide instead of the alkyl bromide, keeping other reaction conditions same (**Scheme 9**).



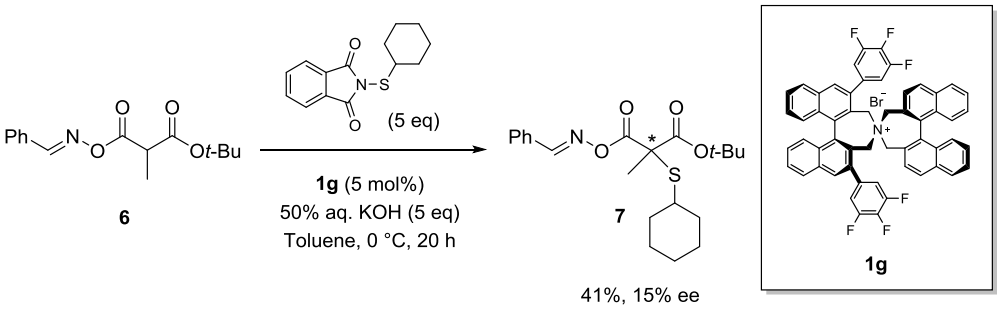

**Scheme 9.** Model study of the asymmetric phase-transfer catalytic sulfenylation

Recently, our research group has developed a malonate substrate for the asymmetric phase-transfer catalytic alkylation whose results have not been published yet. The concept of benzhydrylideneamino[5] functional group was introduced to the substrate for the facile hydrolysis. So we tried the compound **4** containing benzhydrylideneamino group as a novel substrate for the asymmetric phase-transfer catalytic sulfenylation (**Scheme 10**).




**Scheme 10.** The 2nd model study of the asymmetric phase-transfer catalytic sulfenylation

We tried another compound **6** containing *(E)*-benzylideneamino functional group as a substrate for the asymmetric phase-transfer catalytic sulfenylation, but it showed lower chemical yield and ee (**Scheme 11**). Thus, the compound **4** was finally selected as a novel substrate for the asymmetric phase-transfer catalytic sulfenylation.



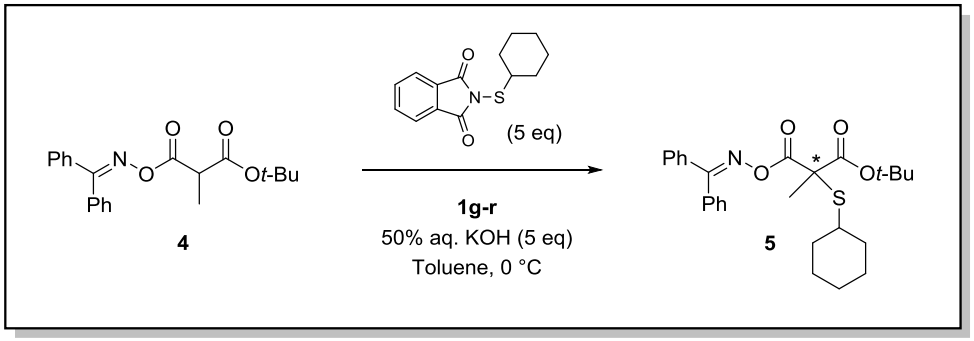

**Scheme 11.** The 3rd model study of the asymmetric phase-transfer catalytic sulfenylation

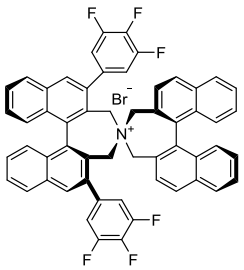
## 2. Enantioselective phase-transfer catalytic sulfenylation of the benzhydrylideneamino *tert*-butyl malonate

### 2.1. Optimization of phase-transfer catalytic sulfenylation

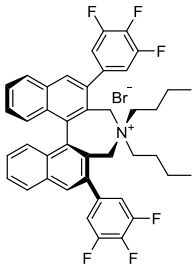
For the optimization of the phase-transfer catalytic sulfenylation, our previous reaction conditions were adapted. The enantioselective phase-transfer catalytic sulfenylation of the preliminary substrate **4** was performed by the representative chiral phase-transfer catalysts (**Scheme 12**). 5 eq. of *N*-(cyclohexylthio)phthalimide, 5 eq. of 50% aqueous potassium hydroxide and toluene was used at 0 ℃. When the hydroquinine-based phase-transfer catalyst **1q** was used, it showed the result of 90% chemical yield and 76% ee, so **1q** was selected as a catalyst. Surprisingly, the only structural difference between **1p** and **1q** was just the existence of one methoxy group, but the difference in ee between them was 30%.

**Scheme 12.** Screening of the PTCs

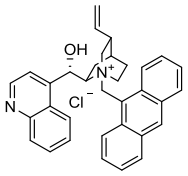




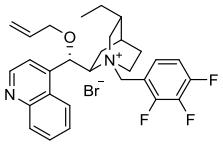
**1g** (5 mol%)
24 h, 87%, 26% ee



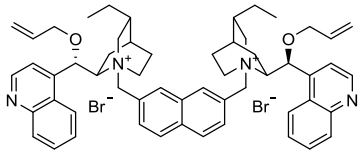
**1h** (5 mol%)
24 h, 78%, 16% ee



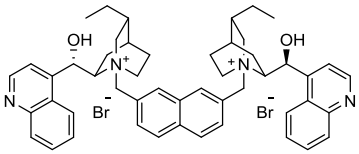
**1i** (10 mol%)
23 h, 36%, 34% ee



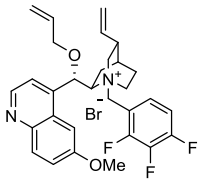
**1j** (10 mol%)
17 h, 86%, 58% ee



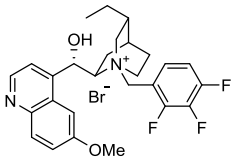
**1k** (10 mol%)
24 h, 44%, 1% ee



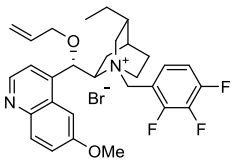
**1l** (10 mol%)
26 h, 35%, 15% ee



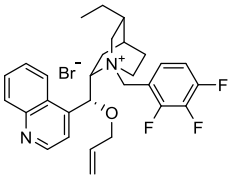
**1m** (10 mol%)
5 h, 87%, 31% ee



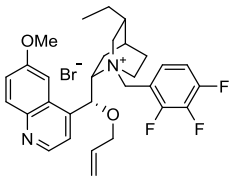
**1n** (10 mol%)
3 h, 59%, 24% ee



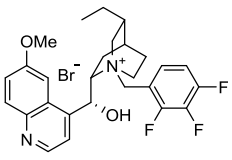
**1o** (10 mol%)
7 h, 90%, 32% ee



**1p** (10 mol%)
17 h, 86%, 46% ee



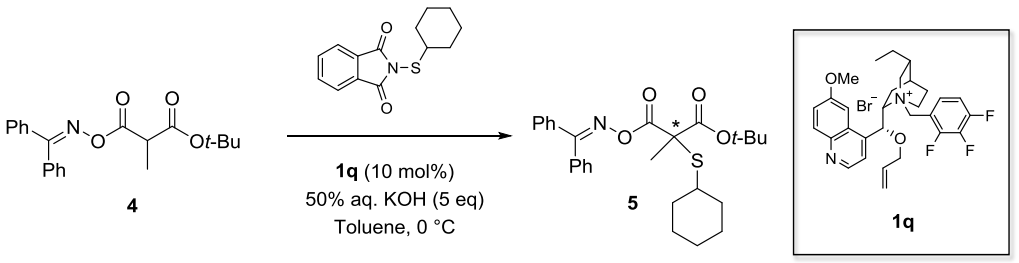
**1q** (10 mol%)
5 h, 90%, 76% ee



**1r** (10 mol%)
5 h, 48%, 57% ee

Then, we optimized the equivalent of electrophile (**Table 1**). 1.25 eq. of *N*-(cyclohexylthio)phthalimide showed the best result and it was chosen.

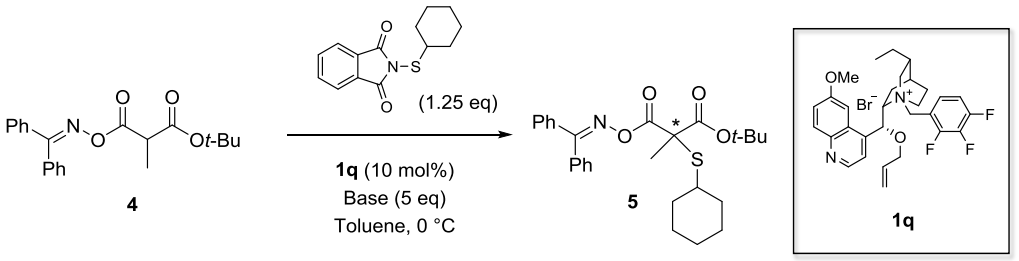
**Table 1.** Optimization of the equivalent of electrophile, *N*-(cyclohexylthio)phthalimide




| Entry | Eq. of *N*-(cyclohexylthio)phthalimide | Time | Yield (%) | ee (%) |
|---|---|---|---|---|
| 1 | 5 | 5 h | 90 | 76 |
| 2 | 2.5 | 6 h | 89 | 81 |
| 3 | 1.25 | 7 h | 91 | 81 |

Next, we optimized the base condition (**Table 2**). When solid potassium hydroxide was used, reaction was finished soon but byproducts were observed on thin-layer chromatography (TLC) plates. 50% aqueous potassium hydroxide showed the best result and it was subsequently selected.

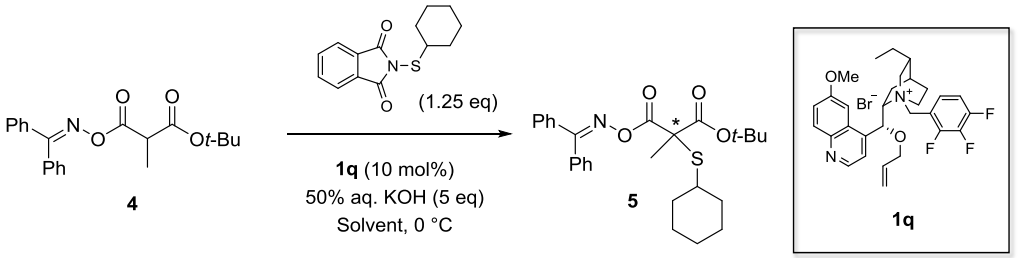
**Table 2.** Optimization of the base



| Entry | Base | Time | Yield (%) | ee (%) |
|---|---|---|---|---|
| 1 | 50% aq. NaOH | 10 h | 91 | 81 |
| 2 | 50% aq. KOH | 7 h | 91 | 81 |
| 3 | 50% aq. CsOH | 10 h | 87 | 80 |
| 4 | Solid KOH | 7 h | 81 | 82 |

Thus, we optimized the solvent (**Table 3**). When using ether solvents such as tetrahydrofuran and diethyl ether, the reaction was finished in such a short time, but chemical yield and ee were rather low. Toluene showed the best result, so it was selected.

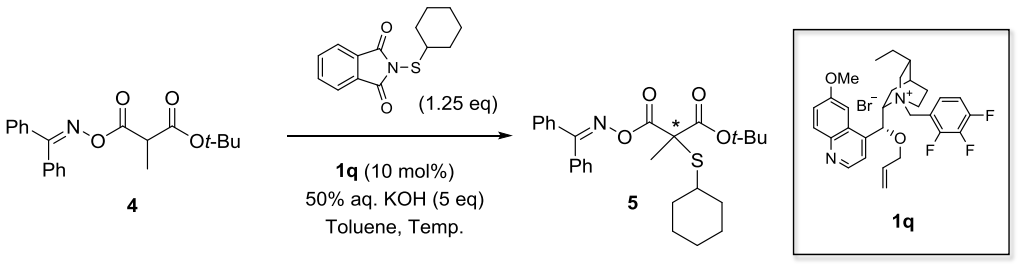
**Table 3.** Optimization of the solvent




| Entry | Solvent | Time | Yield (%) | ee (%) |
|---|---|---|---|---|
| 1 | Toluene | 7 h | 91 | 81 |
| 2 | Dichloromethane | 26 h | 13 | 23 |
| 3 | Tetrahydrofuran | 2 h | 79 | 24 |
| 4 | Diethyl ether | 2 h | 77 | 76 |

Finally, the temperature was optimized (**Table 4**). At -60 ℃, 93% ee was observed but it took so long to be finished. At -40 ℃, it showed relatively high ee and the highest chemical yield among them, so we selected -40 ℃.

**Table 4.** Optimization of the temperature



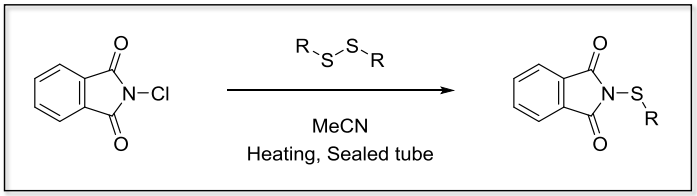

| Entry | Temperature (℃) | Time | Yield (%) | ee (%) |
|---|---|---|---|---|
| 1 | 0 | 7 h | 91 | 81 |
| 2 | -20 | 20 h | 98 | 85 |
| 3 | -40 | 40 h | 92 | 90 |
| 4 | -60 | 7 d | 80 | 93 |

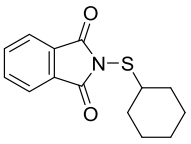
We decided to apply the reaction condition of the benzhydrylideneamino *tert*-butyl malonic ester substrate **4** with the 5 eq. of electrophile, the *N*-(Alkylthio)phthalimide, 10 mol% of chiral phase-transfer catalyst **1q**, 5 eq of 50% aqueous potassium hydroxide, and toluene for further sulfenylations.

## 2.2. The enantioselective phase-transfer catalytic sulfenylations with several electrophiles

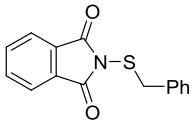
First of all, we synthesized *N*-(alkylthio)phthalimides[13] using symmetric disulfides except commercially available *N*-(cyclohexylthio)phthalimide **8** (**Scheme 13**).

**Scheme 13.** Synthesis of *N*-(alkylthio)phthalimides

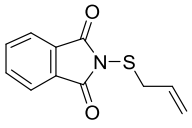


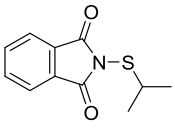
**8**



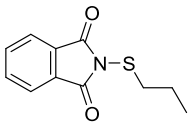

**9**
**24 h, 45%**




**10**
**6 h, 52%**



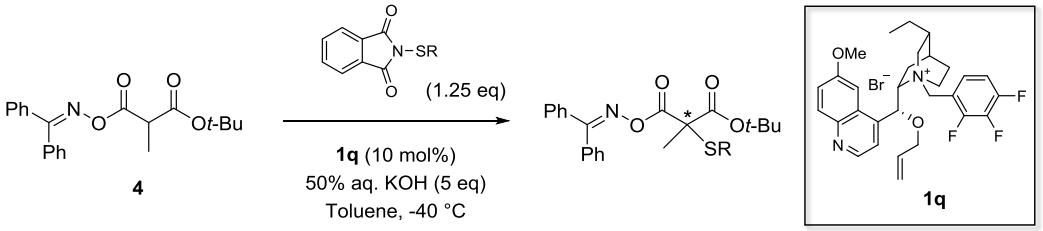

**11**
**25 h, 45%**

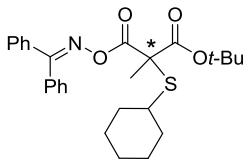



**12**
**15 h, 18%**

Next, we enantioselectively sulfenylated the benzhydrylideneamino *tert*-butyl malonate substrate **4** via asymmetric phase-transfer catalysis using *N*-(alkylthio)phthalimides as electrophiles (**Scheme 14**).

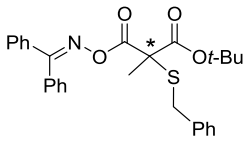
**Scheme 14.** Enantioselective phase-transfer catalytic sulfenylation with *N*-(alkylthio)phthalimides



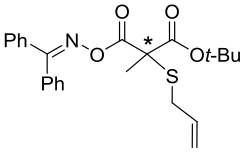

**5**

**40 h, 92%, 90% ee**



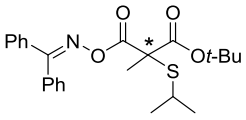

**13**

**17 h, 97%, 61% ee**



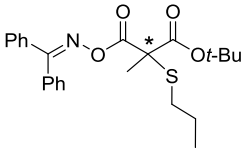

**14**

**18 h, 91%, 70% ee**




**15**

**16 h, 85%, 85% ee**




**16**

**18 h, 77%, 76% ee**

## 3. The application of α-alkylthio-α-alkylmalonates

Under optimized conditions, the phase-transfer catalytic sulfenylation using several electrophiles was performed successfully. Benzhydrylideneamino malonic esters can be easily hydrolyzed without loss of chirality in chiral center. Once hydrolyzed, various functional group, and by subsequent process, it can be oxidized to sulfide, sulfoxide, sulfone and so on (**Figure 5**).

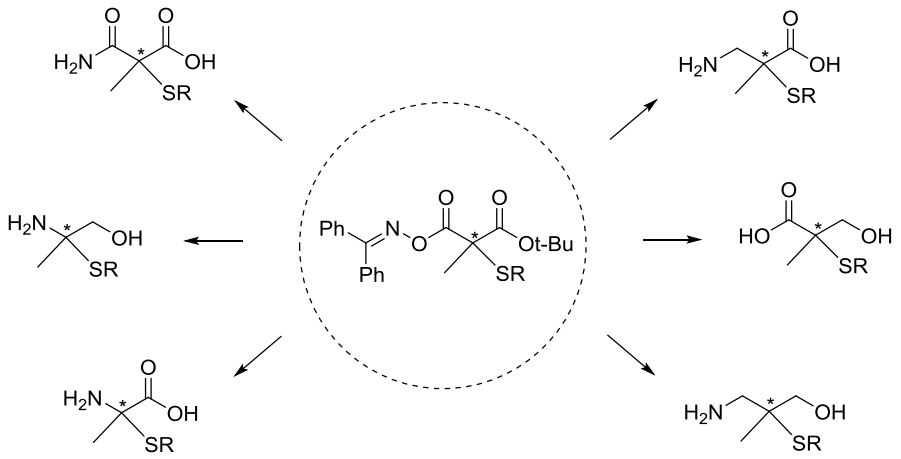
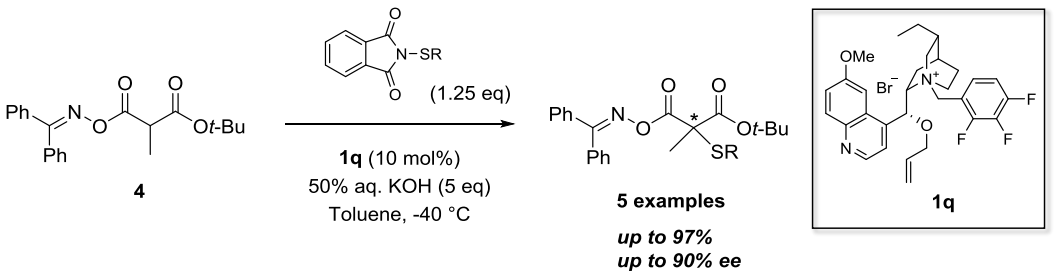



**Figure 5.** Modification methods of α-alkylthio-α-alkylmalonates

Thus, α-alkylthio-α-alkylmalonates can be used as useful building blocks of the synthesis of biologically active natural products and pharmaceuticals. Studies on conversions and applications of α-alkylthio-α-alkylmalonates are currently being investigated.

# CONCLUSION

A novel asymmetric synthetic method to prepare α-alkylthio-α-alkylmalonates for the construction of sulfur-bearing quaternary chiral carbon center via phase-transfer catalytic sulfenlyation has been developed. Malonate derivatives using benzhydrylideneamino group and benzylideneamino group substrates were designed and optimized for furnishing more enantioselective results. Finally we have developed enantioselective synthesis of α-alkylthio-α-alkylmalonate via phase-transfer catalytic sulfenylation in the presence of the chiral phase-transfer catalyst (1*S*,2*S*,4*S*,5*R*)-2-((*R*)-(allyloxy)(6-methoxyquinolin-4-yl)methyl)-5-ethyl-1-(2,3,4-trifluorobenzyl)quinuclidin-1-iumbromide **1q** afforded the corresponding α-alkylthio-α-alkylmalonates in high chemical (up to 97%) and optical (up to 90%) yields at -40 ℃, which can be readily modified to versatile chiral intermediates.




**Scheme 15.** Enantioselective phase-transfer catalytic sulfenylation of a novel benzhydrylideneamino malonate substrate

Our newly developed catalytic system provides attractive synthetic methods for versatile chiral building blocks which can be readily converted to chiral target compounds including sulfur-bearing quaternary chiral carbon centers.

# 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. As the commercially available KOH was a pellet type, solid KOH should be grinded to the powder form. 50% w/v aqueous KOH was used as stock solution from markets.

### 1.2. Chromatography

Analyses using thin-layer chromatography (TLC) were performed using Merck precoated TLC plate (silica gel 60 $GF_{254}$, 0.25 mm). Flash column chromatography was performed using E. Merck Kieselgel 60 (230~400 mesh). Instrument (Hitachi, L-2130) and (Hitachi, Version LaChrom 8908800-07) were used as high-performance liquid chromatography (HPLC) apparatus. The values of the products' enantiomeric excess (ee) were determined by HPLC using 4.6 mm × 250 mm Daicel Chiralpak AD-H, Chiralpak AS-H, Chiralcel OD-H or Chiralcel OJ-H columns.

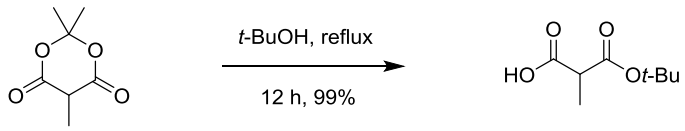
### 1.3. Spectral data

Infrared (IR) spectra recorded on a JASCO FT/IR-300E and Perkin-Elmer 1710 FT

spectrometer. Nuclear magnetic resonance ($^{1}$H-NMR and $^{13}$C-NMR) spectra were measured on JEOL JNM-LA 300 [300 MHz ($^{1}$H), 75 MHz ($^{13}$C)] spectrometer, JEOL JNM-GSX 400 [400 MHz ($^{1}$H), 100 MHz ($^{13}$C)] spectrometer, and Bruker AMX 500 [500 MHz ($^{1}$H), 125 MHz ($^{13}$C)] spectrometer, using $CHCl_3$-*d*, DMSO-$d_6$ or $CH_3OH$-$d_4$ as solvents, were reported in ppm relative to $CHCl_3$ (δ 7.24), DMSO (δ 2.5), and $CH_3OH$ (δ 3.3) for $^{1}$H-NMR and relative to the central $CHCl_3$ (δ 77.23), DMSO (δ 39.52), and $CH_3OH$ (δ 49.15) resonance for $^{13}$C-NMR. Coupling constants (*J*) in $^{1}$H-NMR, $^{13}$C-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 spectrometer. Optical rotations were measured on a JASCO polarimeter P-2000 series. Melting points were measured on a Büchi B-540 melting point apparatus and were not corrected.

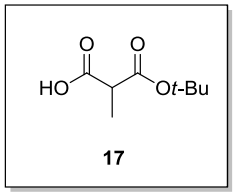
# 2. α-Alkylthio-α-alkylmalonates

## 2.1. Preparation of α-alkylmalonate substrate



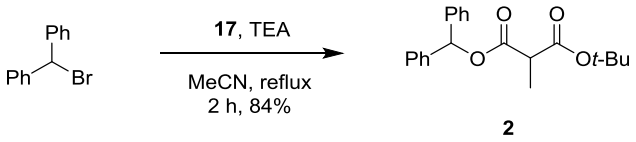

**17**

**3-(*tert*-Butoxy)-2-methyl-3-oxopropanoic acid (17)**

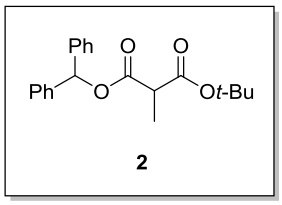



**17**

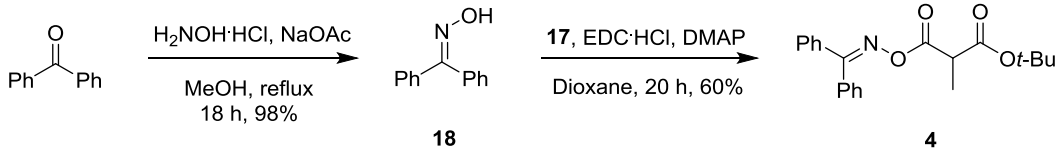
Methyl Meldrum's acid (2.0 g, 12.6 mmol) was added to *tert*-Butyl alcohol (40 mL, 700 mmol). After the reaction mixture being stirred for 5 minutes, it was refluxed for 40 hours, evaporated and concentrated *in vacuo* to afford **17** as colorless oil (2.19 g, 12.6 mmol, 99% yield). $^{1}$H-NMR (300 MHz, $CDCl_3$) δ 11.5 (s, 1H), 3.31 (q, *J* = 7.26 Hz, 1H), 1.37 (s, 9H), 1.32 (d, *J* = 7.35 Hz, 3H) ppm; $^{13}$C-NMR (75 MHz, $CDCl_3$) δ 175.54, 169.19, 82.06, 46.87, 27.75, 13.48 ppm; IR (KBr) 3104, 2982, 2943, 2726, 2639, 1732, 1716, 1458, 1415, 1394, 1370, 1321, 1284, 1250, 1154, 1085, 1024, 927, 912, 840, 747, 672 $cm^{-1}$; HRMS (FAB): calcd. for $[C_8H_{15}O_4]^+$ ($[M+H]^+$): 175.0970 , found : 175.0967.




**Benzhydryl 3-(*tert*-butyl) 2-methylmalonate (2)**

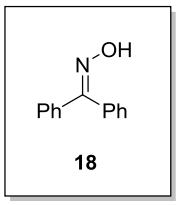



Triethylamine (468.1 μL, 3.36 mmol) was added to a stirred solution of 3-(*tert*-butoxy)-2-methyl-3-oxopropanoic acid (**17**, 531.8mg, 3.05 mmol) in acetonitrile (15.5 mL). α-bromodiphenylmethane (920.6 mg, 3.36 mmol) was added to the reaction mixture. After being refluxed for 2 hours, the reaction mixture was evaporated, diluted with EtOAc (30 mL), quenched with ammonium chloride (15 mL), washed with brine (15 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, hexane : EtOAc = 40 : 1) to afford **2** (8.72g, 84% yield) as pale yellow oil [12]. $^1$H-NMR (300 MHz, $CDCl_3$) δ 7.32~7.25 (m, 10H), 6.90 (s, 1H), 3.42 (q, *J* = 7.21 Hz, 1H), 1.38 (d, *J* =7.14 Hz, 3H), 1.33 (s, 9H) ppm; $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 169.10, 168.67, 139.66, 128.28, 128.23, 127.82, 127.72, 127.08, 126.89, 81.44, 77.26, 47.19, 27.55, 13.35 ppm; IR (KBr) 2980, 1749, 1730, 1496, 1455, 1369, 1248, 1147, 1079, 1026, 966, 849, 744, 699 $cm^{-1}$; HRMS (FAB): calcd. for $[C_{21}H_{24}O_4Na]^+$ ($[M+H]^+$): 363.1572, found: 363.1562.



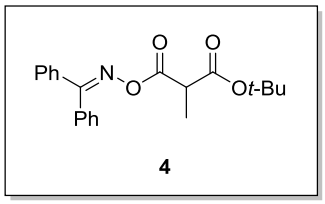

18 4

**Diphenylmethanone oxime (18)**



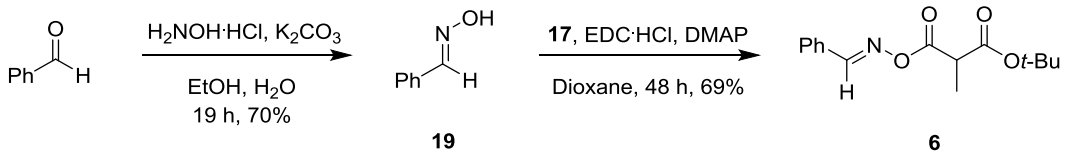
Hydroxylamine hydrochloride (877.1 mg, 12.6 mmol) and sodium acetate (1125.4 mg, 13.7 mmol) were added to a stirred solution of benzophenone (1.0 g, 5.5 mmol) in methanol (20 mL). After being refluxed for 18 hours, it was diluted with EtOAc (40 mL), and washed with brine (10 mL × 3), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to afford **18** (1066 mg, 98%) as white solid. $^1$H-NMR (300 MHz, DMSO) δ 11.35 (s, 1H), 7.48 ~ 7.27 (m, 10H) ppm; $^{13}$C-NMR (75 MHz, DMSO) δ 155.01, 136.71, 133.47, 128.83, 128.76, 128.30, 128.25, 128.06, 126.91 ppm; IR (KBr) 3725, 3273, 3058, 2349, 1494, 1444, 1330, 1162, 998, 934, 920, 785, 766, 697, 660 $cm^{-1}$; HRMS (FAB): calcd. for $[C_{13}H_{12}NO]^+$ ($[M+H]^+$): 198.0919, found : 198.0921; m.p.= 125.4 ℃.

***tert*-Butyl 3-(((diphenylmethylene)amino)oxy)-2-methyl-3-oxopropanoate (4)**

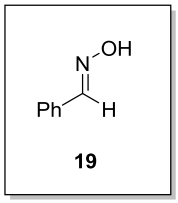


Ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (1978.1 mg, 10.32 mmol) were added to a stirred solution of 3-(*tert*-Butoxy)-2-methyl-3-oxopropanoic acid **17** (898.8 mg, 5.16 mmol) in 1,4-dioxane (17 mL). After 5 minutes, 4-dimethylaminopyridine (63.0 mg, 0.52 mmol) and diphenylmethanone oxime **18** (814.1 mg, 4.13 mmol) were consecutively added to the reaction mixture. After being refluxed for 20 hours, it was diluted with EtOAc (40 mL), and washed with brine (10 mL × 3), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, hexane : acetone = 25 : 1) to afford **4** (1118.2 mg, 60% yield) as white solid. $^1$H-NMR (300 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.86 Hz, 2H), 7.48 ~ 7.42 (m, 4H), 7.39 ~ 7.31 (m,

4H), 3.42 (q, $J$ = 7.32 Hz, 1H), 1.37 (s, 9H), 1.34 (s, 3H) ppm; $^{13}$C-NMR (75 MHz, $CDCl_3$) δ 168.41, 165.00, 134.48, 132.11, 130.94, 129.68, 128.86, 128.12, 81.83, 46.15, 27.74, 13.45 ppm; IR (KBr) 2981, 1774, 1733, 1446, 1328, 1159, 1076, 1031, 985, 917, 877, 848, 781, 697, 647 cm$^{-1}$; HRMS (FAB): calcd. for $[C_{21}H_{24}NO_4]^+$ ($[M+H]^+$): 354.1705, found: 354.1703; m.p.= 83.5 ℃.

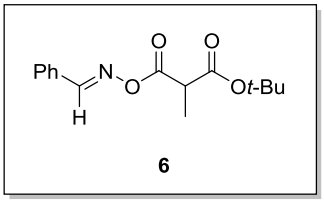



**(*E*)-Benzaldehyde oxime (19)**




Potassium carbonate (1966.4 mg, 14.2 mmol) and benzaldehyde (961.5 μL, 7.11 mmol) were consequently added to a stirred solution of hydroxylamine hydrochloride (988.7 mg, 14.2 mmol) in ethanol (5 mL). After 3 minutes, water (10 mL) was added to the reaction mixture. After being refluxed for 19 hours, it was diluted with EtOAc (40 mL), and washed with brine (10 mL × 3), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, hexane : EtOAc = 10 : 1) to afford **19** (794.9 mg, 70%) as white solid. $^1$H-NMR (300 MHz, DMSO) δ 11.31 (s, 1H), 8.17 (s, 1H), 7.60 (dd, $J_1$ = 7.56Hz, $J_2$ = 2.19Hz, 2H), 7.40~7.32(m, 3H) ppm; $^{13}$C-NMR (75 MHz, DMSO) δ 148.34, 130.54, 129.61, 129.39, 128.83, 128.51 ppm; IR (KBr) 3312, 3064, 3029, 2983, 2897, 1955, 1812, 1632, 1602, 1577, 1494, 1445, 1305, 1290, 121, 1177, 158, 1085, 952, 871, 846, 755, 691, 645 cm$^{-1}$; HRMS (FAB): calcd. for $[C_7H_8NO]^+$ ($[M+H]^+$): 126.0606, found: 126.0607; m.p.= 31.8 ℃.

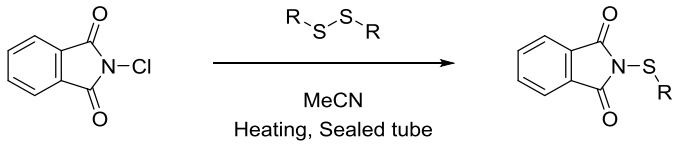
***tert*-Butyl (*E*)-3-((benzylideneamino)oxy)-2-methyl-3-oxopropanoate (6)**



**6**

Ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (1978.1 mg, 10.32 mmol) were added to a stirred solution of 3-(*tert*-Butoxy)-2-methyl-3-oxopropanoic acid **17** (898.8 mg, 5.16 mmol) in 1,4-dioxane (17 mL). After 5 minutes, 4-dimethylaminopyridine (63.0 mg, 0.52 mmol) and (*E*)-benzaldehyde oxime **19** (500 mg, 4.13 mmol) were consecutively added to the reaction mixture. After it being refluxed for 48 hours, diluted with EtOAc (40 mL), and washed with brine (10 mL × 3), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, hexane : acetone = 15 : 1) to afford **6** (785.8 mg, 69% yield) as white solid. $^1$H-NMR(300 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.73 ~ 7.70 (m, 2H), 7.50 ~ 7.35 (m, 3H), 3.54 (q, *J* = 7.32 Hz, 1H), 1.47 (d, *J* = 7.32Hz, 3H), 1.40(s, 9H) ppm; $^{13}$C-NMR (150 MHz, $CDCl_3$) δ 168.51, 168.32, 156.14, 131.79, 129.82, 128.87, 128.39, 82.01, 46.12, 27.82, 13.50 ppm; IR (KBr) 2980, 2941, 2348, 1773, 1732, 1614, 1575, 1455, 1394, 1370, 1330, 1255, 1213, 1162, 1076, 951, 912, 872, 849, 757, 693, 642 $cm^{-1}$; HRMS (FAB): calcd. for $[C_{15}H_{20}NO_4]^+$ ($[M+H]^+$): 278.1392, found: 278.1393; m.p.= 62.0 ℃.

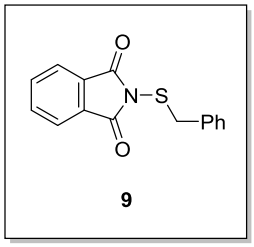
## 2.2 General procedure for synthesis of *N*-(alkylthio)phthalimides




**9-12**

One of the symmetric disulfides (4.4 mmol) was added to a stirred solution of *N*-chlorophthalimide (2.2 mmol) in acetonitrile (15 mL) in a sealed tube, and heated at 100 ℃ overnight. After being cooled to room temperature, the solvent was evaporated. The residue was purified by flash column chromatography (silica gel, hexane : acetone = 15 : 1) to afford *N*-(alkylthio)phthalimides [13].

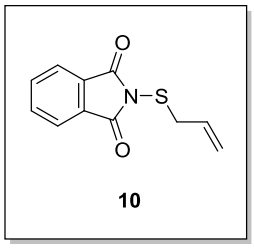
**<u>*N*-(Benzylthio)phthalimide (9)</u>**




**9**

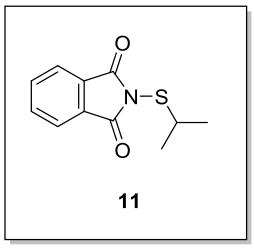
Following the procedure, **9** was obtained as pale yellow solid (45% yield). $^{1}$H-NMR (300 MHz, $CDCl_3$) δ 7.87 ~ 7.83 (m, 2H), 7.78 ~ 7.72 (m, 2H), 7.30 ~ 7.20 (m, 5H), 4.12 (s, 2H), ppm; $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 167.87, 134.46, 134.18, 131.80, 129.45, 128.57, 127.83, 123.72, 42.37 ppm; IR (KBr) 1744, 1715, 1647, 1608, 1220, 867, 772, 706, 650 $cm^{-1}$; HRMS (FAB): calcd. for $[C_{15}H_{11}NO_2S]^+$ ($[M+H]^+$): 270.0589, found: 270.0591; m.p.= 163.2 ℃.

***N*-(Allylthio)phthalimide (10)**



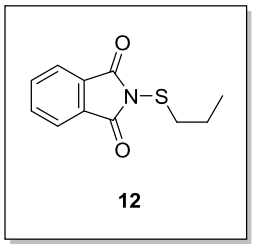

Following the procedure, **10** was obtained as pale yellow solid (52% yield). $^{1}$H-NMR (300 MHz, $CDCl_3$) δ 7.94 ~ 7.89 (m, 2H), 7.81 ~ 7.77 (m, 2H), 5.97 ~ 5.83 (m, 1H), 5.01 ~ 4.93 (m, 2H), 3.54 ~ 3.52 (d, *J* = 3.7 Hz, 2H) ppm; $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 168.30, 134.54, 131.87, 131.57, 123.79, 119.82, 41.53 ppm; IR (KBr) 1745, 1715, 1680, 1647, 1220, 772 $cm^{-1}$; HRMS (FAB): calcd. for $[C_{11}H_{10}NO_2S]^+$ ($[M+H]^+$): 220.0432, found: 220.0437; m.p.= 90.8 ℃.

***N*-(Isopropylthio)phthalimide (11)**



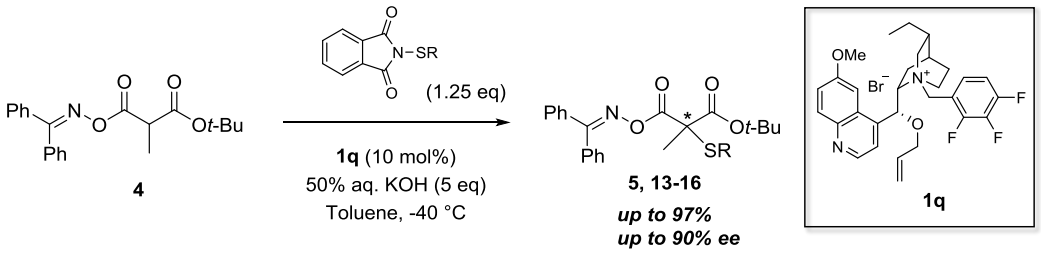

Following the procedure, **11** was obtained as pale red solid (45% yield). $^{1}$H-NMR (300 MHz, $CDCl_3$) δ 7.97 ~ 7.91 (m, 2H), 7.83 ~ 7.77 (m, 2H), 3.54 ~ 3.40 (septet, J = 6.7 Hz, 1H) 1.29 (s, 3H), 1.26 (s, 3H); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 168.69, 134.55, 131.95, 123.84, 41.25, 20.87 ppm; IR (KBr) 1785, 1742, 1714, 1220, 867, 772, 714, 687, 674 $cm^{-1}$; HRMS (FAB): calcd. for $[C_{11}H_{12}NO_2S]^+$ ($[M+H]^+$): 222.0589, found: 222.0588; m.p.= 72.6 ℃.

***N*-(n-Propylthio)phthalimide (12)**



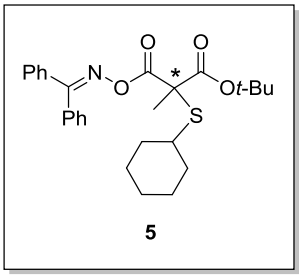

Following the procedure, **12** was obtained as pale yellow solid (18% yield). $^{1}$H-NMR (300 MHz, $CDCl_3$) δ 7.95 ~ 7.90 (m, 2H), 7.82 ~ 7.77 (m, 2H), 2.88 ~ 2.84 (m, 2H), 1.68 ~ 1.56 (sextet, *J* = 6.1 Hz, 2H), 1.06 ~ 1.01 (t, *J* = 7.3 Hz, 3H) ppm; $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 168.77, 167.90, 134.76, 132.28, 131.11, 129.03, 124.06, 40.86, 21.88, 13.20 ppm; IR (KBr) 1786, 1741, 1714, 1609, 1283, 867, 772, 714 $cm^{-1}$; m.p.= 78.2 ℃.

## 2.3 General procedure for asymmetric phase-transfer catalytic sulfenylation




*N*-(Alkylthio)phthalimide (1.25 eq.) and phase-transfer catalyst **1q** (10 mol%) were added to a solution of *tert*-Butyl 3-(((diphenylmethylene)amino)oxy)-2-methyl-3-oxopropanoate **4** (10 mg) in toluene (1 mL) at -40 ℃. After being cooled to designated low temperature, 50% aqueous potassium hydroxide (5 eq.) was added to the reaction mixture. After the starting material disappeared, the reaction mixture was diluted with EtOAc (10 mL), washed with brine (5 mL × 3), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, hexane : EtOAc = 20 : 1) to afford desired chiral products.

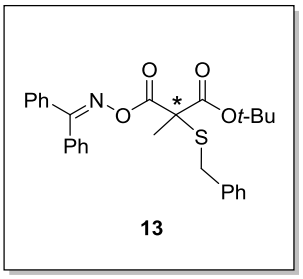
**<u>*tert*-Butyl 2-(cyclohexylthio)-3-(((diphenylmethylene)amino)oxy)-2-methyl-3-oxopropanoate (5)</u>**




Following the procedure, **5** was obtained as pale yellow oil (92% yield). $^1$H-NMR(300 MHz, $CDCl_3$) δ 7.59 ~ 7.56 (m, 2H), 7.45 ~ 7.29 (m, 8H), 2.89 ~ 2.82 (m, 1H), 1.95 ~ 1.87 (t, *J* = 12.3 Hz, 2H), 1.66 ~ 1.63 (m, 2H), 1.53 (s, 3H), 1.46 ~ 1.17 (m, 15H) ppm; $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 168.13, 167.56, 165.45, 134.58, 132.14, 130.98, 129.80, 129.20, 129.09, 128.37, 128.16, 82.79, 56.93, 43.04, 34.96, 34.85, 27.64, 26.13, 25.43, 25.40, 22.59 ppm; IR (KBr) 2931, 1765, 1736, 1219, 875, 847, 772, 697 $cm^{-1}$; HRMS (FAB): calcd. for $[C_{27}H_{34}NO_4S]^+$ ($[M+H]^+$): 468.2209, found: 468.2215; The enantioselectivity

was determined by chiral HPLC analysis (DAICEL Chiralpak AS-H, hexane : 2-propanol = 99 : 1, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm, retention time ; minor isomer 6.89 min, major isomer 10.61 min, 90% ee, $[\alpha]^{25}_{D}$ = -1.83 (*c* 1.0, $CHCl_3$).

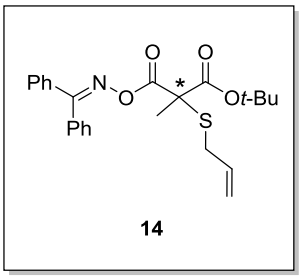
**_tert_-Butyl 2-(benzylthio)-3-(((diphenylmethylene)amino)oxy)-2-methyl-3-oxopropanoate (13)**



13

Following the procedure, **13** was obtained as pale yellow oil (97% yield). $^1$H-NMR (300 MHz, $CDCl_3$) δ 7.63 ~ 7.61 (m, 2.4H), 7.50 ~ 7.31 (m, 12.6H), 3.80 (s, 2H), 1.58 (s, 3H), 1.39 (s, 9H) ppm; $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 167.78, 167.21, 165.92, 136.63, 134.60, 132.45, 131.33, 130.03, 129.56, 129.43, 129.37, 129.07, 128.68, 128.64, 128.57, 128.47, 128.41, 127.43, 83.30, 57.47, 35.52, 27.94, 22.07 ppm; IR (KBr) 2979, 1766, 1736, 1603, 1164, 894, 874, 846, 773, 696 $cm^{-1}$; HRMS (FAB): calcd. for $[C_{28}H_{30}NO_4S]^+$ ($[M+H]^+$): 476.1896, found: 476.1898; The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD-H, hexane : 2-propanol = 99 : 1, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm, retention time ; minor isomer 19.86 min, major isomer 21.34 min, 61% ee, $[\alpha]^{25}_{D}$ = +2.69 (*c* 1.0, $CHCl_3$).

**_tert_-Butyl 2-(allylthio)-3-(((diphenylmethylene)amino)oxy)-2-methyl-3-oxopropanoate (14)**

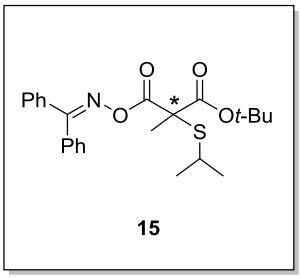


14

Following the procedure, **14** was obtained as pale yellow oil (91% yield). $^1$H-NMR (300 MHz, $CDCl_3$) δ 7.62 ~ 7.59 (m, 2H), 7.49 ~ 7.31 (m, 8H), 5.82 ~ 5.68 (m, 1H), 5.18 ~ 5.04 (m, 2H), 3.24 ~ 3.21 (m, 2H), 1.57 (s, 3H), 1.37 (s, 9H) ppm; $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 167.81, 167.23, 165.88, 134.59, 133.14, 132.45, 131.31, 130.01, 129.35, 129.06, 128.62, 128.45, 118.46, 83.25, 57.04, 33.97, 27.89, 22.16 ppm; IR (KBr) 2979, 1766,

1737, 1636, 1607, 1593, 1165, 846, 774, 697, 673 $cm^{-1}$; HRMS (FAB): calcd. for $[C_{24}H_{28}NO_4S]^+$ ($[M+H]^+$): 426.1739, found: 426.1749; The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AS-H, hexane : 2-propanol = 99 : 1, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm, retention time ; minor isomer 7.65 min, major isomer 11.66 min, 70% ee, $[\alpha]^{25}_D$ = +2.92 (*c* 1.0, $CHCl_3$).

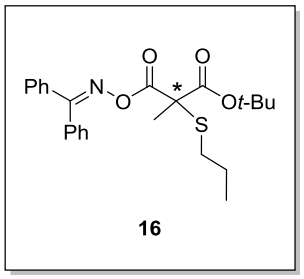
***tert*-Butyl 3-(((diphenylmethylene)amino)oxy)-2-(isopropylthio)-2-methyl-3-oxopropanoate (15)**



**15**

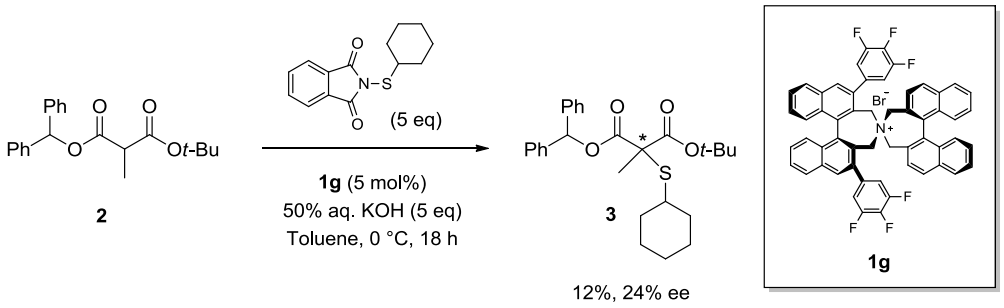
Following the procedure, **15** was obtained as pale yellow oil (85% yield). $^1$H-NMR (300 MHz, $CDCl_3$) δ 7.62 ~ 7.59 (m, 2.2H), 7.49 ~ 7.32 (m, 7.8H), 3.15 ~ 3.02 (septet, *J* = 6.9 Hz, 1H), 1.58 (s, 3H), 1.35 (s, 9H), 1.26 ~ 1.21 (m, 6H) ppm; $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 168.30, 167.74, 165.69, 134.73, 132.39, 131.24, 129.99, 129.39, 129.23, 128.60, 128.39, 83.06, 57.31, 35.45, 27.86, 25.20, 25.08, 22.76 ppm; IR (KBr) 2926, 1766, 1737, 1606, 1593, 1165, 774, 697, 673, 648, 614 $cm^{-1}$; HRMS (FAB): calcd. for $[C_{24}H_{30}NO_4S]^+$ ($[M+H]^+$): 428.1896, found: 428.1892; The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AS-H, hexane : 2-propanol = 99 : 1, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm, retention time ; minor isomer 6.36 min, major isomer 8.54 min, 85% ee, $[\alpha]^{25}_D$ = +2.32 (*c* 1.0, $CHCl_3$).

***tert*-Butyl 3-(((diphenylmethylene)amino)oxy)-2-methyl-3-oxo-2-(n-propylthio)propanoate (16)**

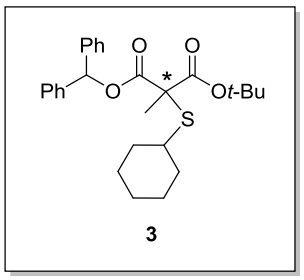



**16**

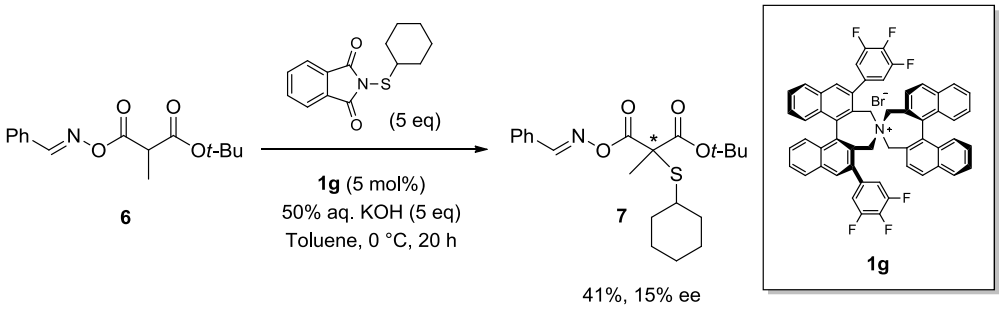
Following the procedure, **16** was obtained as pale yellow oil (77% yield). $^{1}$H-NMR (300 MHz, $CDCl_3$) δ 7.62 ~ 7.59 (m, 2H), 7.49 ~ 7.32 (m, 8H), 2.52 (t, *J* = 7.5 Hz, 2H), 1.57 (s, 3H), 1.57 (s, 3H), 1.51 ~ 1.44 (m, 2H), 1.35 (s, 9H) ppm; $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 168.03, 167.42, 165.72, 134.71, 132.46, 131.25, 129.98, 129.38, 129.17, 129.12, 128.61, 128.42, 83.07, 56.80, 32.46, 28.02, 27.89, 22.39, 22.33, 13.82 ppm; IR (KBr) 2932, 1766, 1737, 1593, 1567, 773, 697 $cm^{-1}$; HRMS (FAB): calcd. for $[C_{24}H_{30}NO_4S]^+$ ($[M+H]^+$): 428.1896, found: 428.1895; The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AS-H, hexane : 2-propanol = 99 : 1, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm, retention time ; minor isomer 6.62 min, major isomer 10.30 min, 76% ee, $[\alpha]^{25}_{D}$ = +1.63 (*c* 1.0, $CHCl_3$).



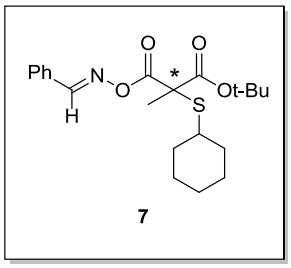

**1-Benzhydryl 3-(*tert*-butyl) 2-(cyclohexylthio)-2-methylmalonate (3)**




*N*-(Cyclohexylthio)phthalimide (5 eq.) and phase-transfer catalyst **1g** (5 mol%) were added to a stirred solution of 1-benzhydryl 3-(*tert*-butyl) 2-methylmalonate **2** (10 mg) in toluene (1 mL). After being cooled to 0 ℃, 50% aqueous potassium hydroxide (5 eq.) was added to the reaction mixture and it was stirred continuously. After 18 hours, the reaction mixture was diluted with EtOAc (10 mL), washed with brine (5 mL × 3), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, hexane : EtOAc = 20 : 1) to afford **3** as colorless oil (12% yield). $^1$H-NMR (300 MHz, $CDCl_3$) δ 7.39 ~ 7.28 (m, 10H), 6.92 (s, 1H), 2.81 ~ 2.75 (m, 1H), 1.81 (m, 1H), 1.72 (s, 3H), 1.46 ~ 1.39 (m, 2H), 1.33 (s, 9H), 1.27 ~ 1.13 (m, 6H) ppm; $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 169.25, 168.65, 139.58, 139.48, 128.46, 128.42, 128.01, 127.90, 127.38, 127.31, 127.27, 127.08, 82.77, 78.28, 42.72, 35.09, 34.91, 27.60, 26.13, 26.07, 25.37, 22.96 ppm; IR (KBr) 1747, 1680, 1647, 1542, 1220, 772, 719, 686, 673 cm$^{-1}$; HRMS (FAB): calcd. for $[C_{27}H_{34}O_4SNa]^+$ ($[M+H]^+$): 477.2076, found: 477.2068; The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD-H, hexane : 2-propanol = 90 : 10, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm, retention time; minor isomer 5.26 min, major isomer 5.74 min, 24% ee.




***tert*-Butyl (*E*)-3-((benzylideneamino)oxy)-2-(cyclohexylthio)-2-methyl-3-oxopropanoate (7)**




*N*-(Cyclohexylthio)phthalimide (5 eq.) and phase-transfer catalyst **1g** (5 mol%) were added to a solution of *tert*-Butyl (*E*)-3-((benzylideneamino)oxy)-2-methyl-3-oxopropanoate **6** (10 mg) in toluene (1 mL). After being cooled to 0 ℃, 50% aqueous potassium hydroxide (5 eq.) was added to the reaction mixture and it was stirred continuously. After 20 hours, the reaction mixture was diluted with EtOAc (10 mL), washed with brine (5 mL × 3), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, hexane : EtOAc = 20 : 1) to afford **7** as white solid (41% yield). $^1$H-NMR(300 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.75 (d, *J* = 6.60 Hz, 2H), 7.52 ~ 7.40 (m, 3H), 2.98 ~ 2.90 (m, 1H), 1.97 (t, *J* = 11.45 Hz, 2H), 1.75 (s, 3H), 1.71 ~ 1.66 (m, 2H), 1.46 (s, 9H), 1.53 ~ 1.16 (m, 6H) ppm ; $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 168.46, 167.80, 156.77, 132.12, 129.94, 129.11, 128.73, 83.26, 56.94, 43.31, 35.29, 35.19, 28.01, 26.41, 25.60, 23.00 ppm ; IR (KBr) 3063, 2978, 2932, 2852, 1766, 1735, 1612, 1574, 1475, 1448, 1393, 1370, 1344, 1316, 1253, 1209, 1162, 1111, 1067, 997, 965, 911, 846, 815, 756, 692, 637 $cm^{-1}$ ; HRMS (FAB) : calcd. for $[C_{21}H_{30}NO_4S]^+$ : 392.1896, found : 392.1894; The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD-H, hexane : 2-propanol = 99 : 1, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm, retention time; minor isomer 13.89 min, major isomer 14.83 min, 15% ee; m.p.= 68.2 ℃.

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# 국 문 초 록

Chiral α-alkylthio-α-alkylmalonate 유도체는 생물학적 활성이 있는 천연물 또는 의약품 합성에 잠재적으로 매우 중요한 중간물질이다. 현재 황을 포함하는 4차 탄소 입체 중심을 도입하기 위해서 주로 쓰는 direct sulfa-Michael addition을 비롯한 다양한 합성적인 접근법이 연구되고 있다. 그러나 sulfenylation은 기질을 합성하거나 화학 작용기를 변환하기가 어렵다는 단점이 있다. 연구를 확장하는 차원에서, 본 연구자는 상전이 촉매를 이용한 α-alkylmalonate의 비대칭적인 sulfenylation을 통해 황을 포함하는 chiral 탄소 입체 중심을 만드는 새로운 합성법을 설계하였다.

본 연구실에서는 최초로 상전이 촉매를 이용해서 malonate의 α위치에 높은 화학적 수율과 광학적 수율로 alkyl 작용기를 도입하는 방법을 보고한 바 있다. 또한 이를 이용하여 4차 탄소 입체 중심을 포함하는 여러 chiral building blocks를 합성하여 성공적으로 응용 가능성을 증명한 바 있다. 상전이 촉매 반응은 반응 조건이 상대적으로 온화하며 반응 진행 시 시약과 촉매로도 경제적이고 환경적으로 지속 가능한 물질들을 사용한다.

본 연구자는 상전이 촉매를 이용해서 α-alkylmalonate의 입체선택 sulfenylation을 성공적으로 수행하였다. (1*S*,2*S*,4*S*,5*R*)-2-((*R*)-(allyloxy)(6-methoxyquinolin-4–yl)methyl)-5-ethyl-1-(2,3,4–trifluorobenzyl)quinuclidin-1-ium bromide 상전이 촉매 존재 하에서 다양한 chiral 중간물질로 변환 가능한 여러 α-alkylthio-α-alkylmalonate를 최대 97%의 화학적 수율과 최대 90%의 광학적 수율로 합성하는데 성공하였다.

**주요어:** 입체선택적 sulfenylation, α-alkylthio-α-alkylmalonate, 비대칭 chiral 상전이 촉매 반응

**학번:** 2013-23456