藥 學 碩 士 學 位 論 文

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

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ABSTRACT

Chiral α-hydroxy malonates and their equivalents are potentially valuable intermediates for the synthesis of natural products and pharmaceuticals. α-Hydroxy malonate itself can be easily modified to chiral glycerols or α,β-dihydroxy esters according to the chemical conversion of two esters. There have been a lot of enantioselective synthetic methods of α-hydroxy-β-ketoesters. However, they have been mostly achieved by the enzymatic desymmetrization of prochiral malonates.

Recently, our research team reported a new synthetic method of chiral α,α-dialkylmalonates in high chemical yields and enantioselectivities by phase-transfer catalytic (PTC) desymmetrization of malonates in the presence of chiral quaternary ammonium salts, and successfully proved its usefulness by applications to the synthesis of various chiral building blocks bearing quaternary carbon center.

Based on this study, highly enantioselective alkylation of *tert*-butyl diphenylmethyl α-benzoxymalonate could be accomplished under phase-transfer catalysis in the presence of (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide as PTC catalyst to afford the corresponding α-benzoxy-α-alkylmalonates in high chemical (up to 99%) and optical yields (up to 93% ee) which could be readily converted to versatile chiral intermediates.

Key words : Chiral α-hydroxy malonates, Enantioselective synthesis, α-benzoxy-α-alkylmalonate, phase-transfer catalysis

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INTRODUCTION

1. Characteristic of α-acyloxy-α-alkylmalonate compound

Chiral α,α-dialkylmalonates have been used for the construction of the chiral quaternary carbon centers of biologically active natural products and pharmaceuticals. Among them, chiral α-hydroxy malonates and their equivalents are a valuable class of compounds utilized in the synthetic intermediates of natural product like eucomol or the synthesis of drug candidates such as chlozolinate and bicalutamide. Chiral α-acyloxy-α-alkylmalonate compound, especially, can be a versatile synthon because the ester groups can be converted to various other functional groups (Figure 1). In addition to chiral malonates, their chiral derivatives can be intermediates in the synthesis of compounds that include α-hydroxy quaternary stereocenters.

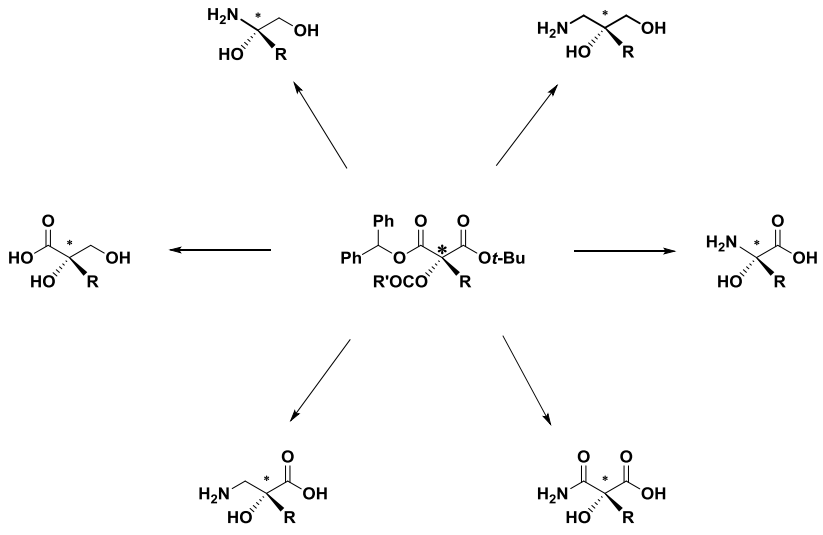
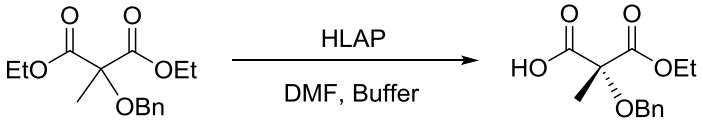


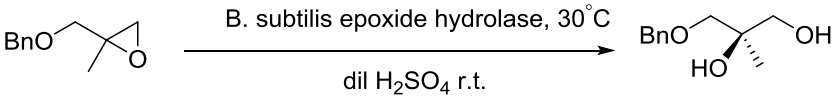
Figure 1. Various modification of α-acyloxy- α-alkylmalonate

Historically, α-hydroxy compounds have been synthesized by the enzymatic desymmetrization of prochiral malonate derivatives, or by the enzymatic and chemical desymmetrization of prochiral glycerols (Scheme 1).[1,2]



92%, 83% ee

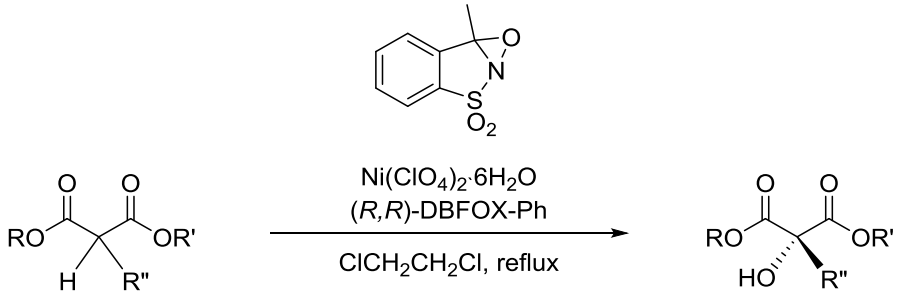
HLAP = horse liver acetone, Buffer - Tis buffer, pH 7.5



82.3% ee

Scheme 1. Enzymatic desymmetrization of prochiral malonates (top)
Enzymatic desymmetrization of prochiral glycerols (bottom)

Recently, in 2009, Shibata and Toru's group reported α-hydroxylation of racemic malonate, which was the first catalytic enantioselective hydroxylation of malonate derivatives. The (R,R)-DBFOX-Ph/Ni complex with oxaziridine was used for production of chiral α-hydroxy malonate (Scheme 2).[3]



up to 98%ee

Scheme 2. Asymmetric transformation in the α-hydroxylation of racemic malonate

However, this approach is inefficient for expanding a scope of α-oxy-α-alkylmalonate and involves a nikel-metal catalysis which is not friendly for environment. Restriction to small-scale process by the metal catalyst makes this inappropriate for an industrial process.

Inspired by recent studies of our research team on , direct α-alkylation of malonates via phase-transfer catalytic (PTC) reaction, new synthetic method of chiral α-oxy-α-alkylmalonate was attempted.

2. Phase-transfer catalysis for asymmetric alkylation

2.1. Phase-transfer catalysis

Phase-transfer catalysis (PTC) indicates a conversion between two or more different phases, generally organic phase and aqueous phase. Without the catalyst, a reaction would be slow and inefficient or does not occur at all. PTC has been recognized as a useful synthetic methodology in organic chemistry owing to those advantages over conventional manner.

- High yield by suppressing side reactions.
- Mild reaction condition
- Inexpensive reagents and solvents
- Green chemistry
- Large-scale preparation

For those merits, PTC expands its scope to alkylation, Michael reaction, aldol reaction etc. Generally, onium salt (ammonium salt, phosphonium salt) and complexing agent (crown ethers, polyethers, polyols) are employed for PTC as a catalyst. Chiral non-racemic phase-transfer catalyst results in asymmetric induction, as, and described in Figure 2, mechanism was studied by asymmetric monoalkylation of active methylene compounds, Schiff base **1** in this illistration. 1) interfacial deprotonation of the active methylene compound **1** with base to be an enolate anion **2**, which occurs at the interface between two different layers in general (e.g. liquid-liquid or solid-liquid). 2)

ion pair formation of the anion with the chiral quaternary ammonium compound to give chiral onium enolate **3**, which makes the lipophilic complex stay in the organic phase. 3) induction of the new chiral center in the optically active monoalkylation product **4** by alkylation of the enolate **3** while the catalyst regenerates simultaneously.

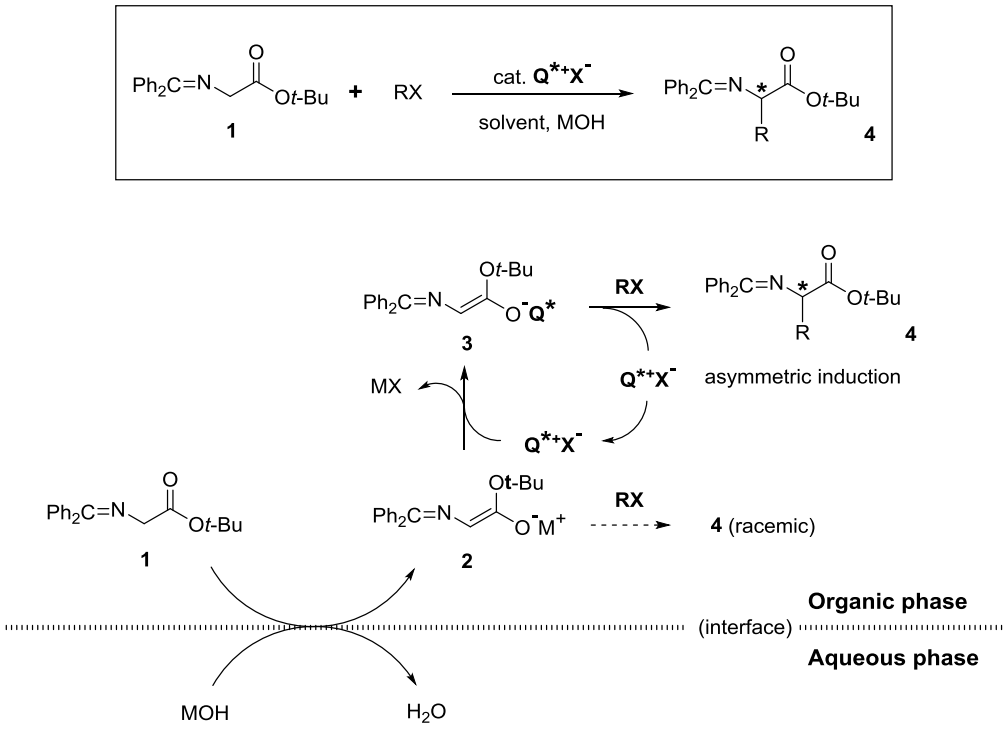


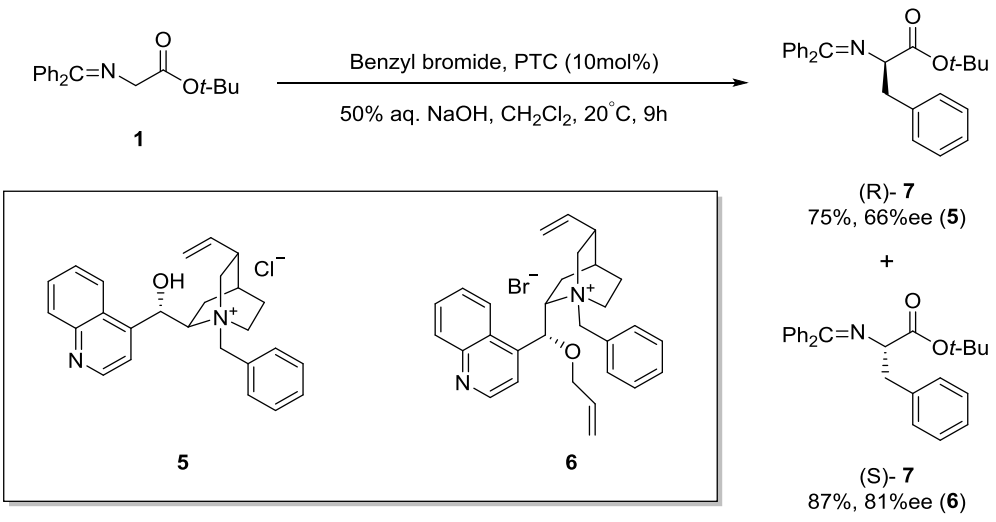
Figure 2. Mechanistic scheme for the asymmetric alkylation

Formation of racemic compound through the direct alkylation of the ion pair **3** can be minimized by fast ion-exchange to give highly reactive chiral onium enolate **3**, and the absolute stereochemistry is determined by effective shielding of one of the two enantiotopic faces of the enolate anion **2**. [4]

2.2. Progress of phase-transfer catalysts

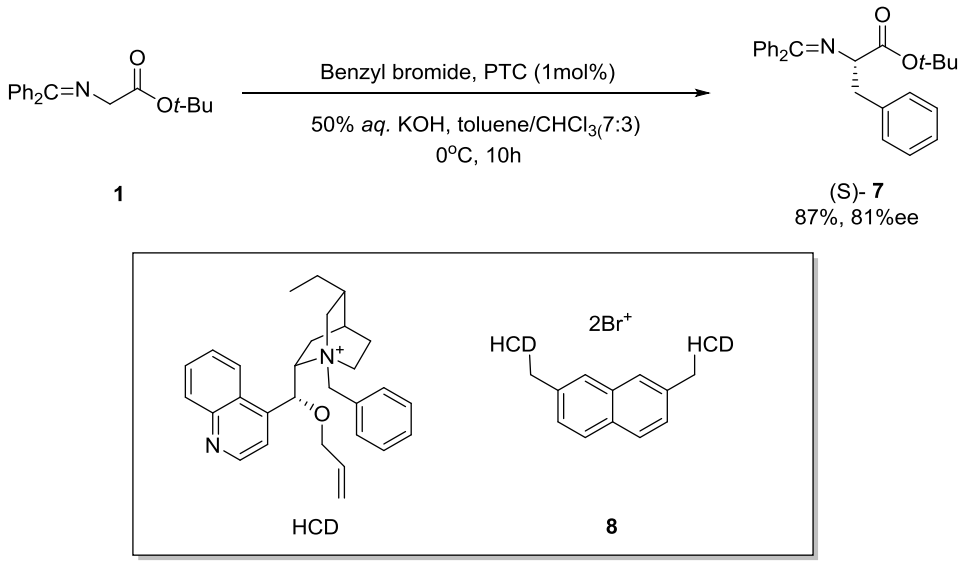
There are two kinds of chiral phase-transfer catalysts, *Cinchona*-derived and non *Cinchona*-derived, which have been developed for excellent enantioselective products in high chemical yields.

As for *Cinchona*-derived phase-transfer catalysts first, they have several advantages that enables to have a dominant occupation in PTC; various functional groups and cheap price. In 1989, M. J. O'Donnell developed α-alkyl-α-amino acid via phase-transfer catalysis as a pioneering practical synthetic method. The cinchonine derivative (first-generation catalyst by Merck in 1984) was employed for a stereoselective alkylation of glycinate Schiff base with benzyl bromide under mild basic conditions (75%, 66%ee). After some catalyst optimization, O-allyl protected cinchonidine derivative (second generation catalyst), diastereomer of cinchonine, shows a higher enantioselectivity, 87% chemical yield and 81%ee (Scheme 4).[5]



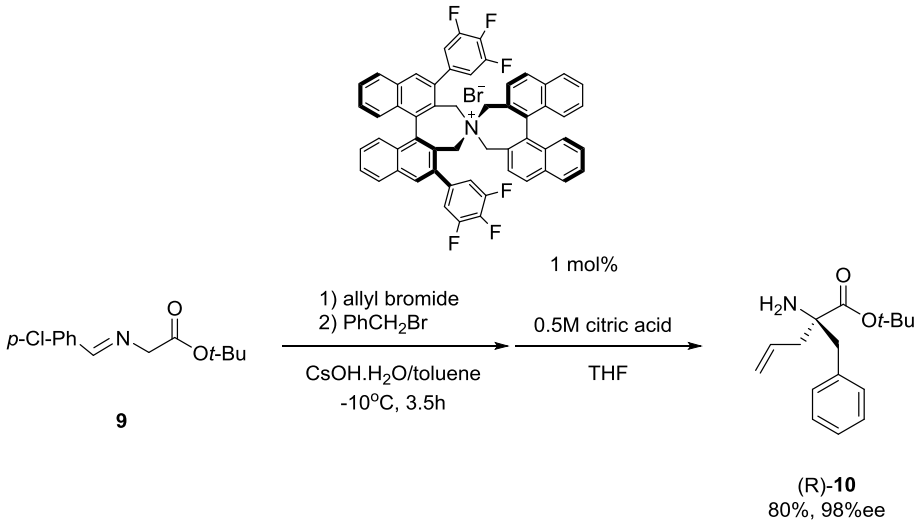
Scheme 3. The first and second generation *Cinchona*-derived catalysts

Jew and Park, recently, reported a development of new kinds of catalysts derived from *Cinchona* alkaloid. Using benzene as a ligand, polymer of cinchona units showed the successful improvement of the stereoselectivity owing to the screening effect between the units that limits the substrate approach only one direction. Higher efficiency was observed with these catalysts than monomeric catalyst, especially naphthyl dimer catalyst **5** showed the highest enantioselectivity, 97%ee (Scheme 5). [6]



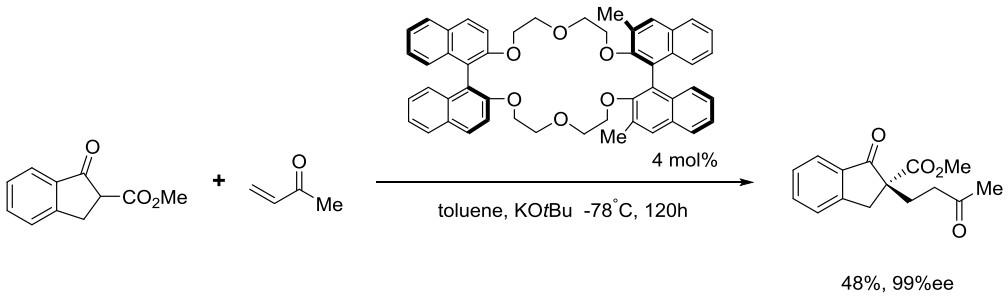
Scheme 4. Dimer cinchona derived catalyst developed by Jew and Park

In 2000, Muraoka group devised C-2 symmetric N-spiro chiral quaternary ammonium bromide for one-pot double alkylation of aldimine Schiff base of glycine *tert*-butyl ester, as a non Cinchona-derived catalytic system. This practical asymmetric method showed 80% yield and 98%ee to provide α,α-dialkyl-α-amino acids (Scheme 5).[7]



Scheme 5. C-2 symmetric chiral PTC developed by Maruoka

Chiral crown ethers can be alternatives to the ammonium salts. High catalyst turnover, easy catalyst design and stability under alkaline conditions are their merits suitable for PTC, but they are expensive and difficult for large-scale preparation. Successful Michael addition under PTC was achieved in the presence of a crown ether (Scheme 6). [8]

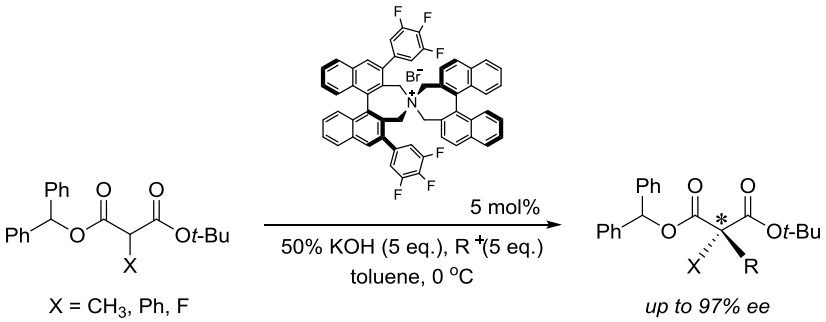


Scheme 6. Chiral crown ether as a phase-transfer catalyst

RESULT AND DISCUSSION

1. Substrate design and preparation for PTC alkylation

In 2001, our research team reported the first enantioselective synthetic method for the construction of a quaternary carbon center from malonates via phase-transfer catalytic alkylation. As briefly discussed in the introduction, malonates is one of the most fundamental chiral building blocks. Over several preliminary studies for the best substrate, high enantioselectivities (up to 97% w) were obtained with malonates that have a *tert*-butyl group with one ester group and diphenyl methyl group with the other ester group. For synthesis of diverse α,α-dialkylmalonates, α-position of substrate malonates was substituted with alkyl, aryl, halogen groups, and underwent substitution with various alkyl halides (Scheme 7).[9]



Scheme 7. Enantioselective alkylation of malonates via phase-transfer catalysis

As mentioned in Scheme 1, direct α-hydroxylation of malonates were reported by Shibata and Toru's group with nikel catalyst to provide chiral α-hydroxy-α-

alkylmalonates. This synthetic method showed high stereoselectivity and ability to be readily transformed to drug candidates.

However, this method has difficulty to examine its applicability because each of various α-alkylmalonate substrates for α-hydroxylation should be synthesized respectively for screening.

Given that phase-transfer catalysis makes it simpler to synthesize a variety of chiral malonates products as our previous research on α,α-dialkylmalonates, a new synthetic approach of chiral α-oxy-α-alkylmalonate was developed via PTC. As for design of malonte substrate for phase-transfer catalysis, firstly, *tert*-butyl group and diphenyl methyl group with each other ester groups were borrowed for the premising result. Next, for the crucial part of this substrate, α-position of malonates was needed to be substituted with acyloxy group as a protection of hydroxyl group (Figure 3). With this α-acyloxymalonate as a substrate, α-alkylation via phase-transfer catalysis was supposed to be performed to furnish α-acyloxy-α-alkylmalonate with a quaternary carbon center.

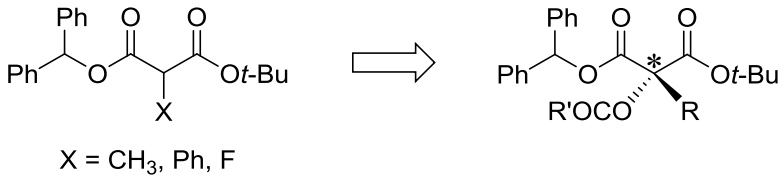
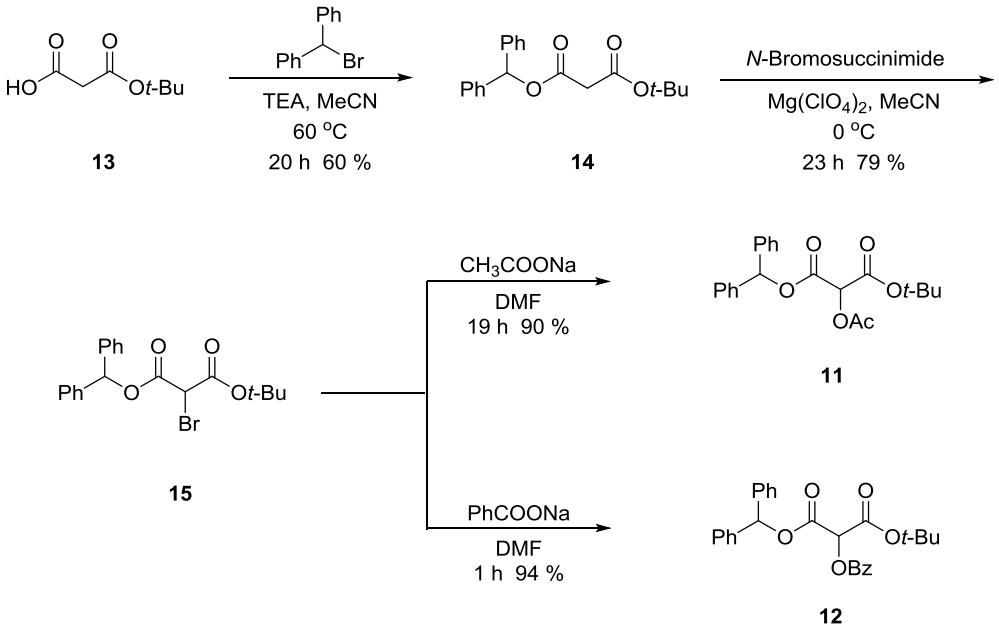


Figure 3. Design of new PTC substrate

α-acyloxymalonate substrate was prepared readily from commercially available *tert*-butyl hydrogen malonates **3** in 3 steps as described in Scheme. First, carboxylate of *tert*-butyl hydrogen malonates underwent substitution with diphenyl methyl group in

basic and warm condition. *N*-bromosuccinimide with magnesium perchlorate was used to provide α-bromomalonate **5** at low temperature, and in the last step, substitution was performed in a quantitative yield with sodium acetate and sodium benzoate to furnish the PTC substrates, α-acetoxymalonate and α-benzoxymalonate, respectively.[10] To select the optimal substrate between these two substrates, PTC alkylation of them was conducted subsequently.

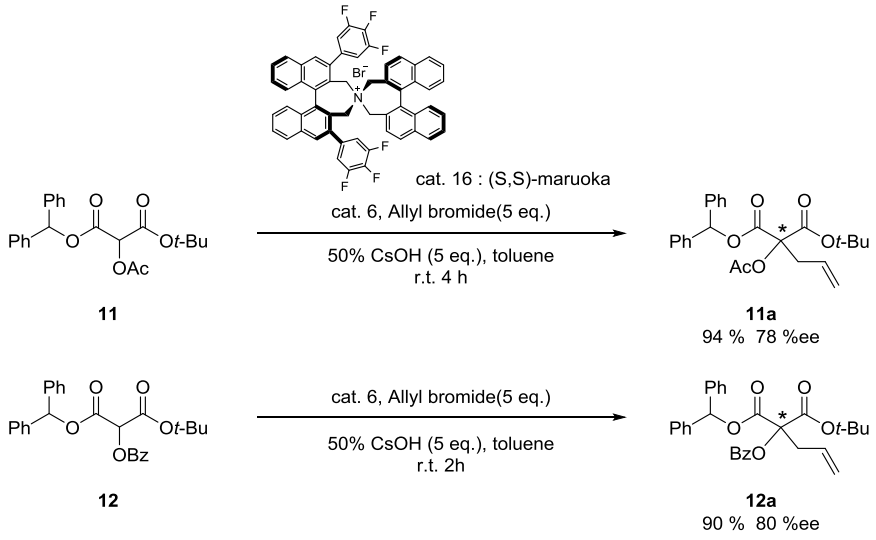


Scheme 8. Preparation of α-acyloxymalonate substrates

2. Enantioselective phase-transfer catalytic reaction of α-benzoxymalonate

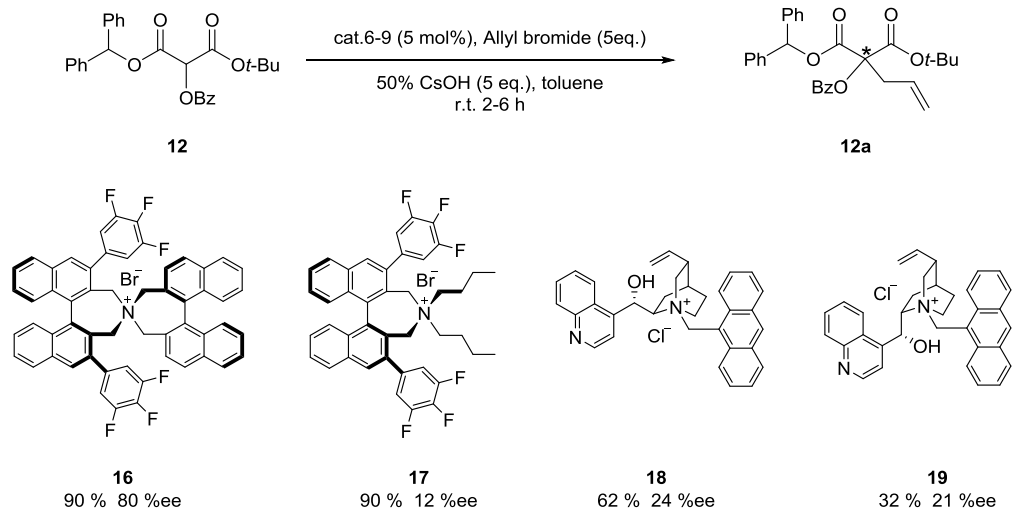
2.1. Optimization of PTC reaction of α-benzoxymalonate

Before searching for the best condition for PTC alkylation, two prepared α-acyloxymalonates were compared under the same circumstance to determine which compound is the best substrate for PTC alkylation. Phase-transfer catalyst, base and solvent condition was referred from our research team's previous studies on PTC; (S,S)-3,4,5-trifluorophenyl-NAS bromide as a catalyst (0.5mol%), 50% CsOH as a base (5eq), toluene (0.3M) is the optimized reaction condition of some former studies. After PTC allylation at room temperature, α-benzoxymalonate **2** showed a higher enantioselectivity and faster reaction rate. Although the chemical yield is lower than α-acetoxymalonate **1**, it was overlooked based on the thought that yield would improve at lower reaction temperatures in future (Scheme 9).



Scheme 9. Comparative PTC reaction of two α-acyloxymalonate substrates

Optimization of phase-transfer catalyst proceeded on the next step. Reaction condition except for the catalyst was set up as the former one, and four catalysts were employed respectively with substrate **2** for comparison. As presumption according to the previous research, both the highest enantioselectivity and chemical yield were observed with catalyst **6**, and other three catalyst; n-butyl substituted (S,S)-maruoka **7**, cinconine derived catalyst **7**, cinchonidine derived **8** possessed significantly lower yields (Scheme 10).



Scheme 10. Optimization of Phase-transfer catalysts

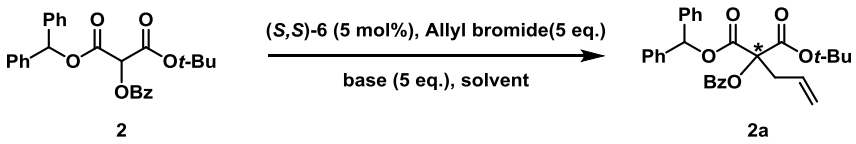
As shown in table 1, optimization of the rest conditions (base, solvent, reaction temperature) was succeeded as the last step. Four kinds of base were chosen according to our past research result; 50% Potassium hydroxide, 50% Cesium hydroxide as an aqueous base (entry 1,2) and their solid form bases (entry 3,4). With solid form bases, substrate was likely to be decomposed, which resulted in much lower chemical yields than PTC allylation with aqueous bases while they have only slight differences on

enantioselectivies. 50% Cesium hydroxide that showed the best yield in both was selected as an optimized base.

It turned out that solvents for PTC allylation have little impact on enantioselectives after solvent screening (entry 2, 5-7). Four all sorts of solvents showed near 80%ee, and only chemical yields were slightly different. Preferable chemical and optical yields were observed with toluene.

Regarding reaction temperature screening (entry 2, 8-9), both chemical yield and enantioselectivity has improved as the temperature decreased until -20^{o}C, but both yields were lowered back under -40^{o}C.

Table 1. Optimization of base, solvent, reaction temperature



2 2a

entry	base	T (^{o}C)	solvent	Time (h)	Yield (%)	ee (%)
1	50% KOH	r.t.	toluene	2	89	79
2	50% CsOH	r.t.	toluene	2	90	80
3	KOH(s)	r.t.	toluene	15	72	80
4	CsOH(s)	r.t.	toluene	15	9	80

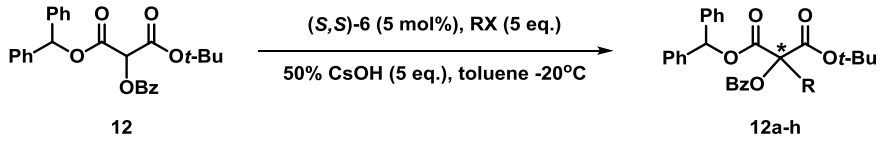
5	50% CsOH	r.t.	xylene	4	99	78
6	50% CsOH	r.t.	mesitylene	4	86	79
7	50% CsOH	r.t.	cyclopentyl methyl ether	4	81	79
8	50% CsOH	0	toluene	4	90	86
9	50% CsOH	-20	toluene	5	94	88
10	50% CsOH	-40	toluene	16	71	75

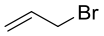
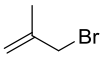
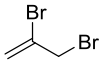
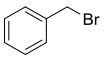
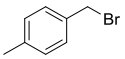
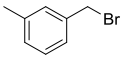
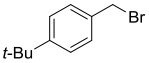
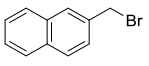
After those optimization of PTC conditions, it turned out that 50% Cesium hydroxide as a base, toluene as a solvent, (S,S)-maruoka as a catalyst and -20^{o}C reaction temperature are the best circumstance for PTC alkylation of α-benzoxymalonate.

2.2. Enantioselective PTC alkylation with various alkyl halides

Under the optimized condition, PTC alkylation with various electrophiles was performed with substrate **2** to investigate its scope. As shown in table 2, screening 8 electrophiles first, aliphatic electrophiles including allyl bromide, examined in the preliminary study, 2-methyl allyl bromide were alkylated quite well giving 87, 91%ee each, and a better enantioselectivity was observed with 2-Bromo substituted allyl bromide (93% ee, entry 3). PTC alkylation with chain aliphatic electrophile such as Iodo hexane was likely to be decomposed, and unable to resolve in HPLC. PTC alkylation of electrophiles that possess aromatic rings were expected to show excellent enantioselectivities, speculated that *pi* stacking effect between an aromatic ring of electrophile and phenyl ring of benzoxy group of PTC substrate would help to accelerate a stereoselctive bonding during the PTC reaction. However, the result was not much satisfactory with our expectation. Benzylated product (entry 4), which has the same Rf value on TLC with the substrate, gave 91%ee, similar with 2-methyl-allylated product. Electrophiles with aromatic rings that bear electron a donating group on their *para* position (entry 5-7) showed identical optical yields with the benzylated product. 2-(Bromomethyl) naphthalene showed low chemical yield and enantioselectivity in both (entry 8).

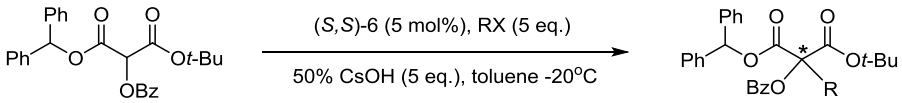
Table 2. Enantioselective PTC alkylation of α-benzoxymalonate (1)



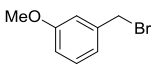
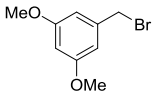
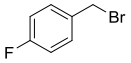
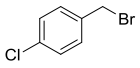
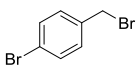
entry	RX	product	Time (h)	Yield (%)	ee (%)
1.		**12a**	2	94	87
2		**12b**	2	75	91
3		**12c**	15	89	93
4		**12d**	3	99	91
5		**12e**	3	93	91
6		**12f**	4	92	91
7		**12g**	4	95	91
8		**12h**	3.5	72	88

The next 5 electrophile screening result is described as table 3. Two more electrophiles bearing electron donating group were alkylated via PTC, and *meta*-methoxy benzylation showed an improved enantioselectivity at entry 1, 93%ee, whereas 3,5-methoxy benzylation gave a similar result with the normal benzylation. Meanwhile, electron withdrawing group-bearing electrophiles showed the opposite effect (entry 3-5). The more polar electron withdrawing group bears, the enantioselectivities lowered.

Table 3. Enantioselective PTC alkylation of α-benzoxymalonate (2)

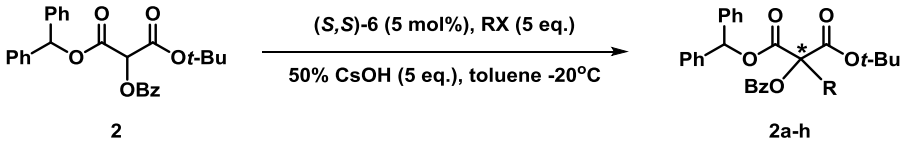


2 **12i-m**

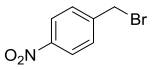
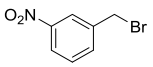
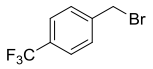
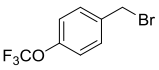
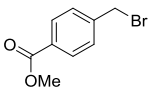
entry	RX	product	Time (h)	Yield (%)	ee (%)
9		**12i**	2	91	93
10		**12j**	2	93	91
11		**12k**	3	90	85
12		**12l**	3	92	82
13		**12m**	3	88	80

As shown in table 4, the rest 5 electrophile screening showed totally poor enantioselectivities compared with the former ones. Nitro substitution on benzyl ring lowered the optical yields (entry 1,2) and trifluoro groups were unhelpful for increasing enantioselectivity (entry 3,4), ester group as well (entry 5).

Table 4. Enantioselective PTC alkylation of α-benzoxymalonate (3)

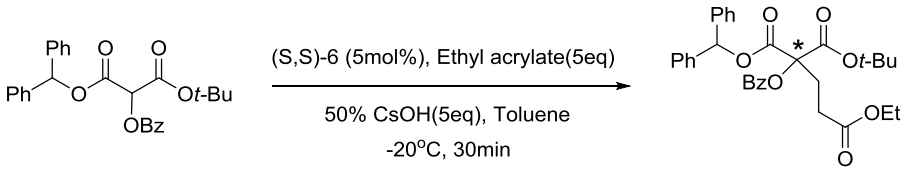


2 2a-h

entry	RX	product	Time (h)	Yield (%)	ee (%)
14		**12n**	2	92	81
15		**12o**	2	88	61
16		**12p**	15	86	80
17		**12q**	3	99	78
18		**12r**	3	90	81

2.3. Limitation of α-benzoxymalonate in enantioselective phase-transfer catalytic Michael reaction

There have been practical experiments of Michael addition via phase-transfer catalysis historically, thereby, scope expansion to Michael addition was attempted with α-benzoxymalonate under the optimal circumstance. Michael donor was α-benzoxymaloate **12**, and ethyl acrylate was chosen as a Michael acceptor.



12 **12s** = 72 % 40 %ee

Scheme 11. Michael reaction of α-benzoxymalonate via PTC

Reaction rate was dramatically fast despite the low reaction temperature, but both chemical and optical yield was not matched with PTC alkylation, which can be speculated that the reactivity is so vigorous that the reaction pathway is not along with phase-transfer catalysis.

3. Application and determination of absolute configuration

As depicted in Figure 4, α-benzoxymalonate products that possess a chiral quaternary carbon via PTC have synthetic potential, transformed to natural products or drug candidates.

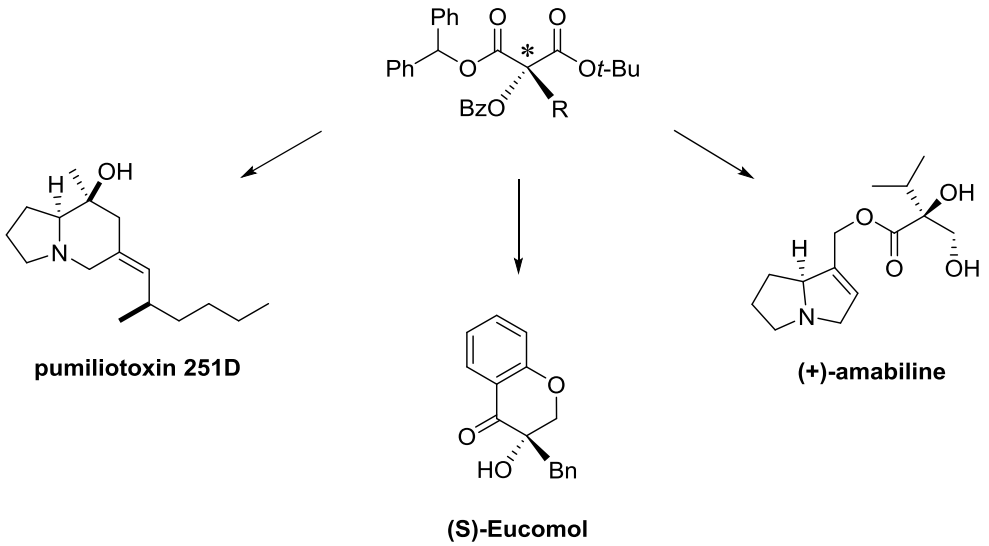
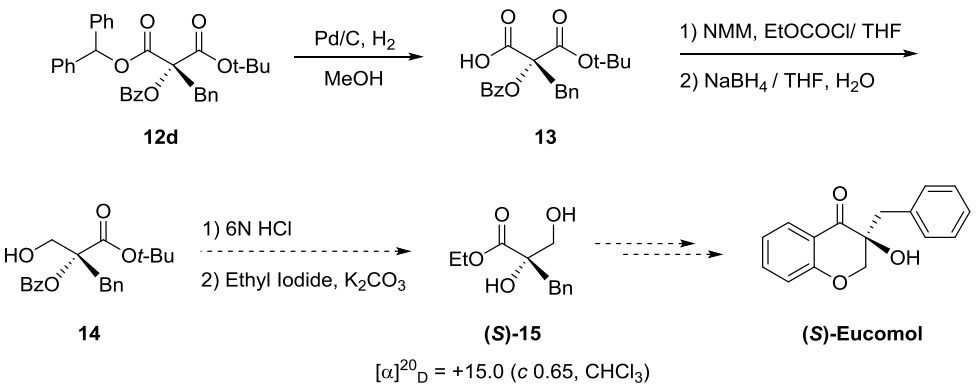


Figure 4. Synthesis of natural products from α-benzoxymalonate products

Currently, to amphasize the synthetic value of so-obtained enantioriched α-hydroxymalonate, transformation to Eucomol intermediate from the benzylated α-benzoxymalonate product is under investigation following Scheme 12. Palladium catalyzed hydrogenation of benzylated product gave carboxylate 13, and activation of carboxylate using ethyl chloroformate followed by reduction of sodium borohydride provided alcohol products 14. Deprotection of benzoyl group and ester reduction under acidic condition and subsequent ethylation is planned to furnish (S)-15, the

known compound as an intermediate of (S)-Eucomol.[11]



Scheme 12. Synthesis of Eucomol intermediate **(S)-15**

The X-ray crystallographic structure of **12m** is displayed in Figure 5. Other absolute configurations of alkylated products in Table 2,3 and 4 were tentatively assigned as R based on the absolute configuration of **12m** and the phase-transfer catalytic mechanism.

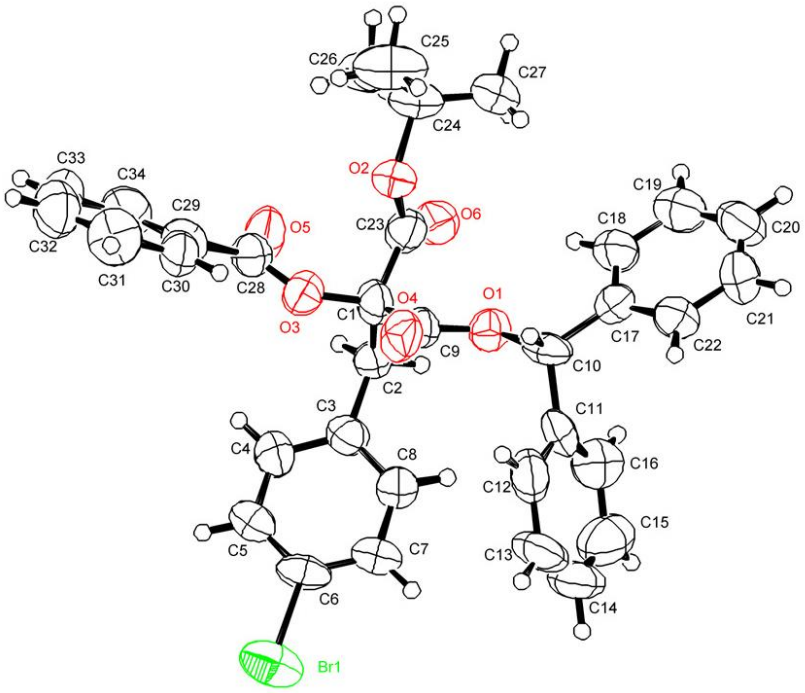


Figure 5. X-ray crystallographic structure of **12m**

CONCLUSION

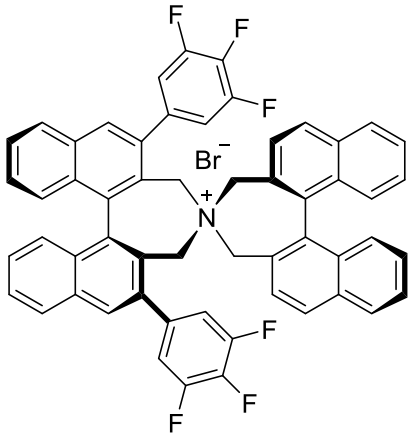
A new synthetic method of α-oxy-α-alkylmalonates with chiral quaternary carbon center has developed. α-oxy-α-alkylmalonates possess a synthetic potential that can be transformed to natural products and pharmaceutical drugs. Thus, Phase-transfer catalytic alkylation of α-acyloxymalonates was attempted to synthesize α-oxy-α-alkylmalonates. Phase-transfer catalysis has several advantages over the conventional synthesis such as mild condition, using inexpensive reagents, simple experimental procedure etc. For synthesis of α-acyloxy-α-alkylmalonates, α-benzoxymalonate was furnished as a PTC substrate. After reaction condition optimization, PTC alkylation of α-benzoxymalonate was performed with several electrophiles in a presence of (S,S)-3,4,5-trifluorophenyl-NAS bromide as a catalyst, and PTC Michael addition also provided α-benzoxy-α-alkylmalonates. Total 19 samples were synthesized via PTC from α-benzoxymalonate, and its absolute configuration was indentified by X-ray crystallography. Synthesis of (S)-Eucomol intermediate, a natural product, is under way to prove the usefulness of the chiral products.

EXPERIMENTAL SECTION

1. General Methods

1.1 Solvents and reagents

All reagents bought from commercial sources were unpurified. Organic solvents were concentrated under reduced pressure using a Büchi rotary evaporator. As the commercially available KOH was a pellet type, solid KOH should be grinded to the powder form for successful reaction and high enantiopurity. 50% v/w aqueous CsOH was used as a stock solution. Phase-transfer catalyst **6**[S1] (Wako) was purchased from the commercial source.



16

1.2. Chromatography and HPLC

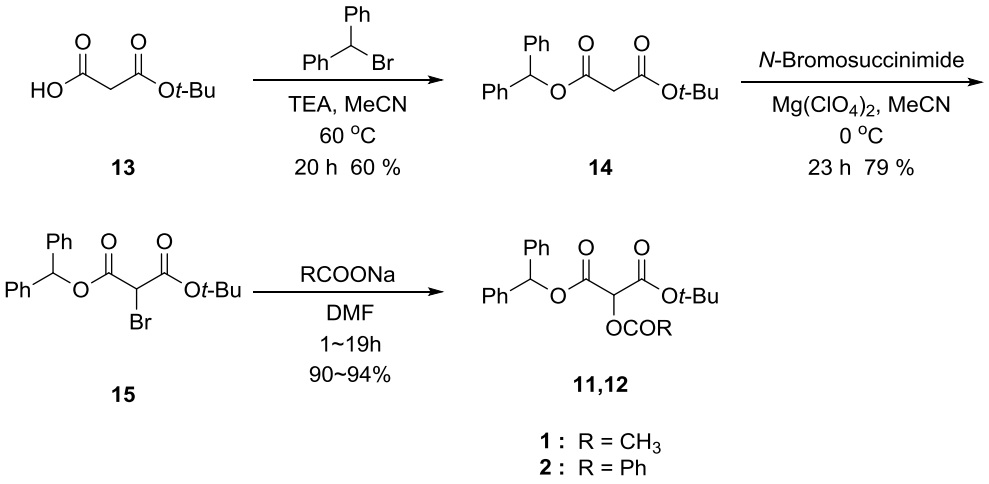
TLC analyses were performed using Merck precoated TLC plate (silica gel 60 GF_{254}, 0.25 mm). Flash column chromatography was carried out using E. Merck Kieselgel 60 (230~400 mesh). Instrument (Hitachi, L-2130) and software (Hitachi, Version LaChrom 8908800-07) were used as HPLC. The enantiomeric excess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

1.3. Spectral data

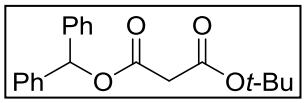
Infrared (IR) spectra were recorded on a JASCO FT/IR-300E and Perkin-Elmer 1710 FT spectrometer. Nuclear magnetic resonance (^{1}H-NMR and ^{13}C-NMR) spectra were measured on JEOL JNM-LA 300 [300 MHz (^{1}H) , 75 MHz (^{13}C)] spectrometer, JEOL JNM-GSX 400 [400 MHz (^{1}H), 100 MHz (^{13}C)] spectrometer,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

2. α-acyloxy-α-alkylmalonates

2.1. Preparation of α-acyloxymalonate substrate



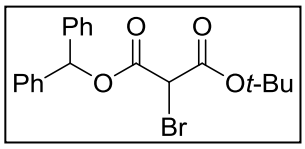
*synthesis of benzhydryl tert-butyl malonate (**14**)*



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

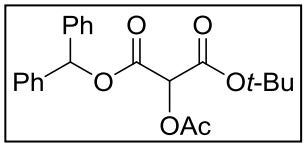
1730, 1496, 1454, 1393, 1369, 1329, 1259, 1144, 1081, 992, 836, 748, 699, 647 cm^{-1} ; HRMS (ESI) : calcd for $[C_{20}H_{22}O_4Na]^+$: 349.1410, found : 349.1422.

*synthesis of α-bromomalonate substrates(**15**)*



A solution of **14** (750 mg, 2.298 mmol) in dry MeCN (23 mL) was added to the *N*-bromosuccinimide (2.757 mmol) and Magnesium perchlorate (154 mg, 0.689 mmol) at 0℃. The reaction mixture was stirred for 23 hours. After solvent was removed on a rotary evaporator, the mixture was diluted with EtOAc (400 mL) and washed with brine (100 mL). The organic layers were dried with $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane:EtOAc = 40:1~20:1), **5** was obtained as colorless oil (736 mg, 79% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.35~7.27 (m, 10H), 6.94 (s, 1H), 4.48 (s, 1H), 1.36 (s, 9H) ppm ; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 163.77, 162.90, 138.91, 138.89, 128.52, 128.48, 128.28, 128.17, 127.29, 127.04, 84.40, 79.26, 44.24, 27.47 ppm ; IR (KBr) 2981, 1740, 1496, 1455, 1370, 1294, 1256, 1139, 989, 848, 748, 699 cm^{-1} ; HRMS (CI) : calcd for $[C_{20}H_{20}FO_4]^+$: 403.0545, found : 403.0545.

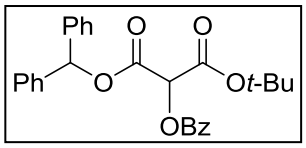
*synthesis of α-acetoxymalonate substrate(**11**)*



Sodium Acetate (228 mg, 0.565 mmol) was added to a stirred solution of **15** (70mg, 0.848 mmol) in dry MeCN (15mL), and Argon gas was substituted. The reaction mixture was stirred for 19 hours.

After solvent was removed on a rotary evaporator, the mixture was diluted with EtOAc (300 mL) and washed with brine (80 mL). The organic layers were dried with $MgSO_4$, and concentrated *in vacuo*. After purification by column chromatography (silica gel, hexane:EtOAc = 10:1), **11** was obtained as white powder (mg, 90% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.32~7.27 (m, 10H), 6.95 (s, 1H), 5.51 (s, 1H), 2.18 (s, 3H), 1.35 (s, 9H) ppm ; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 169.48, 163.82, 162.97, 139.07, 128.54, 128.50, 128.23, 128.20, 127.31, 127.13, 84.02, 78.71, 72.50, 27.69, 20.40 ppm ; IR (KBr) 3489, 2980, 1751, 1587, 1496, 1455, 1371, 1254, 1220, 1150, 1098, 994, 962, 910, 839, 744, 700, 646, 603 cm^{-1} ; HRMS (FAB) : calcd for $[C_{22}H_{24}O_6]^+$: 407.1471, found : 407.1477. ; m.p. = ℃.

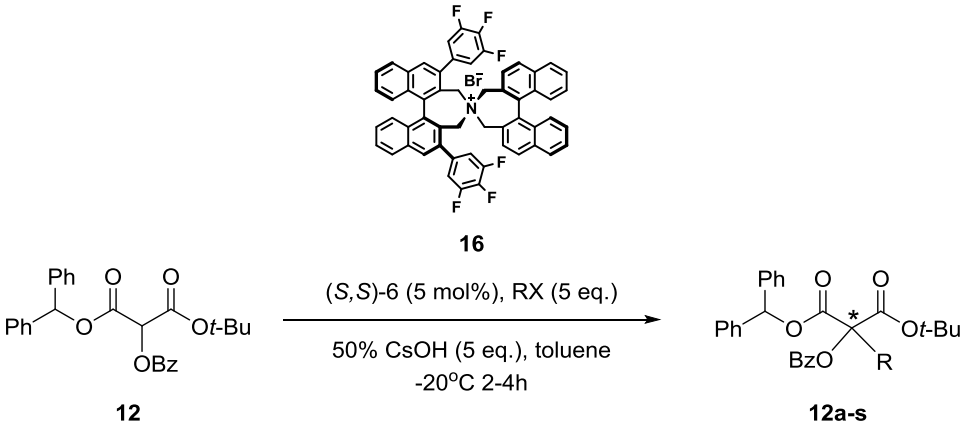
*synthesis of α-benzoxymalonate substrate(**12**)*



Sodium Benzoate (366 mg, 0.905 mmol) was added to a stirred solution of **15** (196 mg, 1.358 mmol) in dry MeCN (20 mL), and Argon gas was substituted. The reaction mixture was stirred for an 1 hour. After solvent was removed on a rotary evaporator, the mixture was diluted with EtOAc (400 mL) and washed with brine (100 mL). The organic layers were dried with $MgSO_4$, and concentrated *in vacuo*. After purification by column chromatography (silica gel, hexane:EtOAc = 10:1), **12** was obtained as white powder (mg, 94% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.13~8.06 (m, 2H), 7.64~7.55 (m, 1H),), 7.48~7.47 (m, 2H), 7.39~7.23 (m, 10H), 7.01 (s, 1H), 5.76 (s, 1H), 1.39 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.09, 163.82, 162.97, 139.11, 133.69, 130.15, 128.64, 128.55,

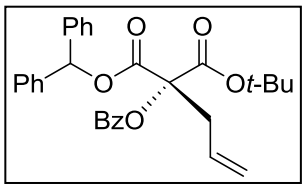
128.49, 128.46, 128.21, 127.27, 127.14, 84.05, 78.72, 72.73, 27.73 ppm ; IR (KBr) 2980, 1768, 1734, 1602, 1496, 1453, 1369, 1235, 1119, 1002, 838, 744, 700 cm^{-1} ; HRMS (FAB) : calcd for $[C_{22}H_{24}O_6]^+$: 447.1808, found : 447.1815 ; m.p. = 97.5 ℃.

2.2. General procedure for asymmetric phase-transfer catalytic alkylation



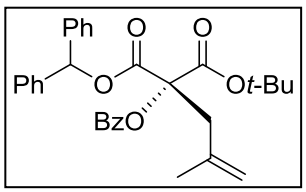
Alkyl halides (0.280 mmol) was added to a solution of α-benzoxymalonate substrates (0.056 mmol) and (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide (**16**, 2.6 mg, 0.003 mmol) in toluene (0.187 mL). At -20℃, 50% CsOH (48.8 μL, 0.280 mmol) was added to the reaction mixtures and stirred for designated time. EYELA PSL-1400 was used for low temperature stirring and the stirring rate was 7. The reaction mixtures was diluted with EtOAc (10 mL), washed with brine (2×3 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane:EtOAc = 10:1) to afford alkylated malonates.

*(R)-1-benzhydryl 3-tert-butyl 2-allyl-2-benzoxymalonate (**12a**)*



Following the general procedure, reaction was started from **12** (25 mg, 0.056 mmol) using allyl bromide (24.2 μL, 0.28 mmol). After 4 hours, **12a** was obtained as white oil (25.5 mg, 94% yield). HPLC analysis (Chiralpak AD-H, hexane:2-propanol = 85:15, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time = major 9.047 min, minor 11.063 min, 87% ee ; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.08~8.05 (m, 2H), 7.59~7.54 (m, 1H), 7.45~7.40 (m, 2H), 7.34~7.22 (m, 10H), 6.98 (s, 1H), 5.76~5.62 (m, 1H), 5.07~5.02 (m, 2H), 3.21~3.07 (m, 2H), 1.33 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.60, 164.67, 164.55, 139.38, 139.20, 133.40, 130.17, 129.99, 129.36, 128.42, 128.38, 128.30, 128.10, 127.94, 127.48, 127.23, 120.08, 83.56, 83.08, 78.48, 38.30, 29.68, 27.66 ppm ; IR (KBr) 3065, 3033, 2980, 2928, 1752, 1731, 1644, 1602, 1496, 4753, 1395, 1370, 1244, 1109, 1069, 1028, 991, 926, 842, 742, 648, 604 cm^{-1} ; HRMS (FAB) : calcd for $[C_{30}H_{31}O_6]^+$: 487.2121, found : 487.2126 ; $[\alpha]^{20}_D$ = 1.27 (*c* 1, $CHCl_3$).

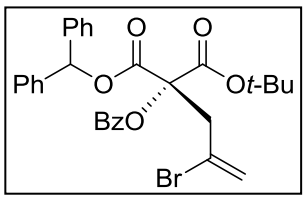
*(R)-1-benzhydryl 3-tert-butyl 2-(2-methylallyl)-2-benzoxymalonate (**12b**)*



Following the general procedure, reaction was started from **12** (25 mg, 0.056 mmol) using 3-bromo-2-methylpropene (28 μL, 0.28 mmol). After 3.5 hours, **12b** was obtained as white oil (21 mg, 75% yield). HPLC analysis (Chiralpak AD-H, hexane:2-propanol = 85:15, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time = major 7.530 min,

minor 10.620 min, 91% ee ; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.09~8.07 (m, 2H), 7.61~7.56 (m, 1H), 7.47~7.42 (m, 2H), 7.36~7.22 (m, 10H), 6.99 (s, 1H), 4.76~4.70 (m, 2H), 3.19 (s, 2H), 1.68 (s, 3H), 1.33 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.77, 164.71, 164.67, 139.33, 139.22, 139.10, 133.37, 129.96, 129.44, 128.41, 128.28, 128.08, 127.92, 127.51, 127.26, 116.16, 83.54, 83.48, 78.46, 40.98, 29.68, 27.62, 23.21 ppm ; IR (KBr) 3931, 3902, 3871, 3840, 3757, 3735, 3724, 3680, 3649, 3614, 3566, 3545, 3525, 3065, 3032, 2978, 2927, 2854, 2371, 2320, 1967, 1868, 1689, 1647, 1601, 1585, 1542, 1508, 1495, 1473, 1395, 1001, 954, 904, 843, 759, 743, 648, 618 cm^{-1} ; HRMS (FAB) : calcd for $[C_{31}H_{33}O_6]^+$: 501.2277, found : 501.2274 ; $[\alpha]^{20}_D$ = 3.98 (*c* 1, $CHCl_3$).

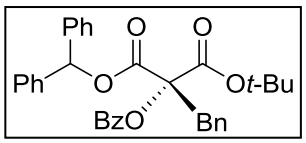
*(R)-1-benzhydryl 3-tert-butyl 2-(2-bromoallyl)-2-benzoxy malonate (**12c**)*



Following the general procedure, reaction was started from **12** (20 mg, 0.045 mmol) using 2,3-bromopropene (21.9 μL, 0.224 mmol). After 4 hours, **12c** was obtained as white oil (22.5 mg, 89% yield). HPLC analysis (Chiralpak AD-H, hexane:2-propanol = 85:15, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time = major 8.970 min, minor 14.590 min, 93% ee ; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.12~8.06 (m, 2H), 7.62~7.57 (m, 1H), 7.48~7.43 (m, 2H), 7.38~7.24 (m, 10H), 7.01 (s, 1H), 5.539~5.537 (m, 1H), 5.43~5.42 (m, 1H), 3.695 (d, *J* = 2.37, 2H), 1.33 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.04, 164.75, 163.89, 139.14, 139.02, 133.52, 130.10, 129.22, 128.46, 128.43, 128.32, 128.18, 128.03, 127.52, 127.30, 125.03, 122.14, 84.13, 82.48, 78.82,

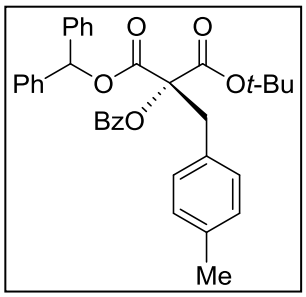
43.63, 27.58 ppm ; IR (KBr) 2979, 1753, 1729, 1627, 1602, 1496, 1453, 1395, 1370, 1289, 1244, 1144, 1069, 956, 903, 839, 742, 700 cm^{-1} ; HRMS (FAB) : calcd for $[C_{30}H_{30}O_6Br]^+$: 565.1226, found : 565.1223 ; $[\alpha]^{20}_D$ = - 3.89 (*c* 1, $CHCl_3$).

*(R)-1-benzhydryl 3-tert-butyl 2-benzyl-2-benzoxy malonate (**12d**)*



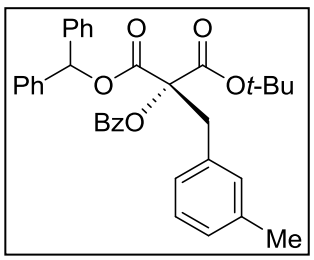
Following the general procedure, reaction was started from **12** (30 mg, 0.067 mmol) using benzyl bromide (39.8 μL, 0.335 mmol). After 4 hours, **12d** was obtained as colorless oil (37.9 mg, 99% yield). HPLC analysis (Chiralpak AD-H, hexane:2-propanol = 85:15, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time = major 9.080 min, minor 11.827 min, 91% ee ; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.01~7.99 (m, 2H), 7.60~7.56 (m, 1H), 7.45~7.43 (m, 2H), 7.35~6.98 (m, 10H), 6.91 (s, 1H), 3.72 (s, 2H), 1.30 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.61, 164.97, 164.46, 139.32, 139.17, 134.08, 133.38, 130.23, 129.98, 129.44, 128.46, 128.39, 128.28, 128.15, 127.87, 127.67, 127.17, 83.83, 83.61, 78.55, 64.39, 39.33, 31.56, 27.59, 25.33, 22.62, 14.08 ppm ; IR (KBr) 3064, 3032, 3979, 1752, 1727, 1601, 1495, 1453, 1394, 1370, 1316, 1284, 1153, 1108, 1084, 1033, 1002, 954, 843, 742, 700, 648 cm^{-1} ; HRMS (FAB) : calcd for $[C_{34}H_{32}O_6Na]^+$: 559.2097, found : 559.2098 ; $[\alpha]^{20}_D$ = 7.24 (*c* 1, $CHCl_3$).

*(R)-1-benzhydryl 3-tert-butyl 2-(4-methylbenzyl)-2-benzoxy malonate (**12e**)*



Following the general procedure, reaction was started from **12** (25 mg, 0.056 mmol) using 4-methylbenzyl bromide (51.8 mg, 0.280 mmol). After 2 hours, **12e** was obtained as white oil (28.1 mg, 91% yield). HPLC analysis (Chiralpak AD-H, hexane:2-propanol = 85:15, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time = major 9.033 min, minor 12.370 min, 91% ee ; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.03~7.35 (m, 2H), 7.60~7.56 (m, 1H), 7.46~7.41 (m, 2H), 7.36~7.26 (m, 10H), 6.98 (s, 1H), 6.95~6.87 (m, 4H), 3.67 (s, 2H), 2.26 (s, 3H), 1.32 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.61, 164.94, 164.52, 139.33, 139.19, 136.66, 133.35, 130.07, 129.99, 128.86, 128.49, 128.44, 128.42, 128.37, 128.24, 128.12, 127.83, 127.66, 127.15, 83.93, 83.53, 78.47, 38.94, 27.61, 21.01 ppm ; IR (KBr) 3839, 3724, 3064, 3032, 2979, 2927, 2310, 1751, 1730, 1602, 1542, 1516, 1496, 1453, 1395, 1370, 1316, 1282, 1176, 1154, 1110, 1069, 1048, 1002, 955, 842, 742, 712, 700, 648 cm^{-1} ; HRMS (FAB) : calcd for $[C_{35}H_{35}O_6]^+$: 551.2434, found : 551.2445 ; $[\alpha]^{20}_D$ = + 4.13 (*c* 1, $CHCl_3$).

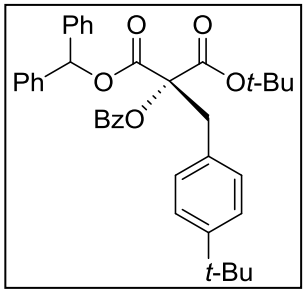
*(R)-1-benzhydryl 3-tert-butyl 2-(3-methylbenzyl)-2-benzoxy malonate (**12f**)*



Following the general procedure, reaction was started from **12** (25 mg, 0.056 mmol) using 3-methylbenzyl bromide (37.8 μL, 0.280 mmol). After 3 hours, **12f** was obtained as white oil (28.2 mg, 92% yield). HPLC analysis

(Chiralpak AD-H, hexane:2-propanol = 85:15, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time = major 7.153 min, minor 9.657 min, 91% ee ; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.01~7.98 (m, 2H), 7.60~7.55 (m, 1H), 7.45~7.40 (m, 2H), 7.37~7.24 (m, 10H), 7.05~6.98 (m, 3H), 6.96 (s, 1H), 6.86~6.81 (m, 1H), 3.67 (s, 2H), 2.13 (s, 3H), 1.31 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.65, 164.99, 164.48, 139.36, 139.23, 137.58, 133.92, 133.36, 131.13, 129.99, 129.51, 128.48, 128.37, 128.28, 128.15, 125.05, 127.91, 127.87, 127.62, 127.26, 127.16, 83.83, 83.56, 78.49, 39.25, 27.62, 21.15 ppm ; IR (KBr) 3063, 3032, 2979, 2930, 2321, 1751, 1729, 1602, 1495, 1453, 1395, 1370, 1316, 1284, 1176, 1154, 1107, 1069, 1047, 1002, 956, 911, 842, 799, 743, 713, 701, 648 cm^{-1} ; HRMS (FAB) : calcd for $[C_{35}H_{35}O_6]^+$: 551.2434, found : 551.2452 ; $[\alpha]^{20}_D$ = + 8.22 (*c* 1, $CHCl_3$).

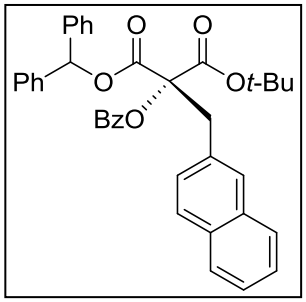
*(R)-1-benzhydryl 3-tert-butyl 2-(4-tert-butylbenzyl)-2-benzoxy malonate (**12g**)*



Following the general procedure, reaction was started from **12** (25mg, 0.056 mmol) using 4-(tert-butyl)benzyl bromide (51.4 μL, 0.280 mmol). After 2.5 hours, **12g** was obtained as white oil (22.5 mg, 89% yield). HPLC analysis (Chiralpak AD-H, hexane:2-propanol = 85:15, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time = major 6.163 min, minor 8.590 min, 91% ee ; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.00~7.97 (m, 2H), 7.60~7.55 (m, 1H), 7.46~7.42 (m, 2H), 7.36~7.28 (m, 10H), 7.15~7.13 (m, 2H), 7.01~6.97 (m, 3H), 3.68 (s, 2H), 1.28 (s, 9H), 1.24 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.75,

165.00, 164.52, 149.91, 139.34, 139.21, 138.65, 138.61, 133.33, 130.97, 130.39, 129.99, 129.90, 129.51, 128.74, 128.60, 128.50, 128.43, 128.35, 128.26, 128.11, 128.02, 127.87, 127.65, 127.42, 127.20, 125.04, 83.89, 83.51, 78.52, 38.96, 34.34, 31.27, 29.68, 27.57, 27.30 ppm ; IR (KBr) 3032, 2962, 2926, 1752, 1729, 1602, 1516, 1496, 1453, 1394, 1370, 1284, 1176, 1155, 1108, 1048, 956, 843, 743, 712, 700, 647 cm^{-1} ; HRMS (FAB) : calcd for $[C_{38}H_{41}O_6]^+$: 593.2903, found : 593.2922 ; $[\alpha]^{20}_D$ = + 7.49 (*c* 1, $CHCl_3$).

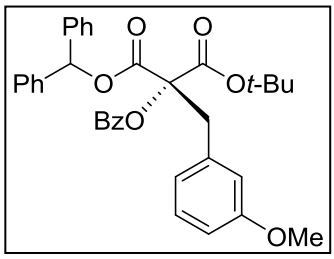
*(R)-1-benzhydryl 3-tert-butyl 2-(naphthalen-2-ylmethyl)-2-benzoxy malonate (**12h**)*



Following the general procedure, reaction was started from **12** (25 mg, 0.056 mmol) using 2-(bromomethyl) naphthalene (61.9 mg, 0.280 mmol). After 4 hours, **12h** was obtained as white oil (29 mg, 88% yield). HPLC analysis (Chiralpak AD-H, hexane:2-propanol = 85:15, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time = major 10.683 min, minor 15.570 min, 88% ee ; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.94~7.92 (m, 2H), 7.68~7.65 (m, 1H), 7.55~7.07 (m, 19H), 6.90 (s, 1H), 3.80 (s, 2H), 1.23 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.57, 165.06, 164.52, 139.31, 139.12, 133.42, 133.19, 132.52, 131.63, 130.00, 129.41, 129.24, 128.49, 128.41, 128.27, 128.24, 128.16, 127.86, 127.70, 127.62, 127.60, 127.51, 127.42, 127.21, 127.09, 125.86, 125.66, 83.99, 83.68, 78.59, 39.49, 27.62 ppm ; IR (KBr) 3840, 3739, 3648, 3614, 2928, 2359, 1748, 1689, 1647, 1602, 1542, 1508, 1489, 1452, 1372, 1288, 1154, 1047, 842, 702 cm^{-1} ; HRMS

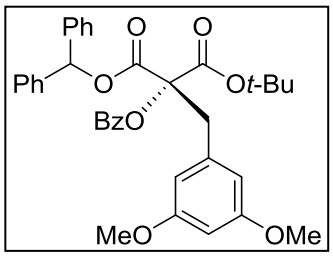
(FAB) : calcd for $[C_{38}H_{35}O_6]^+$: 587.2434, found : 587.2421 ; $[\alpha]^{20}_D$ = + 16.56 (*c* 1, $CHCl_3$).

*(R)-1-benzhydryl 3-tert-butyl 2-(3-methoxybenzyl)-2-benzoxy malonate (**12i**)*



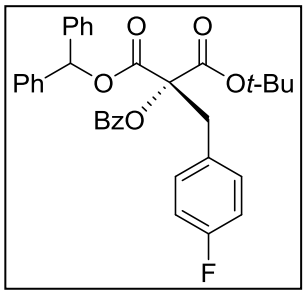
Following the general procedure, reaction was started from **12** (25 mg, 0.056 mmol) using 3-methoxybenzyl bromide (39.2 μL, 0.280 mmol). After 3 hours, **12l** was obtained as white oil (29 mg, 91% yield). HPLC analysis (Chiralpak AD-H, hexane:2-propanol = 85:15, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time = major 9.997 min, minor 12.763 min, 93% ee ; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.02~8.00 (m, 2H), 7.60~7.55 (m, 1H), 7.44~7.40 (m, 2H), 7.34~7.28 (m, 10H), 7.06~7.01 (m, 1H), 6.99 (s, 1H), 6.73~6.70 (m, 1H), 6.62~6.60 (m, 2H), 3.71 (s, 2H), 3.52 (s, 3H), 1.30 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.58, 164.95, 164.42, 159.32, 139.30, 139.18, 135.51, 133.43, 129.99, 129.43, 129.11, 128.47, 128.40, 128.29, 128.12, 127.90, 127.52, 127.18, 122.55, 115.31, 113.36, 83.80, 83.63, 78.52, 54.83, 39.27, 27.59 ppm ; IR (KBr) 3565, 3063, 3032, 2978, 2927, 2854, 2349, 1752, 1729, 1601, 1585, 1541, 1792, 1454, 1438, 1395, 1370, 1316, 1285, 1264, 1154, 1107, 1046, 1002, 956, 912, 841, 784, 744, 712, 699, 649, 618, 604 cm^{-1} ; HRMS (FAB) : calcd for $[C_{35}H_{34}O_7]^+$: 566.2305, found : 566.2310 ; $[\alpha]^{20}_D$ = + 1.68 (*c* 1, $CHCl_3$).

*(R)-1-benzhydryl 3-tert-butyl 2-(3,5-dimethoxybenzyl)-2-benzoxy malonate (**12j**)*



Following the general procedure, reaction was started from **12** (25mg, 0.056 mmol) using 3,5-dimethoxybenzyl bromide (64.7 mg, 0.280 mmol). After 3.5 hours, **12m** was obtained as white solid (31.1 mg, 93% yield). HPLC analysis (Chiralpak AD-H, hexane:2-propanol = 85:15, flow rate = 1.0 mL/min, 23 ℃, λ = 254 nm) retention time = major 11.020 min, minor 14.137 min, 91% ee ; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.04~8.01 (m, 2H), 7.60~7.55 (m, 1H), 7.45~7.40 (m, 2H), 7.37~7.26 (m, 10H), 6.99 (s, 1H), 6.28~6.22 (m, 3H), 3.69 (m, 2H), 3.50 (s, 6H), 1.30 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.56, 164.94, 164.39, 160.43, 139.30, 139.22, 136.21, 133.47, 130.00, 129.45, 128.49, 128.41, 128.31, 128.09, 127.93, 127.36, 127.21, 108.00, 100.00, 83.79, 83.64, 78.50, 54.96, 39.36, 29.68, 27.60 ppm ; IR (KBr) 3648, 3566, 3064, 3032, 2977, 2936, 2838, 2321, 1751, 1728, 1598, 1542, 1496, 1455, 1431, 1395, 1970, 1316, 1289, 1262, 1204, 1153, 1108, 1071, 1002, 958, 841, 793, 742, 712, 701, 648, 604 cm^{-1} ; HRMS (FAB) : calcd for $[C_{36}H_{36}O8]^{+}$: 596.2410, found : 596.2396 ; m.p = 106.8 ℃ ; $[\alpha]^{20}_{D}$ = - 5.22 (*c* 1, $CHCl_3$).

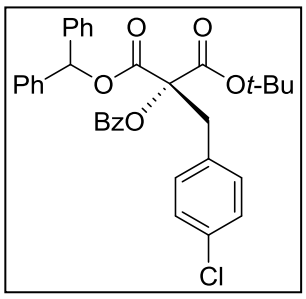
*(R)-1-benzhydryl 3-tert-butyl 2-(4-fluorobenzyl)-2-benzoxy malonate (**12k**)*



Following the general procedure, reaction was started from **12** (25 mg, 0.056 mmol) using 4-fluorobenzyl bromide (34.8 μL, 0.280 mmol). After 4 hours, **12i** was obtained as pale yellow solid (27.9 mg, 90% yield). HPLC analysis

(Chiralpak AD-H, hexane:2-propanol = 85:15, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time = major 10.017 min, minor 12.037 min, 85% ee ; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.01~7.98 (m, 2H), 7.61~7.56 (m, 1H), 7.46~7.41 (m, 2H), 7.37~7.29 (m, 10H), 6.98 (s, 1H), 6.96~6.92 (m, 2H), 6.82~6.74 (m, 2H), 3.68 (s, 2H), 1.31 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.04, 164.75, 163.89, 139.14, 139.02, 133.52, 130.10, 129.22, 128.46, 128.43, 128.32, 128.18, 128.03, 127.52, 127.30, 125.03, 122.14, 84.13, 82.48, 78.82, 77.32, 77.00, 76.68, 43.63, 27.58 ppm ; IR (KBr) 3033, 2962, 2926, 1752, 1729, 1602, 1516, 1496, 1453, 1394, 1370, 1284, 1176, 1155, 1108, 1048, 956, 843, 743, 712, 700, 647 cm^{-1} ; m.p = 111.9 ℃ ; $[\alpha]^{20}_{D}$ = + 5.09 (*c* 1, $CHCl_3$).

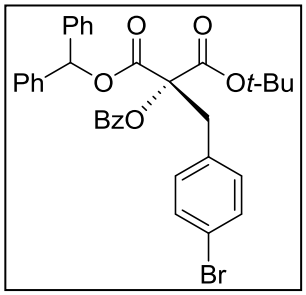
*(R)-1-benzhydryl 3-tert-butyl 2-(4-chlorobenzyl)-2-benzoxy malonate (**12l**)*



Following the general procedure, reaction was started from **12** (25 mg, 0.056 mmol) using 4-chlorobenzyl bromide (57.5 mg, 0.280 mmol). After 4 hours, **12j** was obtained as white powder (28 mg, 88% yield). HPLC analysis (Chiralpak AD-H, hexane:2-propanol = 85:15, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time = major 9.770 min, minor 12.137 min, 80% ee ; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.01~7.98 (m, 2H), 7.62~7.57 (m, 1H), 7.46~7.41 (m, 2H), 7.32~7.24 (m, 10H), 7.07~7.05 (m, 2H), 6.97 (s, 1H), 6.93~6.90 (m, 2H), 3.68 (s, 2H), 1.32 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.36, 165.91, 164.39, 139.20, 139.00, 133.56, 133.14, 139.54, 131.49, 129.94, 129.23,

128.50, 128.32, 128.24, 127.96, 127.65, 127.10, 83.82, 83.65, 78.64, 38.63, 27.61 ppm ; IR (KBr) 3902, 3064, 3033, 2979, 2926, 2854, 2375, 1751, 1729, 1648, 1601, 1585, 1542, 1493, 1453, 1409, 1395, 1370, 1316, 1290, 1176, 1154, 1109, 1094, 1070, 1045, 1016, 1002, 955, 910, 843, 814, 760, 742, 712, 700, 648 cm^{-1} ; HRMS (FAB) : calcd for $[C_{34}H_{32}ClO_6]^+$: 571.1887, found : 571.1884 ; m.p = 145.1 ℃ ; $[\alpha]^{20}_D$ = + 6.06 (*c* 1, $CHCl_3$).

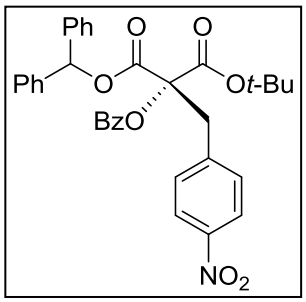
*(R)-1-benzhydryl 3-tert-butyl 2-(4-bromobenzyl)-2-benzoxy malonate (**12m**)*



Following the general procedure, reaction was started from **12** (30 mg, 0.056 mmol) using 4-bromobenzyl bromide (70.0 mg, 0.280 mmol). After 4 hours, **12k** was obtained as colorless crystal (31.7 mg, 92% yield). HPLC analysis (Chiralpak AD-H, hexane:2-propanol = 85:15, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time = major 10.827 min, minor 14.230 min, 86% ee ; ^{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 165.34, 164.90, 164.38, 139.18, 138.99, 133.56, 133.06, 131.85, 131.28, 129.94, 129.22, 128.50, 128.32, 128.23, 127.96, 127.64, 127.10, 121.31, 83.83, 78.65, 38.69, 27.61 ppm ; IR (KBr) 3032, 2979, 2930, 2310, 1750, 1730, 1602, 1489, 1452, 1395, 1370, 1316, 1289, 1176, 1154, 1108, 1070, 1045, 1012, 954, 842, 742, 712, 700, 648 cm^{-1} ; HRMS (FAB) : calcd for $[C_{34}H_{32}BrO_6]^+$: 615.1382, found : 615.1364 ; m.p = 64.3 ℃ ; $[\alpha]^{20}_D$ = + 7.79 (*c* 1,

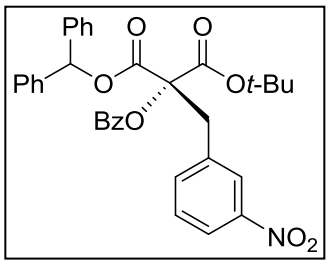
$CHCl_3$).

*(R)-1-benzhydryl 3-tert-butyl 2-(4-nitobenzyl)-2-benzoxy malonate (**12n**)*



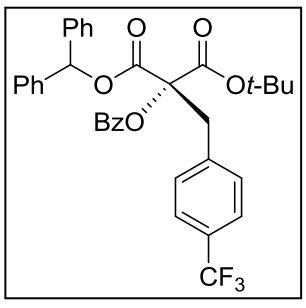
Following the general procedure, reaction was started from **12** (25 mg, 0.056 mmol) using 4-nitrobenzyl bromide (60.5 mg, 0.280 mmol). After 4 hours, **12n** was obtained as white solid (30 mg, 92% yield). HPLC analysis (Chiralpak AD-H, hexane:2-propanol = 80:20, flow rate = 1.0 mL/min, 23 ℃, λ = 254 nm) retention time = major 13.547 min, minor 21.870 min, 81% ee ; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.02~7.99 (m, 2H), 7.93~7.88 (m, 2H), 7.65~7.59 (m, 1H), 7.49~7.43 (m, 2H), 7.33~7.17 (m, 10H), 7.13~7.09 (m, 2H), 6.98 (s, 1H), 3.82 (s, 2H), 1.34 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.03, 164.84, 164.18, 147.13, 141.79, 139.01, 138.79, 133.81, 130.98, 129.90, 128.94, 128.61, 128.55, 128.35, 128.33, 128.10, 127.59, 127.09, 123.26, 84.21, 83.34, 78.82, 38.96, 27.60 ppm ; IR (KBr) 3931, 3902, 3840, 3757, 3735, 3724, 3649, 3614, 1566, 3065, 3032, 2979, 2930, 2372, 2321, 1868, 1731, 1688, 1648, 1603, 1523, 1495, 1474, 1453, 1396, 1374, 1348, 1317, 1284, 1177, 1154, 1109, 1070, 1047, 1002, 954, 711, 841, 760, 742, 712, 700, 649 cm^{-1} ; HRMS (FAB) : calcd for $[C_{34}H_{32}NO_8]^+$: 582.2128, found : 582.2140 ; m.p = 160.3 ℃ ; $[\alpha]^{20}_D$ = - 1.28 (*c* 1, $CHCl_3$).

*(R)-1-benzhydryl 3-tert-butyl 2-(3-nitrobenzyl)-2-benzoxy malonate (**12o**)*



Following the general procedure, reaction was started from **12** (25 mg, 0.056 mmol) using 3-nitrobenzyl bromide (60.5 mg, 0.280 mmol). After 4 hours, **12o** was obtained as white oil (28.6 mg, 88% yield). HPLC analysis (Chiralpak AD-H, hexane:2-propanol = 80:20, flow rate = 1.0 mL/min, 23 ℃, λ = 254 nm) retention time = major 13.187 min, minor 16.717 min, 61% ee ; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.06~8.00 (m, 4H), 7.63~7.57 (m, 1H), 7.48~7.43 (m, 2H), 7.35~7.20 (m, 12H), 6.97 (s, 1H), 3.80 (s, 2H), 1.33 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.19, 164.90, 164.07, 147.95, 139.05, 138.89, 136.37, 136.13, 133.75, 129.94, 129.07, 128.92, 128.57, 128.52, 128.32, 128.26, 128.03, 127.47, 127.09, 125.18, 122.37, 84.27, 83.22, 78.84, 39.07, 27.60 ppm ; IR (KBr) 3066, 3033, 2980, 2933, 1752, 1732, 1602, 1585, 1531, 1495, 1453, 1395, 1370, 1352, 1316, 1283, 1207, 1176, 1153, 1095, 1069, 1048, 1002, 954, 908, 840, 809, 734, 712, 700, 648, 603 cm^{-1} ; HRMS (FAB) : calcd for $[C_{34}H_{32}NO_8]^+$: 582.2128, found : 582.2139 ; $[\alpha]^{20}_{D}$ = + 4.23 (*c* 1, $CHCl_3$).

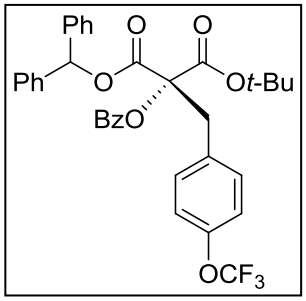
*(R)-1-benzhydryl 3-tert-butyl 2-(4-trifluoromethylbenzyl)-2-benzoxy malonate (**12p**)*



Following the general procedure, reaction was started from **12** (25 mg, 0.056 mmol) using 4-(trifluoromethyl) benzyl bromide (66.9 mg, 0.280 mmol). After 3 hours, **12p** was obtained as white solid (29 mg, 86% yield). HPLC analysis (Chiralpak AD-H, hexane:2-propanol = 85:15, flow rate =

1.0 mL/min, 23 °C, λ = 254 nm) retention time = major 8.003 min, minor 10.960 min, 80% ee ; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.01~7.98 (m, 2H), 7.63~7.57 (m, 1H), 7.49~7.42 (m, 2H), 7.38~7.20 (m, 12H), 7.11~7.08 (m, 2H), 6.98 (s, 1H), 3.78 (s, 2H), 1.32 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.30, 164.91, 164.31, 139.13, 138.93, 138.26, 133.65, 130.49, 129.93, 129.57, 129.25, 129.13, 128.53, 128.33, 128.29, 128.03, 127.65, 127.11, 125.08, 125.04, 125.00, 83.99, 83.52, 78.75, 38.99, 27.59 ppm ; IR (KBr) 3839, 3648, 3566, 3065, 3033, 2980, 2934, 2321, 1922, 1752, 1730, 1619, 1602, 1585, 1542, 1496, 1475, 1453, 1418, 1395, 1371, 1326, 1284, 1165, 1125, 1115, 1068, 1049, 1020, 1002, 954, 911, 859, 843, 796, 789, 743, 712, 700, 648, 630, 618, 603 cm^{-1} ; HRMS (FAB) : calcd for $[C_{35}H_{32}F_3O_6]^+$: 605.2151, found : 605.2160 ; m.p = 138.4 ℃ ; $[\alpha]^{20}_D$ = + 4.24 (*c* 1, $CHCl_3$).

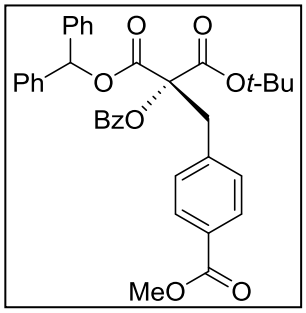
*(R)-1-benzhydryl 3-tert-butyl 2-(4-trifluoromethoxybenzyl)-2-benzoxy malonate (**12q**)*



Following the general procedure, reaction was started from **12** (25 mg, 0.056 mmol) using 4-(trifluoromethoxy) benzyl bromide (44.9 μL, 0.280 mmol). After 2.5 hours, **12q** was obtained as viscous oil (38.6 mg, 99% yield). HPLC analysis (Chiralpak AD-H, hexane:2-propanol = 85:15, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time = major 7.033 min, minor 9.117 min, 78% ee ; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.00~7.97 (m, 2H), 7.62~7.56 (m, 1H), 7.49~7.42 (m, 2H), 7.39~7.17 (m, 10H), 7.04~6.93 (m, 5H), 3.72 (s, 2H), 1.31 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.41, 164.91, 164.37, 148.38, 139.18,

138.99, 133.58, 132.86, 131.55, 130.51, 129.92, 129.21, 128.50, 128.32, 128.25, 127.98, 127.66, 127.12, 121.16, 120.55, 83.87, 83.61, 78.69, 38.61, 27.56 ppm ; IR (KBr) 3931, 3902, 3882, 3871, 3839, 3759, 3735, 3724, 3680, 3649, 3614, 3566, 3545, 3525, 3065, 3033, 3879, 2928, 2855, 2350, 2320, 1908, 1868, 1751, 1730, 1689, 1648, 1602, 1585, 1542, 1509, 1496, 1474, 1453, 1395, 1374, 1315, 1261, 1224, 1200, 1159, 1110, 1069, 1046, 1002, 954, 922, 843, 760, 743, 712, 700, 648, 604 cm^{-1} ; HRMS (FAB) : calcd for $[C_{35}H_{31}F_3O_7Na]^+$: 643.1920, found : 643.1929 ; $[\alpha]^{20}_D$ = + 5.27 (*c* 1, $CHCl_3$).

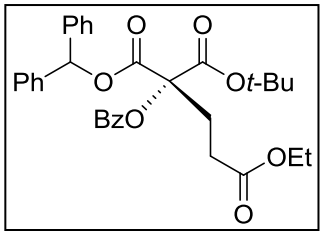
*(R)-1-benzhydryl 3-tert-butyl 2-(mehtylbenoate-4-methyl)-2-benzoxy malonate (**12r**)*



Following the general procedure, reaction was started from **12** (25 mg, 0.056 mmol) using methyl 4-(bromomethyl) benzoate (64.1 mg, 0.280 mmol). After 3.5 hours, **12r** was obtained as white solid (29.8 mg, 90% yield). HPLC analysis (Chiralpak AD-H, hexane:2-propanol = 85:15, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time = major 13.950 min, minor 19.503 min, 81% ee ; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.01~7.99 (m, 2H), 7.80~7.77 (m, 2H), 7.63~7.57 (m, 1H), 7.47~7.42 (m, 2H), 7.36~7.19 (m, 10H), 7.10~7.07 (m, 2H), 6.98 (s, 1H), 3.88 (s, 3H), 3.78 (s, 2H), 1.32 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 166.82, 165.31, 164.90, 164.28, 139.46, 139.17, 138.98, 133.56, 130.22, 129.93, 129.42, 129.17, 129.03, 128.49, 128.29, 128.24, 127.94, 127.60, 127.11, 83.89, 83.52, 78.68, 51.98, 39.20, 27.60 ppm ; IR (KBr) 3757, 3648, 3566, 3032, 2979, 2951,

2319, 1751, 1725, 1612, 1543, 1508, 1496, 1452, 1436, 1416, 1395, 1370, 1317, 1282, 1179, 1154, 1108, 1070, 1046, 956, 842, 760, 743, 703, 648 cm^{-1} ; HRMS (FAB) : calcd for $[C_{36}H_{35}O_8]^+$: 595.2332, found : 595.2331 ; m.p = 95.0 ℃ ; $[\alpha]^{20}_D$ = + 6.55 (*c* 1, $CHCl_3$).

*(R)-3-benzhydryl 3-tert-butyl 3-benzoxy 1-ethyl propane-1,3,3-tricarboxylate (**12s**)*



Following the general procedure, reaction was started from **12** (20 mg, 0.045 mmol) using ethyl acrylate (24.4 μL, 0.224 mmol). After 30 minutes, **12s** was obtained as colorless oil (17.6 mg, 72% yield). HPLC analysis (Chiralpak AD-H, hexane:2-propanol = 85:15, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time = major 15.443 min, minor 19.467 min, 40% ee ; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.07~8.04 (m, 2H), 7.62~7.56 (m, 1H), 7.47~7.42 (m, 2H), 7.37~7.23 (m, 10H), 6.98 (s, 1H), 4.03 (q, *J* = 7.14 Hz, 2H), 2.83~2.67 (m, 2H), 2.42~2.22 (m, 2H), 1.36 (s, 9H), 1.18 (t, *J* = 7.14 Hz, 3H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.93, 165.55, 164.63, 164.55, 139.33, 139.12, 133.48, 129.99, 129.18, 128.47, 128.40, 128.35, 128.13, 127.99, 127.37, 127.21, 83.80, 82.78, 78.69, 60.61, 29.21, 28.59, 27.62, 14.08 ppm ; IR (KBr) 3064, 3033, 2980, 2931, 2375, 1736, 1602, 1585, 1543, 1496, 1475, 1452, 1394, 1371, 1316, 1285, 1181, 1155, 1107, 1096, 1082, 1027, 1010, 951, 912, 894, 842, 759, 743, 701, 648, 618, 604 cm^{-1} ; HRMS (FAB) : calcd for $[C_{32}H_{35}O_8]^+$: 547.2332, found : 547.2318 ; $[\alpha]^{20}_D$ = - 1.02 (*c* 1, $CHCl_3$).

The spectral data was identical with the reported data.

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국문초록

광학활성을 갖는 알파 하이드록시 말로네이트 종류들은 천연물질과 의약품을 합성하는데 귀중한 잠재성을 갖고 있는 화합물이다. 알파 하이드록시 말로네이트는 광학적인 글리세롤이나 알파,베타 다이하이드록시 에스테르로 용이하게 변환될 수 있다. 그 동안 알파 하이드록시 베타 키토이스터의 입체선택적인 합성법들이 있었으나 대부분 프로카이랄 말로네이트의 효소를 이용한 비대칭법을 통해 이루어진 것들이였다.

최근 본 연구실에서는 광학활성이 있는 사차탄소 암모늄 염을 촉매로 한 상전이촉매반응(PTC)을 통해 높은 화학수율과 입체선택성으로 말로네이트의 비대칭 반응으로 광학활성을 갖는 다이알킬말로네이트의 새로운 합성법을 보고한 바 있다. 또한 사차탄소를 갖는 다양한 광학적 탄소 블록으로의 변환을 통해 이 합성법의 유용성을 증명하였다.

이를 기초로 하여 알파 벤족시말로네이트를 기질로 한 상전이 촉매반응을 (*S,S*)-3,4,5-trifluorophenyl-NAS bromide 를 촉매로 하여 매우 입체선택적으로 알킬화하였으며, 합성된 벤족시-알킬말로네이트는 높은 화학수율 (최고 99%)과 광학수율 (최고 93%)를 보였다. 이 화합물은 용이하게 다양한 광학활성 중간체로 변환될 수 있다.

주요어 : 알파 하이드록시 말로네이트, 입체선택적 합성, 상전이 촉매반응, 알파 벤족시 알킬말로네이트

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