약학박사학위논문

Enantioselective construction of α-quaternary carbon centers of α-alkyl malonates and α-amido malonates by asymmetric phase-transfer catalytic alkylation

상전이 촉매 알킬화 반응을 통한 α-alkyl malonate 및 α-amido malonate의 α위치에의 비대칭 4 급 탄소 합성에 관한 연구

2015 년 2 월

서울대학교 대학원

약학과 약품제조화학전공

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지도교수 박 형 근

이 논문을 약학박사 학위논문으로 제출함
2014 년 11 월

서울대학교 대학원
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하 민 우

하 민 우의 약학박사 학위논문을 인준함

2014 년 12 월

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ABSTRACT

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Malonate structure has commonly been utilized as a principle synthetic unit for C-C bond formation thanks to its electronic properties in organic synthetic chemistry. Especially, α-chiral malonate compounds have been quite popularly applyed for the construction of chiral α-quaternary carbon centers of biologically active natural products and pharmaceuticals. Based on their synthetic values, although many methodologies for efficiently obtaining α-chiral malonates have been researched, development of synthetic methods by chemical conversion based on organic chemical theory has not been fully realized. Very recently, our research team succeeded in inducing the chirality at α-position of malonate with high stereoselectivity through asymmetric phase-transfer catalytic alkylation of diphenylmethyl *tert*-butyl α-methylmalonate. It was the first chemically performed enatioseletive α-alkylation of malonate. However, in regard of modification of synthesized chiral compounds, we experienced challenges in chemoselective cleavage of the two different ester parts. Selective deprotection of the *tert*-butyl group was not successful due to partial hydrolysis of the diphenylmethyl group under acidic conditions. In alkali basic conditions the diphenylmethyl ester could not be hydrolyzed due to steric hindrance. In order to fix the shortcomings and extend the usefulness of our synthetic method, we has made efforts to construct an improved method for preparation of chiral malonates.

First, we designed new malonates bearing slightly small sized one ester group, which were examined for their efficiency by phase-transfer catalytic α-alkylation. Through comparision between 13 kinds of designed substrates, 2-methylbenzyl *tert*-butyl malonate has been developed as an efficient hydrolyzable malonate substrate under alkali basic

conditions. Asymmetric phase-transfer catalytic α-alkylation of 2-methylbenzyl *tert*-butyl α-methylmalonate afforded the corresponding α, α-dialkylmalonates in high chemical (up to 99%) and optical yields (up to 91% ee).

Furthemore, The synthesis of optically active nitrogen-containing organic compounds is very important in organic and medicinal chemistry due to their versatile biological activities and pharmaceutical applications. There has been a lot of enantioselective synthetic methods of α-amino-β-ketoester system. However, the enantioselective synthetic methods of α-amino malonate system have been mostly achieved by the enzymatic desymmetrization of prochiral α-amino malonates, and there are only a few cases as a part of studies via chemical conversions. We planned to develop a new synthetic method for chiral α-amino malonates via well- established enantioselective phase-transfer catalytic α-alkylation of malonates. Incorporation of amino group into α-position of malonates, followed by enantioselective α-alkylation via phase-transfer catalysis as a key step for asymmetric induction would provide chiral quaternary α-amino malonates. Herein, we reported that efficient enantioselective α-alkylations of diphenylmethyl *tert*-butyl α-substituted amido malonate was accomplished under phase-transfer catalysis in the presence of (S,S)-3,4,5-trifluorophenyl-NAS bromide to afford the corresponding α-amido α-alkylmalonates in high chemical yields (up to 99%) and optical yields (up to 97% ee), being converted to versatile unnatural amino acids including (*R*)- α-benzyl serine.

Our new catalytic system would provide an attractive synthetic method for various chiral building blocks which could be readily converted to versatile chiral target molecules with involvement of quaternary carbon centers.

Key words: asymmetric synthesis, phase-transfer catalysis, chiral malonate, α, α-dialkyl malonates, nitrogen-containing organic compound, quaternary carbon center

Student ID: 2011-31108

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INTRODUCTION

1. Asymmetric phase-transfer catalysis

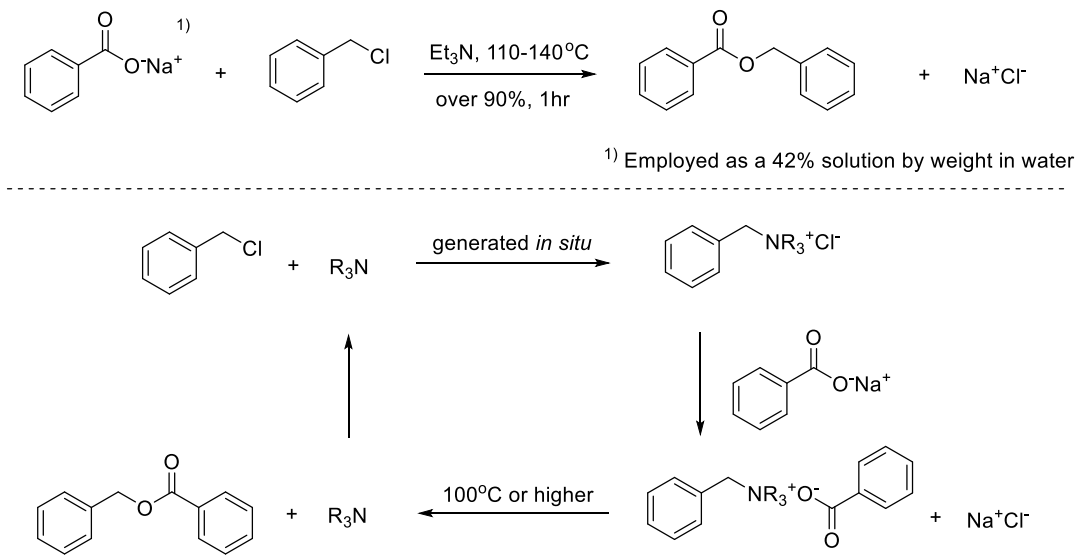
1-1. Nature of phase-transfer catalysis

In principle, reactions between molecules located in different phases of a mixture are inhibited by the inability of the reagents to interact. However, if certain molecules that can transfer between the phases and can serve as vehicles to bring one reactant into the same phase as the second reactant are placed in the reaction condition, then interaction between the chemical species situated in the different phases can occur with the assistance of that molecule. Such a molecule is called a “phase-transfer catalyst”, and the type of reaction in which the phase-transfer catalyst participates is called “phase-transfer catalysis”. In reality, the reaction with no phase-transfer catalyst is extremely slow and regarded as not occurring at all. Using a catalyst that transfers between the two phases, the reaction can commence.

The representative reaction system applied to phase-transfer catalysis is a biphasic system composed of an organic phase, containing an acidic compound and an electrophile, and an aqueous solution of a solid phase of an inorganic base, such as an alkaline metal (Na, K, or Cs) hydroxide or carbonate. The key reactive intermediates in this type of reaction are onium-carbanion species, primarily onium-enolate complexes, which react with the electrophile in the organic phase to afford the desired compound. The most commonly used phase-transfer catalysts are onium (ammonium, phosphonium, and occasionally arsonium) salts or complexing agents (crown ethers, polyethers, and polyols, among others) that may mask and solubilize the inorganic cations, conveying them to their new location.

1-1-1. Origin of phase-transfer catalysis

A molecule acting as a phase-transfer catalyst and the reaction in which the phenomenon occurred were first reported in 1946 by Walter H. C Rueggeberg [1]. The term "phase-transfer catalysis" had not yet appeared, and a concrete description had not yet been provided, making this occurrence the first clear introduction of a phase-transfer catalytic reaction.

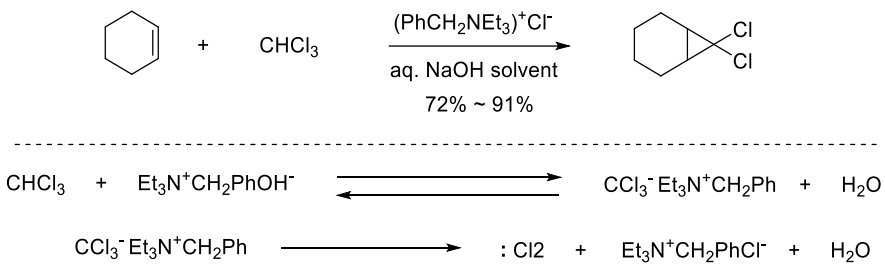


Scheme 1. The first report of phase-transfer catalysis

Rueggeberg recorded the reaction forming benzyl benzoate from benzyl chloride and sodium benzoate in aqueous solution. In the amine-catalyzed reaction between 1 mole of sodium benzoate and 1.4 moles of benzyl chloride, the results indicated that the tertiary amines, such as triethylamine, produced benzyl benzoate in yields of over 90% for a reaction period of approximately 1 hour at 110-140℃. A probable reaction mechanism was postulated that the amine-catalyzed formation of benzyl benzoate might proceed by the formation of a quaternary ammonium intermediate. This suggestion was proposed because

the trialkyl benzyl ammonium salts thermally decomposed, contrary to Hoffmann's rule, to produce a trialkyl amine and benzyl derivatives, depending on the negative ion in the parent salt. The triethyl benzyl ammonium chloride formed in situ by the addition of triethylamine can be regarded as a phase-transfer catalyst, and the above reaction provides indisputable evidence for the first phase-transfer catalysis.

In 1969, M. Makosza, a Polish chemist, formulated the first mechanistic hypothesis on phase-transfer catalysis [2] and described the catalytic method for the preparation of dichlorocyclopropane derivatives in an aqueous medium.

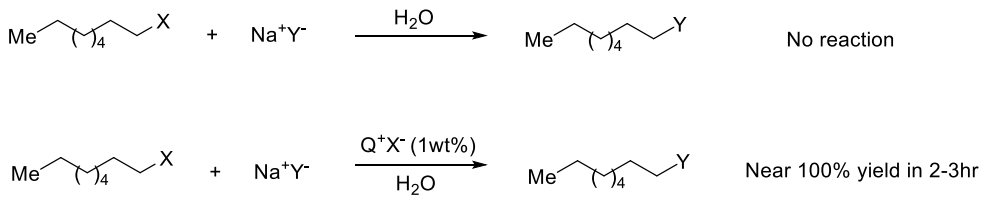


Scheme 2. The first formulation of phase-transfer catalysis

Although the reaction was performed in an aqueous medium and with only an equimolar amount of olefin, the dichlorocyclopropane derivatives were obtained with high yields. The reaction without the catalyst afforded the desired product in only 0.5% yield. This result was explained by the quaternary ammonium compound's catalytic mode of action. In a concentrated sodium hydroxide solution, tetraethylbenzyl ammonium chloride was transformed into the hydroxide, which is insoluble in the reaction medium. Therefore, the quaternary ammonium hydroxide migrated to the boundary between the aqueous and organic phases, where it reacted with chloroform to yield the quaternary ammonium derivative of the trichloromethyl anion. After diffusion into the organic phase, the derivative was transformed into dichlorocarbene and ammonium chloride. Dichlorocarbene

reacted rapidly with the olefin present in the organic layer, while ammonium chloride passed to the phase boundary and reentered the transformation cycle. Therefore, Makosza postulated an ion exchange between the triethylammonium chloride and the aqueous sodium hydroxide to form a base that can react in the organic phase.

In 1970, Charles M. Starks introduced the term "phase-transfer catalysis" to explain the critical role of tetraalkylammonium or phosphonium salts (Q^+X^-) in the reactions between two substances in different immiscible phases [3]. For example, the displacement reactions shown in **Scheme 3** were performed in a heterogeneous system using quaternary salts as anion-transfer catalysts.



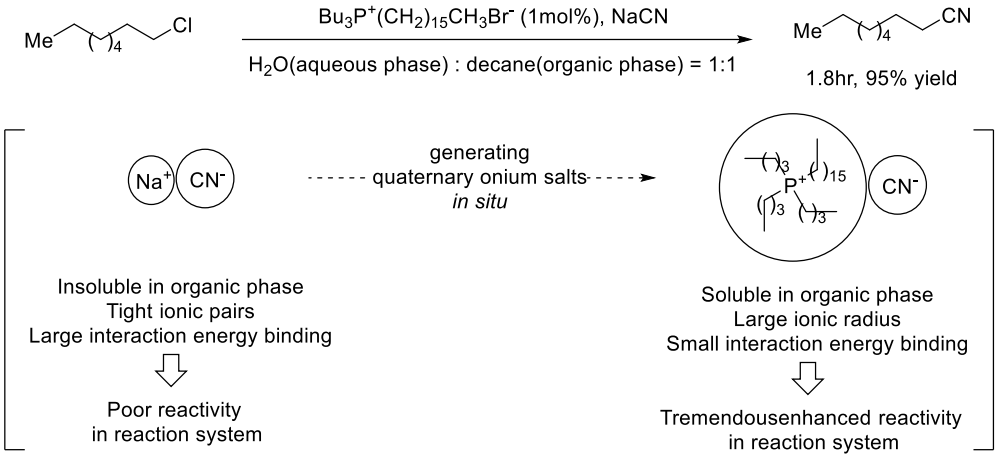
X = Cl, Br, CH_3SO_3
Y = CN, Cl, Br, I, RCO_2, NO_2, NCO, OH, $CH(CN)_2$, C_6H_5CHCN

Scheme 3. The first description of the term "phase-transfer catalysis"

The reactions occurred through small quantities of an agent that transferred one reactant across the interface into the other phase, enabling the reactions to proceed. The phase-transfer agent was not consumed but performed the transport function repeatedly.

Scheme 4 shows the concrete reaction condition of the displacement of 1-chlorooctane with sodium cyanide. The addition of only 1 mol% of hexadecyltributylphosphonium bromide as the phase-transfer catalyst made the reaction possible and accelerated it several thousandfold. The key contribution to this tremendous enhancement of reactivity was the formation of quaternary phosphonium cyanide, making the cyanide anion soluble in the

organic solvents and rendering it sufficiently nucleophilic. The high rate of displacement is primarily due to the properties of the pairing cation (Q^+), namely high lipophilicity and a large ionic radius.



Scheme 4. Tetraalkylonium salts as phase-transfer catalysts

The above study was the first report that emphasized the causal roles of the catalytic activity of the quaternary onium salts. With the above observation, gradation studies on phase-transfer catalysis began to. Since that time, Starks, Makosza, and Brändstörm have systematically laid the foundation for phase-transfer catalysis. However, primarily due to the difficulty of investigating biphasic systems and the multiple parameters that must be analyzed, the mechanistic aspects of phase-transfer catalysis remain relatively obscure.

1-1-2. Mechanism of phase-transfer catalysis

The typical reaction condition of phase-transfer catalysis is an immiscible biphasic system consisting of an organic phase containing an acidic molecule and an electrophile and an aqueous phase containing an inorganic alkaline base. The critical intermediate of this

reaction is an onium-carbanion complex, which encounters the electrophile in the organic solvents. The exact pathway for generating the reactive intermediate, the onium-carbanion complexes, remains the subject of controversy between the Starks extraction mechanism and the Makosza interfacial mechanism.

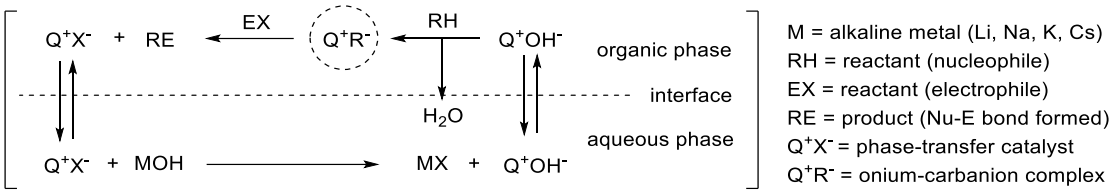


Figure 1. Starks's extraction mechanism of phase-transfer catalysis

In the Starks extraction mechanism [3], the phase-transfer catalyst directly alternates across the organic and aqueous phases. The onium salt, the phase-transfer catalyst (Q^+X^-), equilibrates with the inorganic base (MOH) in the aqueous phase and extracts hydroxide (OH^-) into the organic phase. The onium hydroxide (Q^+OH^-) then extracts hydrogen from the acidic organic compound (RH) to afford the reactive intermediate onium-carbanion complex (Q^+R^-) and one molecule of water. The activated anion, as a form of the onium-carbanion species, can interact with various halides (RX) in the organic solvent, regenerating the phase-transfer catalyst. In the extraction mechanism, the inorganic anion is transferred to the organic phase, and a full-scale phase-transfer catalytic substitution reaction occurs in the organic phase. The catalyst (Q^+X^-) is required for both the transfer step and the reaction step.

In contrast, according to the interfacial mechanism [4], the deprotonation occurs in the interfacial region between the organic and aqueous phases. The carbanion (R^-) formed in this manner is combined in the interfacial region; it cannot enter the aqueous phase due to the strong salting-out effect of the concentrated aqueous metal hydroxide, and it cannot

enter the organic phase because the accompanying metal cation (MR) cannot move into that phase from the aqueous phase.

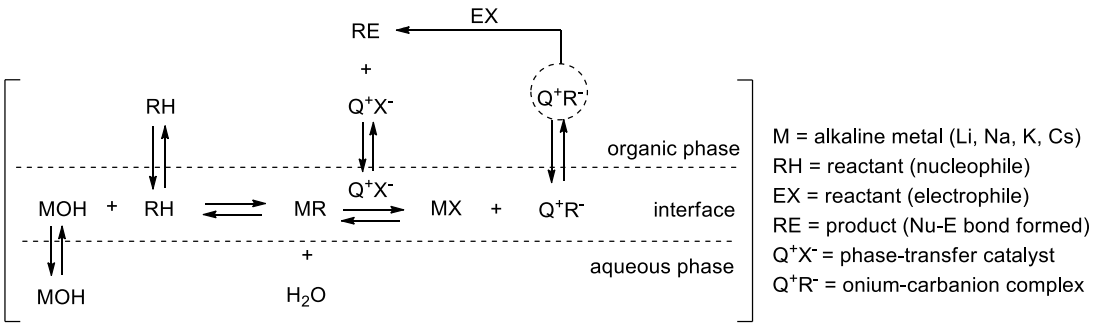
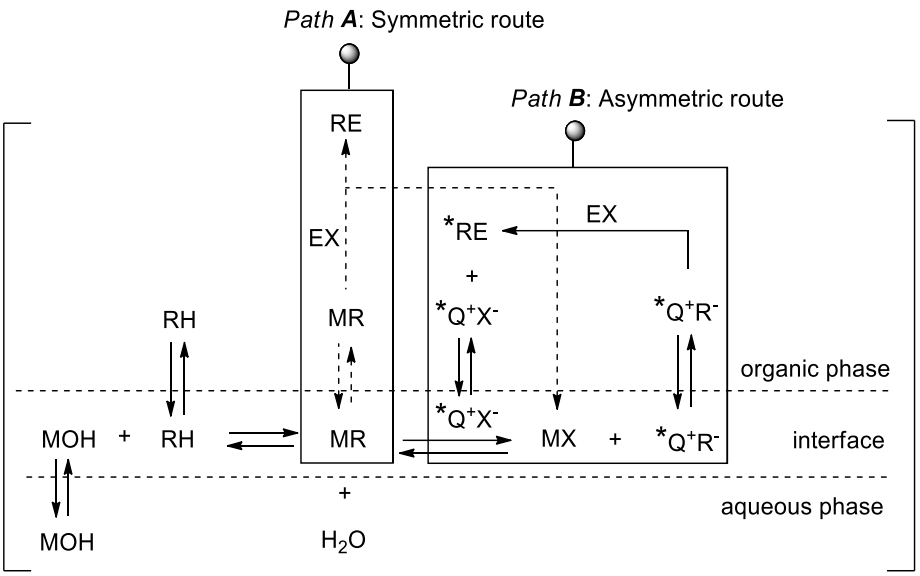


Figure 2. Makosza's interfacial mechanism of phase-transfer catalysis

The proposed pathway of the interfacial mechanism is described from the first generation of the metal carbanion (MR) at the interface of the organic and aqueous phases in the absence of a phase-transfer catalyst, followed by the extraction of the formed metal carbanion species from the interface into the organic phase by the action of a phase-transfer catalyst. When the catalyst, a source of lipophilic cations (Q^+), is added, the ion exchange at the interface causes the metal carbanion (MR) to become lipophilic in pairs (Q^+R^-), which enter the organic phase where further reactions occur. The onium salt (Q^+X^-) regenerated in the alkylation process reenters the ion exchange at the interface, thus introducing the next carbanion into the organic phase. The fate of the onium carbanion (Q^+R^-) incorporated into the organic phase depends on the electrophilic reaction partner.

When chiral no-racemic phase-transfer catalysts ($*Q^+X^-$) are used in reactions affording new stereogenic centers, the reactions may proceed stereoselectively to yield chiral non-racemic products. The common mechanism of the asymmetric phase-transfer catalysis is described as path B in **Scheme 5**.



Scheme 5. General mechanism of asymmetric phase-transfer catalysis

The undesired process in path A can occur in competition with path B, which is the desired step generating the optically active product. The specific explanation of path B is as follows. The first step of the reaction is the interfacial deprotonation of the acidic proton of the reactant (RH) with the base (MOH) to give the corresponding metal enolate (MR), which remains at the interface of the two layers. The subsequent ion exchange of the anion with the chiral catalyst ($*Q^+X^-$) generates a lipophilic chiral onium enolate ($*Q^+R^-$). This step causes the enolate to penetrate into the organic phase where it reacts with an electrophile to afford the optically active chiral product (*RE). Path B is only successful when the chiral onium cation ($*Q^+$) generates the highly reactive chiral onium enolate ($*Q^+R^-$) through a sufficiently fast ion-exchange step and the effective shielding of one of the two enantiotopic faces of the enolate anion; the former minimizes the intervention of the direct reaction of the metal enolate (MR) to give a racemic product (RE), whereas the latter rigorously controls the absolute stereochemistry.

Therefore, to ensure the high optical purity of the chiral product (*RE), the ion exchange step must occur with sufficient speed, preventing the undesired racemic reaction with the metal salt (MR). Additionally, the ion pair between the quaternary onium salt ($*Q^+$) on the catalyst and the enolate (R^-) on the substrate should have a good structural fit to yield high optical purity. Furthermore, to ensure rapid ion exchange and the optimal reaction of the cation of the catalyst and the anion of the substrate in the ion pair, the reaction mixture should be stirred vigorously.

The Starks extraction mechanism and the interfacial mechanism have been suggested as mechanisms of phase-transfer catalysis. As in the previously described case, the interfacial mechanism appears to operate in asymmetric phase-transfer catalysis.

1-1-3. Virtue of phase-transfer catalysis

Phase-transfer catalysis has historically been recognized as a practical methodology for organic synthesis in academia and in industry because of its operational simplicity, high yield process, mild reaction conditions, use of safe and inexpensive reagents and solvents, safety considerations, environmental concerns, and applicability to reactions on a large scale [5]. Therefore, phase-transfer catalysis is currently a basic and useful tool in various chemical applications, such as heterocyclic chemistry, polymer chemistry, and organometallic chemistry. Furthermore, because phase-transfer catalysis increases the rate of the reaction, a quality employed especially in pharmaceutical and agrochemical manufacturing and in the perfume, flavor, and dye industries, it also has a vast spectrum of analytical applications, such as in medicinal and forensic laboratories. In particular, asymmetric phase-transfer catalysis based on structurally well-defined chiral, non-racemic

phase-transfer catalysts has become a versatile tool to introduce a novel chirality on molecules.

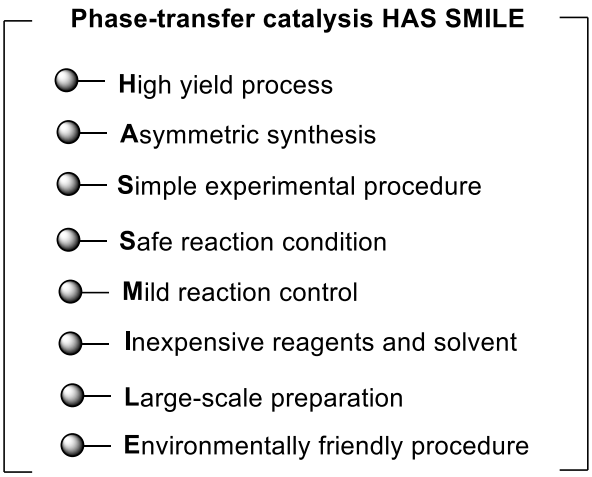


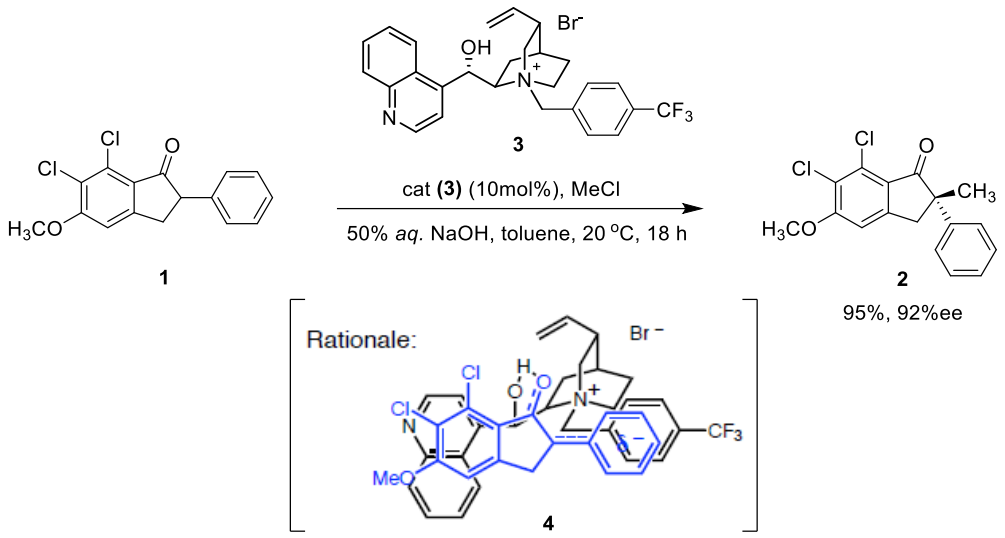
Figure 3. Advantages of phase-transfer catalysis

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

1-2. Progress in asymmetric phase-transfer catalytic alkylation

The asymmetric alkylation of active methylene compounds is central to the field of symmetric phase-transfer catalysis, and its development was triggered by the pioneering study by a Merck research group in 1984 [6]. Dolling and co-workers utilized the cinchonine-derived quaternary ammonium salt **3** as the catalyst for the methylation of phenylindanone **1** under liquid-liquid phase-transfer conditions and succeeded in obtaining

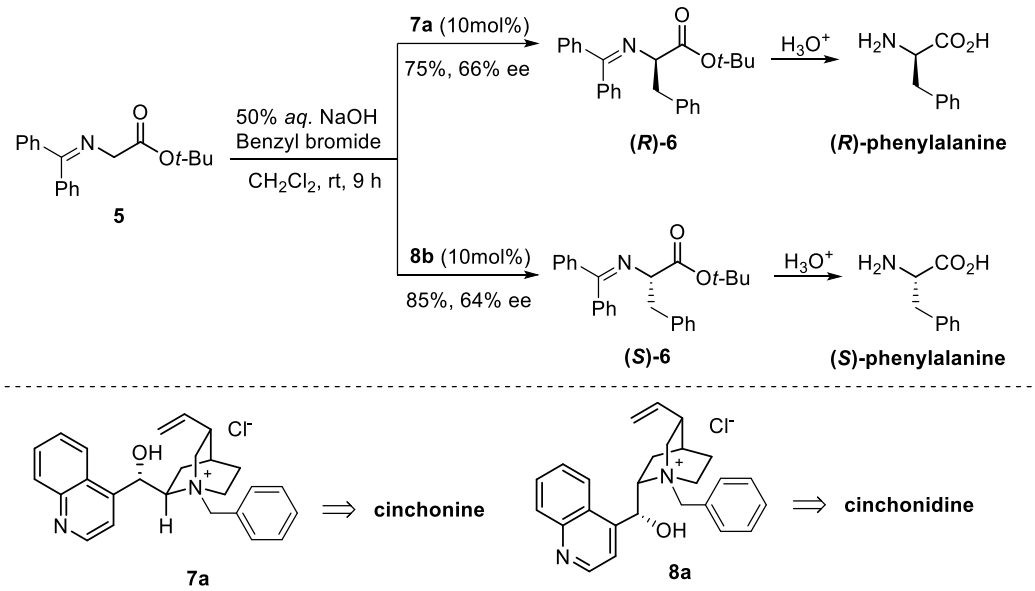
the corresponding methylated product **2** in excellent yield and with high enantioselectivity (**Scheme 6**). These authors conducted systematic studies of this reaction and proposed the tight ion pair intermediate **4**, formed through hydrogen bonding and electrostatic and π-π stacking interactions, to account for the result. This study has been recognized as the first trial of asymmetric phase-transfer catalytic alkylation by the newly designed catalyst that can be prepared from the cinchonine alkaloid.



Scheme 6. The first asymmetric phase-transfer catalytic alkylation

After five years of successful application of the cinchonine-derived quaternary ammonium salt **3** by the Merck research group, M. J. O'Donnell and co-workers applied a similar *Cinchona*-derived quaternary ammonium salt for the alkylation of (*N*)-(diphenylmethylene) glycinate *tert*-butyl ester (**5**) and succeeded in obtaining the alkylated product **6**, which could be hydrolyzed to afford the α-amino acid in high yield and high enantioselectivity [7]. The stereoselective alkylation of the glycinate Schiff base **5** with benzyl bromide proceeded smoothly under mild basic conditions using a chiral catalyst, the cinchonine derivative **7**,

with 75% yield and 66% ee. By changing the catalyst to the cinchonidine derivative **8**, the pseudo-enantiomer compound of **7** was obtained in similar chemical and optical yields (85%, 64% ee). With these studies providing momentum, the glycine Schiff base **5,** which was suggested by O'Donnell, has become a key substrate for the phase-transfer catalytic system. Nearly all of the early studies on asymmetric phase-transfer catalysis were developed using the molecule glycine *tert*-butyl ester **5**.



Scheme 7. Glycinate Schiff base as the phase-transfer catalytic substrate

O'Donnell's successful asymmetric transformations using the *Cinchona*-derived chiral phase-transfer catalysts were explained by Markosza's interfacial mechanism. The asymmetric phase-transfer catalytic alkylation of glycinate Schiff base **5** is illustrated in **Figure 4**. The reaction was initiated by the abstraction of the α-proton of **5** by an aqueous alkaline hydroxide base (NaOH), which affords the active methylene anion **9** at the interface of the two phases. The ion exchange with the quaternary ammonium salt generates the lipophilic salt **10**, which partitions into the organic phase, where it can encounter the

alkyl halide (BnBr) and form the alkylated product **6**. The catalyst is regenerated during the alkylation step, which enables the use of small quantities of the catalyst. To ensure the high optical purity of chiral **6**, this ion exchange step must occur sufficiently rapidly to prevent undesired racemic alkylation with metal salt **9**. Additionally, the ion pair between the quaternary ammonium salt on the catalyst (cation) and the enolate on the substrate (anion) should reasonably interact, yielding a high optical purity.

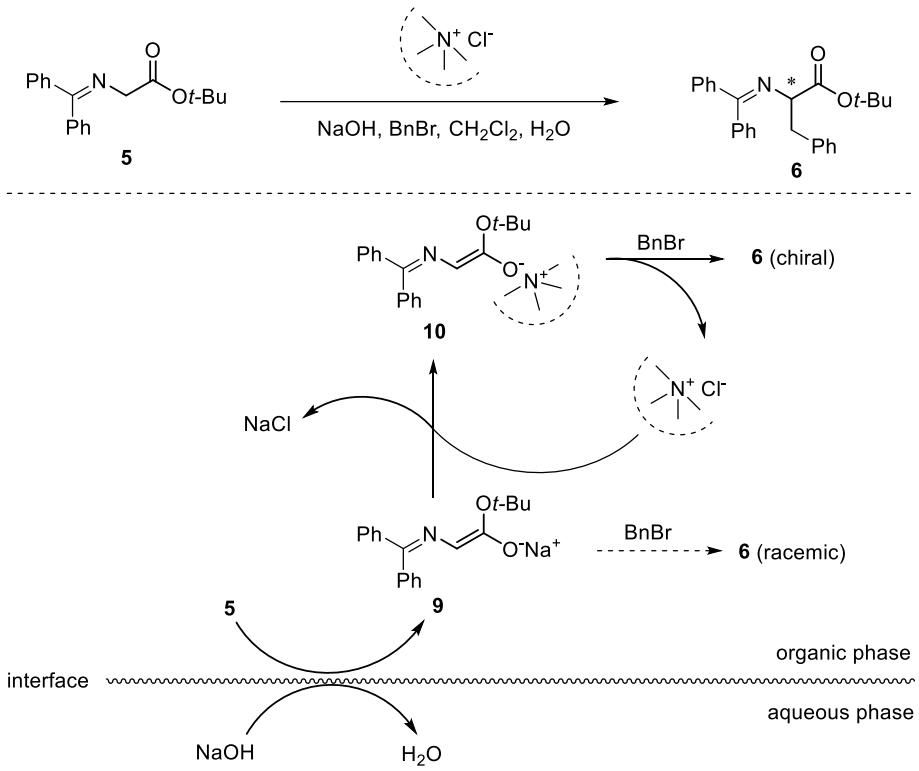


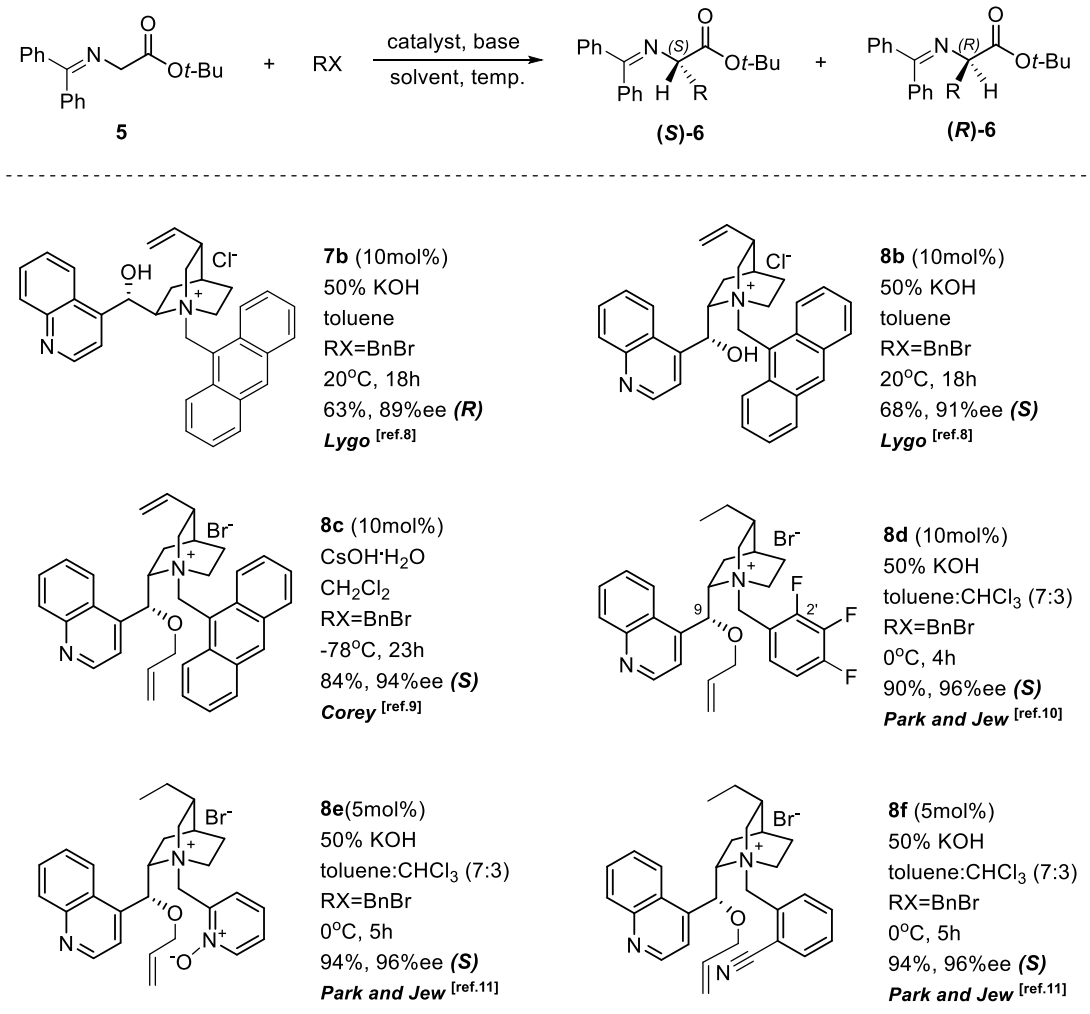
Figure 4. General mechanism of asymmetric phase-transfer catalysis

1-2-1. Development of phase-transfer catalysts

1-2-1-1. *Cinchona* alkaloid-derived mono-ammonium salts

The successful design of the *Cinchona* alkaloid-derived catalysts formed the basis for the development of the asymmetric phase-transfer catalysts depicted in **Scheme 8**. A new class of *Cinchona* alkaloid-derived catalysts, **7b**, **8b**, and **8c,** bearing an *N*-anthracenylmethyl function independently developed by Lygo and Corey has introduced a new era of asymmetric phase-transfer catalysis. In 1997, the Lygo group reported the development of the *N*-anthracenylmethyl *Cinchona* salts **7b** and **8b** and applied them to the phase-transfer alkylation of glycinate Schiff base **5** with significantly higher enantioselectivities [8] compared with the *N*-benzyl analogues [7]. Corey and coworkers designed O-allyl-N-9-anthracenyl-methyl cinchonidium bromide [9]. The phase-transfer catalytic benzylation of **5** under a cesium hydroxide base in dichloromethane at low temperature showed a slightly higher enantioselectivity (94% ee). The increases in the enantioselectivity in both cases were achieved by more efficient screening due to the higher steric hindrance of the anthracenyl moiety compared with the benzyl group. The electronic effect of the fluoroaromatic substituents has been utilized by the Park and Jew research group for the development of efficient catalysts derived from *Cinchona* alkaloids [10]. An evaluation of the effect of the electron-withdrawing groups on the benzylic group of dihydrocinchonidium salt **8d** has revealed that the 2,3,4-trifluoro substituent on the aromatic ring led to a dramatic enhancement of the enantioselectivity. It has been proposed that a hydrogen-bonding interaction between the oxygen atom at C9 and the fluorine atom at C2' in **8d** might increase the rigidity of its conformation, thus leading to high enantioselectivity. In addition, studies from the same research group on the evaluation of

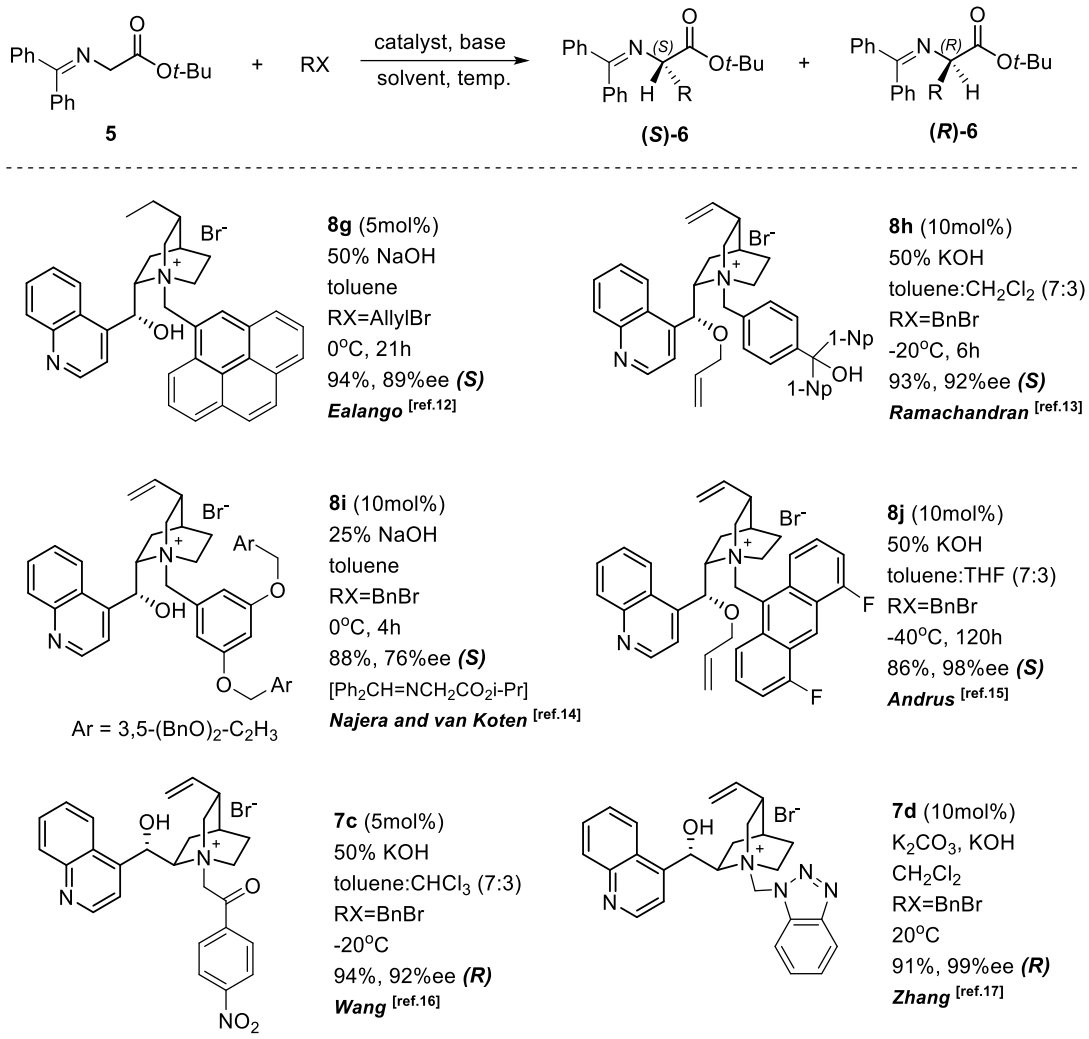
the related chiral quaternary ammonium salts containing the 2'-*N*-oxypyridinyl (**8e**) and 2'-cyanophenyl groups (**8f**) have strongly supported this possibility [11].



Scheme 8. *Cinchona* alkaloid-derived mono-ammonium salts-I

As depicted in **Scheme 9**, many research groups have been interested in the design of new phase-transfer catalysts by adding a large alkyl chain. Elango, in Singapore, has designed catalysts (**8g**) bearing the 1-pyrenyl methyl moiety based on the extension of planarity and steric bulkiness [12]. When the nitrogen on the bicyclic ring of the *Cinchona* alkaloids is

quaternized by a bulky and rigid group, it appears to give the highest rigidity and steric effect to the catalyst's framework and leads to highly enantioselective alkylations.



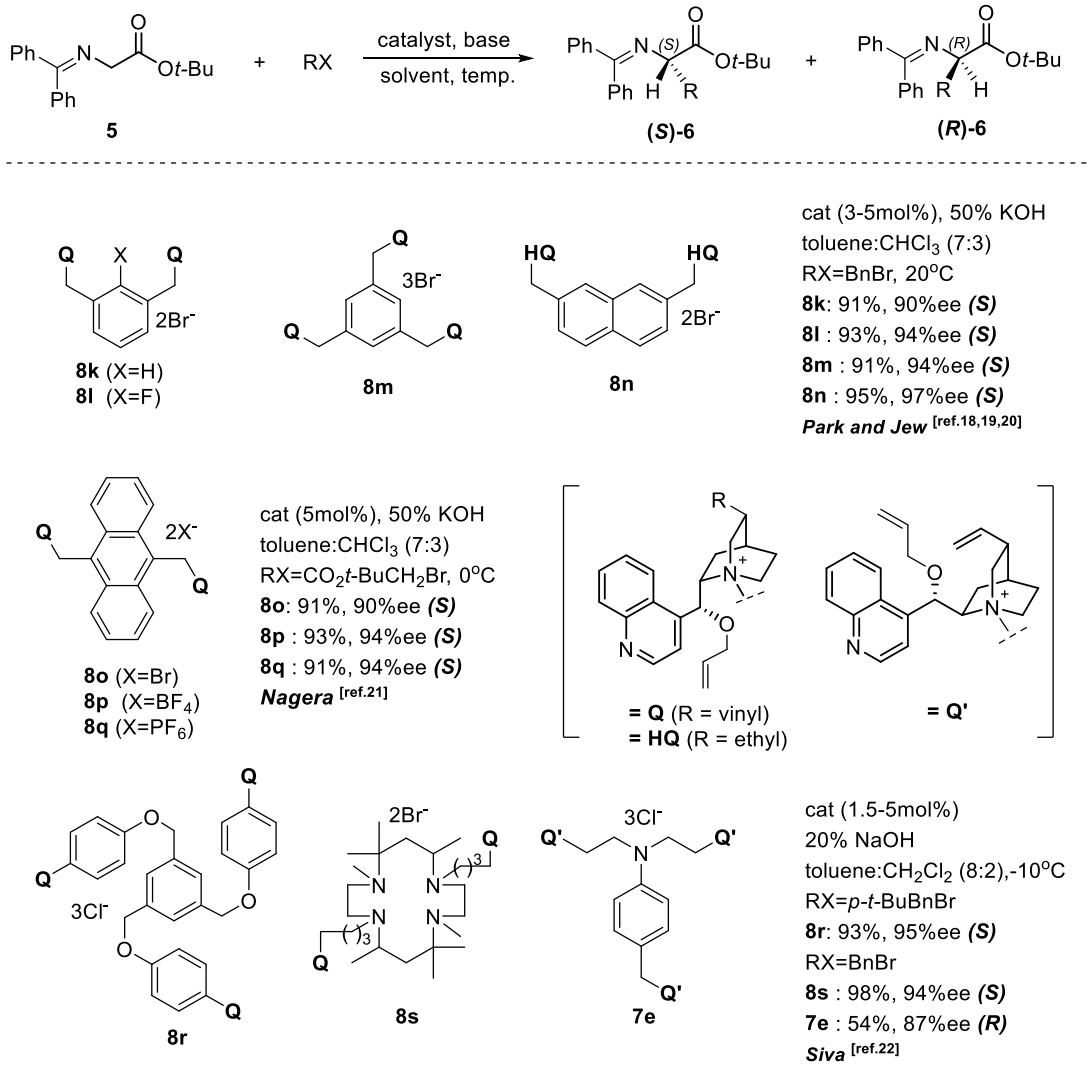
Scheme 9. Cinchona alkaloid-derived mono-ammonium salts-II

In 2005, Ramachandran designed new molecules (**8h**) having a diaryl substitution at the para-position of the *N*-benzyl group in the cinchonidium salts to examine the effect of the substituted aryl moieties on the asymmetric benzylation of **5** compared with flat linear aryl systems [13]. Najera, van Kotem and coworkers have prepared dendritic cinchonidine-

derived ammonium salts (**8i**) using Frechet dendritic wedges [14]. In 2005, Andrus reported a new class of fluorinated anthracenylmethyl cinchonidine-derived catalysts (**8j**) that promote the benzylation of glycinate Schiff base **5** with high reactivity and selectivity [15]. Phase-transfer catalysts containing various alkyl chains have been steadily developed. Novel catalysts possessing an aryl ketone (**7c**) and a benzotriazole (**7d**) moiety have appeared in academic fields by Wang [16] and Zhang [17], respectively. The adjustment of the steric hindrance effect of the catalysts appears essential for high enantiomeric induction. Furthermore, because the asymmetric alkylation of glycine imines is an ion-pair-mediated reaction, the electronic properties of the phase-transfer catalyst may also play an important role in the transformation.

1-2-1-2. *Cinchona* alkaloid-derived bis- and tris-ammonium salts

During the development of the asymmetric Sharpless dihydroxylation, it was found that ligands with two *Cinchona* alkaloid units attached to heterocyclic spacers considerably increased the enantioselectivity and the scope of the substrate. This effect has been successfully utilized by Jew, Park, and co-workers for the design of chiral phase-transfer catalysts **8k**, **8l**, **8m**, and **8n** with two and three *Cinchona* alkaloid units [18,19,20]. These catalysts substantially enhanced the enantioselectivity of the alkylation of **5** and expanded the range of alkyl halides that could be transformed. During their search for the ideal aromatic spacer, Jew, Park, and co-workers found that the catalyst **8n**, consisting of 2,7-bis(bromomethyl)naphthalene and the requisite two *Cinchona* alkaloid units, exhibited remarkable catalytic and chiral efficiency.



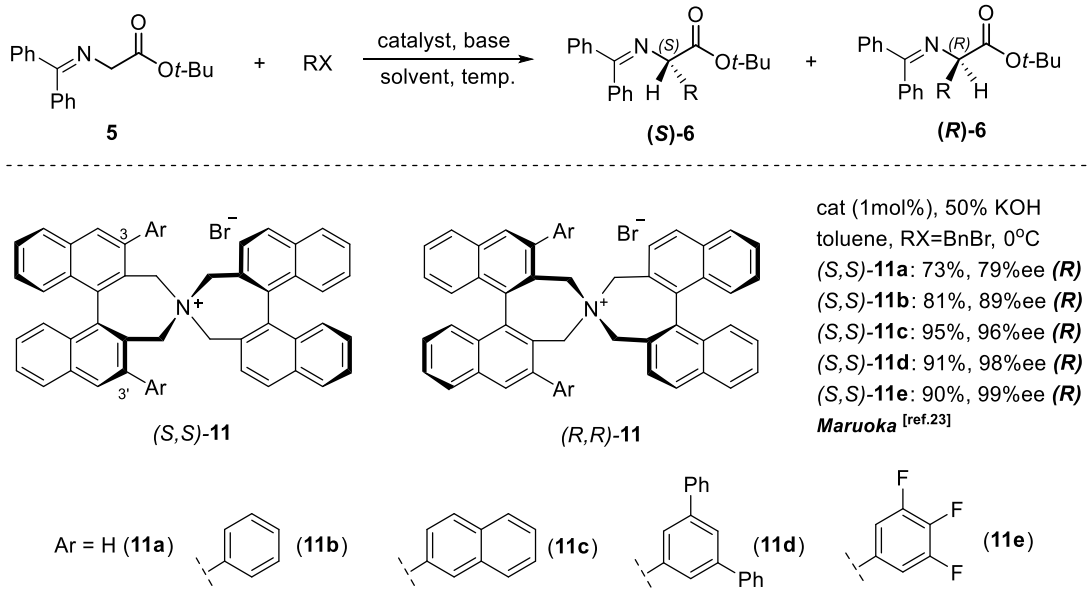
Scheme 10. *Cinchona* alkaloid-derived bis-and tris-ammonium salts

Najera and co-workers have also prepared salts **8o**, **8p**, and **8q**, which incorporate a dimethylanthracenyl bridge as a spacer [21]. This type of catalyst has been utilized for the catalytic enantioselective alkylation of **5** with different alkyl halides in a biphasic system consisting of 50% aqueous KOH and a toluene/$CHCl_3$ mixture. Furthermore, out of interest in the influence of the counterions on the asymmetric alkylation of **5** using chiral

bis(ammonium) salts, the bromide ion of **8o** was exchanged with tetrafluoroborate (**8p**) or hexafluorophosphate (**8q**). The counterion effect was pronounced, with the most remarkable increase in the enantioselectivity observed in the reaction of **8o** with *tert*-butyl bromoacetate. In addition, based on these advances in the development of phase-transfer catalysts, Siva and co-workers in India prepared various dimeric and trimeric molecules for use in the benzylation reaction of glycinate Schiff base **5** and successfully applied them to that reaction [22].

1-2-1-3. Binaphthyl-modified phase-transfer catalysts

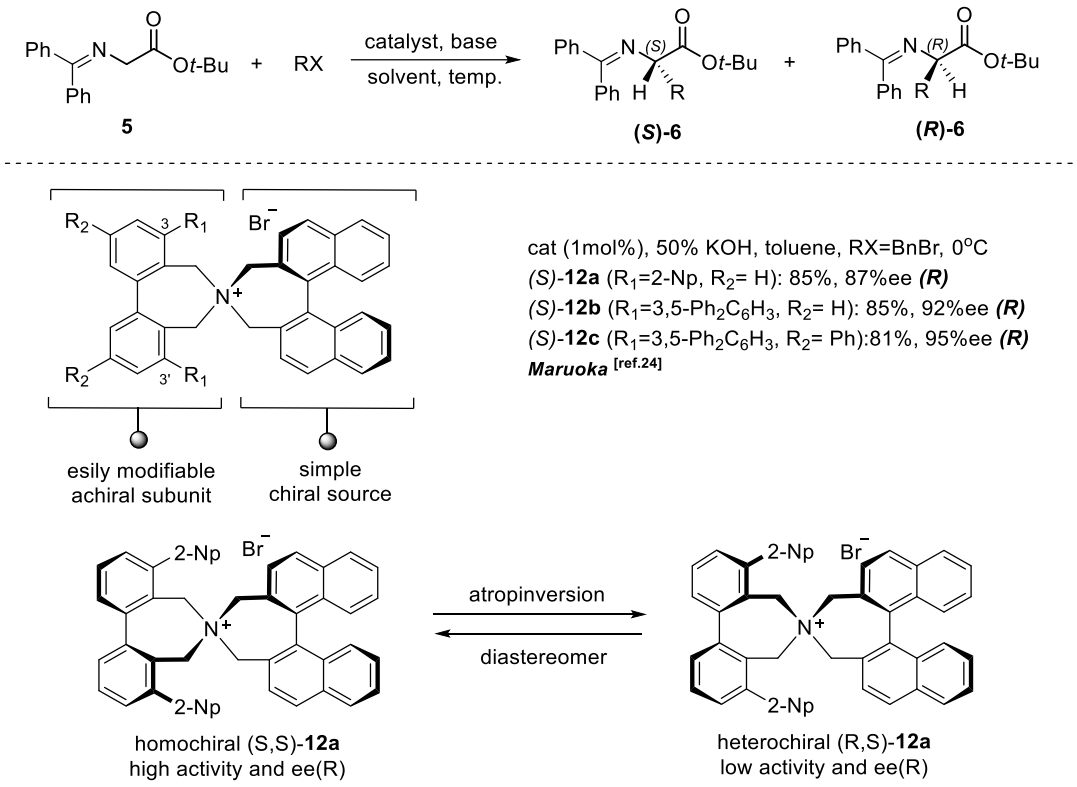
In 1999, considering the available structural modifications and the fine-tuning of the catalysts to attain sufficient reactivity and selectivity, Maruoka's group designed and synthesized the structurally rigid, chiral spiro ammonium salts of the type **11** derivatives from the commercially available (*S*)-or (*R*)-1.1'-bi-2-naphthol as a new C_2 symmetric chiral phase-transfer catalyst. This group successfully applied this molecule to the enantioselective alkylation of *N*-(diphenylmethylene) glycine *tert*-butyl ester (**5**) under mild phase-transfer conditions [23]. The key finding in their study was a significant effect of an aromatic substituent (Ar) at the 3,3'-position of one binaphthyl subunit of catalyst **11** on the enantiofacial discrimination. Compared with the *Cinchona* alkaloid-derived phase-transfer catalysts, 1 mol% of **11a-e** was sufficient for a smooth benzylation (**Scheme 11**).



Scheme 11. Binaphthyl-modified phase-transfer catalysts-I

Although the conformationally rigid *N*-spiro structure created by two chiral binaphthyl subunits is a characteristic feature of **11**, it imposes limitations on the catalyst design due to the use of two different chiral C_2 symmetric chiral binaphthyl moieties. Accordingly, in 2002, Maruoka's research group developed the new C_2 symmetric chiral quaternary ammonium bromide **12** by incorporating an achiral, conformationally flexible biphenyl subunit (**Scheme 12**). The phase-transfer catalytic benzylation of **5** with the catalyst (*S*)-**12a**, with a 2-naphthyl group on the 3,3'-position of the flexible biphenyl moiety, proceeded smoothly at 0℃ to afford the corresponding benzyl-adduct compound (*R*)-**6** in 85% yield with 87% ee after 18 hours. The origin of the observed chiral efficiency could be equilibrated using a diastereomeric homo- and heterochiral catalyst; namely, homochiral (*S*,*S*)-**12a** is primarily responsible for the efficient asymmetric phase-transfer catalysis to give the product with a high enantiomeric excess, whereas the heterochiral (*R*,*S*)-**12a** displays low reactivity and stereoselectivity. This unique phenomenon provided a powerful

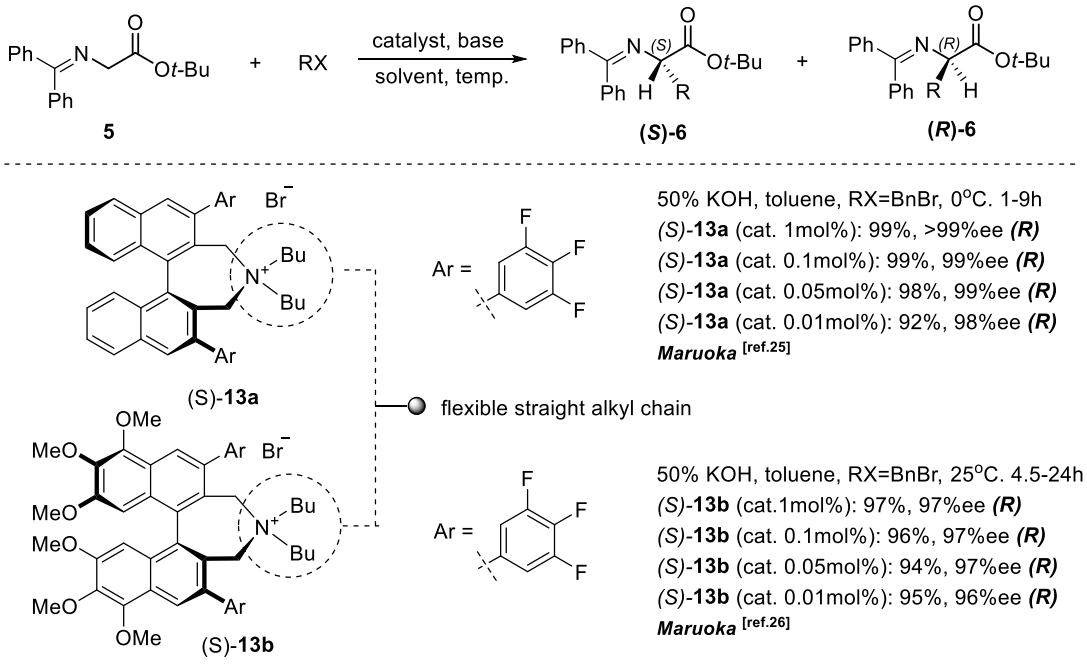
strategy for the molecular design of chiral catalysts. The requisite chirality can be served by the simple binaphthyl moiety, whereas an additional structural requirement for the fine-tuning of the reactivity and selectivity can be fulfilled by an easily modifiable achiral biphenyl structure. A quaternary ammonium bromide possessing a sterically demanding substituent, such as (*S*)-**12b,** was easily obtained, and benzylation with (*S*)-**12b** as the catalyst gave **6** in a 95% yield with 92% ee. In addition, the enantioselectivity was increased to 95% ee with the more sterically hindering catalyst (*S*)-**12c**.



Scheme 12. Binaphthyl-modified phase-transfer catalysts-II

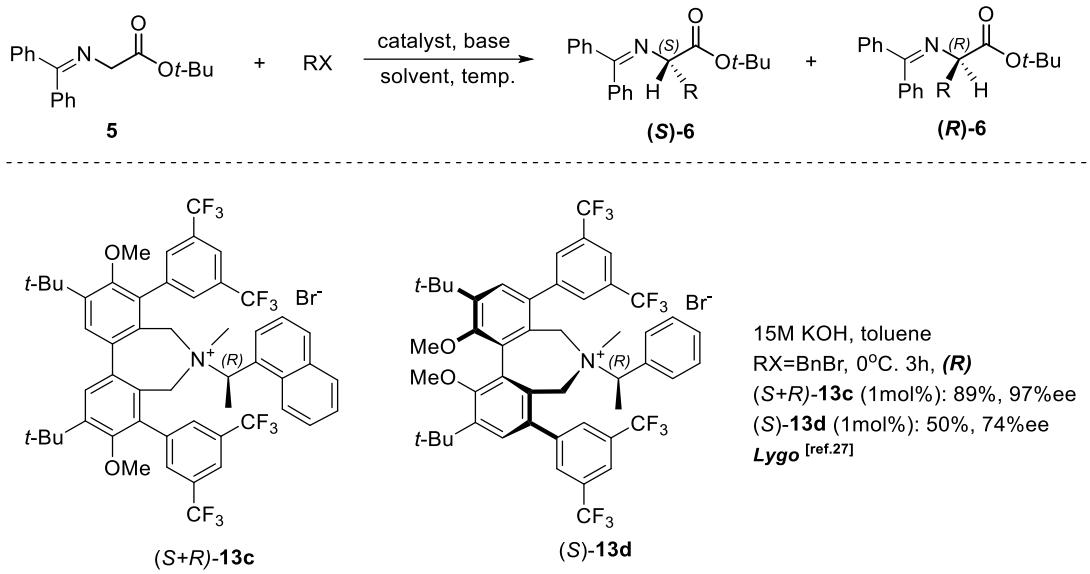
As shown in **Scheme 13**, in 2005, Maruoka and co-workers discovered the powerful chiral quaternary ammonium bromide **13,** possessing flexible straight-chain alkyl groups instead of rigid binaphthyl moiety functions, as an unusually active chiral phase-transfer catalyst.

Most notably, the reaction of **5** with various alkyl halides proceeded smoothly under mild phase-transfer conditions in the presence of only 0.01-0.05 mol % of (*S*)-**13a** to afford the corresponding alkylation products with excellent enantioselectivities [25]. The ready availability of the chiral starting materials is crucial for the design of practical phase-transfer catalysts. Accordingly, the highly practical chiral phase-transfer catalyst **13b** was conveniently prepared from the known, readily available (*S*)-4,5,6,4′,5′,6′-hexamethoxy biphenyldicarboxylic acid derived from gallic acid. This catalyst (*S*)- **13b** also exhibited high catalytic performance (0.01-1 mol%) in the asymmetric alkylation of glycine Schiff base **5** compared with the existing chiral phase-transfer catalysts, thereby providing a general and useful procedure for the highly practical enantioselective synthesis of the structurally diverse natural and unnatural α-alkyl- α -amino acids [26].



Scheme 13. Binaphthyl-modified phase-transfer catalysts-III

Scheme 14 shows the Lygo research group's project to construct a new library of quaternary ammonium salts of type **13c** and **13d** [27]. Since 2009, Lygo has focused on the synthesis of binaphthyl-modified phase-transfer catalysts with conformationally flexible biphenyl units from simple, commercially available amines. A key feature of structure **13c**, which is prepared by the amines, is the conformationally labile (*tropos*) dihydro-5H-dibenz[*c*,*e*]azepinium ring incorporating the amino group of the chiral amine precursor. This fragment allows the fine-tuning of the catalyst by changing the substituents attached to the aromatic rings and appears to be essential for high enantioselectivity.



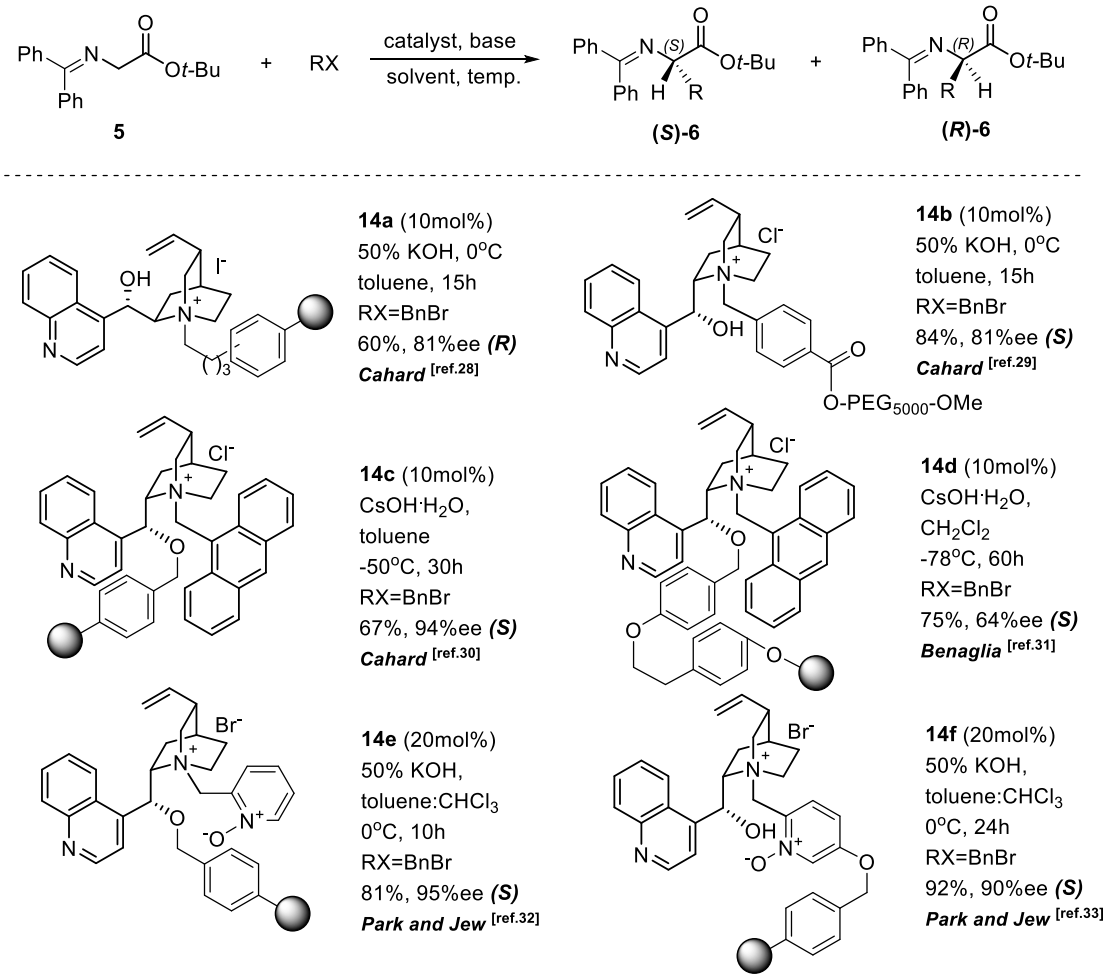
Scheme 14. Binaphthyl-modified phase-transfer catalysts-IV

In conclusion, the Lygo group has developed a short synthetic route to the diastereoisomeric atropos dihydro-5H-dibenz[*c*,*e*]azepinium salts via the reaction of a single enantiomer of (*R*)-α-methylbenzylamine with the racemic *atropos* biphenol derivatives. Compounds prepared *via* this approach have provided strong evidence that the structurally related *tropos* dihydro-5H-dibenz[*c*,*e*]azepinium salts preferentially react *via* a

single conformation in the phase-transfer catalytic reactions involving the glycine imine enolates (**5**) and afford impressive catalytic performance.

1-2-1-4. Polymer-supported phase-transfer catalysts

A further useful development for the phase-transfer catalysts has been the immobilization of the catalyst on an insoluble polymeric support.



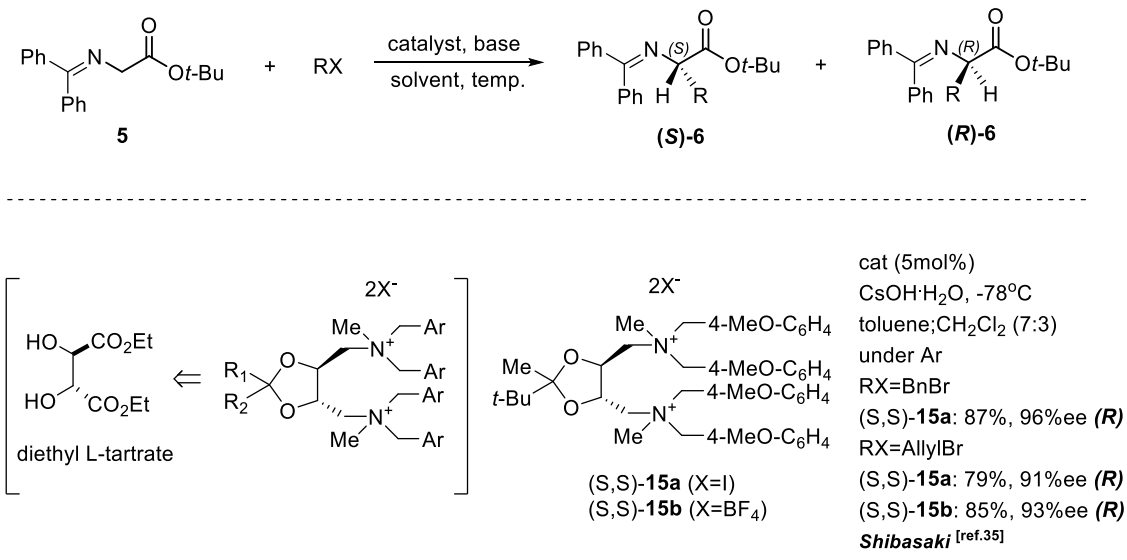
Scheme 15. Polymer-supported phase-transfer catalysts

This strategy presents several practical advantages over the use of the same catalyst in solution, including significantly simplified product purification, the easy recovery of the catalyst by simple filtration and potential for recycling. During the course of this development, Najera reported improved enantioselectivities of up to 58% through using the first polymer-supported *Cinchona* alkaloids for the alkylation of *N*-diphenyl methylene glycine *tert*-butyl ester **5** [28]. Cahard investigated the role of a flexible spacer between the quaternary ammonium and the polymer backbone in the benzylation of **5**. This group found that catalyst **14a** anchored to the matrix through a butyl group was optimal and gave (*R*)-**6** with 81% enantioselectivity [29]. This research group also grafted a quaternary ammonium salt derived from cinchonidine to a poly(ethylene glycol) matrix **14b**. This catalyst was found to be efficient for the homogeneous asymmetric alkylation of 5, and up to 81% enantiopurity was attained in the benzylation under standard liquid–liquid phase-transfer conditions [30]. Cahard, Plaquevent, and co-workers have also succeeded in improving the enantioselectivity by attaching the Merrifield resin to the hydroxy group of catalyst **14c**, which possesses a 9-anthracenylmethyl group on the nitrogen atom [31]. Benaglia and co-workers immobilized the third-generation catalyst on modified poly(ethylene glycol) through the alkylation of the C9 hydroxy group. The obtained chiral ammonium salt **14f** acts as a catalyst in the benzylation of **5** to afford (*S*)-**6** with a maximum of 64% enantioselectivity [32]. The Park and Jew group proposed that water molecule-mediated internal hydrogen bonding between (9)-oxygen and special functional groups, such as 2'-F, 2'-CN, or 2'-N^+–O^-, in the N^+(1)-aryl methyl moieties in the *Cinchona* phase-transfer catalysts played a critical role in enhancing the enantioselectivity in the alkylation of **5** [11]. Subsequently, they reported the design and preparation of the O-supported *Cinchona* phase-transfer catalyst **14e**, in which the hydrogen bonding-inducing functional groups are incorporated in the O-supported polymer portion [32]. As part of their ongoing studies

towards *Cinchona* polymer-supported catalysts, the electronically modified N-supported *Cinchona*-phase-transfer catalyst **14f** was designed, and its capabilities were evaluated using the asymmetric phase-transfer catalytic benzylation of **5** (**Scheme 15**).

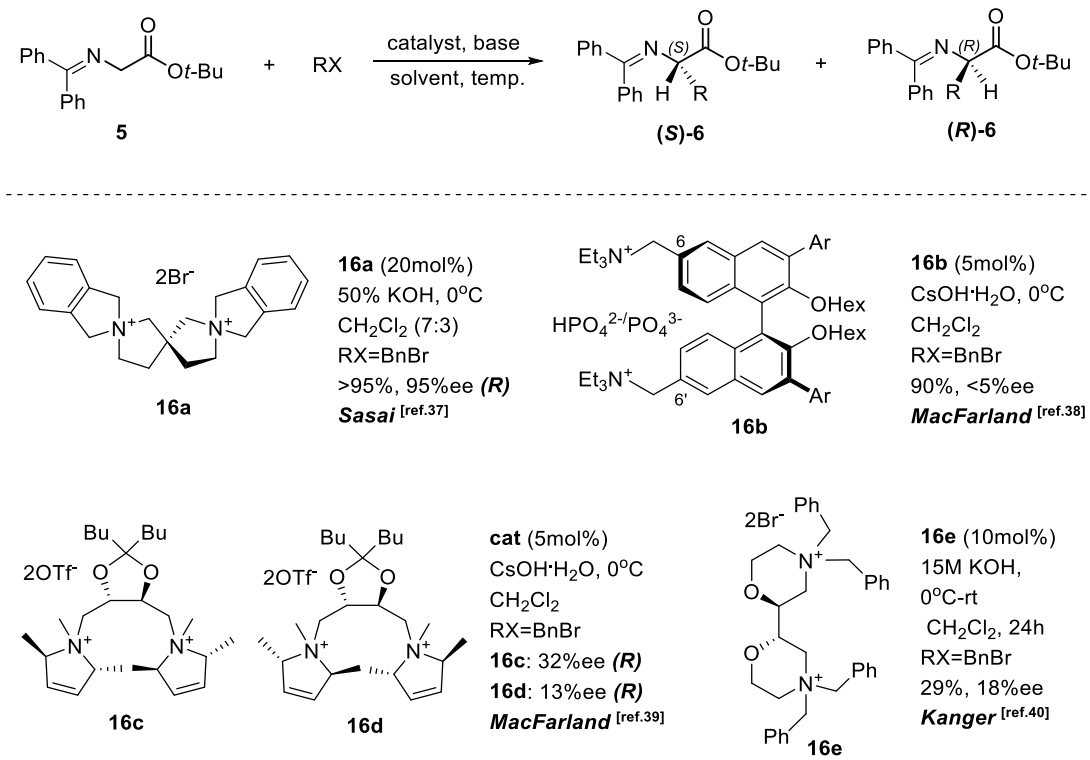
1-2-1-5. Two-center chiral phase-transfer catalysts

A wide variety of metal-mediated asymmetric two-center catalyses based on a multifunctional catalyst concept has been developed [35]. Similarly to an enzymatic reaction, the synergistic functions of two or more active sites in multimetallic catalysts make substrates more reactive and control their position in the transition state so that the functional groups are proximal to each other. To extend this concept to asymmetric organocatalysis, two ammonium salt moieties maintaining an appropriate distance (two-center organocatalyst) were introduced to the catalyst by the Shibasaki group [36].



Scheme 16. Tartrate-derived two-center phase-transfer catalysts

The new two-center catalyst of type **15** could be synthesized from commercially available and relatively inexpensive L- or D-tartrate under operationally simple reaction conditions in which the substrate can be fixed in a chiral environment by two cationic moieties. To achieve the ideal complexation of the two-center catalyst and the substrate, glycine Schiff base **5**, these authors selected a 1,4-diammonium salt rather than a 1,2-diammonium salt or a 1,3-diammonium salt based on the spatial environment created by two cationic moieties and on several preliminary investigations. Using the best catalyst **15a** and **15b**, the reaction conditions were optimized to improve the selectivity (**Scheme 16**).



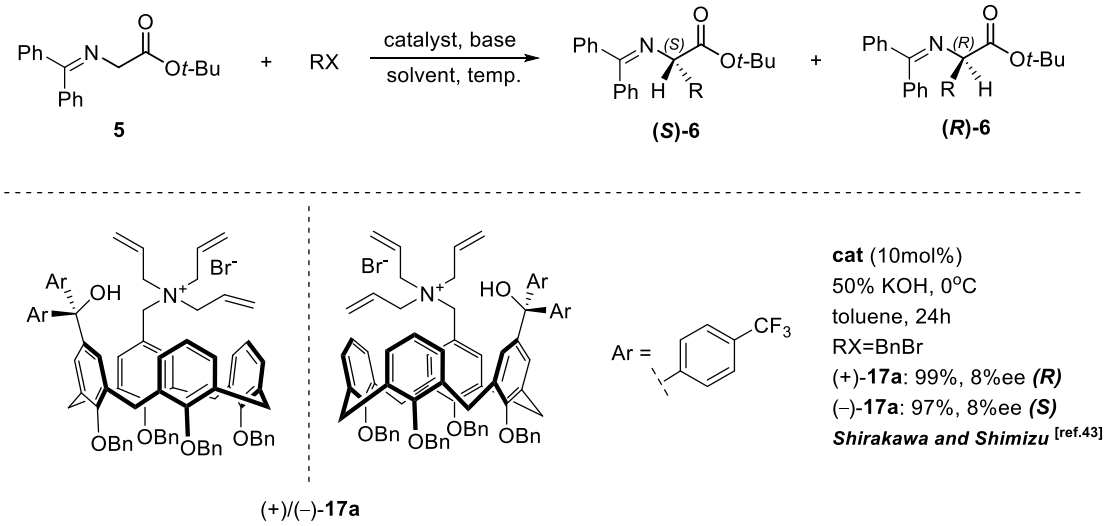
Scheme 17. Two-center chiral phase-transfer catalysts

In 2003, Sasai designed bis(spiroammonium) salt **16a** as a chiral phase-transfer catalyst and applied it to the representative alkylation reaction, the benzylation of glycine Schiff base **5,** achieving 95% enantioselectivity [37]. One year later, MarFarland reported the BINOL-derived two-center phase-transfer catalyst **16b**, in which the bis-ammonium units were introduced at the 6,6'-positions of the BINOL skeleton to act cooperatively [37]. The catalyst **16b** was synthesized from (*R*)-BINOL in five steps and was used as the phase-transfer catalyst. The efficiency of **16b** was compared with the *N*-spiro binaphthyl phase-transfer catalyst **11**. Although the enantioselectivities were reduced, it was worthwhile to introduce the binaphthyl skeleton to the two ammonium salts [38]. In addition, MarFarland and co-workers prepared diastereomeric bis (ammonium) salts **16c** and **16d** by combining a tartrate derivative and 2,5-dimethylpyrroline and tested their ability as chiral phase-transfer catalysts in the asymmetric benzylation of the substrate **5** [39]. A high-yield synthetic scheme to obtain the enantiomeric 2,2'-bimorpholine **16e** in six steps, starting from the tartaric ester, was developed by Kanger [40]. Although the corresponding bimorpholinium salts were found to be inefficient catalysts for the alkylation of the glycine imine ester **5**, affording compound (*R*)-**6** with 18% ee, Kanger promised that further investigations to widen the synthetic scope of this potential organocatalyst in other reactions will be developed.

1-2-1-6. Other phase-transfer catalysts

Calixarenes represent an important class of macrocyclic compounds due to their potential to form host–guest complexes with numerous classes of compounds in supramolecular chemistry. The sites available on these macrocyclic compounds can be easily modified to tailor them for many applications, such as phase-transfer catalysts, ionophores in catalysis,

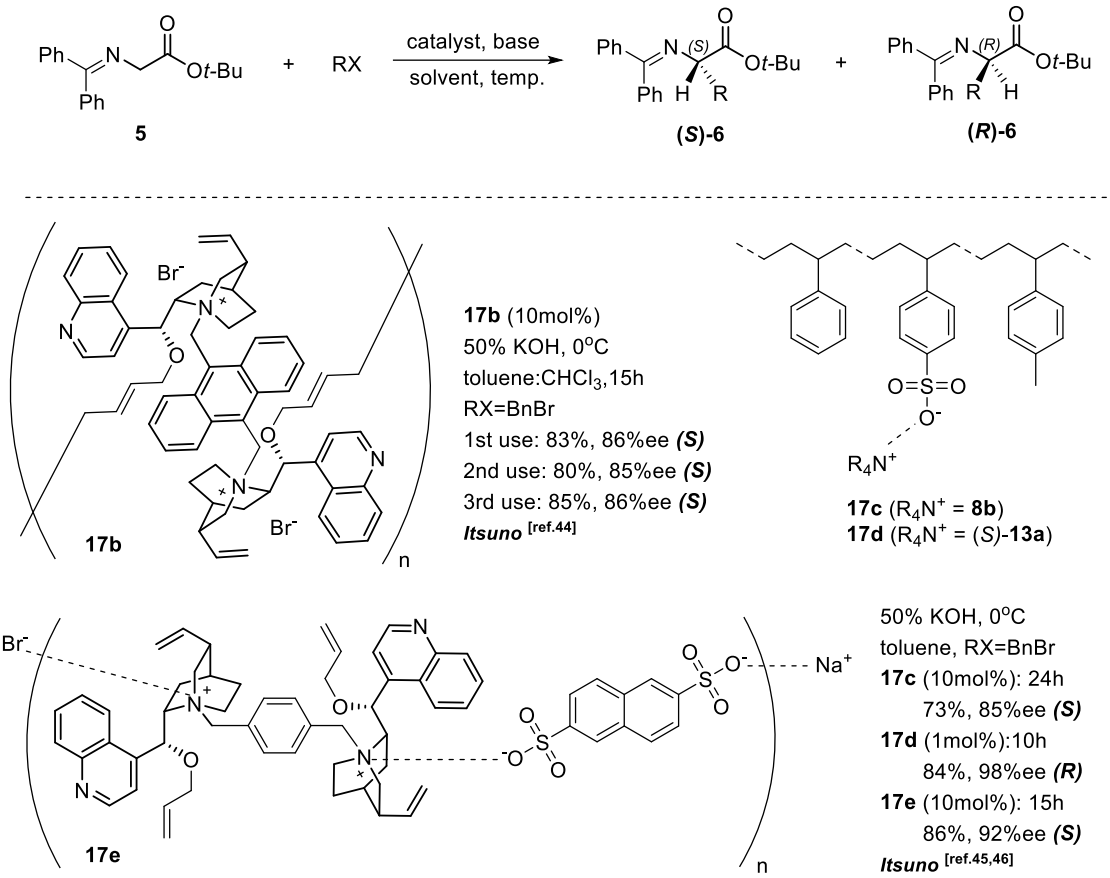
carriers in liquid membrane technology, heavy metal adsorption agents, alkali metal complexation agents, extractants for anions and cations, and chemical sensors [41]. The synthesis of the first calixarene-based chiral phase-transfer catalysts derived from the *Cinchona* alkaloids has been achieved in two steps from *p*-tert-butylcalix[4]arene by Sirit [42]. The catalytic efficiency of the chiral calix[4]arenes has been evaluated through performing the phase-transfer alkylation of *N*-(diphenylmethylene)glycine ethyl ester with benzyl bromide, affording the benzylated compound with up to 57% enantioselectivity. Shirakawa and Shimizu improved on the design of the inherently chiral calix[4]arenes as organocatalysts [43] by demonstrating a new approach for the design of phase-transfer catalysts using the inherently chiral calix[4]arene backbone (**17a, 17b**). Although the enantioselectivity of the obtained product **6** was low, this approach is a valuable example of the application of the inherently chiral calix[4]arene as a chiral catalyst (**Scheme 18**).



Scheme 18. Calix[4]arene-based phase-transfer catalysts

The Itsuno group developed a novel type of polymeric phase-transfer catalyst, **17b**, **17c**, **17d**, and **17e**, based on the successful design of the dimeric catalysts derived from the

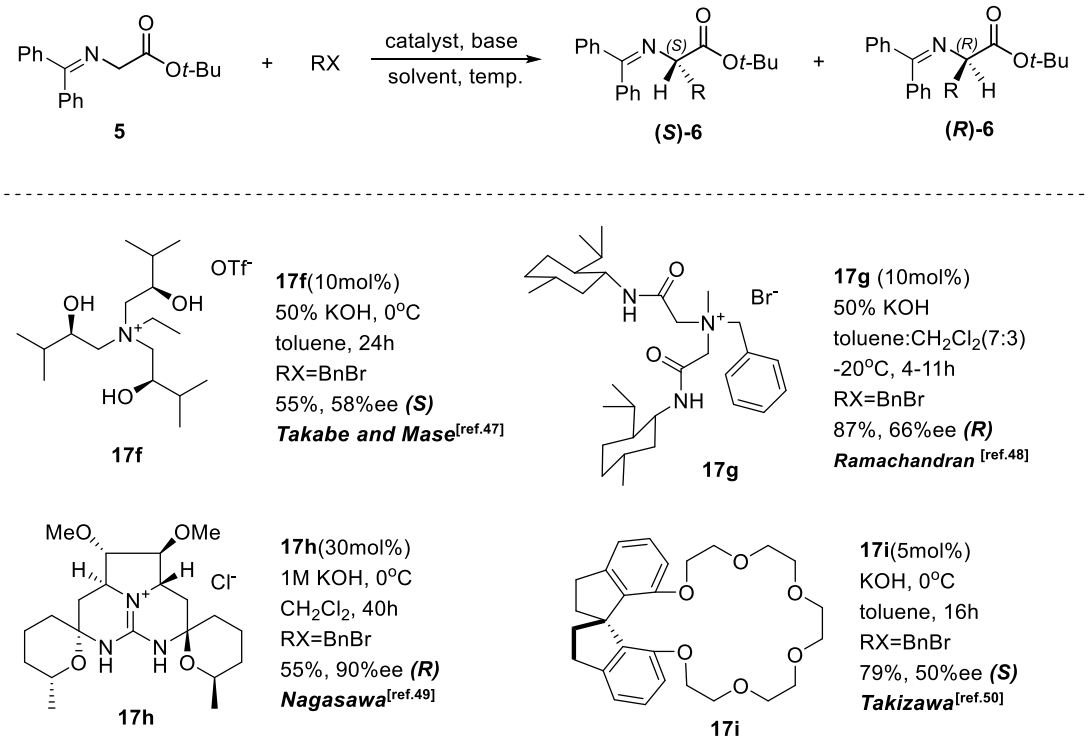
Cinchona alkaloid [18,19,20]. These authors developed the novel optically active polymer **17b** with chiral quaternary ammonium repeating units [44]. These polymers with main chain chirality have efficiently performed as polymeric catalysts in the asymmetric benzylation of *N*-diphenylmethylidene glycine *tert*-butyl ester **5**. In addition, the catalysts can be reused without loss of reactivity and selectivity.



Scheme 19. A novel type of polymeric phase-transfer catalysts

The same research group reported a new type of immobilization method involving the ionic bonding of sulfonate groups to a polymer. The polymer-supported chiral quaternary ammonium salts **17c** and **17d** were readily prepared by the reaction of the sulfonated

polymer with the corresponding chiral ammonium salt. The polymeric catalysts were applied to the alkylation of **5** and afforded a highly enantioselective compound [45]. These findings led to the development of a novel main-chain ionic chiral polymer catalyst **17e** with a quaternary ammonium sulfonate repeating unit [46] (**Scheme 19**).



Scheme 20. Other phase-transfer catalysts

In 2010, the C_3 symmetric amine-derived chiral phase-transfer catalysts were prepared in only two steps by Takabe and Mase [47]. The stereospecific ring-opening of the enantiomerically pure epoxide, which was commercially available or obtained by a short-step synthesis, with ammonia afforded the C_3 symmetric chiral amines. Quaternization of the amine with an alkyl halide gave the chiral compound **17f**. Application of this chiral phase-transfer catalyst (1 mol%) in the alkylation of a *tert*-butyl glycinate-benzophenone Schiff base under mild reaction conditions provided a benzylated product with up to 58%

enantiomeric excess. Ramachandran reported the synthesis of various derivatives using the L-menthol scaffold [48]. The authors designed the catalyst **17g** with two methyl units linked by an amide. The quaternized catalyst **17g** exhibited a moderate level of enantioselectivity. The guanidine group, which contributes to the stabilization of the three-dimensional structures of proteins, is a superbase that forms stabilized complex salts with anionic compounds through parallel interactions, including hydrogen bonding. These features suggest that the guanidine-containing molecules can be used as new "reaction vessels". While developing the guanidine-related compounds, the Nagasawa research group aimed to develop new organocatalysts, and they reported the novel phase-transfer catalyst **17g** [49]. This group determined that the substituent (methyl group) on the spiro ether rings of **17g** played a critical role in the effective asymmetric induction of (*R*)-**6**; the catalyst without the methyl group induced the same product with 13% selectivity. Takiza developed the novel spiro chiral crown ethers **17i** for the asymmetric phase-transfer reaction [50]. The combination of **17i** and solid potassium hydroxide promoted the asymmetric alkylation of glycine derivative (**5**) with moderate enantioselectivity (**Scheme 20**).

1-2-2. Progress of the substrates for phase-transfer catalytic alkylation

As previously mentioned, since *N*-(diphenylmethylene) glycine *tert*-butyl ester (**5**) was developed by O'Donnell and co-workers as a substrate for phase-transfer catalytic alkylation, diverse substrates based on the structure of **5** have been developed that are appropriate in mono- or di-alkylations. Molecules that can be used in phase-transfer catalysis must have common characteristics. The molecules should be activated as nucleophiles by an aqueous base, thus obtaining an appropriate pKa value at the reaction

site. Additionally, the phase-transfer catalytic substrate must be easily converted to useful molecules by convenient chemical synthetic methods. Thus, the asymmetric reaction methods that produce the corresponding substrates occur are more valuable than other synthetic methods. The substrate must be prepared in an environmentally safe and economical manner. The representative structures that have been developed are shown in **Schemes 21-23.**

1-2-2-1. Schiff bases of glycine ester and amides as substrates

In 1992, the aldimine Schiff bases **18**, which incorporate a monocarbonyl moiety, were reported by O'Donnell for the synthesis of the α,α-dialkyl-α-amino acids [51]. The *p*-chlorophenyl aldimine substrate **18** was alkylated with phase-transfer catalyst **7a**, which was developed by Lygo. O'Donnell also developed alternative substrates, the polymer-bound glycine substrates (**19**) [52]. Based on the former approach for the polymer-supported ammonium salts, O'Donnell used the Wang-resin-bound derivative. The bulky aldimine **20**, which carries a naphthalene moiety and was developed by Park and Jew [53], showed improved enantioselectivity. The esters and amides of glycine can be used as prochiral Schiff bases for asymmetric alkylation under the phase-transfer conditions. Kumar and Ramachandran have demonstrated the effectiveness of the cinchonidine-derived catalyst for the benzylation of various Schiff bases of the tertiary glycine amides **21** [54]. The authors have stated that low enantioselectivity was generally observed in the reaction of the substrates with the secondary amide groups. Maruoka introduced the glycine diphenylmethyl (Dpm) amide derived Schiff base **22** as a key substrate, achieving high enantioselectivity even in the alkylation with the less reactive simple secondary alkyl halides [55]. This system offers simple access to the structurally diverse optically active

vicinal diamines after the subsequent reduction. Another Schiff base **23** of the glycine diphenylmethyl (Dpm) ester as an excellent alternative to **5** has been designed by Lygo [56]. The reaction conditions using substrate **23** afforded the desired product quantitatively with a high enantiomeric excess, providing access to a differentially protected L-aspartic acid derivative.

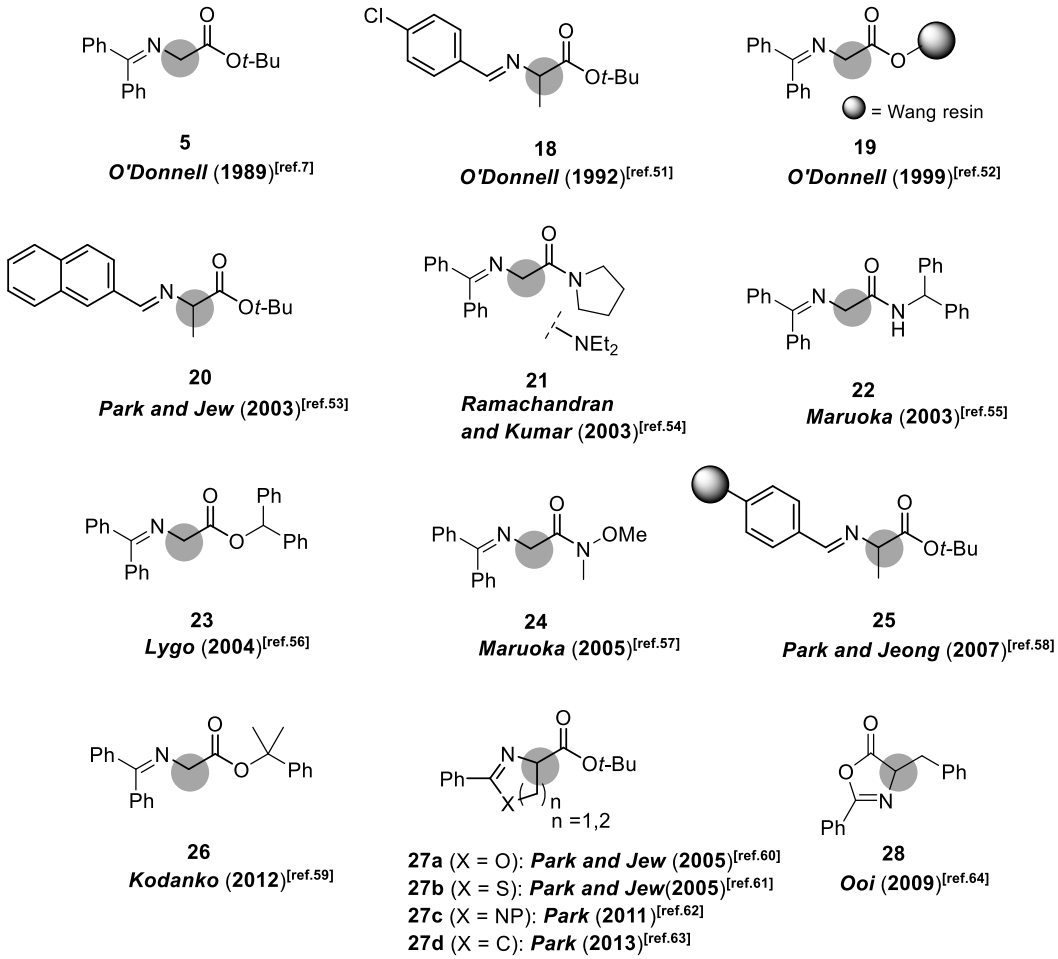


Figure 5. Monocarbonyl imine substrates

Furthermore, Maruoka group's approach was also successful in the asymmetric alkylation of the Weinreb amide derivative **24** [57]. The optically active α-amino acid Weinreb amide benzylated from the substrate **24** was efficiently converted into the corresponding amino ketone by a simple treatment with Grignard reagents. The solid-phase synthesis in which polymer-bound substrates are utilized has advantages over the liquid-phase synthesis, such as easy purification and application to combinatorial chemistry. Park and Jew utilized the Merrifield resin-supported glycine Schiff base **25** for asymmetric alkylation under phase-transfer catalytic conditions [58]. The cumyl ester of glycine benzophenone imine **26** provides an attractive alternative to the analogous *tert*-butyl ester. The substrate bearing the cumyl ester, which could be easily cleaved by hydrogenolysis without acid treatment, has been published in academia by Kodanko [59]. Since 2004, Park and Jew have introduced the "zoline project" for the design of new molecules as substrates. The compounds *tert*-butyl 2-phenyloxazoline-4-carboxylate (**27a**) [60], *tert*-butyl 2-phenylthiazoline-4-carboxylate (**27b**) [61], *N*(1)-Boc-2-phenyl-2-imidazoline-4-carboxylic acid *tert*-butyl ester (**27c**) [62], and 5-phenyl-2-alkylproline *tert*-butyl ester (**27d**) [63] have been successfully prepared and have demonstrated that the phase-transfer catalytic conditions are efficient for the α-alkylation of the "zoline" systems. Ooi and co-workers have used azlactones, such as **28**, derived from α-amino acids [64]. The resulting alkylated azlactone can be readily converted into the corresponding α,α-dialkyl-α-amino acid by acidic hydrolysis.

1-2-2-2. Substrates with the α-position inherently activated by the mono-carbonyl group

In 1998, Corey successfully synthesized β,γ-unsaturated ester **29** [65] and observed that the enantioselectivity varied predictably with the electronic effect of the substituent R. This

finding might be rationalized by the structured contact ion pair model previously postulated for the alkylation of glycinate Schiff base **5**. One year later, Shioiri and Arai studied the asymmetric alkylation of α-fluorotetralone (**30**) under phase-transfer conditions with commercially available chiral quaternary ammonium bromide [66]. In 2006, Maruoka reported the highly enantioselective alkylation of 3,5-diaryloxazolidin-2,4-diones, such as **31**, under mild phase-transfer conditions in the presence of catalyst (*S*,*S*)-**11**, which they also newly designed. This method allows a wide range of *tert*-α-hydroxy-β-aryl carboxylic acid derivatives to be readily obtained in good yield and high enantiomeric excess [67]. In the same year, Bhattacharya introduced the indanone derivative **32** bearing the normal propyl at the α-position as a new substrate for phase-transfer catalysis [68a]. In addition, a group at Merck changed the alkyl chain of **32** from propyl to butyl for asymmetric synthesis of an estrogen receptor β-modulator [68b]. Kawasaki and co-workers reported 2-substituted indolin-3-one **33** [69]. Scheidt and co-workers reported the asymmetric alkylation of isoflavanone **34**, catalyzed by the cinchonidine-derived catalysts, to obtain an alkylated isoflavanone possessing a quaternary carbon center with good enantioselectivity [70]. The highly enantioselective alkylation of cyanoacetates, such as **35**, was achieved by Itoh using the *N*-spiro chiral ammonium salt [71]. In 2009, Maruoka demonstrated the ability of the α-alkyl-α-alkynyl esters, such as **36**, to undergo a highly enantioselective alkylation under phase-transfer conditions, thereby furnishing α-chiral acetylenes with an all-carbon quaternary center [72]. A detailed investigation of this reaction system revealed the formation of an allenyl ester prior to alkylation. In 2011, Ooi designed the novel chiral 1,2,3-triazolium, and its potential as a phase-transfer catalyst has been proven in the asymmetric alkylation of the 3-substituted oxindoles, such as **37**, to give the alkylation products with high enantioselectivity [73].

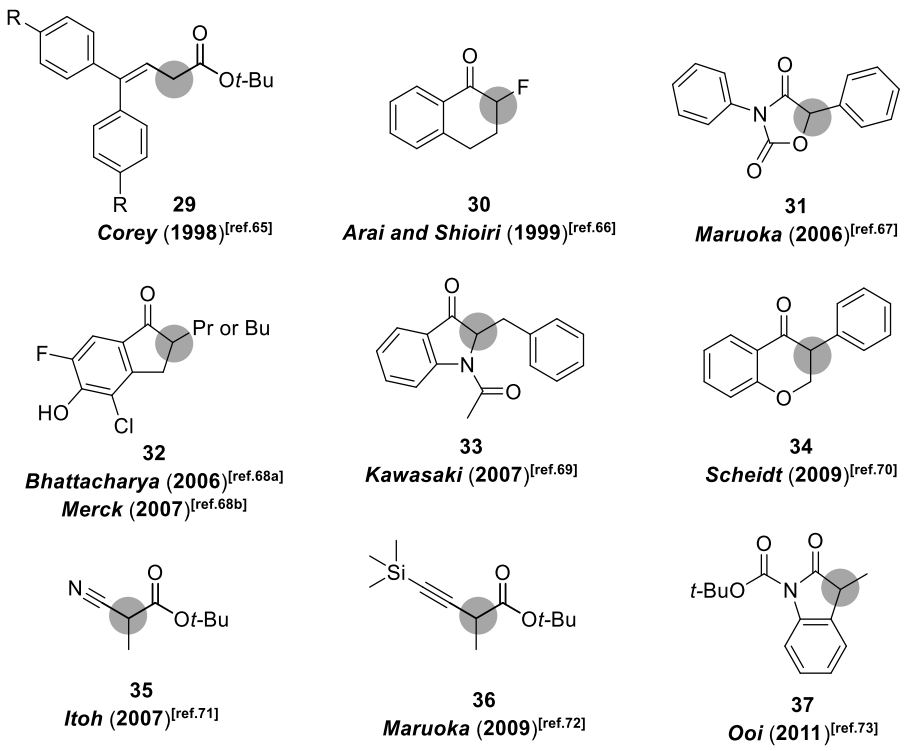


Figure 6. Substrates with the α-position inherently activated by the mono-carbonyl group

1-2-2-3. Substrates with the α-position inherently activated by the di-carbonyl group

One of the most challenging tasks in phase-transfer catalyzed asymmetric alkylation is accessing enantioenriched carbonyl compounds of high value, which possess quaternary α-carbon stereocenters containing heterofunctionalities. In 1998, Manabe designed the β-keto ester **38a** as a phase-transfer catalytic substrate [74], which was the first introduction of a new substrate simultaneously activated by two adjacent carbonyl groups. Although the reactivity and selectivity required improvement (the maximum ee % was 46), this study provided a conceptual advance in the development of new structural substrates. In 2003,

Maruoka modified the structure of **38a** to extend the ring size (**38b**) and add the phenyl adduct (**39**) [75]. Kim in Korea showed the effectiveness of the β-keto esters involving methyl ester **40** as the substrate for the phase-transfer catalytic alkylation [76]. Maruoka suggested the cyclic α-amino-β-keto ester **41** as the ideal substrate in asymmetric alkylation with the C_2- symmetric phase-transfer catalyst to obtain the aza-cyclic amino acids with quaternary stereocenters [77]. Additionally, the highly enantioselective alkylation of α-acyl-γ-butyrolactone **42** was achieved, resulting in the α-alkylated keto lactone, which serves as a valuable chiral building block in organic synthesis [78]. As a complementary approach to the development of the substrates, α-fluoro- and α-benzoyloxy-β-keto esters (**43**) [79] and (**44**) [80] were introduced in 2009. A malonamic ester, dicarbonyl substrate **45**, was designed for monoalkylation and was synthesized by Park in 2009 [81]. Because these substrates can be easily converted to versatile synthetic chiral intermediates, malonamic esters **45** are useful substrates for the generation of a chiral tertiary carbon center. Influenced by the *N*-protecting groups, the enantioselectivities were significantly changed, and the methyl or *p*-methoxyphenyl groups gave high enantioselectivity. The research groups of Park and Itoh independently reported the asymmetric alkylation of the α-substituted malonic esters through the discrimination of two different ester moieties. Park and co-workers employed the malonic ester **47** with a binaphthyl-modified catalyst to obtain α,α-dialkylmalonate with high enantioselectivity [83]. In contrast, Itoh used the malonic ester **48** with a cinchonine-derived catalyst to give the corresponding alkylated compound [84]. After conducting additional studies on dicarbonyl substrates for phase-transfer catalytic alkylation, Park recently developed the lactam **46** [82] and lactone **49** [85] substrates. The quaternary carbon stereocenters of these substrates were successfully formed under phase-transfer catalytic conditions with high chemical yields and stereoselectivities.

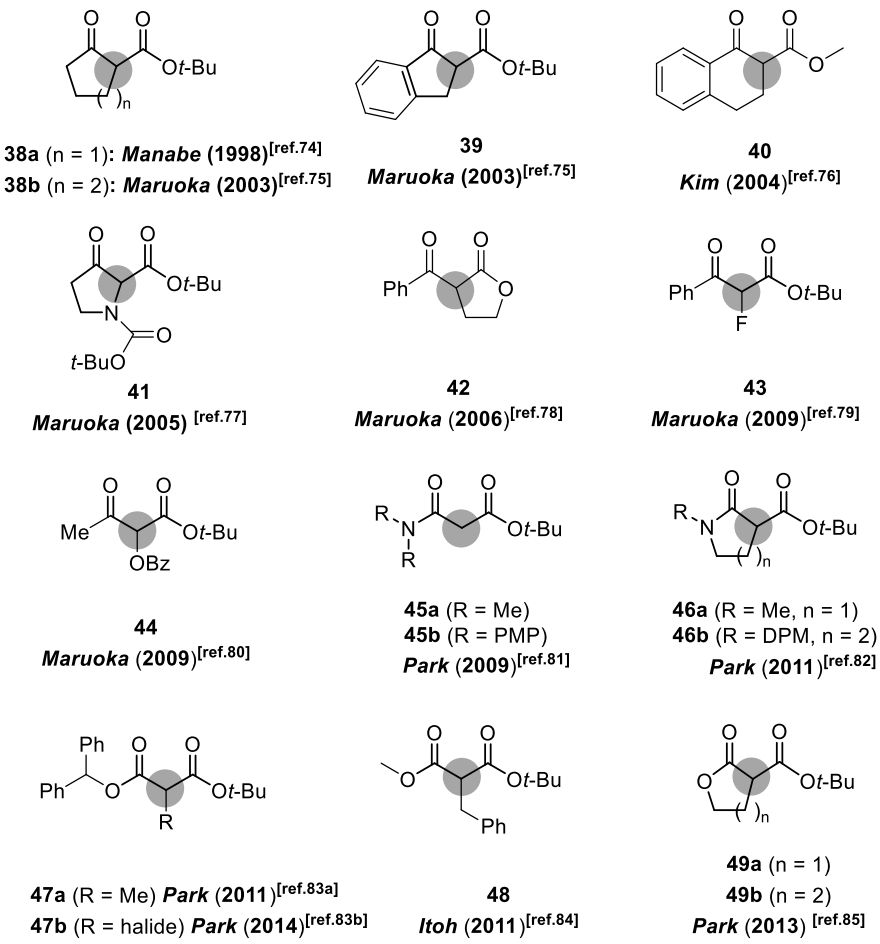


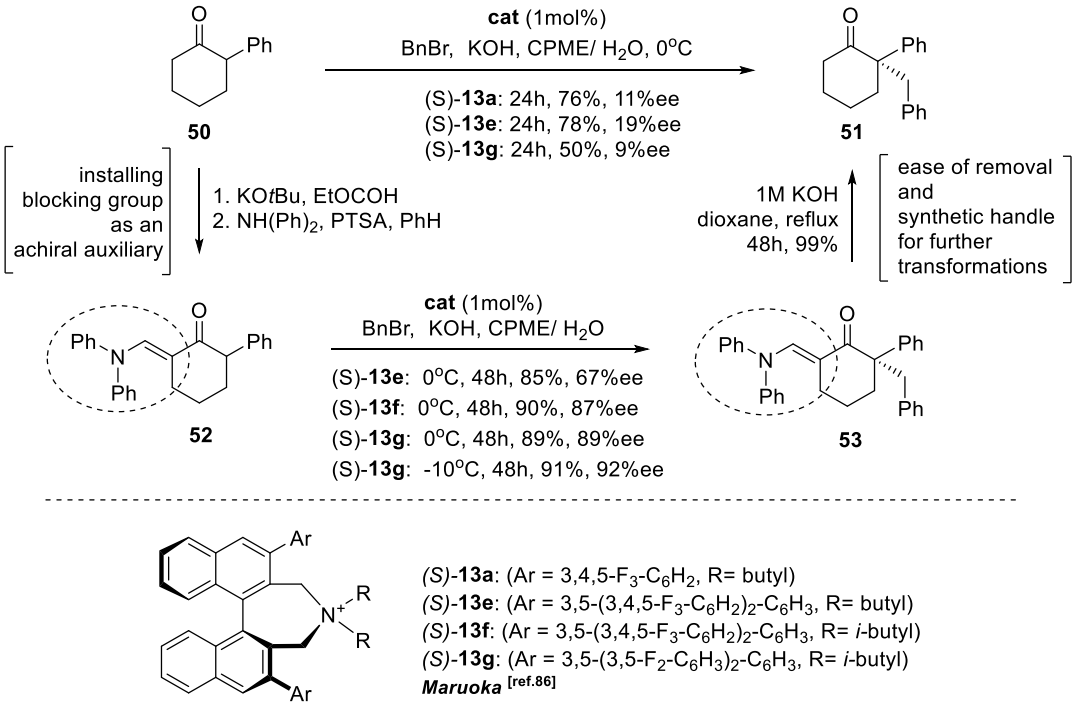
Figure 7. Substrates with the α-position inherently activated by the di-carbonyl group

Although various carbonyl substrates appropriate for α-alkylation using the asymmetric phase-transfer catalytic reaction have been developed, investigations into new substrates to broaden the reaction scope are required. As one of our research programs for the development of new carbonyl substrates for phase-transfer catalytic reactions, our research team attempted to develop malonate derivatives and apply them to develop efficient phase-transfer catalytic reactions.

1-3. Recent advances in asymmetric phase-transfer catalysis

1-3-1. Development of a substrate with an installed achiral auxiliary

In 2013, Maruoka's research group achieved a highly enantioselective alkylation of the 2-arylcyclohexanones by installing an achiral auxiliary, the *N,N*-diphenylaminomethylene group, at the 6-position of the cyclohexanones [86]. The auxiliary was readily removed from the alkylation product by simple basic hydrolysis. This methodology provided a practical entry for the introduction of a steric and electronic tuning auxiliary to the phase-transfer catalytic substrate and expanded the synthetic method of the highly enantioselective asymmetric alkylation of the 2-arylcyclohexanones, overcoming the limited success up to that time.



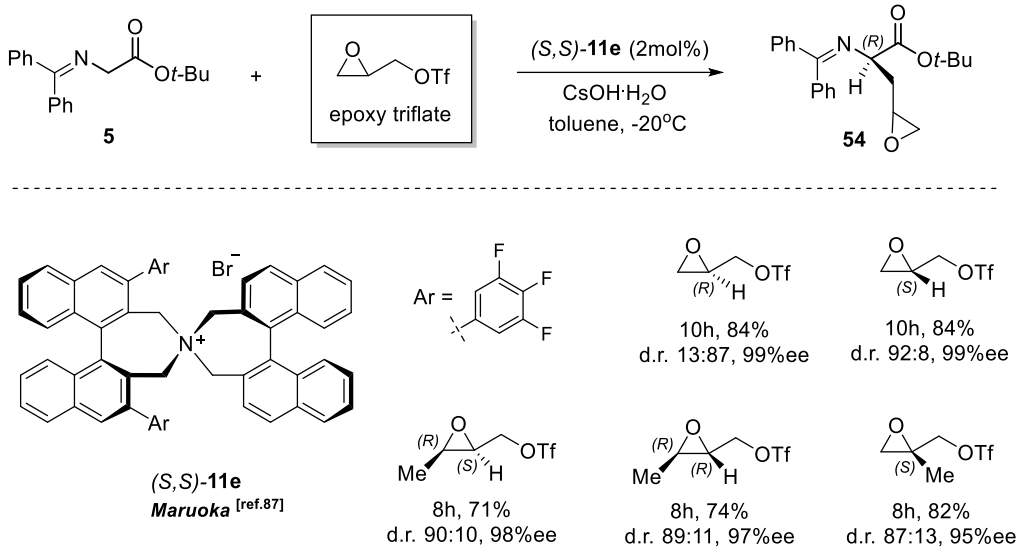
Scheme 21. 2-Arylcyclohexanone modified with a *N,N*-Diphenylaminomethylene group

The reaction between 2-phenylcyclohexanone (**50**) and benzyl bromide under phase-transfer conditions gave the benzylated product (**51**) with low enantioselectivity, and a chiral phase-transfer catalyst, (S)-**13**, was found to be unsuitable for relatively small substrates, such as 2-phenylcyclohexanone, most likely because of the difficulty of the enantioface discrimination. Based on these results, the authors installed *N*,*N*-diphenylaminomethylene as a tunable achiral auxiliary at the 6-position of 2-phenylcyclohexanone with the expectation that the structural modification in the cyclic ketone would result in efficient enantioface discrimination, leading to higher enantioselectivity. A significant improvement in the enantioselectivity was observed in the reaction of modified 2-phenylcyclohexanone (**52**). Fine-tuning of the catalyst and lowering the reaction temperature to −10°C increases the enantioselectivity slightly, although a longer reaction time was required.

1-3-2. Introduction of various electrophiles in the phase-transfer catalytic alkylation

Phase-transfer catalytic alkylation has been utilized as the one of the most fundamental yet versatile reactions for carbon-carbon bond formation in synthetic organic chemistry, and asymmetric alkylation under the phase-transfer catalytic system has been developed with several types of alkylating agents. However, the use of the alkylating agent as the electrophile is relatively limited to alkyl halides, especially electronically activated allylic-like halides. This limitation is inherently problematic when the required alkyl halides are not readily available. Therefore, recent efforts to expand the scope of the electrophiles under the phase-transfer catalytic system have been undertaken by several research groups. Molecules used as electrophiles should be added to or substituted on the substrates with a

high reactivity and enantioselectivity, also serving as versatile chiral building blocks. In 2011, Maruoka and co-workers utilized epoxy sulfonates as alkylating agents, which can be efficiently prepared from the corresponding alcohols by the Sharpless asymmetric epoxidation in two steps [87]. These authors have reported the first practical phase-transfer catalyzed asymmetric alkylation of glycine Schiff base **5** with epoxy triflates for the stereoselective synthesis of the γ,δ-epoxy-α-amino acid derivatives, which are frequently encountered as important scaffolds in several total syntheses (**Scheme 22**).

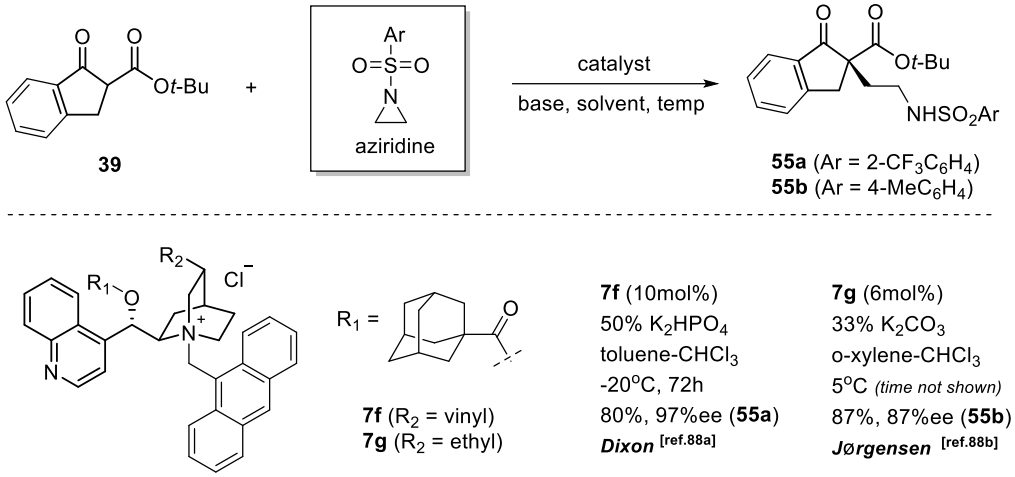


Scheme 22. Asymmetric phase-transfer catalytic alkylation with epoxy triflates

The research groups of Dixon and Jørgensen independently reported the asymmetric ring-opening reaction of the aziridines with the β-ketoesters in 2008 [88]. The reaction of β-ketoester **39** and *N*-sulfonylaziridine catalyzed by **7f** or **7 g** under the phase-transfer conditions gave the products **55a** and **55b,** respectively**,** with good enantioselectivities. These studies reported the direct enantioselective catalytic alkylation reaction with *N*-

sulfonyl aziridines leading to products containing the amino ethylene group attached to a stereogenic quaternary carbon in high enantiomeric excess.

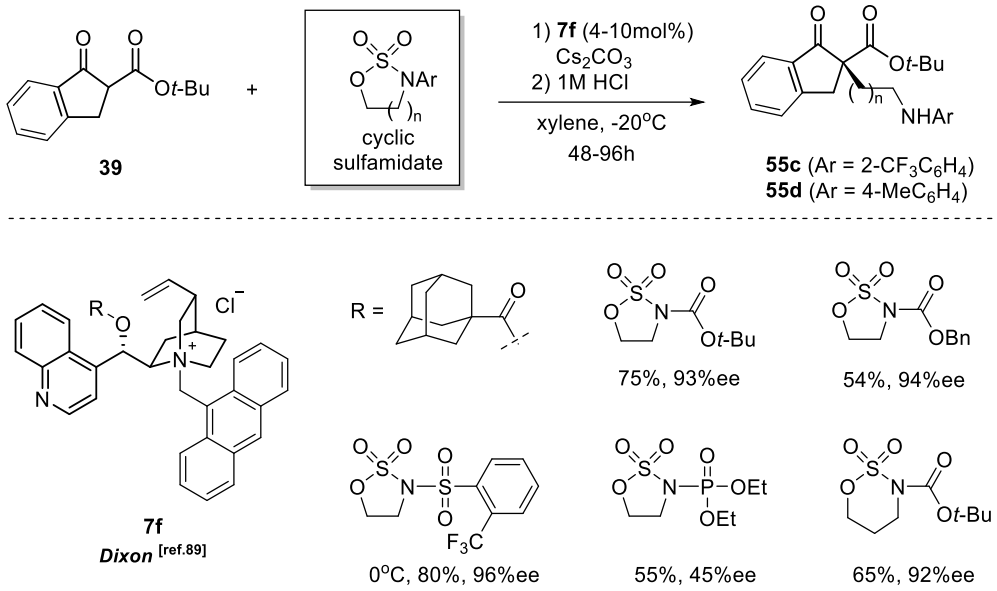
Furthermore, this reaction would directly install a protected amino group and would allow γ-substituents to be incorporated into the produced γ-amino acid backbone (**Scheme 23**).



Scheme 23. Asymmetric phase-transfer catalytic alkylation with aziridine

Two years later, Dixon introduced the cyclic sulfamidates as potential two- or three-carbon electrophile candidates [89], which was the first enantioselective phase-transfer-catalyzed ring-opening of five-membered and six-membered cyclic sulfamidates. Under mild conditions, good to excellent selectivities have been obtained for a range of newly emerged electrophiles. There have been no reports of a catalytic enantioselective nucleophilic ring-opening of cyclic sulfamidates with carbon-centered nucleophiles, despite the synthetic advantages of this approach. Dixon reasoned that a base-catalyzed reaction would be challenging because of the low basicity of the sulfamic acid salts that can be formed from the ring opening of the cyclic sulfamidates. Accordingly, it was believed that an enantioselective ring-opening of the cyclic sulfamidates could be realized using

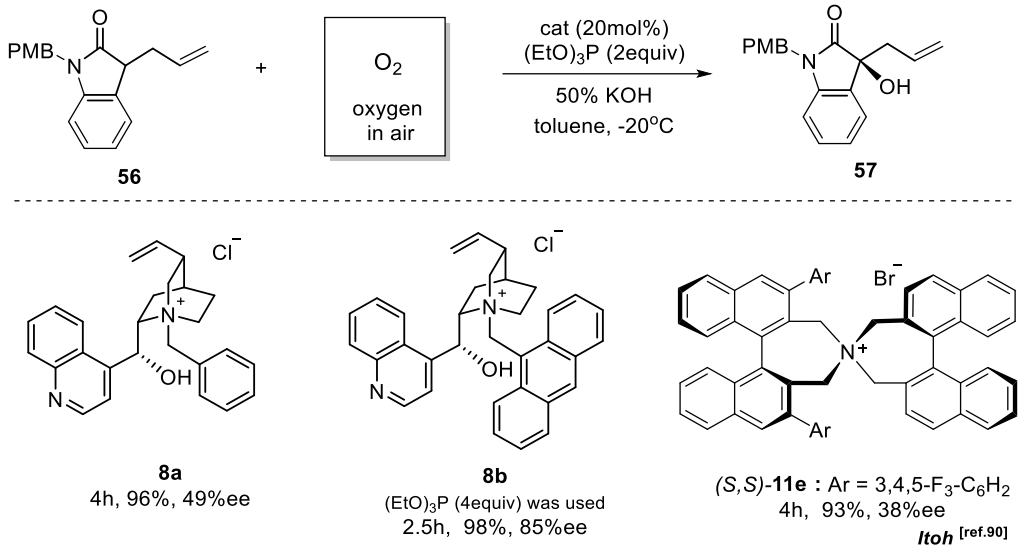
asymmetric phase-transfer catalysis with a stoichiometric base. The synthetic potential of this attractively simple methodological approach was demonstrated (**Scheme 24**).



Scheme 24. Asymmetric phase-transfer catalytic alkylation with the cyclic sulfamidate

Itoh and co-workers reported the asymmetric hydroxylation of the 3-substituted oxindoles, such as **56**, with molecular oxygen used concurrently as an oxidant and an electrophile [90]. The reaction of oxindole **56** was promoted by various catalysts in air to give hydroxylation product **57** with good reactivity and moderate enantioselectivity. The use of O_2 as an oxidant was paramount because it is economical and environmentally benign. During their investigation using air, Itoh and co-workers found that 3-substituted oxindoles react with molecular oxygen in the presence of an alkaline base to give the corresponding 3-hydroxy derivatives quantitatively. Although the reaction with solid KOH proceeded without a catalyst in toluene to give 3-allyl-3-hydroxy-2-oxindole **57**, no product was obtained when the reaction was performed in a toluene/50% KOH aqueous solution when the phase-transfer catalyst was not added. Thus, the chiral reaction was screened in the two-phase

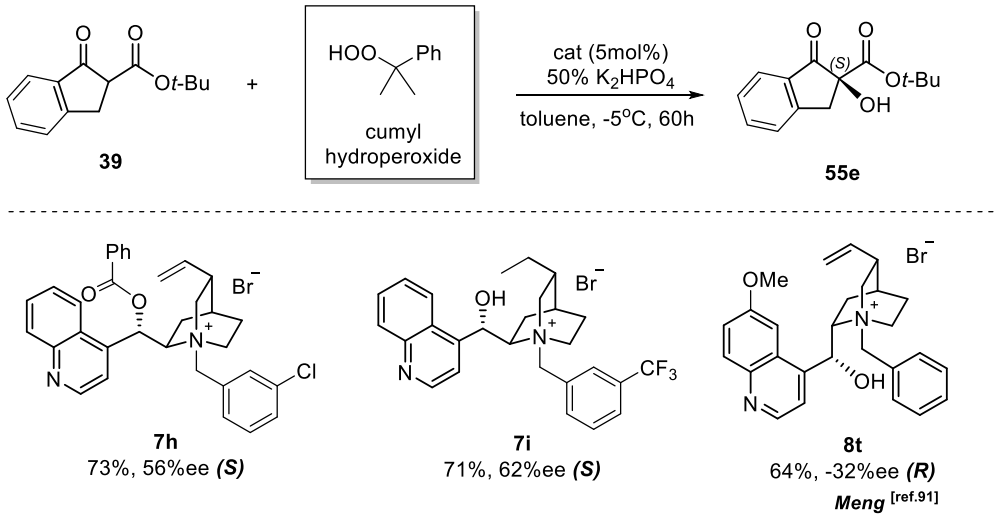
system, and the cinchonidine-derived catalyst **8b** produced the desired product with high yield and good enantioselectivity (**Scheme 25**).



Scheme 25. Asymmetric phase-transfer catalytic hydroxylation with oxygen gas

The development of novel and efficient electrophiles for the stereoselective preparation of chiral molecules was an important synthetic goal for the Meng research group. In 2010, Meng endeavored to prepare optically active chiral hydroxy-containing compounds, which constitute an important class of synthetic intermediates [91]. These authors developed enantioselective phase-transfer catalyzed direct oxidation with the commercially available electrophile cumyl hydroperoxide. Under mild conditions, high selectivities were obtained for a range of substituted indanone derivatives. Moreover, this new methodology was successfully amplified to a gram-quantity scale. The substrate was treated with cumyl hydroperoxide (1.25 equiv.) on a gram-quantity scale under the same conditions as the catalyst loading (5 mol%). Surprisingly, after only 30 hours at –5℃, the hydroxylation product was obtained in 80% yield without any loss of enantioselectivity. The shorter

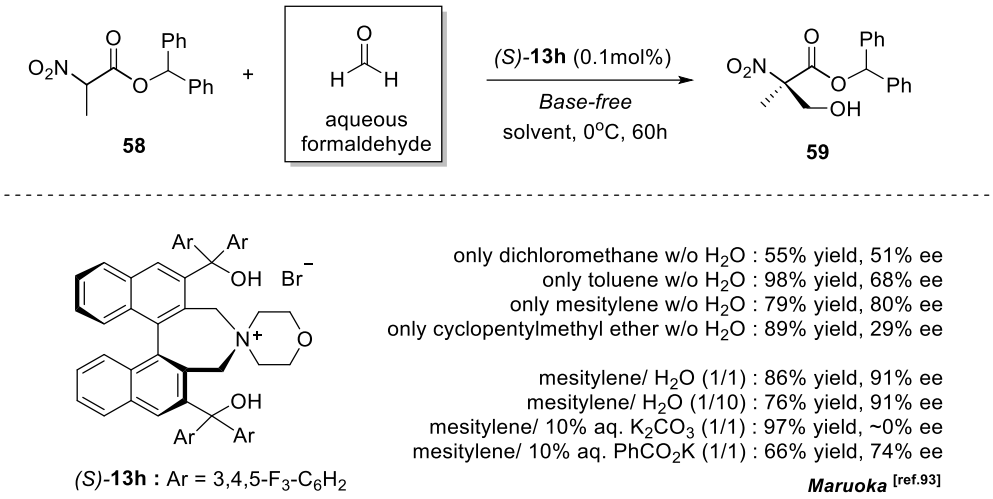
reaction time was ascribed to the intensive mixing conditions by high-speed mechanical agitation (800 rpm). Although this method showed limited stereoselectivity, it has significant value in terms of simplicity and the ready availability of the electrophile (**Scheme 26**).



Scheme 26. Asymmetric phase-transfer catalytic hydroxylation with hydroperoxide

Recently, Maruoka's research group discovered an asymmetric phase-transfer reaction under base-free neutral conditions [92]. Although quaternary onium salt-catalyzed phase-transfer reactions are generally believed to require base additives, Maruoka determined that even without any base additives, the conjugate additions of 3-substituted oxindoles proceeded smoothly in the presence of lipophilic quaternary onium bromide under water-organic biphasic conditions. The mechanism of this novel base-free neutral phase-transfer reaction system was investigated, and the assumed catalytic cycle was presented along with the interesting effects of the weight and lipophilicity of the phase-transfer catalyst. The base-free neutral phase-transfer reaction system has been applied to highly enantioselective conjugate additions, the aldol reaction, sulfenylation, and chlorination under the influence

of chiral bifunctional onium bromides as the key catalysts. During their studies on the development of an efficient asymmetric phase-transfer method, Maruoka's research group reported the difficult, highly enantioselective aldol reaction of α-substituted nitroacetates, such as **58**, with aqueous formaldehyde for the synthesis of α-alkyl serine derivatives under base-free neutral phase-transfer conditions with low catalyst loading (0.1 mol %) of (*S*)-**13h** [93].



Scheme 27. Asymmetric phase-transfer catalytic aldol reaction with formaldehyde

With diphenylmethyl 2-nitropropanoate **58** as a key substrate for the reaction, the solvent effect was investigated. Although the use of dichloromethane and cyclopentyl methyl ether as the organic solvents instead of toluene decreased the enantioselectivities, conducting the reaction in mesitylene and an equal amount of water enhanced the enantioselectivity to a maximum of (91% ee), and in the water-rich biphasic reaction system (with a mesitylene: H_2O ratio of 1:10), the reaction gave the product with same high enantioselectivity. Note that the reaction under ordinary phase-transfer conditions using aqueous base solutions, such as aqueous K_2CO_3, significantly decreased the enantioselectivity. Even using $PhCO_2K$

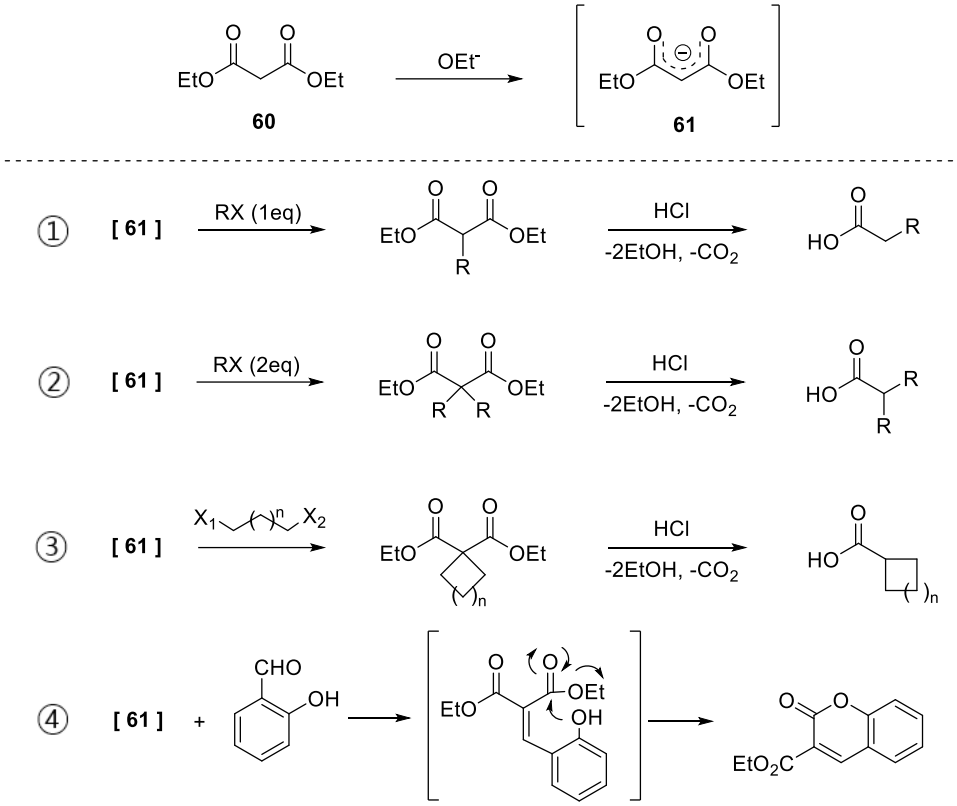
as a relatively mild base, a decrease in enantioselectivity was observed in the reaction. These results clearly indicated that there were certain cases that did not require a basic water solvent under the phase-transfer catalytic system and suggested the possibility of using formaldehyde as an electrophile (**Scheme 27**).

2. Chiral malonate derivatives

2-1. Potential of malonic esters

Malonic ester is a reagent specifically used in a reaction that converts an alkyl halide to a carboxylic acid, called the "malonic ester synthesis". Malonic esters are the esters of malonic acid. Because the most common example of a malonic ester is diethyl malonate, malonic ester typically indicates diethyl malonate (**60**), which is readily available and is a representative active methylene compound. Because the α hydrogens of the malonic ester are adjacent to two carbonyls, the relatively acidity of the α-proton (pK_a value of 13) is appropriate for deprotonation by a weak base (the pKa value of its conjugate acid should be above 13). If one of the carbonyls is absent, then the quantitative generation of the enolate from the ethyl acetate in high yield is difficult because increasing the pKa value of the α-proton causes the reaction to require a very strong base, such as lithium diisopropylamide (LDA), and very low temperature under strictly anhydrous conditions. However, the enolate of malonic ester (**61**) is readily formed and converted to various chemical moieties via several modifications [94]. The sequence of reactions shown in **scheme 28** is as follows. **1)** The active methylene enolate is mono-alkylated by one equivalent of the alkylating reagent, then hydrolyzed and decarboxylated under acidic conditions to give the α-mono-substituted carboxylic acid. **2)** If two equivalents of alkyl halide are used, then the disubstituted malonic ester is smoothly obtained. After alkylation, the product can be converted to a dicarboxylic acid through hydrolysis, and subsequently, one of the carboxylic acids can be removed through a decarboxylation step. **3)** Intramolecular malonic ester synthesis occurs when reacted with a dihalide. This reaction is also called the "Perkin alicyclic synthesis". **4)** The Knoevenagel reaction of salicylaldehyde and malonic ester proceeded efficiently under milder reaction conditions

followed by an intramolecular nucleophilic acyl substitution reaction, affording various types of coumarin derivatives in excellent yield.



Scheme 28. General malonic ester synthesis

Malonates, commonly meaning the ester or salt form of malonic acid, are one of the most fundamental molecular groups in synthetic organic chemistry, especially for carbon-carbon bond formation. These compounds contain adjacent dicarbonyl functional groups with two esters located in the β-positions. When the two ester groups are different, certain products mentioned in **scheme 28** can have chiralities on their molecules. Additionally, dicarbonyl compounds with different ester substituents at the β-positions and either a pro-chiral or chiral α-carbon position have considerable synthetic value because the ester groups can be

modified to various other functional groups. Similarly, chiral malonates can be converted into diverse chiral compounds (**Figure 8**).

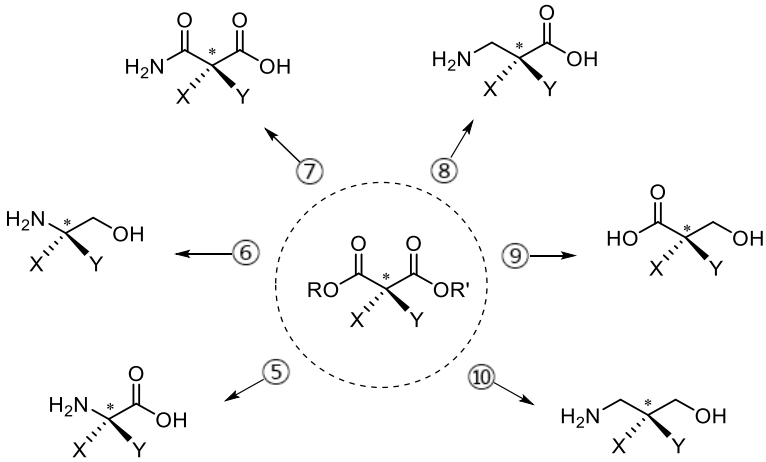


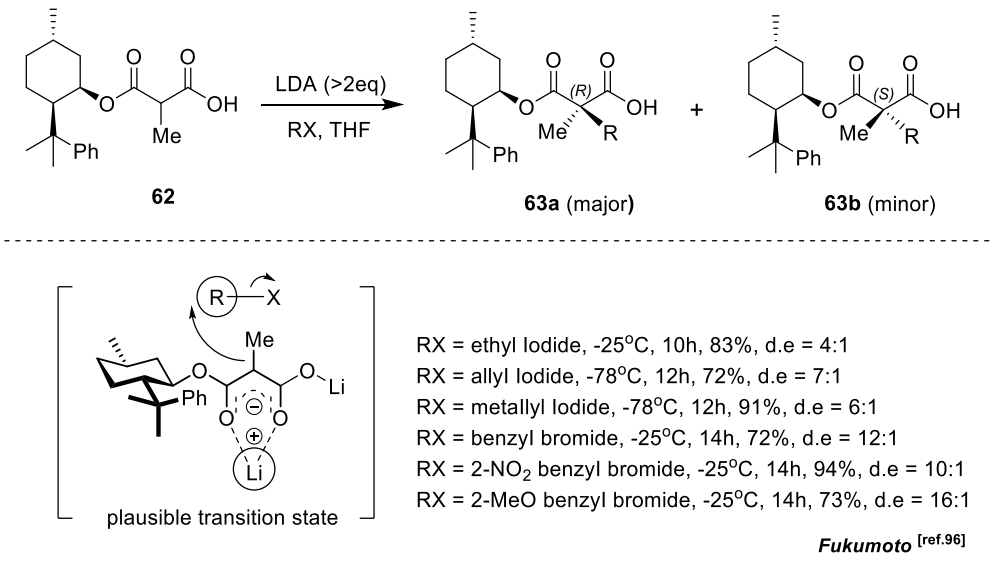
Figure 8. Representative modification of the malonate skeleton

The optically active derivatives of the chiral malonates can also be crucial intermediates in the synthesis of biologically active pharmaceuticals and natural products. Because the chiral α,α-dialkylmalonates are especially resistant to racemization under normal reaction conditions, they can be used in the synthesis of chiral compounds without loss of chirality at quaternary carbon centers. Therefore, achieving chiral α,α-dialkylmalonates has been regarded as challenging but valuable in asymmetric synthetic fields.

2-2. Synthetic method for the chiral malonates

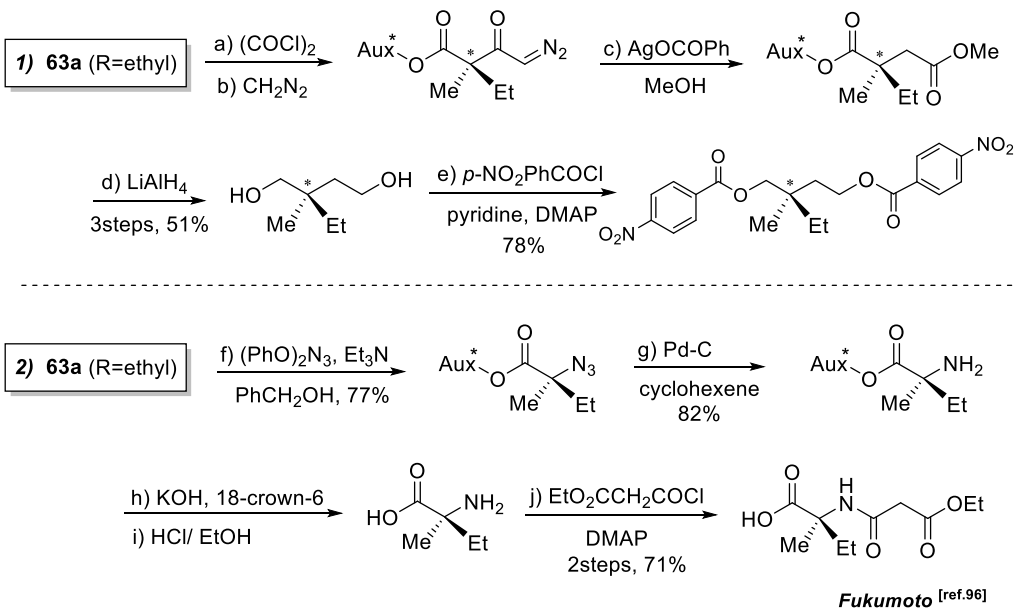
Although the enantioselective transformation of prochiral malonic acids into chiral molecules would be a preferred method for providing versatile chiral building blocks for the synthesis of optically and biologically active compounds, this type of asymmetric synthesis is only common in enzymatic conversions [95], and examples of its use in chemical transformations are rare.

In 1989, Fukamoto and co-workers reported the enantioselective construction of a quaternary asymmetric carbon center at the α-position of malonic acid using a chiral auxiliary through the reaction of dianions derived from the chiral half esters of mono-substituted malonic acids (**62**) with two molar equivalents of LDA and alkyl halides [96]. The investigation by the Fukamoto team led us to the discovery of a novel and enantioselective construction of the α-quaternary asymmetric center in a moderate optical purity (**Scheme 29**).



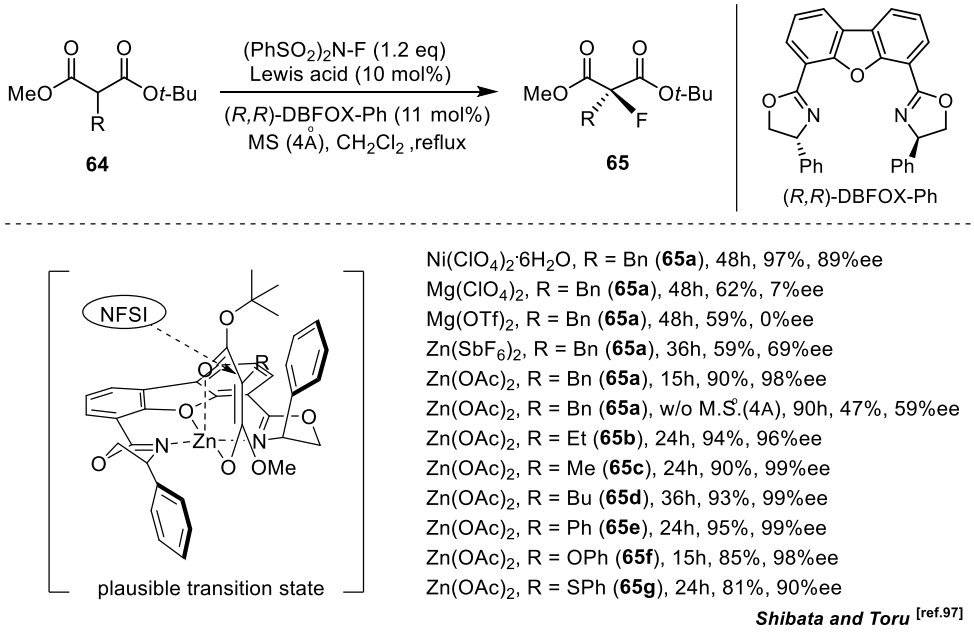
Scheme 29. Enantioselective α-alkylation of malonates using a chiral auxiliary

When the enolate of **62** was formed, the actual *E/Z* distribution and conformations of the dianions were unknown. The diastereofacial selectivity could be attributed to the easier access to the alkyl halides from the less-hindered side of the transition-state geometry depicted in **scheme 29**. The alkylated half esters were transformed into certain derivatives to prove the efficiency of this methodology and to determine the absolute configuration by comparison of the specific rotation with several known compounds. First, chiral **63a** underwent an Arndt-Eistert reaction, gaining one more carbon atom. Following cleavage of the auxiliary and reduction, the chiral malonate bearing two different alcohol functional groups was obtained. Next, the nucleophilic acyl substitution yielded another chiral malonate derivative carrying the aryl ester groups. Second, **63a** was converted into an azide with one fewer carbon by Curtius-type rearrangement followed by hydrogenolysis, which was hydrolyzed using KOH and 18-crown-6 in hot toluene. The resulting α-methyl α-alkyl amino acid also smoothly attacked the acyl chloride as a nucleophile (**Scheme 30**).



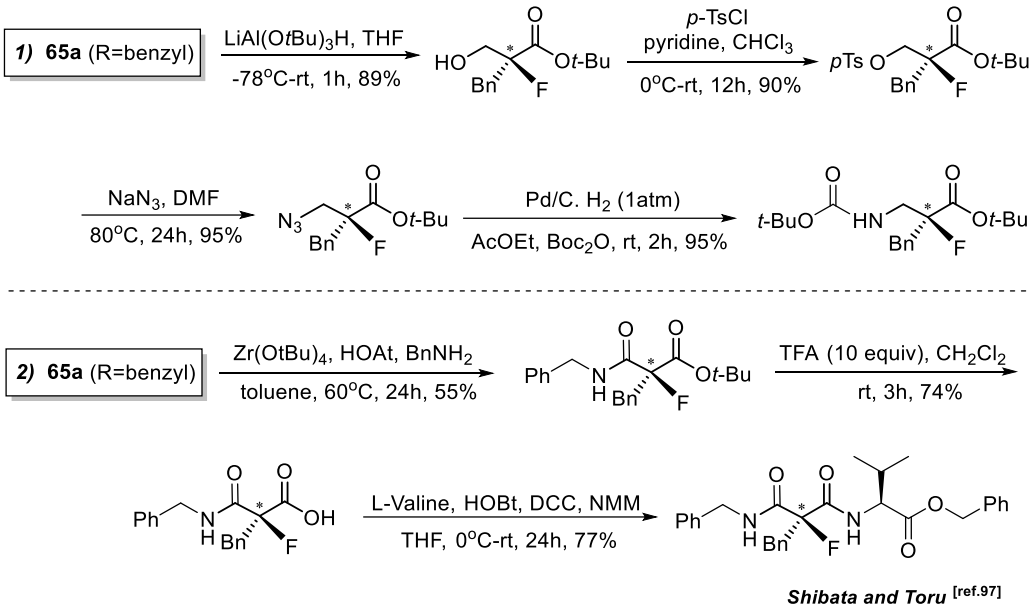
Scheme 30. Modification of chiral malonate (**63a**) into various derivatives

In 2008, the Shibata and Toru research group reported the direct α-fluorination of racemic mixtures of malonates carrying different esters for the synthesis of chiral malonates [97]. The chiral α-fluoro-α-alkylmalonates **65** could be obtained in high chemical yields and up to 99% ee through enantioselective direct α-fluorination using various Lewis acids and (*R,R*)-DBFOX-Ph as a catalyst; this reaction was the first enantioselective fluorination of malonates. The authors attempted fluorination with N-fluorobenzene sulfonimide (NFSI) as a fluorine source. Optimization experiments for the Lewis acid were performed to improve the enantioselectivity of the transformation. $Zn(OAc)_2$ was found to be effective for the desymmetrization-like enantioselective fluorination of malonates. In addition, molecular sieves were indispensable for achieving high enantiocontrol. With the conditions optimized, the scope of the α-fluorination was investigated in terms of the range of substrates that could be tolerated (**Scheme 31**).



Scheme 31. Enantioselective α-fluorination of the malonates

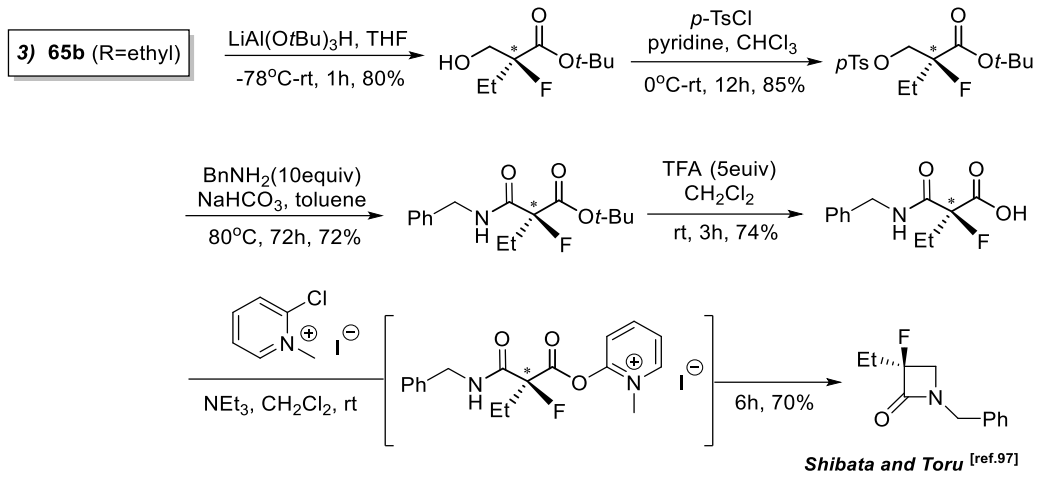
In the described transformation, the observed chemical yields and enantioselectivities are excellent, and the resulting chiral 2-fluorinated malonates **65** are potentially versatile starting materials for the synthesis of biologically important compounds. In this context, a synthetic application of these malonates in producing pharmaceutically attractive molecules was investigated.



Scheme 32. Modification of chiral malonate (**65a**) into various derivatives

The first goal was the transformation of **65a**. Chemoselective reduction of **65a** using LiAl(O*t*Bu)$_3$H followed by tosylation, nucleophilic azidation, and subsequent hydrogenolysis under H_2 atmosphere in the presence of Pd/C and Boc_2O afforded the fluoro α-benzyl-β-alanine target molecule. Additionally, the optically active fluorinated retroamide isostere was synthesized in only three steps via an asymmetric esteramide. The chemoselective ester–amide exchange reaction proceeded successfully in the presence of $Zr(OtBu)_4$ in good yield. The chemoselectivity observed was thought to result from the bulkier *tert*-butyl group compared with the methyl ester moiety. The subsequent treatment

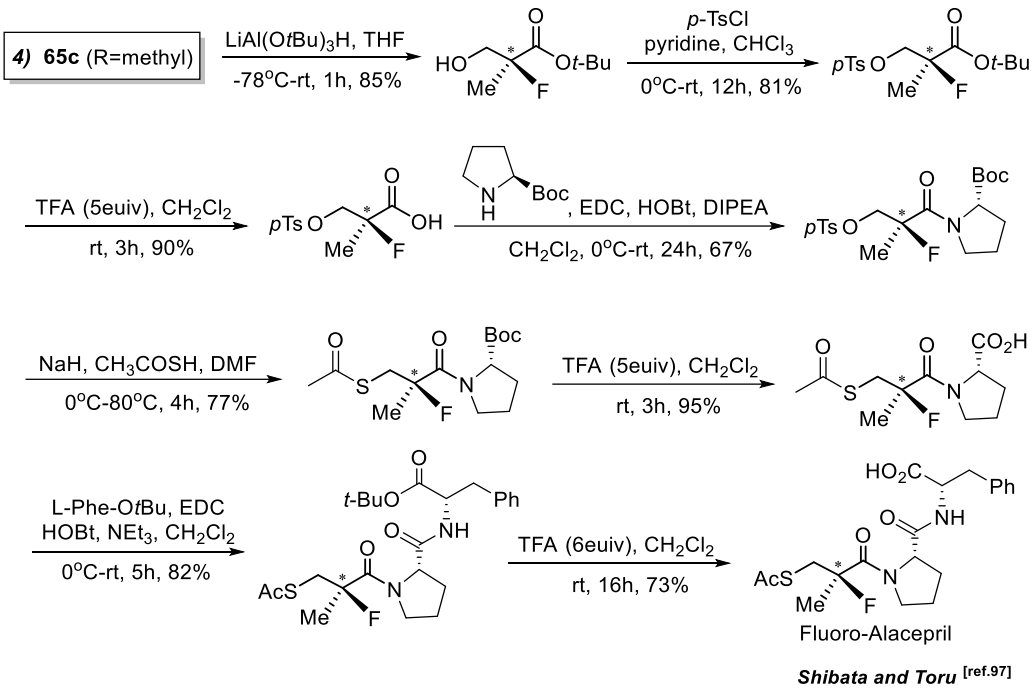
with TFA gave the acid, which was coupled with L-Val-OBn, which proceeded smoothly using 1,3-dicyclohexylcarbodiimide and 1-hydroxy benzotriazole (**Scheme 32**).



Scheme 33. Modification of chiral malonate (**65b**) into various derivatives

The utility of the 2-fluorinated malonates was also demonstrated by synthesizing a 3-fluorinated β-lactam. The chemoselective reduction of the malonate with the $LiAl(OtBu)_3H$ procedure mentioned above and the subsequent tosylation underwent nucleophilic amination using benzylamine. Removal of the *tert*-butyl ester using a strong acid followed by intramolecular cyclization by the Mukaiyama procedure afforded the fluorinated β – lactam (**Scheme 33**).

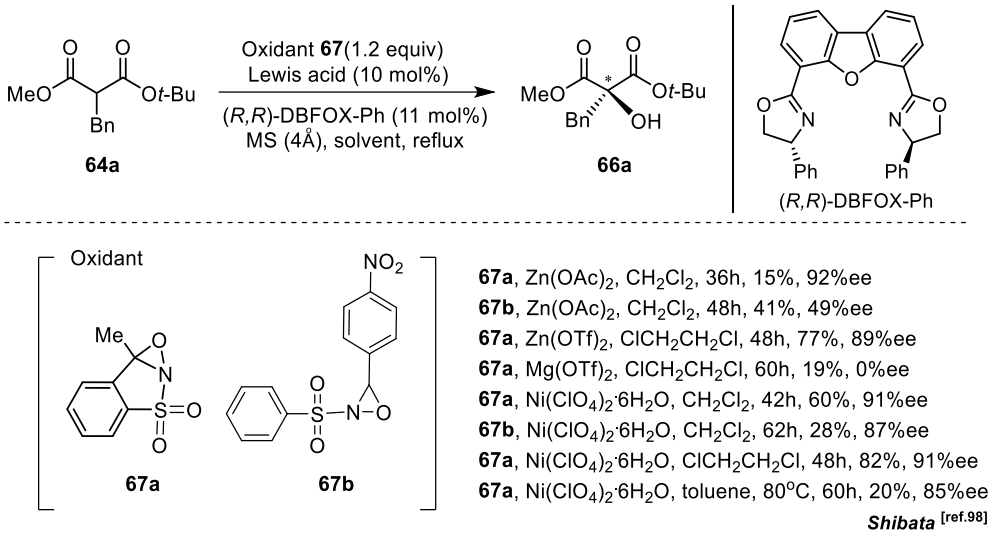
The synthesis of fluoro-alacepril was then examined. Alacepril is an orally active antihypertensive angiotensin-converting enzyme (ACE) inhibitor. Structurally, alacepril is characterized as a tripeptide-like compound consisting of l-phenylalanine, l-proline, and 3-mercapto-(2S)-methylpropionic acid. The total synthesis of (S)-fluoro-Alacepril was accomplished in eight steps starting from chiral malonate (S)-**65c**, based on the strategy outlined in **Scheme 34**.



Scheme 34. Modification of chiral malonate (**65c**) into various derivatives

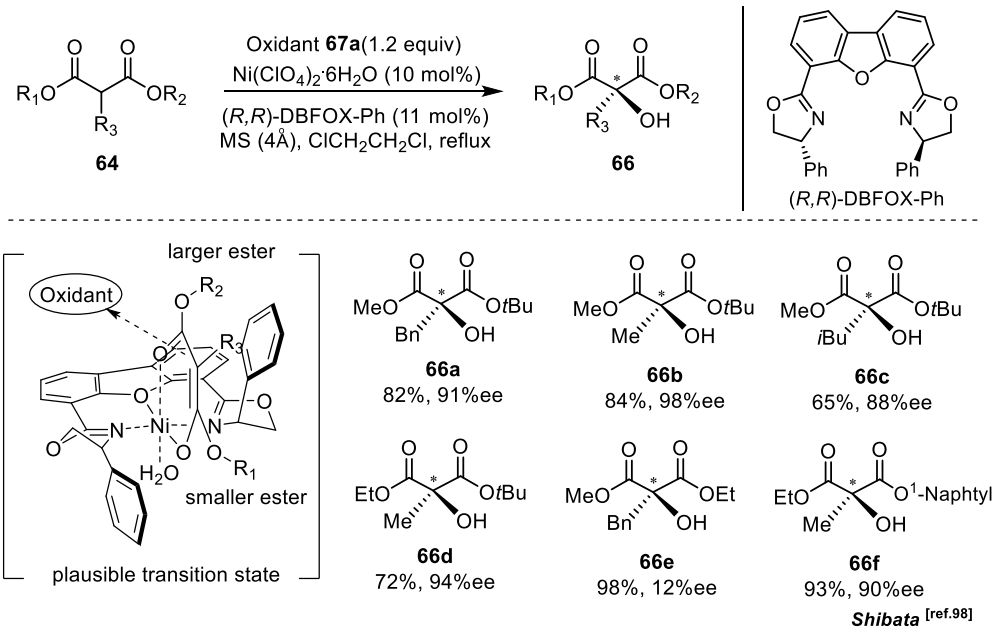
Optically active 2-fluoromalonate (S)-**65c** was treated with reductant, followed by tosylation. Removal of the *tert*-butyl ester was followed by coupling to l-Pro-OtBu under standard peptide coupling conditions. Nucleophilic substitution of CH_3COSNa followed by cleavage of the resulting tert-butyl ester, coupling to l-phenylalanine *tert*-butyl ester and a trifluoroacetic acid treatment afforded fluoro-alacepril in good overall yield.

Thus, Shibata and Toru have described the first highly enantioselective fluorination of malonates. This desymmetrization-like approach for the preparation of fluorinated chiral building blocks showed higher enantioselectivity and generality, which can be easily converted into valuable intermediates for the preparation of pharmaceutically attractive molecules.



Scheme 35. Enantioselective α-hydroxylation of malonates-I

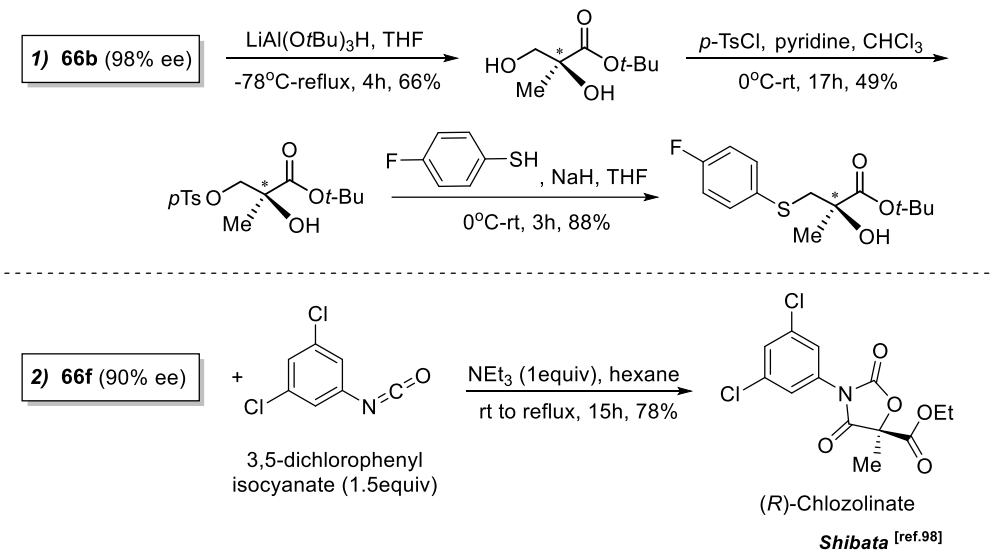
One year later, Shibata presented the first dynamic kinetic asymmetric transformation in the α-hydroxylation of racemic malonate **64a** using the (*R*,*R*)-DBFOX-Ph/Ni II complex with oxaziridine **67** as an oxidant to provide the chiral α-hydroxy malonate **66a**, which has a quaternary stereocenter, in high yield with a high enantioselectivity (**Scheme 35**) [98]. First, Shibata attempted direct α -hydroxylation with oxaziridine **67a** under the best reaction conditions previously reported for the enantioselective fluorination of malonate derivatives [97]. Optimization experiments for the Lewis acid and the solvent were performed to improve the yield and enantioselectivity of the transformations, and the combination of $Ni(ClO_4)_2 \cdot 6H_2O$ in 1,2-dichloroethane at reflux was highly effective for the dynamic kinetic asymmetric transformation in the α-hydroxylation of the malonate derivatives. The structure of the oxidant slightly affected the yield and enantioselectivity of **66a**. Changing the oxidant from cyclic oxaziridine **67a** to acyclic 3-(4-nitrophenyl)-2-(phenylsulfonyl)-1,2-oxaziridine (**67b**) resulted in lower yields with lower ee values.



Scheme 36. Enantioselective α-hydroxylation of malonates-II

With the reaction conditions optimized, the authors explored the range of substrates that could be tolerated during the hydroxylation reaction (**Scheme 36**). First, the group examined the malonate derivatives and studied the effect of the substituents on the stereogenic center at the α position on the hydroxylation reaction. The results showed that the aryl and alkyl substituents at the α position have less of an effect on the yields and enantioselectivities. Hydroxylation with a sterically demanding *i*-Bu group also proceeded smoothly to give **66c** with 88% ee. Next, the group investigated the scope, limitation, and ability of this method to discriminate among the ester moieties of different steric bulk. The (R,R)-DBFOX/Ni^{II} catalyst efficiently discriminated between the Me/tBu ester system and the Et/tBu ester system. Next, the authors attempted discrimination between the Me and Et ester substituents. However, the desired product **66e** was obtained in 98% yield with only 12% ee. These results indicated that the tBu ester moiety is responsible for the enantio

elective transformation. The configuration of the resulting α-hydroxy malonate **66** could be explained by the preferential approach of the hydroxylating agent **67** from the less-hindered *Si* face of the octahedral complex formed between the substrates, a Ni^{II} ion, and (*R*,*R*)-DBFOX-Ph, based on the outlined mechanism.

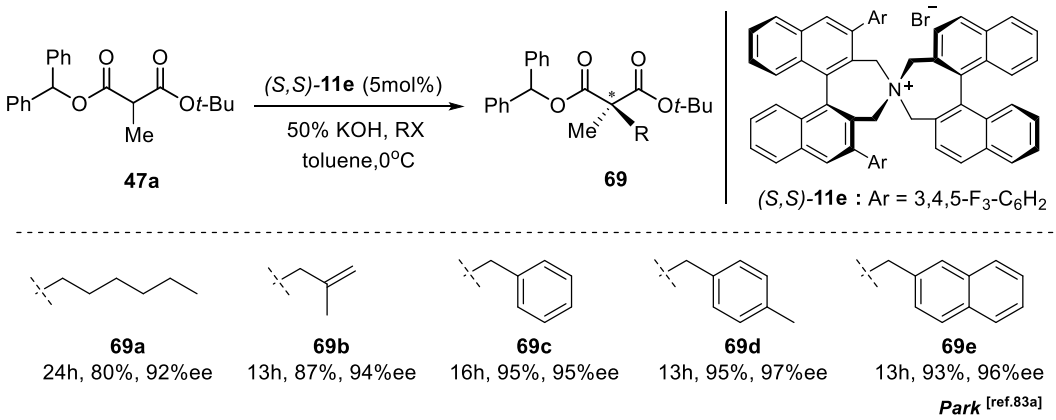


Scheme 37. Modification of chiral malonates (**66b** and **66f**) into various derivatives

The application of these reactions to the synthesis of biologically attractive molecules illustrated the efficiency of this strategy (**Scheme 37**). The authors considered the synthesis of a key intermediate for the bicalutamide derivatives. The chemoselective reduction of **66b** was successfully achieved. The primary hydroxyl group was then protected using *p*-toluenesulfonyl chloride to give the tosylate. Nucleophilic substitution by sodium 4-fluorobenzenethiol furnished the common intermediate for the synthesis of (*R*)-bicalutamide and its derivatives. Next, the utility of α-hydroxy malonate **66f** was demonstrated through the synthesis of chlozolinate, an important antifungal agent, in only two steps from the racemic malonate. In conclusion, Shibata achieved the first highly

enantioselective direct α-fluorination and α-hydroxylation of racemic malonate using the (*R,R*)-DBFOX-Ph/metal complex. Based on this strategy, dynamic kinetic asymmetric transformations in the α-functionalization of racemic malonate with other electrophiles were investigated. However, these methods were limited to fluorination and hydroxylation and were restricted to a small-scale process using the metal catalyst, which could not be applied to an industrial process.

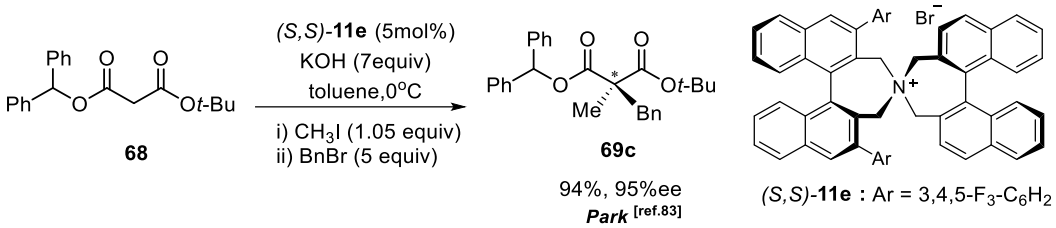
In 2011, Park's research group attempted to develop a method for the enantioselective direct α-alkylation of malonates using a phase-transfer catalytic reaction, which was the first chemical process of direct α-alkylation. Furthermore, the synthesized chiral α-alkylated malonates were then developed by conversion into various building blocks [83a]. This approach was an attractive synthetic method for universal chiral building blocks that could be readily converted to versatile chiral target molecules involving quaternary carbon centers.



Scheme 38. Enantioselective α-alkylation of malonate by Park

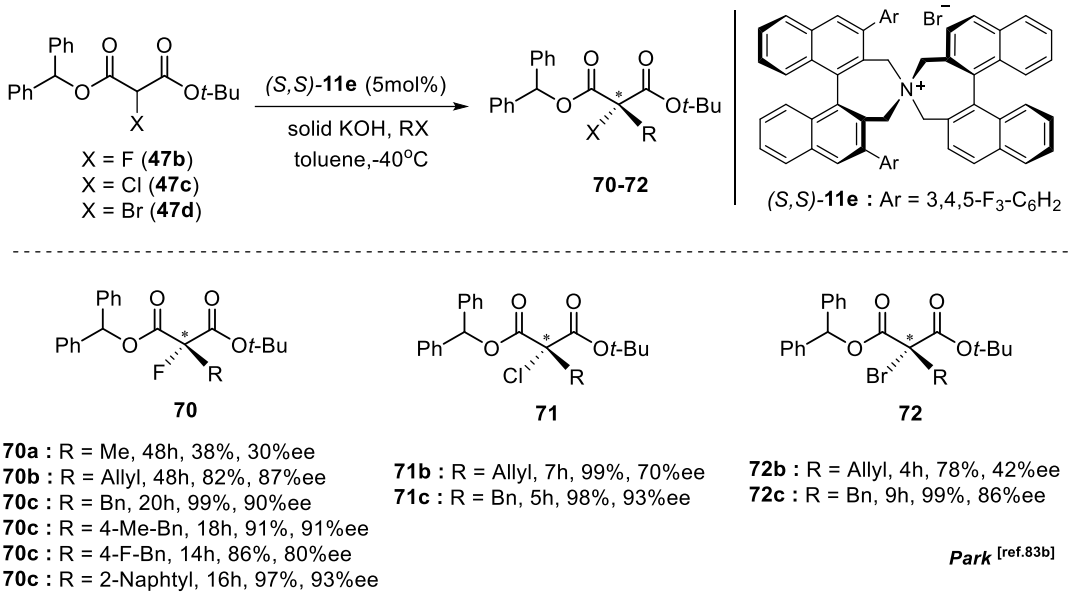
The substrate **47a** was chosen for investigation into the scope and limitations of enantioselective PTC alkylation with various electrophiles. The very high

enantioselectivities (97% ee) shown in **Scheme 38** indicated that this reaction system was a highly efficient enantioselective synthetic method for dialkylmalonates. In addition, the successive double alkylations of malonate **68** could afford the corresponding dialkylmalonates without loss of enantioselectivity with a high chemical yield (**Scheme 39**).



Scheme 39. Enantioselective double α-alkylation of malonate

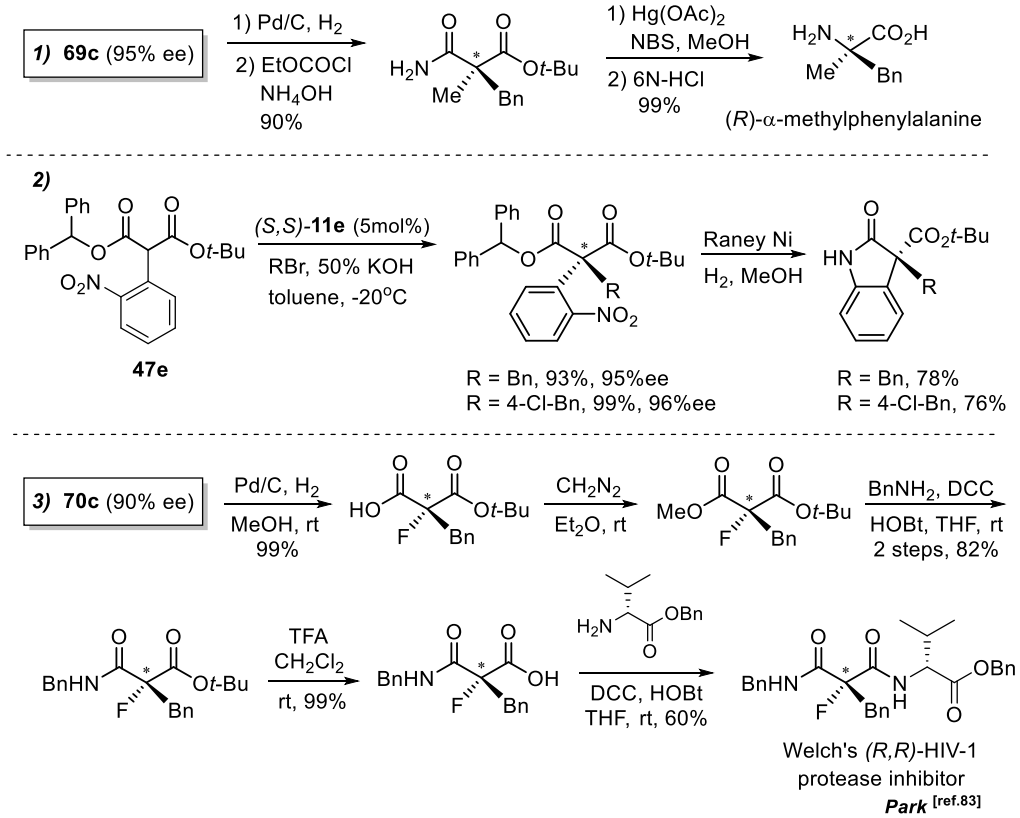
In 2014, Park's research team attempted to further extend PTC alkylation to the enantioselective construction of the quaternary α-halomalonate system based on a series of their previous studies [83b]. The group reported a new and highly efficient enantioselective synthetic method for α-halo-α-alkylmalonates under phase-transfer catalytic conditions. The group selected solid KOH at −40°C as the optimal reaction condition. The α-benzylation of **47b**, **47c**, and **47d** was performed under the optimized phase-transfer catalytic conditions. Similar enantioselectivities and chemical yields were observed, as shown in **Scheme 40**. The scope and limitations of the enantioselective phase-transfer catalytic α-alkylation with various electrophiles were investigated. High enantio selectivities were observed, except for the methylation of **47b** (30% ee) and the allylation of **47d** (42% ee). The very high enantioselectivities (up to 93% ee) indicated that this reaction was a highly efficient enantioselective synthetic method for the quaternary α-halo-α-alkylmalonates.



Scheme 40. Enantioselective α-alkylation of α-halomalonate

As depicted in **Scheme 41**, the optically active α,α-dialkylmalonates could be readily converted to non-natural α-amino acids and indole derivatives. Catalytic hydrogenation of **69c** with Pd/C-H_2, followed by acid activation and ammonolysis, gave *tert*-butyl malonamide ester. The Hofmann rearrangement followed by acidic hydrolysis provided (*R*)-α-methylphenylalanine. Phase-transfer catalytic benzylations of **47e** with benzyl bromide and 4-chlorobenzyl bromide afforded the corresponding α-benzylated products. Reduction by the Raney Nickel hydrogenation provided the α,α-dialkyloxindoles. This method can be applied to the synthesis of the oxindole-based natural products, such as (-)-horsfiline, spirotryprostatin B, aspidospermidine, and mersicarpine. In addition, the synthetic potential of these methods has been demonstrated via the synthesis of a precursor of Welch's (*R*,*R*)-HIV-1 protease inhibitor from **70c**. Hydrogenolysis under one atmosphere of H_2 in the presence of Pd/C in methanol provided the corresponding mono acid. The methyl ester prepared by treatment of an excess of diazomethane was coupled with

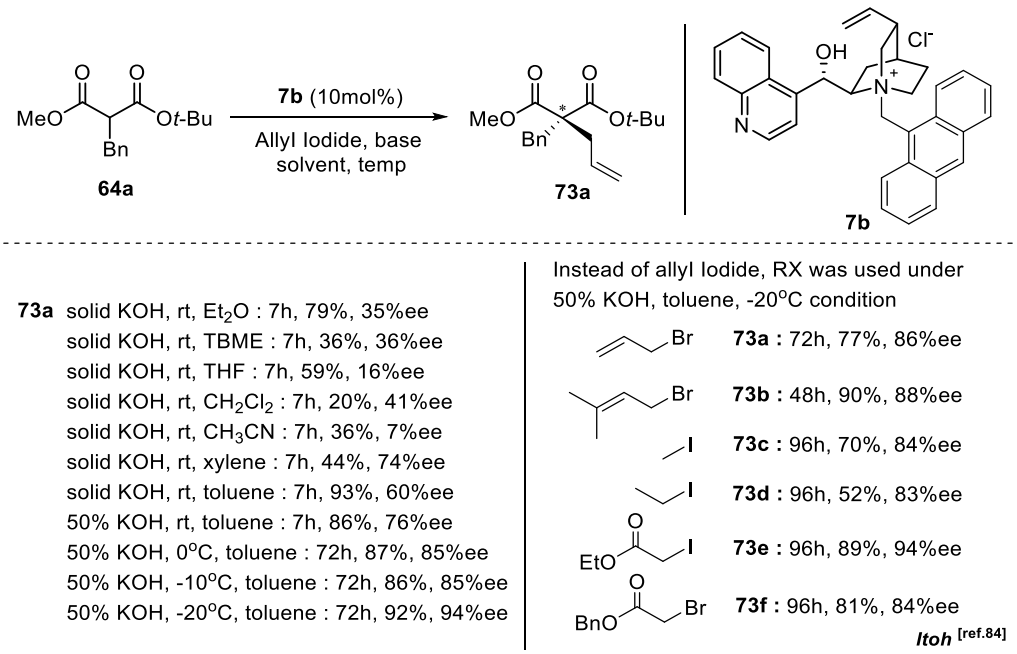
benzylamine in the presence of 1-hydroxy benzotriazole with the aid of DCC, followed by the deprotection of the *tert*-butyl group, to afford the mono acid. Finally, the precursor of Welch's (*R,R*)-HIV-1 protease inhibitor could be obtained by the amide formation with O-benzylated (L)-valine.



Scheme 41. Modification of chiral malonate (**66c**) into various derivatives

Coincidentally, in the same year, Itoh developed an enantioselective phase-transfer catalytic alkylation of α-monosubstituted malonic diester [84]. The alkylation of α-monosubstituted *tert*-butyl methyl malonate in the presence of N-(9-anthracenylmethyl)cinchoninium chloride (**7b**) afforded the α,α-disubstituted products in high yields and with high enantioselectivities. Moreover, a successful gram-scale (10 mmol)

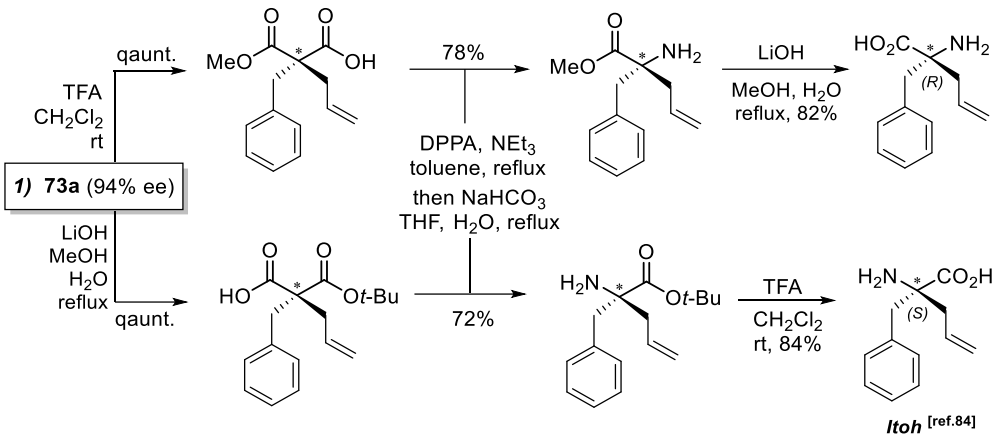
experiment using the *Cinchona* catalyst indicated the potential for practical applications of this methodology. Compared with the results of the Park group, Itoh improved the scope of the ester modification. Because the substrates bearing the diphenylmethyl ester could be efficiently cleaved by catalytic hydrogenation, the substrates and products should not contain substituents sensitive to hydrogenolysis. Therefore, the allylated products would also reduce to the ethylated product when diphenylmethyl ester is cleaved by hydrogenation. To develop a new and convenient method for synthesizing quaternary carbon centers, Itoh investigated an alkylation reaction of *tert*-butyl methyl α-monoalkylated malonate under phase-transfer conditions using a *Cinchona* alkaloid derivative. Methyl ester and *tert*-butyl are simple protecting groups that are readily cleaved chemoselectively under acidic or alkaline conditions. The optimization studies, summarized in **Scheme 42**, showed that the reaction medium significantly influences the rate of the reaction.



Scheme 42. Enantioselective α-alkylation of malonate by Itoh

In ether solvents, such as diethyl ether, *tert*-butyl methyl ether, and tetrahydrofuran, the products were afforded in unsatisfactory enantioselectivities. Dichloromethane gave slightly better selectivity, but the yield was very low. Acetonitrile also provided poor enantioselectivity. In contrast, reactions performed in toluene and xylene gave higher enantioselectivities. Notably, the reaction in toluene afforded the highest chemical yield; therefore, toluene was selected as the reaction solvent of choice. To further improve the reaction, the authors screened certain bases and determined that the use of a KOH aqueous solution provided a higher enantioselectivity than the KOH solid. Moreover, an increase in enantioselectivity was obtained by gradually decreasing the reaction temperature to -20℃. Using these optimized reaction conditions, the group then examined a variety of alkyl halides and malonic diester **64a** to demonstrate the general utility of *Cinchona* catalyst **7b** in the catalytic asymmetric alkylation reaction. Compared with allyl iodide, allyl bromide yielded the α-allyl α-benzyl product **73a** with lower yield and enantioselectivity. The reaction with prenyl bromide was faster and afforded product **73b** in high yield with high enantioselectivity. The alkylation reaction with methyl iodide and ethyl iodide proceeded with good enantioselectivity to give **73c** and **73d,** respectively. In the case of ethyl iodoacetate, the reaction proceeded with high yield and excellent enantioselectivity. Benzyl bromoacetate provided similar enantioselectivity, although with a slightly lower yield (**Scheme 42**).

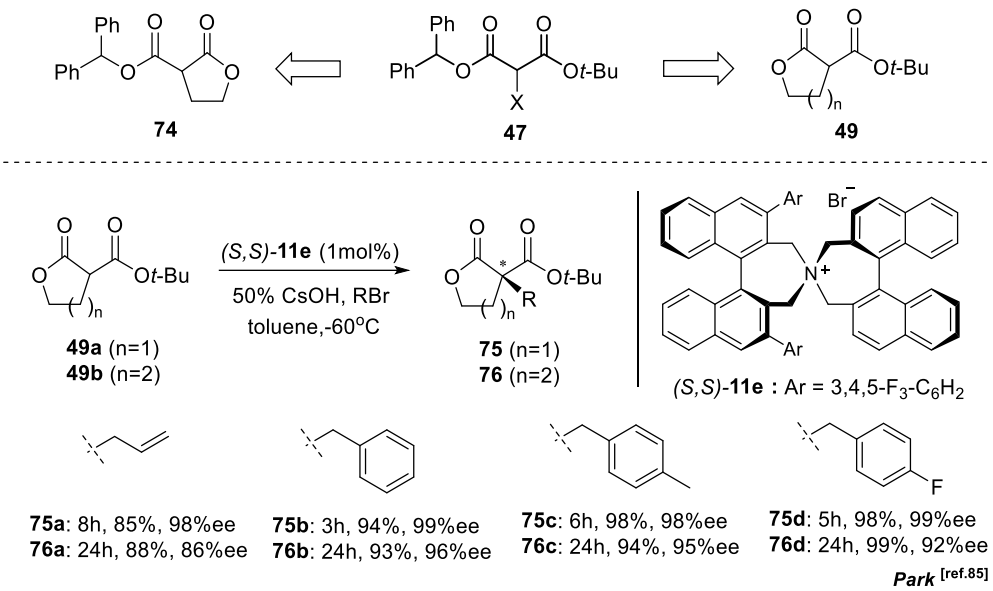
To demonstrate the utility of this method, the product with a quaternary chiral carbon was converted to the (*R*)-and (*S*)-α,α-dialkylated amino acids through alternative chemo selective transformation of the two ester groups. These compounds are of interest because they belong to the broad class of nonproteinogenic amino acids. Due to the quaternary stereocenter, the replacement of the natural amino acids by the α,α-disubstituted amino acids in peptides might result in conformationally rigid and proteolytically stable peptides.



Scheme 43. Modification of chiral malonate (**73a**) into various derivatives

The *tert*-butyl or methyl ester of an α,α-disubstituted malonic diester could be chemoselectively deprotected. Thus, the asymmetric reaction product **73a** could be selectively converted into carboxylic acids that bear different α-configurations in a quantitative yield. The carboxylic acids were converted into amines with the absence of one carbon atom through the Curtius rearrangement with diphenylphosphoryl azide in the presence of triethylamine followed by hydrolysis. Deprotection of the methyl ester by hydrolysis under alkaline conditions provided (*R*)-α-allylphenylalanine. However, *tert*-butyl ester was treated with TFA to obtain (*S*)-α-allylphenylalanine. The (*R*)-and (*S*)-amino acids both exhibited full optical activity (**Scheme 43**).

In 2014, the Park group designed the α-carboxy-lactones as novel substrates based on a series of their previous studies in which ester skeletons were made rigid by ring formation. The *tert*-butyl ester group and the diphenylmethyl ester group are essential for high enantioselectivity in the enantioselective phase-transfer catalytic α-alkylations of the malonate system (**Scheme 44**).

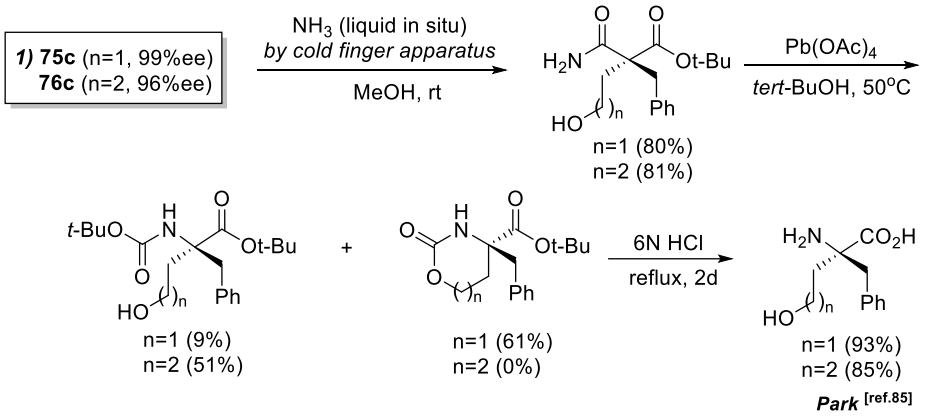


Scheme 44. Enantioselective α-alkylation of α-*tert*-butoxycarbonyllactone

Both of the ester groups were employed as α-carboxy-lactone substrates. For the preliminary study, α-diphenylmethoxycarbonylbutyrolactone (**74**) and α-tert-butoxy carbonylbutyrolactone (**49**) were prepared. The substrate efficiency of these compounds was examined by α-benzylation, and **49** afforded relatively high enantioselectivity with a lower chemical yield than **74**, suggesting that the *tert*-butyl ester group was more efficient for enantioselectivity than the diphenylmethyl ester group.

Optimization of the base and temperature conditions using substrate **49a** was performed. As shown in **Scheme 44**, the best enantioselectivity was observed using the 50% CsOH base conditions at -60℃. The promising results with the 5-membered lactone **49a** encouraged the group to expand the ring size to a 6-membered lactone, **49b**. The lactone substrates **49a** and **49b** were chosen for further investigation into the scope and limitations of our enantioselective α-alkylation with various electrophiles. Generally, butyrolactone gave a slightly higher enantioselectivity than valerolactone.

These new catalytic systems provided attractive synthetic methods for lactone-based chiral intermediates, including quaternary carbon centers. The α-benzylated lactones **75c** (99% ee) and **76c** (96%ee) were converted to the corresponding amides by ammonolysis using saturated ammonia in methanol at room temperature. The Hofmann rearrangement of the amides using lead tetraacetate in *tert*-butyl alcohol followed by hydrolysis with 6 N HCl provided unnatural chiral amino acids. The absolute configuration was confirmed as *S* by comparison of the specific optical rotation value with the reported value (**Scheme 45**).

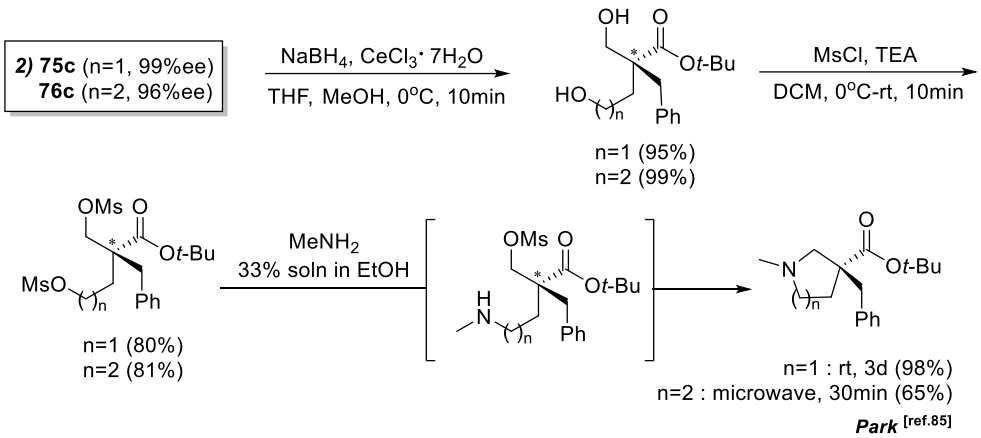


Scheme 45. Modification of chiral malonates (**75c** and **76c**) into various derivatives I

α-Benzylated butyrolactone and valerolactone were also converted to pyrrolidine and piperidine, respectively (**Scheme 46**). Selective reduction with $NaBH_4$ in the presence of $CeCl_3$ afforded diols. Dimesylation of the diols followed by double N-alkylation with methylamine successfully provided pyrrolidine and piperidine.

In conclusion, Park's research group has recently developed enantioselective synthetic methods for the α-benzyl- and allyllactones. The asymmetric reaction afforded the corresponding substituted compound in with high chemical yield (up to 99%) and high optical yields (up to 99%) using only 1 mol% of the catalyst. The synthetic potential of this

method has been successively demonstrated by the synthesis of the unnatural α-quaternary homoserines, the pyrrolidine and piperidine derivatives.



Scheme 46. Modification of chiral malonates (**75c** and **76c**) into various derivatives II

In contrast to the β-keto esters, the malonates are nearly symmetrical and less acidic. Therefore, improvement of the reactivity and discrimination of the two ester moieties is required to achieve high enantiocontrol. Thus, the development of an efficient and practical synthetic method for the synthesis of chiral malonates is challenging. Although a phase-transfer catalytic system has recently been employed to obtain chiral α-alkylated malonates, more active and productive studies should be performed to extend the range of application for the synthesis of bio-active natural products and pharmaceuticals.

3. Chiral α-amino quaternary carbon centers

3-1. Bioactive organic molecules containing chiral α-amino quaternary carbon centers

Organic molecules involving chiral α-amino groups are at the center of modern organic chemistry and are widely used in the pharmaceutical industry, crop protection, natural product chemistry, and in advanced materials [99]. In particular, optically active α-amino acid derivatives are fundamental constituents of numerous natural products, other highly valuable compounds of pharmaceutical significance and biologically important building blocks in organic synthesis [100]. Therefore, from these basic considerations, modern constructive methods for the introduction of chiral α-amino quaternary carbon centers are of major importance to synthetic chemists and product developers. There is a growing requirement for efficient methods because there are many examples of naturally occurring and pharmaceutical drugs that display a chiral α-quaternary center in their structure.

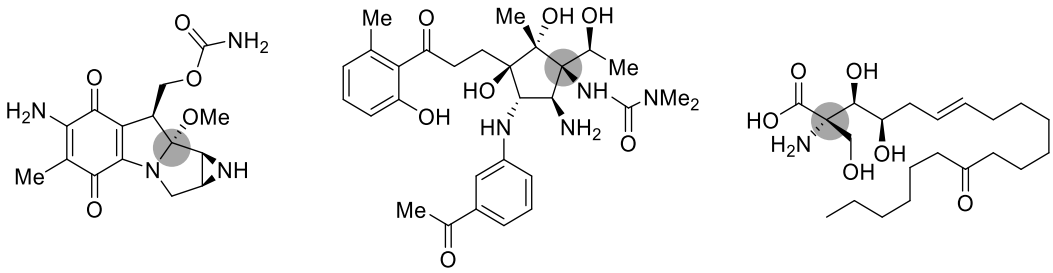


Figure 9. Representatives of natural products bearing a chiral α-quaternary center-I

The mitomycins are a family of aziridine-containing natural products isolated from *Streptomyces caespitosus* or *Streptomyces lavendulae.* One of these compounds, mitomycin C, has been used as a chemotherapeutic agent because of its antitumor antibiotic activity [101].

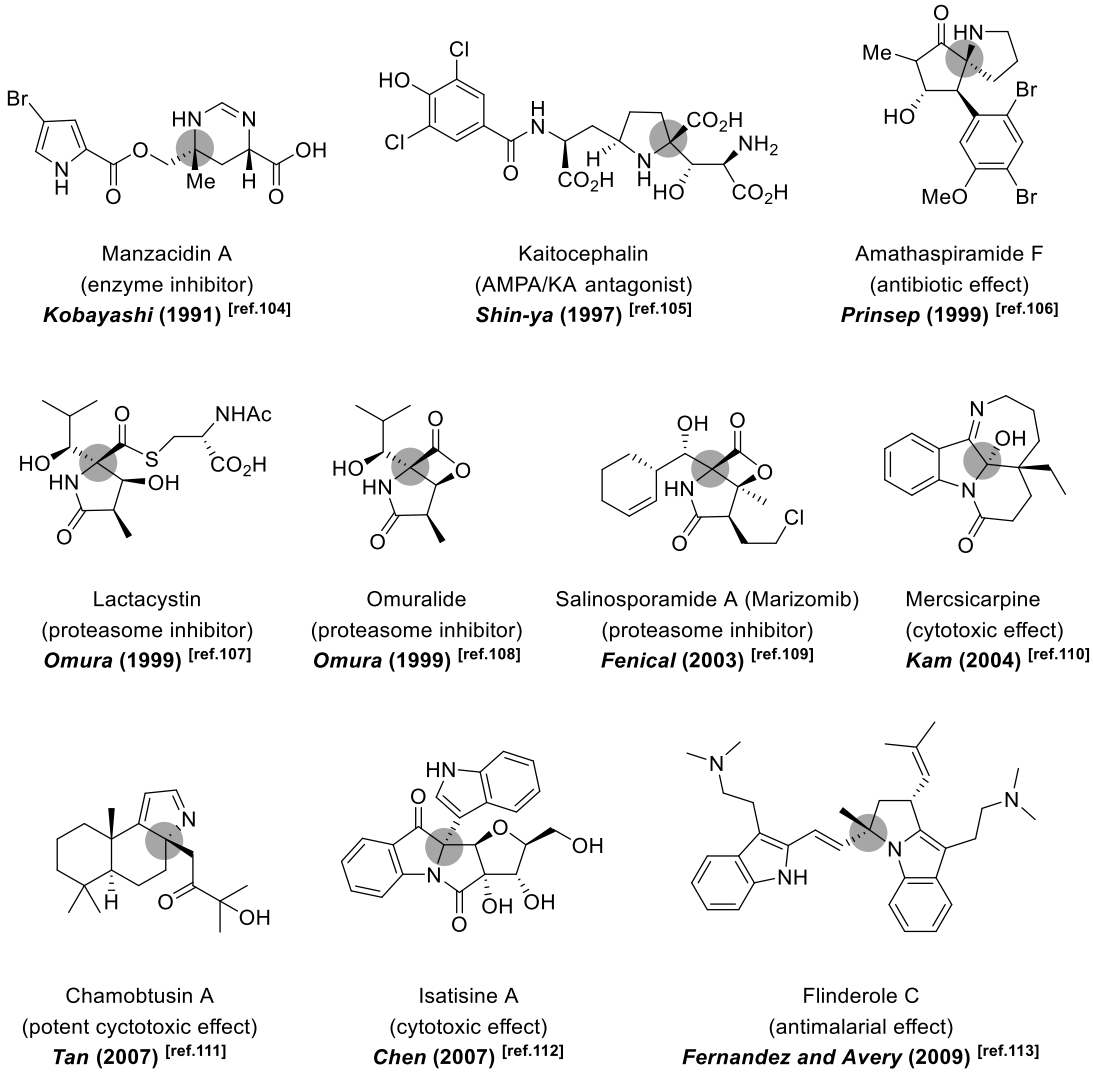


Figure 10. Representatives of natural products bearing a chiral α-quaternary center-II

Among the plethora of microbial secondary metabolites produced by the soil bacteria of the *Streptomyces* family is pactamycin, a structurally unique member of the amino cyclopentitol-containing natural products. Pactamycin was isolated in 1961 from a fermentation broth of *Streptomyces pactum* var *pactum* by scientists at the former Upjohn Company [102]. Pactamycin exhibits activity against Gram-positive and Gram-negative bacteria in addition to potent in vitro and in vivo cytotoxic effects. Fujita and co-workers first isolated (+)-myriocin (also known as thermozymocidine and ISP-1) in 1972 from *Myriococcum albomyces* and *Mycelia sterilia* [103]. Initially of interest for its antifungal properties, considerable attention was engendered by the finding that myriocin is a potent immunosuppressant. The juxtaposition of the quaternary α-amino acid and the neighboring dihydroxylated alkyl chain within myriocin represents a challenging motif that, combined with the interesting biological activity, has made myriocin an attractive target for many total syntheses (**Figure 9**).

In 1991, Kobayashi and his co-workers reported the isolation of a novel class of bromopyrrole alkaloids, manzacidin A, from the marine sponge *Hymeniacidon* sp., collected at the Manza Beach of Okinawa Island in Japan. These alkaloids possess a unique structure consisting of an ester-linked bromopyrrolecarboxylic acid and a 3,4,5,6-tetrahydro pyrimidine ring [104]. The Shin-ya structure determination lab reported the isolation of kaitocephalin from *Eupenicillium shearii* PF1191 in 1997 [105]. Amatha spiramide A was isolated from a New Zealand collection of the marine bryozoan *Amathia wilsoni* by Prinsep in 1999 [106]. The structural features common to these alkaloids are characterized by a novel aza-spirobicyclic framework that consists of three contiguous chiral centers in which one of the amino groups is attached to the quaternary carbon center, a cyclic hemiaminal moiety, and an 11,13-dibrominated aromatic ring. These structures suggest that these alkaloids would have important biological activity. The Omura group

reported the isolation and characterization of lactacystin in 1991 and showed it to be a novel γ-lactam produced by a culture broth of *Streptomyces* sp. OM-6519. Because lactacystin inhibits the 20S proteasome, there has been a flurry of synthetic approaches towards the synthesis of this interesting molecule and its analogues [107]. Omuralide was also isolated from the same culture broth and displayed activities similar to lactacystin [108]. Salinosporamide A (NPI-0052, marizomib) was isolated by Fenical and co-workers from a marine actinomycete, *Salinispora tropica*, that is distributed in ocean sediments around the Bahamas [109]. Salinosporamide A is a potent inhibitor of the 20S proteasome and is currently being tested as an anticancer drug candidate to treat patients with multiple myeloma. In addition to its potent bioactivity, the highly functionalized structure of Salinosporamide A, possessing a β-lactone, an α,α-disubstituted amino acid moiety, a cyclohexene ring, and five contiguous stereogenic centers, has attracted the attention of a number of synthetic chemists. Mersicarpine was isolated from the *Kopsia* genus of plants by Kam and co-workers in 2004 and has an atypical tetracyclic structure in which a nitrogen atom is substituted at the indoline 3-position to form a seven-membered cyclic imine [110]. A hemiaminal and α-quaternary carbon are contiguously arranged adjacent to the imine. The overall structure includes three heterocycles, specifically, indoline, cyclic imine, and *δ*-lactam, fused with each other around a tertiary hydroxy group.

The plant family of *Cupressaceae* has been a rich source of terpenes. Tan and co-workers have isolated chamobtusin A from the branches and leaves of *Chamaecyparis obtusa* cv. Tetragon [111]. Chamobtusin A has a unique and unprecedented molecular architecture characterized by a fused tricyclic skeleton with a 2H-pyrrole ring system. Although no significant biological activity has been identified for chamobtusin A, its novel structure has prompted many organic chemists to attempt the total synthesis. Isatisine A is a complex bisindole natural product isolated from the leaves of *Isatis indigotica* Fort, a shrub prevalent

in the Anhui Province of China [112]. The roots and leaves of *I. indigotica* have been used in traditional Chinese medicine for the treatment of viral diseases, including influenza, viral pneumonia, mumps, and hepatitis. In 2009, flinderole C was isolated through an initial antimalarial natural product extract screening program [113]. The flinderoles have shown impressive selective antimalarial activity against the *P. falciparum parasite*, with flinderole C being the most active (IC_{50} value of 150 nM); thus, flinderoles present new molecular scaffolds for antimalarial drug discovery (**Figure 10**).

3-2. Synthetic methods for the construction of the chiral α-amino quaternary carbon centers

As mentioned in **chapter 3-1**, the synthesis of optically active nitrogen-containing organic compounds is important in organic chemistry and medicinal chemistry due to their versatile biological activities and pharmaceutical applications. The alkaloids are among the most representative nitrogen-containing natural products, showing various biological activity, and most of the pharmaceutics involve a nitrogen in the molecule.

Over the last decade, significant research activity has enabled the construction of the α-amino quaternary carbon center with impressive levels of enantioselectivity using either organometal catalysis or organocatalysis [114]. Although several different approaches for obtaining optically active α-quaternary stereocenters are available, the development of stereoselective transformations for the synthesis of chiral α-amino molecules from simple and readily available starting compounds in the presence of a chiral catalyst remains a challenge for many chemists. There have been many enantioselective synthetic methods for the α-amino-β-ketoester system via electrophilic α-amination [115]. However, the enantioselective synthetic methods of the α-aminomalonate system have been primarily

achieved by the enzymatic desymmetrization [116] of prochiral α-aminomalonates, and only a few cases involve studies via chemical synthesis.

3-2-1. Electrophile α-amination of the carbonyl compound

C-N bonds are typically formed by the attack of a nucleophilic nitrogen atom at an electrophilic carbon bearing a leaving group by an S_N2-type reaction (**Figure 11, on the left**). However, most of the classical processes are hampered by difficult access to the electrophilic precursors, particularly when multifunctional derivatives are considered, and by the frequently recurring difficult reaction conditions. Among the various modern synthetic strategies, the electrophilic amination of carbon nucleophiles appears as an unconventional C-N connective process in organic synthesis (**Figure 11, on the right**).

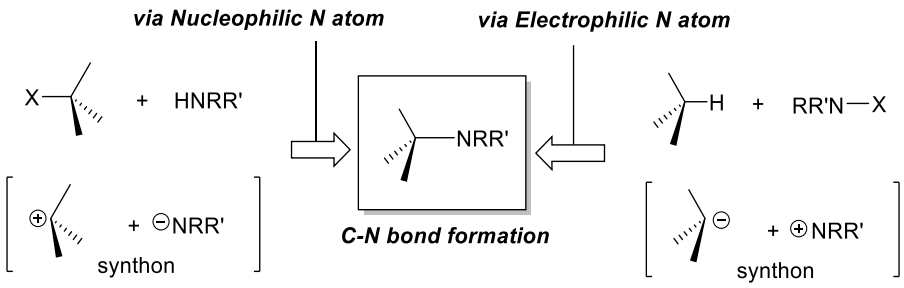
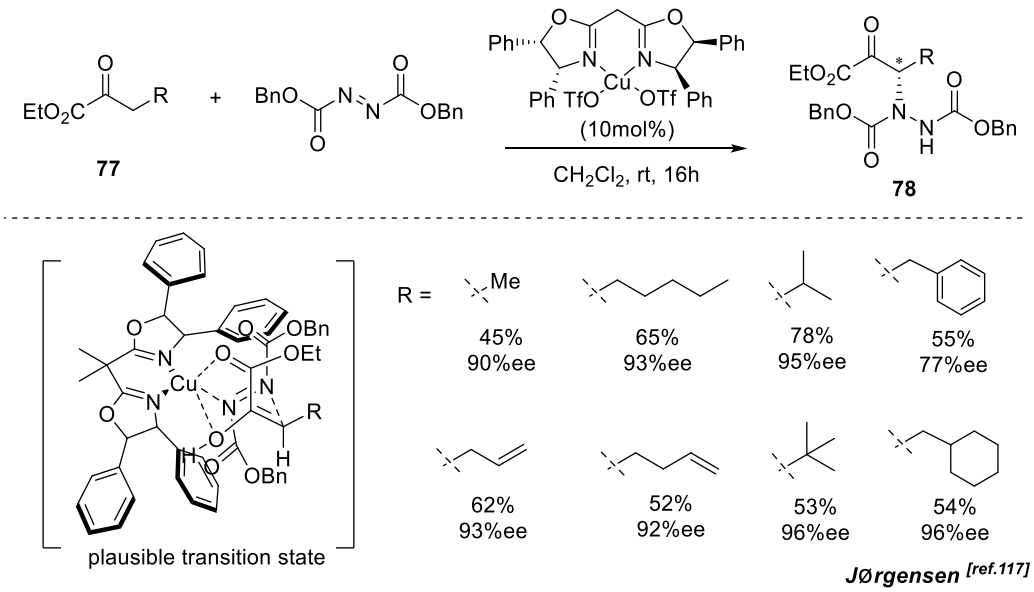


Figure 11. Two general methods of amination for the C-N bond formation

In electrophilic amination, the chemists' demand for practical electrophilic [NH_2^+] equivalents, amenable to C-N bond formation, falls short of the supply of suitable reagents in a process in which a carbon nucleophile replaces a leaving group on an electrophilic nitrogen.

A conceptual development toward electrophilic amination is based on the addition of carbanions to neutral aminating agents. The successful implementation of the above

amination strategy is dependent on the availability of suitable nitrogen sources. Reagents in which no leaving groups are present have recently entered into common use in many applications of organic synthesis and are capable of reacting under mild reaction conditions with explicit or latent carbanions, leading to a new C-N bond in a connective process. Di-alkyl-azodicarboxylate, which exploits the synthetic equivalence of a $[RN\text{-}NHR]^+$ synthon, is a commercially available and highly stable compound. Di-alkyl-azodicarboxylate with a remarkable reactivity towards carbon nucleophiles for achieving the chiral α-amino quaternary carbon center was first demonstrated by the Jørgensen group in 2002 [117].

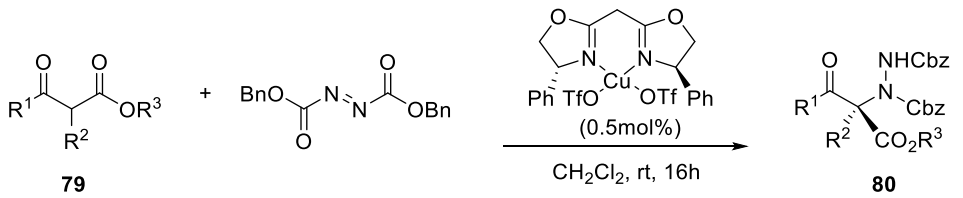


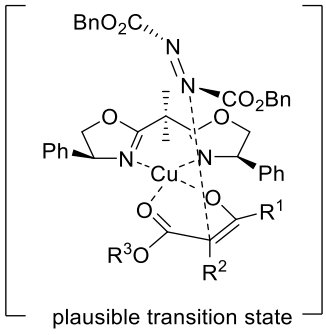
Scheme 47. Asymmetric direct α-amination of an α-keto ester

As depicted in **Scheme 47**, the reaction proceeds relatively well for a variety of α-keto esters and dibenzyl azodi-carboxylates catalyzed by the chiral C_2-symmetric copper (II) bis(oxazoline) Lewis acids. Because the products were prone to racemization, the crude reaction mixture was immediately treated with L-selectride. The reaction most likely proceeds through a complex in which the distorted square-planar Cu(II) center is chelated

to the α-keto ester enolate. The sense of asymmetric induction can be rationalized by the electrophilic attack of the azodicarboxylate onto the less hindered face of the copper (II) enolate.

This type of amination reaction was extended to the β-keto ester substrates in 2003 by Jørgensen [115a]. Again, a C_2-symmetric copper (II)–bis (oxazoline) complex was the optimal catalyst, with very low loadings (0.5 mol%).





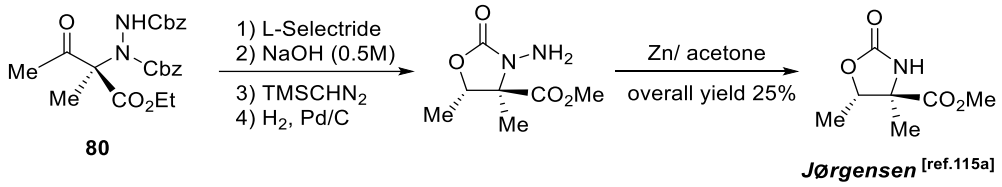
R^1	R^2	R^3	yield (%)	ee%
Me	Me	Et	91	96
Et	Me	Et	98	98
Ph	Me	Et	81	87
*i*Pr	Me	*t*Bu	89	98
Bn	Me	*t*Bu	79	98
Me	allyl	*t*Bu	80	98
Mr	Me	*t*Bu	86	98
$(CH_2)_3$		Et	96	99
$(CH_2)_4$		Et	96	99
$(CH_2)_5$		Et	70	99

Jørgensen **[ref.115a]**

Scheme 48. Asymmetric direct α-amination of a β-keto ester

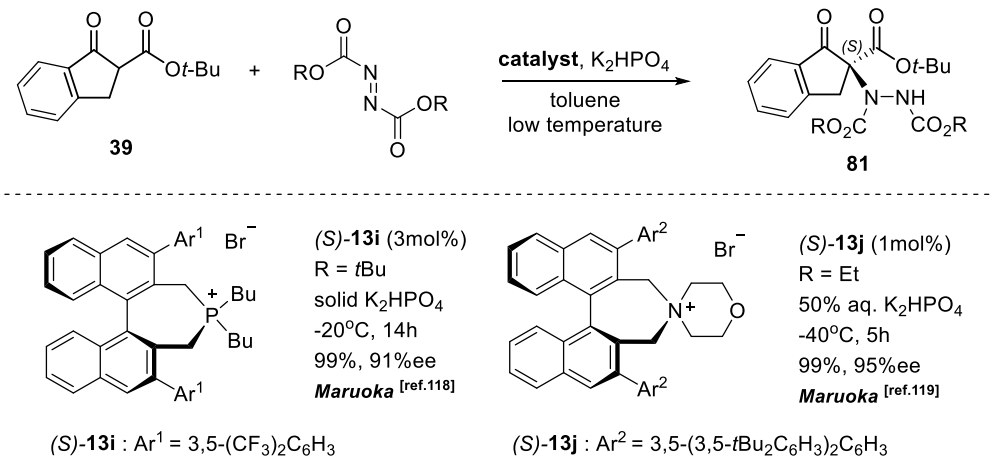
The catalyst showed exceptional levels of selectivity for a variety of cyclic and acyclic keto esters. The proposed mechanism and model for stereoinduction are similar to the ones previously described, and the chelating ability of the substrate explains the high levels of enantioselectivity (**Scheme 48**).

A variety of possible product modifications could be envisioned, for example, as shown in the reaction sequence in **Scheme 49**, which is the reduction of the β-keto functionality in **80**, proceeds in a highly diastereoselective manner and forms *N*-amino oxazolidinone with a diastereomeric ratio of 24:1. Cleavage of the N-N bond gave the oxazolidinone derivative in an overall yield of 25%.



Scheme 49. Modification of the chiral α-amino β-keto ester into its derivatives

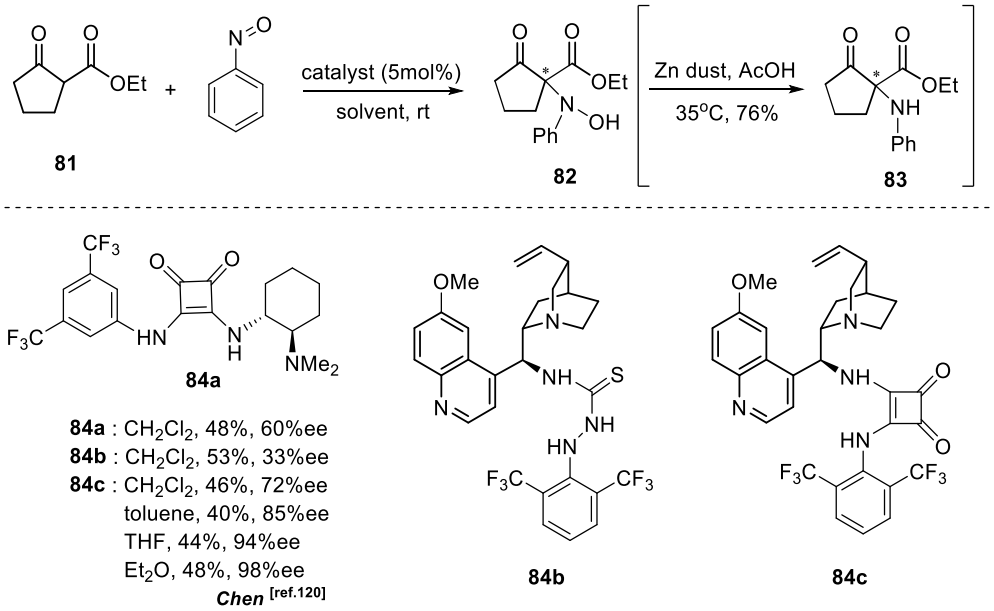
A highly efficient asymmetric amination of the β-keto esters was achieved under phase transfer conditions using chiral quaternary phosphonium (**13i**) [118] or ammonium (**13j**) [119] bromide as a catalyst in 2008 and 2009, respectively, by the Maruoka group. In these reactions, azodicarboxylates were employed as electrophiles to obtain the amination product **81**. This research was the pioneering study that combined catalytic asymmetric α-amination, which directly generates a C–N bond with an asymmetric carbon center, and the phase-transfer catalytic reaction system of a β-keto ester (**Scheme 50**).



Scheme 50. Asymmetric phase-transfer catalytic α-amination of a β-keto ester

The asymmetric *N*-nitroso aldol reaction is a powerful synthetic tool for the expedient formation of the C–N bond, which can be used to construct optically active α-hydroxyamino carbonyl compounds. The enantioselective catalytic version of the *N*-nitroso aldol reaction of a β-keto ester was pioneered in 2012 by Chen, using chiral squaramide derivatives as the catalyst [120]. The reaction of ethyl 2-oxocyclopentanecarboxylate (**81**) and nitrosobenzene was selected as the model. The authors screened the reaction conditions and found that **84c** was an excellent catalyst for the model reaction, giving the corresponding α-hydroxyamino derivatives in 48% yield with 98% ee using diethyl ether as the solvent (**Scheme 51**).

In addition, chirality adduct **82** (98% ee) could be readily transformed to the corresponding amine **83** in 76% yield without affecting the optical purity, using acetic acid and zinc dust as the reducing agent. However, because cleavage of the *N*-aryl bond of the products is difficult, the hydroxyamination reaction is relatively synthetically limited to allow the subsequent nitrogen bond-forming transformations.



Scheme 51. Asymmetric α-amination of a β-keto ester *via* the *N*-nitroso aldol reaction

3-2-2. Asymmetric reaction of the α-amino tertiary substrate

Although the direct electrophilic α-aminations of carbonyl compounds can directly afford amines or protected amines in a simple step, there is a limited source of electrophilic nitrogens. To address the problems associated with the installation of the α-quaternary carbon centers bearing nitrogen, a reverse strategy (described in **Figure 12, on the right**) has been considered as an unconventional method in terms of diversity. The advantage of the reverse strategy, which means an asymmetric reaction of the α-amino tertiary skeleton molecule as the reaction substrate compared with the direct electrophilic α-amination (**Figure 12, on the left**), is that various chiral compounds are easily available simply by changing the alkyl reagent delivering the synthon $[R]^+$.

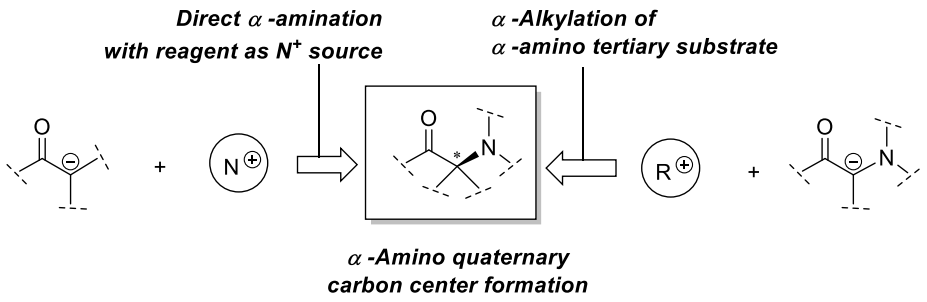
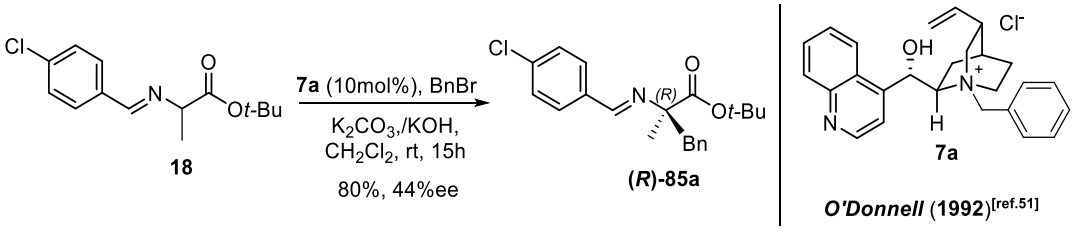


Figure 12. Synthetic strategy for the chiral α-amino quaternary carbon center

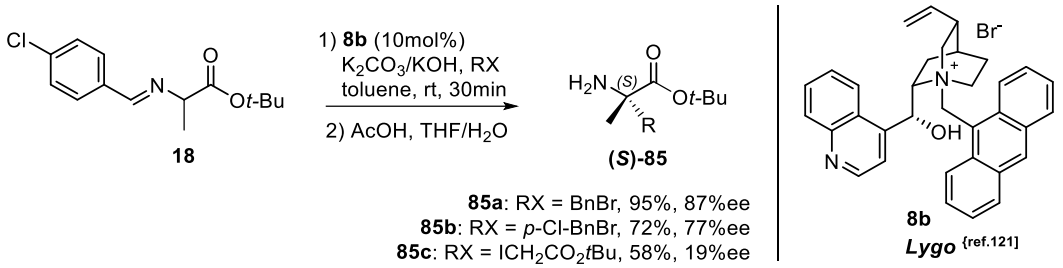
There are numerous asymmetric reactions of the α-amino tertiary substrate. Of these many reactions that introduce a chirality at the α-amino tertiary molecule, several distinguished methods are described below.

First, phase-transfer catalysis has made unique contributions to the preparation of the stable α-amino quaternary carbon center using the substrate bearing α-nitrogen substitution. In 1992, O'Donnell succeeded in obtaining the optically active α-methyl-α-amino acid derivatives **85** by a catalytic phase-transfer alkylation of the *p*-chlorobenzaldehyde imine of alanine *tert*-butyl ester (**18**) with catalyst **7a** (**Scheme 52**) [51]. An examination of the effect of the different base systems revealed the importance of using the mixed solid base KOH/K_2CO_3. Although the enantioselectivities are moderate, this study is the first example of preparing optically active α,α-dialkyl-α-amino acids by asymmetric phase-transfer catalysis.



Scheme 52. Asymmetric synthesis of α-methyl α-amino acid derivatives by O'Donnell

Seven years later, the Lygo group demonstrated that the use of **8b** significantly improved the enantioselectivity of alkylations with benzylic bromides, thus highlighting the utility of this approach for the synthesis of the α,α-dialkyl-α-amino acids [121]. This group found that the solid base KOH/K_2CO_3 must be freshly prepared before use to obtain reproducible results. The lack of stereoselectivity in reactions with other electrophiles was ascribed to competing nonselective alkylation (**Scheme 53**).

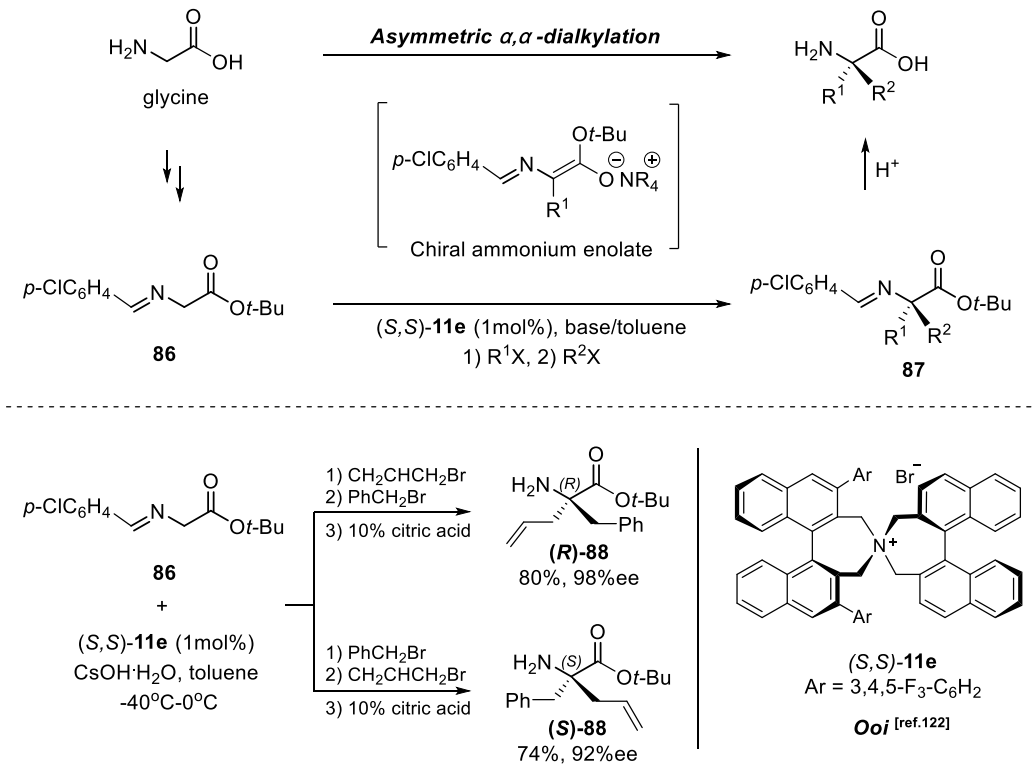


Scheme 53. Asymmetric synthesis of α-methyl α-amino acid derivatives by Lygo

The Ooi research group introduced an efficient method for achieving α,α-dialkyl glycine by a phase-transfer catalytic double reaction in 2002 [122]. Because the aldimine Schiff base **86** can be readily prepared from glycine, the possibility exists for the direct stereoselective introduction of two different side chains into **86** by asymmetric phase-transfer catalysis for the synthesis of structurally diverse chiral α,α-dialkyl-α-amino acids.

This double alkylation has been realized using chiral quaternary *N*-spiroammonium bromide (*S*,*S*)- **11e** in a one-pot reaction. A solution of **86** and a catalyst of 1 mol % in toluene was initially treated with allyl bromide (1 equiv) and $CsOH{\cdot}H_2O$ at −10 °C. A subsequent reaction with benzyl bromide (1.2 equiv) at 0℃ resulted in the formation of the double alkylation product **(*R*)-88** in 80 % yield (98 % *ee*) after hydrolysis. The absolute configuration of product **88** was opposite when the halides were added in the reverse order

during the double alkylation of **86**. This finding indicates the intervention of the chiral ammonium enolate in the second alkylation stage (**Scheme 54**).

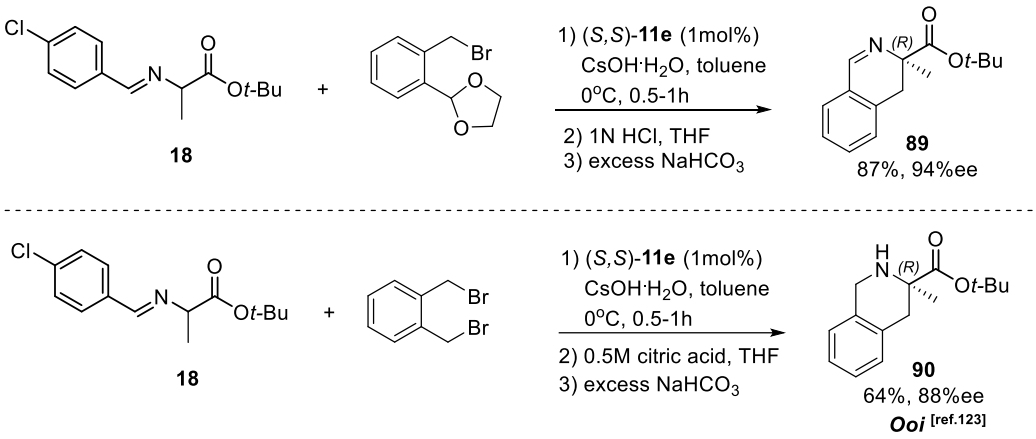


Scheme 54. Asymmetric synthesis of α,α-dialkyl α-amino acid derivatives by Ooi

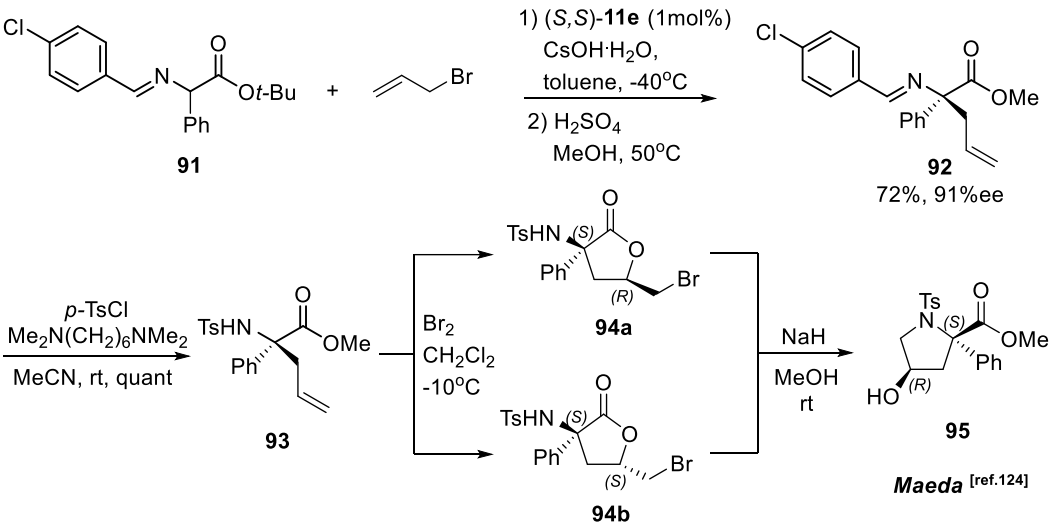
This powerful method enabled the catalytic asymmetric synthesis of the α-amino quaternary isoquinoline derivatives with **18** as a substrate, as depicted in **Scheme 55** [123].

The catalytic asymmetric alkylation of **18** with functionalized benzyl bromide followed by sequential treatment with 1 N HCl and then excess $NaHCO_3$ furnished the corresponding α-amino dihydroisoquinoline derivative **89** in 87 % yield and 94% ee. In addition, treatment of **18** with α,α-dibromo-*o*-xylene under the phase-transfer catalytic system resulted in the rapid generation of the monoalkylation product, which was transformed into the desired α-

amino quaternary carbon adduct **90** with 64% yield and 88% ee during the workup procedure.



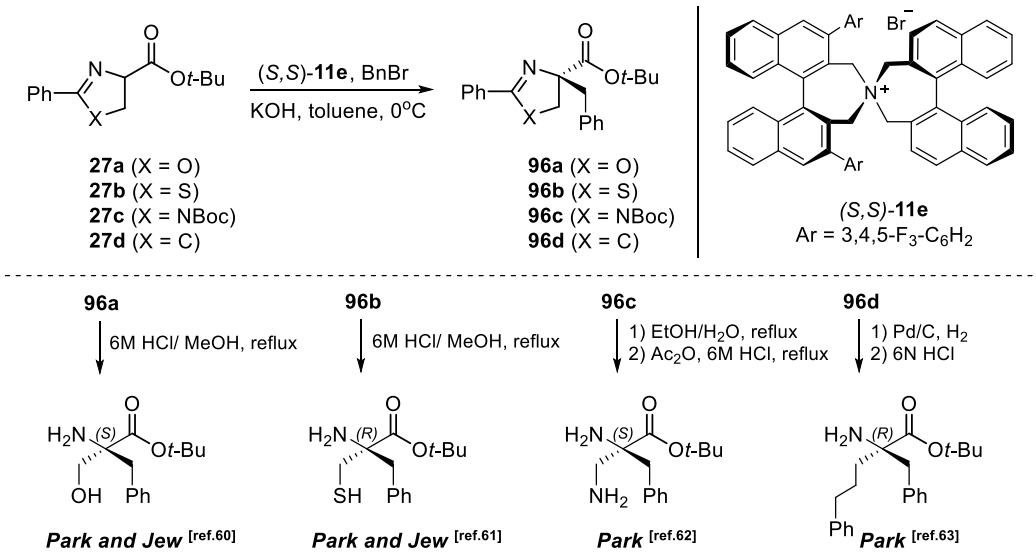
Scheme 55. Asymmetric synthesis of isoquinoline derivatives by Ooi



Scheme 56. Asymmetric synthesis of 4-hydroxy-2-phenylproline derivatives by Ooi

In 2005, the Maeda group utilized (*S*,*S*)-**11e** as a phase-transfer catalyst in the asymmetric alkylation of **91** for the stereoselective synthesis of the 4-hydroxy-2-phenylproline framework [124]. After hydrolysis and transesterification to methyl ester, the resulting chiral **92** was derivatized to its tosylate **93**. Subsequent treatment with Br_2 in CH_2Cl_2 at −10°C resulted in the formation of γ-lactones **94** with high diastereoselectivity (**94a:94b** > 20:1). These compounds were then treated with NaH in methanol to give the essentially pure (2*S*,4*R*)-4-hydroxy-2-phenylproline derivative **95,** including an α-amino quaternary carbon center (**Scheme 56**).

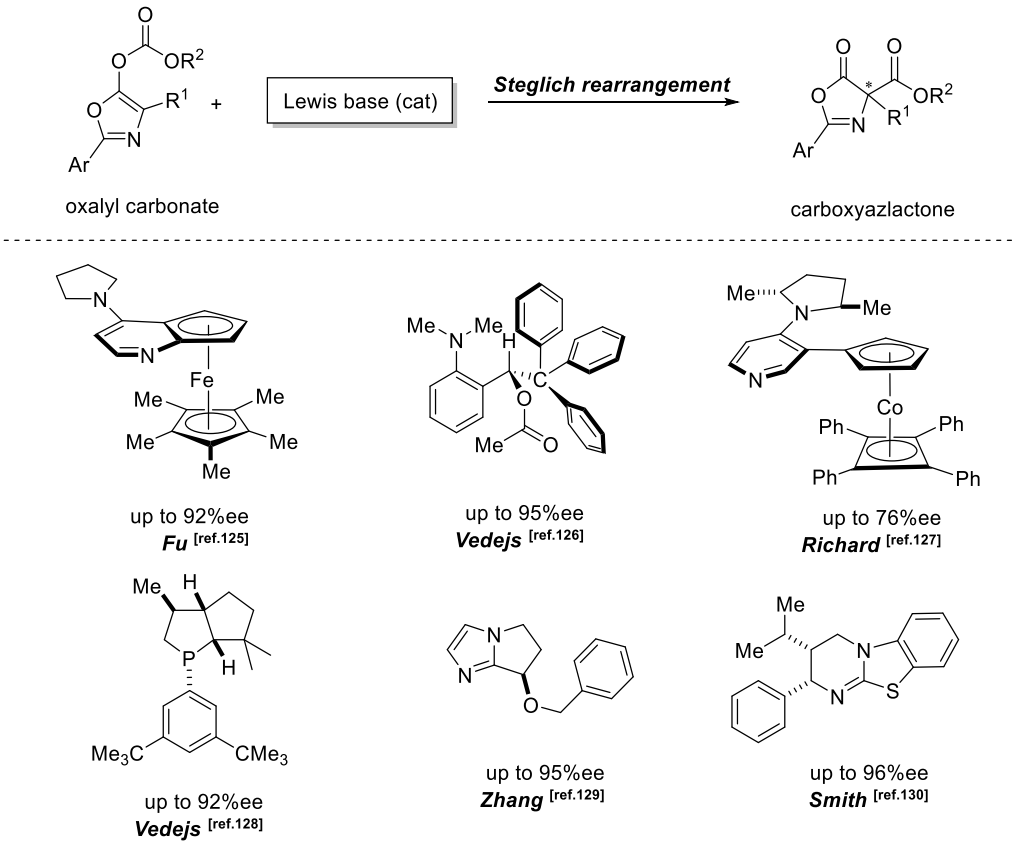
This efficient phase-transfer-catalyzed alkylation strategy was successfully applied by the research group of Jew and Park to the asymmetric synthesis of α,α-dialkyl α-amino acids from several "-zoline" substrates (**Scheme 57**). Because of the rigidity of the substrates based on their ring structure, the reaction afforded significantly high stereoselectivities under phase-transfer catalytic conditions, making them promising methods for industrial application through a few simple hydrolysis steps.



Scheme 57. Asymmetric synthesis of α,α-dialkyl α-amino acids by Park

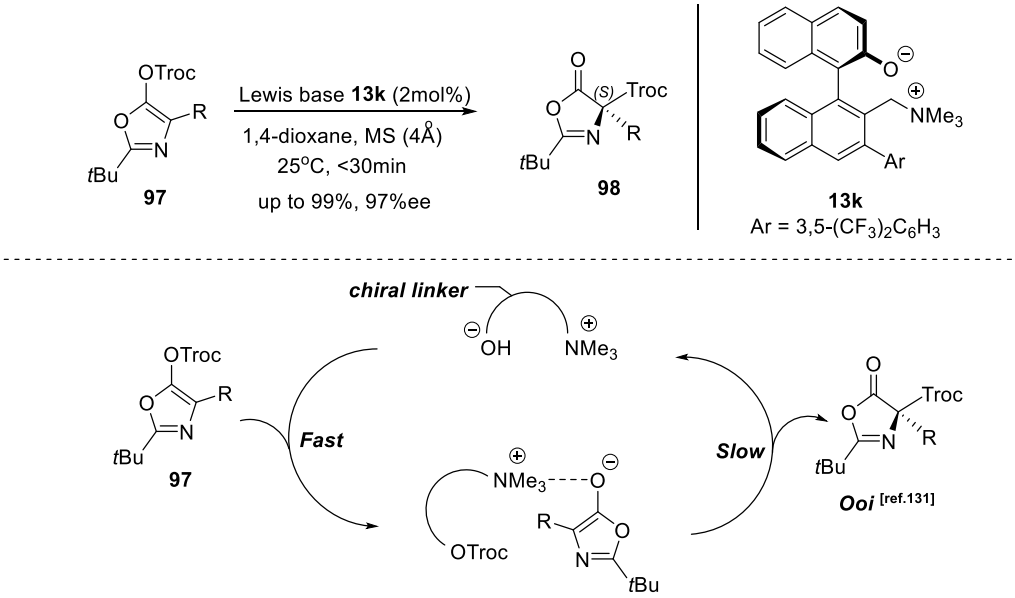
These reaction system of the Park group provided practical access to a variety of optically active α,α-dialkyl α-amino acids, such as α-alkyl serine [60], α-alkyl cysteine [61], α-alkyl-α,α-diaminopropionic acid [62], and dialkyl α-amino acid [63].

Another milestone in this area for introducing the α-quaternary carbon center is the Steglich rearrangement of the oxazolyl carbonate derivatives. This process delivers C-carboxyazlactones bearing a quaternary stereocenter with excellent enantio control. The Steglich rearrangement is a related Lewis base-promoted reaction process, and this transformation has been widely probed to evaluate the stereo directing ability of a range of chiral Lewis bases in asymmetric catalysis.



Scheme 58. Asymmetric Lewis base-promoted Steglich rearrangement

Concerning the Lewis base, the development of the chiral 4-pyrrolidinopyridine (PPY) or 4-dimethylaminopyridine (DMAP) derivatives elegantly introduced by Fu [125], Vedejs [126], and Richards [127], deliver the C-carboxyazlactones with up to 95% ee. Alternative catalyst classes also deliver high enantioselectivity in this process, such as phosphine, utilized by Vedejs [128], and bicyclic imidazole, used by Zhang [129]. In 2012, Smith reported the synthesis and use of tetrahydropyrimidine-based isothioureas as a Lewis base, affording nearly enantiopure chiral malonate derivatives bearing the α-quaternary carbon center [130] (**Scheme 58**).



Scheme 59. Chiral ammonium betaine catalyzed Steglich rearrangement

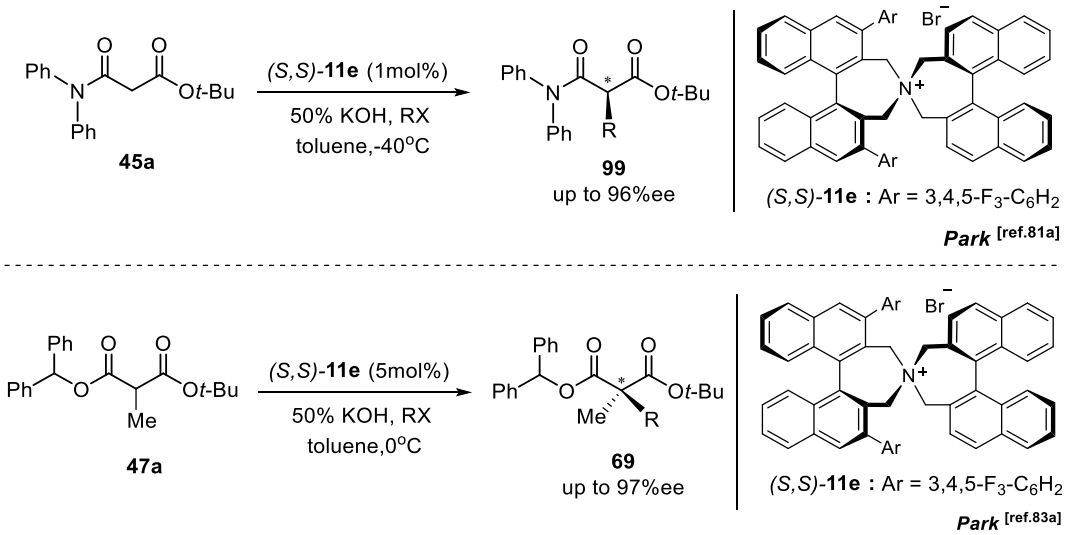
In 2010, Ooi introduced the chiral ammonium betaine **13k** as a new and intriguing structural motif for an organic molecular catalyst [131]. The basic character of its anionic site (aryloxylate) and the hydrogen-bonding capability of its conjugate acid (arylhydroxide) appeared to be the key features for realizing highly enantioselective reactions. The rate-determining step in this rearrangement is the C–C bond-forming reaction, which can be

facilitated using a betaine catalyst in a *quasi*-intramolecular manner to enhance the reactivity and stereoselectivity. The mode of activation with the Lewis base catalyst can be rationalized, as shown in **Scheme 59**. The nucleophilic anionic functionality initially activates the enolcarbonate, and the resulting enolate forms a sterically defined ion pair with the ammonium group. An intramolecular face-selective ester transfer then results in the formation of **98** and the recovery of catalyst **13k**. This catalyst, designed by Ooi, has been successfully applied to a variety of differently functionalized enol carbonates (up to 99%, 97% ee) to yield optically active molecules containing the α-amino quaternary carbon center.

RESULTS AND DISCUSSION

1. α-Alkyl malonates

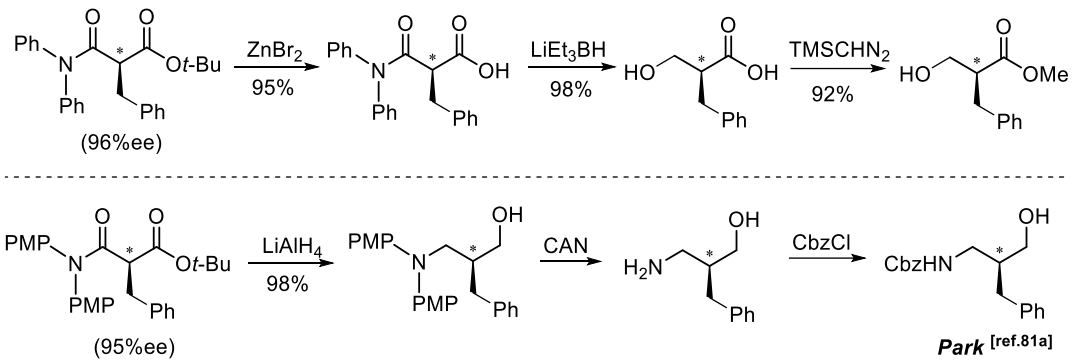
As mentioned in the introduction, the enantioselective direct catalytic α-alkylation of the malonates has not been well studied to date. Recently, our laboratory research group reported a new synthetic method for chiral α-alkylmalonamide esters (**99**) through the phase-transfer catalytic mono-α-alkylation of *N*,*N*-diaryl malonamide esters (**45a**) with high enantioselectivities [81a]. As a continuation of this study, the substrate has been expanded to the malonate system for the construction of quaternary carbon centers using diphenylmethyl *tert*-butyl α-methylmalonate (**47a**) [83a] (**Scheme 60**).



Scheme 60. Enantioselective α-alkylation of the malonamic esters and malonates

To the best of our knowledge, these experiments were the first to accomplish the direct mono-α-alkylation of a 1,3-dicarbonyl system and the first enantioselective direct catalytic α-alkylation process of malonates. Furthermore, the new methods have successfully

applied the compound to the synthesis of various chiral building blocks with several modifications. The optically active α-benzyl-*N*,*N*-diphenylmalonamic *tert*-butyl esters could be readily converted into their corresponding β-hydroxy acid and γ-amino alcohol derivatives without loss of chirality, as exemplified in **Scheme 61**.



Scheme 61. Conversion of the α-alkyl-malonamic esters to versatile chiral building blocks.

Examples of the chemical modifications of the optically active α,α-dialkylmalonates, which were afforded by the asymmetric phase-transfer catalytic α-alkylation of the malonates, are depicted in **Scheme 41**. The resulting diphenylmethyl *tert*-butyl α,α-dialkylmalonates could be successfully converted into various versatile chiral intermediates via the selective deprotection of the diphenylmethyl group by catalytic hydrogenation.

However, selective deprotection of the *tert*-butyl group was unsuccessful due to the partial hydrolysis of the diphenylmethyl group under acidic conditions (trifluoroacetic acid or 1 M HCl). Under an acidic system, because a relatively stable tertiary cation and a diphenylic cation were achieved, double hydrolysis was inevitable, resulting in a complete loss of the induction of α-chirality under acidic hydrolysis. The diphenylmethyl ester was not hydrolyzed under alkaline conditions (aqueous KOH or NaOH solution), causing the compound to remain unchanged. Although diphenylmethylene is a secondary carbon, it

occupies a wide area. Therefore, due to the maintenance of the two ester groups by the steric hindrance, their chemoselective removal under alkaline conditions failed. The reductive cleavage by hydrogenation enabled only the removal of diphenylmethyl ester; however, it also reduced the sensitive functional groups, such as the olefin, enyne, and nitro moieties [132] (**Figure 13**).

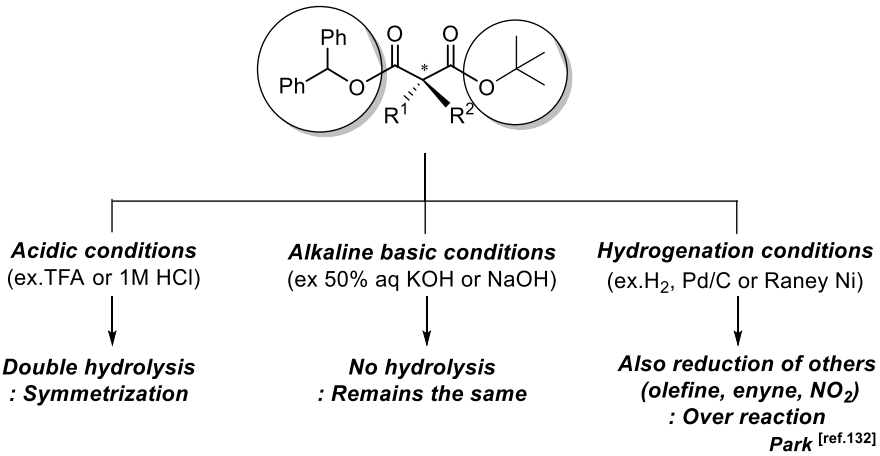


Figure 13. Trial of chemoselective reduction of two different ester groups

To extend the usefulness of our synthetic method to versatile derivatization, especially in the case of the α-substitution with unsaturated electrophiles, the development of a new substrate was required, namely a malonate substrate hydrolyzable under alkaline conditions for enantioselective phase-transfer catalytic alkylation.

1-1. Design of novel α-alkyl malonates as substrates for phase-transfer catalytic alkylation

Our research group designed enantiotopic asymmetric α-alkylmalonates as substrates for phase-transfer catalytic alkylation. First, we installed a primary framework on the malonate skeleton as the basis of the molecular structure, which has many possible applications because malonate can be easily modified using the suitable chemical conversion of two different esters that are different from malonamide ester. Second, a hydrolyzable ester was induced at one of the ester portions of malonate, which could be attacked by a hydroxide anion under alkaline hydrolysis conditions based on the reduced steric hindrance. Therefore, the carbon that attaches beside the ester oxygen must have a primary or secondary atom to have sufficient room to encounter the hydroxide anion. Another portion of the ester was maintained as the *tert*-butyl ester group, which is seldom hydrolyzed under a basic system due to steric hindrance and has historically been essential for high enantioselectivity in the previous enantioselective α-alkylations under phase-transfer catalytic conditions [7]. Finally, the α-substitution of the malonate substrate contained an alkyl group to avoid double α-alkylation and to expand the scope of the substrates (**Figure 14**).

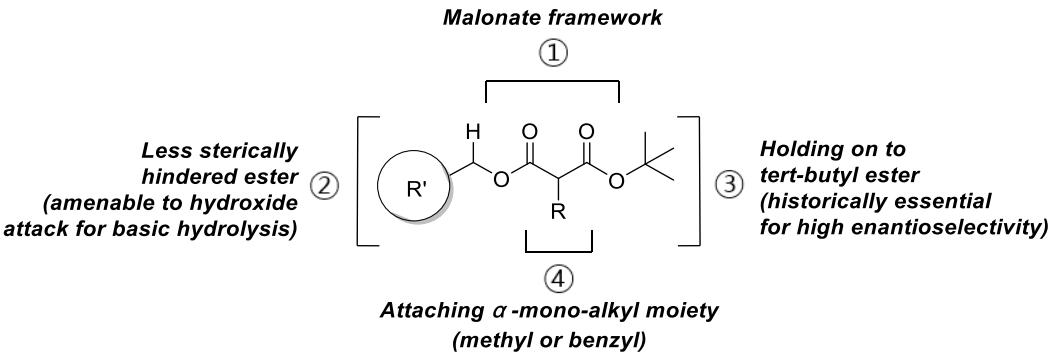
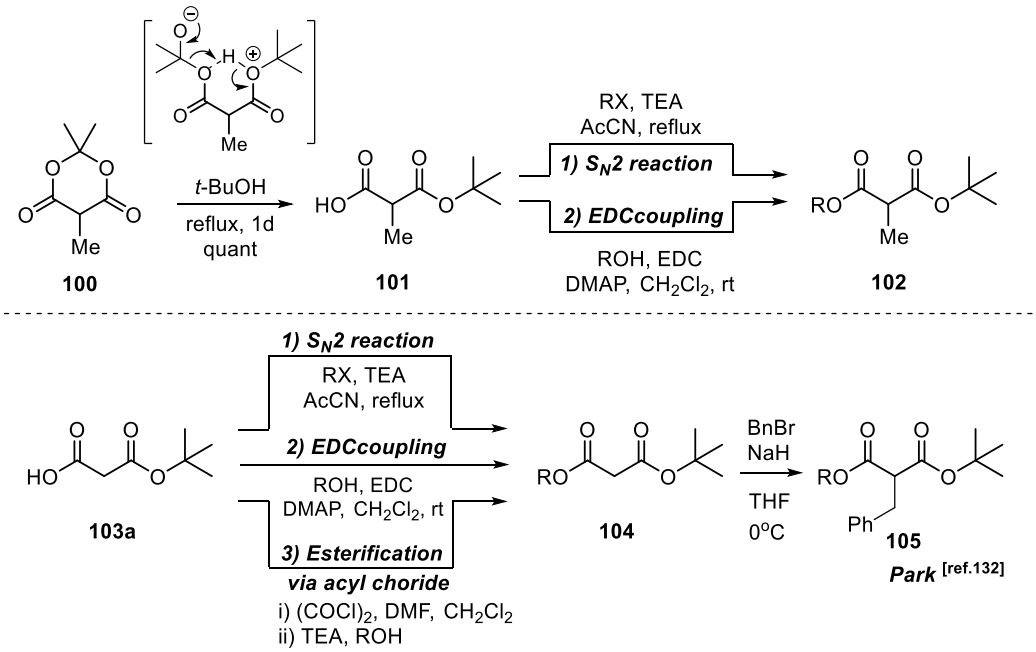


Figure 14. Design of novel phase-transfer catalytic substrates, the α-alkyl malonates

1-2. Synthetic routes for the preparation of the α-alkyl malonates

As mentioned above, our research team designed new phase-transfer catalytic substrates, changing the diphenylmethyl group to a series of less sterically hindered ester groups. All of the various *tert*-butyl alkyl malonates we intended to synthesize were prepared using a convenient method from commercially available compounds. Several α-methyl malonates **102** were obtained in two steps from α-methyl Meldrum's acid. *tert*-Butanolysis of α-methyl Meldrum's acid (**100**), followed by esterification with various alkyl halides or alcohols in the presence of triethylamine or EDC, respectively, resulted in the corresponding α-methyl malonates, which were hydrolyzable under basic conditions. In regard to α-benzyl malonates **105**, hydrogen *tert*-butyl malonate (**103**) was esterified via a S_N2 reaction with triethylamine to afford alkyl *tert*-butyl malonate carrying α-methylene **104**, which was mono substituted with benzyl bromide (**Scheme 62**).



Scheme 62. Synthetic routes for the preparation of α-alkyl malonates

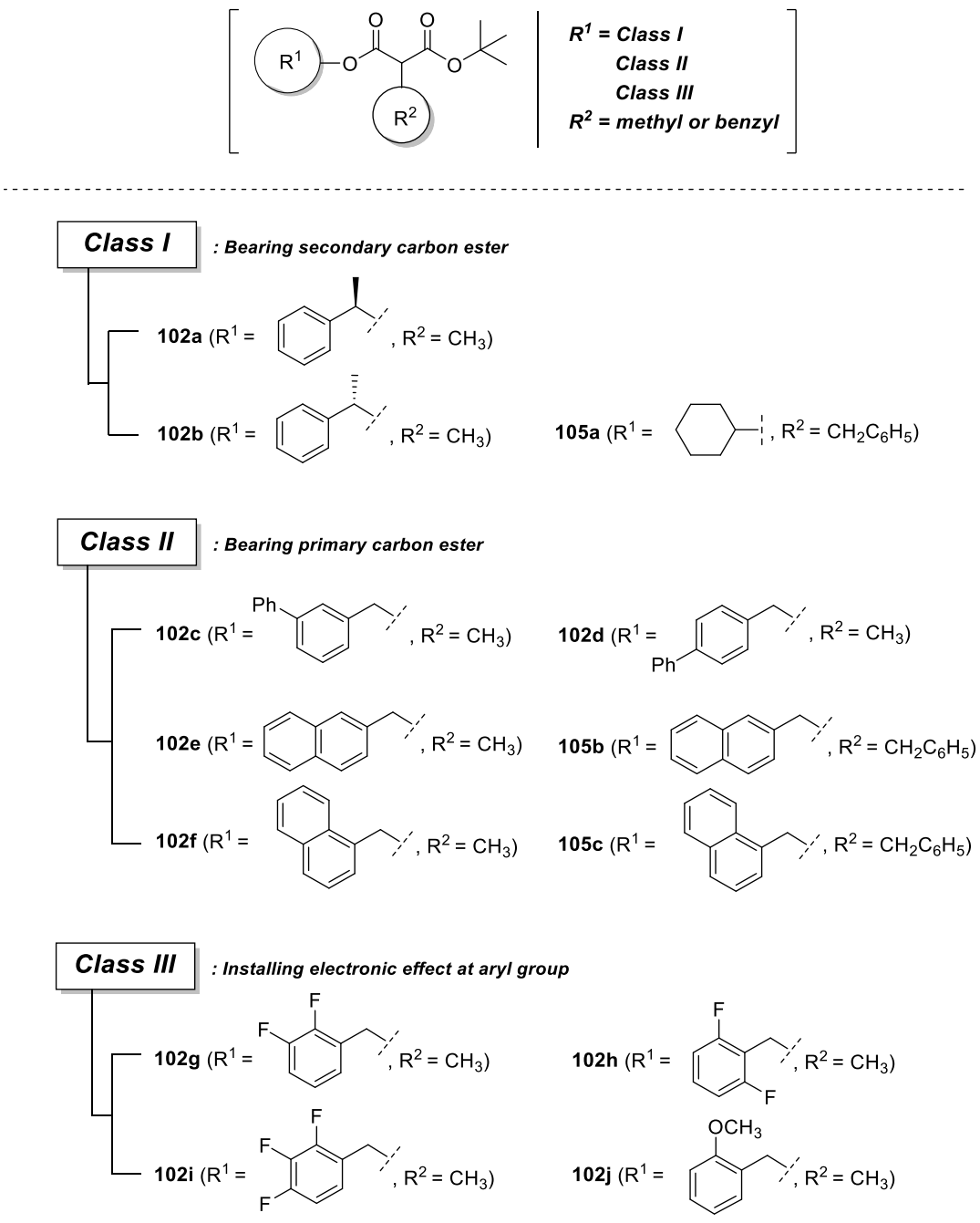
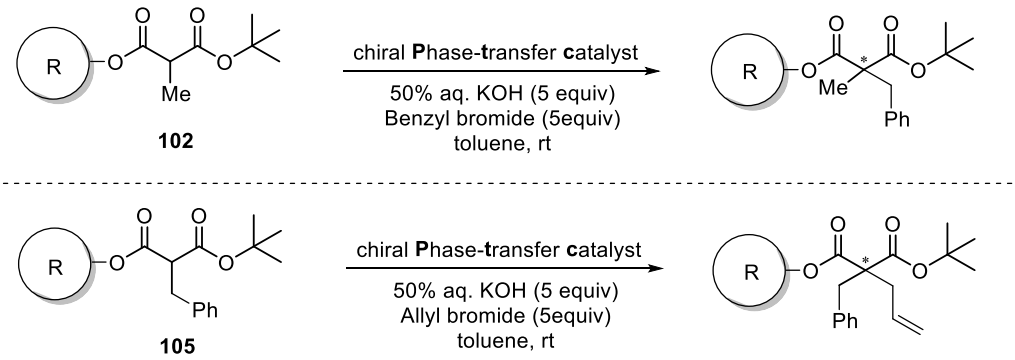


Figure 15. Classes of the prepared α-alkyl malonates

Thirteen molecules prepared by the methods depicted in **Scheme 62**, the α-alkyl malonates, can be categorized according to the structure of one ester group of the main skeleton. First, the initially installed diphenylmethyl ester was changed to the less sterically crowded secondary carbon ester, classified into **Class I**. By reducing the size of the ester to the secondary benzylic ester, formation of the chirality at the benzylic position was inevitable, and the 2-(*R*)-methylbenzyl *tert*-butyl malonates **102a** and 2-(*S*)-methylbenzyl *tert*-butyl malonates **102b** were synthesized. The **Class II** substrates contain primary carbon esters. To partially compensate for the reduced size of the molecule, we added a bulky aryl moiety to the methyl ester, especially the phenyl substituted phenyl and naphthyl group, and we attempted to manipulate an electronic effect between the substrate and the phase-transfer catalyst. As a part of this effort, di- or tri-fluoro substituted **102g**, **102h**, and **102i** and ortho-methoxy substituted **102j** were prepared. The substrates containing benzylic ester substituted with an electron withdrawing or releasing group were assigned to **Class III** (**Figure 15**).

1-3. Examination of the efficiency of the prepared malonates as substrates for phase-transfer catalytic alkylation

The prepared malonates (**102**, **105**) were examined for their efficiency as substrates by α-benzylation or allylation under typical phase-transfer catalytic reaction conditions based on our previous report [83]. The enantioselective alkylations were performed using several phase-transfer catalysts along with benzyl bromide or allyl bromide and a 50% aqueous KOH solution at 0℃ in toluene (**Scheme 63**). Selected examples of the phase-transfer catalysts used to determine the best combination of substrate and catalyst are displayed in **Figure 16**.



Scheme 63. Preliminary condition of the asymmetric phase-transfer catalytic α-alkylation

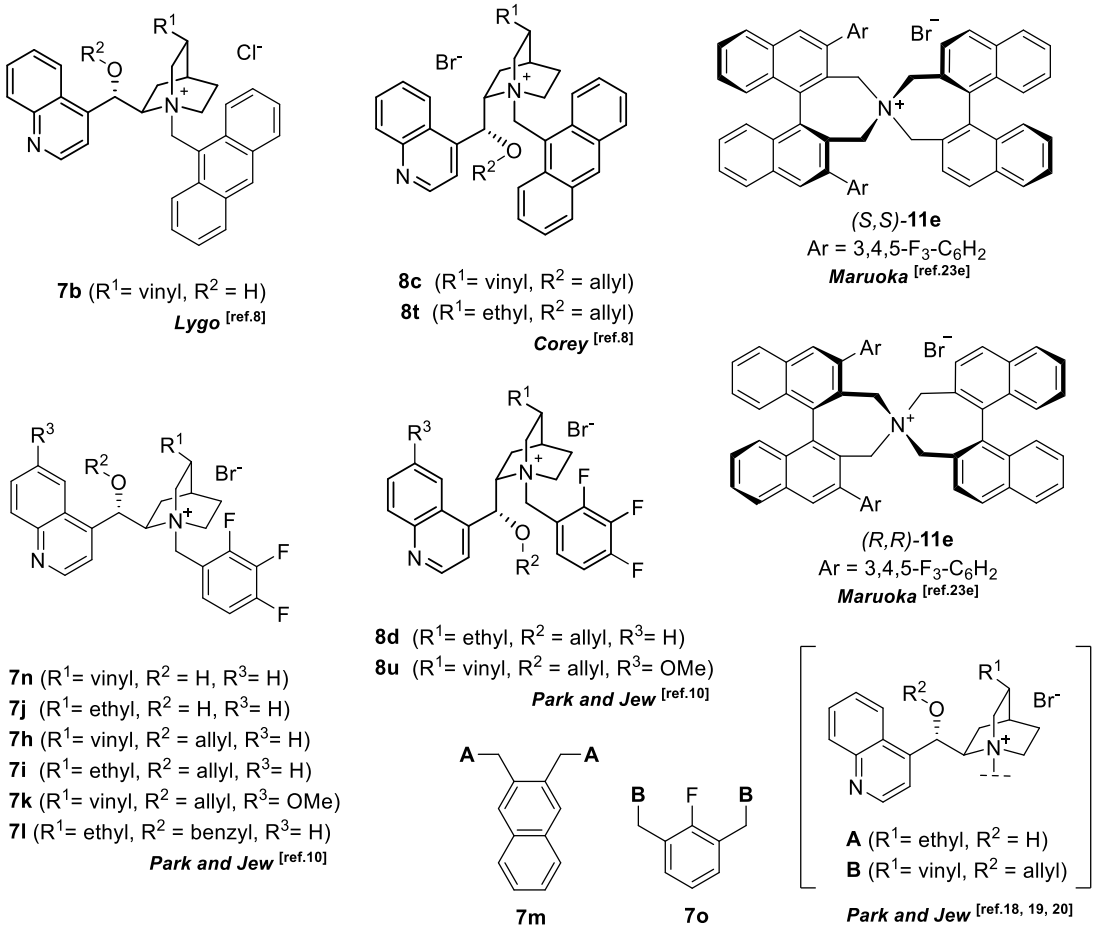


Figure 16. Selected examples of phase-transfer catalysts-I

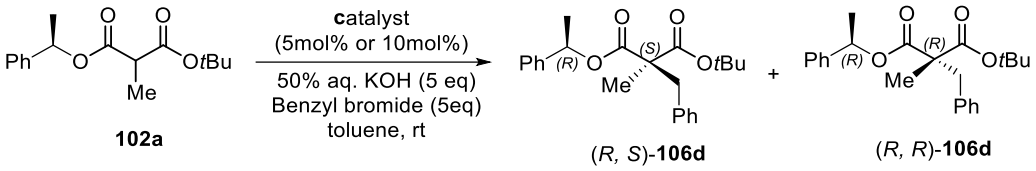
1-3-1. Optimization of the phase transfer catalytic alkylation with various phase-transfer catalysts

The prepared malonates (**102a**, **102b**, **102c**, **102d**, **102e**, **102f**, **102g**, **102h**, **102i**, **102j**, **105a**, **105b**, and **105c**) were examined for their efficiency as substrates by α-benzylation under typical phase-transfer catalytic conditions based on our previous report [83a]. Enantioselective phase-transfer catalytic benzylation was performed using the catalyst (5 mol% or 10 mol%), along with benzyl bromide (5.0 equiv.) and 50% KOH (5.0 equiv.) at room temperature or at 0℃ in toluene.

Substrate **102a**, belonging to **Class I**, was used to determine the best phase-transfer catalysts using 5 mol% of (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide (*S*,*S*)-**11e** and 10 mol% of nine *Cinchona*-derived catalysts. The configuration of the synthesized **106d** was dependent on the conformation of the substrate-catalyst complex. The newly formed chirality at the α-position was of the (*S*)-configuration when (*S*,*S*)-**11e** and the *Cinchonidine*-based catalysts were used. In contrast, the cinchonine-derived catalysts afforded the α-(*R*)-configured benzylated **106d**. As shown in **Table 1**, (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide (*S*,*S*)-**11e** exhibited an 83% de value, which could be improved by the delicate optimization procedure (entry 1). The representative cinchonine-derived **7b**, **7h**, **7i**, **7j**, **7k**, and **7l** showed lower stereo selectivities to a certain degree (entries 2-7). However, unfortunately, the use of **8c**, **8t**, and **8d** presented relatively diminished enantioselectivities, in the lower 20% range. Regarding the conversion extent, most of the reactions afforded the desired structure **106d** with high chemical yields without any detected byproducts. The reaction time was recorded as the moment when the substrate completely disappeared in the TLC. For the reaction in the presence of catalyst (*S*,*S*)-**11e**,

the rate of conversion was significantly slower than the other comparison groups and was finally terminated in 7 days.

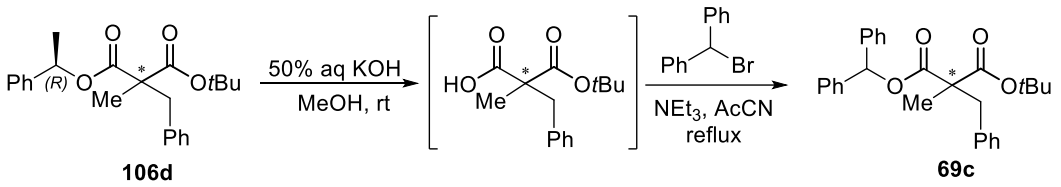
Table 1. Screening of the phase-transfer catalysts combined with substrate **102a**



entry	catalyst (mol%)	time (h)	yield (%)	de (%) [a]
1	(*S*,*S*)-**11e** (5)	168	91	83 (*R*, *S*)
2	**7b** (10)	16	99	60 (*R*, *R*)
3	**7i** (10)	16	98	67 (*R*, *R*)
4	**7h** (10)	14	92	59 (*R*, *R*)
5	**7j** (10)	14	97	53 (*R*, *R*)
6	**7k** (10)	14	99	43 (*R*, *R*)
7	**7l** (10)	18	99	64 (*R*, *R*)
8	**8c** (10)	32	79	24 (*R*, *S*)
9	**8t** (10)	39	92	20 (*R*, *S*)
10	**8d** (10)	19	86	23 (*R*, *S*)

[a] Enantiopurity was determined via **69c**, as obtained from **106d**

A chiral HPLC apparatus analyzed the degree of chiral induction achieved by each catalyst. Optically active **106d** was hydrolyzed under mild basic conditions followed by esterification with α-bromo diphenyl methylester, affording **69c** with an absolute configuration that has been previously determined [83a]. The distinct degree of chirality of **106d** was retained during the modification to **69c**. The enantiopurity of the converted **69c** was calculated by HPLC analysis, reflecting the de values of **106d** (**Scheme 63**).

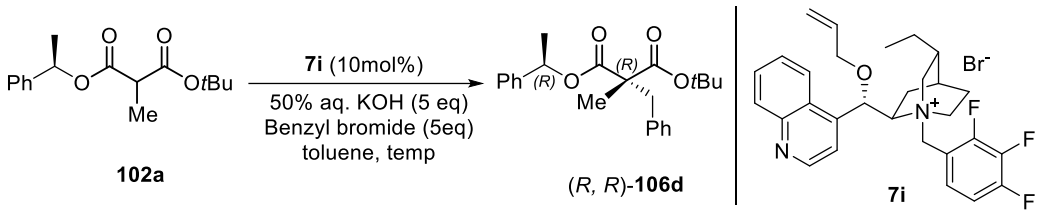


Scheme 63. Modification of **106d** to diphenylmethyl ester for HPLC analysis

While performing the screening experiments with various phase-transfer catalysts coordinating with substrate **102a** (**Table 1**), **7i** showed 67% stereoselectivity, which was expected to increase upon optimization of the changing reaction temperature.

Therefore, the reaction mixture containing substrate **102a** in the presence of 10 mol% of **7i** was gradually brought to the low temperature, and a 15% rise in stereoselectivity was observed at -40℃, as described in **Table 2**. When the temperature decreased to -60℃, the reaction occasionally completely terminated, possibly because of the loss of efficacy of the aqueous base caused by freezing. Twelve days after the reaction began, the reaction mixture was worked up and determined to afford optically active **106d** with moderate yield. The degree of optical purity of the product was also calculated with modification through the two chemical steps in **Scheme 62**.

Table 2. Optimization of the reaction system with substrate **102a** in the presence of **7i**



entry	temperature (°C)	time (h)	yield (%)	de (%) [a]
1	room temperature	16	98	67 (*R*, *R*)
2	0	19	98	74 (*R*, *R*)
3	-10	22	90	71 (*R*, *R*)
4	-20	22	92	74 (*R*, *R*)
5	-40	40	91	82 (*R*, *R*)
6	-60	288	89	81 (*R*, *R*)

[a] Enantiopurity was determined via **69c**, as obtained from **106d**

Furthermore, in **Table 1**, the highest de value was obtained using catalyst (*S*,*S*)-**11e**. The trial to increase the preliminary selectivity by delicately manipulating the reaction condition was thought to be worthwhile. Our research group has secured a supply of two series of *N*-spiro type chiral ammonium bromides (*S*,*S*)-**11e** and (*R*,*R*)-**11e**, which are enantiomers. In addition, the prepared substrates **102a** and **102b** were available for use in the optimization. Therefore, we planned an organized optimization, making a classification with substrates **102a**, **102b**, (*S*,*S*)-**11e**, and (*R*,*R*)-**11e,** as shown in **Figure 17**. To investigate the best pair of substrates, **102a**, **102b** and C_2-symmetric chiral phase-transfer catalyst

(*S*,*S*)-**11e** and (*R*,*R*)-**11e**, four types of combinations required verification by practically conducting the phase-transfer catalytic α-alkylation.

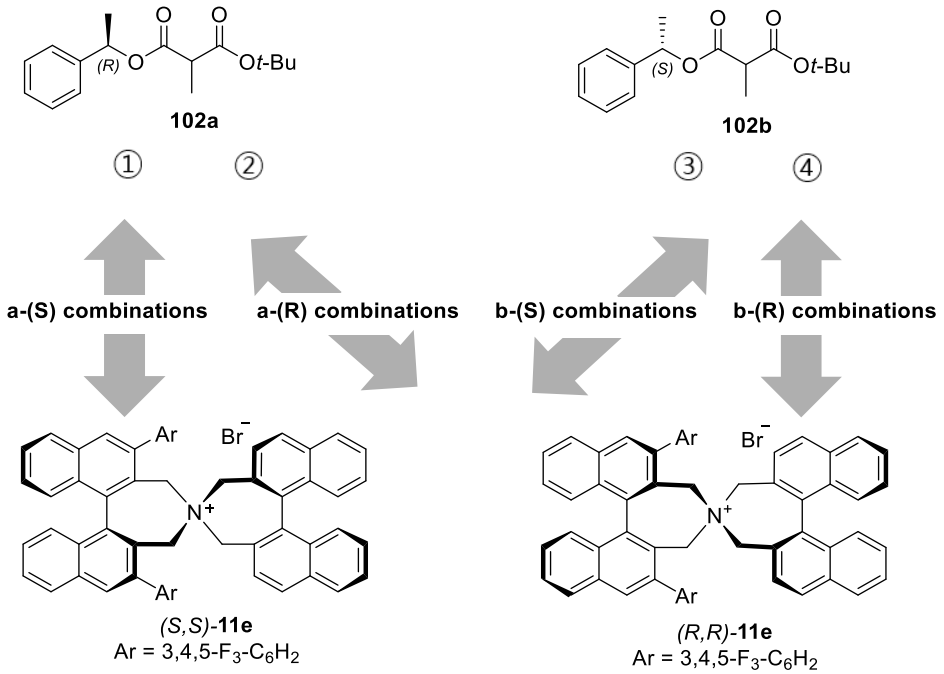
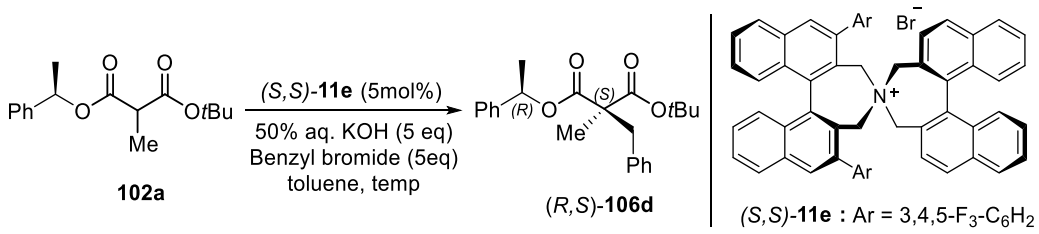


Figure 17. 4 Types of combinations with substrates **102a** and **102b** and catalyst **11e**

The validation experiments commenced with the first group **(1)**, substrate **102a** containing the (*R*)-configured substituted methyl ester and (*S*,*S*)-**11e**. **Table 3** describes the efficacy of pair **(1)**. As depicted in entries **1-4**, seven days are required for nearly complete conversion. As the reaction temperature was reduced to -40℃, gradual advances in stereoselectivity were observed. Finally, our laboratory team determined that the reaction temperature of -40℃ afforded the best results for the chemical yield and optical yield in the reaction using combination **(1)** (**Table 3**).

Using the optimized results for combination **(1)**, we changed the catalyst (*S*,*S*)-**11e** to its enantiomer (*R*,*R*)-**11e**. The use of the opposite axial chiral catalyst resulted in the opposite configuration of product **106d**.

Table 3. Efficiency test with combination **(1)**: substrate **102a** and (*S*,*S*)-**11e**

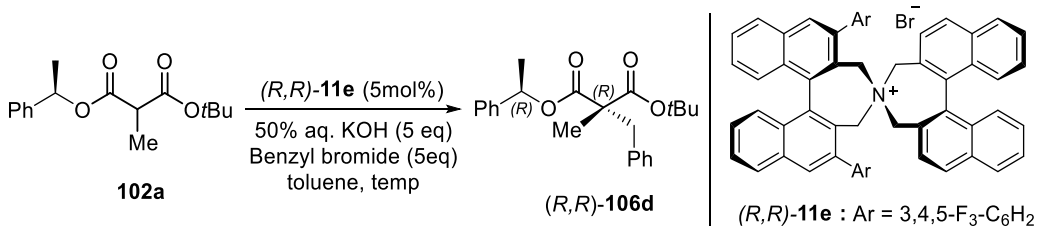


entry	temperature (°C)	time (h)	yield (%)	de (%) [a]
1	room temperature	168	91	83 (*R*, *S*)
2	0	168	91	84 (*R*, *S*)
3	-20	168	87	88 (*R*, *S*)
4	-40	168	92	91 (*R*, *S*)

[a] Enantiopurity was determined via **69c**, as obtained from **106d**

Combination **(2)** consisted of substrate **102a** and (*R*,*R*)-**11e**, which presented slightly lower stereoselectivities than combination **(1)** (**Table 4**). Although each reaction system showed a stepwise increase in the stereoselectivity as the reaction temperature decreased, the respective optical yields were less than expected. When the substrate-catalyst species formed the appropriate conformation during the reaction, the methyl group did not contribute to the optimal structure.

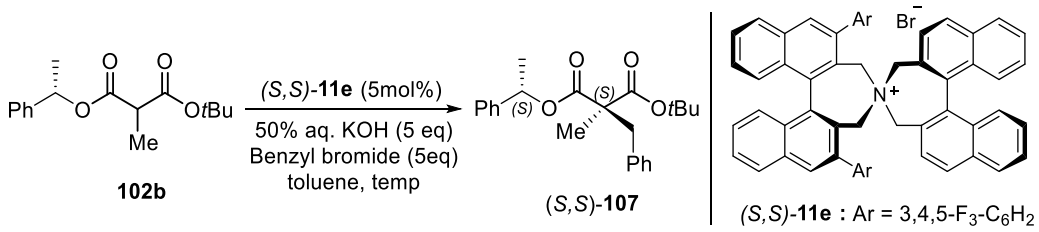
Table 4. Efficiency test with combination **(2)**: substrate **102a** and (*R*,*R*)-**11e**



entry	temperature (°C)	time (h)	yield (%)	de (%) [a]
1	0	168	86	64 (*R*, *R*)
2	-20	168	91	77 (*R*, *R*)
3	-40	168	89	83 (*R*, *R*)

[a] Enantiopurity was determined via **69c**, as obtained from **106d**

Table 5. Efficiency test with combination **(3)**: substrate **102b** and (*S*,*S*)-**11e**

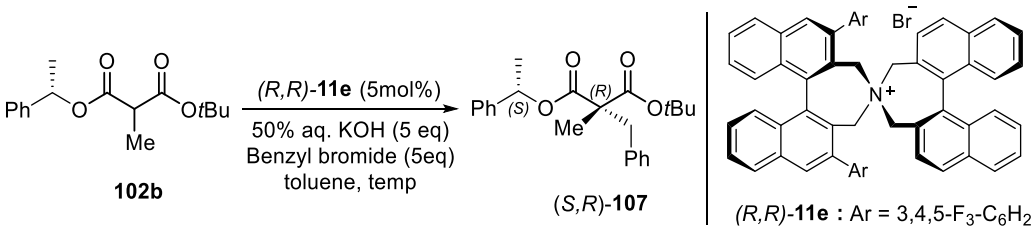


entry	temperature (°C)	time (h)	yield (%)	de (%) [a]
1	0	91	82	77 (*S*, *S*)
2	-20	115	81	80 (*S*, *S*)
3	-40	168	82	82 (*S*, *S*)

[a] Enantiopurity was determined via **69c**, as obtained from **107**

Table 3 reflects the efficacy of combination **(3)**, the complex of substrate **102b** and (*S*,*S*)-**11e**. Similar to combination **(2)**, this pair was mismatched compared to **(1)** or **(4),** as demonstrated by the reduced stereoselectivity of approximately 80% and slower reaction rates. Finally, the combination of **(4)** was validated as having a high optical yield. The best enantioselectivity was observed in the presence of (*R*,*R*)-**11e** at −40°C with a 1% increase compared to combination **(1)** (**Table 3**, entry **4**). However, below -40℃, termination of the reaction was considerably delayed. We were compelled to end the reaction and recovered approximately half the substrate.

Table 6. Efficiency test with combination **(4)**: substrate **102b** and (*R*,*R*)-**11e**



entry	temperature (°C)	time (h)	yield (%)	de (%) [a]
1	room temperature	49	94	83 (*S*, *R*)
2	0	121	89	83 (*S*, *R*)
3	-20	121	88	88 (*S*, *R*)
4	-40	384	84 (BORSM)	92 (*S*, *R*)
5	-60	384	86 (BORSM)	90 (*S*, *R*)

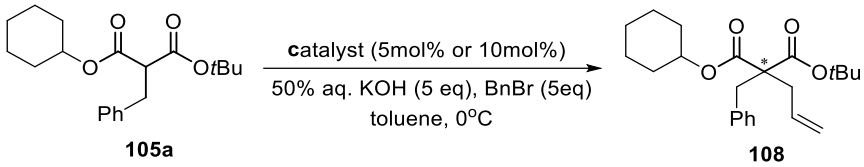
[a] Enantiopurity was determined via **69c**, as obtained from **107**

In summary, our research team investigated the efficacy of four cases with the two substrates **102a** and **102b** and the catalysts (*S*,*S*)-**11e** and (*R*,*R*)-**11e**. Combinations **(1)** and **(4)** matched each other, and combinations **(2)** and **(3)** were slightly mismatched. As shown in entry **4** of **Table 3**, the best results were based on the reaction time, the chemical yield, and the stereoselectivity that the combinations achieved.

Next, molecule **105a** containing cyclohexyl ester and a benzyl group at the α-position was used with the representative catalysts under the preliminary phase-transfer catalytic conditions. By adding the benzyl moiety as the absorbance unit and the sterically bulky unit at the α-position, the screening experiments of the phase-transfer catalyst to **105a** were accomplished (**Table 7**). Because substrate **105a** already contained a benzyl group at the α-position, the phase-transfer catalytic reaction was performed by asymmetric α-allylation with an allyl bromide reagent.

Substrate **105a** was allylated in the presence of the selected phase-transfer catalysts, showing results similar to substrates **102a** and **102b**. The *N*-spiro type chiral ammonium bromides (*S*,*S*)-**11e** resulted in the allylated product **108** with moderate optical purity (entry **1**, 65%). Similarly to the experiments in **Table 1**, the cinchonine-derived catalyst **7** series showed lower enantioselectivities than (*S*,*S*)-**11e,** and cinchonidine-derived **8d** presented a more diminished ee value (entry **2**, 19%). The substrate belongs to **Class I**, the cyclohexyl ester malonates **105a** were regarded as inappropriate for the asymmetric phase-transfer catalytic alkylation (**Table 7**).

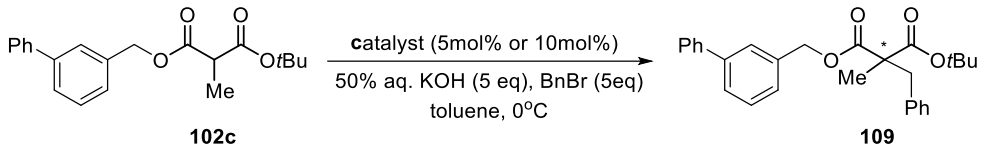
Table 7. Screening of the phase-transfer catalysts combined with substrate **105a**



entry	catalyst (mol%)	time (h)	yield (%)	ee (%)
1	(*S*,*S*)-**11e** (5)	72	53	65
2	**8d** (10)	72	72	19
3	**7b**(10)	72	76	61
4	**7i** (10)	72	35	46
5	**7j** (10)	72	49	33
6	**7l** (10)	72	67	41

Our research group employed substrates **102c** and **102d** in **Class II** along with a binaphthyl-type catalyst (*S*,*S*)-**11e** and the two cinchonine-derived catalysts **7i** and **7l**. Catalyst **7i** afforded the highest selectivities among the analogues of **7**; thus, it was employed again. Catalyst **7l**, which bears a benzyl ether moiety, was expected to interact with the aromatic ring of substrates **102c** and **102d**.

Table 8. Screening of the phase-transfer catalysts combined with substrate **102c**

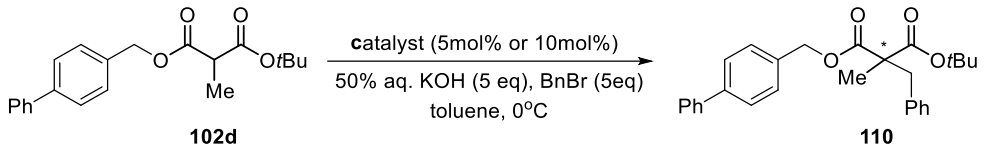


entry	catalyst (mol%)	time (h)	yield (%)	ee (%)
1	(*S*,*S*)-**11e** (5)	83	99	72
2	**7i** (10)	58	99	32
3	**7l** (10)	12	99	26

As shown in **Table 8**, both of the cinchonine-derived catalysts showed lower enantioselectivities compared with the binaphthyl-type catalyst (*S*,*S*)-**11e**. Although the conversions to **109** from **102c** were clear with high yields, the enantioselectivities did not approach our expectations. There appeared to be no effective interaction between the phenyl rings of **102c** and catalyst **7l**.

With the expectation that the substitution of one phenyl group at the *para*-position on the benzyl ester would encourage a more effective interaction between the substrate and catalyst, substrate **102d** was prepared and employed in the asymmetric phase-transfer catalytic alkylation along with three types of catalysts, as shown in **Table 8**. By comparison with the data in **Table 8**, each degree of chiral induction was increased by approximately 8-10%. Thus, we obtained a method that can afford the quaternary carbon center with 81% ee in quantitative chemical yield (**Table 9**).

Table 9. Screening of the phase-transfer catalysts combined with substrate **102d**



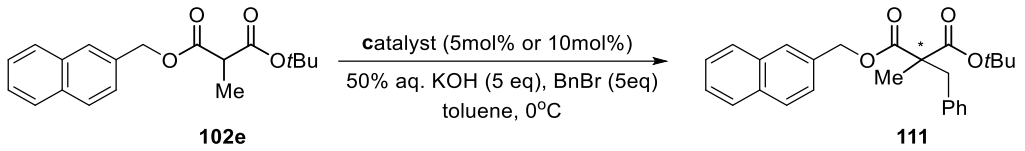
entry	catalyst (mol%)	time (h)	yield (%)	ee (%)[a]
1	(*S*,*S*)-**11e** (5)	60	99	81
2	**7i** (10)	19	99	40
3	**7l** (10)	11	95	37

[a] Enantiopurity was determined via **69c**, as obtained from **110**

The asymmetrically benzylated product **110** was not separated into two enantiomers by chiral HPLC analysis. Unavoidably, **110** was modified to diphenylmethyl ester **69c**, as shown in **Scheme 62,** to determine the ee value of **110**. The ratio of the isomers of each changed compound from the phenyl substituted benzyl ester to the diphenyl methyl ester was then calculated.

To investigate the efficacy of a bulkier ester, the α-naphthylmethyl group **102e** and **105b** and the β-naphthylmethyl group **102f** and **105c** were introduced onto the ester portion of malonate as a phase-transfer catalytic substrate. Each asymmetric reaction was implemented in the presence of eight types of phase-transfer catalysts.

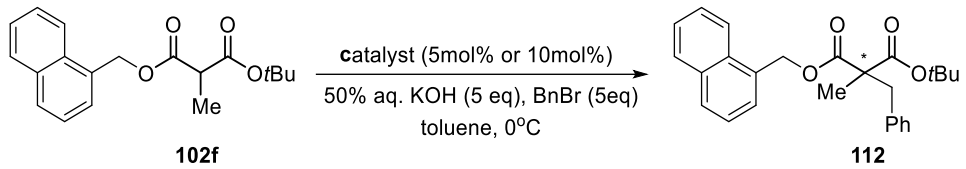
Table 10. Screening of the phase-transfer catalysts combined with substrate **102e**



entry	catalyst (mol%)	time (h)	yield (%)	ee (%)
1	(*S*,*S*)-**11e** (5)	44	91	71
2	**8d** (10)	72	99	43
3	**8u** (10)	20	99	24
4	**7h** (10)	10	95	41
5	**7i** (10)	20	99	41
6	**7j** (10)	20	99	35
7	**7k** (10)	20	98	35
8	**7m** (5)	20	96	25

The α-naphthylmethyl group (**Table 10**) showed slightly higher enantioselectivity than the β-naphthylmethyl group (**Table 11**). It is assumed that the conformation of the naphthyl of **102e** was more suitable than the conformation of **102f**. The trial using dimeric catalyst **7m** did not further increase the enantioselectivity (entry **8**).

Table 11. Screening of the phase-transfer catalysts combined with substrate **102f**

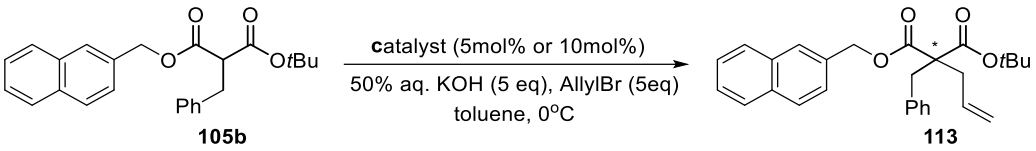


entry	catalyst (mol%)	time (h)	yield (%)	ee (%)
1	(*S*,*S*)-**11e** (5)	18	97	53
2	**8d** (10)	14	98	16
3	**8u** (10)	18	99	9
4	**7h** (10)	18	93	33
5	**7i** (10)	18	92	38
6	**7j** (10)	18	99	31
7	**7k** (10)	18	99	28
8	**7m** (5)	18	99	15

In the reaction of **102e** and **102f**, the chemical yields were satisfactory, but the enantioselectivities were not. Therefore, our research group decided to increase the bulk of the substrate by substituting methyl with the benzyl group.

Initially, the prepared **105b** and **105c** were used in the screening experiments for the appropriate phase-transfer catalysts by asymmetric α-allylation. However, the expectation of the roles of the α-benzyl group was not met.

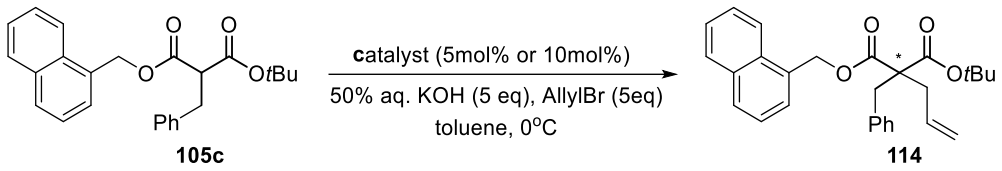
Table 12. Screening of the phase-transfer catalysts combined with substrate **105b**



entry	catalyst (mol%)	time (h)	yield (%)	ee (%)
1	(*S*,*S*)-**11e** (5)	11	91	69
2	**8d** (10)	11	80	31
3	**8u** (10)	11	91	13
4	**7h** (10)	11	93	40
5	**7i** (10)	14	81	44
6	**7j** (10)	11	81	33
7	**7k** (10)	14	92	26
8	**7m** (5)	14	80	15

As shown in **Tables 2** and **3**, the enantioselectivity values were typically low. Especially in the reaction of **105c**, (*S*,*S*)-**11e** afforded the best ee value, at 39% ee. Substrate **105c**, which simultaneously contains β-naphthylmethyl ester and a benzyl group at the reaction site, did not bind favorably to any phase-transfer catalysts. In addition, the cinchonine-derived catalysts **7k** and **7m** did not effectively discriminate the particular area as the electrophile approached (entries **6** and **7**).

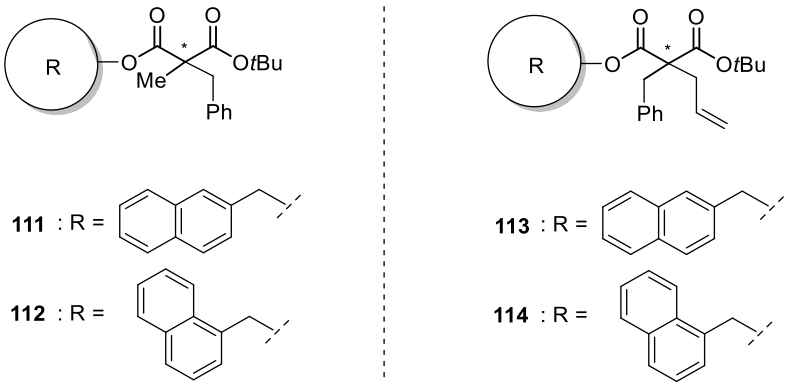
Table 13. Screening of the phase-transfer catalysts combined with substrate **105c**



entry	catalyst (mol%)	time (h)	yield (%)	ee (%)
1	(*S*,*S*)-**11e** (5)	23	87	39
2	**8d** (10)	27	95	12
3	**7i** (10)	27	82	42
4	**7h** (10)	26	97	41
5	**7j** (10)	27	92	29
6	**7k** (10)	23	87	7
7	**7m** (5)	23	83	3

The cumulative results concerning the enantioselectivity of substrates **102e**, **102f**, **105b**, and **105c** are briefly summarized in **Table 14**. Among the four chiral products, **111,** which was the product of **102e** in the presence of the binaphthyl-type catalyst (*S*,*S*)**-11e,** achieved the highest enantioselectivity of 71% ee (entry **1**). Primarily, the cinchonine-derived catalysts (a series of **7**) were superior to the cinchonidine-derived catalysts, **8d** and **8u**. Because we found no steric effect on the enantioselectivity, our research group decided to manipulate the electronic effect occurring on the atoms at the substrate.

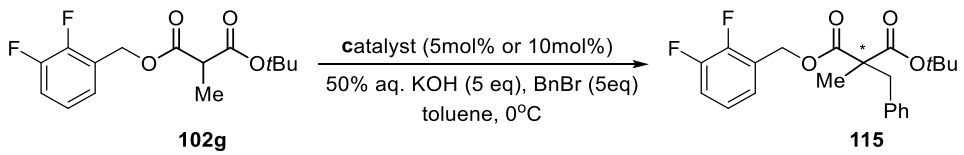
Table 14. Comparison of the efficiency among substrates **102e**, **102f**, **105b**, and **105c**



entry	catalyst (mol%)	ee% (**111**)	ee% (**112**)	ee% (**113**)	ee% (**114**)
1	(*S*,*S*)-**11e** (5)	71	53	69	39
2	**8d** (10)	43	16	31	12
3	**8u** (10)	24	9	13	-
4	**7h** (10)	41	33	40	42
5	**7i** (10)	41	38	44	41
6	**7j** (10)	35	31	33	29
7	**7k** (10)	35	28	26	7
8	**7m** (5)	25	15	15	3

The F atom is approximately the same size as hydrogen. However, in hydrogen bonding, the F atom operates differently from hydrogen as a hydrogen acceptor. In addition, the F atom is the most electronegative element. Thus, we installed fluorine on the phenyl ring to investigate the electronic effect on the enantioselectivities.

Table 15. Screening of the phase-transfer catalysts combined with substrate **102g**



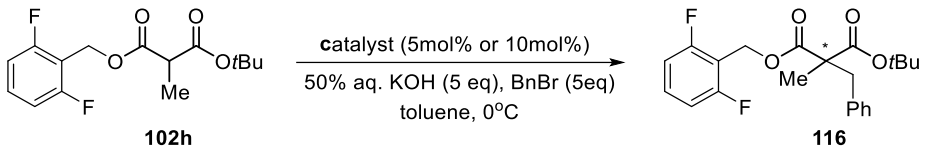
entry	catalyst (mol%)	time (h)	yield (%)	ee (%)
1	(*S*,*S*)-**11e** (5)	96	88	74
2	**8d** (10)	14	99	13
5	**7i** (10)	15	99	17
8	**7o** (5)	24	94	31

We designed and synthesized the substrates belonging to **Class III**. Thus, 1,2-difluorobenzyl ester malonate **102g**, 2,6-difluorobenzyl ester malonate **102h**, and 2,3,4-trifluorobenzyl ester malonate **102i** were prepared and used to perform preliminary asymmetric benzylation under representative phase-transfer catalytic conditions with several types of catalysts.

First, substrate **102g** afforded 74% ee in the presence of the *N*-spiro type chiral ammonium bromides (*S*,*S*)-**11e**. When the *Cinchona*-derived catalysts **8d**, **7i**, and **7o** were used, a

significant decrease in the stereoselectivity was observed. The dimeric catalyst **7o**, which contains the F atom, was employed due to the expectation of a certain interaction during the conversion of **102g** to **115** (**Table 15**).

Table 16. Screening of the phase-transfer catalysts combined with substrate **102h**



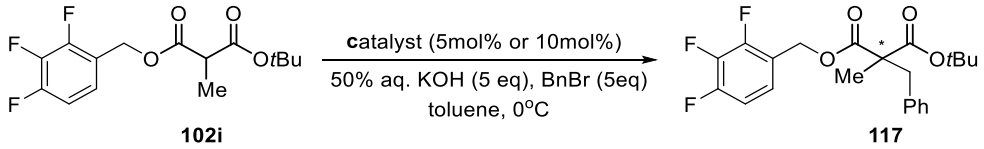
entry	catalyst (mol%)	time (h)	yield (%)	ee (%)
1	(*S*,*S*)-**11e** (5)	72	98	31
2	**8d** (10)	14	99	25
3	**7i** (10)	15	99	2
4	**7o** (5)	24	95	1

Next, we intended to change the position of one fluorine atom from *meta*- to *ortho*- on substrate **120g**. Thus, substrate **102h** bifluorinated at two *ortho*-positions was prepared and uses the screening reaction. As shown in **Table 16**, very low ee values were obtained, and there was no significant contribution from the fluorine element. Catalysts **7i** and **7o** afforded **116** with only 1-2% ee (**Table 16**, entries **3** and **4**).

When an additional fluorine was added at the *para* position of the phenyl ring, we expected that a certain interaction might occur. Thus, 2,3,4-trifluorobenzyl ester malonate **102i** was employed in the screening reaction. *Cinchonidine*-derived **8d** afforded the lowest

enantioselectivities, and the binaphthyl-containing (*S*,*S*)-**11e** furnished the corresponding product **117** with 71% ee (**Table 17**).

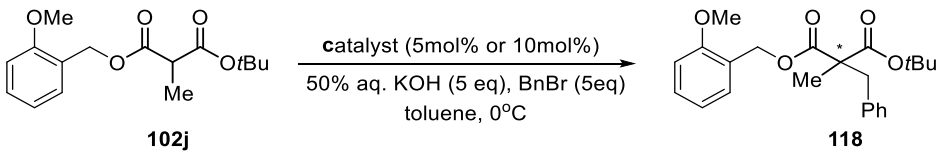
Table 17. Screening of phase-transfer catalysts combined with substrate **102i**



entry	catalyst (mol%)	time (h)	yield (%)	ee (%)
1	(*S*,*S*)-**11e** (5)	72	87	71
2	**8d** (10)	14	95	7
5	**7i** (10)	15	96	16
8	**7o** (5)	24	95	25

After obtaining these unsatisfactory results using fluorinated substrates, we designed substrate **102j**, bearing an electron-donating group, methoxy, at the *ortho*-position. However, this substrate was also unable to yield the expected enantiopure **118**.

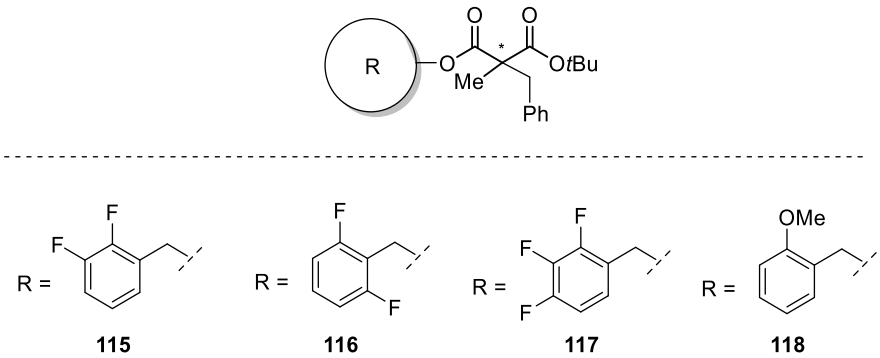
Table 18. Screening of phase-transfer catalysts combined with substrate **102j**



entry	catalyst (mol%)	time (h)	yield (%)	ee (%)
1	(*S*,*S*)-**11e** (5)	72	90	65
2	**8d** (10)	14	97	28
5	**7i** (10)	21	93	26
8	**7o** (5)	24	97	26

The cumulative stereoselectivities of the products **115**, **116**, **117**, and **118** converted from **102g**, **102h**, **102i**, and **102j,** respectively, are briefly summarized in **Table 19**. Comparing **115** and **117**, a very slight decrease in the ee value was determined. Note that the *para*-located fluorine diminishes the interaction between the substrate and catalyst. However, every substrate in the presence of the binaphthyl-type catalyst (*S*,*S*)-**11e** furnished the optically active product, with the highest enantioselectivity reaching 74% ee (entry **1**).

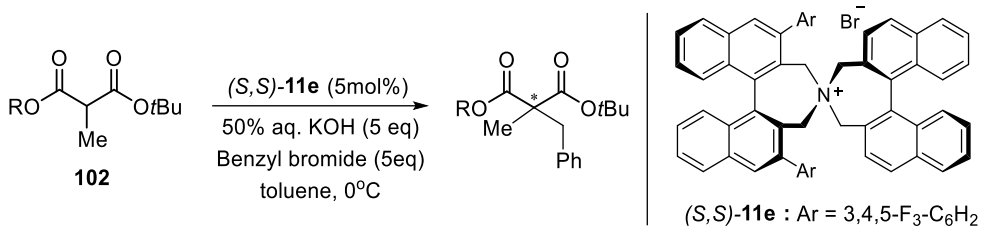
Table 19. Comparison of the efficiency among substrates **102g**, **102h**, **102i**, and **102j**

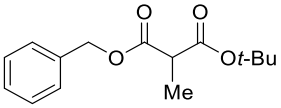
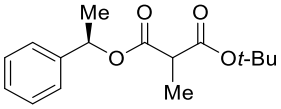
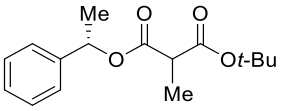
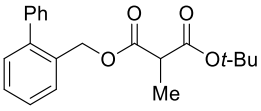
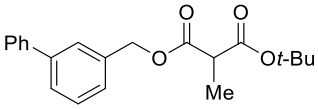
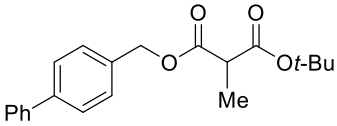


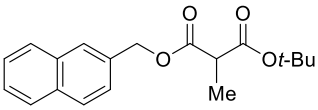
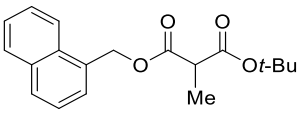
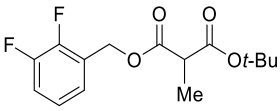
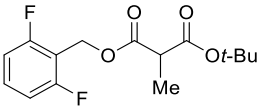
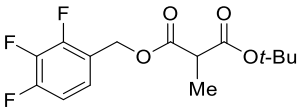
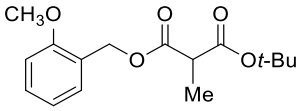
entry	catalyst (mol%)	ee% (**115**)	ee% (**116**)	ee% (**117**)	ee% (**118**)
1	(*S*,*S*)-**11e** (5)	74	31	71	65
2	**8d** (10)	13	25	7	28
3	**7i** (10)	17	2	16	26
4	**7o** (10)	31	1	25	26

Table 20 summarizes the results from the combination of the α-methyl malonate substrates and the binaphthyl-type representative catalyst (*S*,*S*)-**11e**. The enantioselectivity varied depending on the alkyl ester group. The biphenyl groups (entries **4-6**, above 80%) gave an ee value approximately 10% higher or comparable to the benzyl group (entry **1**, 70% ee). Among the bulky groups, the α-naphthylmethyl group (entry **8**, 53% ee) showed lower enantioselectivity than the β-naphthylmethyl group (entry **7**, 71% ee). The functional group on the phenyl ring affected the enantioselectivity slightly (entries **2**–**3**). However, the 2,6-difluorobenzyl group decreased the enantioselectivity (entry **10**, 31% ee). Among the prepared substrates, the 2-methylbenzyl group showed the highest enantioselectivity. Regarding the chirality of the 2-methylbenzyl moiety, the *R*-isomer (entry **2**, 83% ee) showed slightly higher enantioselectivity than the *S*-isomer (entry **3**, 77% ee). We speculated that the slight difference might arise from the match/mismatch of the chirality between the substrate (**102a** and **102b**) and the catalyst (*S*,*S*)-**11e**. These cumulative results suggest that the large ester groups may not be suitable for favorable binding with the catalyst (*S*,*S*)-**11e** and that there is no specific electronic effect on the enantioselectivity.

Table 20. Comparison of efficiency among substrates with (*S*,*S*)-**11e**



entry	substrate (**102**)		time (h)	yield (%)	ee (%)
1		**102k** [ref.83]	16	90	70 (*S*)
2		**102a**	168	91	83[a] (*S*)
3		**102b**	91	82	77[a] (*S*)
4		**102l** [ref.83]	13	90	80 (*S*)
5		**102c**	83	99	72(+)
6		**102d**	60	99	81[a] (+)

7		**102e**	44	91	71(+)
8		**102f**	18	97	53(+)
9		**102g**	96	88	74(+)
10		**102h**	72	98	31(+)
11		**102i**	72	87	71(+)
12		**102j**	72	90	65(+)

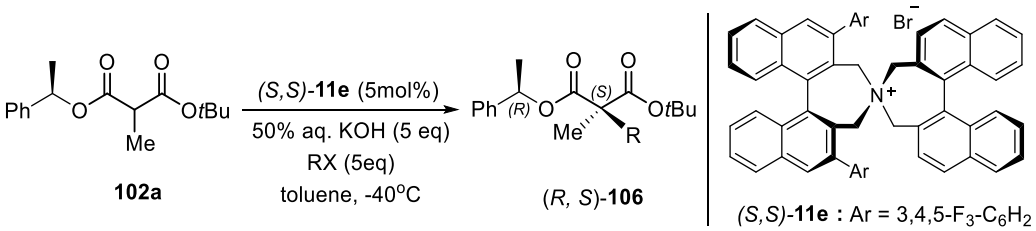
[a] Enantiopurity was determined via **69c**, as obtained from **106, 107,** and **110**

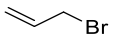
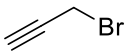
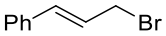
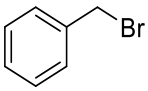
1-3-2. Scope and limitations of α-alkyl malonates on phase-transfer catalytic alkylation

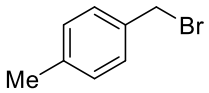
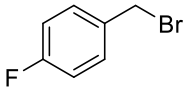
A further investigation into the scope and limitations of the unsaturated alkylating agents, including benzyl bromide, was performed under the optimized phase-transfer catalytic conditions (**Table 3**, entry **4**). The high enantioselectivities (up to 91% ee) in **Table 21**

indicate that this reaction system is an efficient enantioselective synthetic method for the preparation of α,α-dialkylmalonates. However, inactivated alkyl halide, such as methyl iodide, provided a poor chemical yield, which was a rare occurrence under the conditions used. Substitution of the allyl group by asymmetric phase-transfer catalysis was terminated within 1 day with excellent chemical yield and moderately high stereoselectivity (entry **1**). The cinnamyl group was also substituted with similar stereopurity to the allyl group (entry **3**). Asymmetric propargylation was completed within 3 days with only a slight reduction in stereoselectivity (entry **2**). The commonly *para*-substituted benzyl groups were substituted smoothly with nearly 90% diastereoselectivity (entries **4**-**6**).

Table 21. Asymmetric PTC α-alkylation of **102a** with various electrophiles



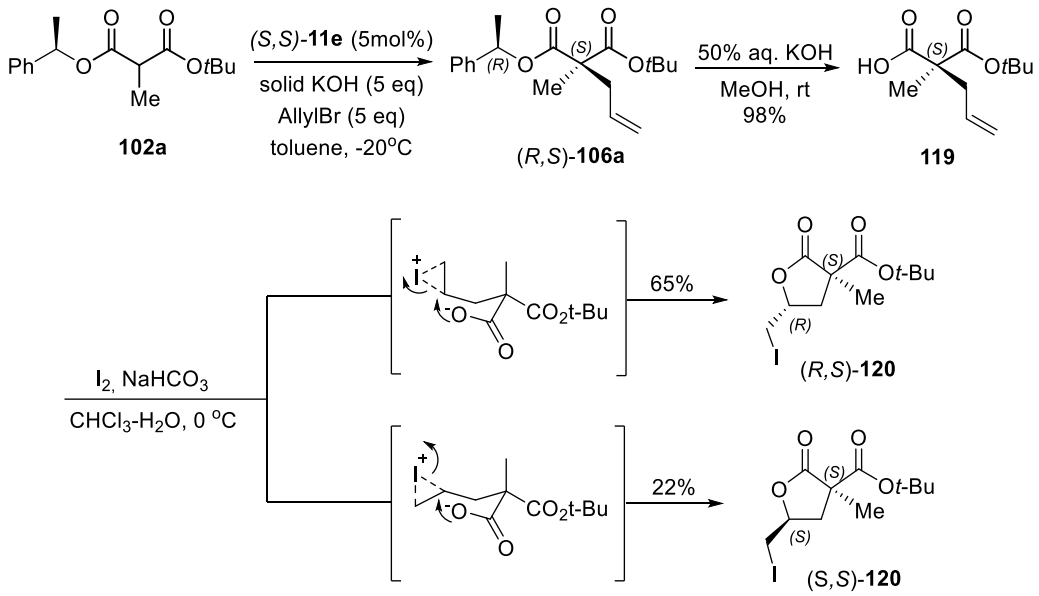
entry	RX	product	time (h)	yield (%)	de (%)
1[a]		**106a**	21	99	81 (*R*, *S*)
2		**106b**	72	80	75 (*R*, *S*)
3		**106c**	72	72	82 (*R*, *S*)
4		**106d**	168	91	91 (*R*, *S*) [b]

5		**106e**	168	99	90 (*R*, *S*)
6		**106f**	168	95	91 (*R*, *S*)

[a] Solid KOH (85%) was used at -20°C. [b] Enantiopurity was determined via **69c**, as obtained from **106d.**

1-4. Application and confirmation of the absolute configuration of the newly induced chirality

Optically enriched α-methyl-α-allylmalonate (**106a**) was successfully hydrolyzed to the corresponding acid **119** by 50% KOH (**Scheme 64**). (*R*)-2-Methylbenzyl alcohol was also successfully recovered during the workup process. However, the selective hydrolysis of *tert*-butyl ester failed. The TFA acidic conditions hydrolyzed not only *tert*-butyl ester but also 2-methylbenzyl ester. Iodolactonization of **119** with iodine in the presence of sodium bicarbonate under a mixture of $CHCl_3$–H_2O successfully afforded the corresponding iodolactones **120** with 3:1 diastereoselectivity.

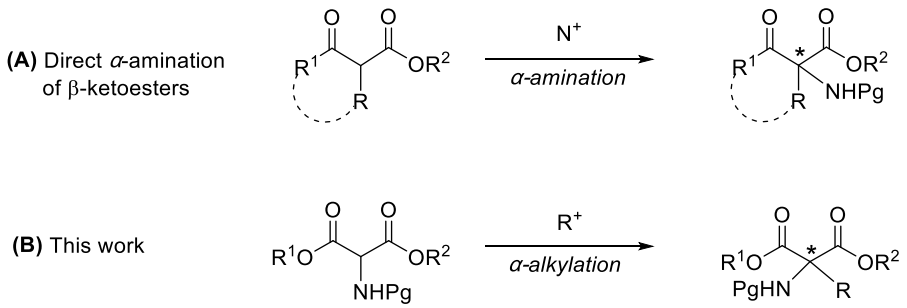


Scheme 64. Selective hydrolysis of **106a** and iodolactonization of **119**

2. α-Amido malonates

As mentioned in the introduction, the synthesis of optically active nitrogen-containing organic compounds is important in organic chemistry and medicinal chemistry due to their versatile biological activities and pharmaceutical applications [99]. Alkaloids are among the most representative nitrogen-containing natural products, showing various biological activities, and they are the nitrogen-containing molecules of most pharmaceutics.

During the last decade, significant progress has enabled the construction of α-amino quaternary carbon centers with impressive levels of enantioselectivity, using either organometal catalysis or organocatalysis [114]. Many enantioselective synthetic methods have been developed for α-amino-β-ketoesters via electrophilic α-amination of β-ketoesters (**Scheme 65**, **A**) [115, 117]. However, the enantioselective synthetic methods for the α-amino malonates have primarily been achieved by enzymatic desymmetrization [116] of the prochiral α-amino malonates, and only two cases exist as part of a study via chemical synthesis (each case was a malonate sample) [115t, 133].



Scheme 65. Two synthetic strategies for the preparation of the chiral α-amino malonates

2-1. Design of novel α-amido malonate as a substrate for phase-transfer catalytic alkylation

We planned to develop a new method for the synthesis of chiral α-quaternary amino malonates via the well-established enantioselective phase-transfer catalytic α-alkylation of malonates. Incorporation of an amino group into the α-position of the malonates followed by enantioselective α-alkylation under phase-transfer catalysis conditions as the key step in asymmetric induction would produce chiral α-amino malonates. This approach is a reverse strategy of the direct α-amination process (**Scheme 65**, **B**). Although the direct electrophilic α-aminations of the carbonyl compounds can directly afford amines or protected amines in a single step, there is a limited availability of electrophilic nitrogen sources. The advantage of the reverse strategy compared to direct electrophilic α-amination is that a variety of chiral compounds can be easily prepared by changing the alkylating reagent. Therefore, our research team attempted to develop a new and highly efficient enantioselective synthetic method for α-amino-α-alkylmalonates, which can be converted into valuable chiral building blocks bearing α-amino quaternary carbon centers.

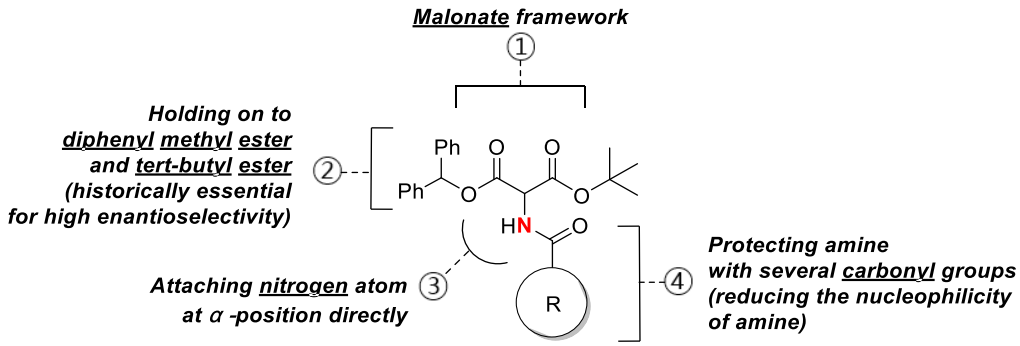
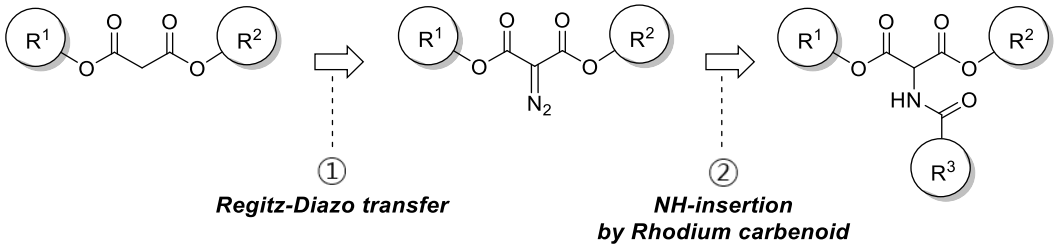


Figure 18. Design of a novel phase-transfer catalytic substrate, α-amido malonates

First, we had to design enantiotopic asymmetric α-amino malonates possessing non-nucleophilic nitrogen as substrates for phase-transfer catalytic α-alkylation. We installed the malonate skeleton as the basis of a molecular structure that could be readily modified by several chemical conversions of two different esters. It was thought that the ester portions must be diphenylmethylester and *tert*-butyl ester, which has been historically regarded as crucial for high enantioselectivity. Most importantly, the amine should not participate in the conversion as a nucleophile during the reaction. Thus, to reduce the nucleophilicity of the nitrogen attached at the α-position, protection with a carbonyl group was necessary (**Figure 18**).

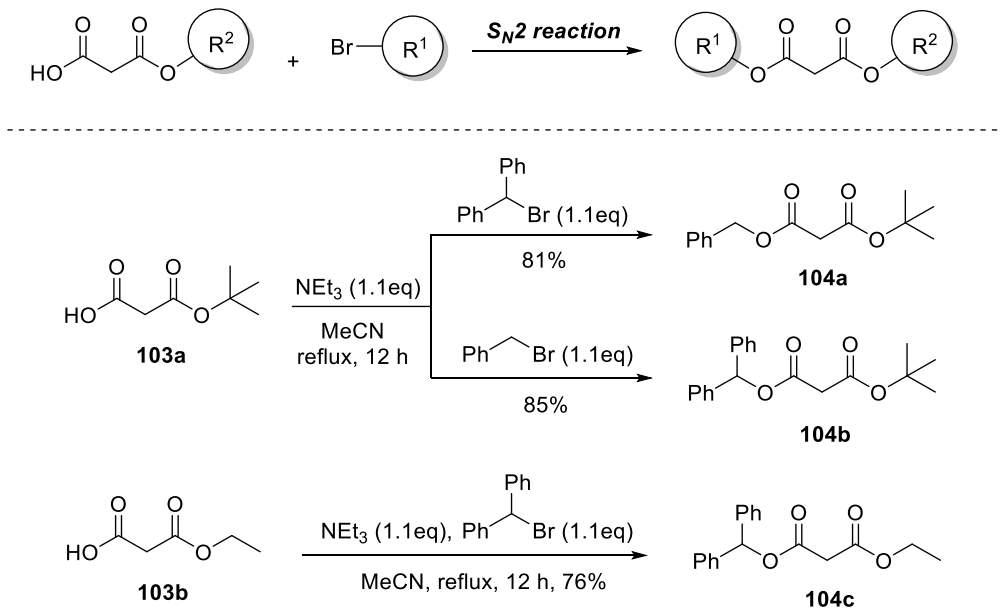
2-2. Synthetic routes for preparation of the α-amido malonates

Because several α-amido malonates were used as substrates in the phase transfer catalytic reaction, we obtained sufficient amounts of the designed molecules by the most efficient methods. As depicted in **Scheme 66**, the strategy of direct addition of nitrogen to the main malonate framework by the Regitz-Diazo transfer reaction followed by rhodium (II)-catalyzed nitrogen insertion was successful.



Scheme 66. Synthetic routes for preparation of the α-amido malonates

First, the malonic esters that contain α-methylene and the two desired ester groups were afforded by a simple and convenient bimolecular nucleophilic substitution reaction (**Scheme 67**). The commercially available hydrogen alkyl malonates **103a** and **103b** were substituted by α-bromodiphenylmethylene and benzyl bromide, furnishing the corresponding dialkyl malonates under basic conditions. When the reactions were stirred for excessive time, an undesired decarboxylation was discovered that increased gradually but could be minimized by shortening the reaction times to provide the desired product in a respectable yield. Therefore, during the best reaction time, benzyl *tert*-butyl malonate (**104a**), diphenylmethyl *tert*-butyl malonate (**104b**), and diphenylmethyl ethyl malonate (**104c**) were prepared successfully.

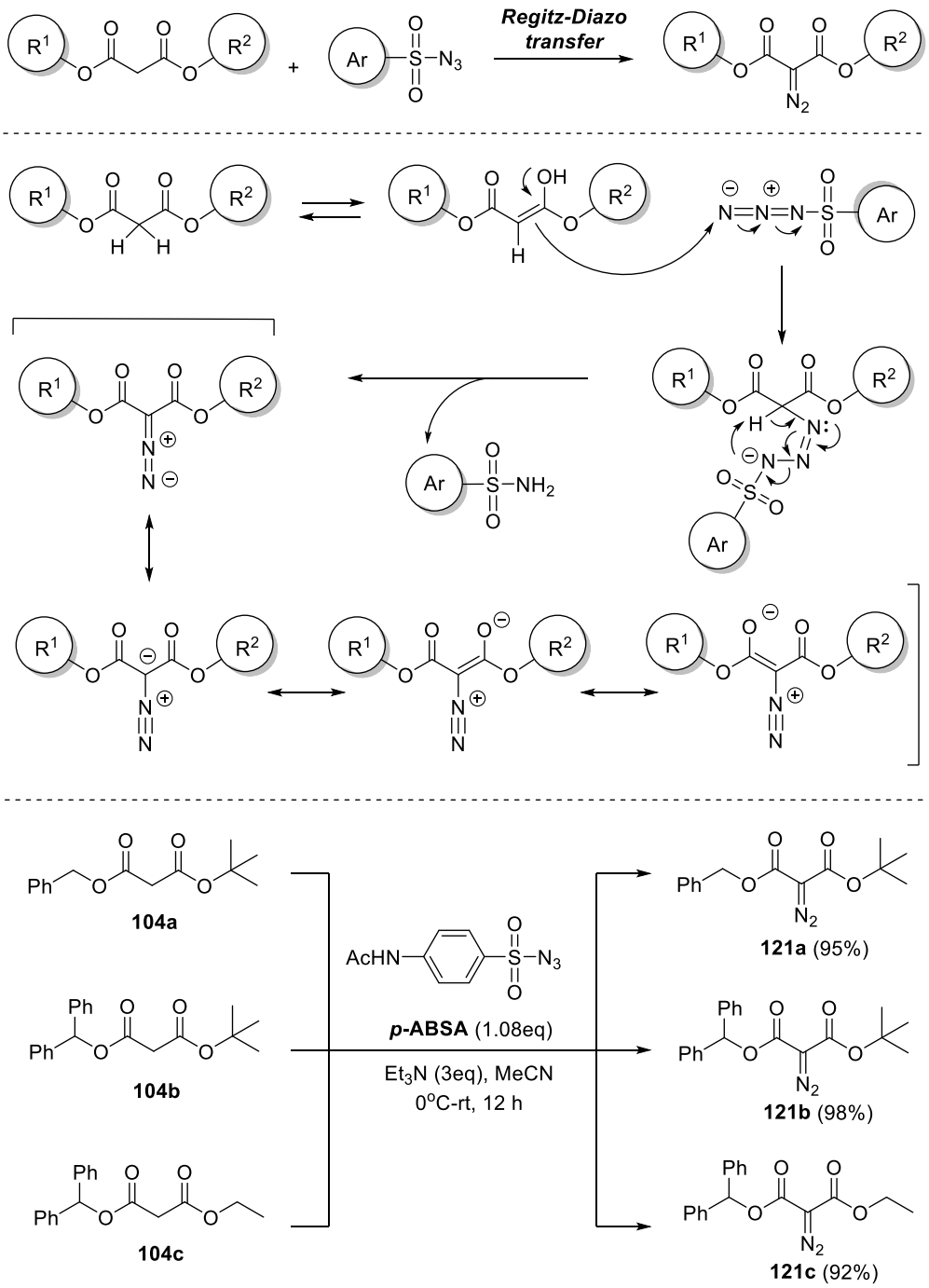


Scheme 67. Synthesis of dialkyl malonates by an S_N2 reaction

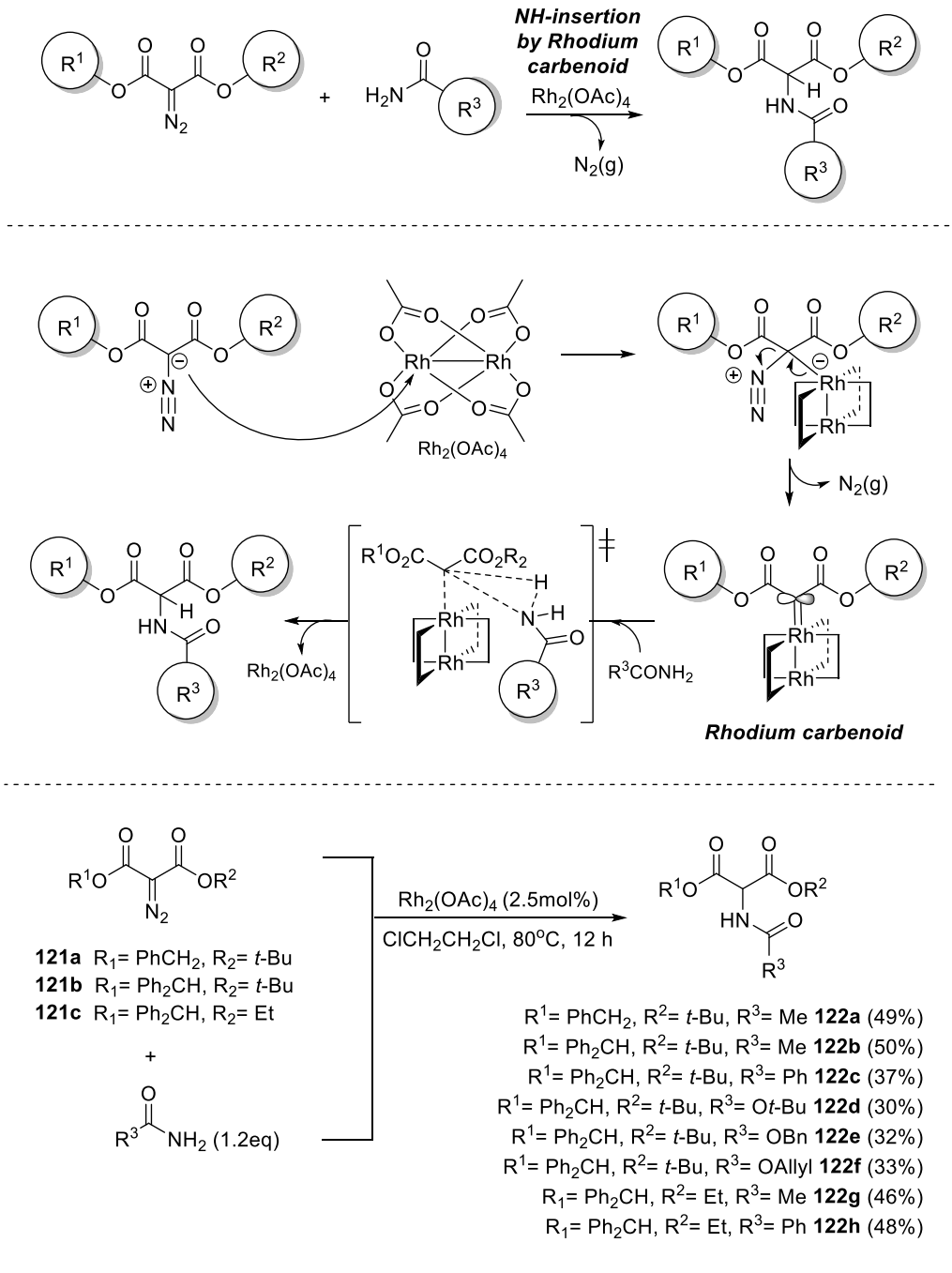
Second, dialkyl malonates **104** obtained using the above procedure were used in the Regitz-Diazo transfer reaction, which was diazotization using arenesulfonyl azide reacted in the presence of a base with a compound containing an active methylene group. In this reaction, the two hydrogen atoms of the active methylene group are replaced by a diazo group to form a diazo compound and an arenesulfonamide [134]. This reaction was a base-promoted transfer of a diazo group from an azide to an active methyl or methylene moiety of a substrate with electron-withdrawing groups. In this reaction, the common *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) was used as a source of nitrogens [135]. Note that this reaction of **104** had been performed nearly quantitatively without any byproducts, such as the azo-coupled compounds of the diazocompound with the starting material.

The concrete reaction pathway is illustrated in **Scheme 68**. Typically, α-methylene malonic ester is in rapid equilibrium with an enol tautomer, which contains a pair of doubly bonded carbon atoms adjacent to a hydroxyl group. Although the keto form predominates at equilibrium, the enol form plays a crucial role in starting the reaction. With the aid of an appropriate base, the enol form affords the corresponding deprotonated intermediate in the interconversion of the two forms, referred to as an enolate anion, and makes it a strong nucleophile. Then, the enol or enolate of α-methylene malonic ester attacks the terminal nitrogen of arenesulfonyl azide, forming the triazene-like intermediate. The capture of an α-proton followed by the consequent electron dispersion furnishes α-diazo malonate, which has certain resonance structures.

Using these mechanisms, the α-methylene malonates **104** were converted into the corresponding diazo malonates **121** with high yield in the presence of *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) and triethylamine under acetonitrile solvent at low temperature.



Scheme 68. Synthesis of α-diazo malonates by the Regitz-Diazo transfer reaction



Scheme 69. Synthesis of α-amido malonates by N-H insertion *via* rhodium carbenoid

Finally, we established a simple, general route to synthesize α-amido malonates from α-diazo malonates, and we determined that direct N-H insertion using the rhodium catalyst accompanied by releasing nitrogen gas produced the desired product. The subsequent N-H insertion of acetamide, benzamide or carbamates to **121** via a carbenoid in the presence of rhodium(II) acetate [$Rh_2(OAc)_4$] successfully provided the corresponding α-amido malonates **122**.

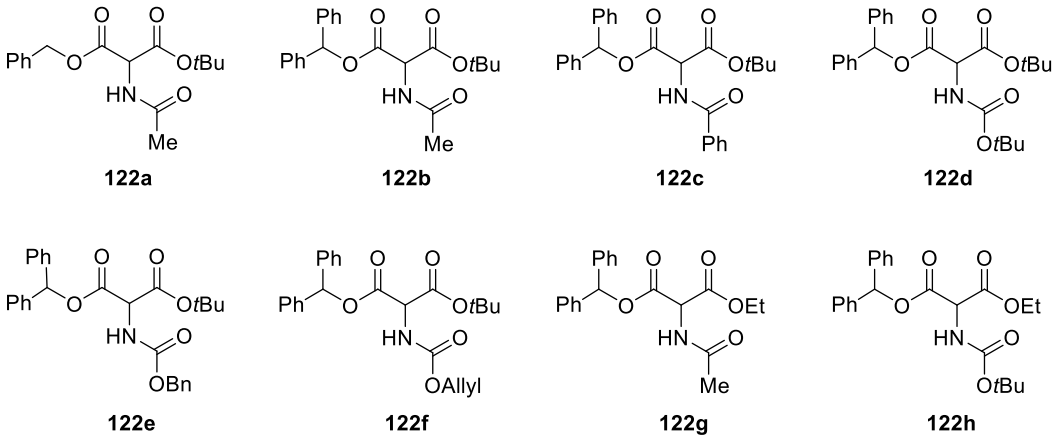
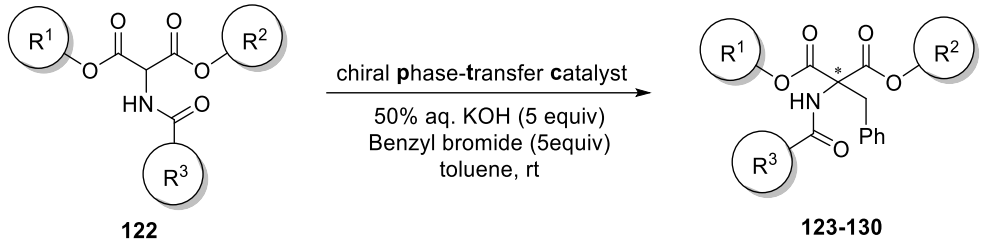


Figure 19. Prepared α-amido malonates as the phase-transfer catalytic substrates

Eight of the α-amido malonates **122** were prepared from various malonates **121** in only 2 steps and from the commercially available molecules **103** in 3 steps. Acetamide was inserted into the three types of malonate, **121a**, **121b**, and **121c**, producing the respective α-amido malonates **122a**, **122b**, and **122 g**. For the malonate simultaneously bearing the diphenylmethyl ester and the *tert*-butyl ester, the insertion of benzamide, *tert*-butyl carbamate, benzyl carbamate, allyl carbamate, and *tert*-butyloxy carbamate into **122b,** afforded the corresponding products with moderate yields (**Figure 19**).

2-3. Progress of optimization of phase-transfer catalytic alkylation

For the preliminary study, the substrate efficiency of the prepared α-amido malonates **122** was examined by α-benzylation under typical phase-transfer catalytic conditions, benzyl bromide (5.0 equiv.) and 50% KOH (aq., 5.0 equiv.) at room temperature in toluene, based on previous reports (**Scheme 70**) [83].

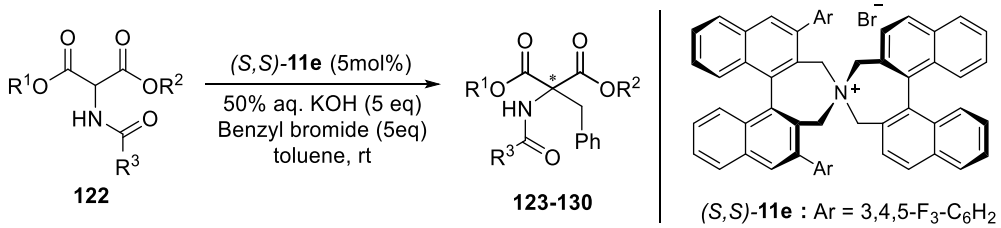


Scheme 70. Preliminary conditions of the asymmetric phase-transfer catalytic α-alkylation

Initially, the enantioselective phase-transfer catalytic α-benzylation of **122** was performed in the presence of the representative chiral quaternary ammonium salt (S,S)-**11e**. As shown in **Table 22**, all of the substrates successfully gave the corresponding α-benzylated products in high chemical yields with variable enantioselectivities in the presence of Maruoka's catalyst, (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide ((S,S)-**11e**). The substrates carrying diphenylmethyl ester and *tert*-butyl ester groups showed relatively higher enantioselectivities (entries **2**-**6**) than substrates carrying benzyl ester and the ethyl ester groups, respectively (entries **1**, **7**, and **8**), which is consistent with the previous report of the synthesis of chiral quaternary α,α-disubstituted malonates [83]. For the amide groups, the acetyl group gave better enantioselectivity than Bz and Boc. Additionally, the Cbz and Alloc groups afforded the same enantioselectivity, with lower chemical yield, as the acetyl

group. Therefore, our research group decided to optimize several reaction factors, such as the catalyst, base, temperature, and solvent performance with substrate **122b**.

Table 22. Efficacy comparison of the substrates combined with catalyst (*S*,*S*)-**11e**



entry	substrate	product	time (h)	yield (%)	ee (%)
1	**122a**	**123**	0.5	92	46
2	**122b**	**124i**	0.5	99	87
3	**122c**	**125**	0.5	94	82
4	**122d**	**126**	0.5	98	80
5	**122e**	**127**	0.5	85	87
6	**122f**	**128**	0.5	93	87
7	**122g**	**129**	0.5	95	59
8	**122h**	**130**	0.5	97	55

Note that *N*-benzylation was not observed as a minor product, even in the presence of excess base and benzyl bromide under the phase-transfer catalytic conditions. This result might be due to the properties of the amide, in which the geometry of the nitrogen atom is

trigonal planar (sp^2), not tetrahedral (sp^3). A large number of subsequent experiments have verified that amides should be best represented as the resonance hybrid of three resonance-contributing structures. In the unique third contributing structure of an amide, the lone pair on the nitrogen donates electron density to create a pi bond between carbon and nitrogen [136]. Additionally, the presence of a partial double bond in the resonance hybrid indicates restricted bond rotation around the C-N bond. In addition, because the lone pair on nitrogen is delocalized into the pi bond, it is less available to interact with Lewis acids, such as protons. Thus, amide nitrogens are not basic and nucleophilic. Therefore, due to the nitrogen lone pair electron delocalization, nitrogen did not participate in the phase-transfer reaction (**Figure 20**).

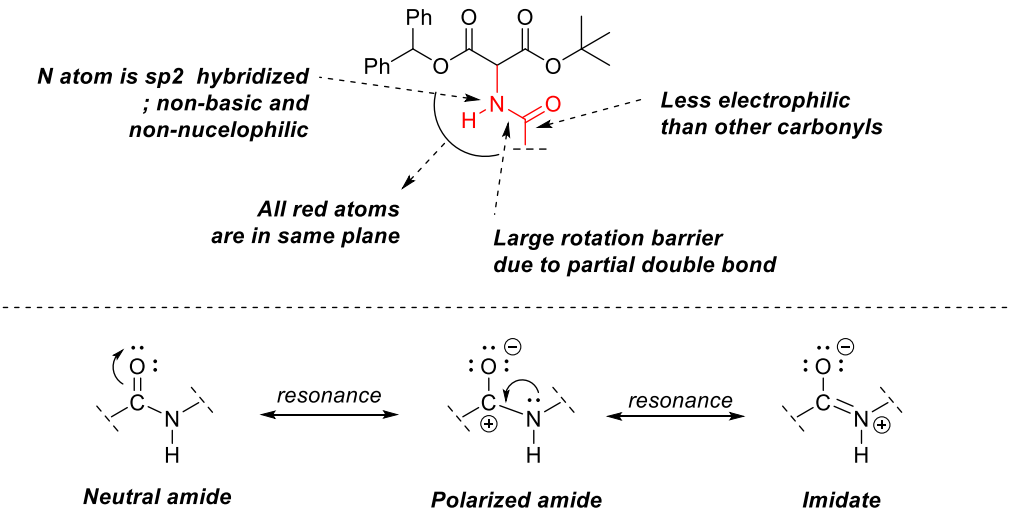


Figure 20. Characteristics of the amide structure

2-3-1. Phase-transfer catalyst optimization

To determine the best phase-transfer catalyst that interacts with substrate **122b** sterically and electronically, we prepared and synthesized representative catalysts in accordance with the literature or purchased them from the market. Selected examples of the phase-transfer catalysts that were used to determine the best combination of substrate and catalyst are displayed in **Figure 21**.

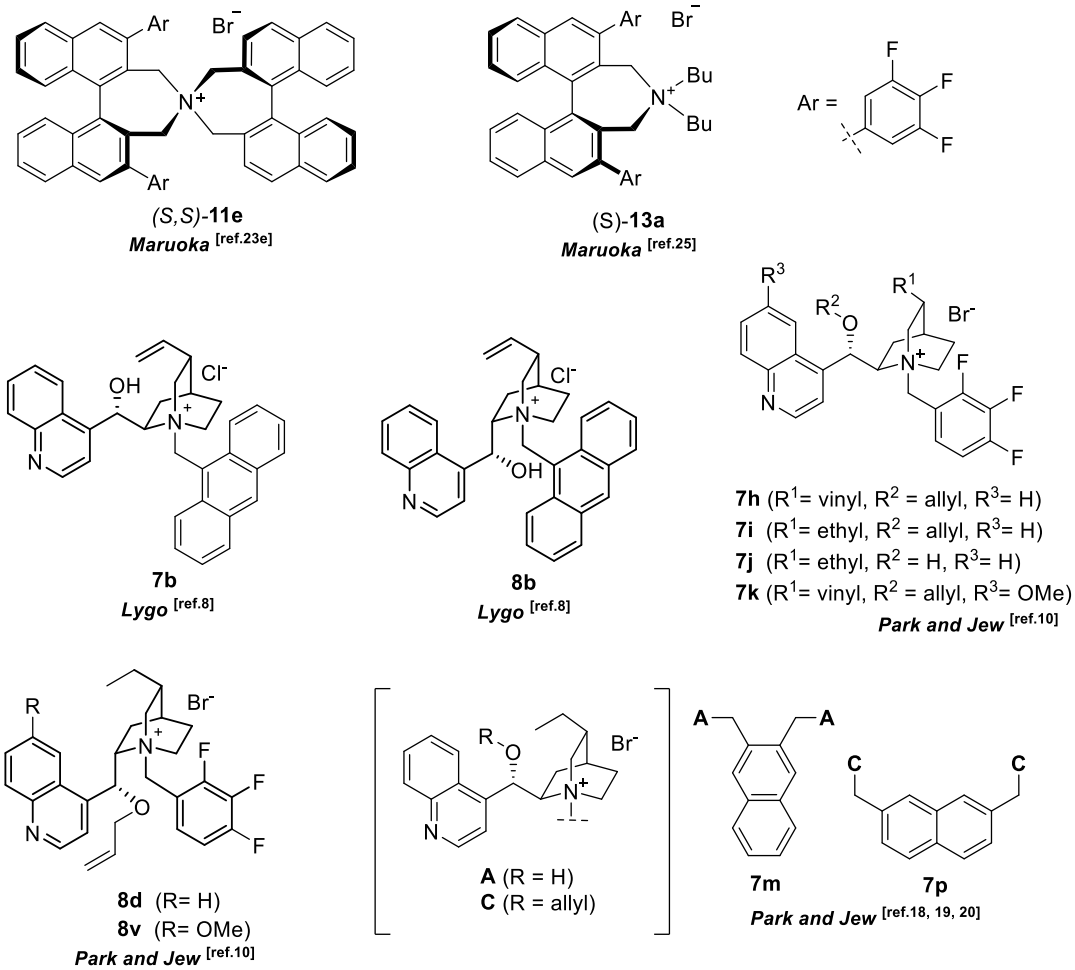
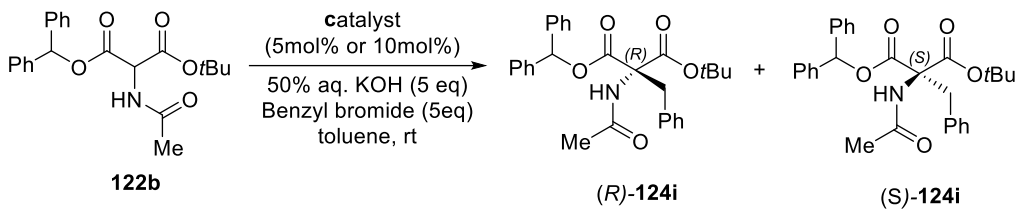


Figure 21. Selected examples of phase-transfer catalysts-II

Using the selected phase-transfer catalysts, we performed a screening experiment with substrate **122b**. Among the employed catalysts, (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide ((*S*,*S*)-**11e**) afforded the highest enantioselectivity in the asymmetric α-benzylation of **122b** (entry **1**). The other Maruoka catalyst, (*S*)-**13a**, which possesses flexible straight-chain butyl groups, gave reduced enantioselectivity (entry **2**). All of the *Cinchona*-derived catalysts, including Lygo's catalysts (**7b**, **8b**), resulted in significantly lower enantio selectivities than (*S*,*S*)-**11e**. Generally, the cinchonine-derived catalysts predominantly produced the (*R*)-configured α-benzyl product **124i** rather than the (*S*)-configuration. However, the catalysts derived from *cinchonidine* showed the opposite tendency, affording the major (*S*)-configured isomer. Regarding the dimeric catalysts that had a principal skeleton of cinchonine, a larger amount of (*S*)-**124i** was obtained than (*R*)-**124i**; the quantity of (*R*)-**124i** was so low that it was difficult to determine the tendency (**Table 23**).

Table 23. Screening of the phase-transfer catalysts combined with substrate **122b**

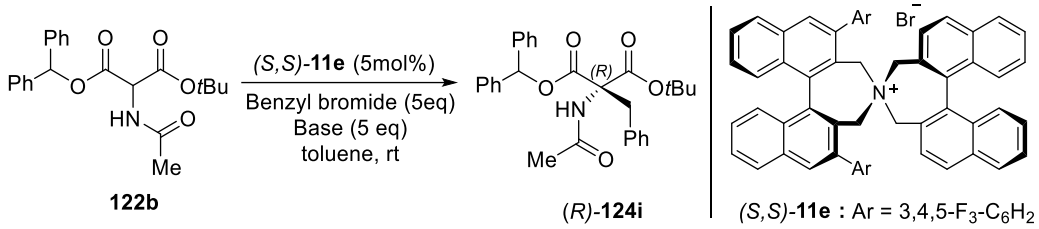


entry	catalyst (mol%)	time (h)	yield (%)	ee (%)
1	(*S*,*S*)-**11e** (5)	0.5	99	87(*R*)
2	(*S*)-**13a** (5)	0.5	95	47*(R)*
3	**7b** (10)	0.3	91	23*(R)*
4	**7h** (10)	0.3	95	20*(R)*
5	**7i** (10)	0.3	91	21*(R)*
6	**7j** (10)	0.3	93	23*(R)*
7	**7k** (10)	0.3	95	13*(R)*
8	**8b** (10)	0.3	92	19*(S)*
9	**8d** (10)	0.3	93	11*(S)*
10	**8v** (10)	0.3	96	12*(S)*
11	**7m** (5)	0.3	96	23*(S)*
12	**7p** (5)	0.3	95	18*(S)*

2-3-2. Base and temperature optimization

Next, the best substrate **122b** chosen to optimize the reaction conditions was used in the base and temperature screening experiment. Phase-transfer catalytic α-benzylation of **122b** was performed in the presence of the best catalyst, (*S*,*S*)-**11e**, under variable base and temperature conditions.

Table 24. Screening of the bases using substrate **122b** and catalyst (*S*,*S*)-**11e**

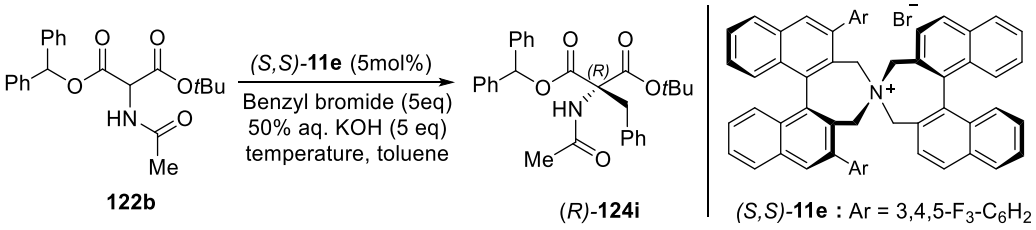


entry	base	time (h)	yield (%)	ee (%)
1	50% aq. NaOH	0.5	90	86
2	50% aq. KOH	0.5	99	87
3	50% aq. CsOH	0.5	97	86
4	solid NaOH	1	92	85
5	solid KOH[a]	0.3	91	84
6	solid K_2CO_3	12	93	85
7	solid Cs_2CO_3	12	85	82

[a] Anhydrous KOH with 95% purity was used

Generally, the chemical yield and enantioselectivity were not significantly dependent on the base conditions at room temperature (**Table 24**). However, the bases diluted by 50% with water showed a slightly higher enantioselectivity than the solid neat bases (entries **1-3** and **4-7**). When the solid KOH, which was available in the anhydrous condition, was used, the reaction was rapidly terminated in 30 minutes, whereas using a weak base (types of carbonate bases), the reaction required half a day to terminate. Based on these base screening results, we found the potential to upgrade the enantioselectivity by manipulating the temperature factors.

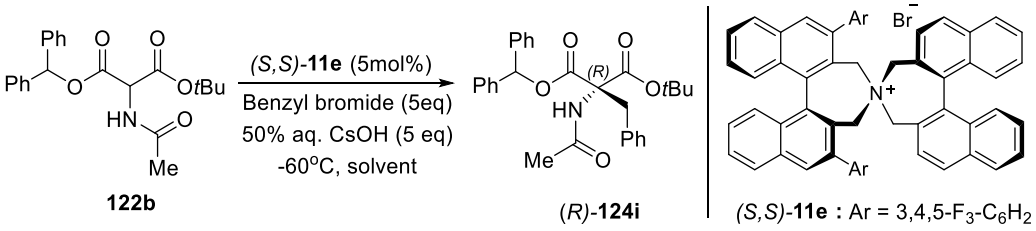
Table 25. Temperature screening using **122b** and (*S*,*S*)-**11e** under 50% KOH



entry	temperature (℃)	time (h)	yield (%)	ee (%)
1	room temperature	0.5	99	87
2	0	0.7	98	88
3	-20	2	96	91
4	-40	4	97	95
5	-60	23	92	94

Initially, the results using 50% aqueous KOH prompted us to decrease the temperature to -60℃ (**Table 25**). When the reaction was performed under the low-temperature condition, the reaction time increased due to the reduced molecular mobility. The reaction at -60℃ required nearly 1 day to convert the substrate **122b** into the product **124i** (entry **5**). In proportion to the long reaction time caused by the reduced temperature, the corresponding enantioselectivities increased as the temperature was reduced to -40℃. However, the reaction at -60℃ presented a slightly diminished ee value compared to -40℃. The reaction condition displayed in entry **4** of **Table 25** was considered to be the best condition until this process was performed.

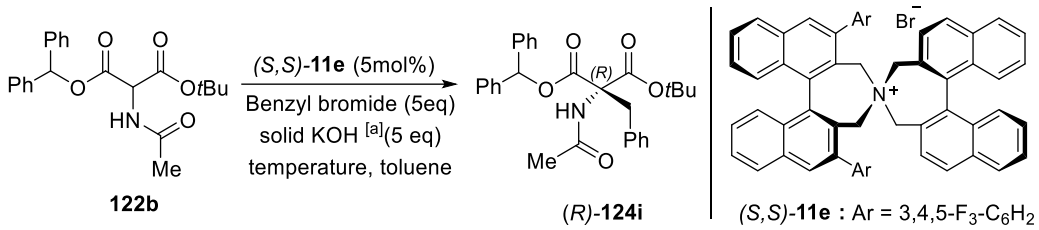
Table 26. Temperature screening using **122b** and (*S*,*S*)-**11e** under 50% CsOH



entry	temperature (°C)	time (h)	yield (%)	ee (%)
1	room temperature	0.5	97	86
2	0	0.7	96	89
3	-20	1	93	91
4	-40	2	94	94
5	-60	21	95	95

In the case of the temperature screening experiments with 50% aqueous CsOH, lower reaction temperatures clearly resulted in higher enantioselectivity (**Table 26**). In addition, the reaction time increased with decreasing temperature, resulting in a longer reaction time at –60℃ (entry **5**). In this system with 50% aqueous CsOH, the highest enantioselectivity was 95% at -60℃.

Table 27. Temperature screening using **122b** and (*S*,*S*)-**11e** under solid KOH



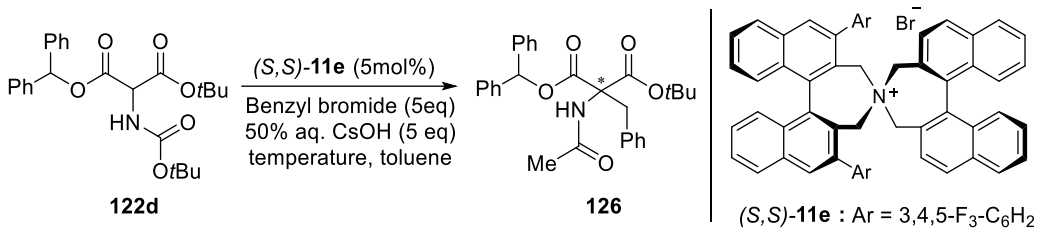
entry	temperature (ºC)	time (h)	yield (%)	ee (%)
1	room temperature	0.3	91	84
2	0	0.5	95	87
3	-20	1	73	88
4	-40	3.5	58	90

[a] Anhydrous KOH with 95% purity was used

From the base screening results in the presence of substrate **122b** and catalyst (*S*,*S*)-**11e** in **Table 24**, we selected solid KOH to confirm the efficacy of the solid base at low temperature (**Table 27**). A similar tendency was observed with the diluted base, the reaction time and the enantioselectivity. However, the reactions below -20℃ did not prove to be efficient because of the low chemical yield (entry **4**).

Additionally, substrate **112d** containing the *tert*-butyloxy carbonyl protected amine was used to perform temperature optimization with the expectation of increased enantio selectivity (**Table 28**). Although these reaction systems in the presence of **122d** and (*S*,*S*)-**11e** under 50% CsOH afforded the benzylated product **126** within an appropriate reaction time, the selectivities were unable to exceed the value of 90%. The results in **Table 28** revealed that substrate **122b** was, once again, more efficient than **122d**.

Table 28. Temperature screening using **122d** and (*S*,*S*)-**11e** under 50% CsOH

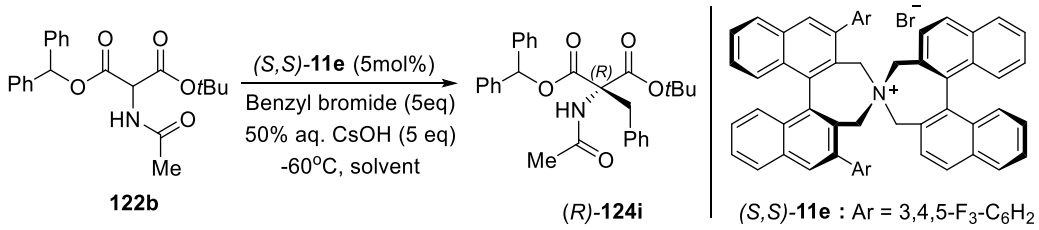


entry	temperature (°C)	time (h)	yield (%)	ee (%)
1	room temperature	0.3	81	80
2	0	2	81	85
3	-20	2.5	82	87
4	-40	3.5	84	90
5	-60	21	87	88

2-3-3. Organic solvent optimization

Using the optimized results on the substrates, phase-transfer catalysts, bases, and temperatures, a 50% aqueous KOH base under toluene at –40℃ was chosen as the optimized reaction condition, considering the enantioselectivity, chemical yield and reaction time (entry **4**, Table **25**). As the last phase of optimization, our research team performed a further screening process by varying the solvents under the best conditions identified prior to this stage (**Table 29**). When we added chloroform to the toluene reaction system, the enantioselectivities decreased to a certain degree, and changing the solvent to dichloromethane significantly decreased the ee value (entry **5**).

Table 29. Screening of the solvents using **122b** and (*S*,*S*)-**11e** under 50% CsOH

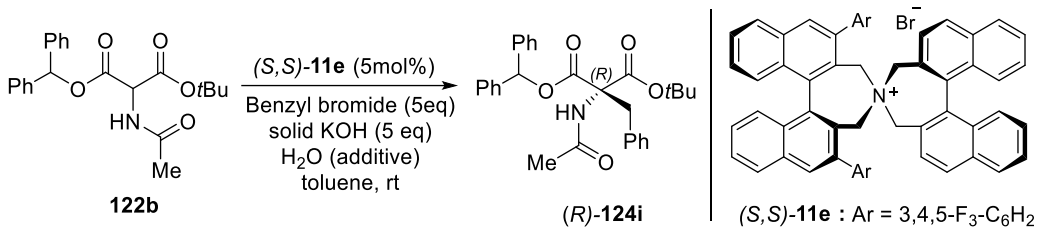


entry	temperature (ºC)	time (h)	yield (%)	ee (%)
1	toluene	21	95	95
2	toluene:$CHCl_3$ = 8:2	21	97	93
3	toluene:$CHCl_3$ = 7:3	21	96	90
4	xylene	21	84	85
5	CH_2Cl_2	21	88	56

2-3-4. Water content optimization

Recently, the important roles of water in the phase-transfer catalytic system were introduced [92]. To verify the best water content under our sufficiently optimized conditions, we conducted experiments increasing the water content to varying degrees. To manipulate the ratio of the water in the solvent, extra amounts of water were added.

Table 30. Changing water content under the phase-transfer catalytic reaction of **122b**-I

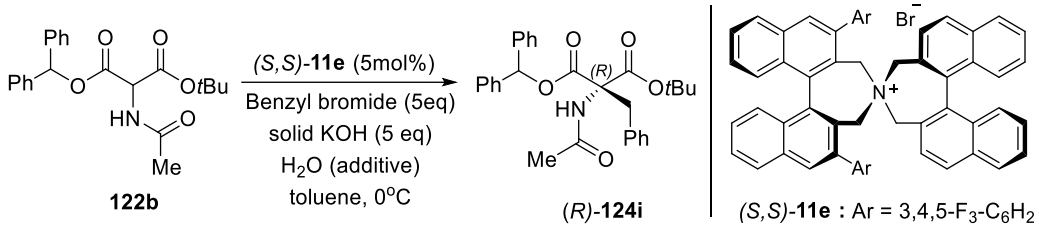


entry	H_2O content (%) [a]	time (h)	yield (%)	ee (%)
1	0.46 [b]	0.3	91	84
2	1.72 [b]	0.5	92	86
3	3	0.5	93	86
4	6	0.5	99	86
5	8	0.5	93	87
6	11 [c]	0.5	99	87
7	25	0.5	97	87

[a] The percentage of water in the solvent. [b] Water contributes 0.46% of the solvent due to the formation of water molecules after the reaction without any instant addition. [c] The solvent contains 1.72% water when using

85% solid KOH, considering that the remaining impurities contributing 15% are all in the water. [d] The solvent contains 11% water when using 50% aqueous KOH.

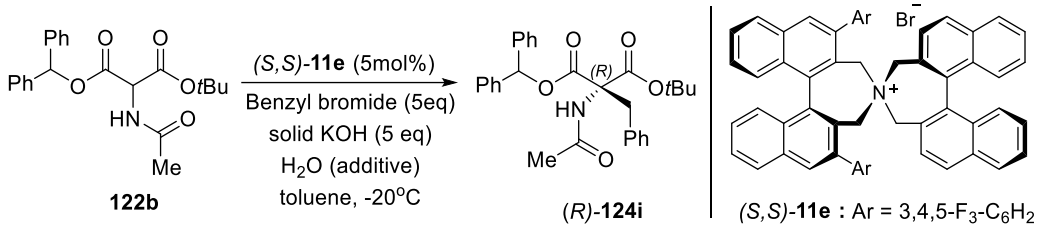
Table 31. Changing water content under the phase-transfer catalytic reaction of **122b**-II



entry	H_2O content (%) [a]	time (h)	yield (%)	ee (%)
1	0.46 [b]	0.5	95	87
2	1.72 [b]	0.5	96	88
3	3	0.5	89	89
4	6	0.5	93	88
5	8	0.7	98	88
6	11 [c]	0.7	98	88
7	25	0.7	95	89

[a] The percentage of water in the solvent. [b] Water contributes 0.46% of the solvent due to the formation of water molecules after the reaction without any instant addition. [c] The solvent contains 1.72% water when using 85% solid KOH, considering that the remaining impurities contributing 15% are all in the water. [d] The solvent contains 11% water when using 50% aqueous KOH.

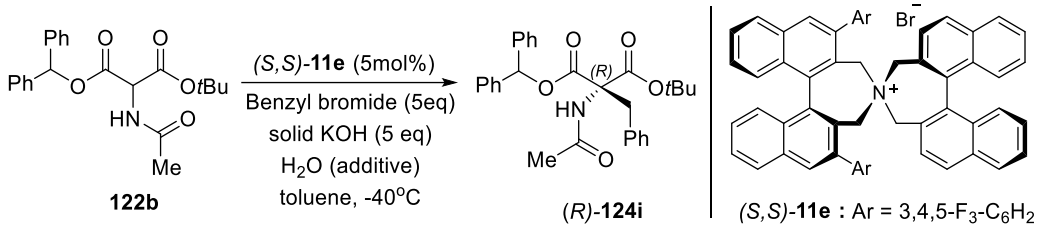
Table 32. Changing water content under the phase-transfer catalytic reaction of **122b**-III



entry	H_2O content (%) [a]	time (h)	yield (%)	ee (%)
1	0.46 [b]	1	73	88
2	1.72 [b]	2	93	92
3	3	2	92	92
4	6	2	96	91
5	8	2	90	91
6	11 [c]	2	96	91
7	25	2	93	91

[a] The percentage of water in the solvent. [b] Water contributes 0.46% of the solvent due to the formation of water molecules after the reaction without any instant addition. [c] The solvent contains 1.72% water when using 85% solid KOH, considering that the remaining impurities contributing 15% are all in the water. [d] The solvent contains 11% water when using 50% aqueous KOH.

Table 33. Changing water content under the phase-transfer catalytic reaction of **122b**-IV



entry	H_2O content (%) [a]	time (h)	yield (%)	ee (%)
1	0.46 [b]	3.5	58	89
2	1.72 [b]	4	97	94
3	3	4	93	95
4	6	4	93	95
5	8	4	94	94
6	11 [c]	4	97	95
7	25	4	99	94

[a] The percentage of water in the solvent. [b] Water contributes 0.46% of the solvent due to the formation of water molecules after the reaction without any instant addition. [c] The solvent contains 1.72% water when using 85% solid KOH, considering that the remaining impurities contributing 15% are all in the water. [d] The solvent contains 11% water when using 50% aqueous KOH.

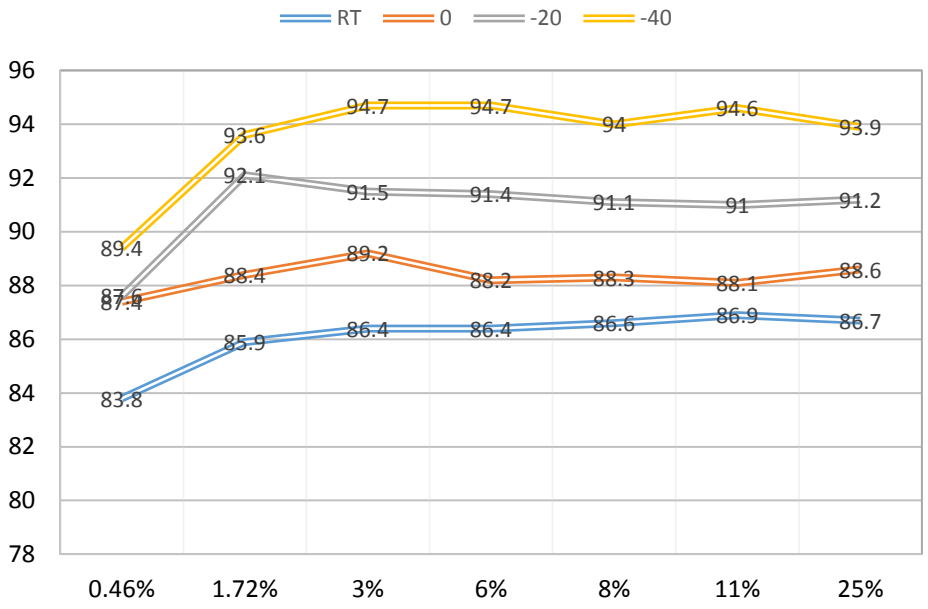


Figure 22. Summary of the water content optimization

As described in **Tables 30-33**, the water content was regulated by the injection of additional distilled water. Typically, the smallest amount of water was 0.46% due to the formation of water molecules during the reaction (entry **1**). The value of 1.72% in every entry **2** was interpreted from the use of 85% solid KOH, as the remaining 15% impurities are all in the water. When 50% aqueous KOH was used, the reaction system was considered to contain 11% water. To summarize these empirical results, we could obtain the tendency of the enantioselectivities regarding the increase in water content at every temperature. It was tentatively understood that when the reaction system was performed under a scarcity of water, it produced the non-chiral product until it generated water molecules from the progress of the reaction (**Figure 22**).

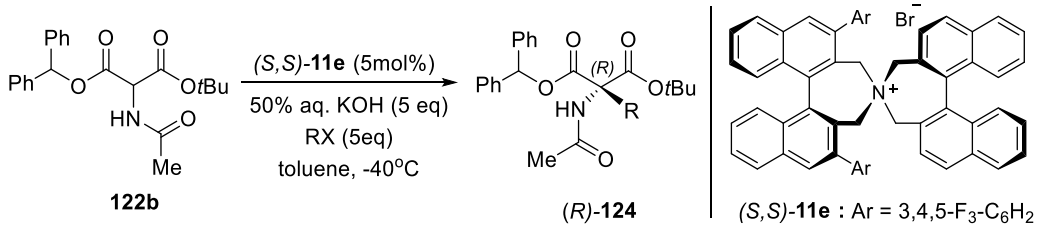
2-4. Scope and limitations of the α-amido malonates on phase-transfer catalytic alkylation

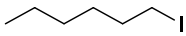
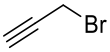
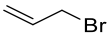
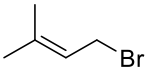
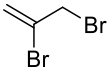
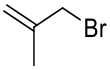
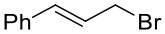
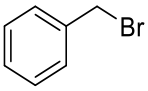
We analyzed the scope and limitations of the enantioselective phase-transfer catalytic alkylation of **122b** with various electrophiles performed under the final optimized reaction conditions, as shown in **Table 34**.

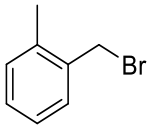
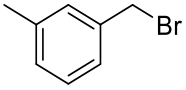
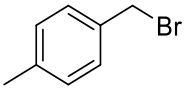
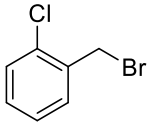
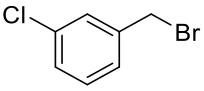
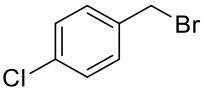
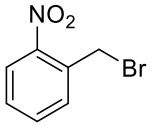
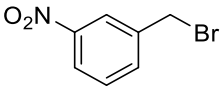
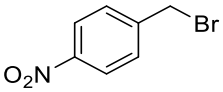
Most of the alkylating agents showed high enantioselectivities, except for certain examples. Using small alkylating agents, methyl iodide converted **122b** to the methylated product **124a** with relatively low enantioselectivity (entry **1**, 30% ee). Using the inactivated alkylating agent, normal hexyl iodide rarely substituted the substrate, even at 0℃, with only 26% chemical yield, also affording relatively low enantioselectivity (entry **2**, 65% ee). Propargyl bromide also resulted in lower enantioselectivities but demonstrated quantitative conversion (entry **3**, 54% ee). The allyl and prenyl moieties substituted the substrate with excellent chemical yields and with ee values in the upper 70% range (entry **4**, **5**). However, the substituted allyl group resulted in greater increases in enantioselectivity (entry **6**, 86% ee and entry **7**, 91% ee). When the bulkier phenyl adduct to allyl bromide, cinnamyl bromide, was used, a lower than expected selectivity was observed (entry **8**, 71% ee).

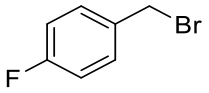
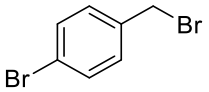
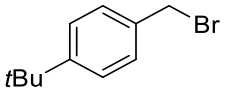
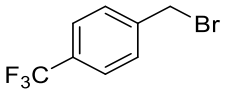
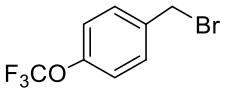
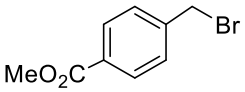
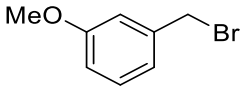
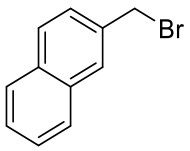
Generally, the substituted benzyl bromides used as electrophiles produced highly stereoselective products. In particular, all of the *para*-substituted benzyl groups presented an ee value above 95% (entries **12**, **15**, **19**, and **20-24**). We determined that the location of the substitution had a certain effect on their enantioselectivities. As described in entries **10-18**, the *ortho*-substituted compounds showed lower ee values than the *meta*- or *para*-substituted compounds.

Table 34. Asymmetric PTC α-alkylation of **122b** with various electrophiles I



entry	RX	product	time (h)	yield (%)	ee (%)
1 [a]	$H_3C—I$	**124a**	4	99	30
2 [a]		**124b**	4	26 [b]	65
3		**124c**	4	99	54
4		**124d**	4	99	76
5		**124e**	4	99	77
6		**124f**	4	98	86
7		**124g**	4	98	91
8		**124h**	4	99	71
9		**124i**	4	97	95

10		**124j**	4	99	91
11		**124k**	4	99	94
12		**124l**	4	99	97
13		**124m**	4	93	93
14		**124n**	4	84	90
15		**124o**	4	86	97
16		**124p**	4	99	78
17		**124q**	4	99	92
18		**124r**	4	99	96

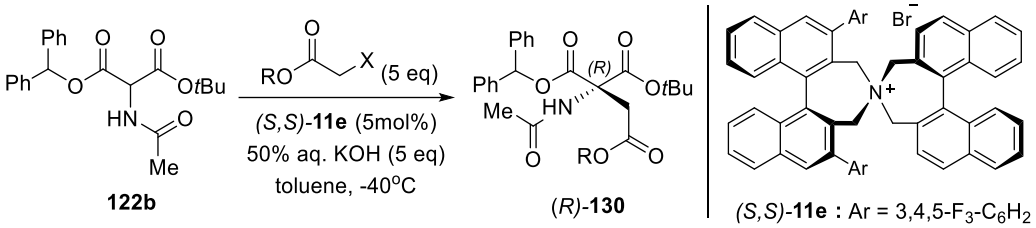
19		**124s**	4	99	96
20		**124t**	4	98	97
21		**124u**	4	99	95
22		**124v**	4	95	95
23		**124w**	4	91	95
24		**124x**	4	99	95
25		**124y**	4	96	94
26		**124z**	4	98	91

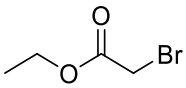
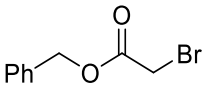
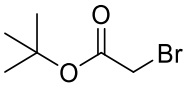
[a] Performed at 0℃. [b] Considering the recovery of the substrate, a 92% chemical yield was observed.

Based on the strength of various allylic and benzylic agents, we attempted to expand the scope of the method using different structural electrophiles. As shown in **Table 35**, ethyl

bromoacetate, benzyl bromoacetate, and *tert*-butyl bromoacetate were used under the optimized conditions. Although these stereoselectivities were relatively low, the experiment was useful as an effort to expand the scope of the method. In summary, the maximum enantioselectivity of 97% ee indicated that this reaction system was a very efficient enantioselective synthetic method for α-amino-α-alkylmalonates.

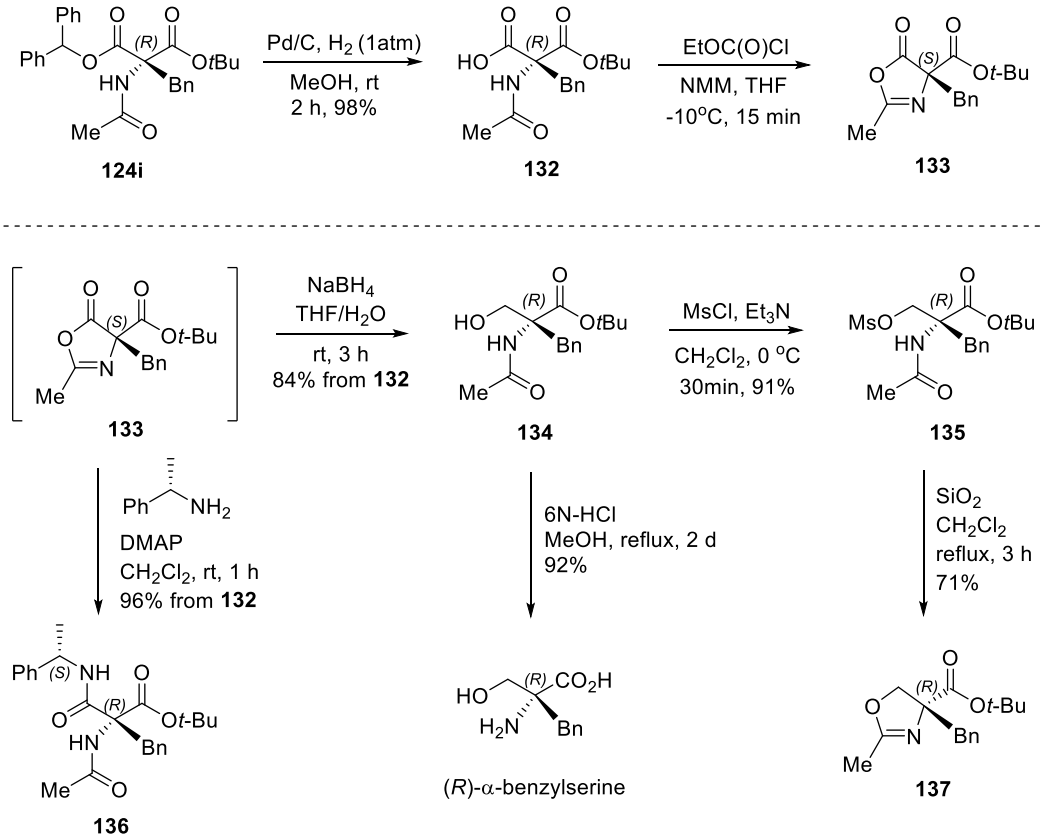
Table 35. Asymmetric PTC α-alkylation of **122b** with various electrophiles-II



entry	$ROCOCH_2X$	product	time (h)	yield (%)	ee (%)
1		**131a**	6	99	40
2		**131b**	6	99	40
3		**131c**	6	67	63

2-5. Application and confirmation of the absolute configuration of the newly induced chirality

The synthetic potential of the above method was demonstrated via the synthesis of an unnatural amino acid, α-benzylserine, from the optically active α-acetamido-α-benzylmalonate (**124i**), as exemplified in **Scheme 71**.



Scheme 71. Conversion of chiral compound **124i** to several optically active compounds

Catalytic hydrogenation of **124i** with Pd/C-H_2 in methanol afforded the corresponding mono acid **132**. The activation of **132** via a mixed anhydride using ethyl chloroformate in the presence of *N*-methylmorpholine (NMM) gave azlactone **133** via intramolecular

cyclization. The reduction of **133** using $NaBH_4$ provided the corresponding alcohol **134**. Finally, the acidic hydrolysis of **17** using 6 N HCl afforded (*R*)-α-benzylserine {$[\alpha]_D^{20}$ = –15.5 (*c* 1.0, H_2O); literature value [137] (*S*)-α-benzylserine, $[\alpha]_D^{20}$ = 16.4 (*c* 0.80, H_2O), 98% ee}. The mesylation of **134** followed by intramolecular cyclization in the presence of triethylamine under methylene chloride afforded oxazoline **137**. Additionally, opening of the ring of azlactone **133** was attempted via nucleophilic substitution of the amine. The treatment of (*R*)-methylbenzylamine with azlactone **133** in the presence of DMAP under methylene chloride successfully afforded amide **136**. To our knowledge, this procedure is the first systematic synthetic method for chiral α-amino-α-alkylmalonates.

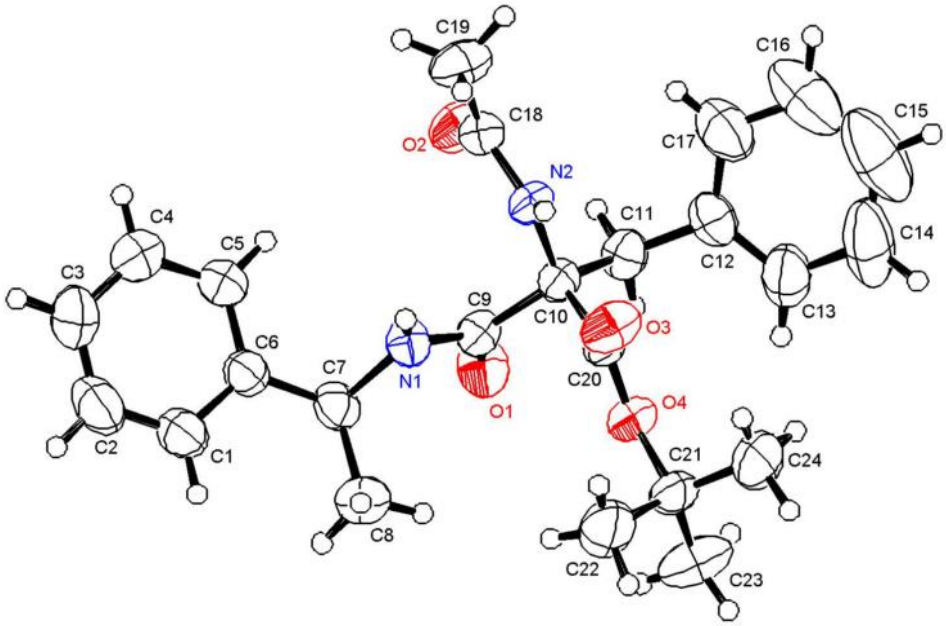


Figure 23. X-ray crystallographic structure of **136**

As shown in **Figure 23**, the X-ray crystallographic structure of compound **136** was obtained, showing the (*R*)-configured **136**. During the several modification steps from optically active **124i**, it was obvious that the chirality of **124i** did not change. Therefore, the induced chirality was also determined by the (*R*)-configuration. The other absolute configurations of the alkylated products in **Tables 34** and **35** were tentatively assigned as (*R)* based on the absolute configuration of **136** and the phase-transfer catalytic mechanism.

CONCLUSION

A new asymmetric synthetic method to prepare α,α-dialkylmalonates for the construction of a quaternary carbon center via phase-transfer catalytic alkylation was developed. Thirteen hydrolyzable substrates were designed and utilized in the optimization process to obtain higher stereoselectivities. Finally, we determined that the enantioselective α-alkylation of the 2-methylbenzyl *tert*-butyl α-methylmalonates under phase-transfer catalytic conditions in the presence of (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide ((*S*,*S*)-**11e**) afforded the corresponding α,α-dialkylmalonates in high chemical yields (up to 99%) and optical yields (up to 91% ee), which were then selectively hydrolyzed to malonic mono acids under basic conditions for the conversion to versatile chiral intermediates.

In addition, an enantioselective synthetic method for α-amido-α-alkylmalonates via phase-transfer catalytic α-alkylation was successfully developed. The asymmetric phase-transfer catalytic α-alkylations of diphenylmethyl-*tert*-butyl α-acetamidomalonate afforded the corresponding α-acetamido-α-alkylmalonates in high chemical yields (up to 99%) and optical yields (up to 97% ee).

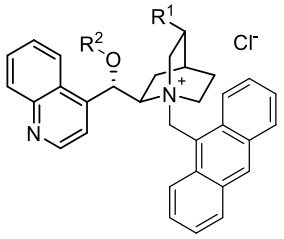
Our newly developed catalytic system provides an attractive synthetic method for versatile chiral building blocks, which can be readily converted to chiral target molecules containing α-amino quaternary carbon centers.

EXPERIMENTAL SECTION

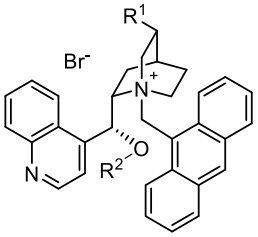
1. General Methods

1-1. Solvents and reagents

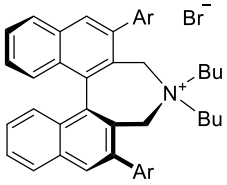
All reagents bought from commercial sources were used without further purification. Organic solvents were concentrated under reduced pressure using a Büchi rotary evaporator. As the commercially available KOH was a pellet type, solid KOH should be grinded to the powder form. 50% w/v aqueous KOH and 50% w/w aqueous CsOH was used as stock solution from markets. Some phase-transfer catalysts (**7b, 8c, 8t,** (*S,S*)**-11e,** (*R,R*)**-11e,** and **(S)-13a)** were purchased from the commercial source (Wako and Sigma Aldrich).



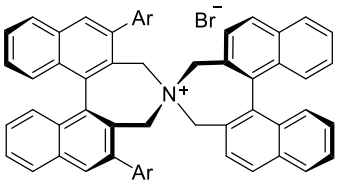
7b (R^1= vinyl, R^2 = H)
Lygo [ref.8]
Supplied from ***Sigma Aldrich***



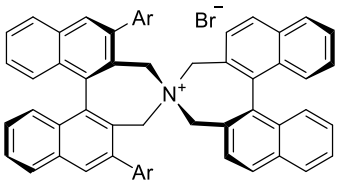
8c (R^1= vinyl, R^2 = allyl)
8t (R^1= ethyl, R^2 = allyl)
Corey [ref.8]
Supplied from ***Sigma Aldrich***



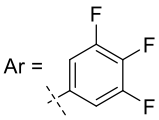
(S)-**13a**
Maruoka [ref.25]
Supplied from ***Sigma Aldrich***



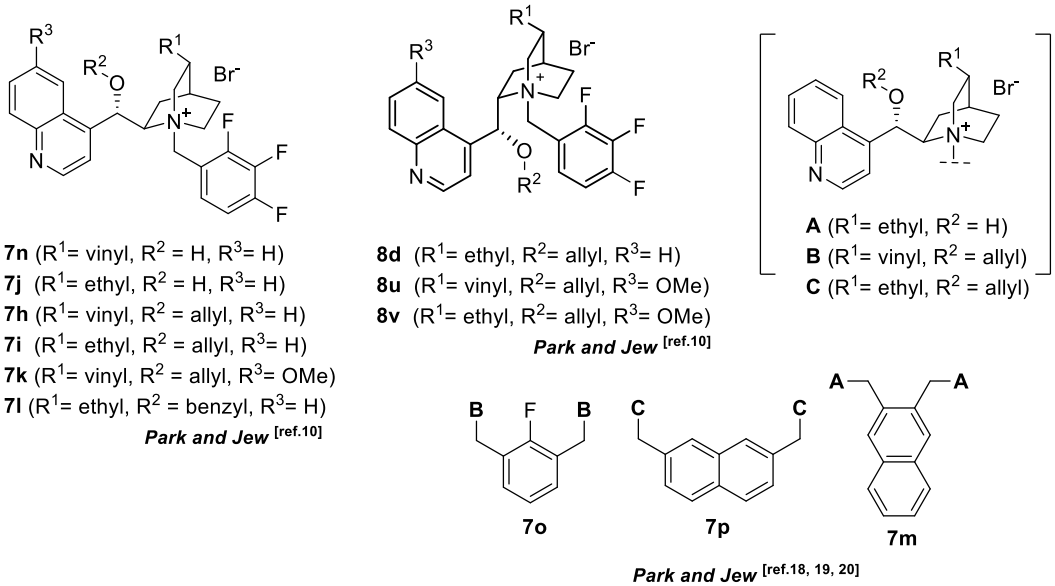
(S,S)-**11e**
Maruoka [ref.23e]
Supplied from ***Wako***



(R,R)-**11e**
Maruoka [ref.23e]
Supplied from ***Wako***



Other phase-transfer catalysts (**7h-p, 8d, 8u,** and **8v)** were prepared according to ther reported procedures as shown below.



1-2. Chromatography and HPLC

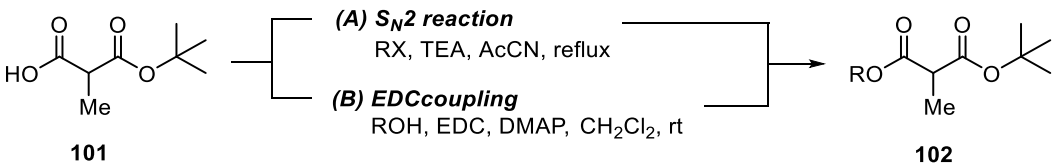
TLC analyses were performed using Merck precoated TLC plate (silica gel 60 GF_{254}, 0.25 mm). Flash column chromatography was performed using E. Merck Kieselgel 60 (230~400 mesh). Instrument (Hitachi, L-2130) and software (Hitachi, Version LaChrom 8908800-07) were used as HPLC apparatus. The enantiomeric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

1-3. Spectra 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 [500 MHz (^{1}H), 125 MHz (^{13}C)] spectrometer, 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. 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. Melting points were measured on a Büchi B-540 melting point apparatus and were not corrected. Optical rotations were measured on a JASCO polarimeter P-2000 series.

2. α-Alkyl malonate

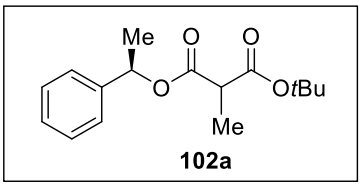
2-1. General procedures for α-methylmalonates



Procedure (A): Bimolecular nucleophilic substitutions of α-methyl-malonate mono-*tert*-butyl ester (**101**) with various alkyl halides in the presence of triethylamine resulting in the corresponding esterified *tert*-butyl α-methylmalonates (**102**). Triethylamine (0.88 ml, 6.31 mmol) was added to a stirred solution of α-methyl-malonate mono-*tert*-butyl ester (**101**, 1g, 5.74 mmol) in dichloromethane (19 ml). Alkyl halide (6.31 mmol) was added to the reaction mixture. After reflux average 15 hours, the reaction mixture was diluted with dichloromethane (100 ml), quenched with ammonium chloride (150 ml), washed with brine (150 ml), dried over anhydrous $MgSO_4$, filtered, and concentrated in *vacuo*. The residue was purified by column chromatography (silica gel, hexane: EtOAc = 30:1 ~40:1) to afford **102c, 102d, 102e, 102g, 102h, 102i,** and **102j,** respectively.

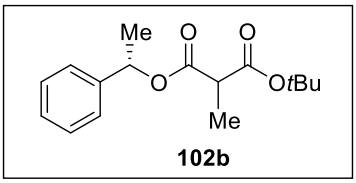
Procedure (B): Esterifications of α-methyl-malonate mono-*tert*-butyl ester (**101**) with various alcohols by EDC coupling reaction. α-Methyl-malonate mono-*tert*-butyl ester (**101**, 531 mg, 3.05 mmol) was dissolved with alkyl alcohol (3.96 mmol) in dichloromethane (7 ml) under argon air. 4-Dimethylaminopyridine (522 mg, 4.27 mmol) and 1-(3-dimethyl aminopropyl)-3-ethylcarbodiimide hydrochloride (760 mg, 3.96 mmol) was added to a stirred solution. After stirring for 15 hours, water (15 ml) was added to the reaction mixture. The reaction mixture was extracted with dichlromethane (2×100 ml), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane : EtOAc = 40:1) to afford **102a, 102b,** and **102f.**

1-*tert*-Butyl 3-((*R*)-1-phenylethyl) 2-methylmalonate (102a)



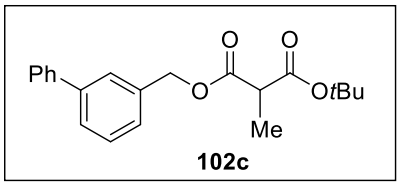
Following the general procedure (B), **102a** was obtained as pale yellow oil (81% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.34 ~ 7.25 (m, 5H), 5.94 ~ 5.88 (q, J = 6.6 Hz, 1H), 3.37 ~ 3.29 (ddd, J_1 = 14.5 Hz, J_2 = 7.3 Hz, J_3 = 4.8 Hz, 1H), 1.55 ~ 1.52 (d, J = 6.6 Hz, 3H), 1.41 ~ 1.33 (m, 12H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.67, 169.61, 169.13, 169.04, 141.16, 141.13, 128.44, 128.40, 127.93, 127.84, 126.09, 126.01, 81.55, 81.54, 73.01, 72.94, 47.38, 47.27, 27.90, 27.81, 27.75, 27.68, 21.97, 21.87, 13.44, 13.37 ppm; IR (KBr) 3064, 2936, 1732, 1604, 1496, 1370, 1294, 1175, 1108, 1064, 910, 849, 742 cm^{-1}; HRMS (FAB): calcd for $[C_{16}H_{23}O_4]^+$ ($[M+H]^+$): 279.1596, found: 279.1590. $[\alpha]^{25}_D$ = + 59.18 (c 1.0, $CHCl_3$).

1-*tert*-Butyl 3-((*S*)-1-phenylethyl) 2-methylmalonate (102b)



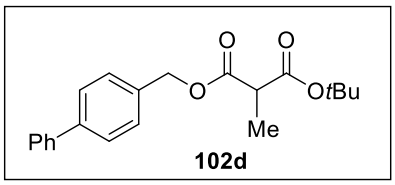
Following the general procedure (B), **102b** was obtained as pale yellow oil (79% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.25 ~ 7.17 (m, 5H), 5.87 ~ 5.80 (q, J = 6.5 Hz, 1H), 3.30 ~ 3.21 (m, 1H), 1.47 ~ 1.45 (d, J = 6.5 Hz, 1H), 1.38 ~ 1.26 (m, 12H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.55, 169.49, 169.02, 168.93, 141.10, 141.07, 128.37, 128.32, 127.85, 127.77, 126.01, 125.93, 81.41, 72.92, 72.85, 47.28, 47.18, 27.73, 27.66, 21.90, 21.80, 13.36, 13.29 ppm; IR (KBr) 2981, 1748, 1730, 1496, 1369, 1149, 1064, 996, 762 cm^{-1}; HRMS (FAB): calcd for $[C_{16}H_{23}O_4]^+$ ($[M+H]^+$): 279.1596, found: 279.1597. $[\alpha]^{25}_D$ = - 62.22 (c 1.0, $CHCl_3$).

1-([1,1'-Biphenyl]-3-ylmethyl) 3-*tert*-butyl 2-methylmalonate (102c)



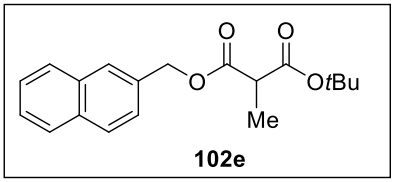
Following the general procedure (A), **102c** was obtained as pale yellow oil (63% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.60 ~ 7.54 (m, 4H), 7.47 ~ 7.33 (m, 5H), 5.28 ~ 5.18 (dd, J_1 = 17.0 Hz, J_2 = 12.3 Hz, 2H), 3.44 ~ 3.37 (dd, J_1 = 14.5 Hz, J_2 = 7.3 Hz, 1H), 1.42 ~ 1.39 (d, J = 7.3 Hz, 3H), 1.36 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.20, 168.96, 141.52, 140.62, 136.08, 128.88, 128.68, 127.37, 127.06, 127.03, 127.01, 81.58, 66.70, 47.08, 27.67, 13.45 ppm; IR (KBr) 3060, 2979, 2941, 1952, 1748, 1730, 1600, 1577, 1481, 1392, 1331, 1281, 1146, 1080, 1029, 958, 898, 799 cm^{-1}; HRMS (FAB): calcd for $[C_{21}H_{24}O_4]^+$ ($[M]^+$): 340.1675, found: 340.1677.

1-([1,1'-Biphenyl]-4-ylmethyl) 3-*tert*-butyl 2-methylmalonate (102d)



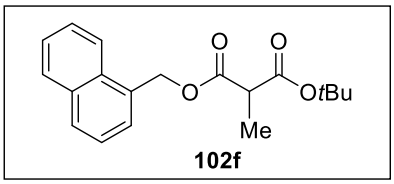
Following the general procedure (A), **102d** was obtained as pale yellow oil (83% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.60 ~ 7.56 (m, 4H), 7.47 ~ 7.33 (m, 5H), 5.26 ~ 5.16 (dd, J_1 = 17.0 Hz, J_2 = 12.3 Hz, 2H), 3.44 ~ 3.37 (q, J = 7.3 Hz, 1H), 1.42 ~ 1.39 (m, 12H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.20, 168.95, 141.19, 140.54, 134.55, 128.70, 128.68, 127.36, 127.16, 127.00, 81.58, 66.44, 47.10, 27.69, 13.43 ppm; IR (KBr) 3461, 3058, 2941, 1908, 1748, 1730, 1602, 1488, 1455, 1392, 1228, 1093, 1079, 1030, 947, 901, 848 cm^{-1}; HRMS (FAB): calcd for $[C_{21}H_{24}O_4]^+$ ($[M]^+$): 340.1675, found: 340.1665.

1-*tert*-Butyl 3-(naphthalen-2-ylmethyl) 2-methylmalonate (102e)



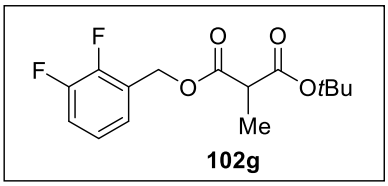
Following the general procedure (A), **102e** was obtained as a white solid (mp 53°C, 78% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.83 ~ 7.81 (m, 4H), 7.50 ~ 7.42 (m, 3H), 5.36 ~ 5.27 (m, 2H), 3.43 ~ 3.36 (dd, J_1 = 14.5 Hz, J_2 = 7.1 Hz, 1H), 1.40 ~ 1.35 (m, 12H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.25, 168.99, 133.07, 133.05, 132.96, 128.24, 127.86, 127.59, 127.30, 126.20, 126.18, 125.77, 81.59, 66.86, 47.12, 27.69, 13.47 ppm; IR (KBr) 3057, 2883, 1916, 1748, 1730, 1636, 1510, 1456, 1328, 1274, 1252, 1146, 1093, 964, 853, 750 cm^{-1}; HRMS (FAB): calcd for $[C_{19}H_{22}O_4]^+$ ($[M]^+$): 314.1518, found: 314.1516,

1-*tert*-Butyl 3-(naphthalen-1-ylmethyl) 2-methylmalonate (102f)



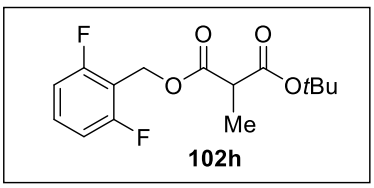
Following the general procedure (B), **102f** was obtained as pale yellow oil (65% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.04 ~ 8.00 (m, 1H), 7.90 ~ 7.82 (m, 2H), 7.57 ~ 7.40 (m, 4H), 5.66 ~ 5.57 (dd, J_1 = 4.9 Hz, J_2 = 12.4 Hz, 2H), 3.41 ~ 3.34 (q, J = 7.3 Hz, 1H), 1.39 ~ 1.37 (d, J = 7.1 Hz, 3H), 1.27 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.28, 168.95, 133.61, 131.55, 131.01, 129.27, 128.57, 127.51, 126.50, 125.84, 125.11, 123.50, 81.54, 65.09, 47.10, 27.56, 13.47 ppm; IR (KBr) 3460, 2979, 2291, 1747, 1730, 1600, 1512, 1329, 1281, 1146, 1093, 957, 901, 798, 647 cm^{-1}; HRMS (FAB): calcd for $[C_{19}H_{22}O_4]^+$ ($[M]^+$): 314.1518, found: 314.1518.

1-*tert*-Butyl 3-(2,3-difluorobenzyl) 2-methylmalonate (102g)



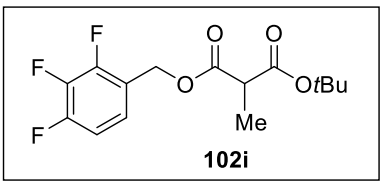
Following the general procedure (A), **102g** was obtained as pale yellow oil (90% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.15 ~ 7.00 (m, 3H), 5.25 ~ 5.15 (ddd, J_1 = 16.7 Hz, J_2 = 12.6 Hz, J_3 = 1.3 Hz, 2H), 3.39 ~ 3.32 (q, J = 7.3 Hz, 1H), 1.36 ~ 1.34 (m, 12H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.02, 168.79, [151.67 - 151.55, 149.21 - 149.08 (dd, J_1 = 247.0 Hz, J_2 = 12.3 Hz)], [150.22 - 150.09, 147.73 - 147.60 (dd, J_1 = 249.1 Hz, J_2 = 13.0 Hz)], 125.25 - 125.14 (m), 124.13 - 124.08 (d, J = 4.7 Hz), 124.06 - 124.02 (d, J = 4.8 Hz), 117.50 - 117.33 (d, J = 17 Hz), 81.76, 60.11, 60.11 - 60.04 (t, J = 3.5 Hz), 47.00, 27.67, 13.40 ppm; IR (KBr) 2982, 1752, 1631, 1458, 1370, 1331, 1222, 1094, 947, 899, 827, 785, 690 cm^{-1}; HRMS (FAB): calcd for $[C_{15}H_{19}F_2O_4]^+$ ($[M+H]^+$): 301.1251, found: 301.1252.

1-*tert*-Butyl 3-(2,6-difluorobenzyl) 2-methylmalonate (102h)



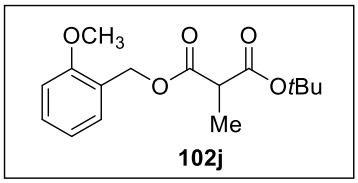
Following the general procedure (A), **102h** was obtained as pale yellow oil (96% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.29 ~ 7.19 (m, 1H), 6.87 ~ 6.78 (m, 2H), 5.16 (s, 2H), 3.30 ~ 3.23 (q, J = 7.3 Hz, 1H), 1.30 ~ 1.27 (d, J = 6.8 Hz, 12H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.04, 168.79, [163.13 - 163.05, 160.62 - 160.55 (dd, J_1 = 250.5 Hz, J_2 = 7.3 Hz)], 131.01 - 130.81 (t, J = 10.3 Hz), [111.43 - 111.37, 111.24 - 111.18 (dd, J_1 = 18.8 Hz, J_2 = 6.1 Hz)], 81.65, 54.60 - 54.52 (t, J = 4.1 Hz), 46.96, 27.63, 13.36 ppm; IR (KBr) 3078, 2943, 1752, 1658, 1596, 1370, 1275, 1238, 1147, 1060, 1029, 936, 730 cm^{-1}; HRMS (FAB): calcd for $[C_{15}H_{19}F_2O_4]^+$ ($[M+H]^+$): 301.1251, found: 301.1254.

1-*tert*-Butyl 3-(2,3,4-trifluorobenzyl) 2-methylmalonate (102i)



Following the general procedure (A), **102i** was obtained as pale yellow oil (95% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.15 ~ 7.07 (m, 1H), 7.00 ~ 6.90 (m, 1H), 5.22 ~ 5.12 (m, 2H), 3.39 ~ 3.31 (dd, J_1 = 14.5 Hz, J_2 = 7.3 Hz, 1H), 1.37 ~ 1.34 (d, J = 8.1 Hz, 12H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.03, 168.78, [152.66 - 152.63, 152.57 - 152.54, 150.17 - 150.14, 150.07 - 150.04 (ddd, J_1 = 249.9 Hz, J_2 = 9.9 Hz, J_3 = 3.0 Hz)] [151.27 - 151.24, 151.17 - 151.13, 148.76 - 148.73, 148.66, 148.63 (ddd, J_1 = 250.9 Hz, J_2 = 10.3 Hz, J_3 = 3.6 Hz)], [141.28 - 140.97, 138.77 - 138.47 (dt, J_1 = 250.6 Hz, J_2 = 15.2 Hz)], 124.39 - 124.23 (p, J = 4.2 Hz), [120.55 -120.51, 120.43 - 120.40, (dd, J_1 = 11.8 Hz, J_2 = 3.6 Hz), [112.18 - 112.14, 112.00 - 111.97 (dd, J_1 = 17.5 Hz, J_2 = 3.9 Hz)], 81.84, 59.88 - 59.82 (t. J = 2.8 Hz), 47.00, 27.71, 13.42 ppm; IR (KBr) 3471, 2942, 1753, 1733, 1638, 1517, 1490, 1370, 1330, 1235, 1094, 1030, 964, 881, 747, 679 cm^{-1}; HRMS (FAB): calcd for $[C_{15}H_{18}F_3O_4]^+$ ($[M+H]^+$): 319.1157, found : 319.1155.

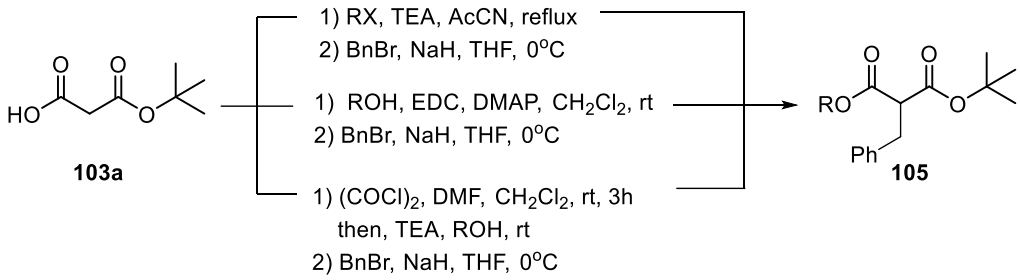
1-*tert*-Butyl 3-(2-methoxybenzyl) 2-methylmalonate (102j)



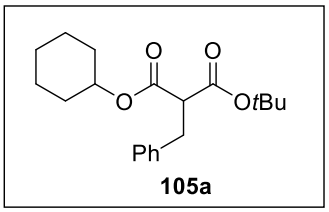
Following the general procedure (A), **102j** was obtained as pale yellow oil (88% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.27 ~ 7.19 (m, 2H), 6.89 ~ 6.79 (m, 2H), 5.15 (s, 2H), 3.75 (s, 3H), 3.35 ~ 3.28 (q, J = 7.3 Hz, 1H), 1.33 ~ 1.31 (t, J = 3.6 Hz, 12H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.39, 136.13, 157.40, 129.54, 129.50, 123.96, 120.32, 110.31, 81.50, 62.23, 55.30, 47.15, 27.73, 13.50 ppm; IR

(KBr) 3461, 2942, 1747, 1730, 1605, 1591, 1461, 1370, 1290, 1250, 1093, 1050, 1030, 954, 929, 755 cm^{-1}; HRMS (FAB): calcd for $[C_{16}H_{22}O_5]^+$ ($[M]^+$): 294.1467, found: 294.1472.

2-2. General procedures for α-benzylmalonates



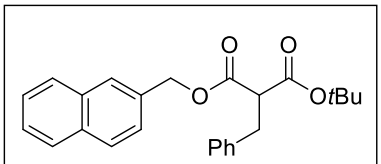
<u>1-(*tert*-Butyl) 3-cyclohexyl 2-benzylmalonate (105a)</u>



Oxalyl chloride (1.3 ml, 15.0 mmol) was added to a stirred solution of mono *tert*-butyl hydrogen malonate (**103a,** 2g, 12.5 mmol) in dichloromethane (60 ml). One or two drops of *N*,*N*-dimethylformamide (1.2 mmole) was added to the reaction mixture. After stirring for 3 hours at room temperature with releasing CO and CO_2 gas, cyclohexanol (1.6 mL, 15.0 mmole) and triethylamine (2.0 mL, 13.8 mmole) was added to the reaction mixture. After 5 hours, the reaction mixture was diluted with dichloromethane (100 ml), washed with ammonium chloride (100 ml), extracted with brine (150 ml) twice, dried over anhydrous $MgSO_4$, filtered, and concentrated in *vacuo*. The residue (approximately 1.9 g, 7.8 mmole) was solvated with anhydrous THF (20mL) under Ar atmosphere at 0°C. Sodium hydride (187mg, 7.8 mmole) was added to the reaction

mixture to activate the substrate. Then, benzyl bromide (0.93mL, 7.8 mmole) was added very slowly. After 5 hours, the reaction mixture was diluted with EtOAc (200 ml), washed with ammonium chloride (150 ml), extracted with brine (200 ml) twice, dried over anhydrous $MgSO_4$, filtered, concentrated, and purified by column chromatography (silica gel, hexane: EtOAc = 30 : 1) to afford **105a** as yellow oil (982 mg, 20%). ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.26 ~ 7.17 (m, 5H), 4.80~ 4.76 (m, 1H), 3.56 ~ 3.53 (t, *J* = 7.8 Hz, 1H), 3.17 ~ 3.16 (d, *J* = 7.8 Hz, 2H), 1.80 ~ 1.22 (m, 10H), 1.40 (s, 9H) ppm; ^{13}C-NMR (150 MHz, $CDCl_3$) δ 168.50, 167.92, 138.09, 128.78, 128.25, 126.43, 81.58, 73.32, 54.76, 34.52, 31.22, 27.73, 25.20, 23.42 ppm; IR (KBr) 3030, 2937, 2860, 1744, 1730, 1496, 1454, 1392, 1368, 1278, 1233, 1146, 1122, 1082, 1054, 1038, 910, 847, 748, 700 cm^{-1}; HRMS (FAB): calcd for $[C_{20}H_{29}O_4]^+$ ($[M+H]^+$): 333.2066, found: 333.2070.

<u>1-(*tert*-Butyl) 3-(naphthalen-2-ylmethyl) 2-benzylmalonate (105b)</u>

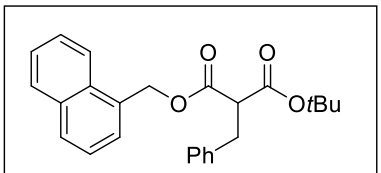


105b

Triethylamine (0.94 ml, 6.7 mmol) was added to a stirred solution of mono *tert*-butyl hydrogen malonate (**103a,** 900mg, 5.6 mmol) in acetonitrile (20 ml). 2-(Bromomethyl) naphthalene (1.5g, 6.7 mmol) was added to the reaction mixture. After reflux for 1 day, the reaction mixture was evaporated and diluted with EtOAc (200 ml), quenched with ammonium chloride (150 ml), washed with brine (150 ml), dried over anhydrous $MgSO_4$, filtered, and concenturated in *vacuo*. The residue (approximately 1.4 g, 4.7 mmole) was solvated with anhydrous THF (15 mL) under Ar atmosphere at 0°C. Sodium hydride (111 mg, 4.7 mmole) was added to the reaction mixture to activate the substrate. Then, benzyl bromide (0.55 mL, 4.7 mmole) was added very slowly. After 5 hours, the reaction mixture was diluted with EtOAc (100 ml), washed

with ammonium chloride (80 ml), extracted with brine (100 ml) twice, dried over anhydrous $MgSO_4$, filtered, concentrated, and purified by column chromatography (silica gel, hexane: EtOAc = 30 : 1) to afford **105b** as pale yellow oil (515 mg, 28%). ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.83 ~ 7.79 (m, 3H), 7.74 (s, 1H), 7.49 ~ 7.46 (m, 2H), 7.36 ~ 7.34 (dd, J_1 = 8.4 Hz, J_2 = 1.7 Hz, 1H), 7.24 ~ 7.17 (m, 5H), 5.32 ~ 5.24 (dd, J_1 = 22.2 Hz, J_2 = 12.3 Hz, 2H), 3.67 ~ 3.64 (t, J = 7.9 Hz, 1H), 3.22 ~ 3.20 (d, J = 7.9 Hz, 2H), 1.32 (s, 9H) ppm; ^{13}C-NMR (150 MHz, $CDCl_3$) δ 169.08, 167.71, 137.91, 133.10, 132.87, 128.85, 128.41, 128.27, 127.94, 127.65, 127.36, 126.61, 126.24, 125.81, 82.02, 67.02, 54.69, 34.68, 27.72 ppm; IR (KBr) 2978, 2931, 1747, 1729, 1456, 1369, 1220, 1143, 913, 772, 700 cm^{-1}; HRMS (FAB): calcd for $[C_{25}H_{26}O_4]^+$ ($[M]^+$): 390.1831, found: 390.1825.

<u>1-(*tert*-Butyl) 3-(naphthalen-1-ylmethyl) 2-benzylmalonate (105c)</u>

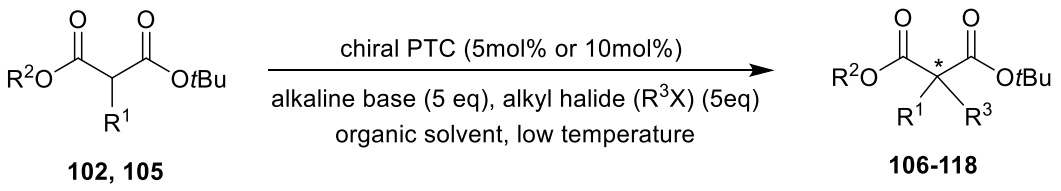


105c

Mono *tert*-butyl hydrogen malonate (**103a,** 931 mg, 5.8 mmol) was dissolved with 1-naphthalene methanol (1.2g, 7.6 mmol) in dichloromethane (10 ml) under Ar atmosphere. 4-Dimethylaminopyridine (1.0 g, 8.2 mmol) and 1-(3-dimethyl aminopropyl)-3-ethylcarbodiimide hydrochloride (1.5g, 7.6 mmol) was added to a stirred solution. After stirring for 12 hours, water (10 ml) was added to the reaction mixture. The reaction mixture was extracted with dichlromethane (2×100 ml), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue (approximately 1.1 g, 3.7 mmole) was solvated with anhydrous THF (15 mL) under Ar atmosphere at 0°C. Sodium hydride (88 mg, 3.7 mmole) was added to the reaction mixture to activate the substrate. Then, benzyl bromide (0.43 mL, 3.7 mmole) was added very slowly. After 5 hours, the reaction mixture was diluted with EtOAc (100 ml), washed with

ammonium chloride (80 ml), extracted with brine (100 ml) twice, dried over anhydrous $MgSO_4$, filtered, concentrated, and purified by column chromatography (silica gel, hexane: EtOAc = 30 : 1) to afford **105c** as pale yellow oil (702 mg, 31%). ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.90 ~ 7.82 (m, 3H), 7.52 ~ 7.40 (m, 4H), 7.28 ~ 7.15 (m, 5H), 5.61 ~ 5.52 (dd, J_1 = 21.9 Hz, J_2 = 12.4 Hz, 2H), 3.64 ~ 3.61 (t, J = 7.9 Hz, 1H), 3.19 ~ 3.18 (d, J = 7.9 Hz, 2H), 1.23 (s, 9H) ppm; ^{13}C-NMR (150 MHz, $CDCl_3$) δ 169.11, 167.66, 137.91, 133.65, 131.59, 130.92, 129.34, 128.83, 128.60, 128.38, 127.59, 126.58, 125.89, 125.17, 123.54, 81.98, 65.27, 54.68, 34.67, 27.61 ppm; IR (KBr) 2977, 1930, 1747, 1730, 1454, 1369, 1233, 1142, 1004, 970, 846, 799, 775, 699 cm^{-1}; HRMS (FAB): calcd for $[C_{25}H_{26}O_4]^+$ ($[M]^+$): 390.1831, found: 390.1830.

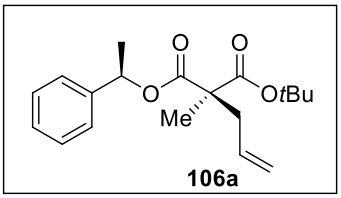
2-3. General procedure of asymmetric phase-transfer catalytic α-alkylation



Alkyl halide (5 equiv.) was added to a solution of 1-*tert*-butyl 3-alkyl (R^2) 2-alkyl (R^1) malonate (**102** and **105**, 30mg) and phase transfer catalyst (5-10 mol%) in organic solvent at room temperature. At the designated low temperature, alkaline base (5 equiv.) was added to the reaction mixture and stirred until the starting material disappeared. After completion of the reaction, the reaction mixture was diluted with ethyl acetate (20 ml), washed with brine (10 mL x 2), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The

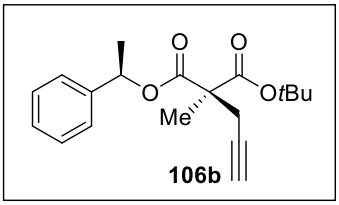
residue was purified by column chromatography (silica gel, hexane : EtOAc = 40 : 1) to afford desired chiral product.

(*S*)-1-*tert*-Butyl 3-((*R*)-1-phenylethyl) 2-methyl-2-allylmalonate (106a)



Following the general eanatioselective PTC alkylation procedure from **102a** with allyl bromide, **106a** was obtained as pale yellow oil (99% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.28 ~ 7.16 (m, 5H), 5.87 ~ 5.80 (q, J = 6.6 Hz, 1H), 5.70 ~ 5.45 (m, 1H), 5.06 ~ 4.8 (m, 2H), 2.52 ~ 2.46 (m, 2H), 1.47 ~ 1.44 (dd, J_1 = 6.1 Hz, J_2 = 2.0 Hz, 3H), 1.27 ~ 1.23 (m, 12H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.40, 170.79, 141.18, 132.78, 128.42, 127.93, 126.21, 118.90, 81.45, 72.94, 53.81, 40.06, 27.73, 22.00, 19.65 ppm; IR (KBr) 3460, 2980, 2934, 1953, 1729, 1641, 1586, 1496, 1392, 1369, 1250, 1207, 1146, 1030, 920, 848 cm^{-1}; HRMS (FAB) : calcd for $[C_{19}H_{27}O_4]^+$ ($[M+H]^+$): 319.1909, found: 319.1909. The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralcel OJ-H, hexane : 2-propanol = 99: 1, flow rate = 1.0 ml/min, 23 ℃, λ = 210 nm, retention time ; Major isomer(*S*) 5.3 min, minor isomer(*R*) 6.6 min, 81% ee, $[\alpha]^{25}_{D}$ = + 57.40 (*c* 1.0, $CHCl_3$).

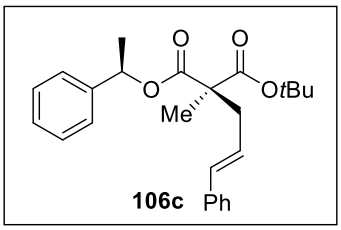
(*S*)-1-*tert*-Butyl 3-((*R*)-1-phenylethyl) 2-methyl-2-propynlmalonate (106b)



Following the general eanatioselective PTC alkylation procedure from **102a** with progargyl bromide, **106b** was obtained as pale yellow oil (80% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.35 ~ 7.23 (m, 5H), 5.95 ~ 5.88 (qd, J_1 =

6.6 Hz, J_2 = 2.9 Hz, 1H), 2.74 ~ 2.71 (dd, J_1 = 7.2 Hz, J_2 = 2.7 Hz, 2H), 1.55 ~ 1.52 (dt, J_1 = 17.0 Hz, J_2 = 2.7 Hz, 1H), 1.54 ~ 1.46 (m, 6H), 1.35 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.39, 169.63, 140.97, 128.44, 127.94, 126.13, 81.95, 79.40, 73.31, 71.14, 53.51, 27.64, 25.77, 21.82, 19.60 ppm; IR (KBr) 3088, 2980, 2854, 2123, 1955, 1732, 1605, 1496, 1393, 1370, 1250, 1196, 1030, 937, 847, 743 cm^{-1}, HRMS (FAB): calcd for $[C_{19}H_{25}O_4]^+$ ($[M+H]^+$): 317.1753, found: 317.1747. The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralcel OJ-H, hexane : 2-propanol = 99: 1, flow rate = 1.0 ml/min, 23 ℃, λ = 210 nm, retention time ; Major isomer(S) 5.8 min, minor isomer(*R*) 7.0 min, 75% ee, $[\alpha]^{25}_D$ = + 53.87 (*c* 1.0, $CHCl_3$).

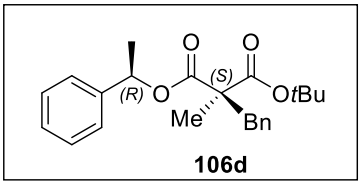
(*S*)-1-*tert*-Butyl 3-((*R*)-1-phenylethyl) 2-cinnamyl-2-methylmalonate (106c)



106c

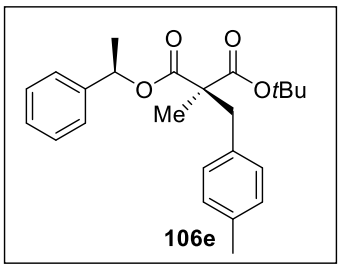
Following the general eanatioselective PTC alkylation procedure from **102a** with cinnamyl bromide, **106c** was obtained as pale yellow oil (72% yield). ^{1}H-NMR (300MHz, $CDCl_3$) δ 7.35 ~ 7.18 (m, 10H), 6.35 ~ 6.30 (m, 1H), 6.03 ~ 5.91 (m, 2H), 2.75 ~2.64 (m, 2H), 1.57 ~ 1.54 (d, *J* = 6.8 Hz, 3H), 1.41~ 1.37 (m, 12H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.35, 170.86, 141.04, 137.12, 133.81, 128.47, 128.38, 127.98, 127.20, 126.31, 126.15, 124.34, 81.57, 73.03, 54.28, 39.28, 27.78, 21.79, 19.96 ppm; IR (KBr) 3060, 2933, 1951, 1877, 1728, 1599, 1496, 1452, 1369, 1291, 1274, 1209, 1110, 1008, 995, 849, 697 cm^{-1}; HRMS (FAB): calcd for $[C_{25}H_{31}O_4]^+$ ($[M+H]^+$): 395.2222, found: 395.2226. The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralcel OJ-H, hexane : 2-propanol = 99: 1, flow rate = 1.0 ml/min, 23 ℃, λ = 210 nm, retention time ; Major isomer(*S*) 10.4 min, minor isomer(*R*) 14.8 min, 82% ee, $[\alpha]^{25}_D$ = + 63.39 (*c* 1.0, $CHCl_3$).

(*S*)-1-*tert*-Butyl 3-((*R*)-1-phenylethyl) 2-benzyl-2-methylmalonate ((*R*,*S*)-106d)



Following the general eanatioselective PTC alkylation procedure from **102a** with benzyl bromide, **106d** was obtained as pale yellow oil (91% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.41 ~ 6.94 (m, 10H), 5.98 ~ 5.91 (q, J = 6.6 Hz, 1H), 3.21 ~ 3.10 (dd, J_1 = 21.6 Hz, J_2 = 13.0 Hz, 2H), 1.58 ~ 1.26 (m, 15H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.30, 170.96, 140.87, 136.29, 130.27, 128.51, 128.08, 127.98, 126.66, 126.50, 81.65, 73.11, 55.24, 40.92, 31.92, 29.69, 27.77, 21.68, 19.73 ppm; IR (KBr) 3087, 3064, 2929, 2855, 1950, 1879, 1805, 1730, 1604, 1585, 1496, 1369, 1279, 1250, 1114, 1008, 995, 760 cm^{-1}; HRMS (FAB): calcd for $[C_{23}H_{29}O_4]^+$ ($[M+H]^+$): 369.1988, found: 368.1983. The enantioselectivity was determined by chiral HPLC analysis after modification into (*S*)-α-Benzyl-α-methyl-malonic acid diphenylmethyl ester *tert*-butyl ester (**69c**) (DAICEL Chiralpak AD-H, hexane : 2-propanol = 98 : 2, flow rate = 1.0 ml/min, 23 ℃, λ = 254 nm, retention time ; Major isomer(*S*) 15.1 min, minor isomer(*R*) 13.7 min, 90% ee). $[\alpha]^{25}_{D}$ = + 59.18 (*c* 1.0, $CHCl_3$).

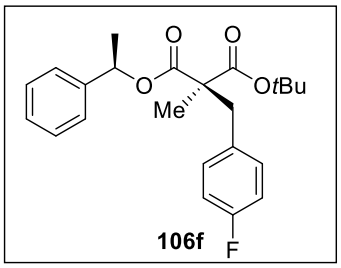
(*S*)-1-*tert*-Butyl 3-((*R*)-1-phenylethyl) 2-methyl-2-(4-methylbenzyl)malonate (106e)



Following the general eanatioselective PTC alkylation procedure from **102a** with *para*-methyl benzyl bromide, **106e** was obtained as pale yellow oil (99% yield). ^{1}H-NMR (400MHz, $CDCl_3$) δ 7.39 ~ 7.30 (m, 5H), 6.94 ~ 6.92 (d, J = 7.9 Hz, 2H), 6.83 ~ 6.81 (d, J = 7.9 Hz, 2H), 5.93 ~ 5.90 (q, J = 6.5 Hz, 1H), 3.15 ~3.04 (dd, J_1 = 30.0 Hz, J_2 = 13.8 Hz, 2H), 2.24 (s, 3H), 1.53 ~ 1.52 (d, J = 6.6 Hz), 1.37 (s, 9H), 1.27 (s, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.37,

171.05, 140.92, 136.15, 133.13, 130.13, 128.70, 128.50, 128.07, 126.51, 81.59, 73.07, 55.27, 40.50, 27.79, 21.72, 20.98, 19.70 ppm; IR (KBr) 2978, 2873, 1727, 1455, 1395, 1324, 1271, 1253, 1121, 1060, 843, 794, 638 cm^{-1}; HRMS (FAB): calcd for $[C_{24}H_{31}O_4]^+$ ($[M+H]^+$): 383.2222, found: 383.2216. The enantioselectivity was determined by chiral HPLC analysis after modification to (*S*)-α-(4′-Methyl-benzyl)-α-methyl-malonic acid diphenylmethyl ester *tert*-butyl ester (DAICEL Chiralpak AD-H, hexane : 2-propanol = 98 : 2, flow rate = 1.0 ml/min, 23 ℃, λ = 254 nm, retention time ; Major isomer(*S*) 21.2 min, minor isomer(*R*) 15.5 min, 90% ee). $[\alpha]^{25}_D$ = + 64.18 (*c* 1.0, $CHCl_3$).

(*S*)-1-*tert*-Butyl 3-((*R*)-1-phenylethyl) 2-methyl-2-(4-fluorobenzyl)malonate (106f)

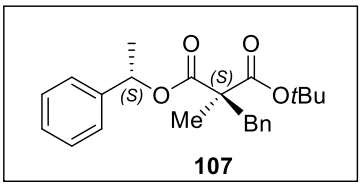


106f

Following the general eanatioselective PTC alkylation procedure from **102a** with *para*-fluoro benzyl bromide, **106f** was obtained as pale yellow oil (95% yield). ^{1}H-NMR (400MHz, $CDCl_3$) δ 7.38 ~ 7.28 (m, 5H), 6.90 ~ 6.86 (m, 2H), 6.81 ~ 6.77 (m, 2H), 5.95 ~ 5.90 (q, *J* = 6.6 Hz, 1H), 3.15 ~3.04 (dd, J_1 = 32.0 Hz, J_2 = 13.9 Hz, 2H), 1.55 ~ 1.52 (m, 3H), 1.37 (s, 9H), 1.28 (s, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.11, 170.86, 163.03-130.60 (d, *J* = 243.3 Hz), 140.77, 131.98 – 131.94 (d, *J* = 3.2 Hz), 131.74 - 131.66 (d, *J* = 8 Hz), 128.54, 128.17, 126.54, 114.90 - 114.70 (d, *J* = 20.8 Hz), 81.77, 73.19, 55.21, 40.12, 27.77, 21.65, 19.74 ppm; IR (KBr) 3072, 2979, 2874, 1604, 1510, 14791396, 1327, 1272, 1254, 1224, 1156, 1085, 1061, 874, 801, 641 cm^{-1}; HRMS (FAB): calcd for $[C_{23}H_{28}FO_4]^+$ ($[M+H]^+$): 387.1972, found: 387.1974. The enantioselectivity was determined by chiral HPLC analysis after modification to (*S*)-α-(4′-Fluoro-benzyl)-α-methyl-malonic acid diphenylmethyl ester *tert*-butyl ester (DAICEL Chiralpak AD-H, hexane : 2-propanol = 95 : 5, flow rate = 1.0 ml/min,

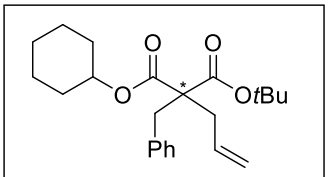
23 ℃, λ = 254 nm, retention time ; Major isomer(*S*) 10.0 min, minor isomer(*R*) 9.2 min, 91% ee). $[\alpha]^{25}_{D}$ = + 70.64 (*c* 1.0, $CHCl_3$).

(*S*)-1-*tert*-Butyl 3-((*S*)-1-phenylethyl) 2-benzyl-2-methylmalonate ((*S*,*S*)-107)



Following the general eanatioselective PTC alkylation procedure from **102a** with benzyl bromide, **107** was obtained as pale yellow oil (82% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.33 ~ 6.86 (m, 10H), 5.90 ~ 5.81 (p, *J* = 6.6 Hz, 1H), 3.13 ~ 3.02 (m, 2H), 1.50 ~ 1.45 (m, 3H), 1.32 ~ 1.28 (m, 9H), 1.22 ~ 1.20 (d, *J* = 6.6 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.41, 170.95, 141.16, 136.46, 130.26, 128.50, 128.05, 126.74, 126.48, 126.10, 81.64, 73.15, 55.25, 40.96, 29.68, 27.75, 22.01, 19.91 ppm; IR (KBr) 2932, 1726, 1490, 1392, 1355, 1251, 1154, 1058, 1028, 1000, 993, 761, 740 cm^{-1}; HRMS (FAB): calcd for $[C_{23}H_{29}O_4]^+$ ($[M+H]^+$): 369.2066, found: 369. 2072. The enantioselectivity was determined by chiral HPLC analysis after modification to (*S*)-α-benzyl-α-methyl-malonic acid diphenylmethyl ester *tert*-butyl ester (**69c**) (DAICEL Chiralpak AD-H, hexane : 2-propanol = 98 : 2, flow rate = 1.0 ml/min, 23 ℃, λ = 254 nm, retention time ; Major isomer(*S*) 15.1 min, minor isomer(*R*) 13.7 min, 90% ee. $[\alpha]^{25}_{D}$ = -47.36 (*c* 1.0, $CHCl_3$).

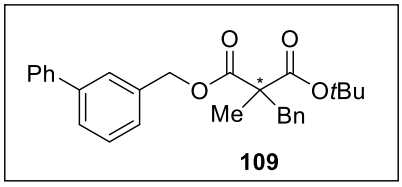
1-(*tert*-Butyl) 3-(naphthalen-2-ylmethyl) 2-allyl-2-benzylmalonate (108)



108

Following the general eanatioselective PTC alkylation procedure from **105b** with allyl bromide, **108** was obtained as pale yellow oil (% yield). ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.26 ~ 7.15 (m, 5H), 5.82 ~ 5.74 (m, 1H), 5.16 ~ 5.13 d, J = 15.2 Hz, 1H), 4.84 ~ 4.80 (m, 1H), 3.20 (s, 2H), 2.53 ~ 2.52 (d, J = 8.3 Hz, 2H), 2.04 ~ 1.26 (m, 10H), 1.44 (s, 9H) ppm; ^{13}C-NMR (150 MHz, $CDCl_3$) δ 170.48, 169.86, 136.41, 132.90, 130.20, 128.09, 126.75, 118.98, 81.75, 73.52, 58.89, 37.78, 36.51, 31.52, 27.92, 25.29, 23.69 ppm; IR (KBr) 3032, 2978, 2938, 2860, 1729, 1454, 1368, 1285, 1210, 1187, 1153, 1039, 1012, 917, 848, 741, 701 cm^{-1}; HRMS (FAB): calcd for $[C_{23}H_{33}O_4]^+$ ($[M+H]^+$): 373.2379, found: 373.2382. The enantioselectivity was determined by chiral HPLC analysis (DAIPAK Chiralpak AD-H, hexane : 2-propanol = 99 : 1, flow rate = 1.0 ml/min, 23 ℃, λ = 254 nm, retention time ; Major isomer 5.1 min, minor isomer 5.9 min, 65% ee). $[\alpha]^{25}_{D}$ = + 8.30 (c 1.0, $CHCl_3$).

(S)-1-([1,1'-Biphenyl]-3-ylmethyl) 3-*tert*-butyl 2-benzyl-2-methylmalonate (109)

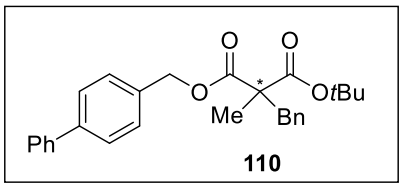


109

Following the general eanatioselective PTC alkylation procedure from **102d** with benzyl bromide, **109** was obtained as pale yellow oil (99% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.58 ~ 7.56 (m, 4H), 7.47 ~ 7.33 (m, 6H), 7.22 ~ 7.19 (m, 2H), 7.11 ~ 7.08 (m, 2H), 5.23 (s, 2H), 3.29 ~ 3.13 (dd, J_1 = 32.3 Hz, J_2 = 13.7 Hz, 2H), 1.34 ~ 1.32 (m, 12H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.91, 170.78, 141.57, 140.66, 136.61, 136.04, 130.24, 128.94, 128.75, 128.06, 127043, 127.38, 127.11, 126.76, 81.71, 66.81, 55.38, 41.03, 27.66, 19.82 ppm; IR (KBr) 3031, 2979, 1950,

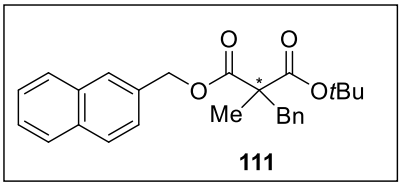
1730, 1603, 1481, 1424, 1369, 1279, 1154, 1030, 848, 700 cm^{-1}; HRMS (FAB): calcd for $[C_{28}H_{30}O_4]^+$ ($[M]^+$): 430.2144, found: 430.2143. The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralcel OD-H, hexane : 2-propanol = 99.5 : 0.5, flow rate = 1.0 ml/min, 23 ℃, λ = 254 nm, retention time ; Major isomer 23.9 min, minor isomer 20.6 min, 72% ee, $[\alpha]^{25}_D$ = + 11.60 (*c* 1.0, $CHCl_3$).

(*S*)-1-([1,1'-Biphenyl]-4-ylmethyl) 3-*tert*-butyl 2-benzyl-2-methylmalonate (110)



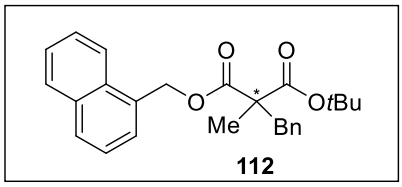
Following the general eanatioselective PTC alkylation procedure from **102e** with benzyl bromide, **110** was obtained as a white solid (mp 110°C, 99% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.58 ~ 7.55 (d, *J* = 7.86, 4H), 7.46 ~ 7.32 (m, 5H), 7.21 ~ 7.19 (dd, J_1 = 5.0 Hz, J_2 = 1.7 Hz, 3H), 7.10 ~ 7.07 (m, 2H), 5.18 (s, 2H), 3.27 ~ 3.12 (dd, J_1 = 30.9 Hz, J_2 = 13.7 Hz, 2H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.89, 170.76, 141.26, 140.60, 136.30, 134.51, 130.24, 129.00, 128.76, 128.05, 127.41, 127.20, 127.04, 126.75, 81.69, 66.52, 55.36, 41.01, 27.68, 13.78 ppm; IR (KBr) 3031, 2978, 1951, 1730, 1604, 1567, 1454, 1392, 1323, 1251, 1112, 1009, 849, 827, 738 cm^{-1}; HRMS (FAB): calcd for $[C_{28}H_{30}O_4]^+$($[M]^+$): 430.2144, found: 430.2148. The enantioselectivity was determined by chiral HPLC analysis after modification to (*S*)-α-benzyl-α-methyl-malonic acid diphenylmethyl ester *tert*-butyl ester (**69c**) (DAICEL Chiralpak AD-H, hexane : 2-propanol = 98 : 2, flow rate = 1.0 ml/min, 23 ℃, λ = 254 nm, retention time ; Major isomer(*S*) 15.1 min, minor isomer(*R*) 13.7 min, 81% ee). $[\alpha]^{25}_D$ = + 19.27 (*c* 1.0, $CHCl_3$).

(*S*)-1-*tert*-Butyl 3-(naphthalen-2-ylmethyl) 2-benzyl-2-methylmalonate (111)



Following the general eanatioselective PTC alkylation procedure from **102e** with benzyl bromide, **111** was obtained as a white solid (mp 66°C, 91% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.84 ~ 7.81 (m, 4H), 7.54 ~ 7.42 (m, 3H), 7.22 ~ 7.07 (m, 5H), 5.32 (s, 2H), 3.29 ~ 3.15 (dd, J_1 = 30.0 Hz, J_2 = 13.53 Hz, 2H), 1.34 ~ 1.32 (d, J = 5.3 Hz, 12H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.98, 170.80, 136.31, 133.11, 132.93, 130.25, 128.29, 128.05, 127.95, 127.64, 126.75, 126.26, 126.08, 81.72, 66.97, 55.43, 41.06, 27.68, 19.83 ppm; IR (KBr) 3461, 3030, 2929, 1950, 1730, 1635, 1583, 1496, 1392, 1323, 1252, 1066, 853, 702 cm^{-1}; HRMS (FAB) calcd for $[C_{26}H_{28}O_4]^+$ ($[M]^+$): 404.1988, found: 404.1988, The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralcel OJ-H, hexane : 2-propanol = 95 : 5, flow rate = 1.0 ml/min, 23℃, λ = 254 nm, retention time ; Major isomer 21.3 min, minor isomer 24.7 min, 72% ee). $[\alpha]^{25}_{D}$ = + 17.70 (*c* 1.0, $CHCl_3$).

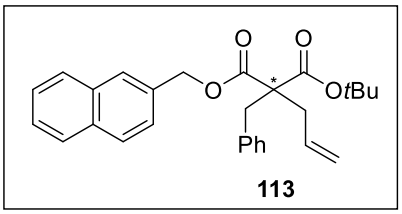
(*S*)-1-*tert*-Butyl 3-(naphthalen-1-ylmethyl) 2-benzyl-2-methylmalonate (112)



Following the general eanatioselective PTC alkylation procedure from **102g** with benzyl bromide, **112** was obtained as pale yellow oil (97% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.06 ~ 8.03 (m, 1H), 7.93 ~ 7.88 (m, 2H), 7.62 ~ 7.46 (m, 4H), 7.26 ~ 7.13 (m, 5H), 5.68 (s, 2H), 3.36 ~ 3.19 (dd, J_1 = 35.5 Hz, J_2 = 13.7 Hz, 2H), 1.39 (s, 3H), 1.28 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.87, 170.71, 136.25, 133.60, 131.62, 131.01, 130.20, 129.25, 128.54, 127.97, 127.64, 126.67, 126.52, 125.84, 125.10, 123.51, 81.58, 64.96, 55.46, 41.00, 27.46, 19.82 ppm; IR

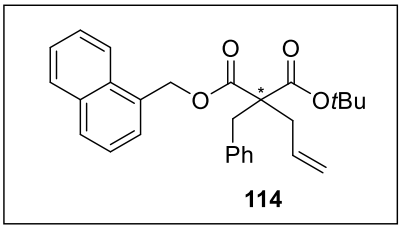
(KBr) 3031, 2978, 1950, 1730, 1601, 1512, 1455, 1369, 1279, 1154, 1112, 968, 877, 848, 790 cm^{-1}; HRMS (FAB): calcd for $[C_{26}H_{28}O_4]^+$ ($[M]^+$): 404.1988, found: 404.1990. The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralcel OJ-H, hexane : 2-propanol = 80 : 20, flow rate = 1.0 ml/min, 23 ℃, λ = 254 nm, retention time ; Major isomer 9.3 min, minor isomer 22.4 min, 53% ee, $[\alpha]^{25}_D$ = + 14.71 (*c* 1.0, $CHCl_3$).

<u>1-(*tert*-Butyl) 3-(naphthalen-2-ylmethyl) 2-allyl-2-benzylmalonate (113)</u>



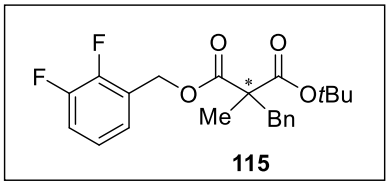
Following the general eanatioselective PTC alkylation procedure from **105b** with allyl bromide, **113** was obtained as pale yellow oil (% yield). ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.85 ~ 7.82 (m, 4H), 7.51 ~ 7.44 (m, 3H), 7.20 ~ 7.11 (m, 5H), 5.85 ~ 5.77 (m, 1H), 5.34 ~ 5.29 (dd, J_1 = 14.1 Hz, J_2 = 12.3 Hz, 2H), 5.17 ~ 5.14 (m, 2H), 3.31 ~ 3.21 (dd, J_1 = 24.9 Hz, J_2 = 13.9 Hz, 2H), 2.64 ~ 2.55 (m, 2H), 1.33 (s, 9H) ppm; ^{13}C-NMR (150 MHz, $CDCl_3$) δ 170.90, 169.49, 136.14, 133.11, 133.08, 132.75, 132.67, 130.09, 128.27, 128.13, 127.94, 127.81, 127.63, 126.80, 126.29, 126.25, 126.22, 119.15, 81.93, 66.97, 59.16, 37.89, 36.49, 27.72 ppm; IR (KBr) 3036, 2978, 2932, 1730, 1455, 1368, 1281, 1249, 1178, 1153, 913, 854, 817, 772 745, 702 cm^{-1}; HRMS (FAB): calcd for $[C_{28}H_{30}O_4]^+$ ($[M]^+$): 430.2144, found: 430.2139. The enantioselectivity was determined by chiral HPLC analysis (DAIPAK AD-H, hexane : 2-propanol = 99 : 1, flow rate = 1.0 ml/min, 23℃, λ = 254 nm, retention time ; Major isomer 11.64 min, minor isomer 14.53 min, 69% ee). $[\alpha]^{25}_D$ = + 14.22 (*c* 1.0, $CHCl_3$).

1-(*tert*-Butyl) 3-(naphthalen-1-ylmethyl) 2-allyl-2-benzylmalonate (114)



Following the general eanatioselective PTC alkylation procedure from **105c** with allyl bromide, **114** was obtained as pale yellow oil (% yield). ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.97 ~ 7.96 (m, 1H), 7.87 ~ 7.84 (m, 2H), 7.54 ~ 7.48 (m, 3H), 7.45 ~ 7.42 (m, 1H), 7.18 ~ 7.16 (m, 3H), 7.08 ~ 7.06 (m, 2H), 5.79 ~ 5.72 (m, 1H), 5.62 ~ 5.55 (dd, J_1 = 17.7 Hz, J_2 = 12.3 Hz, 2H), 5.10 ~ 5.07 (m, 2H), 3.24 ~ 3.15 (dd, J_1 = 24.0 Hz, J_2 = 13.9 Hz, 2H), 2.57 ~ 2.49 (m, 2H), 1.20 (s, 9H) ppm; ^{13}C-NMR (150 MHz, $CDCl_3$) δ 170.98, 169.47, 136.19, 133.67, 132.72, 131.72, 130.97, 130.14, 129.38, 128.62, 128.13, 127.86, 126.81, 126.63, 125.94, 125.19, 123.62, 119.09, 81.94, 64.97, 59.27, 37.99, 36.61, 27.63 ppm; IR (KBr) 2979, 2924, 1430, 1456, 1285, 1249, 1220, 1153, 1083, 913, 774, 744 cm^{-1}; HRMS (FAB): calcd for $[C_{28}H_{30}O_4]^+$ ($[M]^+$): 430.2144, found: 430.2140. The enantioselectivity was determined by chiral HPLC analysis (DAICEL AD-H, hexane : 2-propanol = 99 : 1, flow rate = 1.0 ml/min, 23℃, λ = 254 nm, retention time ; Major isomer 11.2 min, minor isomer 12.4 min, 39% ee). $[\alpha]^{25}_{D}$ = + 8.01 (*c* 1.0, $CHCl_3$).

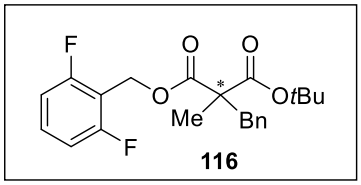
(*S*)-1-*tert*-Butyl 3-(2,3-difluorobenzyl) 2-benzyl-2-methylmalonate (115)



Following the general eanatioselective PTC alkylation procedure from **102h** with benzyl bromide, **115** was obtained as pale yellow oil (96% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.29 ~ 7.22 (m, 3H), 7.21 ~ 7.06 (m, 5H), 5.25 (d, *J* = 1.3 Hz, 2H), 3.29 ~ 3.15 (dd, J_1 = 29.3 Hz, J_2 = 13.7 Hz, 2H), 1.39 (s, 9H), 1.35 (s, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.75, 170.62, [151.73 ~ 151.61, 149.26

~ 149.14 (dd, J_1 = 247 Hz, J_2 = 12.3 Hz)], [150.33 ~ 150.20, 147.84 ~ 147.71 (dd, J_1 = 249.2 Hz, J_2 = 13.0 Hz)], 136.20, 130.23, 128.11, 126.84, 125.50 ~ 125.44 (t, J = 2.8 Hz), 125.20 ~ 125.08 (d, J = 11.3 Hz), 124.17 ~ 124.05 (dd, J_1 = 6.6 Hz, J_2 = 4.8 Hz), 117.61 ~ 117.44 (d, J = 16.9 Hz), 81.88, 60.15 ~ 60.08 (t, J = 3.4 Hz), 55.40, 41.02, 27.68, 19.83 ppm; IR (KBr) 3031, 2965, 2933, 1950, 1732, 1631, 1494, 1370, 1258, 1111, 1030, 847, 702 cm^{-1}; HRMS (FAB): calcd for $[C_{22}H_{25}F_2O_4]^+$ ($[M+H]^+$): 391.1721, found: 391.1720. The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralcel OD-H, hexane : 2-propanol = 99 : 1, flow rate = 1.0 ml/min, 23℃, λ = 254 nm, retention time ; Major isomer 6.3 min, minor isomer 5.9 min, 74% ee, $[\alpha]^{25}_D$ = + 29.97 (c 1.0, $CHCl_3$).

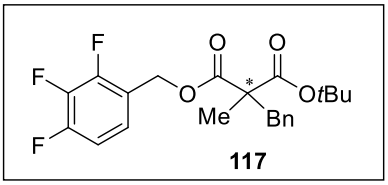
<u>1-*tert*-Butyl 3-(2,6-difluorobenzyl) 2-benzyl-2-methylmalonate (116)</u>



Following the general eanatioselective PTC alkylation procedure from **102i** with benzyl bromide, **116** was obtained as pale yellow oil (98% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.41 ~ 7.20 (m, 4H), 7.15 ~ 7.12 (m, 2H), 6.97 ~ 6.91 (m, 2H), 5.25 (s, 2H), 3.29 ~ 3.12 (dd, J_1 = 31.3 Hz, J_2 = 13.8 Hz, 2H), 1.39 (s, 9H), 1.32 (s, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.66, 170.69, [163.19 - 163.12, 160.69 - 160.61 (dd, J_1 = 250.2 Hz, J_2 = 7.3 Hz)], 136.25, 131.10 - 130.90 (t, J = 10.3 Hz), 130.20, 128.10, 126.78, [111.49 – 111.43, 111.30 - 111.24 (dd, J_1 = 19.0 Hz, J_2 = 6.1 Hz)], 81.77, 55.26, 54.57 – 54.49 (t, J = 4.1 Hz), 40.91, 27.61, 19.72 ppm; IR (KBr) 3087, 3031, 2979, 1950, 1732, 1656, 1562, 1370, 1279. 1238, 1156, 1058, 848, 702 cm^{-1}; HRMS (FAB): calcd for $[C_{22}H_{25}F_2O_4]^+$ ($[M+H]^+$): 391.1721, found: 391.1719. The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD-H, hexane : 2-propanol = 99 :

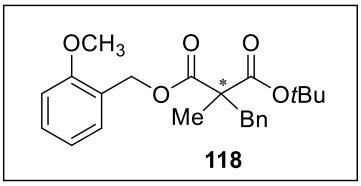
1, flow rate = 1.0 ml/min, 23℃, λ = 254 nm, retention time ; Major isomer 7.2 min, minor isomer 7.6 min, 31% ee, $[\alpha]^{25}_{D}$ = + 16.67 (*c* 1.0, $CHCl_3$).

(*S*)-1-*tert*-Butyl 3-(2,3,4-trifluorobenzyl) 2-benzyl-2-methylmalonate (117)



Following the general eanatioselective PTC alkylation procedure from **102j** with benzyl bromide, **117** was obtained as pale yellow oil (87% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.29 ~ 7.21 (m, 3H), 7.17 ~ 7.09 (m, 3H), 7.03 ~ 6.94 (m, 1H), 5.20 (s, 2H), 3.28 ~ 3.14 (dd, J_1 = 28.9 Hz, J_2 = 13.5 Hz, 2H), 1.40 ~ 1.35 (d, *J* = 14.8 Hz, 12H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.73, 170.56, [152.70 ~152.57, 151.20 ~150.07 (ddd, J_1 = 250 Hz, J_2 = 10 Hz, J_3 = 3.2 Hz)], [151.33 ~151.20, 148.82 ~148.68 (ddd, J_1 = 250.7 Hz, J_2 = 10.1 Hz, J_3 = 3.6 Hz)], [141.30 ~141.00, 138.79 ~138.49 (dt, J_1 = 250.7 Hz, J_2 = 15.1 Hz), 130.22, 128.11, 126.86, 124.61 ~124.45 (p, *J* = 4.1 Hz), [120.48 ~120.44, 120.36 ~120.32 (dd, J_1 = 12 Hz, J_2 = 4 Hz)], [112.20 ~ 2.16, 112.02 ~111.99 (dd, J_1 = 17.4 Hz, J_2 = 4 Hz)], 81.90, 59.87 ~59.81 (t, *J* = 2.6 Hz), 55.42, 41.03, 27.48, 19.85 ppm; IR (KBr) 3064, 3032, 2937, 1952, 1732, 1639, 1605, 1516, 1370, 1279, 1160, 1065, 945, 702, 623 cm^{-1}; HRMS (FAB): calcd for $[C_{22}H_{24}F_3O_4]^+$ ($[M+H]^+$): 409.1627, found: 409.1631. The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralcel OD-H, hexane : 2-propanol = 99 : 1, flow rate = 1.0 ml/min, 23 ℃, λ = 254 nm, retention time ; Major isomer 7.9 min, minor isomer 6.5 min, 71% ee, $[\alpha]^{25}_{D}$ = + 15.77 (*c* 1.0, $CHCl_3$).

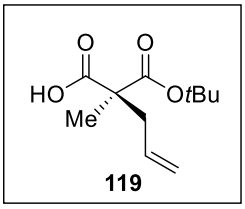
(*S*)-1-*tert*-Butyl 3-(2-methoxybenzyl) 2-benzyl-2-methylmalonate (118)



Following the general eanatioselective PTC alkylation procedure from **102k** with benzyl bromide, **118** was obtained as pale yellow oil (90% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.29 ~ 7.03 (m, 7H), 6.88 ~ 6.79 (m, 2H), 5.18 ~ 5.09 (dd, J_1 = 15.4 Hz, J_2 = 12.6 Hz, 2H), 3.75 (s, 3H), 3.21 ~ 3.05 (dd, J_1 = 32.5 Hz, J_2 = 13.7 Hz, 2H), 1.28 (s, 9H), 1.24 (s, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.00, 170.91, 157.48, 136.45, 130.25, 129.83, 129.55, 128.03, 126.68, 123.89, 120.32, 110.29, 81.56, 62.30, 55.36, 55.25, 40.99, 27.67, 19.73, 0.97 ppm; IR (KBr) 3032, 2857, 1729, 1640, 1496, 1392, 1285, 1209, 1153, 1038, 848, 701, 645 cm^{-1}; HRMS (FAB): calcd for $[C_{23}H_{28}O_5]^+$ ($[M]^+$): 384.1937, found: 384.1939. The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD-H, hexane : 2-propanol = 99 : 1, flow rate = 1.0 ml/min, 23 ℃, λ = 254 nm, retention time ; Major isomer 8.9 min, minor isomer 10.1 min, 65% ee, $[\alpha]^{25}_{D}$ = + 29.39 (*c* 1.0, $CHCl_3$).

2-4. Application of chiral α, α'-dialkyl malonic esters

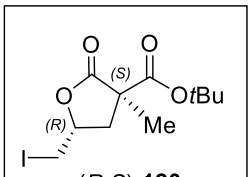
(*S*)-2-(*tert*-Butoxycarbonyl)-2-methylpentenoic acid (119)



50 w/v % aq. KOH (0.12 ml, 1.07 mmol) was added to a stirred solution of (*S*)-1-*tert*-butyl 3-((*R*)-1-phenylethyl) 2-methyl-2-allylmalonate (**106a**, 34 mg, 0.107 mmol) in MeOH (0.12 ml). After stirring for 24 hours, the reaction mixture was evaporated, diluted with EtOAc (10 ml), extracted with 5% $NaHCO_3$ (10 ml) and acidified by 1 M HCl (up to

pH 5-6). The residue was extracted with EtOAc (20 ml), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane: EtOAc = 1:1) to afford **119** (22.4 mg, 98% yield) as pale yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.81 (s, 1H), 5.74 ~ 5.64 (m, 1H), 5.12 ~ 5.07 (m, 2H), 2.62 ~ 2.51 (n, J = 7.5 Hz, 2H), 1.43 (s, 9H), 1.36 (s, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 177.99, 170.97, 132.44, 119.20, 82.24, 54.00, 40.18, 27.78, 27.78, 19.91 ppm; IR (KBr) 2982, 1712, 1643, 1460, 1301, 1150, 921, 847, 649 cm^{-1}; HRMS (FAB): calcd for $[C_{11}H_{19}O_4]^+$ ($[M+H]^+$): 215.1283, found: 215.1281. $[\alpha]^{25}_D$ = - 10.96 (c 1.0, $CHCl_3$).

(3*S*,5*R*)-*tert*-Butyl 5-(iodomethyl)-3-methyl-2-oxotetrahydrofuran-3-carboxylate

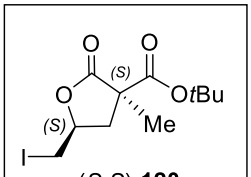


(*R*,*S*)-**120**

(*R*,*S*)-**120**: A mixture of **119** (97.9 g, 0.46 mmol) and $NaHCO_3$ (115.2 mg, 1.37 mmol) in water (2.91 mL) was stirred at room temp. for 10 min before adding chloroform (2.91 mL). The mixture was cooled to 0 ℃ and stirred for 15 min before adding I_2 (232 mg, 0.91 mmol) in the dark. The mixture was stirred at 0 ℃ for 6 h, and then it was quenched with saturated aqueous NaS_2O_3 and the mixture agitated until the solution turned colorless. Et_2O (100 mL) was added, and the layers were separated. The aqueous layer was extracted with Et_2O (100 mL), and the combined organic layers were washed successively with water (100 mL) and then brine (100 mL). The organic layer was dried with anhydrous MgSO4, filtered, and concentrated in vacuo. The diastereomeric mixture was separated by silica gel column chromatography (12% EtOAc in Hexane; R_f = 0.55) to afford (*R*,*S*)-**120** (101.36 mg, 65% yield) as pale yellow oil.^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.53 ~ 4.46 (m, 1H), 3.42 ~ 3.39 (dd, J_1 = 10.4 Hz, J_2 = 4.3 Hz, 1H), 3.31 ~ 3.27 (dd, J_1 = 10.4 Hz, J_2 = 7.2 Hz, 1H), 2.85 ~ 2.80 (dd, J_1 = 13.4 Hz, J_2 = 6.2 Hz, 1H), 1.83 ~ 1.77 (dd, J_1 = 13.4 Hz, J_2 = 9.5 Hz, 1H),

1.47 ~ 1.45 (m, 12H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 174.67, 169.00, 83.31, 52.95, 41.95, 27.78, 20.53, 6.95 ppm; IR (KBr) 2872, 1781, 1737, 1456, 1394, 1338, 1272, 1229, 1098, 952, 844, 744 cm^{-1}; HRMS (FAB) : calcd for $[C_{11}H_{18}IO_4]^+$ ($[M+H]^+$): 341.0250, found: 340.0247. $[\alpha]^{25}_D$ = + 2.78 (*c* 1.0, $CHCl_3$).

(3*S*,5S)-*tert*-Butyl 5-(iodomethyl)-3-methyl-2-oxotetrahydrofuran-3-carboxylate



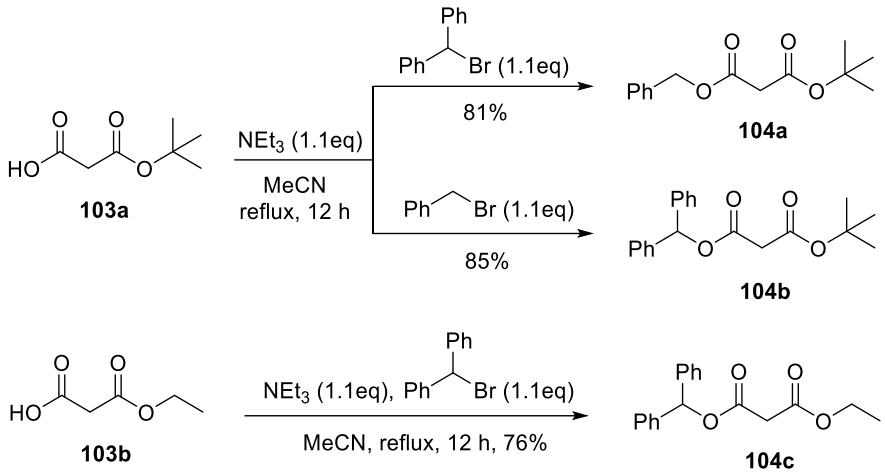
(*S*,*S*)-**120**

(*S*,*S*)-**120**: A stereoisomer of (*R*,*S*)-**120** was monitored on TLC (12% EtOAc in Hexane; R_f = 0.48) and purified to achieve (S,*S*)-**120** (34.8 mg, 22%) as pale yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.58 ~ 4.54 (m, 1H), 3.46 ~ 3.42 (dd, J_1 = 10.1 Hz, J_2 = 4.8 Hz, 1H), 3.21 ~ 3.28 (dd, J_1 = 10.1 Hz, J_2 = 8.5 Hz, 1H), 2.61 ~ 2.56 (dd, J_1 = 13.4 Hz, J_2 = 7.2 Hz, 1H), 2.35 ~ 2.29 (dd, J_1 = 13.4 Hz, J_2 = 7.2 Hz, 1H), 1.48 ~ 1.45 (m, 12H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 175.13, 169.28, 83.10, 52.09, 40.25, 27.79, 20.63, 5.87 ppm; IR (KBr) 2876, 1781, 1457, 1338, 1281, 1151, 1008 cm^{-1}; HRMS (FAB): calcd for $[C_{11}H_{18}IO_4]^+$ ($[M+H]^+$): 341.0250, found: 340.0253. $[\alpha]^{25}_D$ = - 39.51 (*c* 1.0, $CHCl_3$).

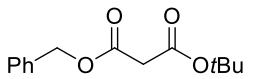
3. α-Amido malonate

3-1. General procedures for α-amido malonates

3-1-1. Synthetic route for α-methylene malonic esters



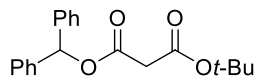
Benzyl *tert*-butyl malonate (104a)



104a

Commercially available hydrogen *tert*-butyl malonate (**103a**, 1g, 6.24 mmol) was dissolved in acetonitrile (20 mL) and heated to reflux. To this solution was added benzyl bromide (816 mg, 6.87 mmol) and triethylamine (0.96mL, 6.87 mmol) in sequence. The reaction was stirred until the TLC analysis showed that the reaction was complete. Water mixable solvent was evaporated and diluted with dichloromethane. Quenching with ammonium chloride (200 mL), washing with brine (150 mL x 2), drying over anhydrous $MgSO_4$, filtration, and purifying by flash column chromatography (silica gel, hexane : EtOAc = 20 : 1) afforded **104a** (1.27 g, 81% yield) as pale yellow oil. ^{1}H-NMR (300 MHz, CDCl3) δ 7.36 ~ 7.28 (m, 5H), 5.15 (s, 2H), 3.31 (s, 2H), 1.41 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 166.69, 165.46, 135.35, 128.46, 128.28, 128.25, 81.98, 66.90, 42.84, 27.77 ppm; IR (KBr) 2979, 1750, 1731, 1369, 1333, 1280, 1143, 1001, 772, 698 cm^{-1}; HRMS (FAB): calcd for $[C_{14}H_{19}O_4]^+$ ($[M+H]^+$): 251.1283, found: 251.1282

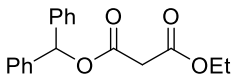
Benzhydryl *tert*-butyl malonate (104b)



104b

Commercially available hydrogen *tert*-butyl malonate (**103a**, 1g, 6.24 mmol) was dissolved in acetonitrile (20 mL) and heated to reflux. To this solution was added α-bromo diphenylmethane (1.7 g, 6.87 mmol) and triethylamine (0.96 mL, 6.87 mmol) in sequence. The reaction was stirred until the TLC analysis showed that the reaction was complete. Water mixable solvent was evaporated and diluted with dichloromethane. Quenching with ammonium chloride (200 mL), washing with brine (150 mL x 2), drying over anhydrous $MgSO_4$, filtration, and purifying by flash column chromatography (silica gel, hexane : EtOAc = 15: 1) afforded **104b** (1.73 g, 85% yield) as yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.34 ~ 7.18 (m, 10H), 6.89 (s, 1H), 3.33 (s, 2H), 1.36 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.79, 165.27, 139.57, 128.37, 127.92, 127.08, 81.99, 77.61, 43.16, 27.73 ppm; IR (KBr) 2960, 2924, 2853, 1732, 1680, 1462, 1377, 1021, 773 cm^{-1}; HRMS (ESI): calcd for $[C_{20}H_{22}O_4Na]^+$ ($[M+Na]^+$): 349.1410, found: 349.1422.

Benzhydryl ethyl malonate (104c)

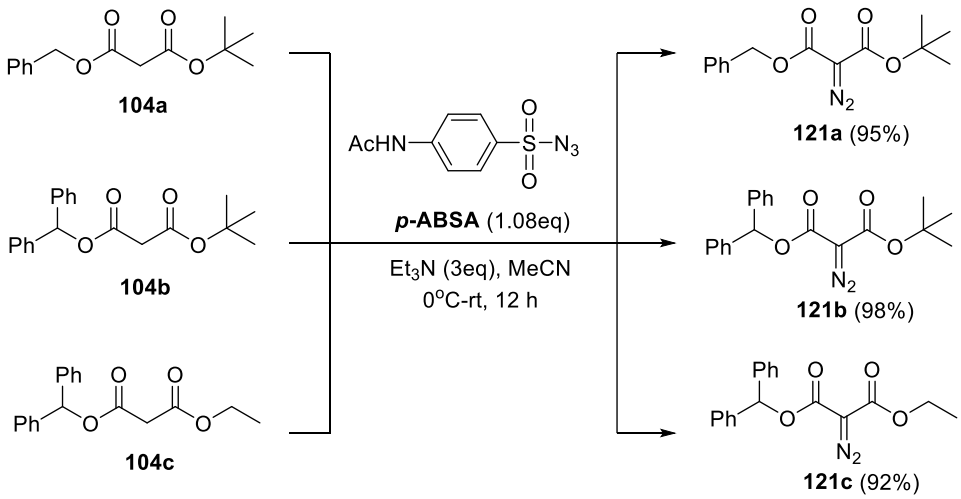


104c

Commercially available mono-ethyl malonate (**103b**, 1g, 7.57 mmol) was dissolved in acetonitrile (25 mL) and heated to reflux. To this solution was added α-bromodiphenylmethane (2.06 g, 8.33 mmol) and triethylamine (1.16 mL, 8.33 mmol) in sequence. The reaction was stirred until the TLC analysis showed that the reaction was complete. Water mixable solvent was evaporated and diluted with dichloromethane. Quenching with ammonium chloride (200 mL), washing with brine (150 mL x 2), drying over anhydrous $MgSO_4$, filtration, and purifying by flash column chromatography (silica gel, hexane : EtOAc

solution = 10 : 1) afforded **104c** (1.72 g, 76% yield) as yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.34 ~ 7.24 (m, 10H), 6.93 ~ 6.92 (d, 1H, *J* = 1.65 Hz), 4.24 ~ 4.14 (p, 2H, *J* = 7.1 Hz), 3.46 (s, 2H), 1.25 ~ 1.19 (t, 3H, *J* = 7.1 Hz) ppm; ^{13}C-NMR (125MHz, $CDCl_3$) δ 166.25, 165.53, 165.27, 139.56, 139.47, 128.48, 128.04, 128.01, 127.14, 127.12, 127.04, 139.56, 139.47, 128.48, 128.04, 128.01, 127.14, 127.12, 127.04, 77.96, 61.55, 41.92, 13.97 ppm; IR (KBr) 3033, 1751, 1734, 1220, 1148, 1032, 772, 699 cm^{-1} ; HRMS (CI): calcd for $[C_{18}H_{17}O_4]^+$ ($[M-H]^+$): 297.1127, found: 297.1125

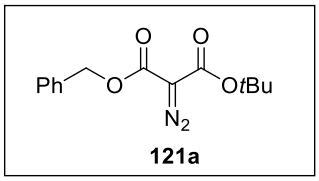
3-1-2. Synthetic route for α-diazo malonic esters



Triethylamine (1.28 mL, 9.19 mmol) was added to a stirred solution of benzhydryl *tert*-butyl malonate (**104b**, 1.0 g, 3.06 mmol) and *p*-(acetamido)benzenesulfonyl azide (*p*-ABSA) (795 mg, 3.31 mmol) in acetonitrile (15 mL) at 0°C under Ar atmosphere. The reaction was gradually warmed to room temperature overnight. Unexpectedly, the product spot had the same R_f value with the substrate spot on TLC. Therefore the reaction was stirred during 12 hours for complete conversion of the substrate into the product. The

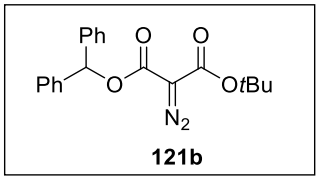
expected duration of the reaction might have been shorter than the actual reaction time. The reaction mixture was then filtered through a pad of celite and washed with EtOAc, and the filtrate was purified by flash column chromatography on silica gel eluting with hexane-EtOAc (15:1) to afford **121b** (1.058 g, 98% yield) as a yellow solid.

<u>1-Benzyl 3-(*tert*-butyl) 2-diazomalonate (121a)</u>



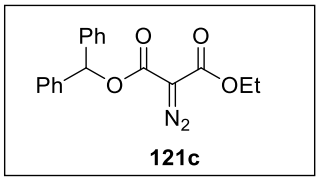
Following the procedure of Regitz-Diazo transfer from **104a**, **121a** was obtained quantitatively as pale yellow oil (95% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.37 ~ 7.27 (m, 5H), 5.24 (s, 2H), 1.49 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 161.21, 159.66, 135.41, 128.51, 128.32, 128.21, 83.07, 66.73, 28.16 ppm; IR (KBr) 2979, 2137, 1757, 1731, 1687, 1370, 1328, 1276, 1165, 1095, 772, 697 cm^{-1}; HRMS (FAB) : calcd for $[C_{14}H_{17}N_2O_4]^+$ ($[M+H]^+$): 277.1188, found: 277.1180

<u>1-Benzhydryl 3-(*tert*-butyl) 2-diazomalonate (121b)</u>



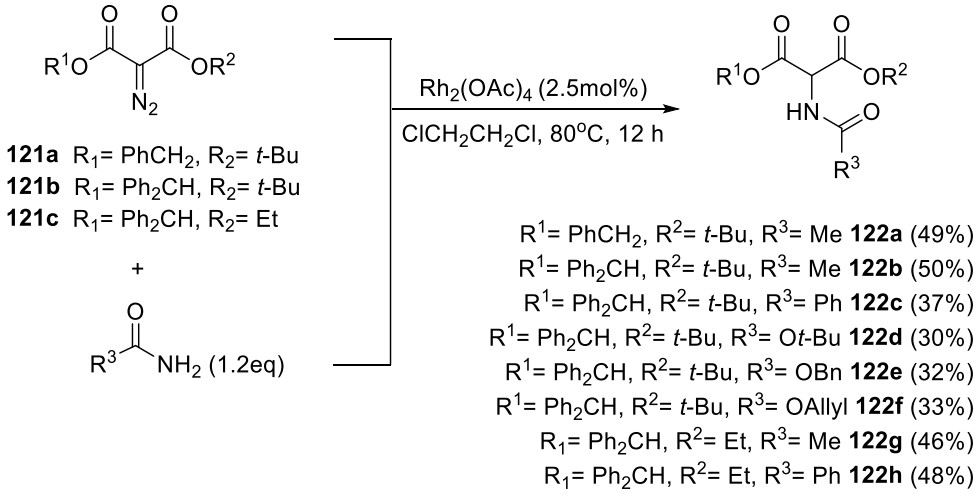
Following the procedure of Regitz-Diazo transfer from **104b**, **121b** was obtained quantitatively as yellow solid (mp 68.8 ^{o}C, 98% yield).; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.37 ~ 7.20 (m, 10H), 7.03 (s, 1H), 1.50 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.34, 159.34, 139.52, 128.28, 127.78, 126.81, 82.83, 77.34, 65.90, 27.97 ppm; IR 2979, 2139, 1954, 1755, 1727, 1687, 1325, 1276, 1166, 1097, 760, 700 (KBr) cm^{-1}; HRMS (FAB) : calcd for $[C_{20}H_{20}N_2NaO_4]^+$ ($[M+Na]^+$): 375.1321, found: 375.1316

1-Benzhydryl 3-ethyl 2-diazomalonate (121c)



Following the procedure of Regitz-Diazo transfer from **104c**, **121c** was obtained quantitatively as pale yellow oil (92% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.40 ~ 7.24 (m, 10H), 7.01 (s, 1H), 4.37 ~ 4.28 (q, 2H, *J* = 7.1 Hz), 1.34 ~ 1.30(t, 3H, *J* = 7.1 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 160.78, 160.46, 139.65, 128.52, 128.03, 126.97, 77.94, 66.20, 61.66, 14.29 ppm; IR (KBr) 2941, 2143, 1759, 1733, 1692, 1372, 1320, 1307, 1269, 1098, 1076, 772, 701 cm^{-1}; HRMS (CI): calcd for $[C_{18}H_{15}N_2O_4]^+$ ([M-H]$^+$): 323.1032, found: 323.1036

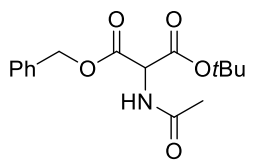
3-1-3. Synthetic route for α-amido malonic esters



A solution of acetamide (101 mg, 1.70 mmol) and rhodium(II) acetate (2.5mol%) in 1,2-dichloroethane(10 mL) was heated to reflux. To this solution was added a solution of the diazocompound **121b** (500 mg, 1.42 mmol) in 1,2-dichloroethane(5 mL) dropwise over 1

hour. The reaction was stirred for a further 12 hours until the reaction was complete. The mixture was evaporated and concentrated for loading on flash column chromatography without further work-up procedure. Eluting with hexane-EtOAc (5:1) afforded purified α-acetamidomalonate **122b** (272 mg, 50% yield) as a white solid

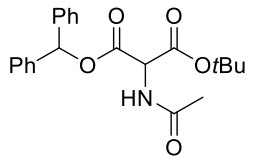
1-Benzyl 3-(*tert*-butyl) 2-acetamidomalonate (122a)



122a

Following the procedure above from **121a** using acetamide, the title compound **122a** was obtained as colorless oil (49% yield). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.33 ~ 7.29 (m, 5H), 6.54 ~ 6.53 (d, 1H, *J* = 5.8 Hz), 5.28 ~ 5.26 (d,1H, *J* =12.1 Hz), 5.13 ~ 5.10 (d, 1H, *J* =12.1 Hz), 5.09 ~ 5.08 (d, 1H, *J* = 7.0 Hz), 2.03 (s, 3H), 1.33 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 169.71, 166.63, 165.00, 134.90, 128.52, 128.40, 83.84, 67.75, 57.03, 27.59, 22.69 ppm; IR (KBr) 3286, 2980, 2939, 1756, 1666, 1524, 1500, 1371, 1149, 1003, 770, 754, 699 cm^{-1}; HRMS (FAB): calcd for $[C_{16}H_{22}NO_5]^+$ ($[M+H]^+$): 308.1498, found: 308.1494

1-Benzhydryl 3-(tert-butyl) 2-acetamidomalonate (122b)

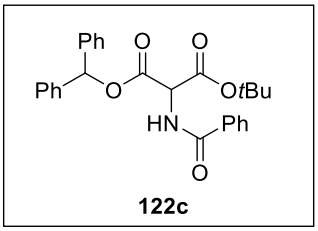


122b

Following the procedure above from **121b** using acetamide, the title compound **122b** was obtained as a white solid (mp 120.3 ºC, 50% yield).; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.33 ~ 7.25 (m, 10H), 6.92 (s, 1H), 6.56 ~ 6.54 (d, 1H, *J* = 6.7 Hz), 5.20 ~ 5.18 (d, 1H, *J* = 7.0 Hz), 2.01 (s, 3H), 1.33 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.63, 165.87, 164.92, 139.16, 139.02, 128.46, 128.40, 128.16, 128.06, 127.33, 126.95,

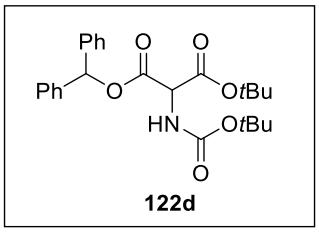
83.84, 78.73, 57.21, 27.59, 22.61 ppm; IR (KBr) 3299, 2980, 1756, 1666, 1371, 772, 700 cm^{-1}; HRMS (FAB): calcd for $[C_{22}H_{26}NO_5]^+$ ($[M+H]^+$): 384.1811, found: 384.1803

1-Benzhydryl 3-(*tert*-butyl) 2-benzamidomalonate (122c)



Following the procedure above from **121b** using benzamide, the title compound **122c** was obtained as colorless oil (37% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.84 ~ 7.81 (m, 2H), 7.55 ~ 7.20 (m, 13H), 7.13 ~ 7.11 (d, 1H, *J* = 6.6 Hz), 6.97 (s, 1H), 5.38 ~ 5.36 (d, 1H, *J* = 6.8Hz), 1.37(s, 1H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 166.80, 165.81, 164.92, 139.17, 139.04, 133.13, 131.95, 128.54, 128.50, 128.43, 128.18, 128.11, 127.33, 127.18, 127.03, 84.08, 78.85, 57.62, 27.64 ppm; IR (KBr) 3430, 2980, 1755, 1667, 1483, 1369, 1339, 1220, 1148, 772, 699 cm^{-1}; HRMS (FAB): calcd for $[C_{27}H_{28}NO_5]^+$ ($[M+H]^+$): 446.1967, found: 446.1967

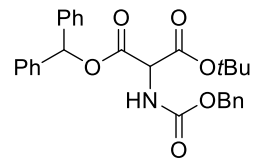
1-Benzhydryl 3-(*tert*-butyl) 2-((*tert*-butoxycarbonyl)amino)malonate (122d)



Following the procedure above from **121b** using *tert*-butyloxycarboxamide, the title compound **122d** was isolated as pale yellow oil (30% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.30 ~ 7.21 (m, 10H), 6.89 (s, 1H), 5.52 ~ 5.49 (d, 1H, *J* = 7.3 Hz), 4.93 ~ 4.90 (d, 1H, *J* = 7.7 Hz), 1.39 (s, 9H), 1.29 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 166.10, 165.13, 154.71, 139.30, 139.20, 128.49, 128.43, 128.22, 128.12, 127.28, 127.11, 83.63, 80.39, 78.55, 58.43, 28.20, 27.64 ppm; IR (KBr) 3440, 2979, 2932, 1759,

1720, 1496, 1368, 1220, 1161, 772 cm-1, HRMS (CI): calcd for $[C_{25}H_{32}NO_6]^+$ ($[M+H]^+$): 442.2230, found: 442.2229

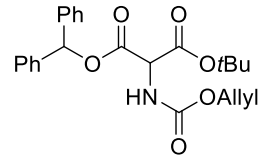
1-Benzhydryl 3-(*tert*-butyl) 2-(((benzyloxy)carbonyl)amino)malonate (122e)



122e

Following the procedure above from **121b** using benzyl carbamate, the title compound **122e** was isolated as colorless oil (32% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.33 ~ 7.24 (m, 15H), 6.93 (s, 1H), 5.81 ~ 5.78 (d, 1H, *J* = 7.5Hz), 5.10 (s, 2H), 5.06 ~ 5.01 (d, 1H, *J* = 7.53 Hz), 1.33 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 165.80, 164.79, 155.28, 139.20, 139.09, 136.01, 128.53, 128.50, 128.47, 128.20, 128.15, 128.08, 127.32, 127.07, 83.94, 78.80, 67.29, 58.63, 27.64 ppm; IR (KBr) 1759, 1730, 1622, 1497, 1339, 1220, 1148, 840, 772 cm^{-1}; HRMS (CI): calcd for $[C_{28}H_{30}NO_6]^+$ ($[M+H]^+$): 476.2073, found: 476.2071

1-Benzhydryl 3-(tert-butyl) 2-(((allyloxy)carbonyl)amino)malonate (122f)

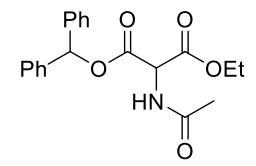


122f

Following the procedure above from **121b** using allyl carbamate, the title compound **122f** was isolated as colorless oil (33% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.33 ~ 7.26 (m, 10H), 6.94 (s, 1H), 5.92 ~ 5.83 (m, 1H), 5.79 ~ 5.78 (d, 1H, *J* = 7.4 Hz), 5.31 ~ 5.28 (d, 1H, *J* = 17.2 Hz), 5.20 ~ 5.18 (d, 1H, *J* = 10.4 Hz), 5.03 ~ 5.01 (d, 1H, *J* = 7.7 Hz), 4.57 ~ 4.56 (d, 2H, *J* = 5.4 Hz), 1.34 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 165.79, 164.79, 155.21, 139.15, 139.03, 132.31, 128.48, 128.43, 128.17, 128.10, 127.29, 127.01, 83.89, 78.73, 66.05, 58.51, 27.59 ppm; IR (KBr) 2980, 1759, 1731, 1648,

1497, 1220, 1148, 1059, 772, 700 cm^{-1};HRMS (FAB): calcd for $[C_{24}H_{28}NO_6]^+$ ($[M+H]^+$): 426.1917, found: 426.1931

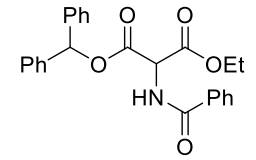
1-Benzhydryl 3-ethyl 2-acetamidomalonate (122g)



122g

Following the procedure above from **121c** using acetamide, the title compound **122g** was obtained as a white solid (mp 106.1 °C, 46% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) 7.36 ~ 7.24 (m, 10H), 6.90 (s, 1H), 6.60 ~ 6.57 (d, 1H, *J* = 7.0 Hz), 5.31 ~ 5.29 (d, 1H, *J* = 7.0 Hz), 4.21 ~ 4.14 (q, 2H, *J* = 7.2 Hz), 2.02 (s, 3H), 1.19-1.14 (t, 3H, *J* = 7.2 Hz) ppm; ^{13}C-NMR (150 MHz, $CDCl_3$) δ 169.71, 166.11, 165.52, 139.06, 138.92, 128.53, 128.42, 128.20, 128.17, 127.04, 127.03, 79.03, 62.65, 56.55, 22.63, 13.79 ppm; IR (KBr) 3284, 3063, 3033, 2983, 1760, 1743, 1666, 1221, 1158, 1028, 771, 700 cm^{-1}; HRMS (FAB): calcd for $[C_{20}H_{22}NO_5]^+$ ($[M+H]^+$): 356.1498, found: 356.1489

1-Benzhydryl 3-ethyl 2-benzamidomalonate (122h)

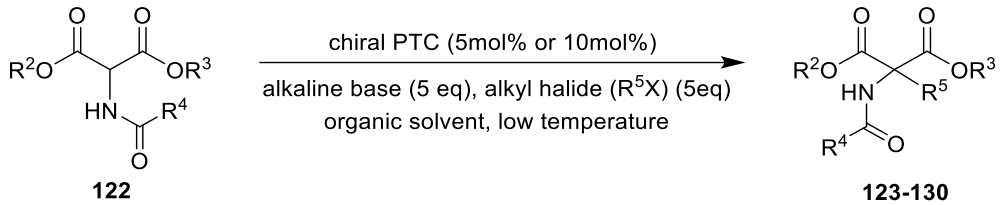


122h

Following the procedure above from **121c** using benzamide, the title compound **122h** was obtained as a white solid (mp 120.4 °C, 48% yield). ^{1}H-NMR (300MHz, $CDCl_3$) δ 7.83 ~ 7.80 (d, 2H, *J* = 7.6 Hz), 7.60 ~ 7.24(m, 13H), 7.16 ~ 7.14(d, 1H, *J* = 6.8 Hz), 6.95 (s, 1H), 5.50 ~ 5.48(dd, 1H, J_1 = 7.0 Hz J_2 = 0.9 Hz), 4.26 ~ 4.16 (qd, 2H, J_1 = 6.7 Hz J_2 = 0.9 Hz), 1.25 ~ 1.15 (t, 3H, *J* = 6.7 Hz) ppm; ^{13}C-NMR (125MHz, $CDCl_3$) δ 166.84, 166.10, 165.49, 139.07, 138.94, 132.95, 132.06, 128.58, 128.56, 128.45, 128.23, 128.19, 127.22, 127.08, 127.03, 79.16, 62.77, 56.98, 13.84 ppm; IR (KBr) 3566,

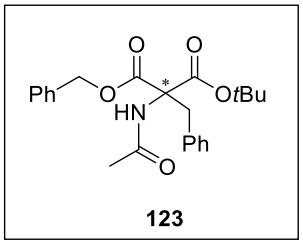
1758, 1665, 1509, 1338, 1220, 772, 673 cm^{-1}; HRMS (FAB): calcd for $[C_{25}H_{24}NO_5]^+$ ($[M+H]^+$): 418.1654, found: 418.1653.

3-2. General procedure of asymmetric phase-transfer catalytic α-alkylation



Alkyl halide (5 equiv.) was added to a solution of prepared α-amido malonates (**122**, 30mg) and phase transfer catalyst (5-10 mol%) in organic solvent at room temperature. At the designated low temperature, alkaline base (5 equiv.) was added to the reaction mixture and stirred until the starting material disappeared. After completion of the reaction, the reaction mixture was diluted with ethyl acetate (20 ml), washed with brine (10 mL x 2), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane : EtOAc = 10 : 1) to afford desired chiral product.

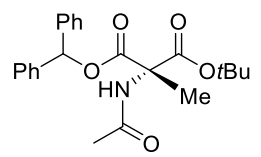
<u>1-Benzyl 3-(*tert*-butyl) 2-acetamido-2-benzylmalonate (123)</u>



Following the PTC procedure from **122a**, the title compound **123** was obtained as colorless oil (92% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.40 ~ 7.30 (m, 5H), 7.21 ~ 7.18 (m, 3H), 7.00 ~ 6.94 (m, 2H), 6.50 (s, 1H), 5.29 ~ 5.25 (d,1H, *J* =12.0 Hz), 5.17 ~ 5.13 (d, 1H, *J* =12.0 Hz), 3.68 ~ 3.63 (d, 1H, *J* =14.0 Hz), 3.58 ~ 3.53 (d, 1H, *J* =14.0

Hz), 1.99 (s, 3H), 1.32 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 168.95, 167.62, 166.13, 135.31, 135.04, 129.95, 128.90, 128.54, 128.52, 128.13, 127.04, 83.90, 67.27, 67.37, 37.63, 27.55, 22.97 ppm; IR (KBr) 3412, 2979, 2933, 1739, 1681, 1496, 1370, 1217, 1198, 1150, 1048, 771, 701 cm^{-1}; HRMS (FAB): calcd for $[C_{23}H_{28}NO_5]^+$ ($[M+H]^+$): 398.1967, found: 398.1966; The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD-H, hexane : 2-propanol = 80 : 20, flow rate = 1.0 mL/min, 23 ºC, λ = 254 nm, retention time ; minor isomer 6.99 min, major isomer 8.03 min, 47% ee, $[\alpha]^{25}_D$ = + 6.92 (*c* 1.0, $CHCl_3$).

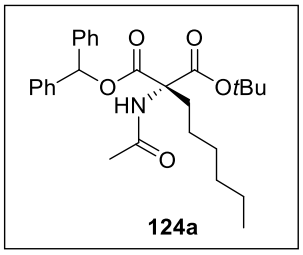
<u>1-Benzhydryl 3-(*tert*-butyl) 2-acetamido-2-methylmalonate (124a)</u>



124a

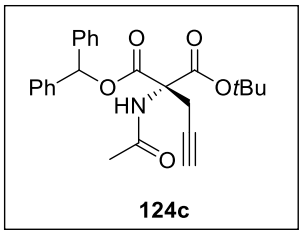
Following the PTC procedure from **122b**, the title compound **124a** was obtained as a white solid (mp 151.6 ºC, 99% yield). ^{1}H-NMR (300MHz, $CDCl_3$) δ 7.33 ~ 7.22 (m, 10H), 6.90 (s, 1H), 6.81 (s, 1H), 1.94 (s, 3H), 1.72 (s, 3H), 1.23 (m, 9H) ppm; ^{13}C-NMR (400MHz, $CDCl_3$) δ 168.82, 167.80, 167.63, 139.30, 139.28, 128.46, 128.33, 128.09, 128.02, 127.40, 127.36, 83.63, 78.43, 63.46, 27.47, 23.00, 20.88 ppm; IR (KBr) 3412, 1681, 1292, 2928, 1737, 1497, 1370, 1117, 700 cm^{-1}; HRMS (FAB): calcd for $[C_{23}H_{28}NO_5]^+$ ($[M+H]^+$): 398.1967, found: 398.1957; The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD-H, hexane : 2-propanol = 80 : 20, flow rate = 1.0 mL/min, 23 ºC, λ = 254 nm, retention time ; minor isomer 7.57 min, major isomer 25.22 min, 30% ee, $[\alpha]^{25}_D$ = - 4.28 (*c* 1.0, $CHCl_3$).

1-Benzhydryl 3-(*tert*-butyl) 2-acetamido-2-hexylmalonate (124b)



Following the PTC procedure from **122b**, the title compound **124b** was obtained as a white solid (mp 90.9 ºC, 26% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.27 ~ 7.17 (m, 10H), 6.87 (s, 1H), 6.70 (s, 1H), 2.38 ~ 2.15 (m, 2H), 1.92 (s, 3H), 1.20 ~ 1.11 (m, 15H), 0.95 ~ 0.90 (s, 2H), 0.79 ~ 0.74 (t, 3H, *J* = 6.9 Hz) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.68, 167.53, 166.98, 139.36, 139.27, 128.45, 128.33, 128.16, 127.99, 127.61, 127.28, 83.51, 78.33, 67.14, 32.08, 31.56, 28.94, 27.54, 23.41, 23.04, 22.46, 13.99 ppm; IR (KBr) 2956, 2926, 2856, 1738, 1682, 1496, 1219, 1155, 772 cm^{-1}; HRMS (FAB) calcd for $[C_{28}H_{38}NO_5]^+$ ($[M+H]^+$): 468.2750, found: 468.2764; The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD-H, hexane : 2-propanol = 80 : 20, flow rate = 1.0 mL/min, 23 ºC, λ = 254 nm, retention time ; minor isomer 8.50 min, major isomer 17.66 min, 65% ee, $[\alpha]^{25}_{D}$ = + 4.49 (*c* 1.0, $CHCl_3$).

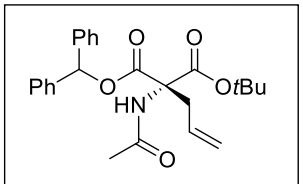
1-Benzhydryl 3-(*tert*-butyl) (*R*)-2-acetamido-2-(prop-2-yn-1-yl) malonate (124c)



Following the PTC procedure from **122b**, the title compound **124c** was obtained as a white solid (mp 135.2 ºC, 99% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.31 ~ 7.18 (m, 10H), 6.91 ~ 6.88 (m, 2H), 3.37 ~ 3.30 (dd,1H, J_1 = 17.2 Hz, J_2 = 2.8 Hz), 3.21 ~ 3.15 (dd,1H, J_1 = 17.2 Hz, J_2 = 2.8 Hz) 1.96 (m, 3H), 1.87 ~ 1.85 (t, 1H, *J* = 2.66 Hz), 1.23 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.16, 165.86, 165.25, 139.00, 128.41, 128.34, 128.14, 128.11, 127.49, 127.38, 84.38, 78.82, 78.36, 71.28, 65.66, 27.44, 23.70, 22.83 ppm; IR (KBr) 3413, 3294, 2979, 2926, 2854, 2122, 1740, 1682, 1496, 1314, 1218, 1151, 963, 772, 699, 648 cm^{-1}; HRMS(FAB): calcd for $[C_{25}H_{28}NO_5]^+$ ($[M+H]^+$):

422.1967, found: 422.1977; The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD-H, hexane : 2-propanol = 80 : 20, flow rate = 1.0 mL/min, 23 ºC, λ = 254 nm, retention time ; minor isomer 10.46 min, major isomer 25.78 min, 54% ee, $[\alpha]^{25}_{D}$ = + 5.39 (*c* 1.0, $CHCl_3$)

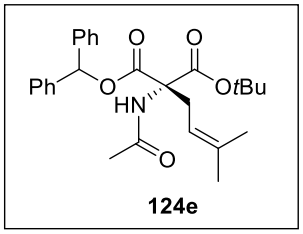
<u>1-Benzhydryl 3-(*tert*-butyl) (*R*)-2-acetamido-2-allylmalonate (124d)</u>



124d

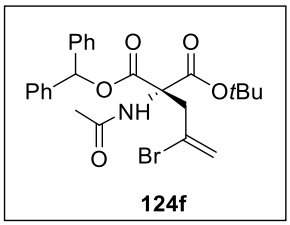
Following the PTC procedure from **122b**, the title compound **124d** was obtained as a white solid (mp 71.9 ºC, 99% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.30 ~ 7.22 (m, 10H), 6.90 (s, 1H), 6.71 (s, 1H), 5.53 ~ 5.39 (m, 1H), 5.01 ~ 4.94 (m, 2H), 3.19 ~ 3.12 (m, 1H), 3.02 ~ 2.94 (m, 1H), 1.95 (s, 3H), 1.22 (m, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.83, 166.88, 166.39, 139.23, 131.20, 128.45, 128.32, 128.16, 128.01, 127.62, 127.30, 119.72, 83.90, 78.46, 66.50, 36.84, 27.55, 22.93 ppm; IR (KBr) 3408, 2926, 1736, 1683, 1496, 1219, 1154, 959, 772, 699 cm^{-1}; HRMS(FAB): calcd for $[C_{25}H_{30}NO_5]^+$ ($[M+H]^+$): 424.2124, found: 424.2111; The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD-H, hexane : 2-propanol = 80 : 20, flow rate = 1.0 mL/min, 23 ºC, λ = 254 nm, retention time ; minor isomer 9.42 min, major isomer 19.04 min, 76% ee, $[\alpha]^{25}_{D}$ = + 6.02 (*c* 1.0, $CHCl_3$).

1-Benzhydryl 3-(*tert*-butyl) (*R*)-2-acetamido-2-(3-methylbut-2-en-1-yl) malonate (124e)



Following the PTC procedure from **122b**, the title compound **124e** was obtained as a white solid (mp 108.8 °C, 99% yield). ^{1}H-NMR (300MHz, $CDCl_3$) δ 7.26 ~ 7.17 (m, 10H), 6.87 (s, 1H), 6.69 (s, 1H), 4.75 ~ 4.70 (t, 1H, J = 7.41 Hz), 3.08 ~ 2.91 (qd, 2H, J_1 = 15.3 Hz, J_2 = 7.5 Hz), 1.90 (s, 3H), 1.55 (s, 3H), 1.46 (s, 3H), 1.19 (s, 9H); ^{13}C-NMR (400MHz, $CDCl_3$) δ 168.70, 167.15, 166.65, 139.29, 136.53, 128.40, 128.29, 128.08, 127.96, 127.63, 127.32, 116.58, 83.61, 78.36, 66.74, 31.31, 27.47, 25.88, 22.93, 17.99; IR (KBr) 3415, 2925, 1736, 1682, 1496, 1219, 1152, 772, 699 cm^{-1}; HRMS(FAB): calcd for $[C_{27}H_{34}NO_5]^+$ ($[M+H]^+$): 452.2437, found: 452.2430; The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD-H, hexane : 2-propanol = 80 : 20, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm, retention time ; minor isomer 8.03 min, major isomer 17.28 min, 77% ee, $[\alpha]^{25}_D$ = + 10.84 (*c* 1.0, $CHCl_3$)

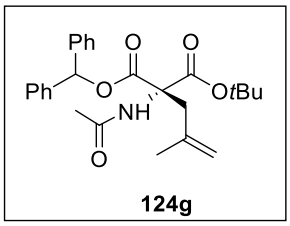
1-Benzhydryl 3-(*tert*-butyl) (*R*)-2-acetamido-2-(2-bromoallyl) malonate (124f)



Following the PTC procedure from **122b**, the title compound **124f** was obtained as a white solid (mp 93.9 °C, 99% yield). ^{1}H-NMR (300MHz, $CDCl_3$) δ 7.28 ~ 7.19 (m, 10H), 6.89 (s, 1H), 6.83 (s, 1H), 5.44 (s, 1H), 5.41 ~ 5.41 (d, 1H, J = 1.5 Hz), 3.65 ~ 3.41 (dd, 2H, J_1 = 55.3 Hz, J_2 = 15.0 Hz), 1.93 (s, 3H), 1.20 (s, 9H) ppm; ^{13}C-NMR (400MHz, $CDCl_3$) δ 169.08, 166.60, 165.69, 139.11, 138.94, 128.48, 128.36, 128.24, 128.10, 127.71, 127.33, 126.45, 122.15, 84.44, 78.93, 65.97, 42.91, 27.53, 22.87 ppm; IR (KBr) 3412, 2979, 2930, 1739, 1682, 1628, 1496, 1151, 961, 903, 840, 742, 700 cm^{-1}; HRMS (FAB): calcd for $[C_{25}H_{29}BrNO_5]^+$ ($[M+H]^+$): 502.1229, found: 502.1221 ; The

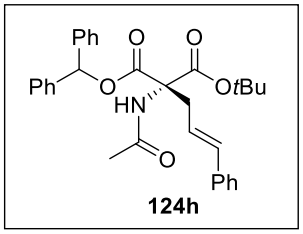
enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD-H, hexane : 2-propanol = 80 : 20, flow rate = 1.0 mL/min, 23 ^{o}C, λ = 254 nm, retention time ; minor isomer 12.20 min, major isomer 18.20 min, 86 % ee, $[\alpha]^{25}_{D}$ = + 2.01 (*c* 1.0, $CHCl_3$)

<u>1-Benzhydryl 3-(*tert*-butyl) (*R*)-2-acetamido-2-(2-methylallyl) malonate (124g)</u>



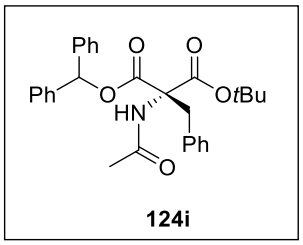
Following the PTC procedure from **122b**, the title compound **124g** was obtained as a white solid (mp 112.0 ^{o}C, 98% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.32 ~ 7.20 (m, 10H), 6.90 (s, 1H), 6.76 (s, 1H), 4.74 (m, 1H), 4.56 (s, 1H), 3.19 ~ 3.14 (d, 1H, *J* = 14.2 Hz), 3.04 ~ 2.99 (d, 1H, *J* = 14.2 Hz), 1.93 (s, 3H), 1.55 (s, 3H), 1.20 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.77, 167.32, 166.71, 140.02, 139.28, 139.13, 128.44, 128.31, 128.16, 128.00, 127.69, 127.31, 115.80, 83.91, 78.52, 66.57, 39.57, 27.52, 23.32, 22.94 ppm; IR (KBr) 3413, 2979, 1736, 1682, 1370, 1277, 1219, 841, 772 cm^{-1}; HRMS(FAB) calcd for $[C_{26}H_{32}NO_5]^+$ ($[M+H]^+$): 438.2280, found: 438.2277; The enantio selectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD-H, hexane : 2-propanol = 80 : 20, flow rate = 1.0 mL/min, 23 ^{o}C, λ = 254 nm, retention time ; minor isomer 8.97 min, major isomer 17.43 min, 91% ee, $[\alpha]^{25}_{D}$ = + 8.16 (*c* 1.0, $CHCl_3$).

1-Benzhydryl 3-(*tert*-butyl) (*R*)-2-acetamido-2-cinnamylmalonate (124h)



Following the PTC procedure from **122b**, the title compound **124h** was obtained as a white solid (mp 130.2 ºC, 99% yield). ^{1}H-NMR (300MHz, $CDCl_3$) δ 7.30 ~ 7.10 (m, 15H), 6.89 (s, 1H), 6.72 (s, 1H), 6.29 ~ 6.23 (d, 1H, *J* = 15.8 Hz), 5.82 ~ 5.72 (m, 1H), 3.29 ~ 3.09 (m, 2H), 1.93 (s, 3H), 1.21 (s, 9H) ppm; ^{13}C-NMR (400MHz, $CDCl_3$) δ 168.93, 166.89, 166.30, 139.19, 139.17, 136.88, 134.54, 128.48, 128.40, 128.32, 128.20, 128.00, 127.67, 127.39, 127.23, 126.16, 122.65, 83.88, 78.53, 66.85, 36.21, 27.58, 22.97 ppm; IR (KBr) 3406, 3028, 2979, 1735, 1676, 1495, 1219, 967, 772 cm^{-1}; HRMS (FAB): calcd for $[C_{31}H_{34}NO_5]^+$ ($[M+H]^+$): 500.2437, found: 500.2423. The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD-H, hexane : 2-propanol = 80 : 20, flow rate = 1.0 mL/min, 23 ºC, λ = 254 nm, retention time ; minor isomer 11.67 min, major isomer 22.87 min, 71 % ee, $[\alpha]^{25}_{D}$ = + 18.67 (*c* 1.0, $CHCl_3$).

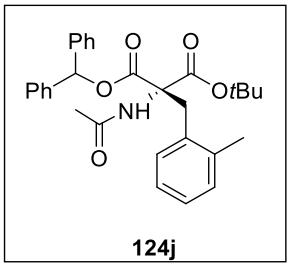
1-Benzhydryl 3-(*tert*-butyl) (*R*)-2-acetamido-2-benzylmalonate (124i)



Following the PTC procedure from **122b**, the title compound **124i** was obtained as a white solid (mp 164.5 ºC, 97% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.41 ~ 7.26 (m, 10H), 7.17 ~ 7.11 (m, 3H), 6.98 (s, 1H), 6.87 ~ 6.85 (d, 2H, *J* = 6.4 Hz), 6.53 (s, 1H), 3.73 ~ 3.69 (d,1H, *J* =14.0 Hz), 3.63 ~ 3.59 (d, 1H, *J* =14.0 Hz), 1.96 (s, 3H), 1.28 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.86, 167.01, 166.13, 139.20, 139.13, 135.30, 129.99, 128.57, 128.34, 128.09, 128.02, 127.95, 127.23, 126.98, 83.98, 78.66, 67.59, 37.63, 27.60, 22.97 ppm; IR (KBr) 3410, 2927, 1736, 1682,

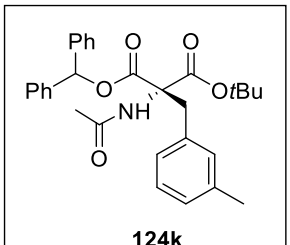
1370, 1219, 772, 700 cm^{-1}; HRMS(CI): calcd for $[C_{29}H_{32}NO_5]^+$ ($[M+H]^+$): 474.2280, found: 474.2277; The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD-H, hexane : 2-propanol = 80 : 20, flow rate = 1.0 mL/min, 23 ºC, λ = 254 nm, retention time ; minor isomer 10.20 min, major isomer 17.04 min, 95% ee, $[\alpha]^{25}_D$ = + 23.06 (*c* 1.0, $CHCl_3$).

<u>1-Benzhydryl 3-(*tert*-butyl) (*R*)-2-acetamido-2-(2-methylbenzyl) malonate (124j)</u>



Following the PTC procedure from **122b**, the title compound **124j** was obtained as a white solid (mp 125.9 ºC, 99% yield). ^{1}H-NMR (300MHz, $CDCl_3$) δ 7.40 ~ 7.26 (m, 10H), 7.08 ~ 7.03 (m, 2H), 6.97 (s, 1H), 6.95 ~ 6.87 (m, 1H), 6.83 ~ 6.81 (d, 1H, *J* = 7.3 Hz), 6.65 (s, 1H), 3.77 ~ 3.66 (dd, 2H, J_1 = 16.8 Hz, J_2 = 14.8 Hz), 2.18 (s, 3H), 1.93 (s, 3H), 1.24 (s, 9H) ppm; ^{13}C-NMR (400MHz, $CDCl_3$) δ 169.01, 167.37, 166.37, 139.17, 138.98, 137.75, 133.73, 130.45, 130.11, 128.52, 128.31, 128.26, 128.03, 127.82, 127.32, 126.88, 125.41, 84.00, 78.80, 67.59, 34.53, 27.48, 22.97, 19.56 ppm; IR (KBr) 3407, 2979, 1736, 1677, 1495, 1219, 1150, 772, 699 cm^{-1}; HRMS (FAB): calcd for $[C_{30}H_{34}NO_5]^+$ ($[M+H]^+$): 488.2437, found: 488.2438. The enantio selectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD-H, hexane : 2-propanol = 80 : 20, flow rate = 1.0 mL/min, 23 ºC, λ = 254 nm, retention time ; minor isomer 7.87 min, major isomer 12.29 min, 91 % ee, $[\alpha]^{25}_D$ = + 9.62 (*c* 1.0, $CHCl_3$)

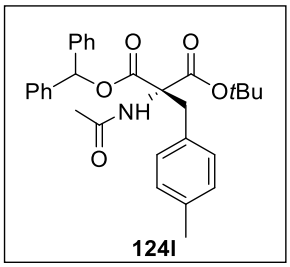
1-Benzhydryl 3-(*tert*-butyl) (*R*)-2-acetamido-2-(3-methylbenzyl) malonate (124k)



124k

Following the PTC procedure from **122b**, the title compound **124k** was obtained as a white solid (mp 143.8 ºC, 99% yield). ^{1}H-NMR (300MHz, $CDCl_3$) δ 7.42 ~ 7.26 (m, 10H), 7.10 ~ 6.97 (m, 3H), 6.69 ~ 6.66 (d, 2H, J = 8.0 Hz), 6.53 (s, 1H), 3.70 ~ 3.54 (dd, 2H, J_1 = 23.0 Hz, J_2 = 9.3 Hz), 2.17 ~ 2.15 (d, 3H, J = 6.8 Hz), 1.96 (s, 3H), 1.27 (s, 9H) ppm; ^{13}C-NMR (400MHz, $CDCl_3$) δ 168.86, 166.99, 166.12, 139.23, 139.12, 137.52, 135.14, 130.76, 128.55, 128.31, 128.28, 127.99, 127.94, 127.82, 127.71, 127.22, 126.99, 83.91, 78.56, 67.59, 37.47, 27.56, 22.91, 21.19 ppm; IR (KBr) 3413, 2979, 2929, 1737, 1682, 1496, 1370, 1219, 1150, 1043, 772, 701 cm^{-1}; HRMS (FAB): calcd for $[C_{30}H_{34}NO_5]^+$ ($[M+H]^+$): 488.2437, found: 488.2426. The enantio selectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD-H, hexane : 2-propanol = 80 : 20, flow rate = 1.0 mL/min, 23 ºC, λ = 254 nm, retention time ; minor isomer 9.85 min, major isomer 13.20 min, 94 % ee, $[\alpha]^{25}_{D}$ = + 23.15 (*c* 1.0, $CHCl_3$).

1-Benzhydryl 3-(*tert*-butyl) (*R*)-2-acetamido-2-(4-methylbenzyl) malonate (124l)

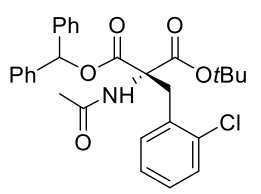


124l

Following the PTC procedure from **122b**, the title compound **124l** was obtained as a white solid (mp 165.6 ºC, 99% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.35 ~ 7.18 (m, 10H), 6.91 ~ 6.86 (m, 3H), 6.69 ~ 6.66 (m, 2H), 6.46 (s, 1H), 3.63 ~ 3.58 (d, 1H, J = 14.0 Hz), 3.52 ~ 3.47 (d, 1H, J = 14.0 Hz), 2.19 (s, 3H), 1.90 (s, 3H), 1.21 (m, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.85, 167.06, 168.19, 139.21, 139.13, 136.52, 132.08, 129.84, 128.82, 128.56, 128.32, 128.00, 127.93, 127.22, 83.89, 78.60, 67.64, 37.20, 27.60, 22.97, 21.02 ppm; IR (KBr) 3416, 2925, 1736, 1683, 1281,

1220, 1150, 772 cm^{-1}, HRMS (FAB) calcd for $[C_{30}H_{33}NO_5]^+$ ($[M+H]^+$): 488.2437, found: 488.2441; The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD-H, hexane : 2-propanol = 80 : 20, flow rate = 1.0 mL/min, 23 ºC, λ = 254 nm, retention time ; minor isomer 11.53 min, major isomer 17.09 min, 97% ee, $[\alpha]^{25}_D$ = + 22.59 (*c* 1.0, $CHCl_3$).

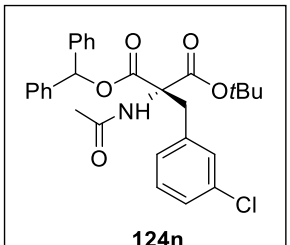
<u>1-Benzhydryl 3-(*tert*-butyl) (*R*)-2-acetamido-2-(2-chlorobenzyl) malonate (124m)</u>



124m

Following the PTC procedure from **122b**, the title compound **124m** was obtained as a white solid (mp 122.0 ºC, 93% yield). ^{1}H-NMR (300MHz, $CDCl_3$) δ 7.42 ~ 7.25 (m, 10H), 7.13 ~ 7.07 (m, 1H), 7.01 ~ 6.94 (m, 4H), 6.55 (s, 1H), 3.90 ~ 3.77 (dd, 2H, J_1 = 25.3 Hz, J_2 = 14.3 Hz), 1.94 (s, 3H), 1.26 (s, 9H) ppm; ^{13}C-NMR (400MHz, $CDCl_3$) δ 169.04, 167.22, 166.09, 139.22, 138.97, 135.22, 133.49, 132.04, 129.62, 128.55, 128.42, 128.34, 128.25, 128.05, 127.74, 127.35, 126.33, 84.02, 78.98, 67.03, 35.07, 27.52, 22.99 ppm; HRMS (FAB): calcd for $[C_{29}H_{31}ClNO_5]^+$ ($[M+H]^+$): 508.1891, found: 508.1887. The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD-H, hexane : 2-propanol = 80 : 20, flow rate = 1.0 mL/min, 23 ºC, λ = 254 nm, retention time ; minor isomer 8.34 min, major isomer 16.67 min, 93 % ee, $[\alpha]^{25}_D$ = + 5.18 (*c* 1.0, $CHCl_3$)

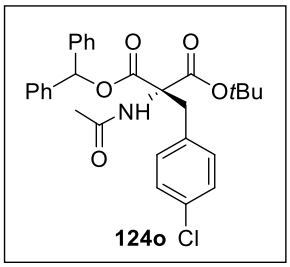
1-Benzhydryl 3-(*tert*-butyl) (*R*)-2-acetamido-2-(3-chlorobenzyl) malonate (124n)



124n

Following the PTC procedure from **122b**, the title compound **124n** was obtained as a white solid (mp 137.5 °C, 84 % yield). ^{1}H-NMR (300MHz, $CDCl_3$) δ 7.40 ~ 7.26 (m, 10H), 7.17 ~ 7.14 (m, 1H), 7.09 ~ 7.03 (t, 1H, J = 7.8 Hz), 6.96 (s, 1H), 6.90 (m, 1H), 6.74 ~ 6.72 (m, 1H), 6.55 (s, 1H), 3.71 ~ 3.55 (dd, 2H, J_1 = 35.6 Hz, J_2 = 14.0 Hz), 1.98 (s, 3H), 1.27 (s, 9H) ppm; ^{13}C-NMR (400MHz, $CDCl_3$) δ 169.08, 166.73, 165.90, 139.11, 139.00, 137.36, 133.91, 130.11, 129.34, 128.63, 128.41, 128.37, 128.15, 128.08, 127.88, 127.24, 127.21, 84.40, 78.81, 67.43, 37.22, 27.59, 22.95 ppm; IR (KBr) 3409, 2925, 1738, 1496, 1219, 1081, 772, 2853, 1681, 1370, 1150, 699 cm^{-1}; HRMS (FAB): calcd for $[C_{29}H_{31}ClNO_5]^+$ ($[M+H]^+$): 508.1891, found: 508.1901. The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD-H, hexane : 2-propanol = 80 : 20, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm, retention time ; minor isomer 9.45 min, major isomer 15.46 min, 90 % ee, $[\alpha]^{25}_{D}$ = + 23.83 (*c* 1.0, $CHCl_3$).

1-Benzhydryl 3-(*tert*-butyl) (*R*)-2-acetamido-2-(4-chlorobenzyl) malonate (124o)

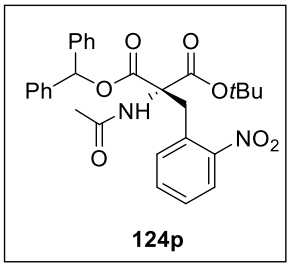


124o

Following the PTC procedure from **122b**, the title compound **124o** was obtained as a white solid (mp 158.9 °C, 86 % yield). ^{1}H-NMR (300MHz, $CDCl_3$) δ 7.39 ~ 7.26 (m, 10H), 7.09 ~ 7.06 (m, 2H), 6.96 (s, 1H), 6.74-6.72 (m, 2H), 6.52 (s, 1H), 3.68 ~ 3.55 (dd, 2H, J_1 = 24.0 Hz, J_2 = 14.1 Hz), 1.96 (s, 3H), 1.27 (s, 9H) ppm; ^{13}C-NMR (400MHz, $CDCl_3$) δ 169.00, 166.85, 165.94, 139.00, 138.99, 133.78, 132.95, 131.24, 128.63, 128.47, 128.37, 128.27, 128.08, 128.00, 127.13, 84.13, 78.80, 67.45, 36.98, 27.60, 22.96 ppm; IR (KBr) 3410, 2926, 1738, 1219, 1150, 1092, 2854, 1680,

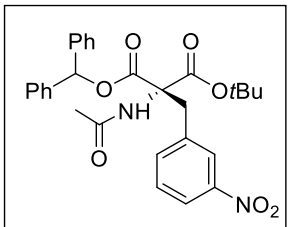
1493, 772 cm^{-1} ; HRMS (FAB): calcd for $[C_{29}H_{31}ClNO_5]^+$ ($[M+H]^+$): 508.1891, found: 508.1901. The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD-H, hexane : 2-propanol = 80 : 20, flow rate = 1.0 mL/min, 23 ºC, λ = 254 nm, retention time ; minor isomer 11.76 min, major isomer 18.48 min, 97 % ee, $[\alpha]^{25}_D$ = + 20.33 (*c* 1.0, $CHCl_3$).

<u>1-Benzhydryl 3-(*tert*-butyl) (*R*)-2-acetamido-2-(2-nitrobenzyl) malonate (124p)</u>



Following the PTC procedure from **122b**, the title compound **124p** was obtained as a white solid (mp 156.7 ºC, 99% yield). ^{1}H-NMR (300MHz, $CDCl_3$) δ 7.69 ~ 7.67 (d, 1H, *J* = 7.7 Hz) 7.30 ~ 7.19 (m, 12H), 7.04 ~ 7.02 (d, 1H, *J* = 7.3 Hz), 6.83 (s, 1H), 6.46 (s, 1H), 4.05 ~ 3.94 (dd, 2H, J_1 = 18.9 Hz, J_2 = 14.5 Hz), 1.84 (s, 3H), 1.16 (s, 9H); ^{13}C-NMR (400MHz, $CDCl_3$) δ 169.28, 166.85, 165.82, 150.86, 139.04, 138.94, 133.57, 132.04, 129.84, 128.57, 128.35, 128.15, 128.08, 127.86, 127.27, 124.61, 84.47, 79.15, 67.10, 34.41, 27.47, 22.69 ppm; IR (KBr) 3402, 2928, 1685, 1357, 1219, 1150, 860, 772, 1737, 1608, 1528 cm^{-1}; HRMS (FAB) calcd for $[C_{29}H_{31}N_2O_7]^+$ ($[M+H]^+$): 519.2131, found: 519.2130. The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD-H, hexane : 2-propanol = 80 : 20, flow rate = 1.0 mL/min, 23 ºC, λ = 254 nm, retention time ; minor isomer 13.38 min, major isomer 32.97 min, 78 % ee, $[\alpha]^{25}_D$ = + 37.81 (*c* 1.0, $CHCl_3$).

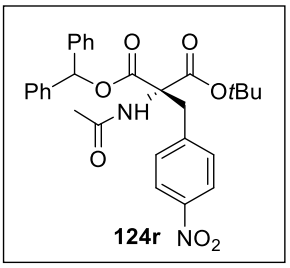
1-Benzhydryl 3-(*tert*-butyl) (*R*)-2-acetamido-2-(3-nitrobenzyl) malonate (124q)



124q

Following the PTC procedure from **122b**, the title compound **124n** was obtained as a white solid (mp 153.0 ºC, 99% yield). ^{1}H-NMR (300MHz, $CDCl_3$) δ 8.00 ~ 7.98 (d, 1H, *J* = 8.1 Hz), 7.78 (s, 1H), 7.31 ~ 7.19 (m, 11H), 7.12 ~ 7.09 (d, 1H, *J* = 7.5 Hz), 6.92 (s, 1H), 6.51 (s, 1H), 3.81 ~ 3.62 (dd, 2H, J_1 = 43.0 Hz, J_2 = 14.1 Hz), 1.94 (s, 3H), 1.22 (s, 9H) ppm; ^{13}C-NMR (400MHz, $CDCl_3$) δ 169.34, 166.49, 165.74, 148.03, 138.95, 138.89, 137.44, 136.23, 129.02, 128.64, 128.46, 128.39, 128.14, 127.84, 127.18, 124.73, 122.20, 84.84, 78.97, 67.30, 37.18, 27.57, 22.93 ppm; IR (KBr) 3403, 1678, 1530, 1220, 1149, 838, 772, 2925, 1737, 1353, 699 cm^{-1}; HRMS (FAB): calcd for $[C_{29}H_{31}N_2O_7]^+$ ($[M+H]^+$): 519.2131, found: 519.2134. The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD-H, hexane : 2-propanol = 80 : 20, flow rate = 1.0 mL/min, 23 ºC, λ = 254 nm, retention time ; minor isomer 18.40 min, major isomer 29.43 min, 92 % ee, $[\alpha]^{25}_{D}$ = + 29.92 (*c* 1.0, $CHCl_3$).

1-Benzhydryl 3-(*tert*-butyl) (*R*)-2-acetamido-2-(4-nitrobenzyl) malonate (124r)

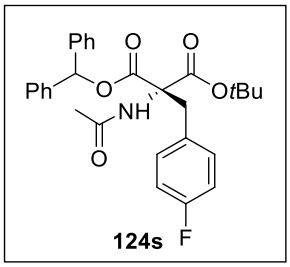


124r

Following the PTC procedure from **122b**, the title compound **124r** was obtained as a white solid (mp 168.8 ºC, 99% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.92 ~ 7.89 (d, 2H, *J* = 8.6 Hz), 7.34 ~ 7.19 (m, 10H), 6.92 ~ 6.86 (t, 3H, *J* = 9.1 Hz), 6.47 (s, 1H), 3.75 ~ 3.65 (dd, 2H, J_1 = 18.3 Hz, J_2 = 14.1 Hz), 1.93 (s, 3H), 1.24 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.24, 166.64, 165.67, 147.13, 143.19, 138.83, 138.78, 130.78, 128.75, 128.70, 128.45, 128.21, 128.08, 127.76, 127.08, 123.78, 123.26, 84.52, 79.12, 67.28, 37.51, 31.92, 29.70, 29.35, 27.63, 23.00, 22.68, 14.10

ppm; IR (KBr) 2979, 2925, 1738, 1522, 1348, 1219, 1149 cm^{-1}; HRMS(FAB): calcd for $[C_{29}H_{31}N_2O_7]^+$ ($[M+H]^+$): 519.2131, found: 519.2131; The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD-H, hexane : 2-propanol = 80 : 20, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm, retention time ; minor isomer 23.37 min, major isomer 34.80 min, 96% ee, $[\alpha]^{25}_D$ = +25.54 (*c* 1.0, $CHCl_3$).

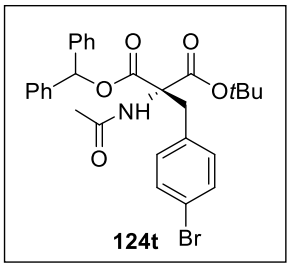
<u>1-Benzhydryl 3-(*tert*-butyl) (*R*)-2-acetamido-2-(4-fluorobenzyl) malonate (124s)</u>



124s

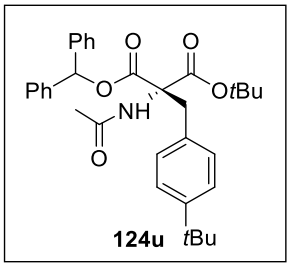
Following the PTC procedure from **122b**, the title compound **124s** was obtained as a white solid (mp 154.4 °C, 99% yield). ^{1}H-NMR (300MHz, $CDCl_3$) δ 7.40 ~ 7.24 (m, 10H), 6.96 (s, 1H), 6.84 ~ 6.74 (m, 4H), 6.52 (s, 1H), 3.69 ~ 3.56 (dd, 2H, J_1 = 25.3 Hz, J_2 = 14.3 Hz), 1.96 (s, 3H), 1.27 (m, 9H) ppm; ^{13}C-NMR (400MHz, $CDCl_3$) δ 168.97, 166.93, 166.02, 163.18 ~ 160.74(d, *J* = 243.8 Hz), 139.05, 139.03, 131.45-131.37(d, *J* = 7.9 Hz), 130.98~ 130.94 (d, *J* = 3.1 Hz), 128.63, 128.44, 128.37, 128.07, 128.00, 127.15, 115.09, 114.88, 84.09, 78.76, 67.56, 36.82, 27.61, 22.97 ppm; IR (KBr) 3408, 2926, 1736, 1676, 1510, 1220, 1150, 841, 772 cm^{-1}; HRMS (FAB): calcd for $[C_{29}H_{31}FNO_5]^+$ ($[M+H]^+$): 492.2186, found: 492.2195. The enantio selectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD-H, hexane : 2-propanol = 80 : 20, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm, retention time ; minor isomer 10.77 min, major isomer 16.01 min, 96 % ee, $[\alpha]^{25}_D$ = + 23.41 (*c* 1.0, $CHCl_3$).

1-Benzhydryl 3-(*tert*-butyl) (*R*)-2-acetamido-2-(4-bromobenzyl)malonate (124t)



Following the PTC procedure from **122b**, the title compound **124t** was obtained as a white solid (mp 182.5 °C, 98% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.40 ~ 7.20 (m, 12H), 6.96 (s, 1H), 6.68 ~ 6.65 (m, 2H), 6.51 (s, 1H), 3.66 ~ 3.54 (dd, 2H, J_1 = 23.3 Hz, J_2 = 14.0 Hz), 1.95 (s, 3H), 1.27 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.00, 166.82, 165.90, 138.98, 138.96, 134.28, 131.60, 131.21, 128.62, 128.46, 128.36, 128.07, 127.98, 127.11, 121.08, 84.12, 78.79, 67.37, 37.03, 27.59, 22.95 ppm; IR (KBr) 3408, 2924, 1736, 1676, 1491, 1370, 1219, 1149, 1012, 772 cm^{-1}; HRMS (FAB) calcd for $[C_{29}H_{31}BrNO_5]^+$ ($[M+H]^+$): 552.1386, found: 552.1381; The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD-H, hexane : 2-propanol = 80 : 20, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm, retention time ; minor isomer 11.86 min, major isomer 19.32 min, 97 % ee, $[\alpha]^{25}_{D}$ = +29.97 (*c* 1.0, $CHCl_3$).

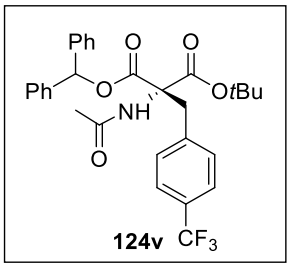
1-Benzhydryl 3-(*tert*-butyl) (*R*)-2-acetamido-2-(4-(*tert*-butyl)benzyl) malonate (124u)



Following the PTC procedure from **122b**, the title compound **124u** was obtained as a white solid (mp 156.5 °C, 99% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.53 ~ 7.34 (m, 10H), 7.27 ~ 7.23 (m, 2H), 7.09 (s, 1H), 6.92 ~ 6.90 (m, 2H), 6.66 (s, 1H), 3.81 ~ 3.76 (d, 1H, *J* = 14.1 Hz), 3.71 ~ 3.66 (d, 1H, *J* = 14.1 Hz), 2.08 (s, 3H), 1.38-1.36 (m, 18H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.87, 167.08, 166.21, 149.72, 139.25, 139.14, 132.08, 129.66, 128.55, 128.33, 128.28, 128.01, 127.90, 127.28, 124.99, 83.90, 78.59, 67.63, 37.14, 34.34, 31.29, 27.59, 22.99 ppm; IR (KBr) 3410, 2963, 2927, 1736, 1676, 1496, 1369, 1219, 772 cm^{-1}; HRMS (FAB) calcd for $[C_{33}H_{40}NO_5]^+$

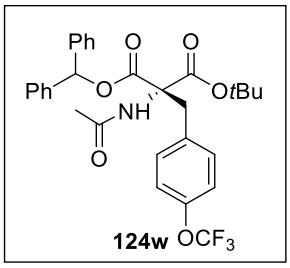
([M+H]$^+$): 530.2906, found: 530.2902; The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD-H, hexane : 2-propanol = 80 : 20, flow rate = 1.0 mL/min, 23 ^{o}C, λ = 254 nm, retention time ; minor isomer 6.88 min, major isomer 11.26 min, 95 % ee, $[\alpha]^{25}_D$ = + 22.86 (*c* 1.0, $CHCl_3$)

1-Benzhydryl 3-(*tert*-butyl) (*R*)-2-acetamido-2-(4-(trifluoromethyl)benzyl) malonate



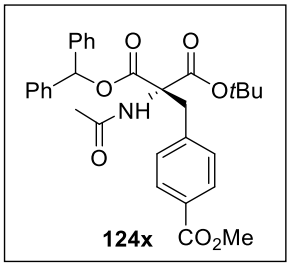
(124v) Following the PTC procedure from **122b**, the title compound **124v** was obtained as a white solid (mp 158.5 ^{o}C, 95% yield). ^{1}H-NMR (300MHz, $CDCl_3$) δ 7.41 ~ 7.25 (m, 12H), 6.98 (s, 1H), 6.93 ~ 6.90 (d, 2H, *J* = 8.0 Hz), 6.53 (s, 1H), 3.77 ~ 3.65 (dd, 2H, J_1 = 22.2 Hz, J_2 = 14.0 Hz), 1.97 (s, 3H), 1.28 (s, 9H) ppm; ^{13}C-NMR (400MHz, $CDCl_3$) δ 169.13, 166.75, 165.83, 139.52, 138.92, 130.25, 128.66, 128.52, 128.39, 128.12, 128.00, 127.11, 125.03, 125.00, 124.96, 124.93, 84.28, 78.90, 67.36, 37.41, 27.58, 22.94 ppm; IR (KBr) 3410, 3298, 2981, 1737, 1676, 1371, 1326, 1219, 1165, 772, 699 cm^{-1}; HRMS (FAB): calcd for $[C_{30}H_{31}F_3NO_5]^+$ ([M+H]$^+$): 542.2154, found: 542.2153. The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD-H, hexane : 2-propanol = 80 : 20, flow rate = 1.0 mL/min, 23 ^{o}C, λ = 254 nm, retention time; minor isomer 8.26 min, major isomer 14.10 min, 95 % ee, $[\alpha]^{25}_D$ = + 25.74 (*c* 1.0, $CHCl_3$).

1-Benzhydryl 3-(*tert*-butyl) (*R*)-2-acetamido-2-(4-(trifluoromethoxy)benzyl) malonate



(124w) Following the PTC procedure from **122b**, the title compound **124w** was obtained as a white solid (mp 130.5 °C, 91% yield). ^{1}H-NMR (300MHz, $CDCl_3$) δ 7.40 ~ 7.22 (m, 10H), 6.97 ~ 6.94 (d, 3H, J = 9.2 Hz), 6.84 ~ 6.81 (d, 2H, J = 8.8 Hz), 6.55 (s, 1H), 3.71 ~ 3.59 (dd, 2H, $J_{1`}$ = 22.4 Hz, J_2 = 14.1 Hz), 1.97 (s, 3H), 1.27 (s, 9H) ppm; ^{13}C-NMR (400MHz, $CDCl_3$) δ 169.05, 166.84, 165.92, 148.29, 148.27, 138.99, 134.04, 131.27, 128.63, 128.48, 128.38, 128.09, 128.00, 127.14, 121.68, 120.47, 119.11, 84.18, 78.83, 67.45, 36.92, 27.58, 22.95 ppm; IR (KBr) 2925, 1739, 1508, 1262, 1153, 839, 3411, 1680, 1220, 699 cm^{-1}; HRMS (FAB): calcd for $[C_{30}H_{31}F_3NO_6]^+$ ($[M+H]^+$): 558.2103, found: 558.2093. The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD-H, hexane : 2-propanol = 80 : 20, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm, retention time ; minor isomer 7.28 min, major isomer 11.90 min, 95 % ee, $[\alpha]^{25}_D$ = + 24.73 (*c* 1.0, $CHCl_3$).

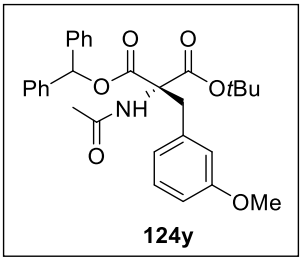
1-Benzhydryl 3-(*tert*-butyl) (*R*)-2-acetamido-2-(4-(methoxycarbonyl)benzyl) malonate



(124x) Following the PTC procedure from **122b**, the title compound **124x** was obtained as a white solid (mp 160.8 °C, 99% yield). ^{1}H-NMR (300MHz, $CDCl_3$) δ 7.76 ~ 7.73 (d, 2H, J = 8.2 Hz), 7.34 ~ 7.19 (m, 10H), 6.91 (s, 1H), 6.86 ~ 6.83 (d, 2H, J = 8.2 Hz), 6.46 (s, 1H), 3.81 (s, 3H), 3.72 ~ 3.58 (dd, 2H, J_1 = 26.9 Hz J_2 = 13.9 Hz), 1.91 (s, 3H), 1.22 (s, 9H) ppm; ^{13}C-NMR (125MHz, $CDCl_3$) δ 169.04, 166.85, 166.77, 165.86, 140.77, 139.00, 138.95, 129.99, 129.35, 128.92, 128.64, 128.48, 128.37, 128.08, 127.95, 127.1484.25, 78.83, 67.35, 52.02, 37.58, 27.59, 22.96, ppm; IR

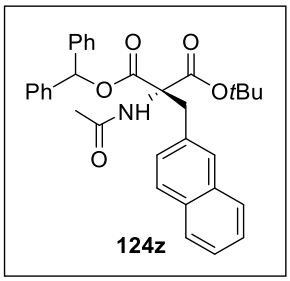
(KBr) 2927, 1723, 1680, 1281, 1219, 1150, 772, 700 cm^{-1}; HRMS (FAB) calcd for $[C_{31}H_{34}NO_6]^+$ ($[M+H]^+$): 532.2335, found: 532.2337. The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD-H, hexane : 2-propanol = 80 : 20, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm, retention time ; minor isomer 14.48 min, major isomer 27.74 min, 95 % ee, $[\alpha]^{25}_D$ = +29.78 (*c* 1.0, $CHCl_3$).

<u>1-Benzhydryl 3-(*tert*-butyl) (*R*)-2-acetamido-2-(3-methoxybenzyl)malonate (124y)</u>



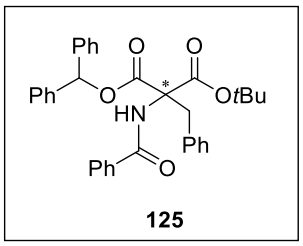
Following the PTC procedure from **122b**, the title compound **124y** was obtained as a white solid (mp 130.5 °C, 96% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.41 ~ 7.29 (m, 10H), 7.07 ~ 7.02 (t, 1H, *J* = 7.9 Hz), 6.98 (s, 1H), 6.73 ~ 6.70 (m, 1H), 6.56 (s, 1H), 6.48 ~ 6.44 (m, 2H), 3.72 ~ 3.56 (m, 5H), 1.96 (s, 3H), 1.26 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.86, 166.95, 166.06, 159.34, 139.22, 139.08, 136.78, 129.00, 128.56, 128.33, 128.25, 128.04, 127.69, 127.31, 122.31, 115.58, 112.59, 83.97, 78.58, 67.53, 54.93, 37.66, 27.55, 22.95 ppm; IR (KBr) 2984, 1736, 1676, 1370, 1220, 1151, 1043, 772 cm^{-1}; HRMS (FAB) calcd for $[C_{30}H_{34}NO_6]^+$ ($[M+H]^+$): 504.2386, found: 504.2395; The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD-H, hexane : 2-propanol = 80 : 20, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm, retention time ; minor isomer 11.56 min, major isomer 20.53 min, 94 % ee, $[\alpha]^{25}_D$ = +15.05 (*c* 1.0, $CHCl_3$).

1-Benzhydryl 3-(*tert*-butyl) (*R*)-2-acetamido-2-(naphthalen-2-ylmethyl) malonate (124z)



Following the PTC procedure from **122b**, the title compound **124z** was obtained as a white solid (mp 162.4 ºC, 98% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.78 ~ 7.73 (m, 1H), 7.64 ~ 7.61 (d, 1H, *J* = 8.6 Hz), 7.56 ~ 7.52 (m, 1H), 7.46 ~ 7.24 (m, 13H), 7.01 ~ 6.98 (m, 2H), 6.53 (s, 1H), 3.91 ~ 3.86 (d, 1H, *J* = 14.1 Hz), 3.81 ~ 3.76 (d, 1H, *J* = 14.1 Hz), 1.98 (s, 3H), 1.30 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.05, 167.01, 166.11, 139.21, 139.15, 133.18, 132.88, 132.42, 128.83, 128.65, 128.39, 128.37, 128.08, 128.06, 127.90, 127.62, 127.54, 127.51, 127.23, 125.92, 125.64, 84.05, 78.71, 67.79, 37.74, 27.63, 22.99, ppm; IR (KBr) 3331, 2978, 1736, 1667, 1496, 1298, 1219, 1151, 772, 700 cm^{-1}, HRMS(FAB): calcd for $[C_{33}H_{34}NO_5]^+$ ($[M+H]^+$): 524.2437, found: 524.2424; The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD-H, hexane : 2-propanol = 80 : 20, flow rate = 1.0 mL/min, 23 ºC, λ = 254 nm, retention time ; minor isomer 12.11 min, major isomer 19.45 min, 91% ee, $[\alpha]^{25}_{D}$ = + 29.48 (*c* 1.0, $CHCl_3$).

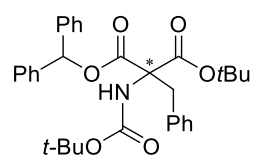
1-Benzhydryl 3-(*tert*-butyl) 2-benzamido-2-benzylmalonate (125)



Following the PTC procedure from **122c**, the title compound **125** was obtained as a white solid (mp 101.9 ºC, 94% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.70 ~ 7.67 (m, 2H), 7.58 ~ 7.49 (m, 1H), 7.49 ~ 7.29 (m, 7H), 7.29 ~ 7.20 (m, 6H), 7.19 ~ 7.09 (m, 3H), 7.05 (s, 1H), 6.93 ~ 6.91 (d, 2H, *J* = 6.6 Hz), 3.88 ~ 3.83 (d,1H, *J* =14.1Hz), 3.76 ~ 3.71 (d, 1H, *J* =14.1 Hz), 1.28 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 166.89, 166.18, 166.16, 139.19, 139.11, 135.16, 133.80, 131.75, 130.07, 128.54, 128.53, 128.32, 128.22,

128.16, 128.06, 128.03, 127.84, 127.04, 127.00, 84.15, 78.54, 67.68, 37.64, 27.55 ppm; IR (KBr) 3415, 3032, 3006, 2979, 1734, 1667, 1508, 1479, 1287, 1219, 1201, 1150, 839, 772, 700 cm^{-1}; HRMS (FAB): calcd for $[C_{34}H_{34}NO_5]^+$ ($[M+H]^+$): 536.2437, found: 536.2439; The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralcel OD-H, hexane : 2-propanol = 99 : 1, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm, retention time ; minor isomer 9.85 min, major isomer 11.26 min, 82% ee, $[\alpha]^{25}_D$ = + 15.03 (*c* 1.0, $CHCl_3$).

<u>1-Benzhydryl 3-(*tert*-butyl) 2-benzyl-2-((*tert*-butoxycarbonyl)amino)malonate (126)</u>



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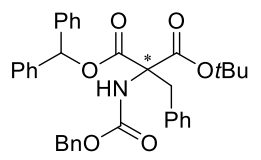
Following the PTC procedure from **122d**, the title compound **126** was obtained as a white solid (mp 104.0 °C, 98% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.34 ~ 7.18 (m, 10H), 7.11 ~ 7.05 (m, 3H), 6.93 (s, 1H), 6.82 ~ 6.80 (m, 2H), 5.56 (s, 1H), 3.63 ~ 3.58 (d,1H, *J* = 14.0 Hz), 3.52 ~ 3.47 (d, 1H, *J* = 14.0 Hz), 1.35 (s, 9H), 1.19 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.18, 166.19, 153.82, 139.27, 135.35, 130.14, 128.56, 128.32, 128.06, 128.01, 127.09, 83.63, 79.95, 78.49, 67.30, 38.16, 28.26, 27.55 ppm; IR (KBr) 3410, 2927, 1736, 1682, 1370, 1219, 772, 700 cm^{-1}, HRMS (CI): calcd for $[C_{32}H_{38}NO_6]^+$ ($[M+H]^+$): 532.2699, found: 532.2703; The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD-H, hexane : 2-propanol = 85 : 15, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm, retention time ; minor isomer 8.55 min, major isomer 10.16 min, 80% ee, $[\alpha]^{25}_D$ = + 11.67 (*c* 1.0, $CHCl_3$)

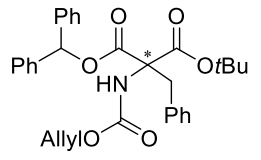
1-Benzhydryl 3-(*tert*-butyl) 2-benzyl-2-(((benzyloxy)carbonyl)amino)malonate (127)



127

Following the PTC procedure from **122e**, the title compound **127** was obtained as colorless oil (85% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.37 ~ 7.24 (m, 15H), 7.17 ~ 7.04 (m, 3H), 6.98 (s, 1H), 6.81 ~ 6.79 (d, 2H, *J* = 7.0 Hz), 6.00 (s, 1H), 5.15 ~ 5.11 (d,1H, *J* =12.3 Hz), 5.02 ~ 4.98 (d, 1H, *J* =12.3 Hz), 3.68 ~ 3.63 (d,1H, *J* =14.1Hz), 3.60 ~ 3.55 (d, 1H, *J* =14.1Hz), 1.22 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 166.87, 165.86, 154.28, 139.20, 139.13, 136.38, 134.97, 130.07, 128.58, 128.48, 128.34, 128.13, 128.06, 127.98, 127.94, 127.10, 126.93, 83.94, 78.61, 67.65, 66.78, 38.00, 27.52 ppm; IR (KBr) 3421, 2979, 2932, 1727, 1496, 1286, 1261, 1219, 1150, 1023, 772, 699 cm^{-1}; HRMS (CI) calcd for $[C_{35}H_{36}NO_6]^+$ ($[M+H]^+$): 566.2543, found: 566.2548; The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralcel AD-H, hexane : 2-propanol = 80 : 20, flow rate = 1.0 mL/min, 23 ^{o}C, λ = 254 nm, retention time ; minor isomer 13.42 min, major isomer 16.37 min, 87% ee, $[\alpha]^{25}_{D}$ = + 15.63 (*c* 1.0, $CHCl_3$).

1-Benzhydryl 3-(*tert*-butyl) 2-(((allyloxy)carbonyl)amino)-2-benzylmalonate (128)

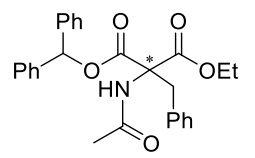


128

Following the PTC procedure from **122f**, the title compound **128** was obtained as colorless oil (93% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.37 ~ 7.26 (m, 10H), 7.20 ~ 7.10 (m, 3H), 6.98 (s, 1H), 6.92 ~ 6.89 (m, 2H), 6.00 (s, 1H), 5.94 ~ 5.81(m, 1H), 5.31 ~ 5.28 (d, 1H, *J* = 17.1 Hz), 5.22 ~ 5.18 (d, 1H, *J* = 11.0 Hz), 4.60 ~ 4.45 (m, 2H), 3.70 ~ 3.65 (d,1H, *J* =14.2 Hz), 3.61 ~ 3.56 (d, 1H, *J* =14.2Hz), 1.25 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 166.86, 165.87, 154.20, 139.21, 139.18, 135.04, 132.62, 130.11, 128.55, 128.32, 128.07, 127.95, 127.92, 127.61, 127.10, 126.98, 117.76, 84.01, 78.54,

67.61, 65.63, 38.04, 27.54ppm; IR (KBr) 3421, 2925, 2854, 1728, 1495, 1258, 1219, 1150, 1095, 1027, 772 cm^{-1}; HRMS (FAB): calcd for $[C_{31}H_{34}NO_6]^+$ ($[M+H]^+$): 516.2386, found: 516.2396; The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralcel AD-H, hexane : 2-propanol = 80 : 20, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm, retention time ; minor isomer 8.83 min, major isomer 13.71 min, 87% ee, $[\alpha]^{25}_D$ = + 16.16 (*c* 1.0, $CHCl_3$)

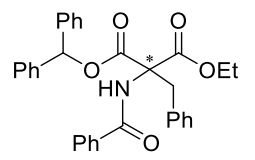
1-Benzhydryl 3-ethyl 2-acetamido-2-benzylmalonate (129)



129

Following the PTC procedure from **122g**, the title compound **129** was obtained as a white solid (mp 120.0 °C, 95% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.39 ~ 7.21 (m, 10H), 7.21 ~ 7.10 (m, 3H), 6.96 ~ 6.92 (s, 1H), 6.82 ~ 6.79 (d, 2H, *J* = 6.4 Hz**)**, 6.53 (s, 1H), 4.16 ~ 4.08(q, 2H, *J* = 7.1 Hz), 3.73 ~ 3.63 (m, 2H), 1.99 (s. 3H), 1.13 ~ 1.08 (t, 3H, *J* = 7.1 Hz) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 169.04, 167.29, 166.59, 139.08, 138.89, 134.98, 129.83, 128.61, 128.43, 128.37, 128.23, 128.06, 127.73, 127.08, 126.93, 78.86, 67.34, 62.68, 37.70, 22.92, 13.77 ppm; IR (KBr) 3411, 3032, 2983, 1742, 1680, 1496, 1281, 1218, 1196, 771, 701 cm^{-1}; HRMS (FAB): calcd for $[C_{27}H_{28}NO_5]^+$ ($[M+H]^+$): 446.1967, found: 446.1976; The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD-H, hexane : 2-propanol = 80 : 20, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm, retention time ; minor isomer 16.38 min, major isomer 32.22 min, 59% ee, $[\alpha]^{25}_D$ = + 16.8 (*c* 1.0, $CHCl_3$)

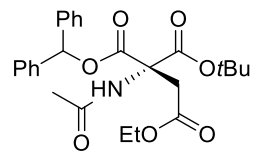
1-Benzhydryl 3-ethyl 2-benzamido-2-benzylmalonate (130)



130

Following the PTC procedure from **122h**, the title compound **130** was obtained as a white solid (mp 102.5 ºC, 97% yield). ^{1}H-NMR (300MHz, $CDCl_3$) δ 7.70 ~ 7.68 (d, 2H, *J* = 7.3 Hz), 7.59 ~ 7.49 (m, 1H), 7.44 ~ 7.29(m, 7H), 7.25 ~ 7.20(m, 7H), 7.20 ~ 7.08(m, 2H), 7.00 (s, 1H), 6.90 ~ 6.83 (d, 2H, *J* = 7.0 Hz), 4.18 ~ 4.11 (q, 2H, *J* = 7.1 Hz), 3.86 ~ 3.76 (dd, 2H, J_1 = 16.3 Hz J_2 = 14.1 Hz), 1.12 ~ 1.08 (t, 3H, *J* = 7.1 Hz) ppm; ^{13}C-NMR (125MHz, $CDCl_3$) δ 167.38, 166.59 166.27, 139.04, 138.99, 134.93, 133.55, 131.91, 129.94, 128.60, 128.43, 128.31, 128.23, 127.97, 127.80, 127.11, 127.07, 126.87, 78.85, 67.55, 62.77, 37.75, 13.78 ppm; IR (KBr) 3418, 3031, 1740, 1667, 1508, 1479, 1285, 1216, 1050, 770, 701 cm^{-1}, HRMS (FAB): calcd for $[C_{32}H_{30}NO_5]^+$ ($[M+H]^+$): 508.2124, found: 508.2130; The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD-H, hexane : 2-propanol = 80 : 20, flow rate = 1.0 mL/min, 23 ºC, λ = 254 nm, retention time ; major isomer 16.10 min, minor isomer 26.01 min, 55% ee, $[\alpha]^{25}_{D}$ = + 7.72 (*c* 1.0, $CHCl_3$).

1-benzhydryl 1-(*tert*-butyl) 2-ethyl (*R*)-1-acetamidoethane-1,1,2-tricarboxylate (131a)

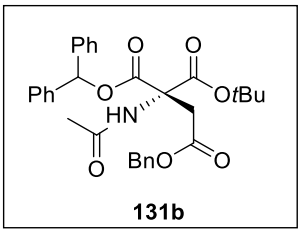


131a

Following the PTC procedure from **122b**, the title compound **131a** was obtained as a white solid (mp 87.4 ºC, 99% yield). ^{1}H-NMR (300MHz, $CDCl_3$) δ 7.29 ~ 7.20 (m, 10H), 6.95 (s, 1H), 6.88 (s, 1H), 4.01 ~ 3.94 (dd, 2H, J_1 = 14.2 Hz, J_2 = 7.1 Hz), 3.58 ~ 3.38 (dd, 2H, J_1 = 42.2 Hz, J_2 = 17.1 Hz), 1.91 (s, 3H), 1.21 (s, 9H), 1.14 ~ 1.09 (t, 3H, *J* = 7.1 Hz) ppm; ^{13}C-NMR (400MHz, $CDCl_3$) δ 170.09, 169.31, 166.11, 165.28, 139.08, 139.06, 128.39, 128.35, 128.09, 127.40, 127.38, 84.12, 78.80, 64.50, 60.70, 37.75,

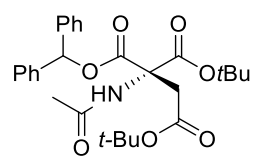
27.41, 22.86, 14.03 ppm; IR (KBr) 3410, 2980, 1681, 1371, 770, 2929, 1742, 1496, 1217, 1150, 700 cm^{-1}; HRMS (FAB): calcd for $[C_{26}H_{32}NO_7]^+$ ($[M+H]^+$): 470.2179, found: 470.2165; The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralcel AD-H, hexane : 2-propanol = 80 : 20, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm, retention time ; minor isomer 26.37 min, major isomer 45.50 min, 40% ee, $[\alpha]^{25}_D$ = + 1.84 (*c* 1.0, $CHCl_3$).

<u>1-Benzhydryl 2-benzyl 1-(*tert*-butyl) (*R*)-1-acetamidoethane-1,1,2-tricarboxylate (131b)</u>



Following the PTC procedure from **122b**, the title compound **131b** was obtained as a white solid (mp 94.6 °C, 99% yield). ^{1}H-NMR (300MHz, $CDCl_3$) δ 7.32 ~ 7.19 (m, 15H), 6.91 (s, 1H), 6.87 (s, 1H), 5.02 ~ 4.93 (m, 2H), 3.66 ~ 3.45 (dd, 2H, J_1 = 44.5 Hz, J_2 = 17.2 Hz), 1.85 (s, 3H), 1.18 (s, 9H) ppm; ^{13}C-NMR (500MHz, $CDCl_3$) δ 169.94, 169.33, 166.02, 165.22, 139.04, 139.01, 135.52, 128.51, 128.41, 128.36, 128.30, 128.26, 128.10, 127.39, 84.23, 78.85, 66.42, 64.48, 37.78, 27.36, 22.79 ppm; IR (KBr) 3409, 2925, 1743, 1496, 1217, 1149, 963, 2957, 2853, 1681, 1299, 769, 699 cm^{-1}; HRMS (FAB): calcd for $[C_{31}H_{34}NO_7]^+$ ($[M+H]^+$): 532.2335, found: 532.2334; The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralcel AD-H, hexane : 2-propanol = 80 : 20, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm, retention time ; minor isomer 32.53 min, major isomer 53.23 min, 40% ee, $[\alpha]^{25}_D$ = + 0.86 (*c* 1.0, $CHCl_3$).

1-Benzhydryl 1,2-di-*tert*-butyl (*R*)-1-acetamidoethane-1,1,2-tricarboxylate (131c)

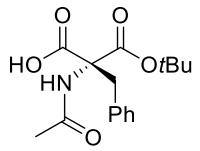


131c

Following the PTC procedure from **122b**, the title compound **131c** was obtained as a white solid (mp 120.5 °C, 67% yield). ^{1}H-NMR (300MHz, $CDCl_3$) δ 7.28 ~ 7.18 (m, 10H), 6.96 (s, 1H), 6.88 (s, 1H), 3.50 ~ 3.32 (dd, 2H, J_1 = 36.7 Hz, J_2 = 17.3 Hz), 1.91 (s, 3H), 1.29 (s, 9H), 1.19 (s, 9H) ppm; ^{13}C-NMR (500MHz, $CDCl_3$) δ 169.42, 169.21, 166.31, 165.43, 139.15, 139.10, 128.40, 128.36, 128.10, 128.06, 127.44, 127.37, 83.91, 81.34, 78.71, 64.51, 38.71, 27.92, 27.43, 28.88 ppm; IR (KBr) 3413, 2979, 1682, 1153, 772, 2926, 1741, 1496, 1370, 1220, 961, 700 cm^{-1}; HRMS (FAB): calcd for $[C_{28}H_{36}NO_7]^+$ ($[M+H]^+$): 498.2492, found: 498.2483; The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralcel AD-H, hexane : 2-propanol = 80 : 20, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm, retention time ; minor isomer 20.34 min, major isomer 41.45 min, 67% ee, $[\alpha]^{25}_D$ = - 2.97 (*c* 1.0, $CHCl_3$).

3-3. Application of chiral α-amino α-alkyl malonic esters

(*R*)-2-Acetamido-2-benzyl-3-(*tert*-butoxy)-3-oxopropanoic acid (132)

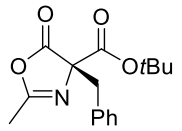


132

Palladium carbon (5 mol%) was added to a stirred solution of 1-benzhydryl 3-(*tert*-butyl) (*R*)-2-acetamido-2-benzylmalonate (**124i**, 300 mg, 0.63 mmol) in methanol (20 mL) under hydrogen gas. After being stirred for 2 ~ 4 hours, the substrate spot disappeared on TLC. The reaction mixture was filtered through a pad of celite and the filtrate was concentrated. The residue was purified by flash column chromate

graphy on silica gel eluting with hexane / EtOAc (3:1 ~ only EtOAc) to afford mono acid **132** as a white solid (mp 135.7 °C, 98% yield). ^{1}H-NMR (500MHz, CD_3OD) 7.25 ~ 7.18 (m, 3H), 7.07 ~ 7.06 (d, 2H, J = 6.8 Hz), 3.57 ~ 3.49 (dd, 2H, J_1 = 26.4 Hz, J_2 = 13.9 Hz), 1.98 (s, 3H), 1.46 (s, 9H) ppm; ^{13}C-NMR (125MHz, CD_3OD) δ 173.07, 171.01, 168.78, 137.85, 131.89, 130.02, 128.82, 84.84, 70.00, 39.37, 28.79, 23.27 ppm; IR (KBr) 3378, 3351, 2979, 2490, 1738, 1370, 1216, 1152, 757 cm^{-1}; HRMS (FAB): calcd for $[C_{16}H_{22}NO_5]^+$ ($[M+H]^+$): 308.1498, found: 308.1497; $[\alpha]^{20}_D$ = - 20.50 (*c* 1.0, MeOH)

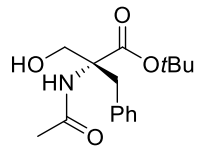
***tert*-Butyl (*S*)-4-benzyl-2-methyl-5-oxo-4,5-dihydrooxazole-4-carboxylate (133)**



133

The mono acid **132** (660 mg, 2.15 mmol) was dissolved in dry THF (9 mL) under argon atmosphere under -10 °C which was maintained by acetone/ice (1:1) mixture. Then *N*-methylmorpholine (354 μL, 3.22 mmol) and ethyl chloroformate (307 μL, 3.22mmol) was added sequentially. Formation of azlactone took less than 15 minutes on TLC analysis. The reaction mixture was filtered for removal of NMM•HCl salt precipitate. All volatile were also removed under reduced pressure to afford **133** as colorless oil. Actually, separation of azlactone **133** on silica gel did not work well which might be caused by decomposition occurring when it becomes solubilized in any solvents or so heated. Fortunately the crude ^{1}H NMR spectroscopy and high resolution mass spectrometry of **133** were able to be measured and the results are attached below. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.26 ~ 7.23 (m, 3H), 7.17 ~ 7.14 (m, 2H), 3.45 ~ 3.32 (dd, 2H, J_1 = 25.4 Hz, J_2 = 13.7 Hz), 2.02 (s, 3H), 1.48 (s, 9H) ppm; HRMS (FAB): calcd for $[C_{26}H_{20}NO_4]^+$ ($[M+H]^+$): 290.1392, found: 290.1392

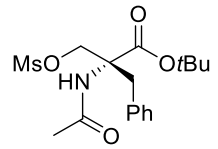
***tert*-Butyl (*R*)-2-acetamido-2-benzyl-3-hydroxypropanoate (134)**



134

The title compound **134** was prepared by consecutive two reaction steps from **132**. A solution of (*R*)-2-acetamido-2-benzyl-3-(*tert*-butoxy)-3-oxopropanoic acid (**132**, 500 mg, 1.63mmol) in dry THF (7 mL) at –10 ºC was stirred for 15 minutes with *N*-methyl morpholine (268 μL, 2.44 mmol) and ethyl chloroformate (232 μL, 2.44 mmol). *N*-methylmorpholine hydrochloride was removed by filtration and the clear organic solution containing the intermediate **133** was added over a period of 10 minutes to vigorously stirred suspension of sodium borohydride (215 mg, 5.70 mmol) in H_2O (2.5 mL) at 5 ºC. The reaction was maintained for a further 3 hours at room temperature until the TLC analysis showed that the reaction was complete. The mixture was then cooled to 0 ºC, acidified to pH 2 with conc. HCl, diluted with water and extracted with diethyl ether (100 mL x 2). The organic phase was collected, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel eluting hexane/EtOAc (1:2) to afford primary alcohol **134** as a white solid (398.8 mg, mp 142.7 ºC, 84% yield). ^{1}H-NMR (600 MHz, $CDCl_3$) 7.24 ~ 7.19 (m, 3H), 7.09 ~ 7.07 (m, 2H), 6.38 (s, 1H), 4.31 ~ 4.29 (d,1H, *J*=11.2 Hz), 3.86 ~ 3.84 (d, 1H, *J*=11.2 Hz), 3.50 ~ 3.47 (d,1H, *J*=13.7 Hz), 3.03 ~ 3.01 (d, 1H, *J*=13.7 Hz), 1.96 (s, 3H), 1.45 (s, 9H) ppm; ^{13}C-NMR (150 MHz, $CDCl_3$) δ 170.75, 135.57, 129.79, 128.17, 126.95, 83.41, 67.61, 66.08, 36.64, 27.84, 23.98 ppm; IR (KBr) 3400, 2978, 1731, 1659, 1514, 1370, 1248, 1157, 741 cm^{-1}; HRMS (FAB): calcd for $[C_{16}H_{24}NO_4]^+$ ($[M+H]^+$): 294.1705, found: 294.1706; $[\alpha]^{20}_D$ = +119.39 (*c* 1.0, $CHCl_3$).

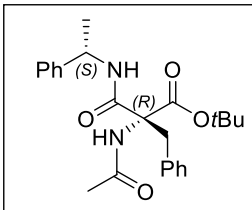
<u>*tert*-Butyl (R)-2-acetamido-2-benzyl-3-((methylsulfonyl)oxy)propanoate (135)</u>



135

The title compound **135** was prepared by mesylation of primary alcohol **134**. A solution of *tert*-butyl (*R*)-2-acetamido-2-benzyl-3-hydroxypropanoate (**134**, 100 mg, 0.34 mmol) in dichloromethane (3 mL) at 0 ^{o}C was stirred for 30 minutes with triethylamine (119 μL, 0.85 mmol) and methanesulfonyl chloride (66 μL, 0.85 mmol). The mixture was then diluted with dichloromethane and washed with saturated NH_4Cl solution (25 mL) and brine (25 mL). The organic phase was collected, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel eluting hexane/EtOAc (2:1) to afford mesylated compound **135** as a white solid (115 mg, mp 117.5 ^{o}C, 91% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) 8.27 (bs, 1H), 7.30 ~ 7.27 (m, 5H), 4.57 ~ 4.48 (dd, 2H, J_1 = 22.2 Hz, J_2 = 11.8 Hz), 3.35 ~ 3.25 (dd, 2H, J_1 = 24.1 Hz, J_2 = 14.1 Hz), 2.69 (s, 3H), 2.10 (s, 3H), 1.36 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.35, 166.73, 132.14, 130.49,. 128.80, 127.97, 85.14, 64.66, 63.72, 39.33, 38.50, 27.66, 20.61 ppm; IR (KBr) 3398, 3279, 2979, 2935, 1737, 1674, 1497, 1370, 1360, 1177, 1154, 989, 964, 838, 740, 704cm^{-1}; LRMS (FAB): calcd for $[C_{17}H_{26}NO_6S]^+$ ($[M+H]^+$): 372, found: 372; $[\alpha]^{20}_D$ = + 14.41 (*c* 1.0, $CHCl_3$).

<u>*tert*-Butyl (*R*)-2-acetamido-2-benzyl-3-oxo-3-(((*S*)-1-phenylethyl)amino)propanoate (136)</u>

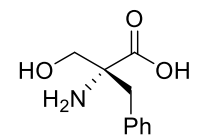


136

To the crude *tert*-butyl (*S*)-4-benzyl-2-methyl-5-oxo-4,5-dihydro oxazole-4-carboxylate (**133**, 95 mg, 0.33 mmol) synthesized according to the method mentioned above were added catalytic amount of 4-methylamino pyridine (10 mol%) and anhydrous dichloromethane (1mL). An excess of (*S*)-(-)-α-methylbenzyl

amine (2 mL, 16 mmol) was added to open the azlactone ring structure. After being stirred for 1 hour at room temperature, the reaction mixture was acidified with 6N HCl in ice bath. The crude residue was purified by column chromatography on silica gel (hexane : EtOAc = 5 : 1 as eluent) and subsequent recrystallization (hexane : EtOAc = 6:1 solvent system at room temperature) yielded stereochemically pure amide **136** as a white solid (129.6 mg, mp 122.5 ^{o}C, 96% yield). For your information; In case of reaction starting from racemic mixture of **132**, the diastereomer bearing the different α-configuration appeared right below the title isomer **136** on TLC analysis. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.35-7.25 (m, 8H), 7.10 ~ 7.07 (m, 2H), 6.78 (s, 1H), 6.52 ~ 6.49 (d, 1H, *J* = 7.9 Hz), 5.14 ~ 5.04 (p, 1H, *J* = 7.2 Hz), 3.82 ~ 3.78 (d, 1H, *J* = 14.0 Hz), 3.51 ~ 3.46 (d, 1H, *J* = 14.0 Hz), 1.98 (s, 3H). 1.57 ~ 1.55 (d, 3H, *J* = 7.2 Hz), 1.37 (s, 9H) ppm ^{13}C-NMR (150 MHz, $CDCl_3$) δ 169.01, 168.96, 165.39, 142.27, 135.26, 129.86, 128.61, 128.12, 127.53, 127.10, 125.94, 83.47, 67.42, 49.29, 38.59, 27.53, 23.11, 21.26 ppm ; IR (KBr) 3353, 2978, 2927, 1731, 1496, 1155, 772 cm^{-1}; HRMS (FAB): calcd for $[C_{24}H_{31}N_2O_4]^+$ ($[M+H]^+$): 411.2284, found: 411.2285; $[\alpha]^{25}_{D}$ = –35.86 (*c* 1.0, $CHCl_3$).

(*R*)-α-Benzylserine

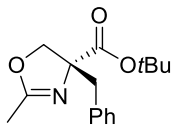


(*R*)-α-benzylserine

tert-Butyl (*R*)-2-acetamido-2-benzyl-3-hydroxypropanoate (**134**, 235 mg, 0.80 mmol) was dispersed in 6N HCl (12 mL) and methanol (3 mL) and refluxed for 2 days. The mixture was diluted with water (50 mL) and washed with EtOAc (50 mL x 2). The aqueous layer was concentrated and purified by ion-exchange column chromatography through DOWEX® 50WX8-100 column eluting with 15% aqueous NH_4OH to afford (*R*)-α-benzylserine as a white solid (143.5 mg, 92% yield, decomposed around at 230 ^{o}C) ^{1}H-

NMR (500 MHz, D_2O) 7.34 ~ 7.27 (m, 3H), 7.20 ~ 7.18 (m, 2H), 3.98 ~ 3.95 (d, 1H, *J* = 12.0 Hz), 3.71 ~ 3.69 (d, 1H, *J* = 12.0 Hz), 3.19 ~ 3.16 (d, 1H, *J* = 14.3 Hz), 2.90 ~ 2.87 (d, 1H, *J* = 14.3 Hz) ppm; ^{13}C-NMR (125 MHz, D_2O) δ 173.99, 133.93, 130.34, 129.41, 128.28, 67.38, 64.49, 38.24 ppm; IR (ATR) 3240, 3141, 2844, 2771, 1593, 1492, 1389, 1055, 697 cm^{-1}; HRMS (FAB): calcd for $[C_{10}H_{14}NO_3]^+$ ($[M+H]^+$): 196.0974, found: 196.0978. $[\alpha]^{20}_D$ = –15.50 (c 1.0, H_2O) {lit [142] (*S*)-α-benzylserine, $[\alpha]_D^{20}$ = + 16.4 (*c* 0.80, H_2O), 98% ee}.

***tert*-Butyl (R)-4-benzyl-2-methyl-4,5-dihydrooxazole-4-carboxylate (137)**



137

The methanesulfonate **135** (100 mg, 0.27 mmol) was dissolved in dichloromethane (20 mL) and stirred for over 3 hours with silica gel under reflux. The mixture was then evaporated and then yielded silica gel powder coated with organic compounds including desired product **137**, which silica gel was loaded into column chromatography directly. Eluting solvent (hexane : EtOAc = 1: 1), the ring-formated product from **135** was obtained successfully as pale yellow oil (71% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) 7.30 ~ 7.19 (m, 5H), 4.50 ~ 4.47 (d, *J* = 9.0 Hz), 4.14 ~ 4.11 (d, *J* = 9.0 Hz), 3.11 (s, 2H), 1.92 (s, 3H), 1.46 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.54, 166.01, 135.61, 130.33, 128.11, 126.86, 82.12, 78.40, 72.70, 43.12, 27.91, 13.78 ppm; IR (KBr) 3433, 2979, 2931, 1726, 1670, 1369, 1256, 1163, 1096, 994, 915, 703, 618 cm^{-1}; HRMS (FAB): calcd for $[C_{16}H_{22}NO_3]^+$ ($[M+H]^+$): 276.1600, found: 276.1609; $[\alpha]^{20}_D$ = – 47.28 (*c* 1.0, $CHCl_3$).

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국문초록

유기합성분야에서 malonate 분자는 그 분자가 가지는 전자적인 특성으로 인하여 탄소-탄소 결합 형성을 위해 기본 출발물질로 많이 사용되어 왔다. 특히 malonate의 α-위치에 비대칭 입체중심탄소을 가지고 있는 광학활성 화합물의 경우, 절대구조가 알려진 많은 생리활성 천연물들과 그 유도체들로 개발된 의약품으로의 전환에 사용될 수 있기에 실제 생리활성 천연물들과 우수 의약품들의 합성 및 신약개발에 다양하게 응용된 바 있다. 이러한 합성학적 가치에 근거하여 학계에서는 α-chiral malonate를 얻기 위한 많은 합성방법들이 연구되어왔으나, 유기화학적 이론에 의한 순수 화학적 비대칭 합성법은 많이 보고되지 않았다. 본 연구실에서는 최근 비대칭 상전이 촉매 알킬화 반응을 malonate에 적용하여 α-위치의 탄소에 입체선택적으로 높은 광학활성을 도입하는 유기합성법을 최초로 개발한 바 있다. 이에 본 연구자는 상기 합성법의 단점을 개선하고 그 적용범위를 넓히기 위해 보다 향상된 합성 방법들을 개발하고자 하였다.

지난 2011년, 본 연구실에서는 최초로 diphenylmethyl *tert*-butyl α-methyl malonate를 출발물질로 사용하는 비대칭 상전이 촉매반응을 이용하여 높은 광학수율로 4급 입체탄소의 도입에 성공하였으나, 합성된 광학활성 화합물의 화학변환과정에서 양쪽 ester의 선택적인 가수분해에 어려움이 있었다. 염기성 조건에서는 ester 분자단들의 공간적 입체장애로 인해 hydroxide의 공격이 어려워 ester의 가수분해 반응이 양쪽 모두 진행되지 않았으며, 산성 조건의 경우 양쪽 ester의 동반 가수분해가 진행되었다. 이는 양성자 부가와 전자의 이동에 의해 안정한 diphenylmethyl cation과 *tert*-butyl cation의 생성이 동시에 일어나기 때문인 것으로 판단 된 바, 본 연구자는 malonate의 기질에서 한 쪽 ester의 크기와 전자적 환경에 변화를 가해 산과 염기 각 조건에서 선택적인

가수분해가 일어날 수 있는 malonate기질을 개발하고자 하였다. 이를 위하여 다양한 ester를 도입한 새로운 malonate기질 13종을 설계하였고 이를 비대칭 상전이 촉매 알킬화 반응에 적용하였다. 본 연구진이 구축하여 보유하고 있는 15종의 상전이 촉매와 기질 간의 다양한 조합으로 95회의 최적화 과정을 수행하였고, 그 결과 2-methylbenzyl *tert*-butyl α-methyl malonate에서 최대 99%의 화학수율과 92%의 광학수율로 α,α-dialkyl malonate를 합성할 수 있었으며, 나아가 처음에 수립한 연구목표와 같이 염기성 조건에서 2-methylbenzyl ester를 선택적으로 가수분해 할 수 있었다. 가수분해된 mono-acid 중간체는 iodolactonization반응에 적용되어 성공적으로 광학수율의 손실 없이 chiral lactone을 높은 화학수율로 얻는데 응용되었다.

생리활성이 높은 다양한 알칼로이드 천연물들과 의약품들의 화학구조에는 광학활성 탄소에 결합된 질소 원자를 포함하는 경우가 많아 상기 골격의 입체 선택적 합성법 개발은 천연물 전합성이나 의약품의 개발에 매우 중요하다. 본 연구자는 비대칭 상전이 촉매반응의 적용범위를 확장하기 위해 α-위치에 질소 원자를 가지는 malonate의 비대칭 알킬화 반응을 이용하여 α-quternary-amine을 얻을 수 있는 새로운 합성법을 개발하고자 하였다. 이를 위하여 질소원자의 친핵성을 다양한 acyl 작용기로 보호시킨 8종의 α-amidomalonate 기질을 설계하였고, 이 들을 해당 malonate들로부터 Regitz 디아조 전환반응과 rhodium 촉매 하의 직접적인 N-H 삽입반응을 이용하여 성공적으로 α-amidomalonate를 확보할 수 있었다. 확보된 α-amidomalonate 기질 8종은 상전이 반응계에서 최적의 촉매, 염기, 온도, 및 용매 조건들을 도출하기 위해 최적화 과정을 진행하였고, 그 결과 –40°C의 온도에서 1-benzhydryl 3-(*tert*-butyl) 2-acetamidomalonate 기질을 출발물질로 사용하고 *N*-spiro 타입의 4급 암모늄염인 (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide의 촉매의 존재 하에 toluene을 용매로 사용하면, 최대 99%의 화학수율과 97%의 광학수율로 성공적인 비대칭 상전이 촉매반응이 진행됨을 확인할 수 있었다. 이 결과는 α-amino 4차 입체탄소의

합성을 가능하게 하는 최초의 상전이 촉매반응으로서, 상기 합성법을 통하여 합성된 일킬화 화합물은 다양한 화학 변환을 통하여 유용한 광학활성 중간체 7종을 합성하는데 성공적으로 응용되었다.

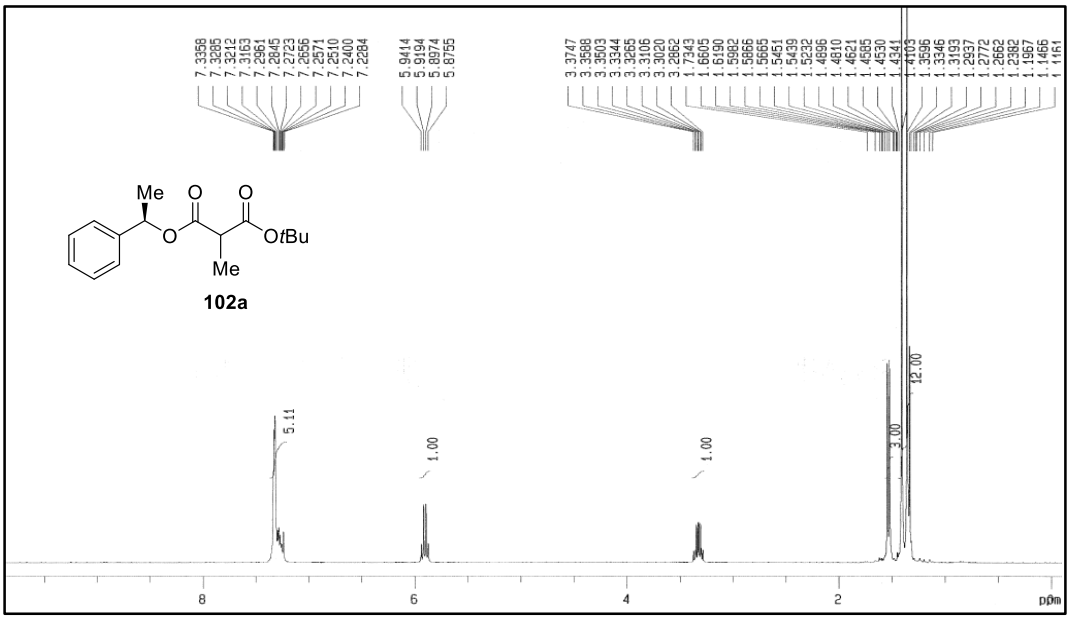
본 연구자가 도출한 상기의 연구결과들은 비대칭 입체탄소를 구축하는 새로운 합성법으로서, 완만하고 안전한 반응조건과 환경 및 경제적인 장점이 있는 입체선택적 상전이 촉매반응의 영역을 확장하고 개선하였다는 점에서 큰 의의가 있다. 본 반응 통하여 다양한 chiral building block의 구축과 다양한 유효활성 화합물들의 개발에 활발히 응용될 수 있을 것으로 예상된다.

주요어: 비대칭 상전이 촉매 알킬화 반응, 키랄성, α-chiral malonate, α-amido malonate, 비대칭 4차탄소, 광학활성 물질

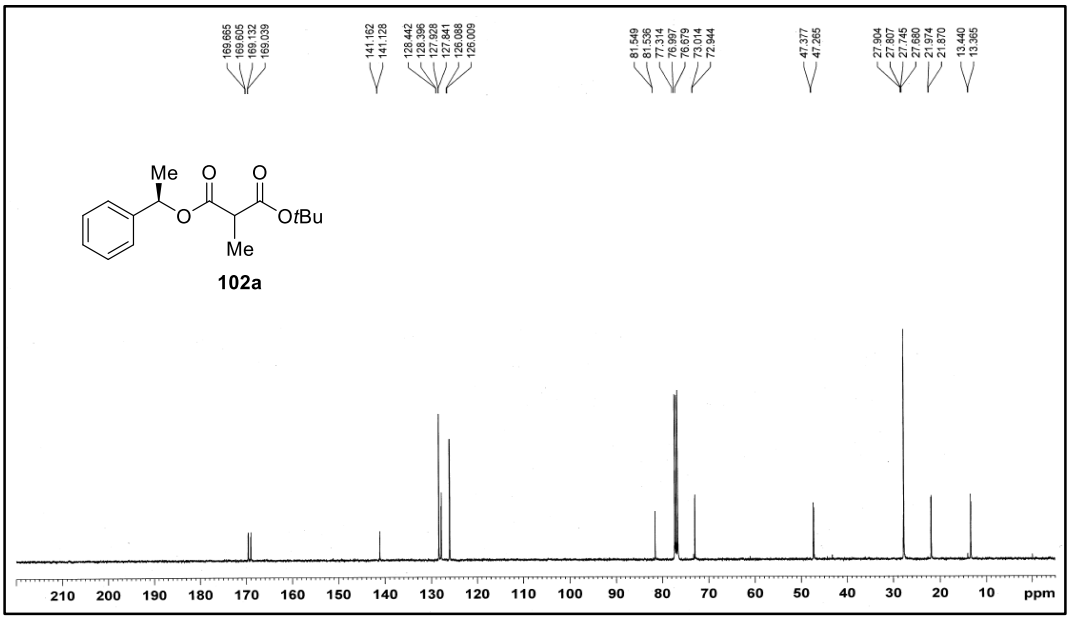
학번: 2011-31108

APPENDIX

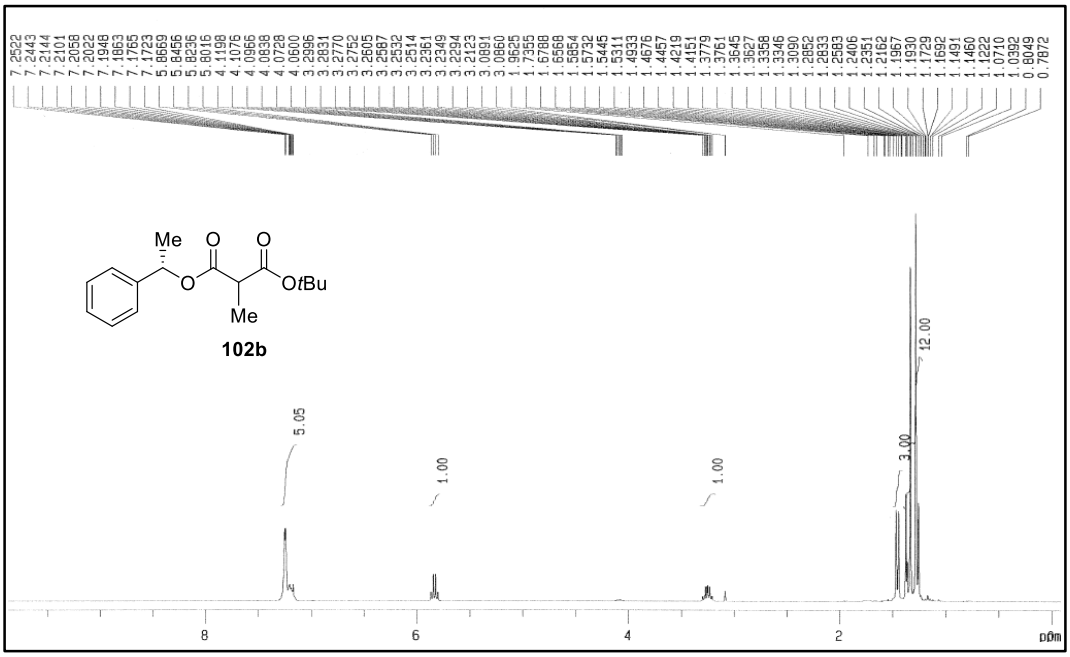
^{1}H-NMR of compound **102a** (300 MHz, $CDCl_3$)



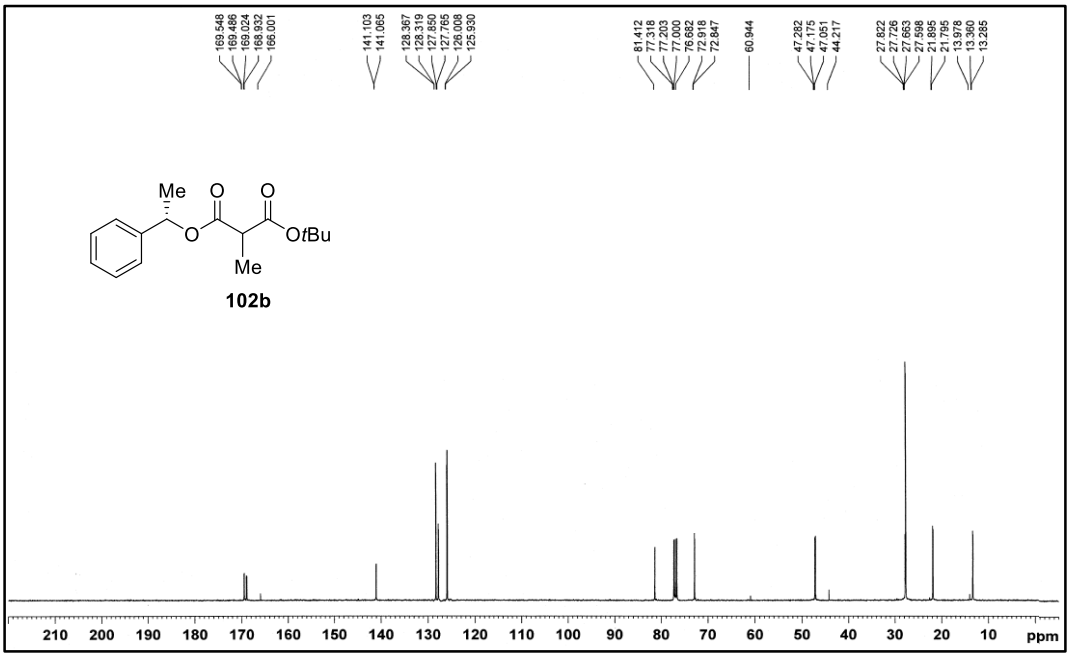
^{13}C-NMR of compound **102a** (100 MHz, $CDCl_3$)



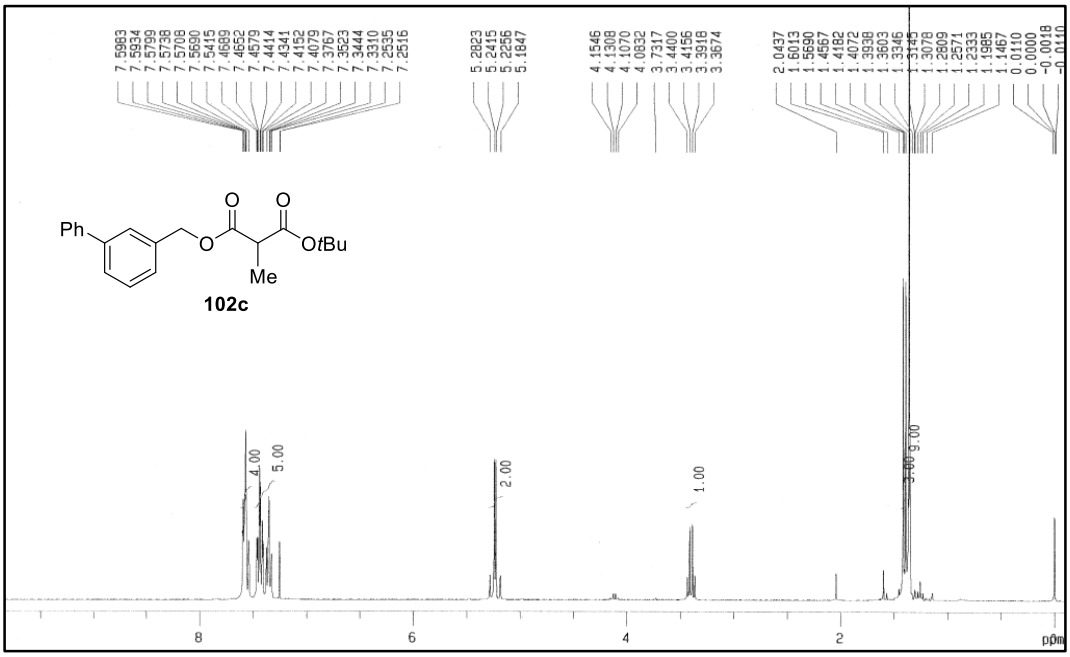
^{1}H-NMR of compound **102b** (300 MHz, $CDCl_3$)



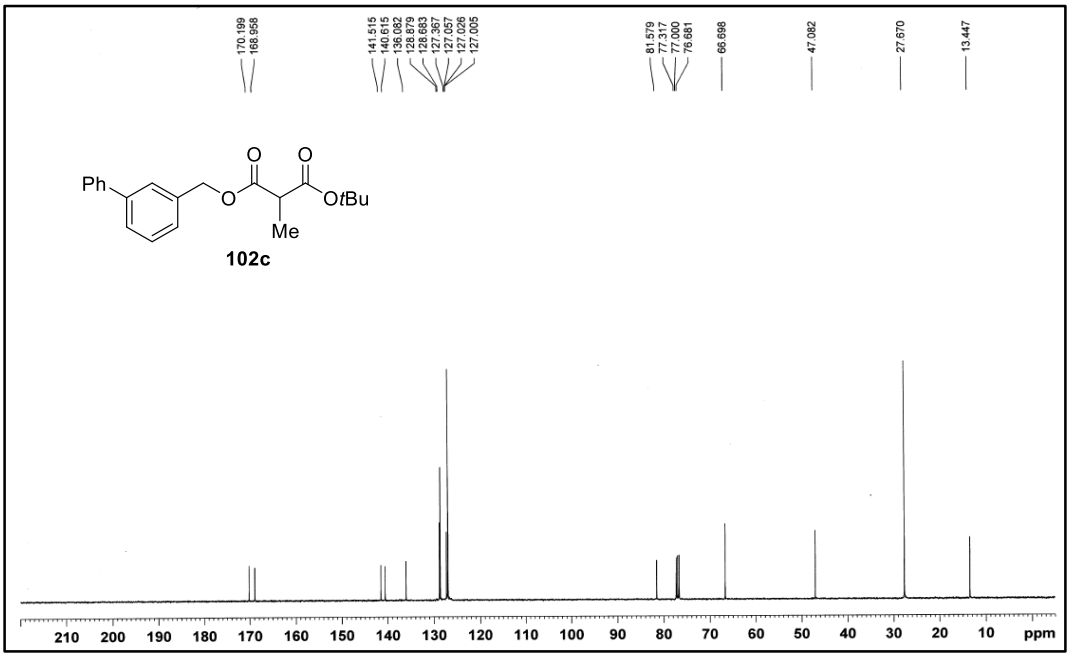
^{13}C-NMR of compound **102b** (100 MHz, $CDCl_3$)



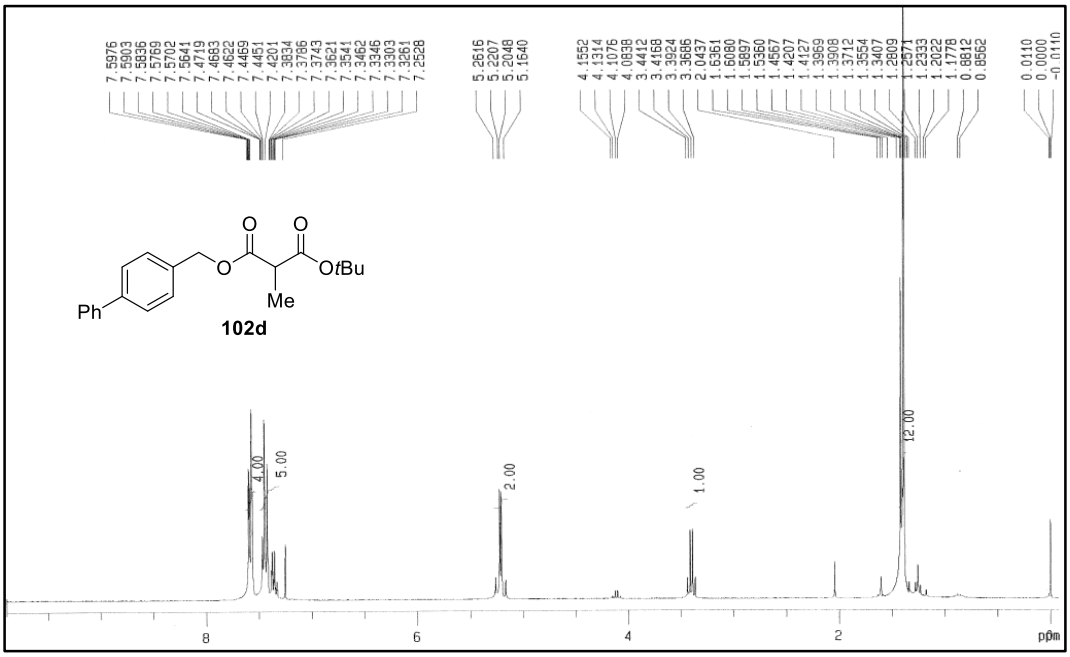
^{1}H-NMR of compound **102c** (300 MHz, $CDCl_3$)



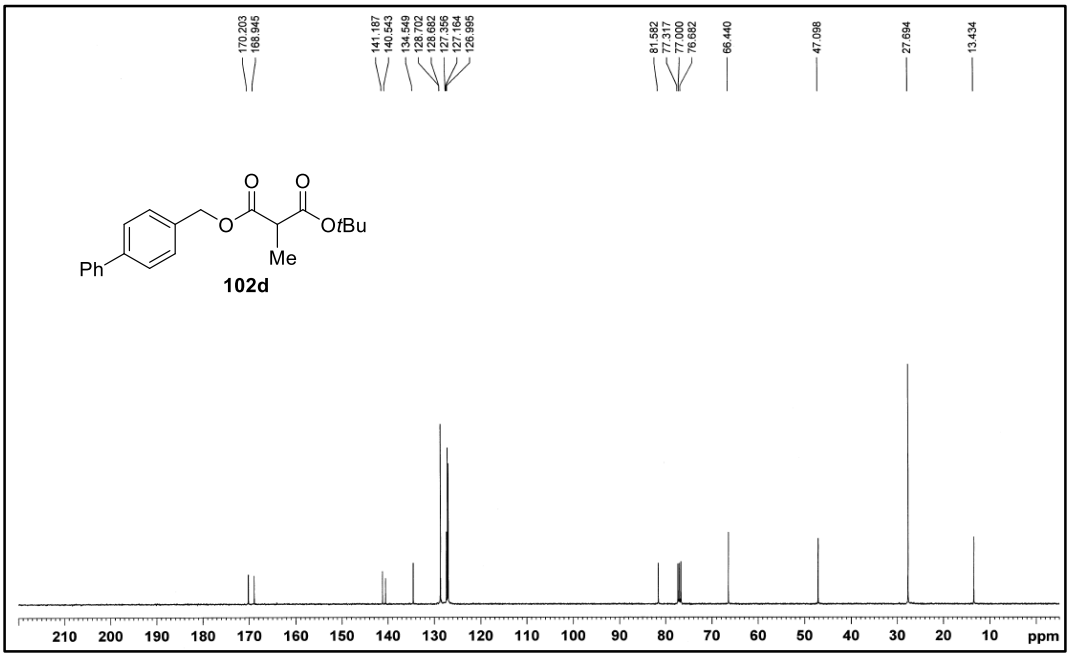
^{13}C-NMR of compound **102c** (100 MHz, $CDCl_3$)



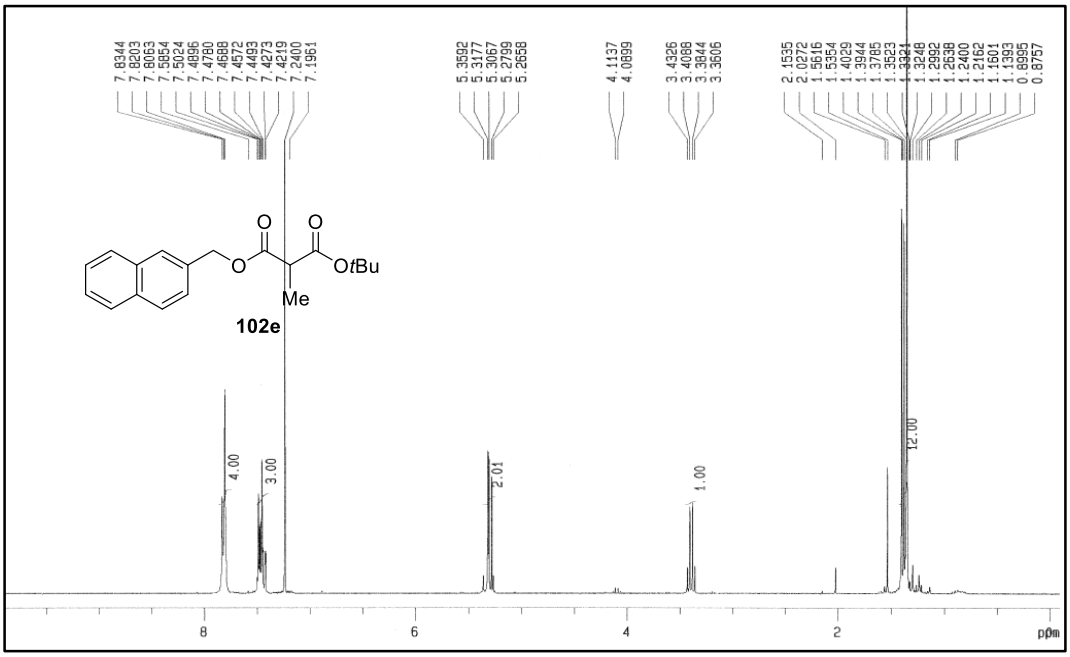
^{1}H-NMR of compound **102d** (300 MHz, $CDCl_3$)



^{13}C-NMR of compound **102d** (100 MHz, $CDCl_3$)



^{1}H-NMR of compound **102e** (300 MHz, $CDCl_3$)



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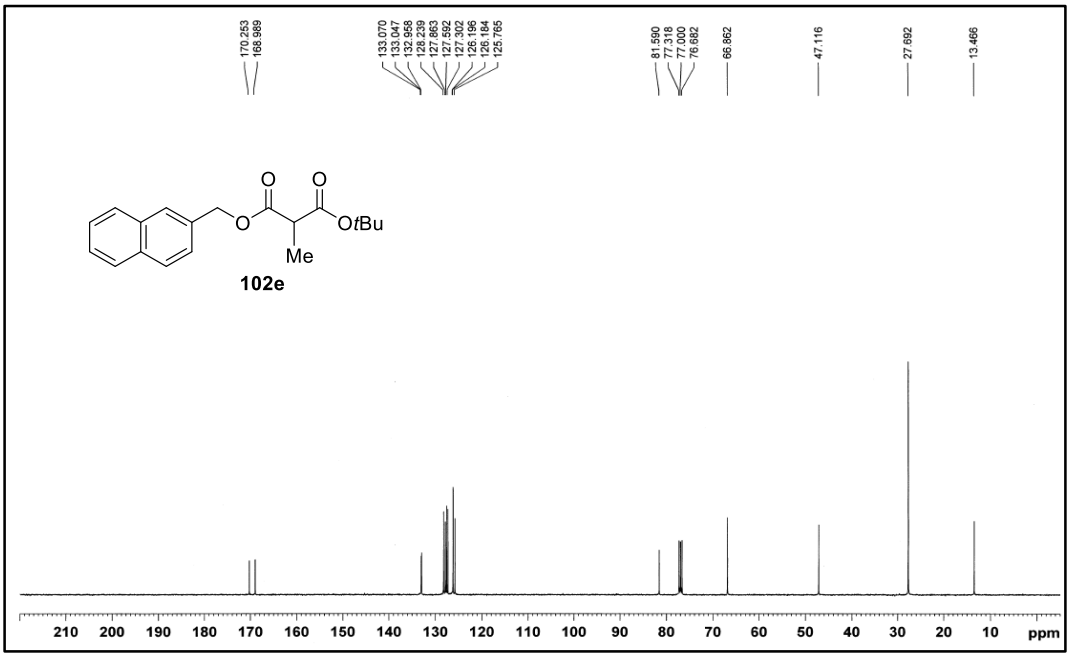
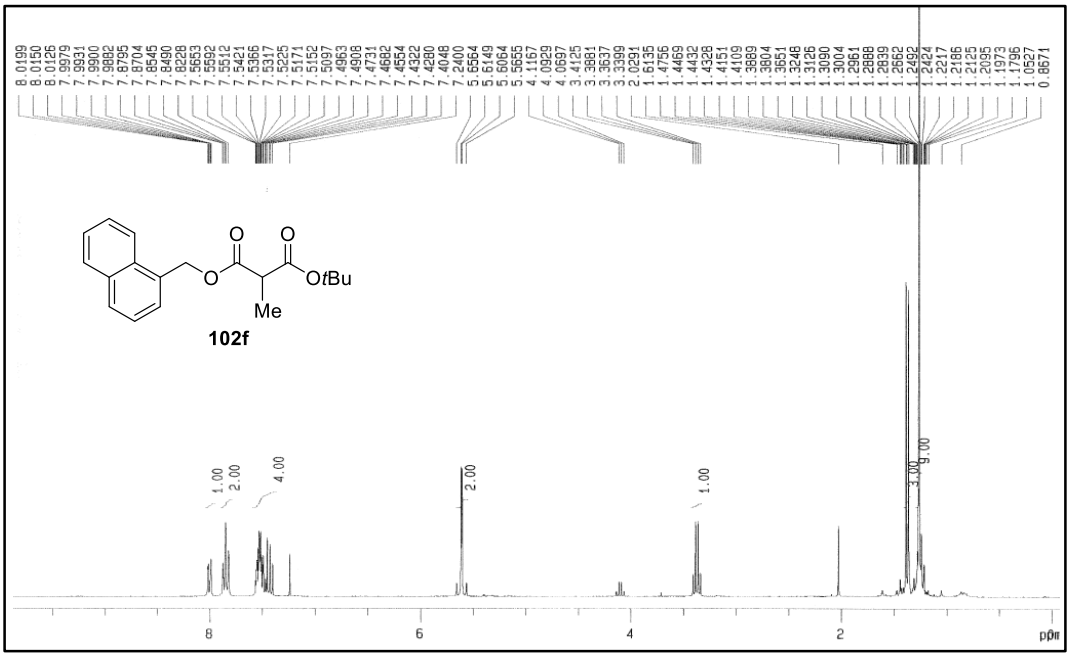
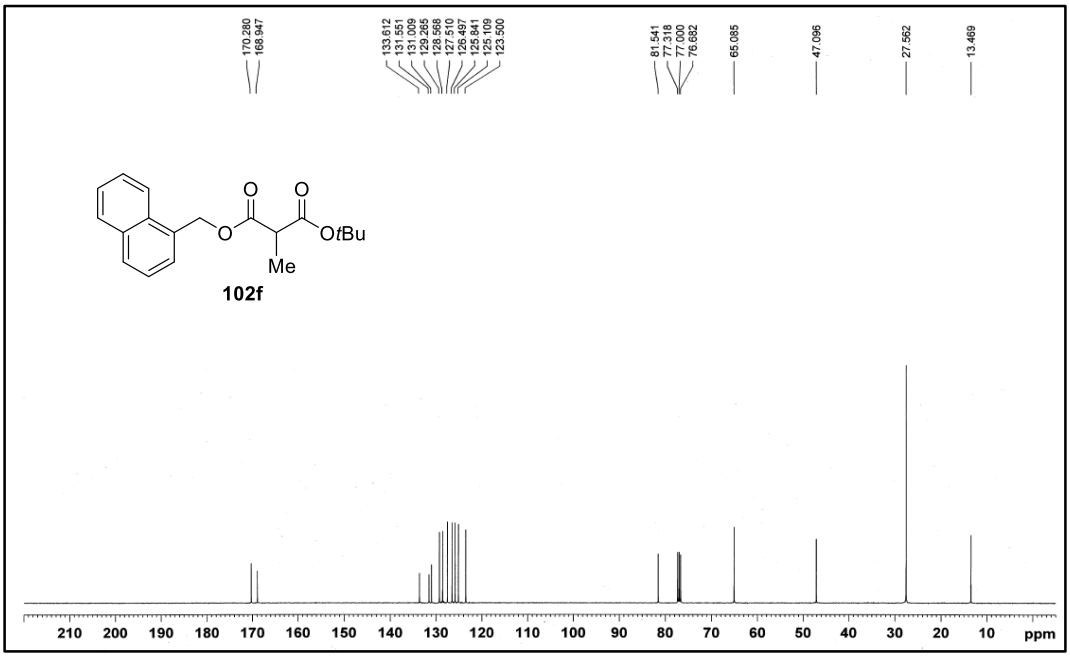


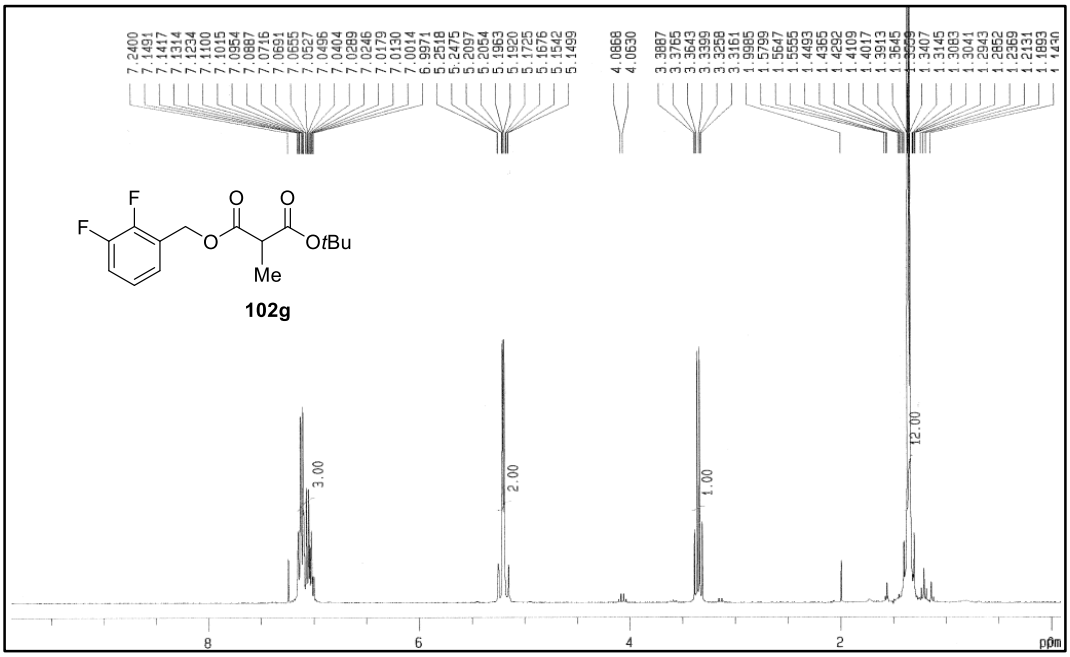
^{1}H-NMR of compound **102f** (300 MHz, $CDCl_3$)



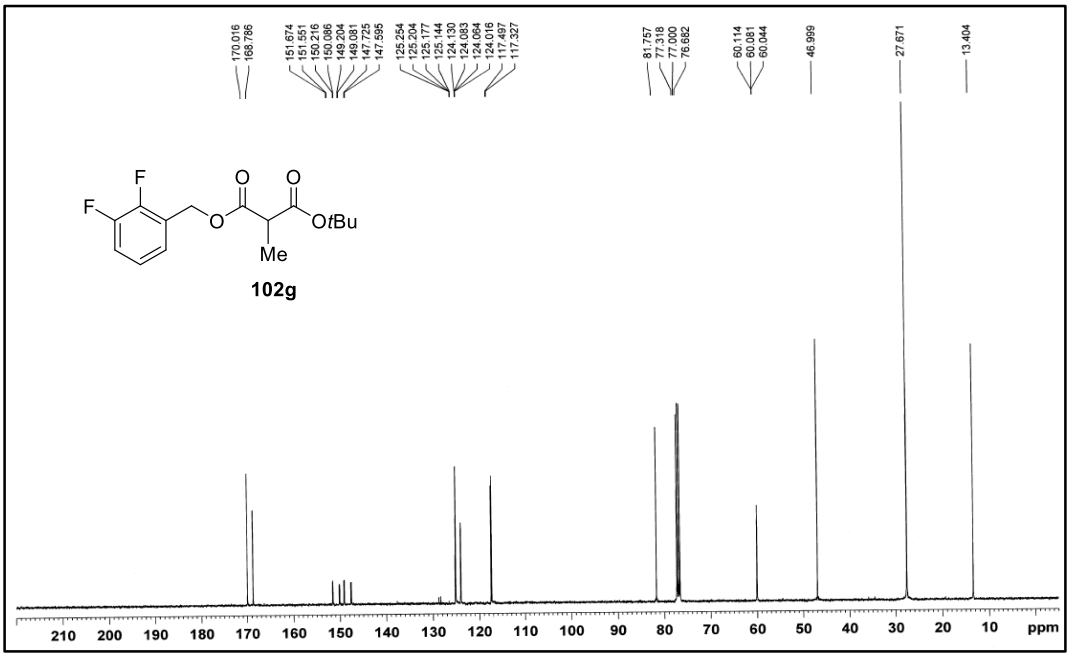
^{13}C-NMR of compound **102f** (100 MHz, $CDCl_3$)



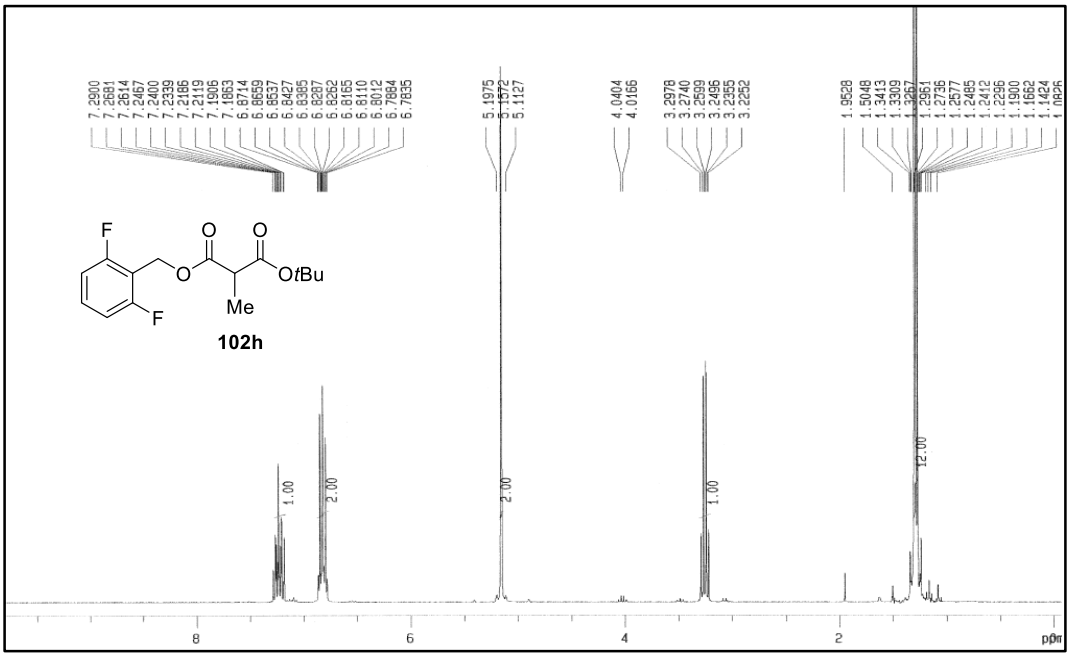
^{1}H-NMR of compound **102g** (300 MHz, $CDCl_3$)



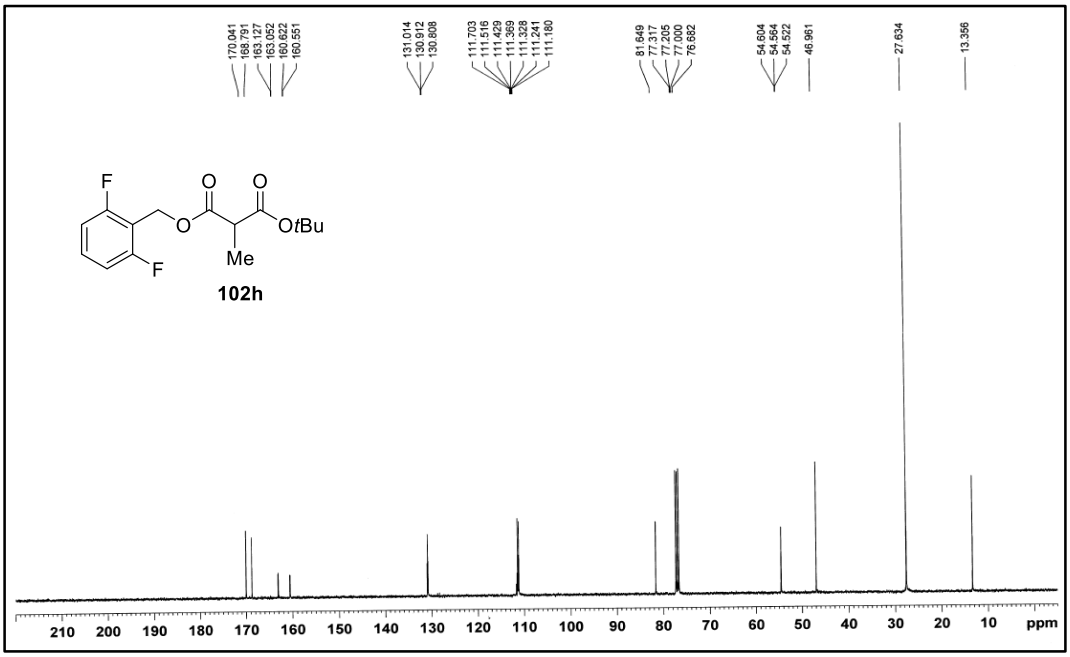
^{13}C-NMR of compound **102g** (100 MHz, $CDCl_3$)



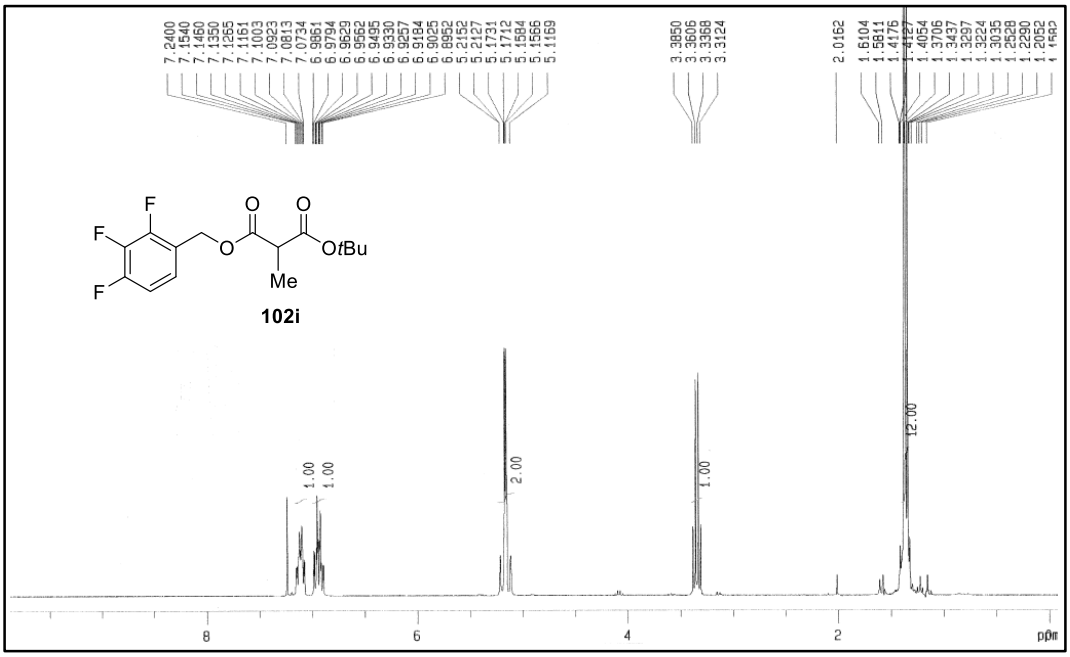
^{1}H-NMR of compound **102h** (300 MHz, $CDCl_3$)



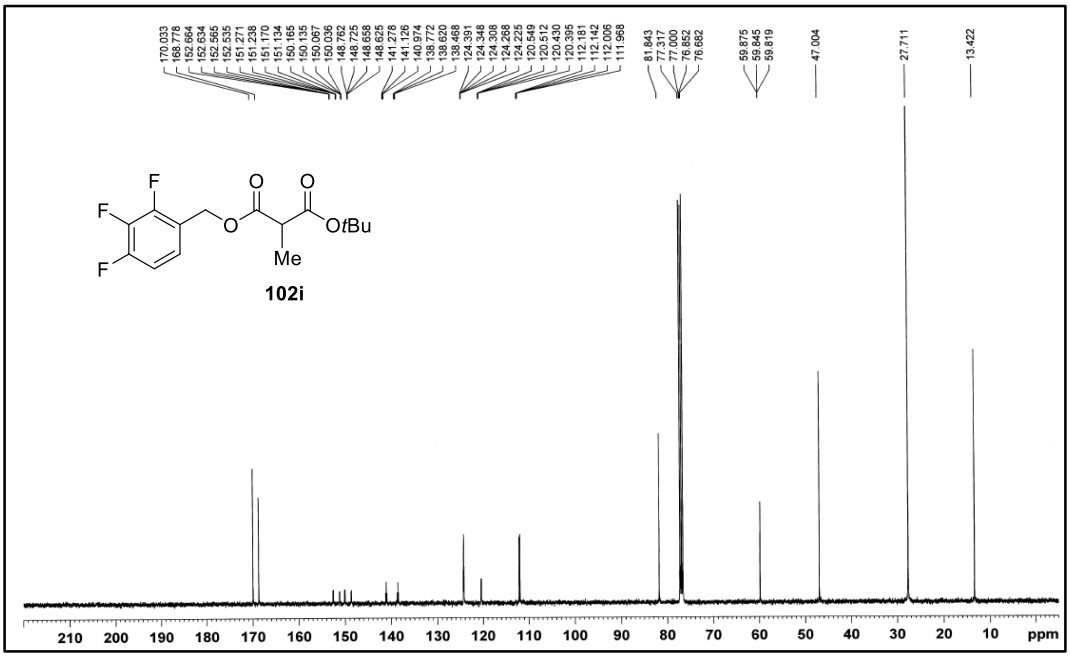
^{13}C-NMR of compound **102h** (100 MHz, $CDCl_3$)



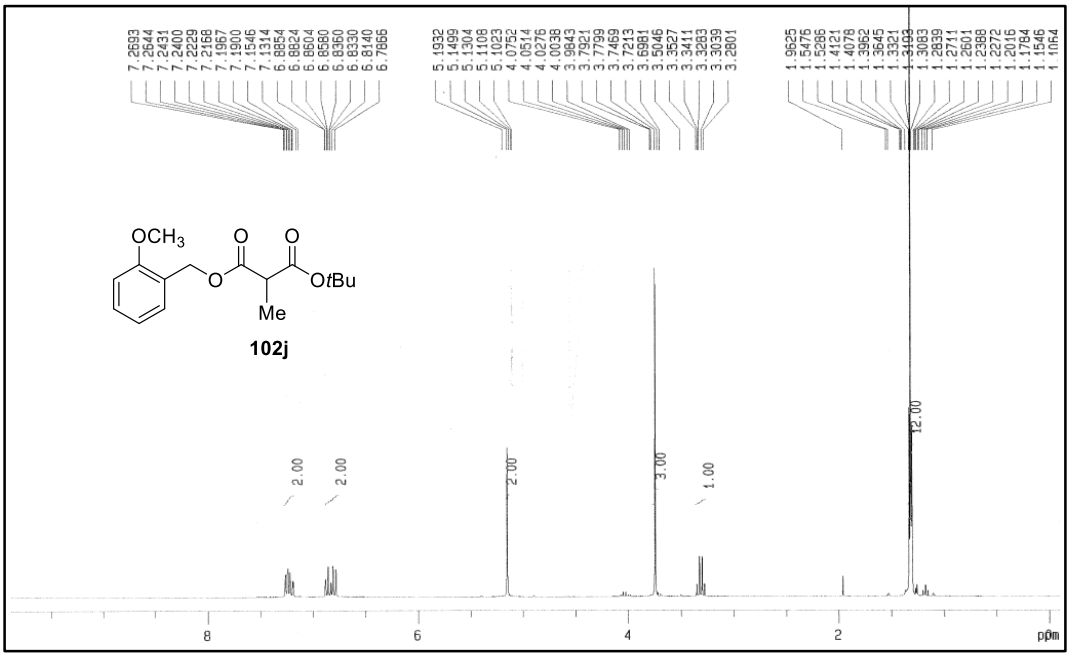
^{1}H-NMR of compound **102i** (300 MHz, $CDCl_3$)



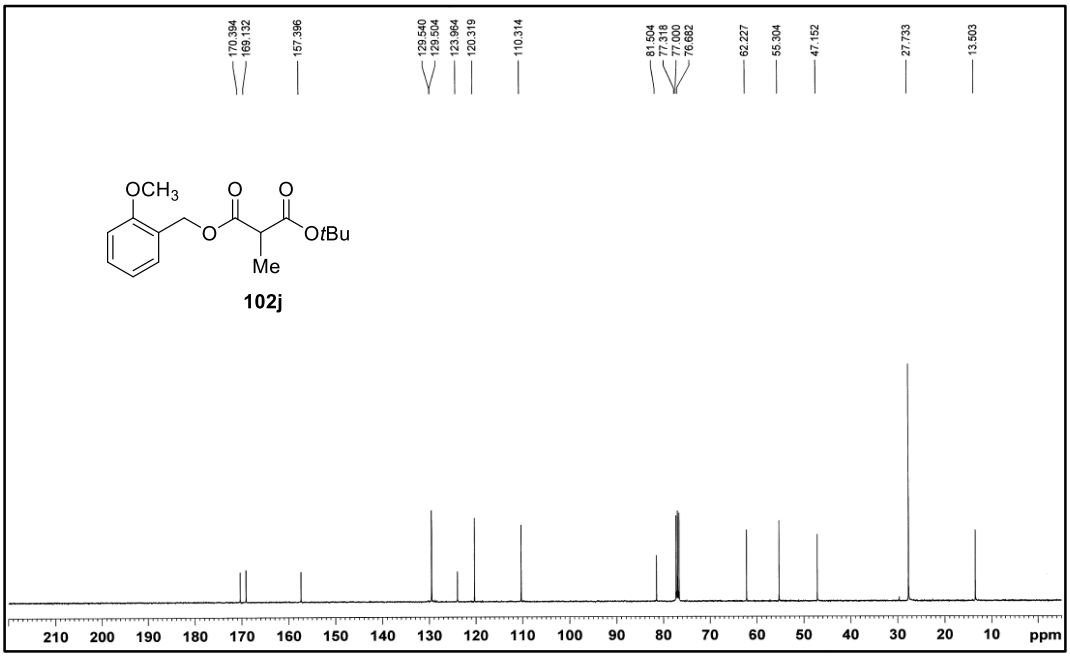
^{13}C-NMR of compound **102i** (100 MHz, $CDCl_3$)



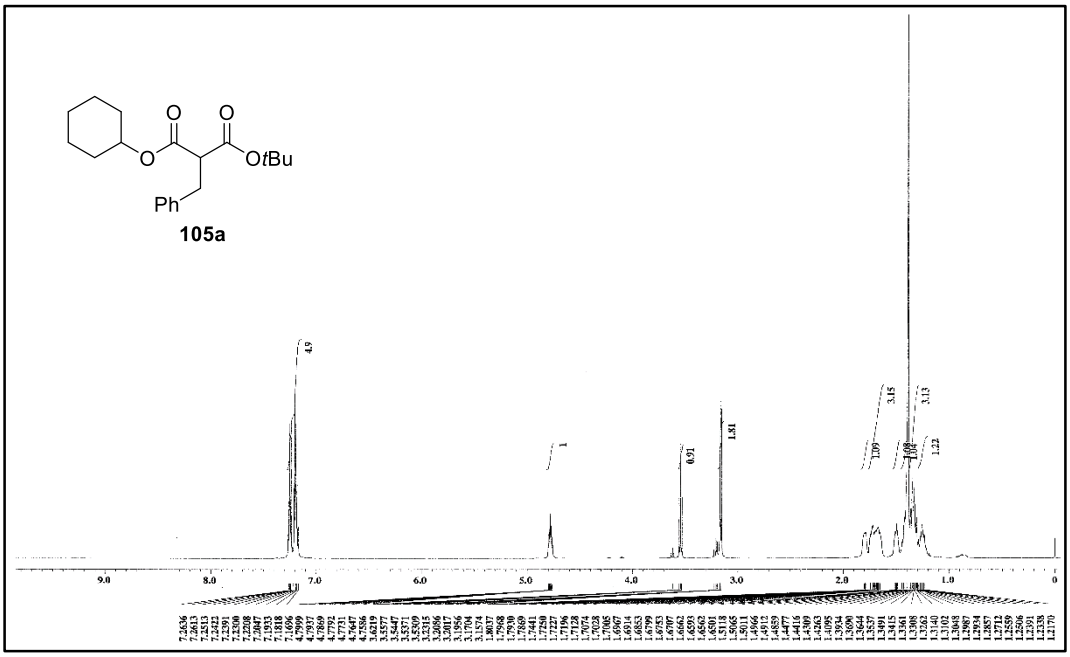
^{1}H-NMR of compound **102j** (300 MHz, $CDCl_3$)



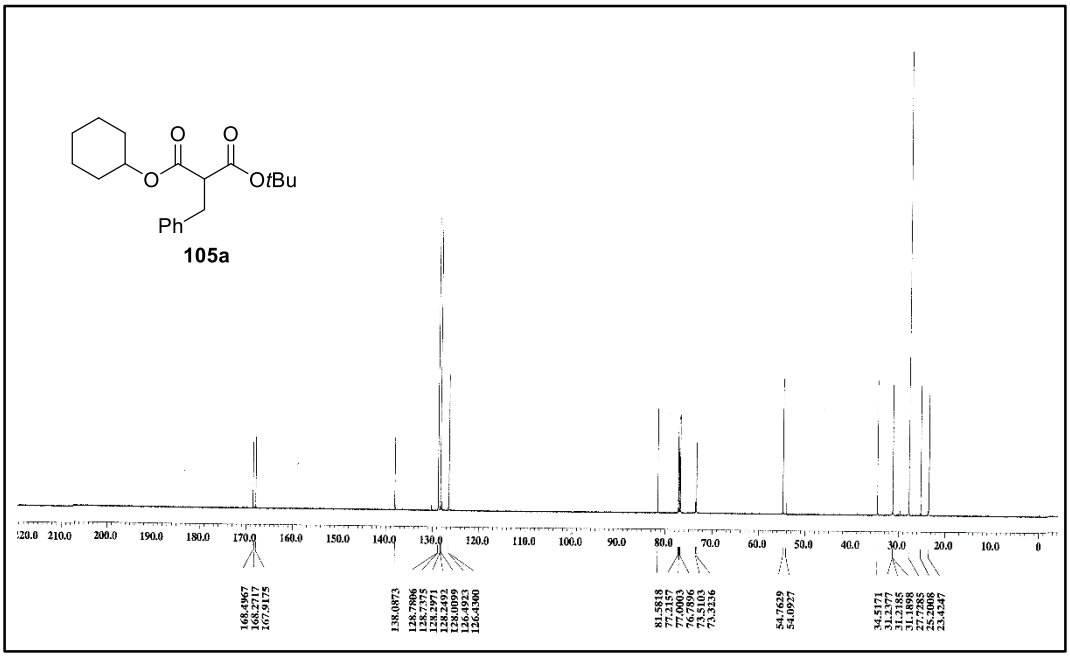
^{13}C-NMR of compound **102j** (100 MHz, $CDCl_3$)



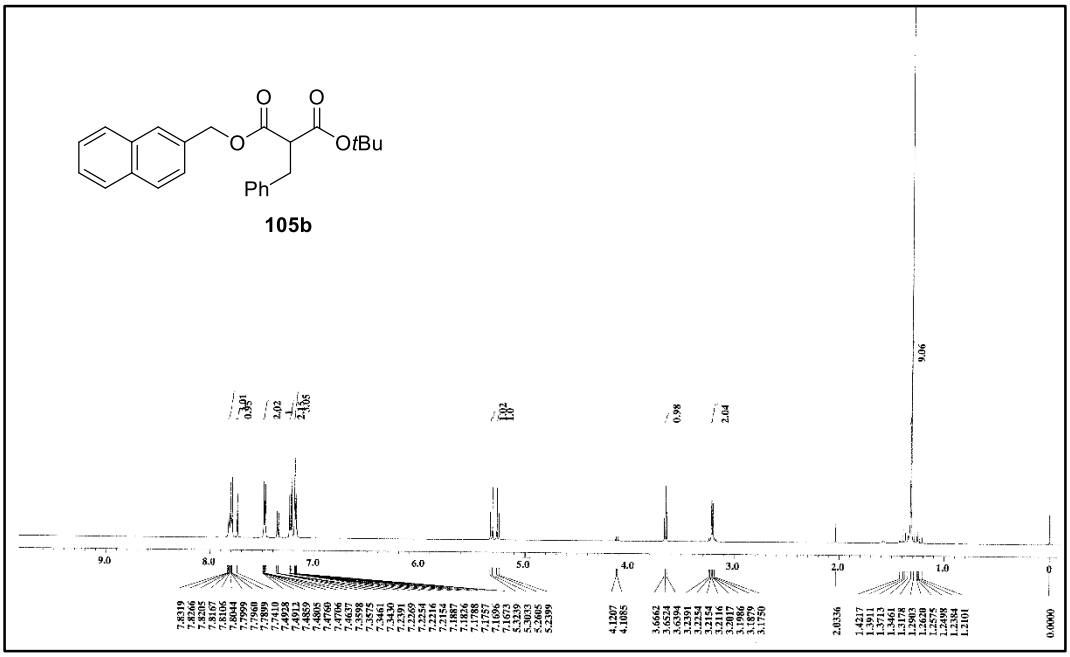
^{1}H-NMR of compound **105a** (600 MHz, $CDCl_3$)



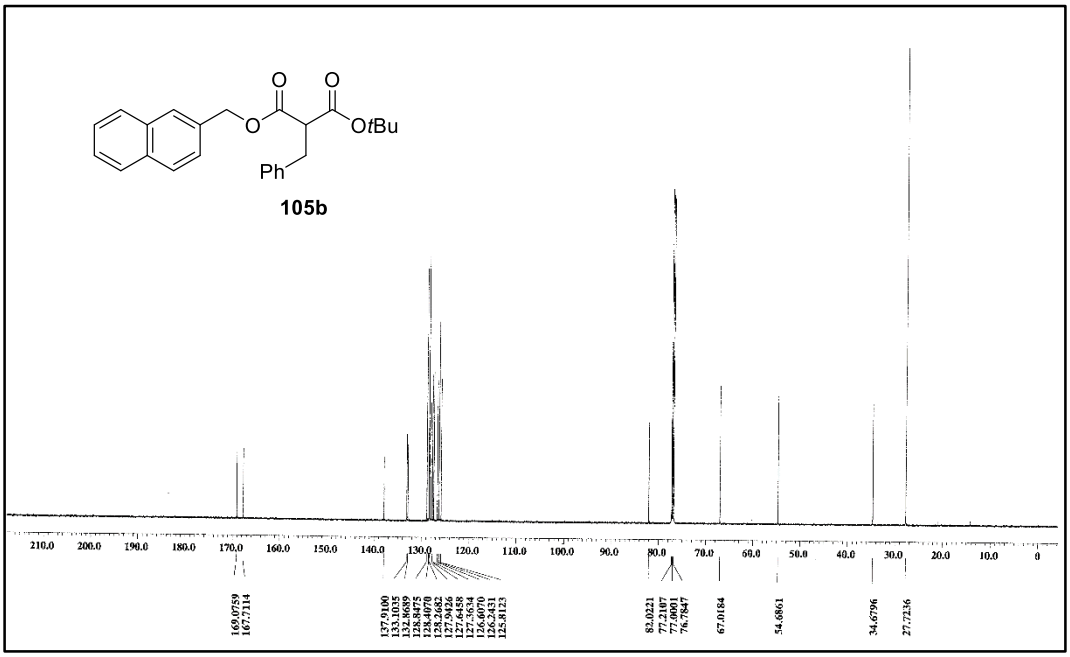
^{13}C-NMR of compound **105a** (150 MHz, $CDCl_3$)



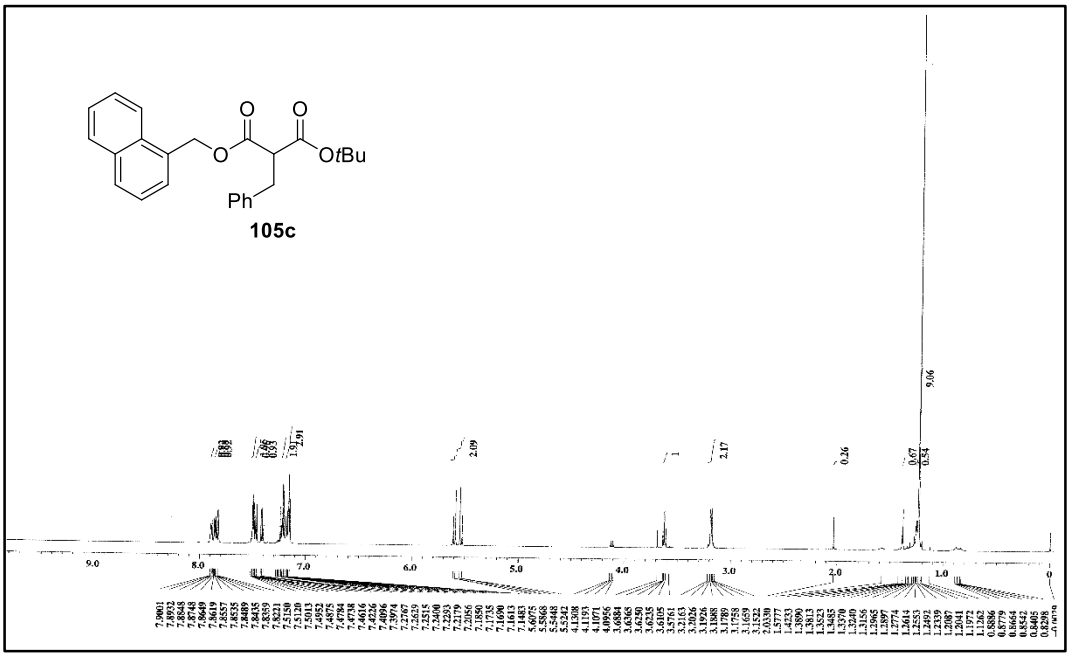
^{1}H-NMR of compound **105b** (600 MHz, $CDCl_3$)



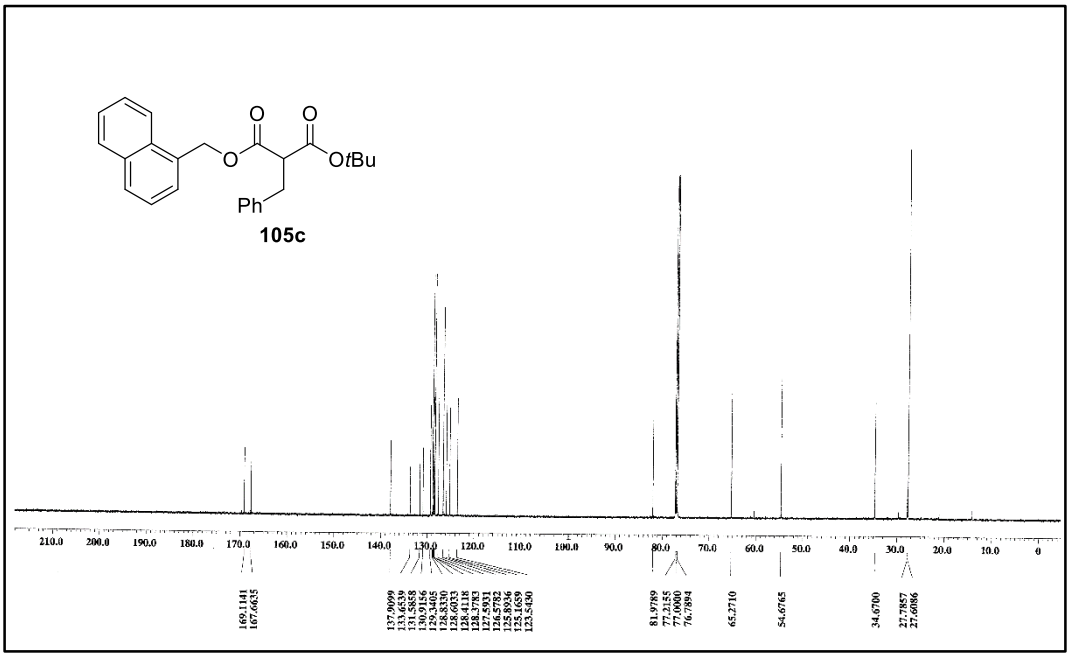
^{13}C-NMR of compound **105b** (150 MHz, $CDCl_3$)



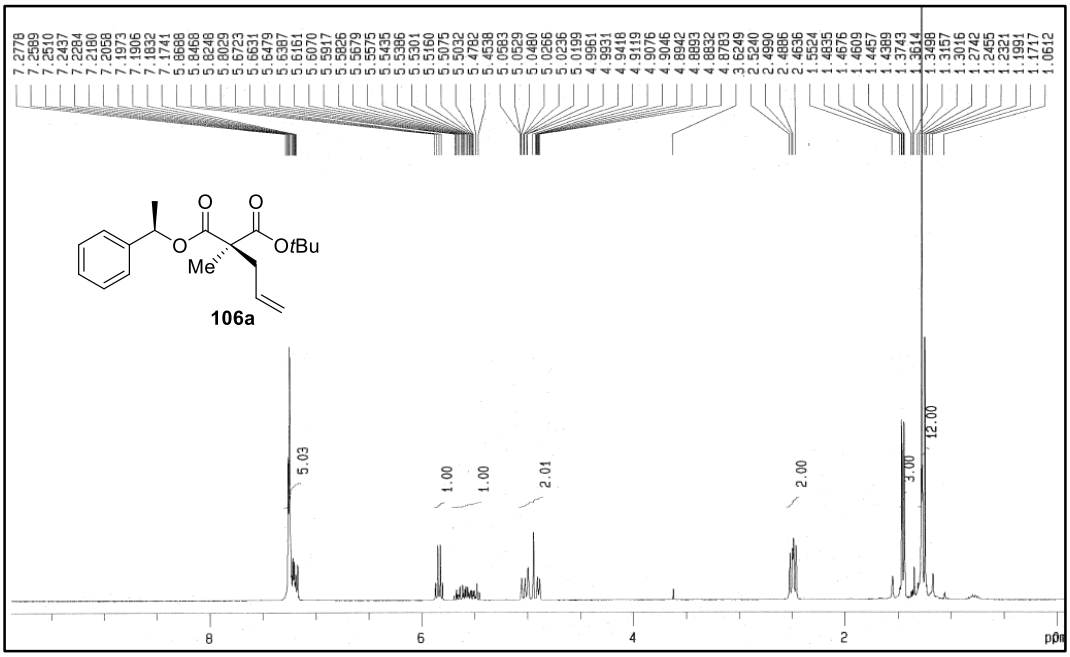
^{1}H-NMR of compound **105c** (300 MHz, $CDCl_3$)



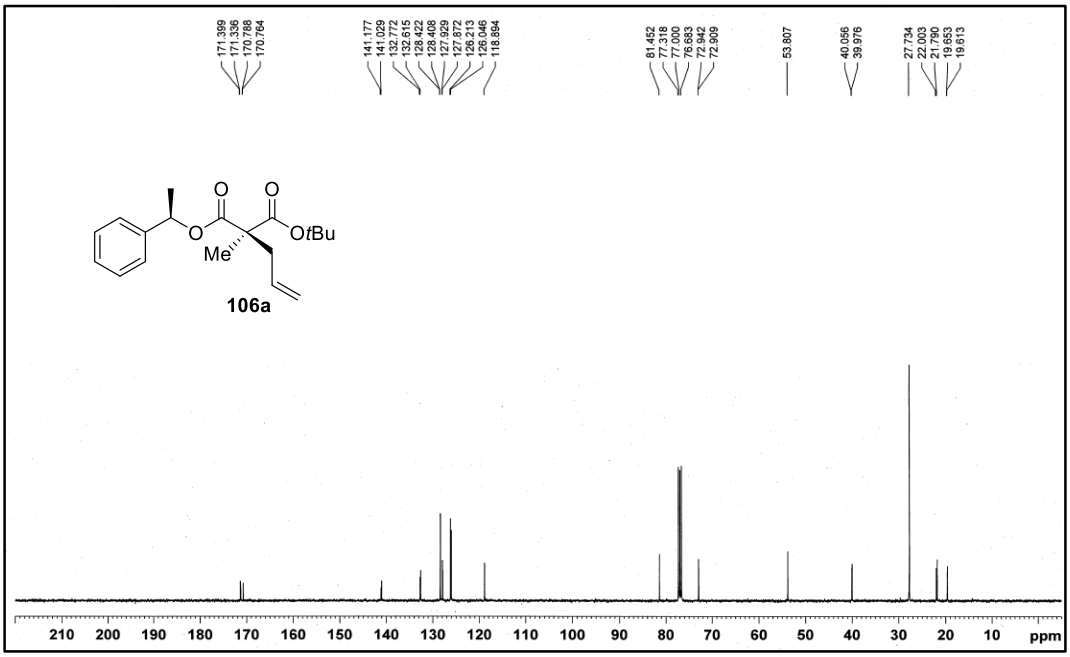
^{13}C-NMR of compound **105c** (100 MHz, $CDCl_3$)



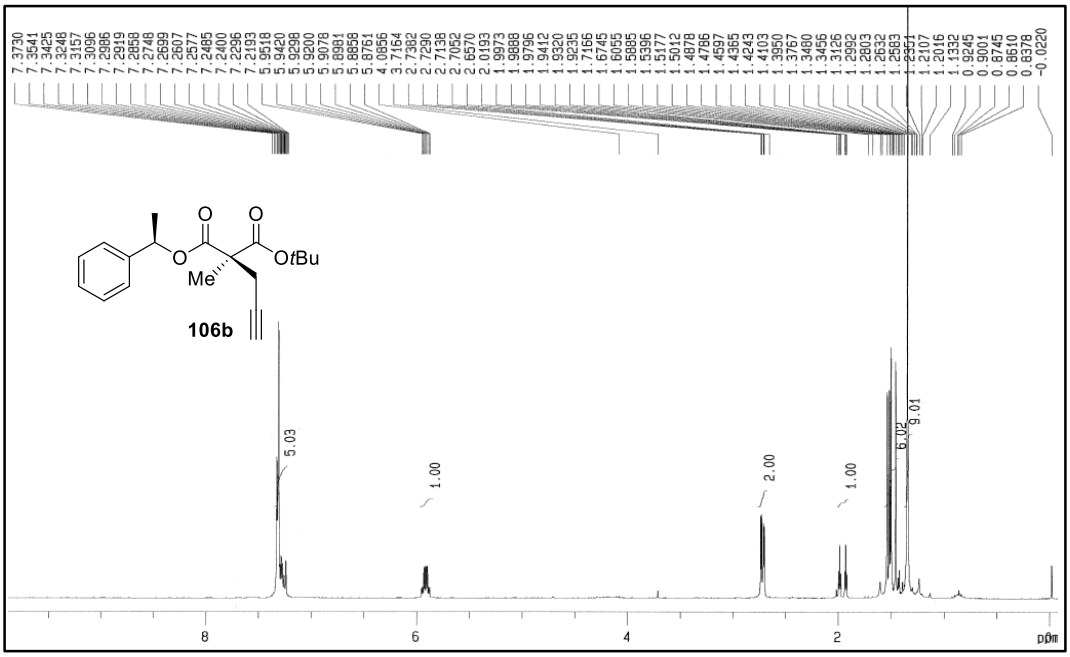
^{1}H-NMR of compound **106a** (300 MHz, $CDCl_3$)



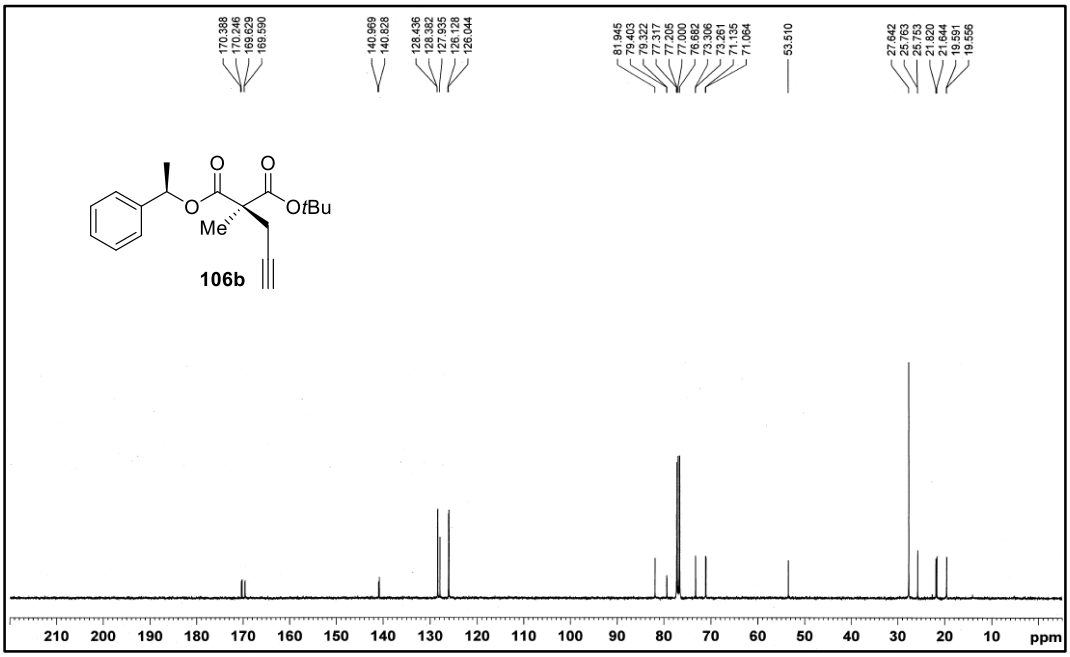
^{13}C-NMR of compound **106a** (100 MHz, $CDCl_3$)



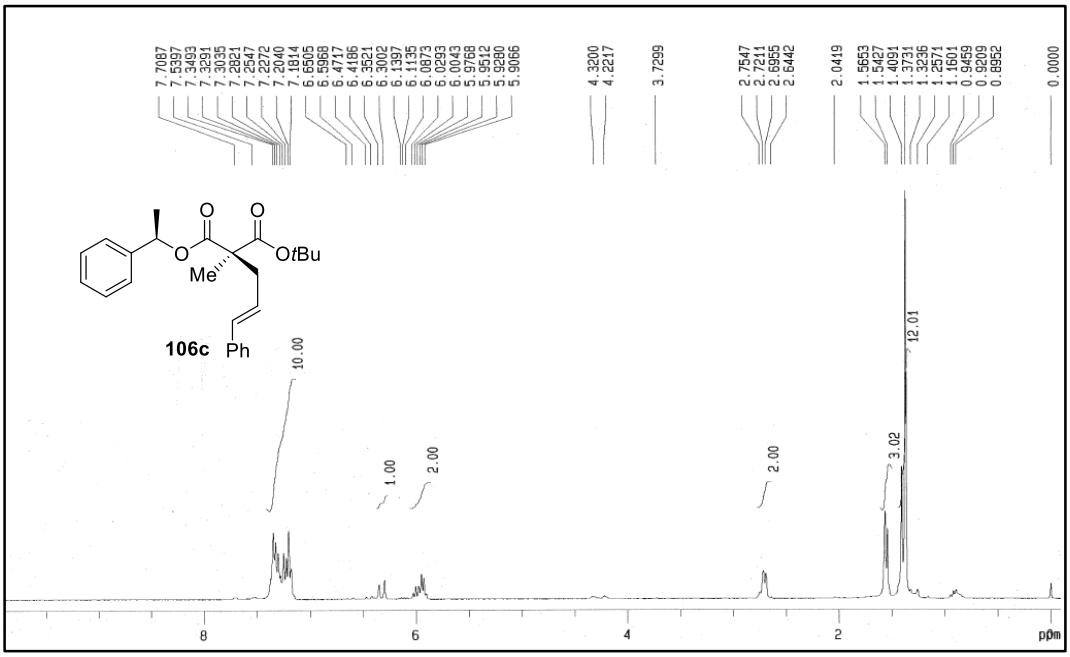
^{1}H-NMR of compound **106b** (300 MHz, $CDCl_3$)



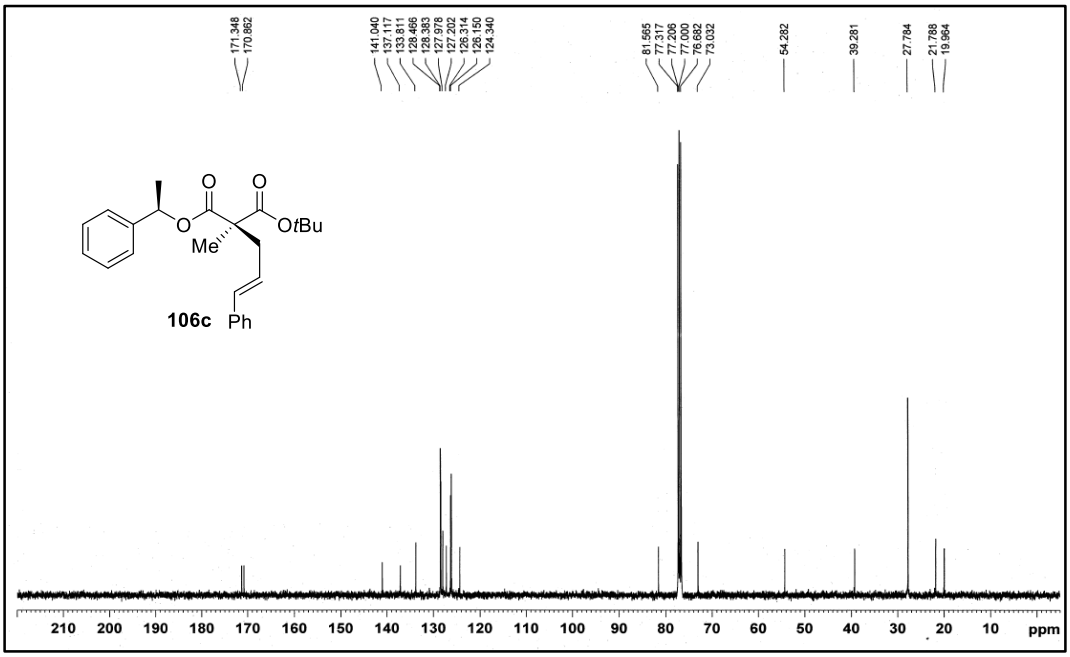
^{13}C-NMR of compound **106b** (100 MHz, $CDCl_3$)



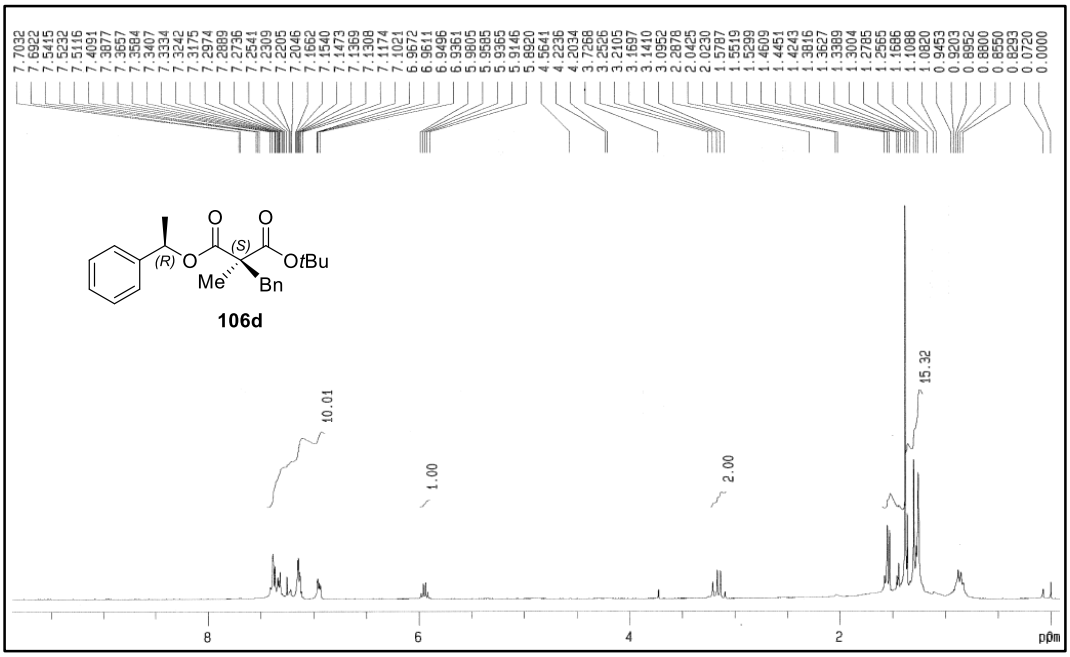
^{1}H-NMR of compound **106c** (300 MHz, $CDCl_3$)



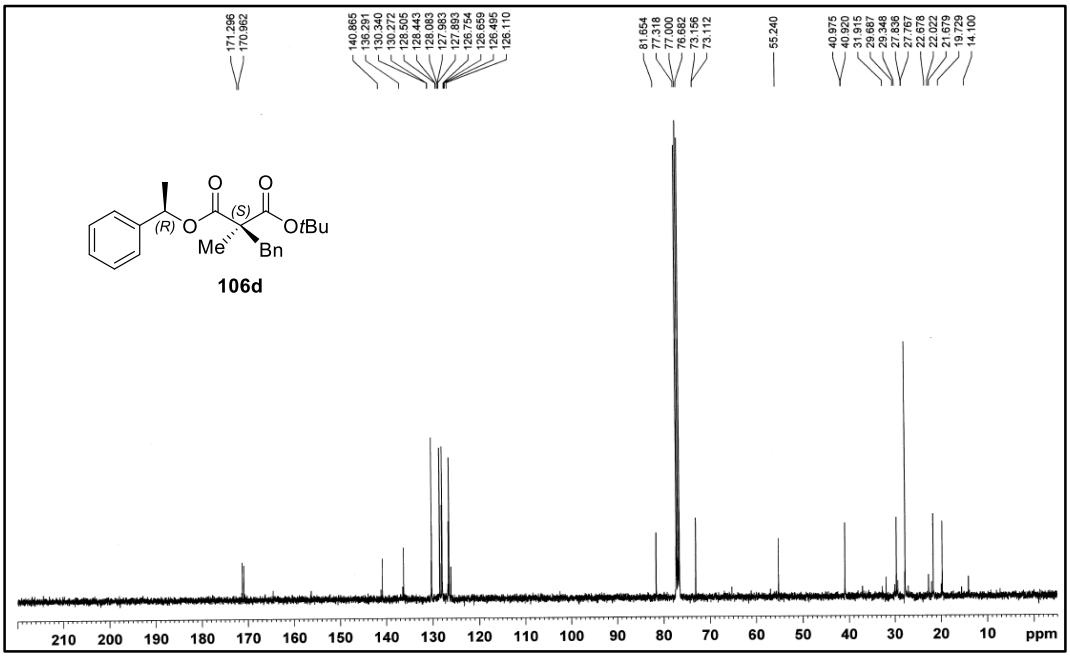
^{13}C-NMR of compound **106c** (100 MHz, $CDCl_3$)



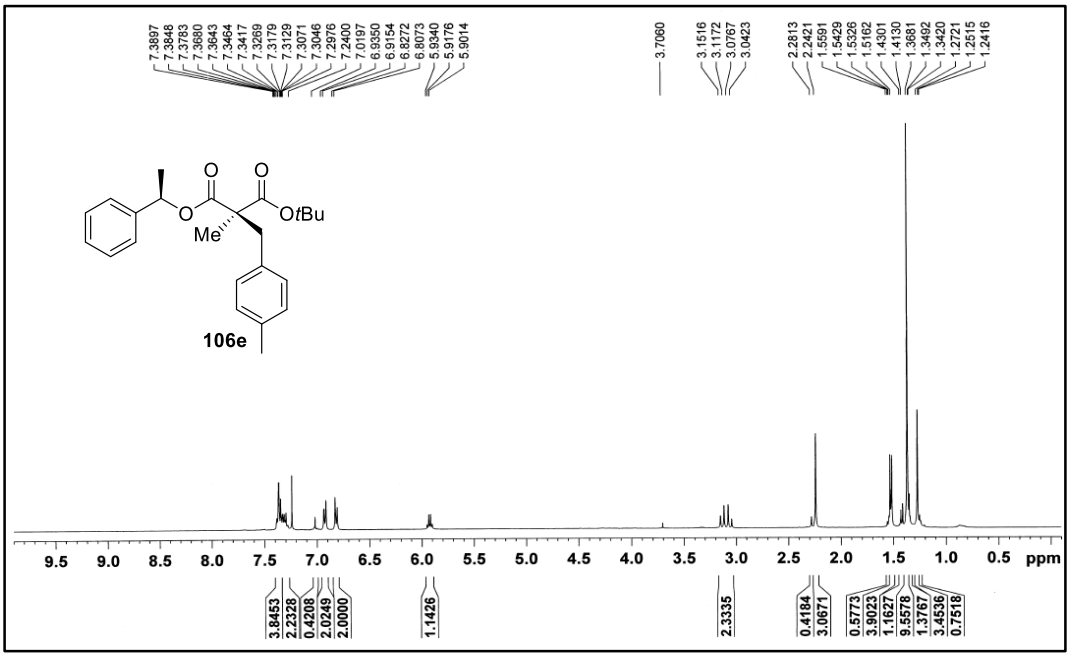
^{1}H-NMR of compound **106d** (300 MHz, $CDCl_3$)



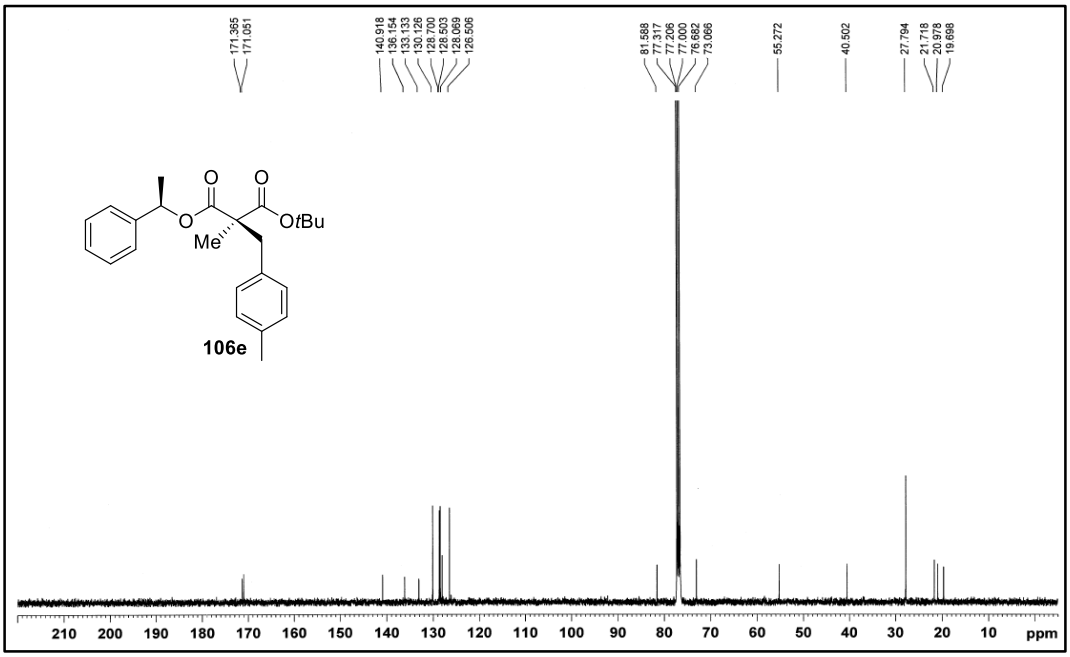
^{13}C-NMR of compound **106d** (100 MHz, $CDCl_3$)



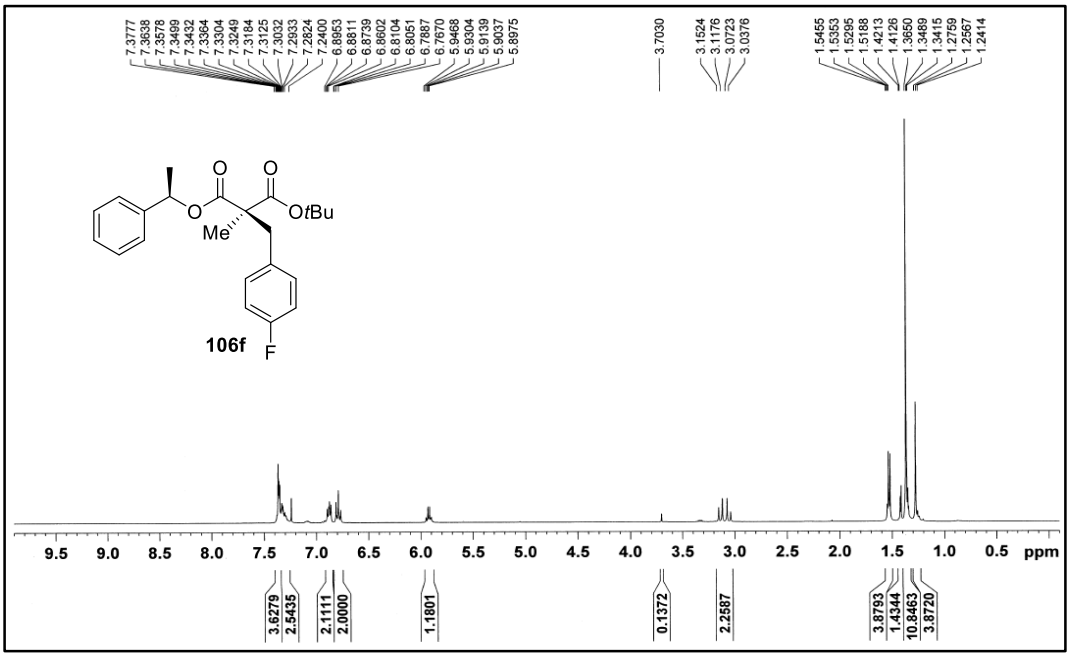
^{1}H-NMR of compound **106e** (400 MHz, $CDCl_3$)



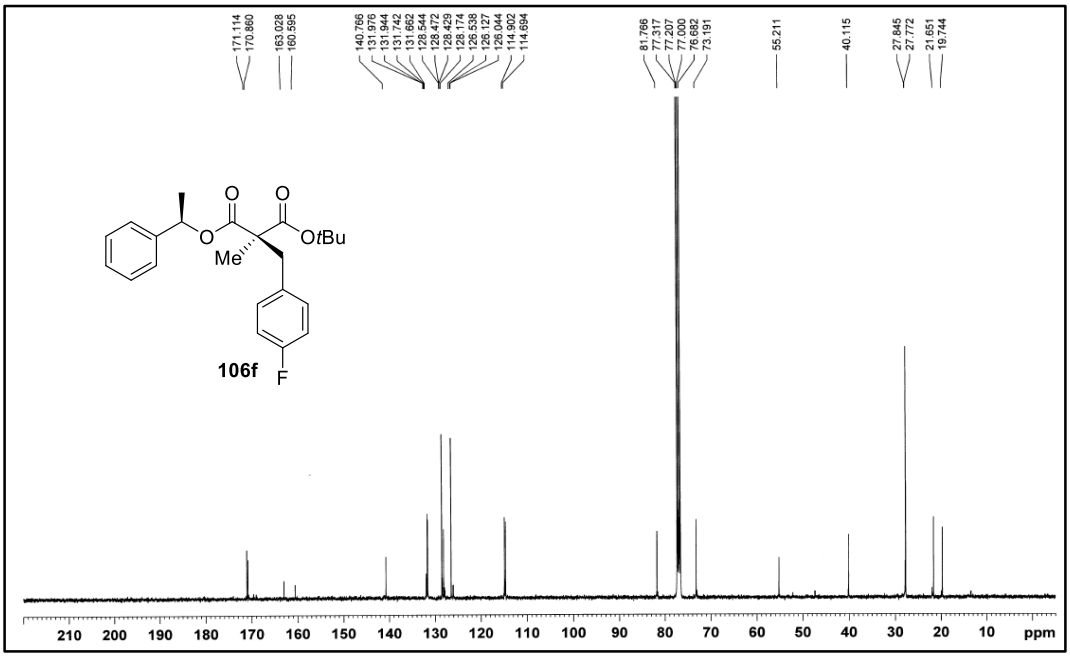
^{13}C-NMR of compound **106e** (100 MHz, $CDCl_3$)



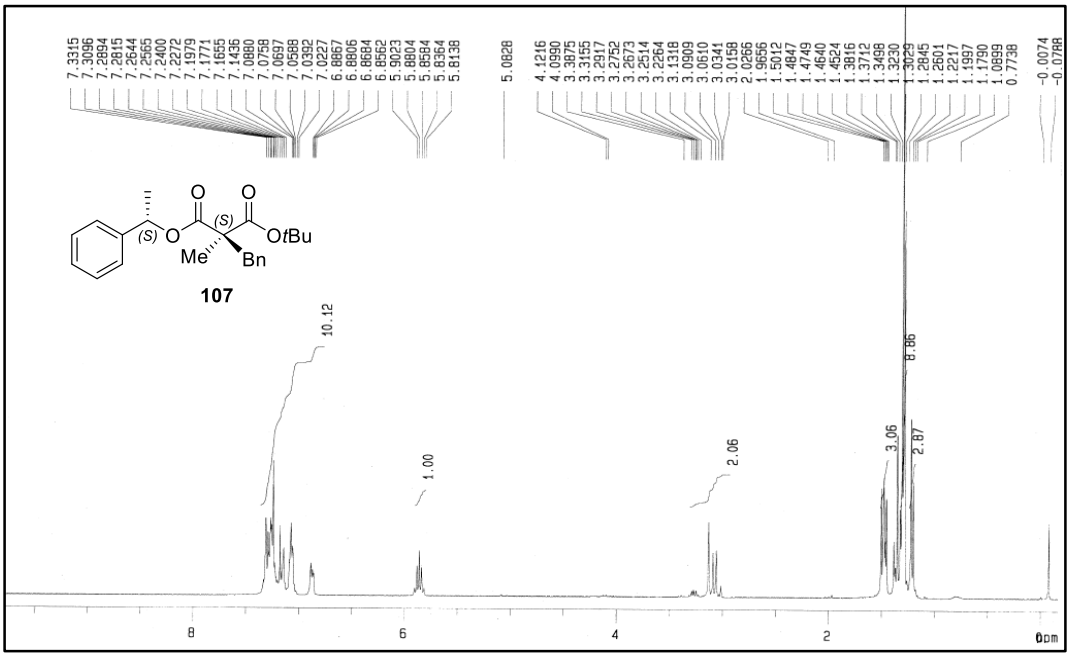
^{1}H-NMR of compound **106f** (400 MHz, $CDCl_3$)



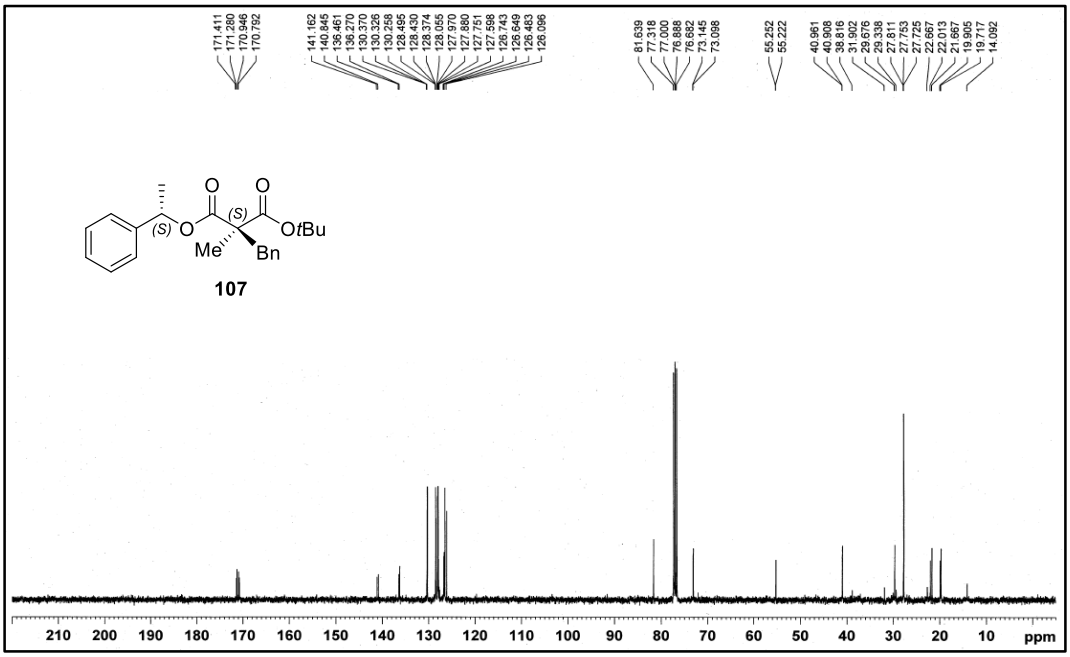
^{13}C-NMR of compound **106f** (100 MHz, $CDCl_3$)



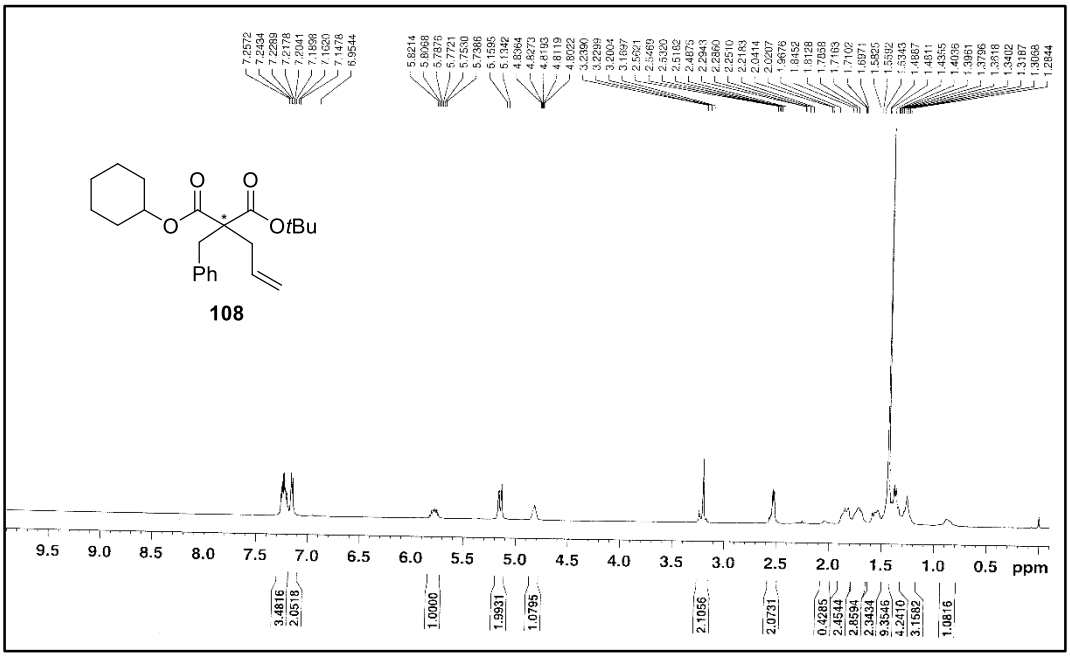
^{1}H-NMR of compound **107** (300 MHz, $CDCl_3$)



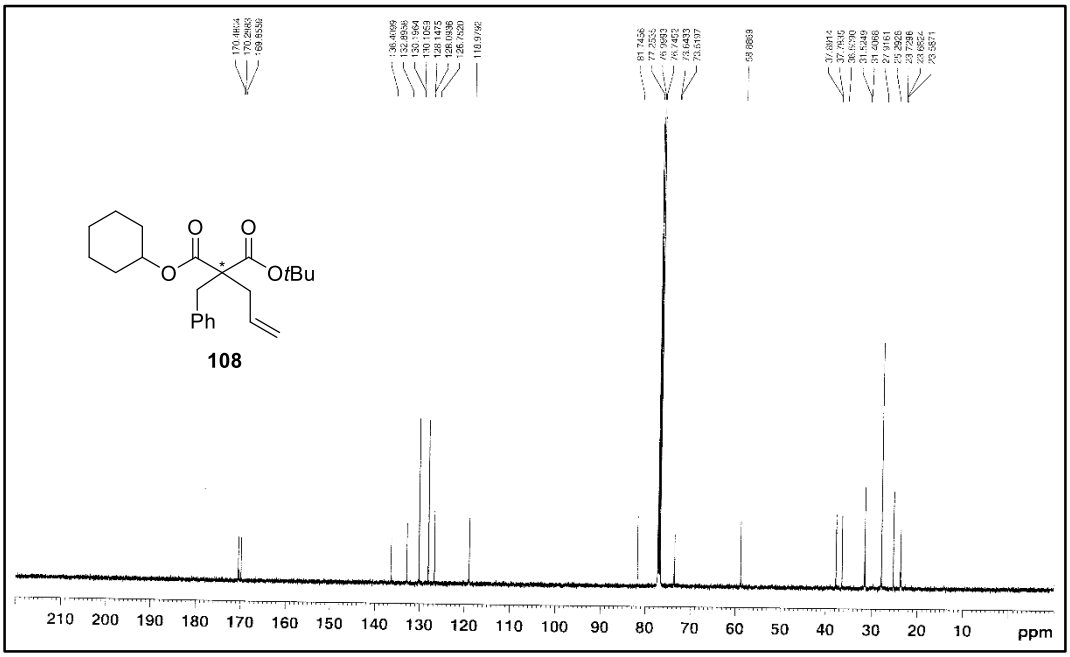
^{13}C-NMR of compound **107** (100 MHz, $CDCl_3$)



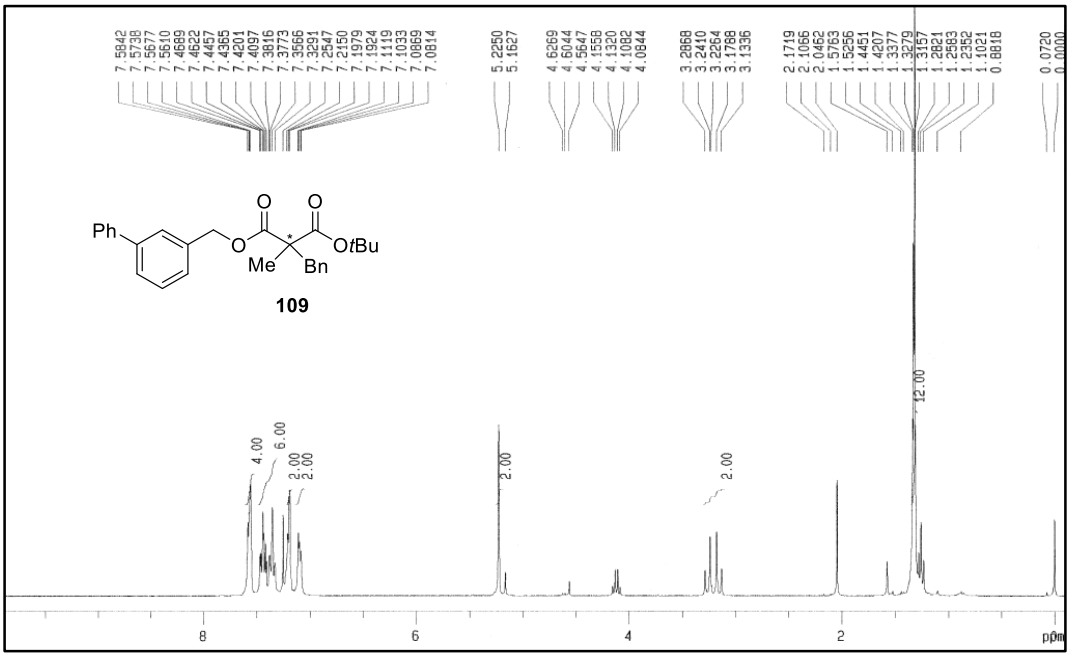
^{1}H-NMR of compound **108** (500 MHz, $CDCl_3$)



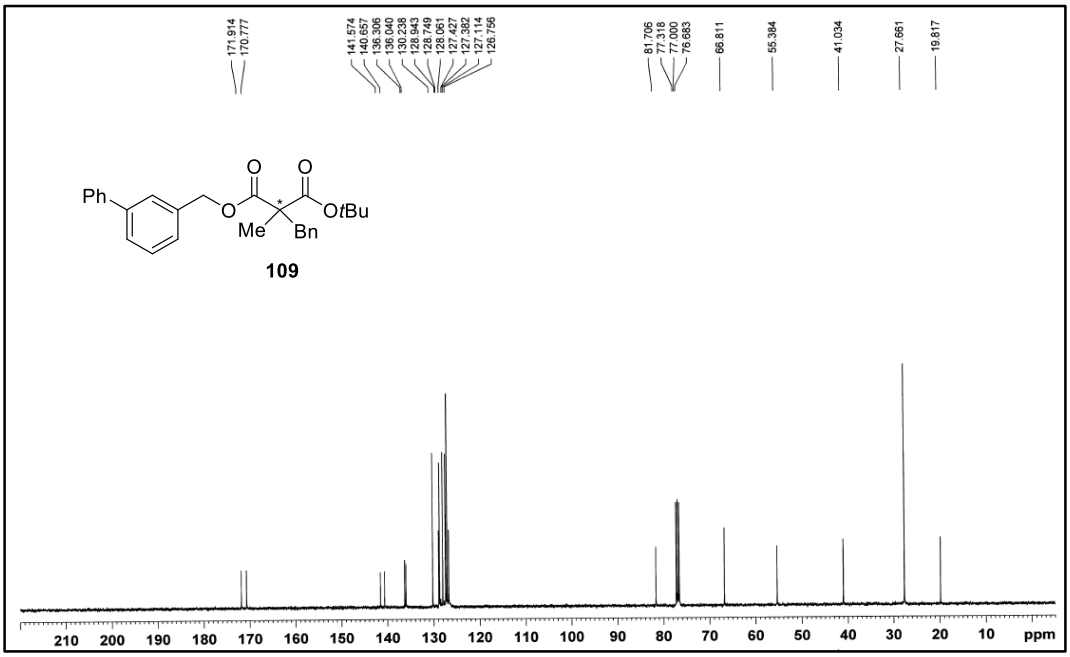
^{13}C-NMR of compound **108** (125 MHz, $CDCl_3$)



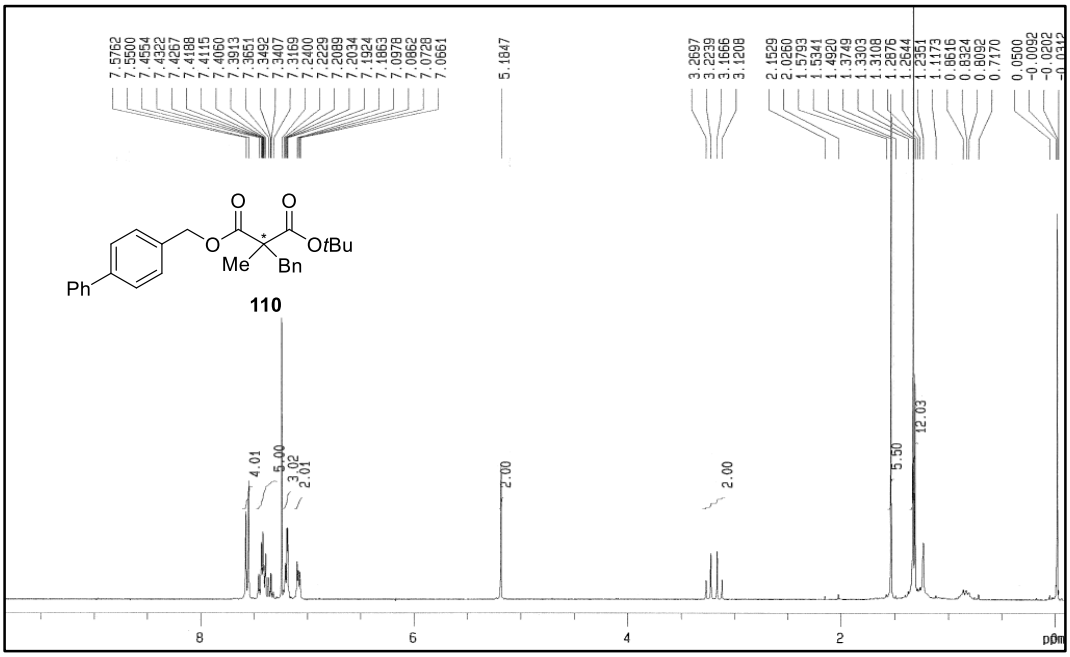
^{1}H-NMR of compound **109** (300 MHz, $CDCl_3$)



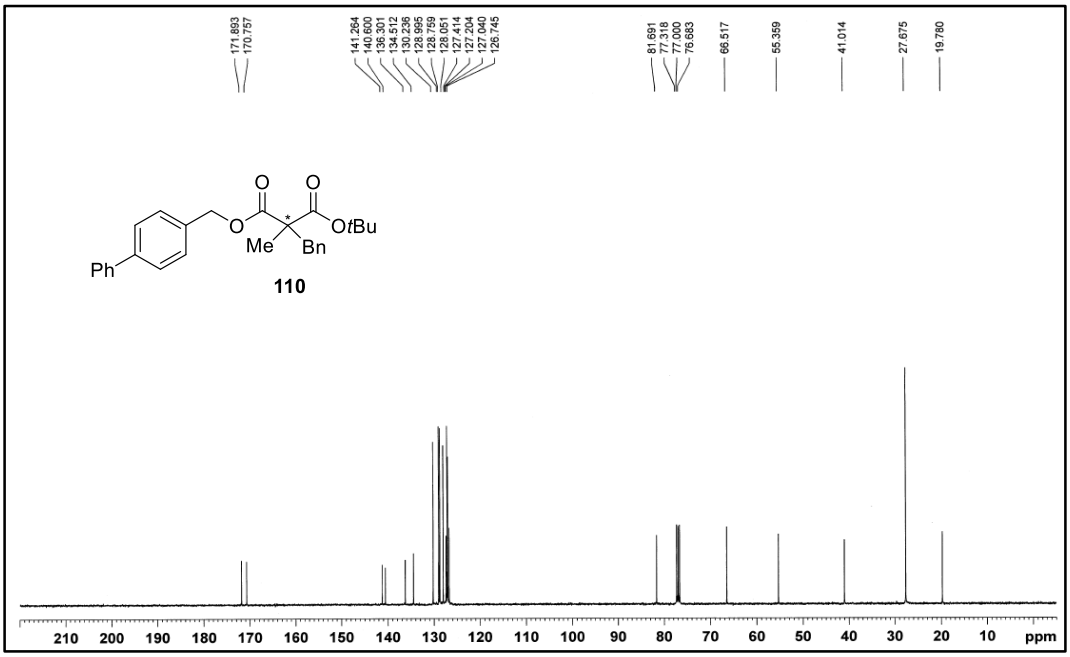
^{13}C-NMR of compound **109** (100 MHz, $CDCl_3$)



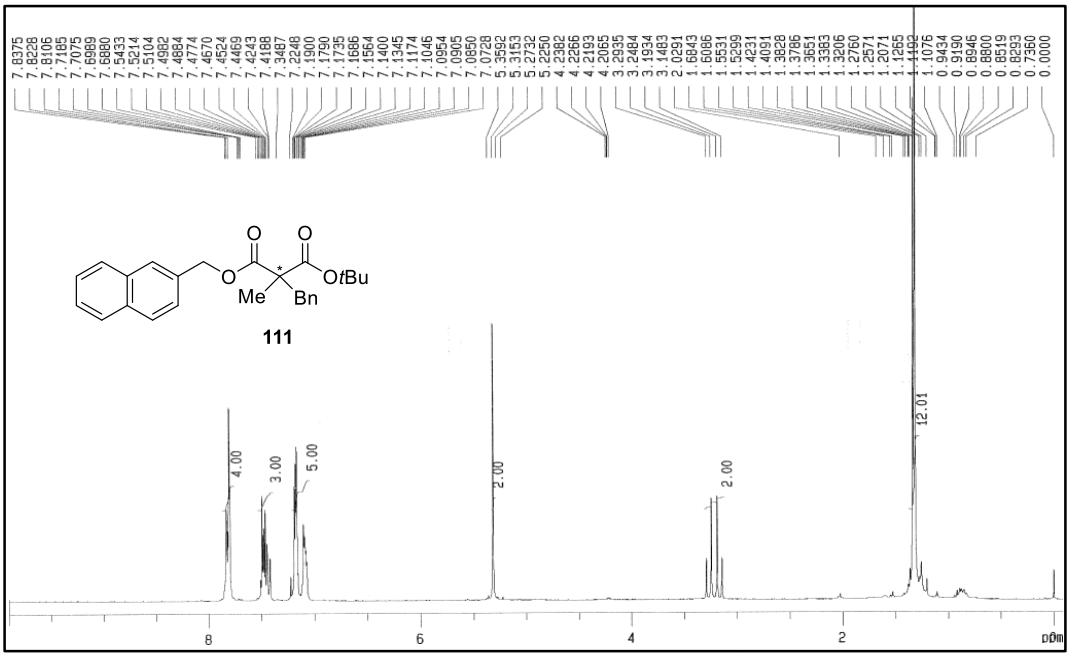
^{1}H-NMR of compound **110** (300 MHz, $CDCl_3$)



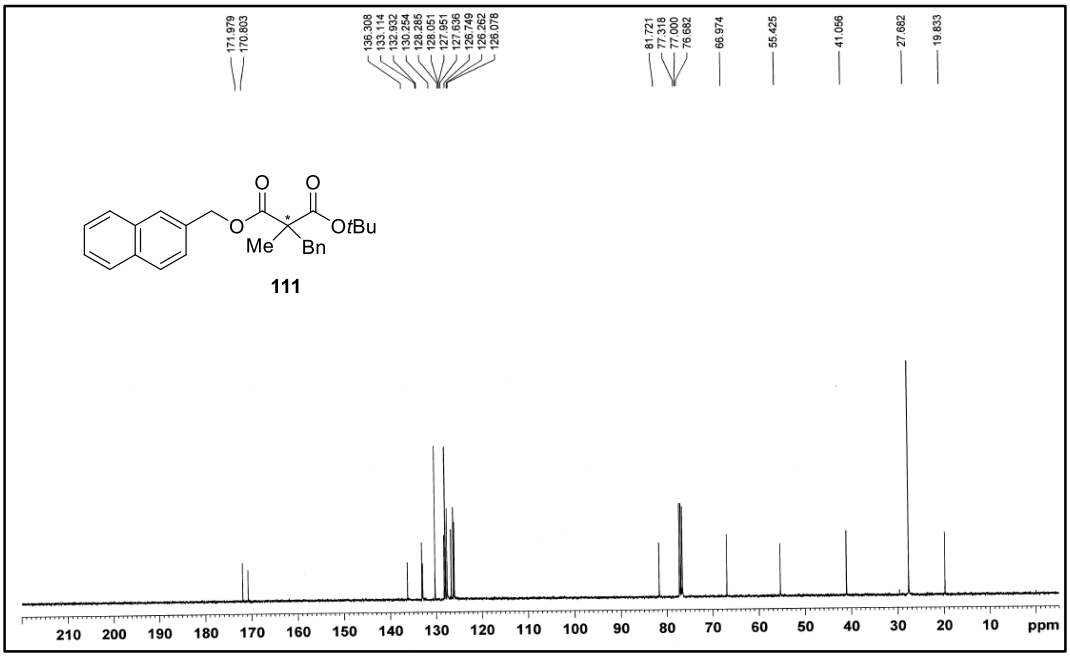
^{13}C-NMR of compound **110** (100 MHz, $CDCl_3$)



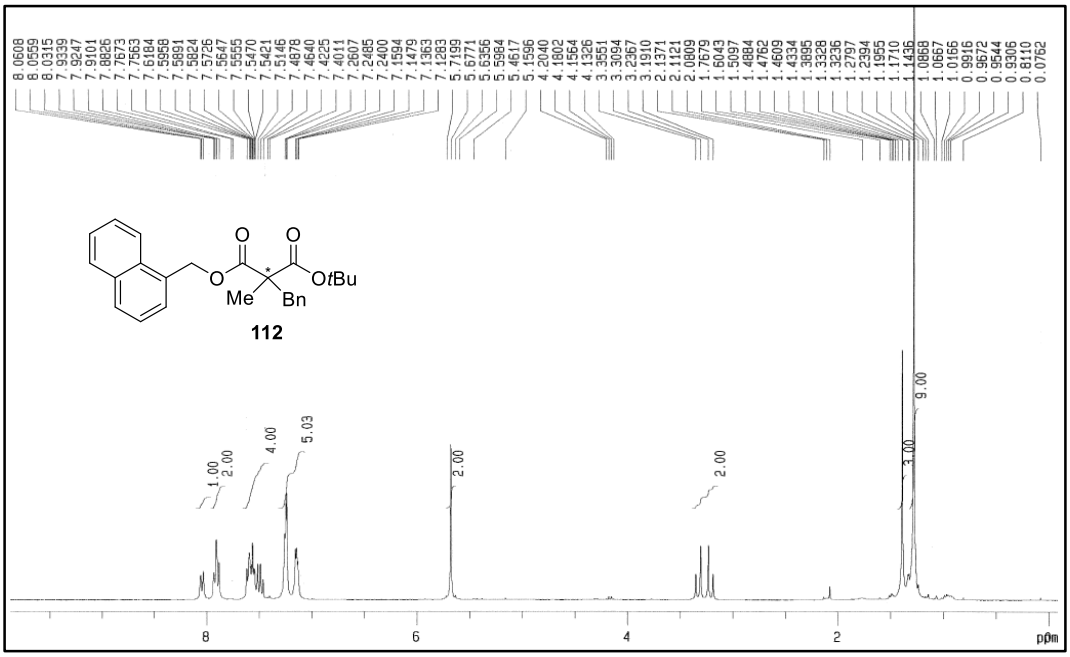
^{1}H-NMR of compound **111** (300 MHz, $CDCl_3$)



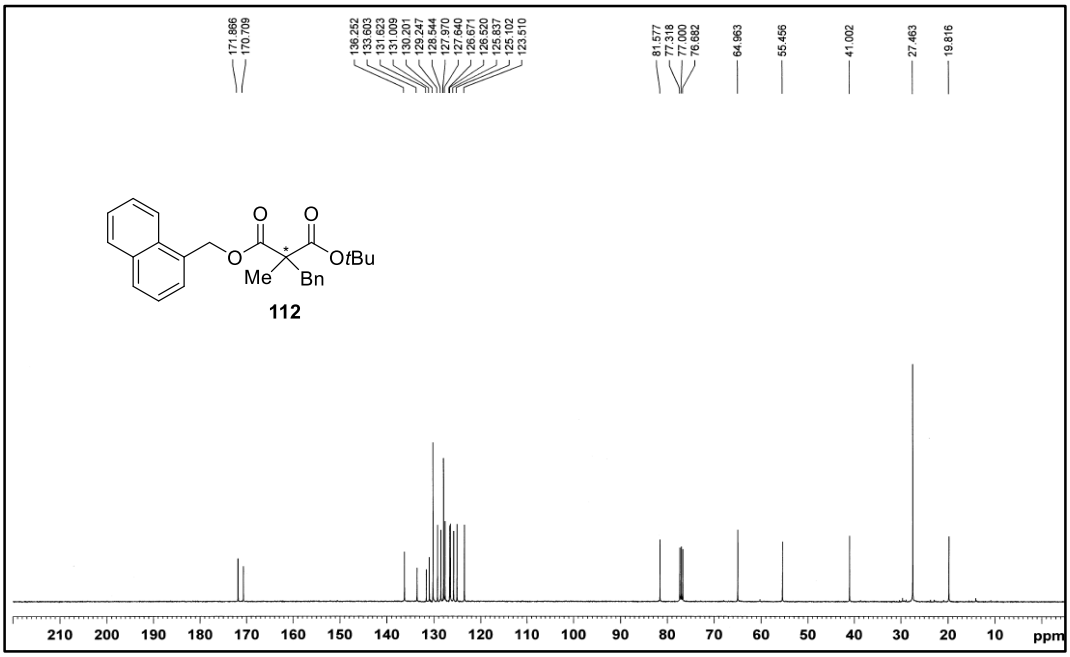
^{13}C-NMR of compound **111** (100 MHz, $CDCl_3$)



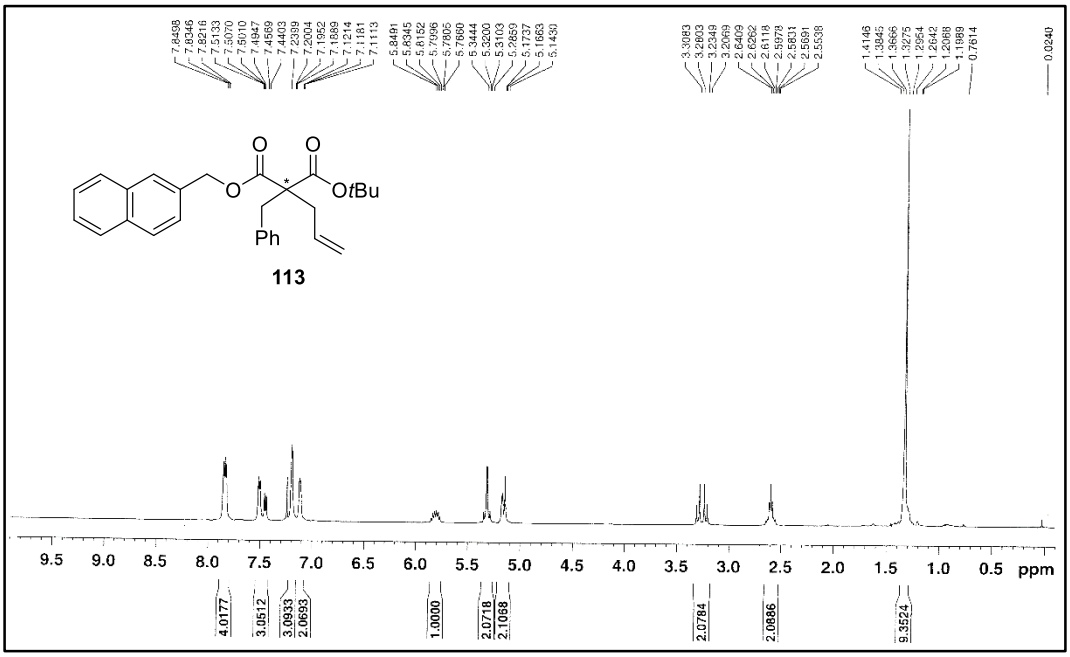
^{1}H-NMR of compound **112** (300 MHz, $CDCl_3$)



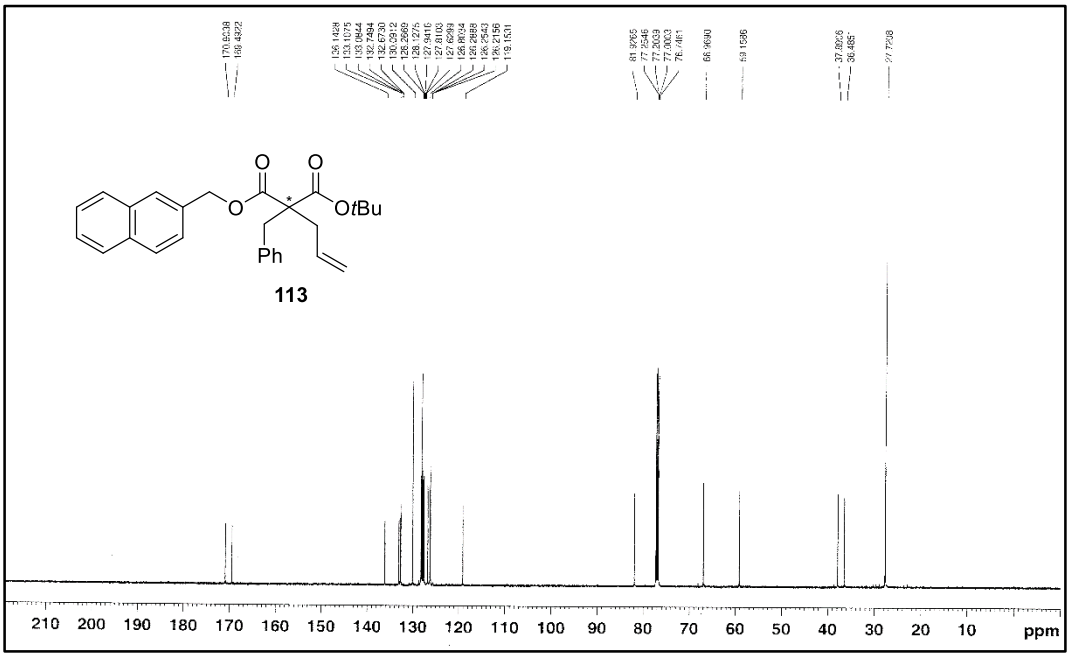
^{13}C-NMR of compound **112** (100 MHz, $CDCl_3$)



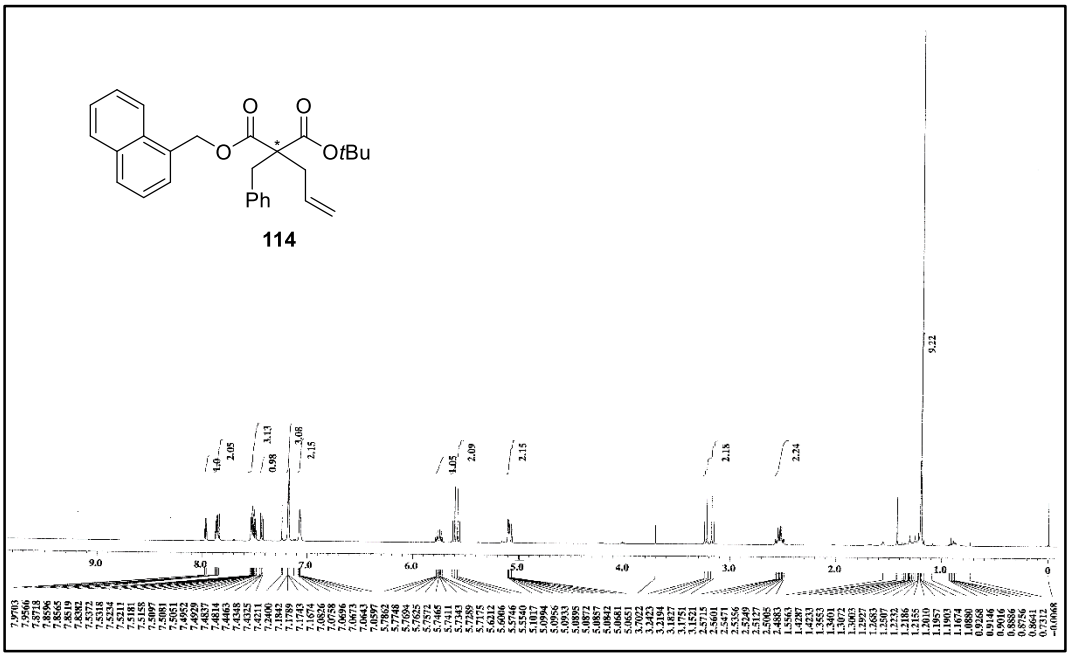
^{1}H-NMR of compound **113** (500 MHz, $CDCl_3$)



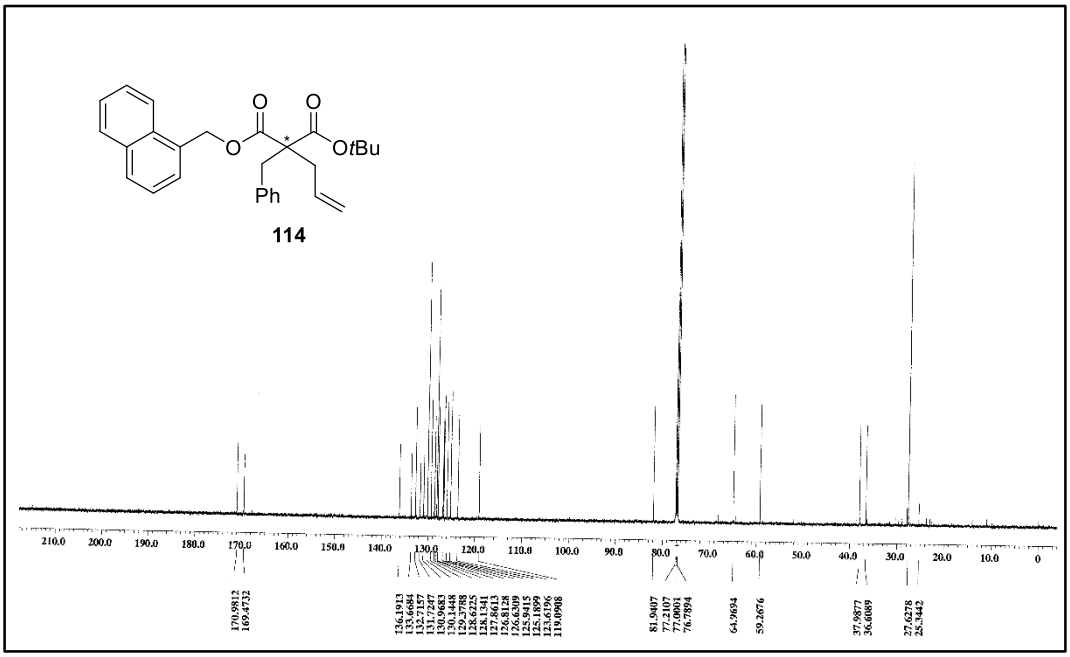
^{13}C-NMR of compound **113** (125 MHz, $CDCl_3$)



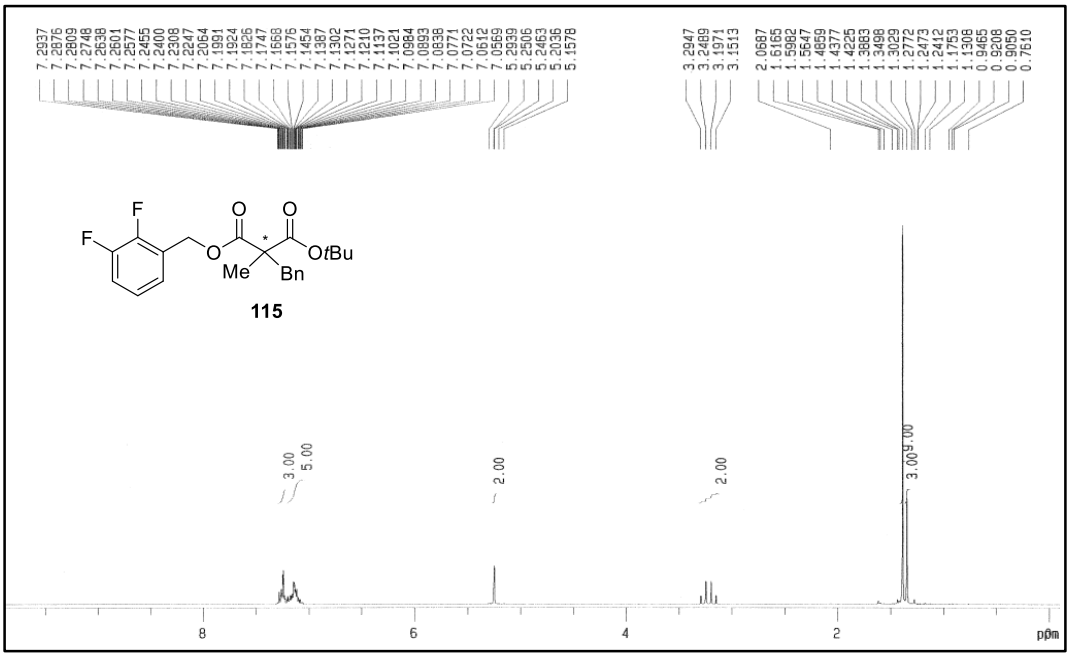
^{1}H-NMR of compound **114** (600 MHz, $CDCl_3$)



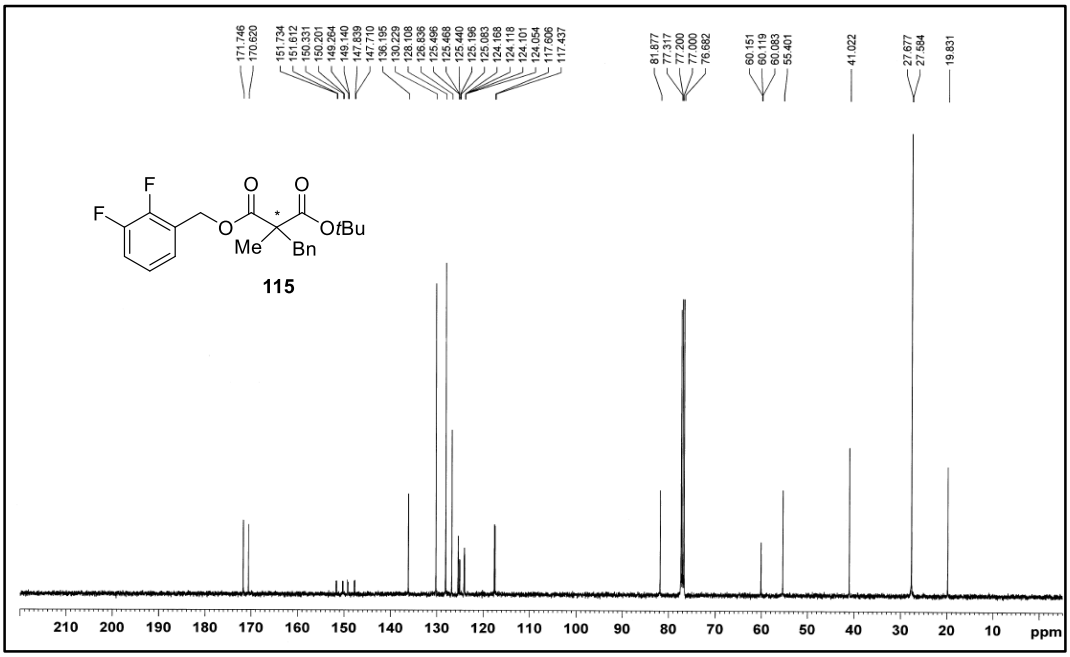
^{13}C-NMR of compound **114** (150 MHz, $CDCl_3$)



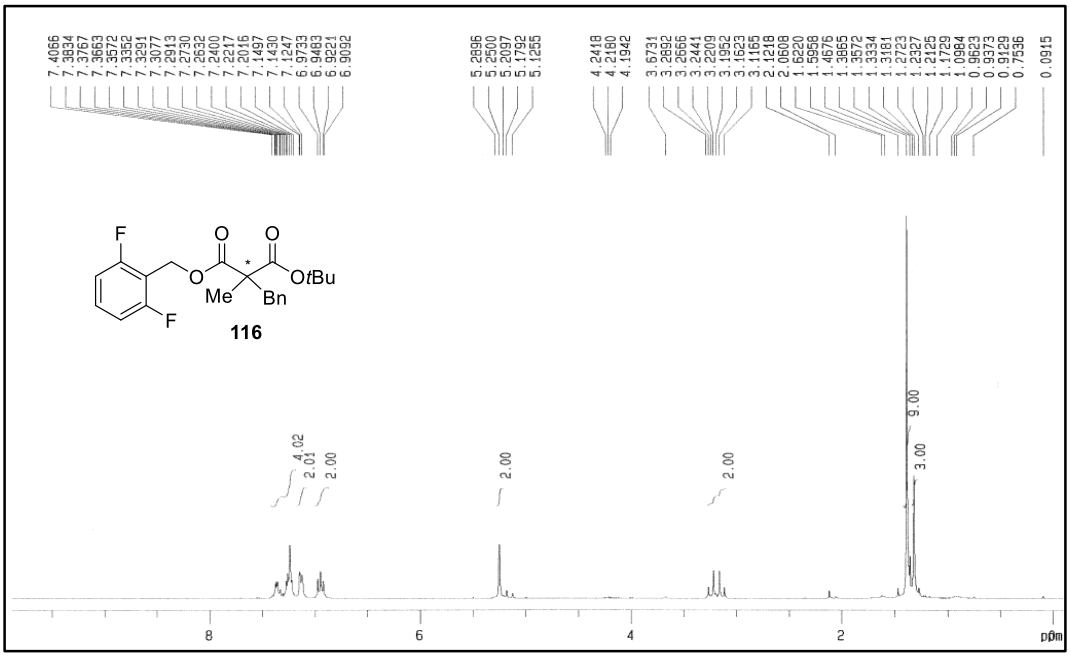
^{1}H-NMR of compound **115** (300 MHz, $CDCl_3$)



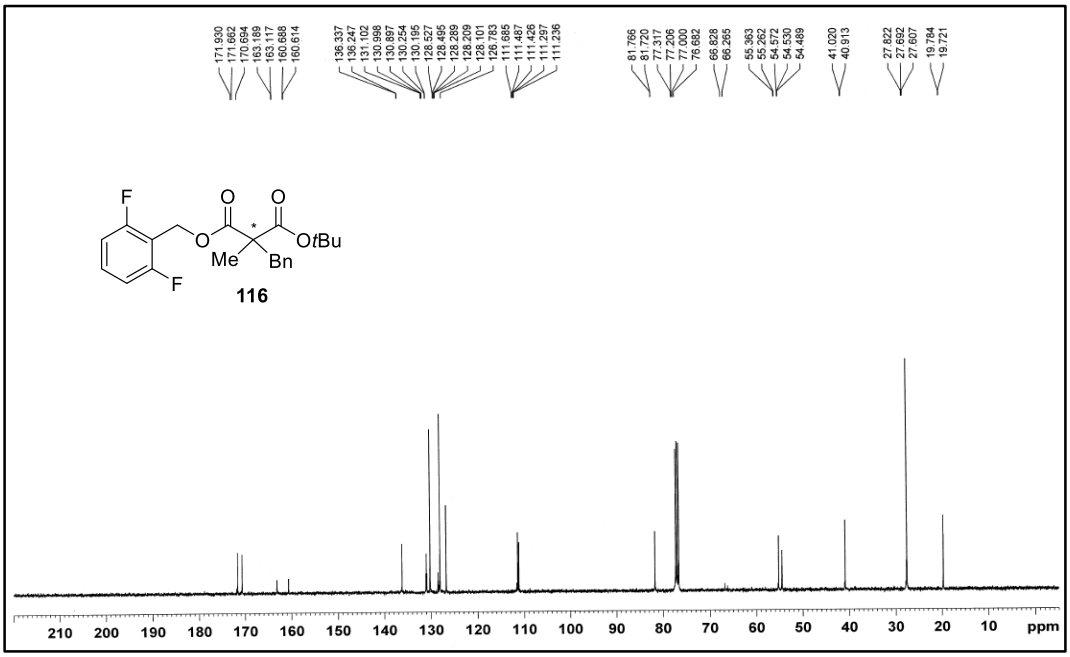
^{13}C-NMR of compound **115** (100 MHz, $CDCl_3$)



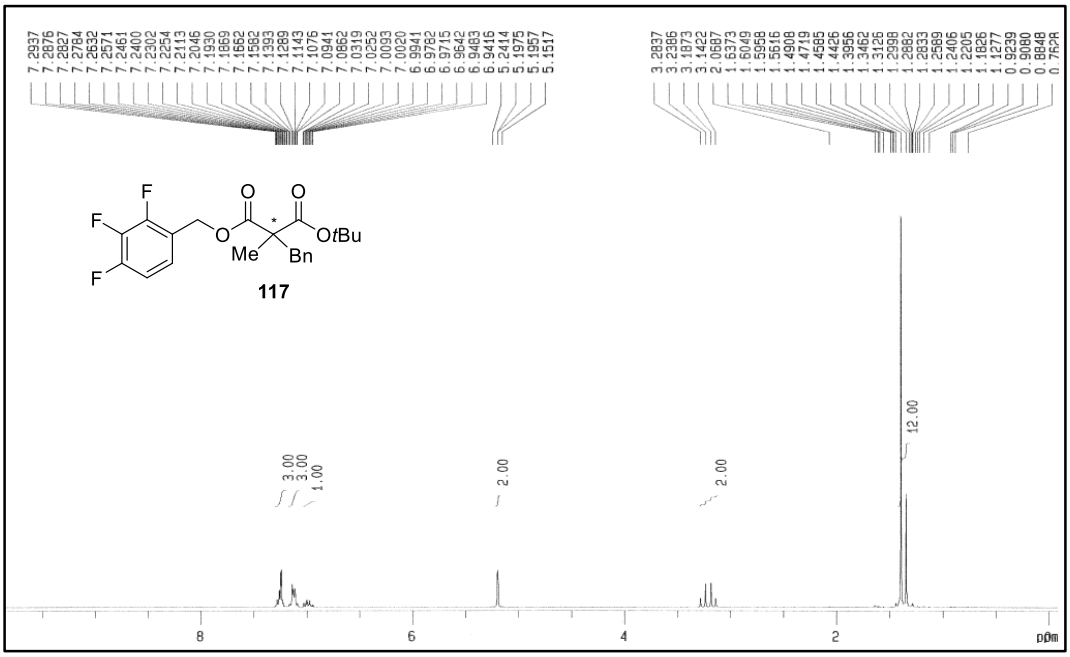
^{1}H-NMR of compound **116** (300 MHz, $CDCl_3$)



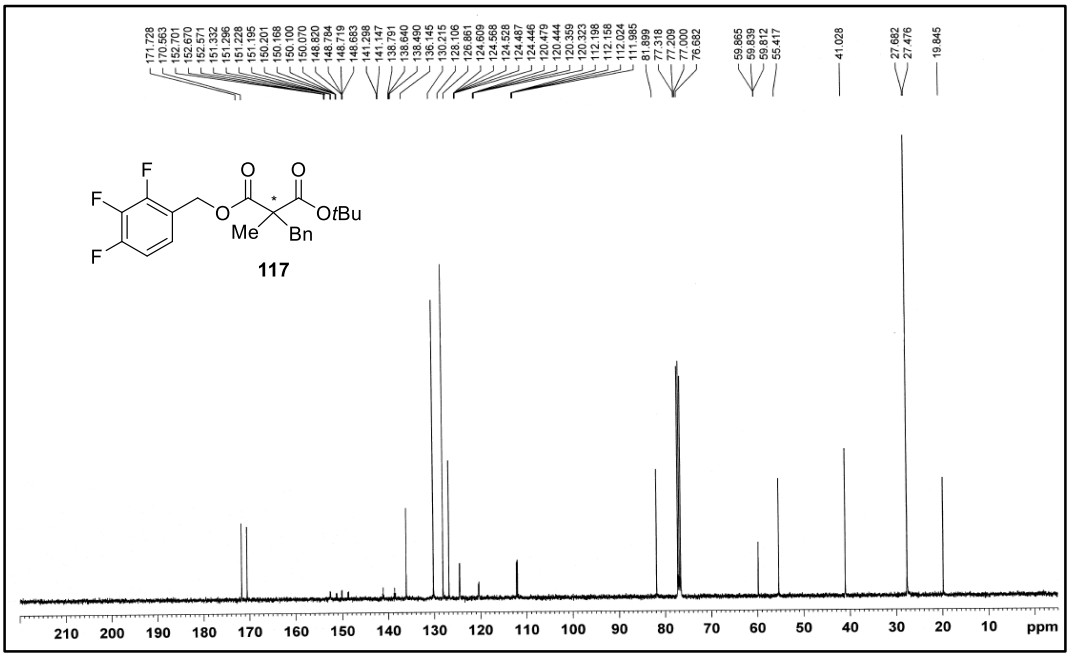
^{13}C-NMR of compound **116** (100 MHz, $CDCl_3$)



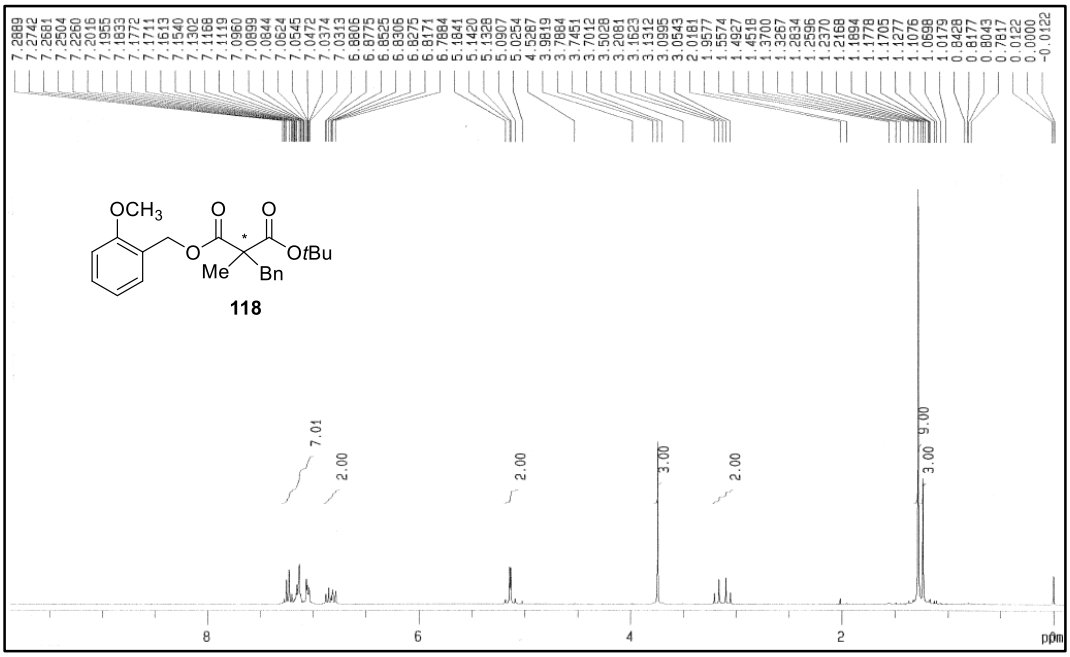
^{1}H-NMR of compound **117** (300 MHz, $CDCl_3$)



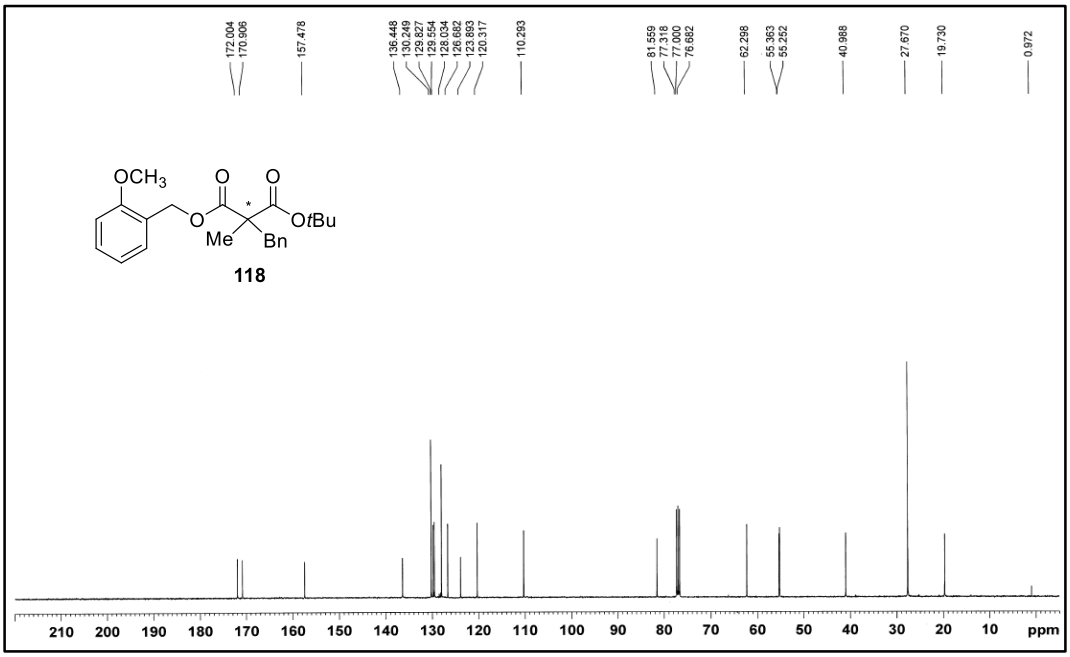
^{13}C-NMR of compound **117** (100 MHz, $CDCl_3$)



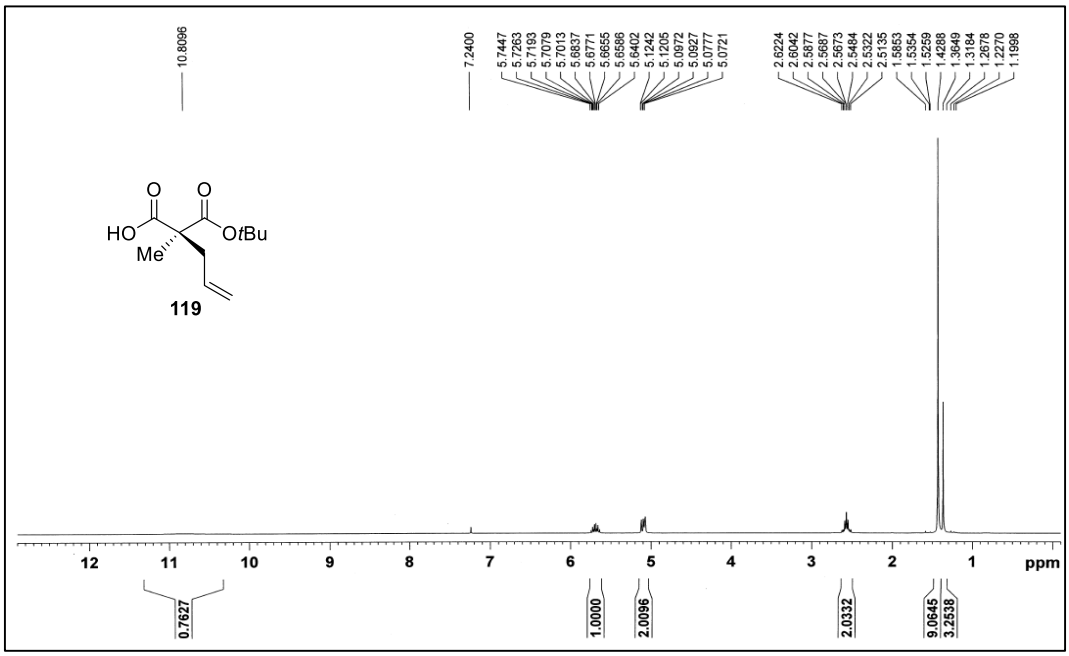
^{1}H-NMR of compound **118** (300 MHz, $CDCl_3$)



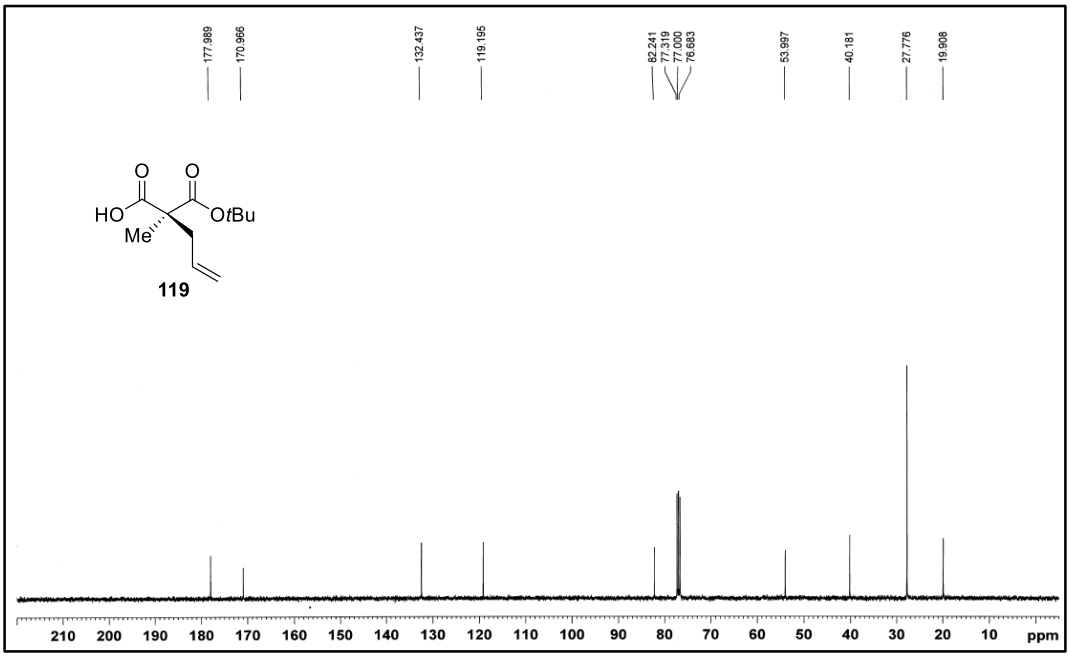
^{13}C-NMR of compound **118** (100 MHz, $CDCl_3$)



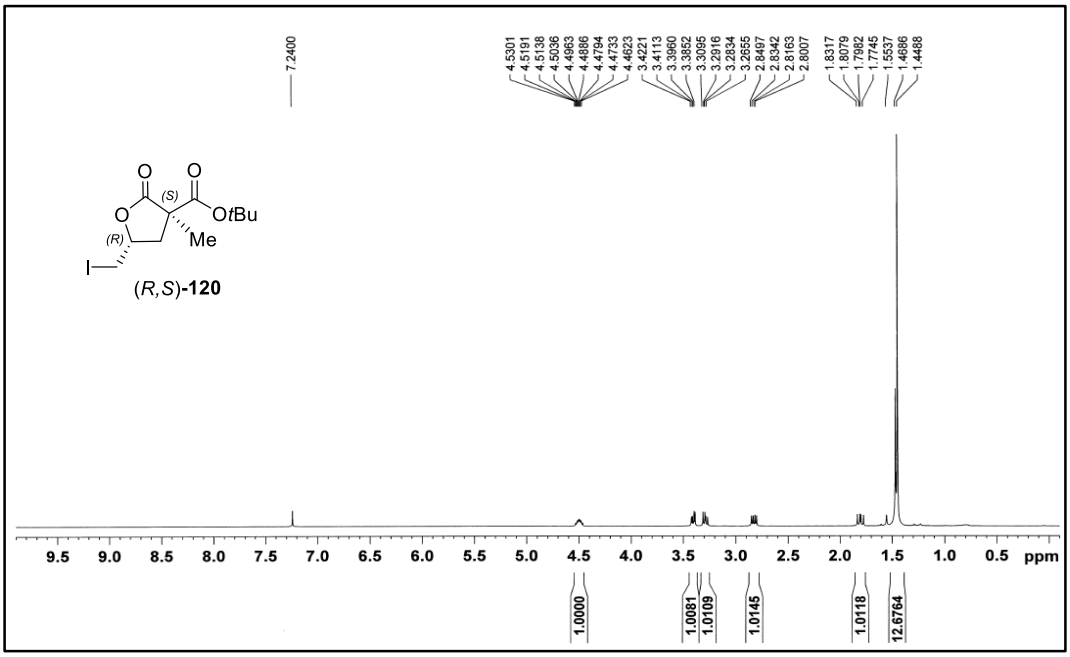
^{1}H-NMR of compound **119** (400 MHz, $CDCl_3$)



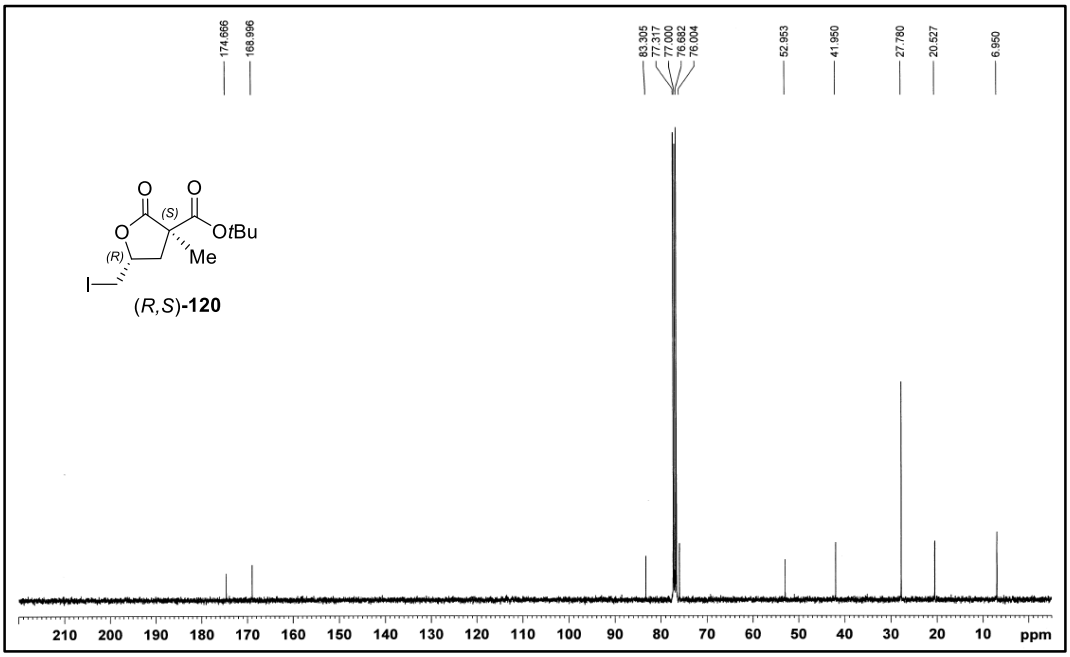
^{13}C-NMR of compound **119** (100 MHz, $CDCl_3$)



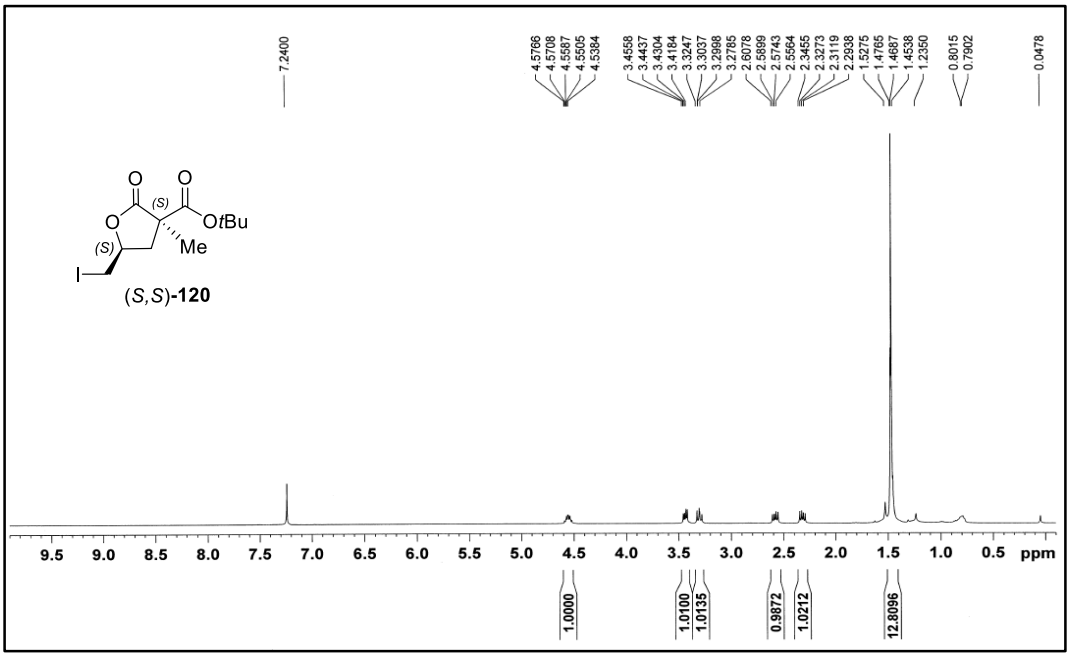
^{1}H-NMR of compound (*R*,*S*)-**120** (400 MHz, $CDCl_3$)



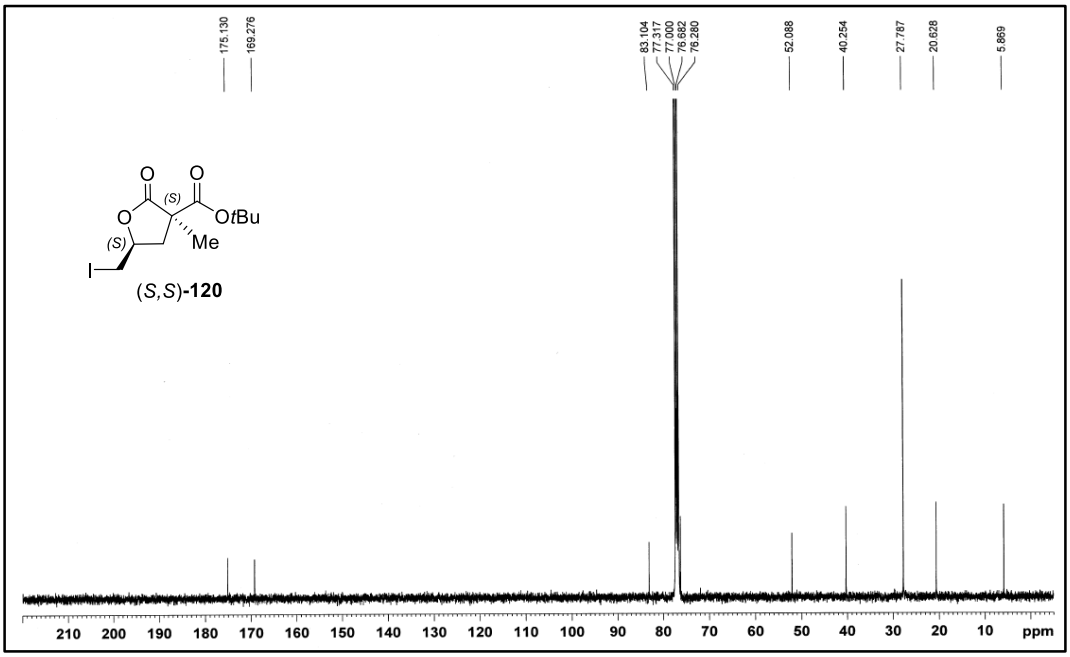
^{13}C-NMR of compound (*R*,*S*)-**120** (100 MHz, $CDCl_3$)



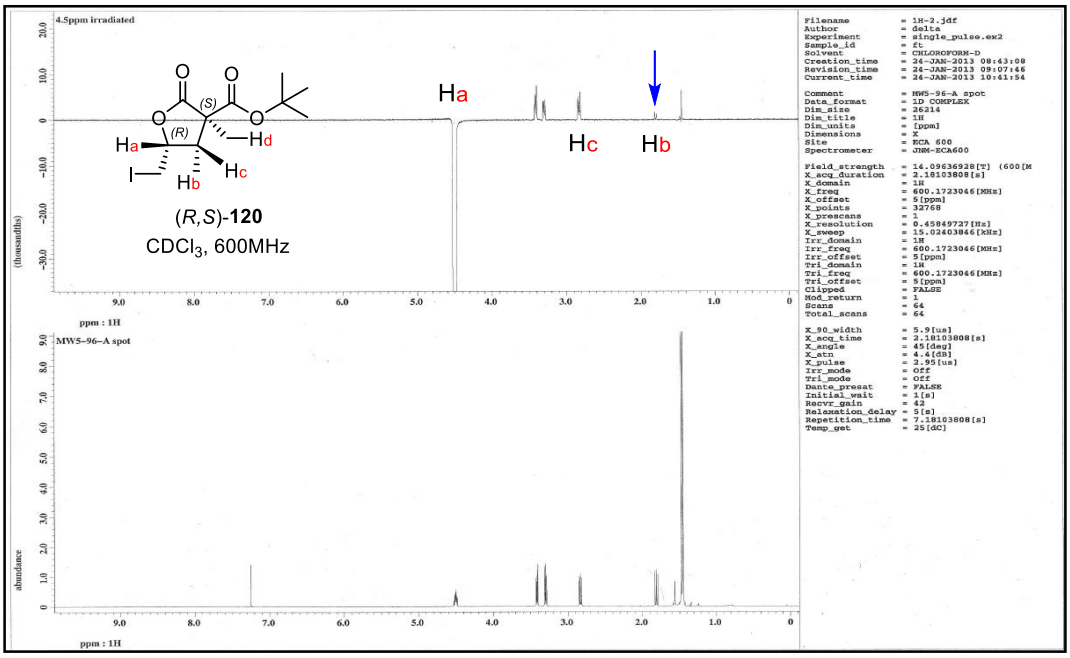
^{1}H-NMR of compound (*S*,*S*)-**120** (400 MHz, $CDCl_3$)

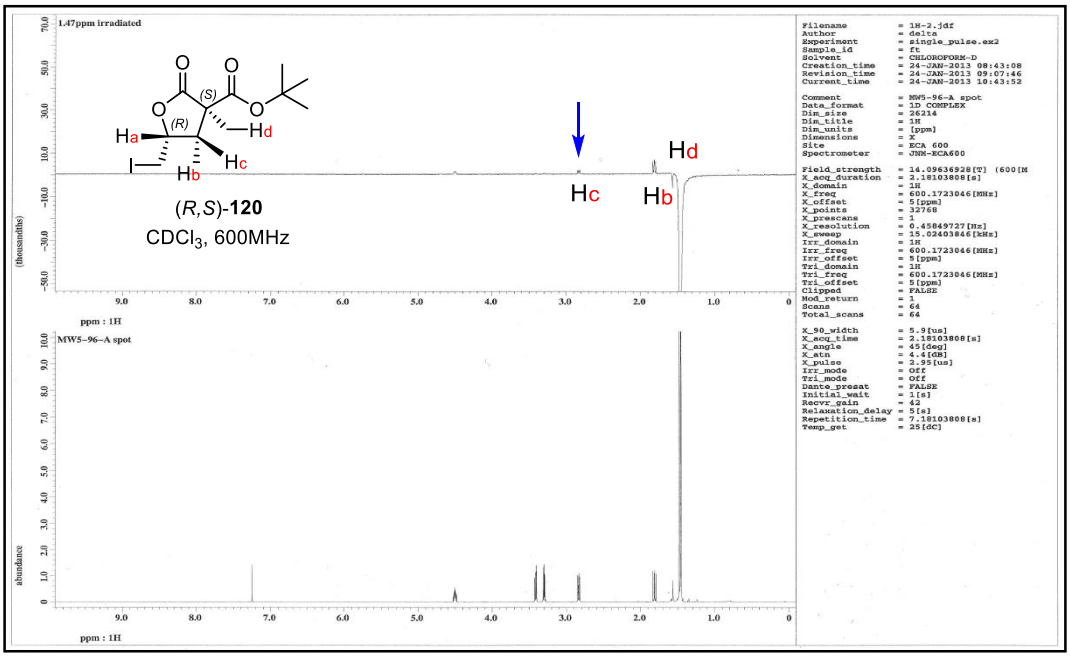


^{13}C-NMR of compound (*S*,*S*)-**120** (100 MHz, $CDCl_3$)

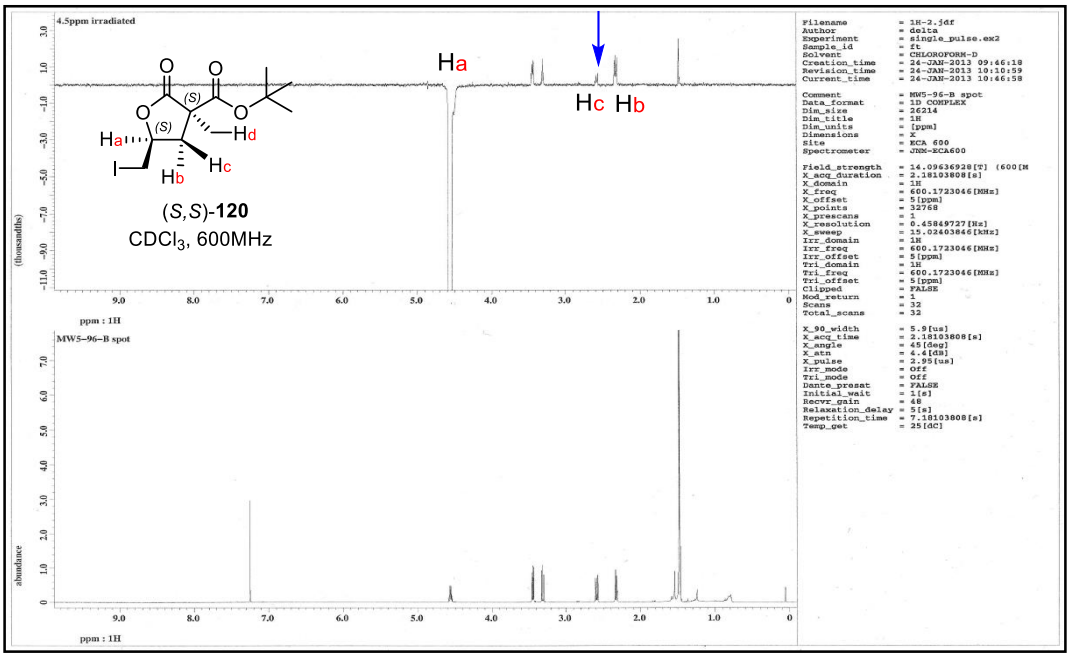


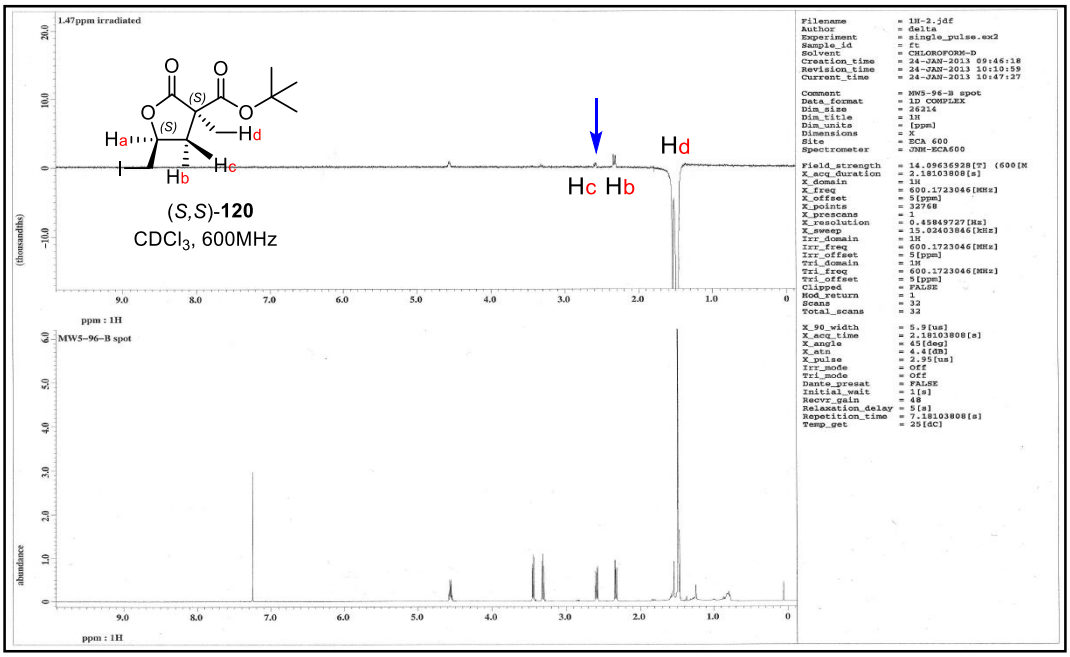
nOe of compound **((*R*,*S*)-120)**



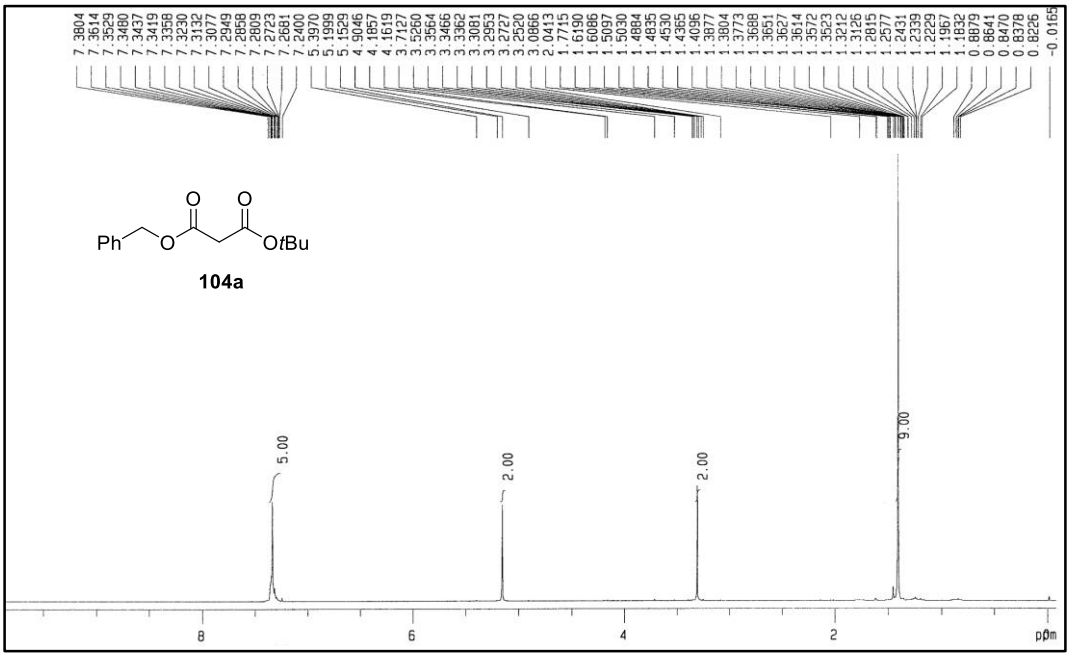


nOe of compound **((*S*,*S*)-120)**

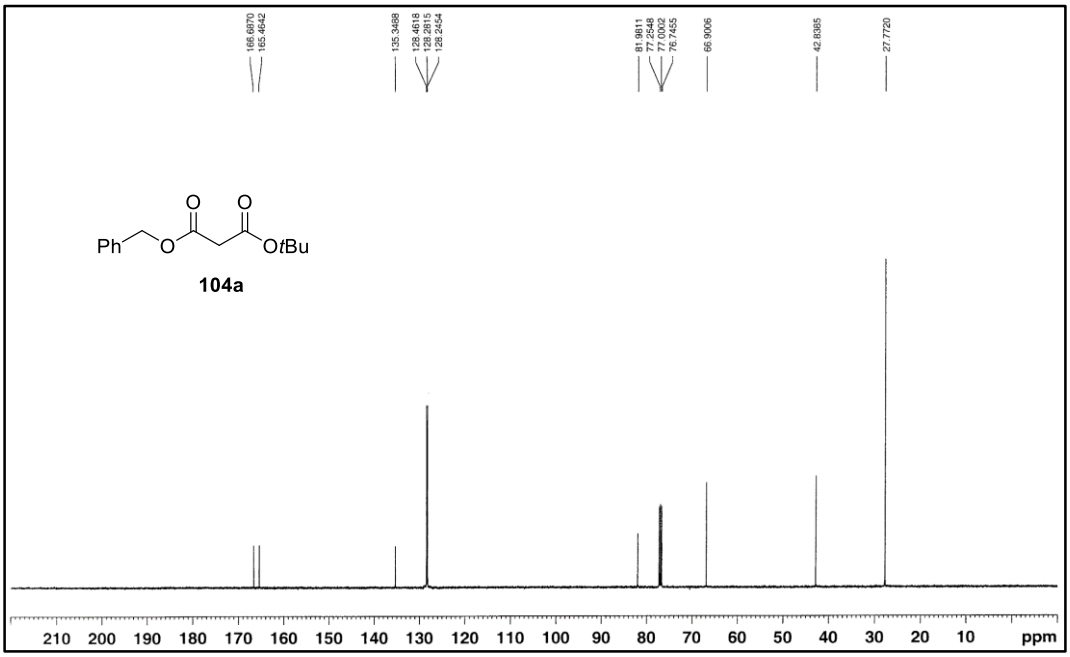




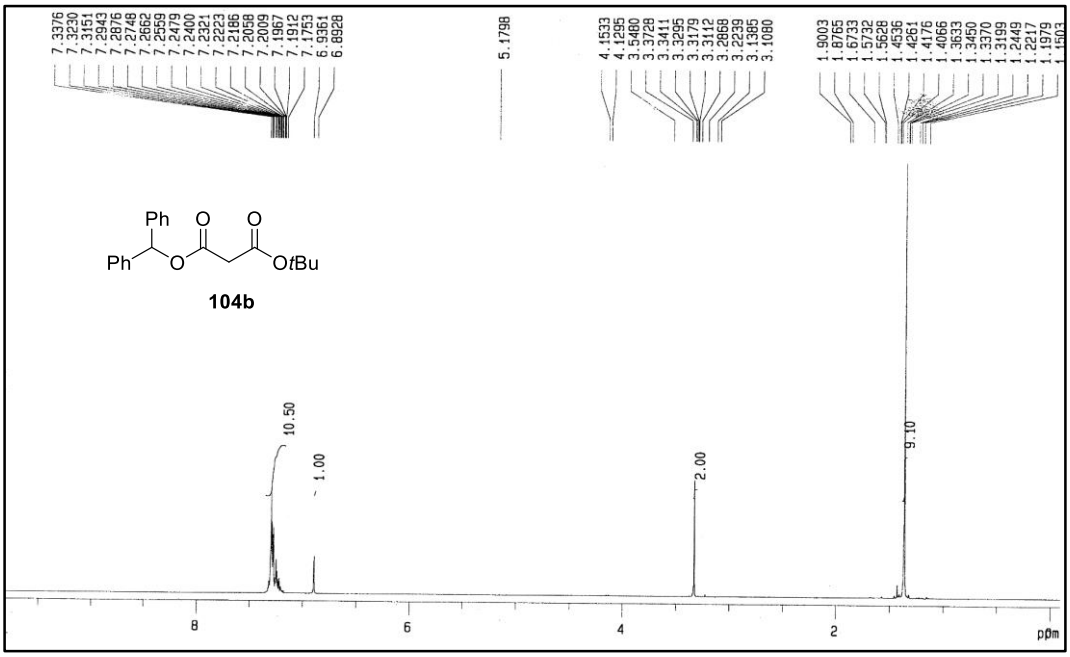
^{1}H-NMR of compound **104a** (300 MHz, $CDCl_3$)



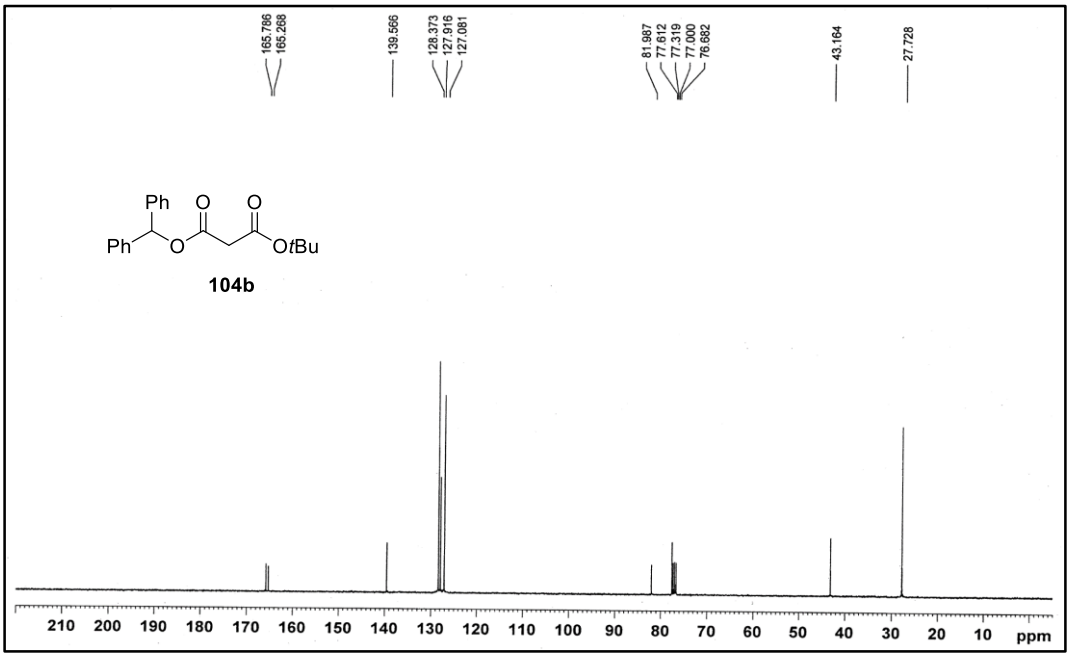
^{13}C-NMR of compound **104a** (125 MHz, $CDCl_3$)



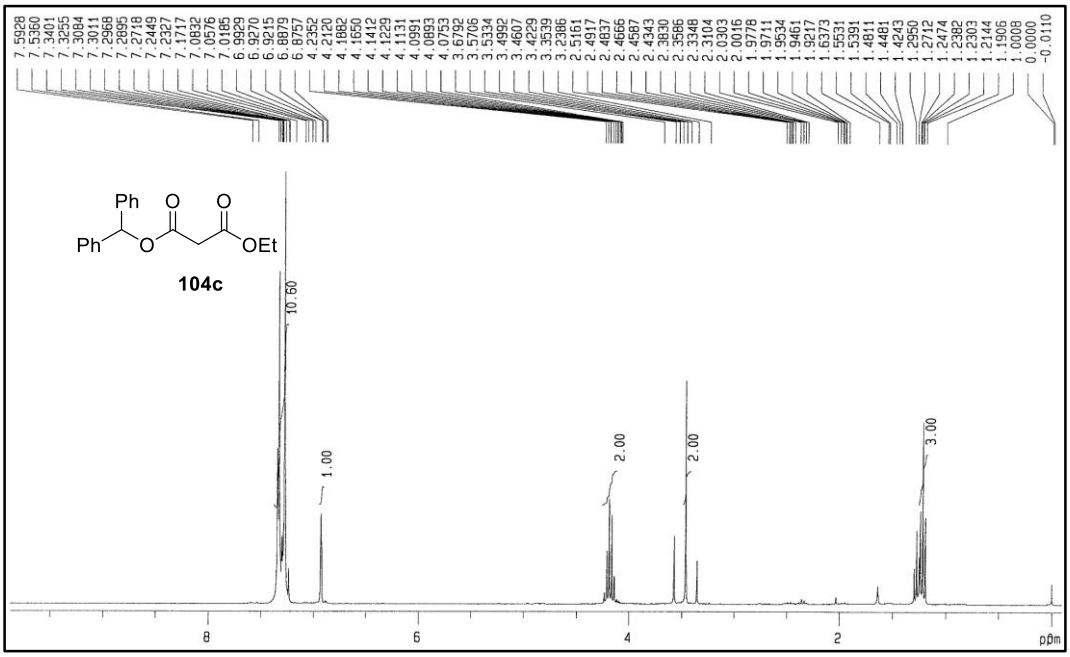
^{1}H-NMR of compound **104b** (300 MHz, $CDCl_3$)



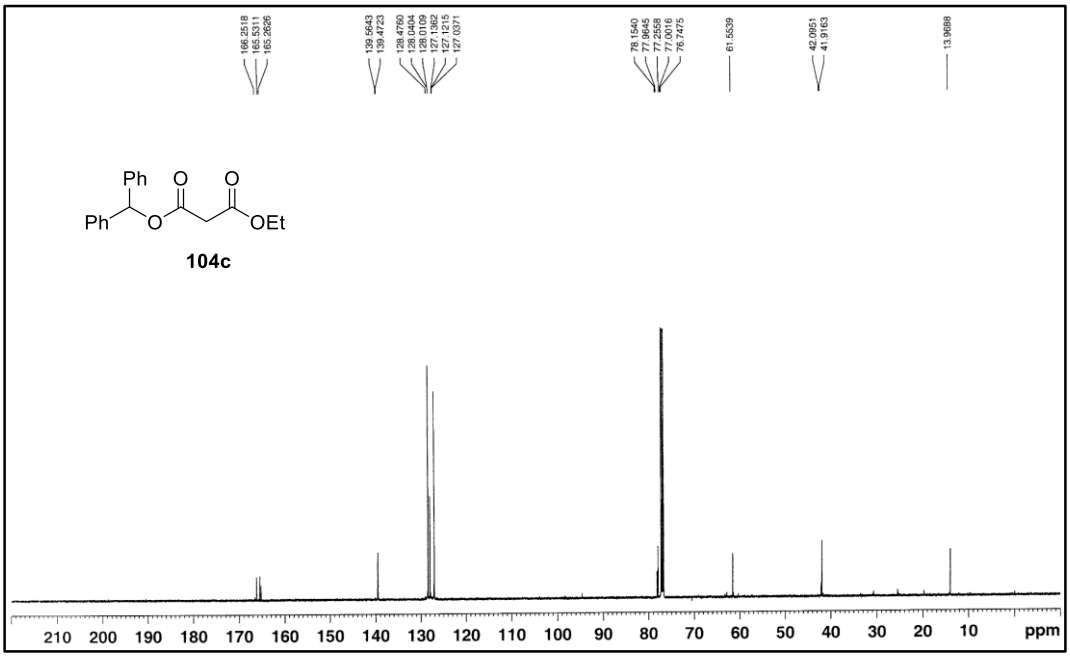
^{13}C-NMR of compound **104b** (125 MHz, $CDCl_3$)



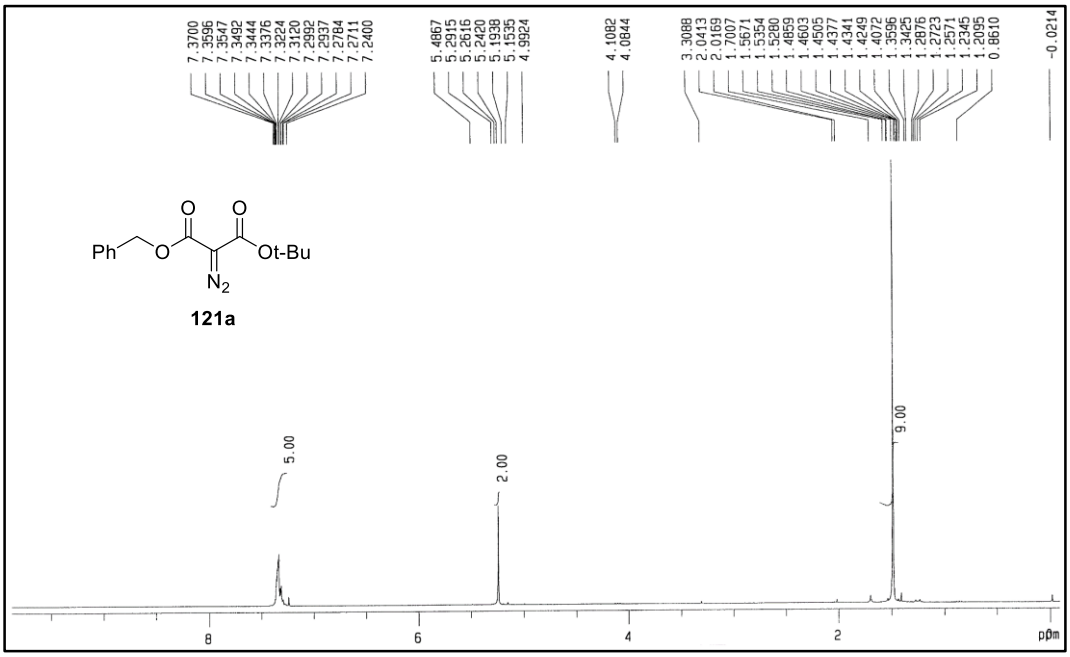
^{1}H-NMR of compound **104c** (300 MHz, $CDCl_3$)



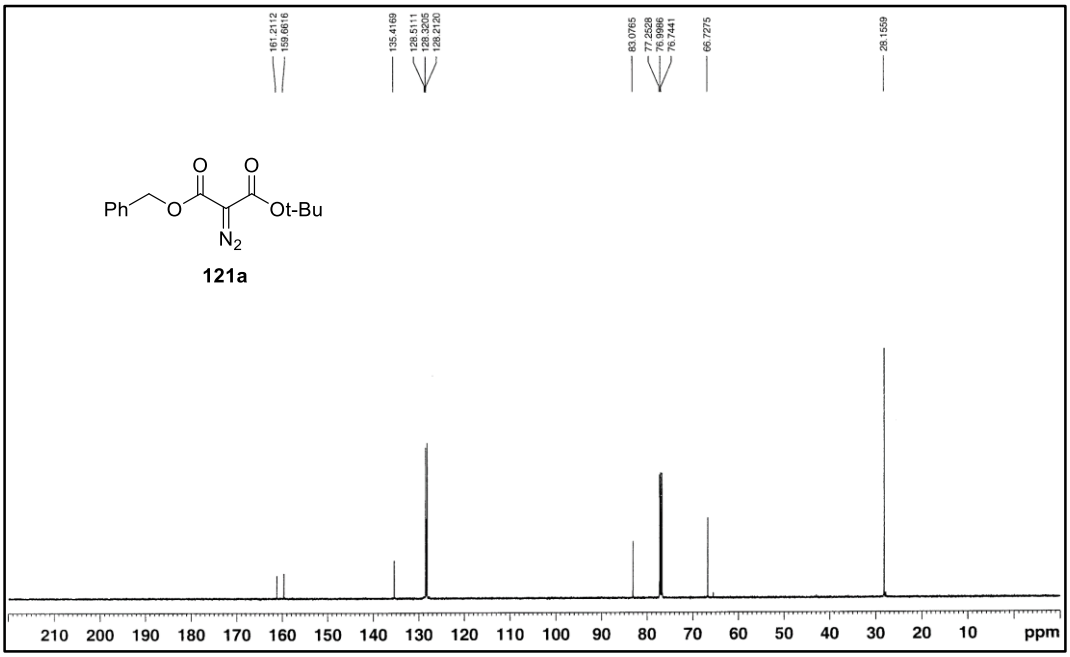
^{13}C-NMR of compound **104c** (125 MHz, $CDCl_3$)



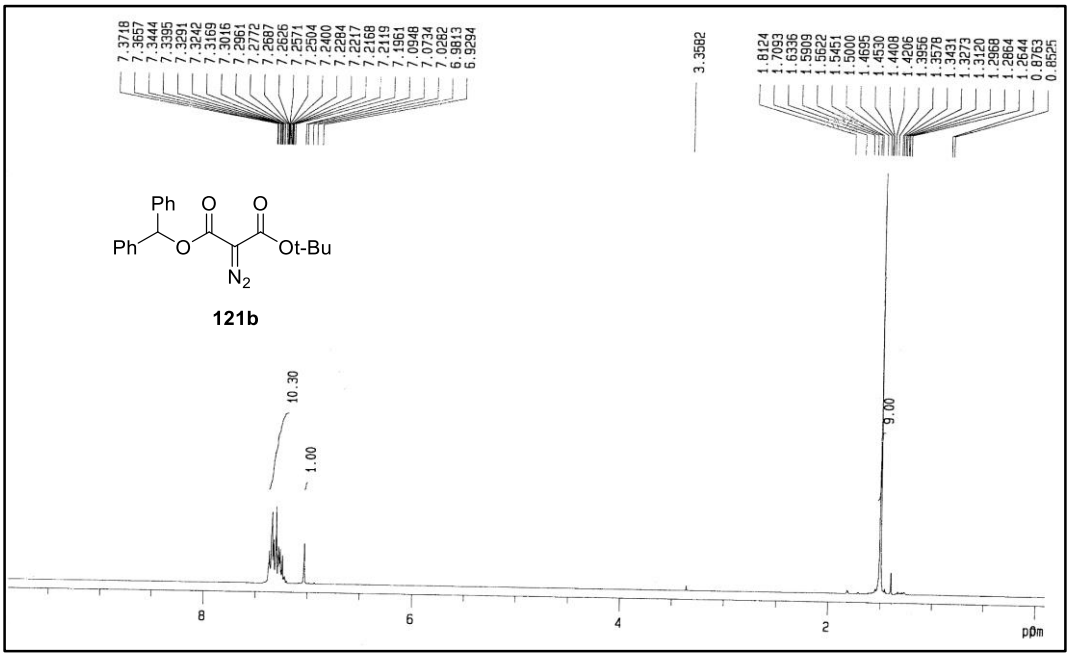
^{1}H-NMR of compound **121a** (300 MHz, $CDCl_3$)



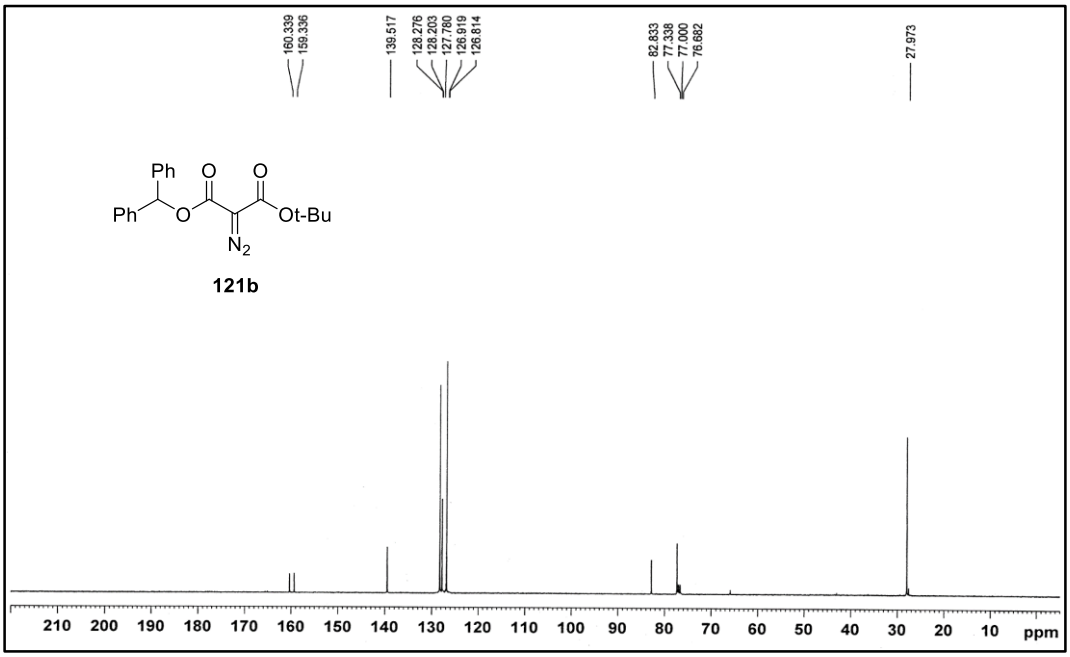
^{13}C-NMR of compound **121a** (125 MHz, $CDCl_3$)



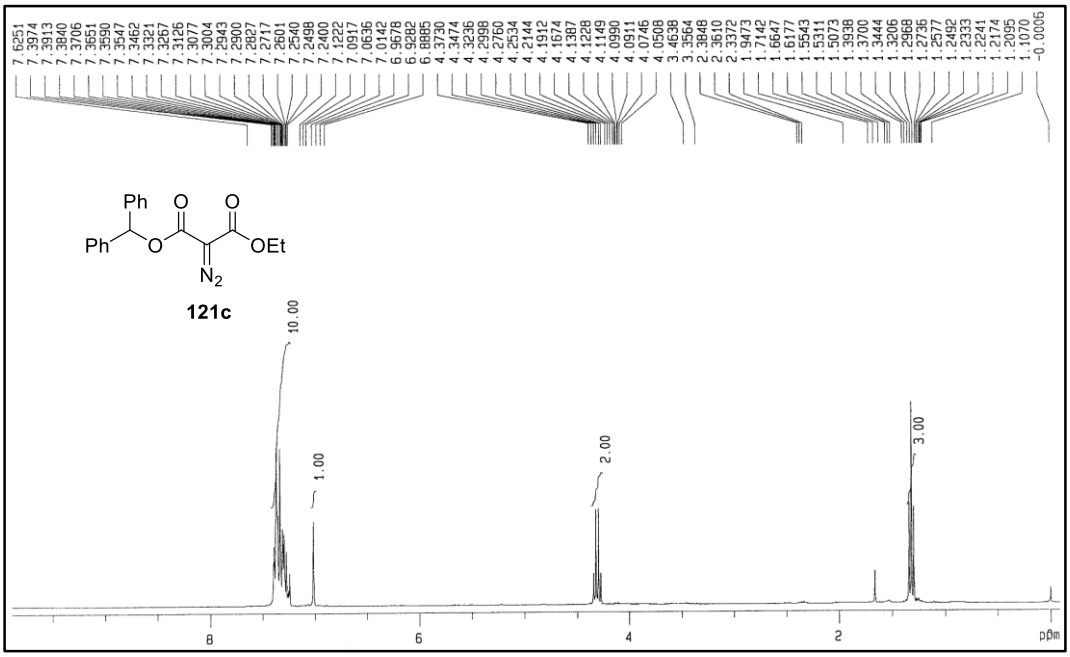
^{1}H-NMR of compound **121b** (300 MHz, $CDCl_3$)



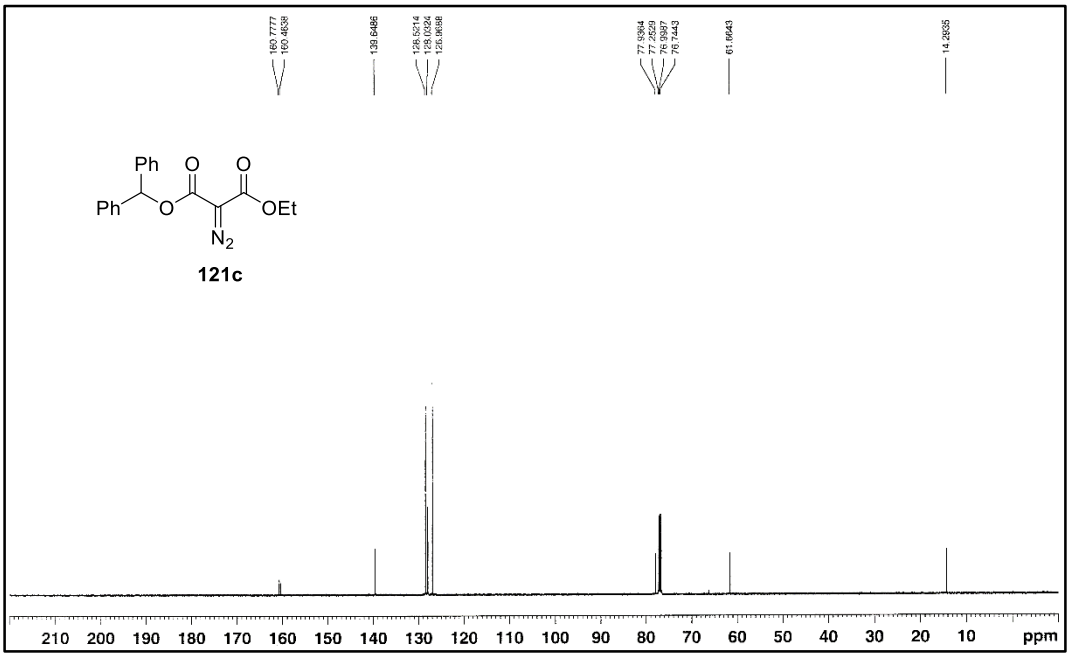
^{13}C-NMR of compound **121b** (125 MHz, $CDCl_3$)



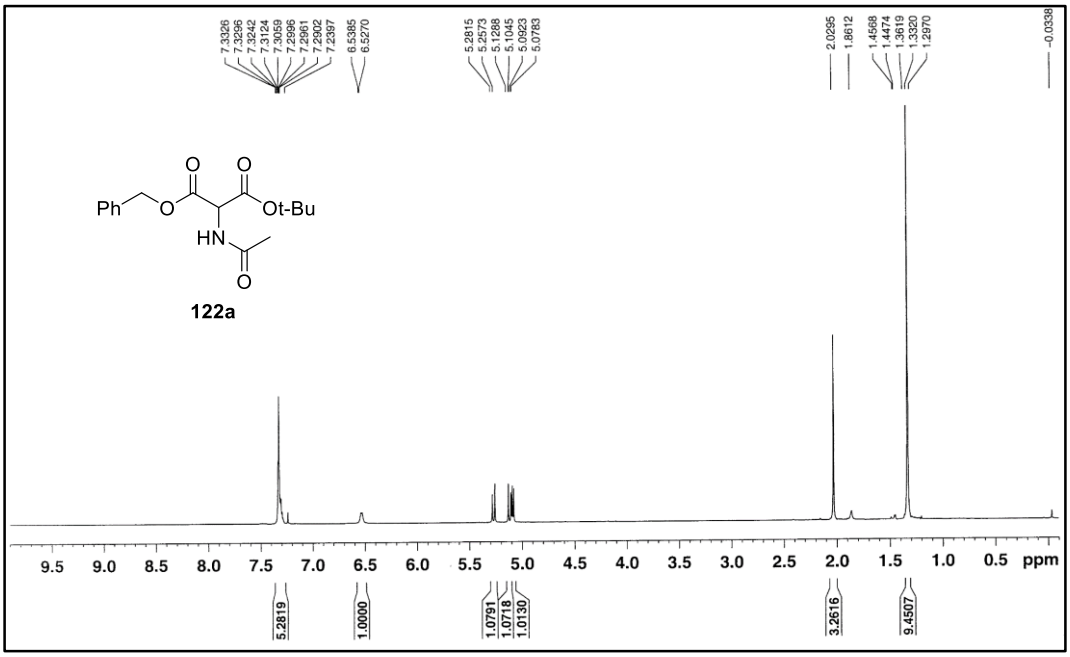
^{1}H-NMR of compound **121c** (300 MHz, $CDCl_3$)



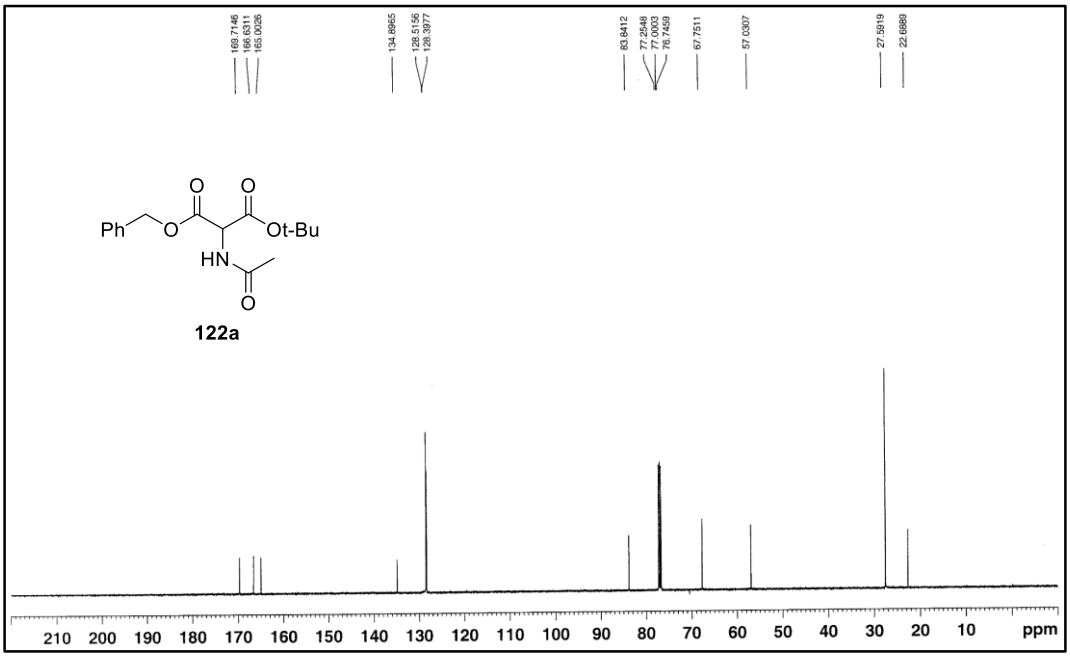
^{13}C-NMR of compound **121c** (125 MHz, $CDCl_3$)



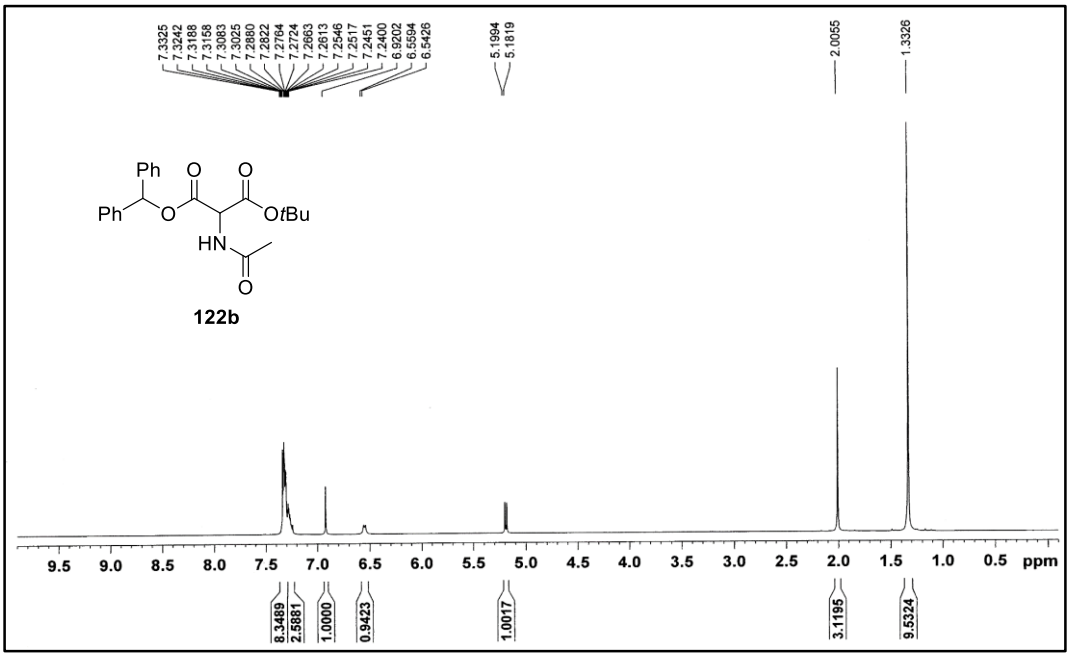
^{1}H-NMR of compound **122a** (500 MHz, $CDCl_3$)



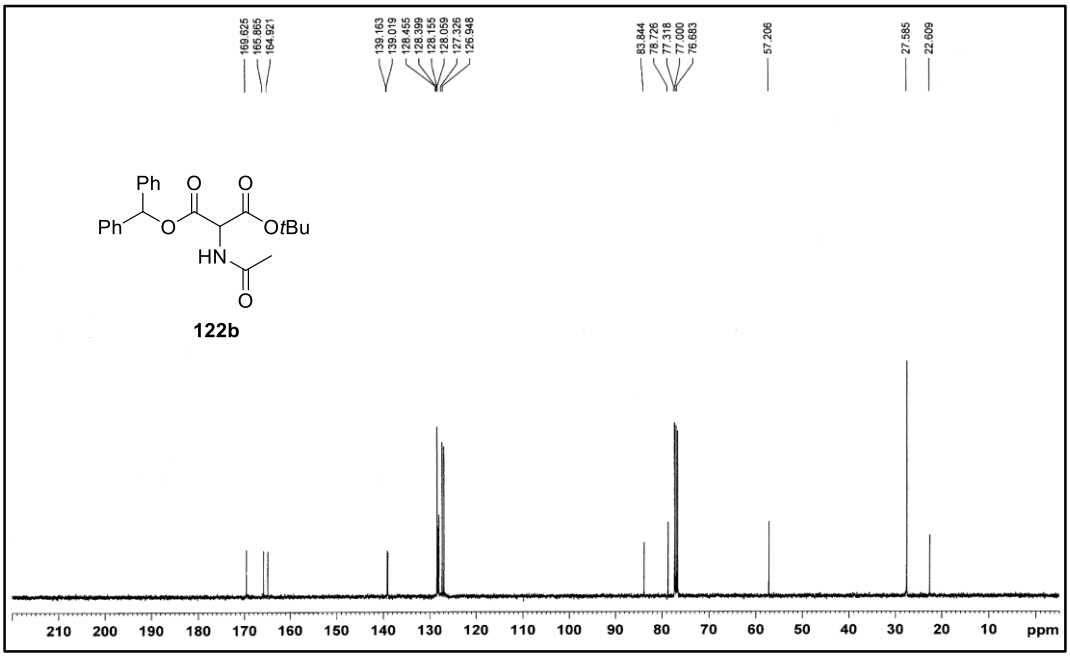
^{13}C-NMR of compound **122a** (125 MHz, $CDCl_3$)



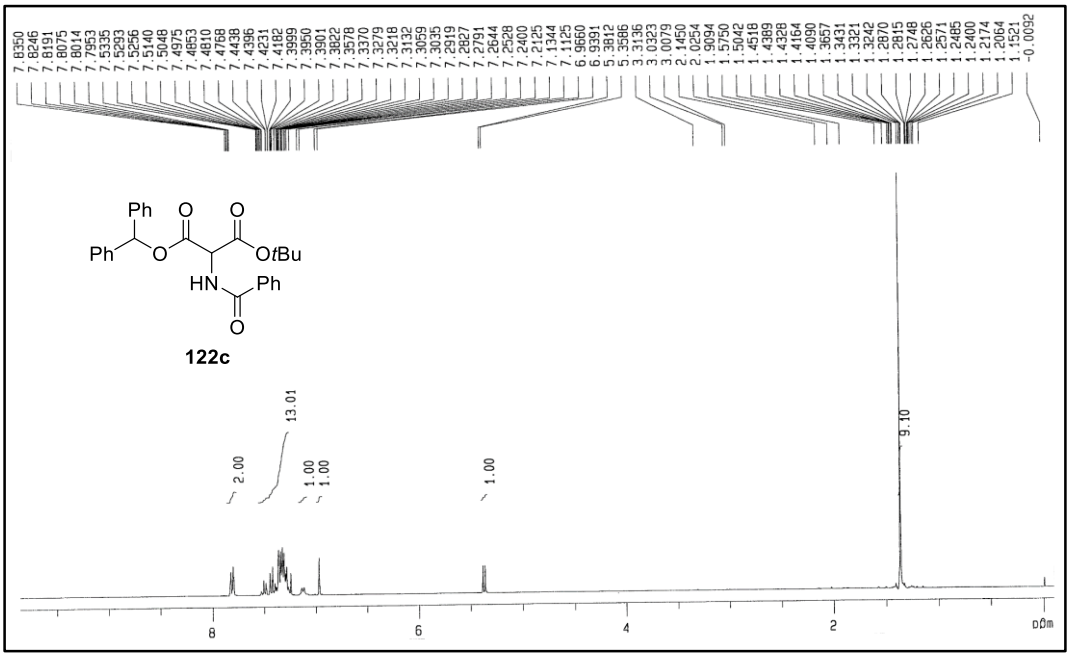
^{1}H-NMR of compound **122b** (500 MHz, $CDCl_3$)



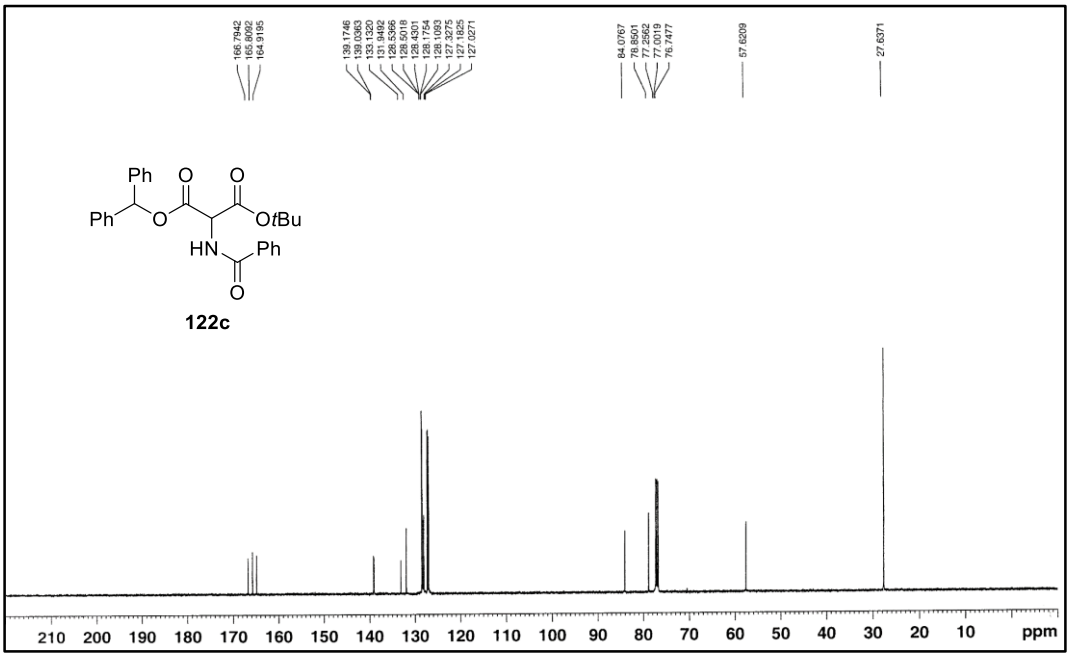
^{13}C-NMR of compound **122b** (125 MHz, $CDCl_3$)



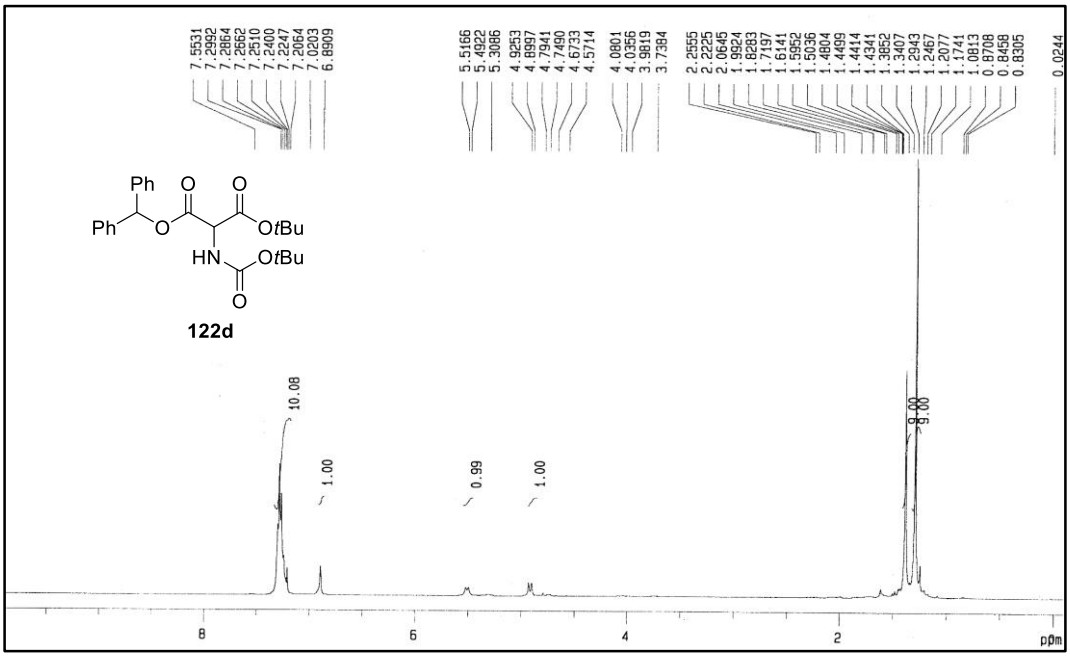
^{1}H-NMR of compound **122c** (300 MHz, $CDCl_3$)



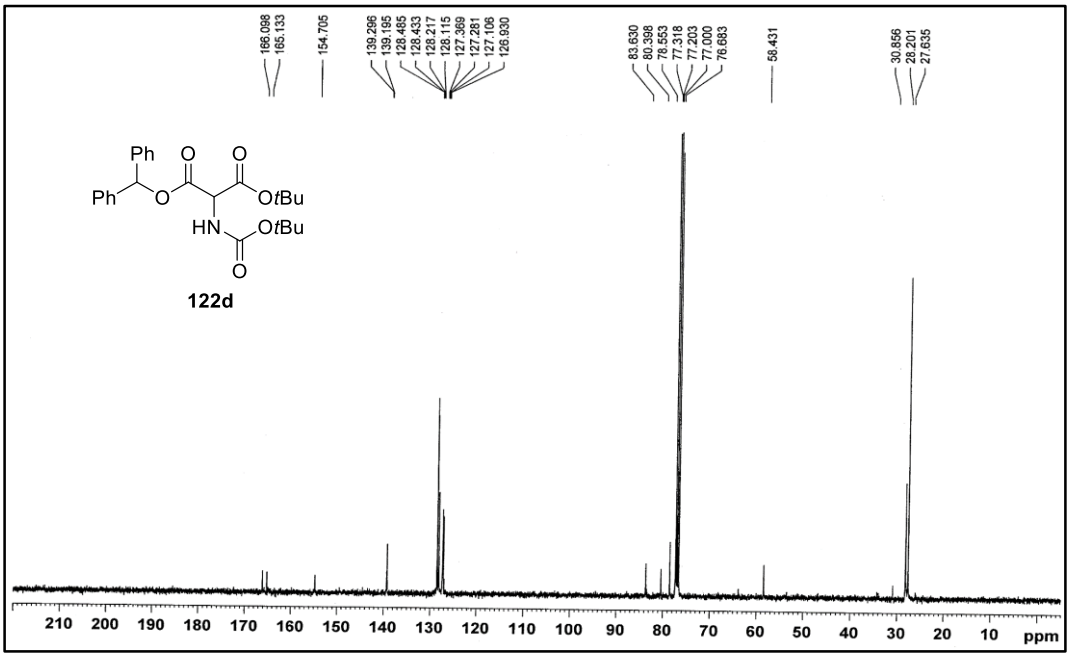
^{13}C-NMR of compound **122c** (125 MHz, $CDCl_3$)



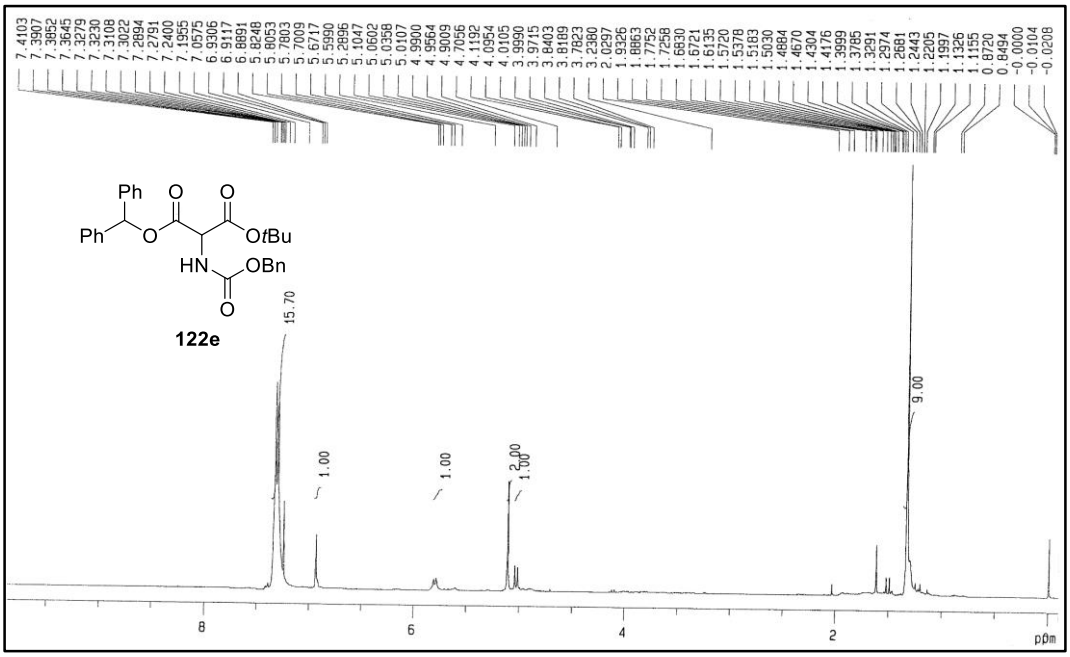
^{1}H-NMR of compound **122d** (300 MHz, $CDCl_3$)



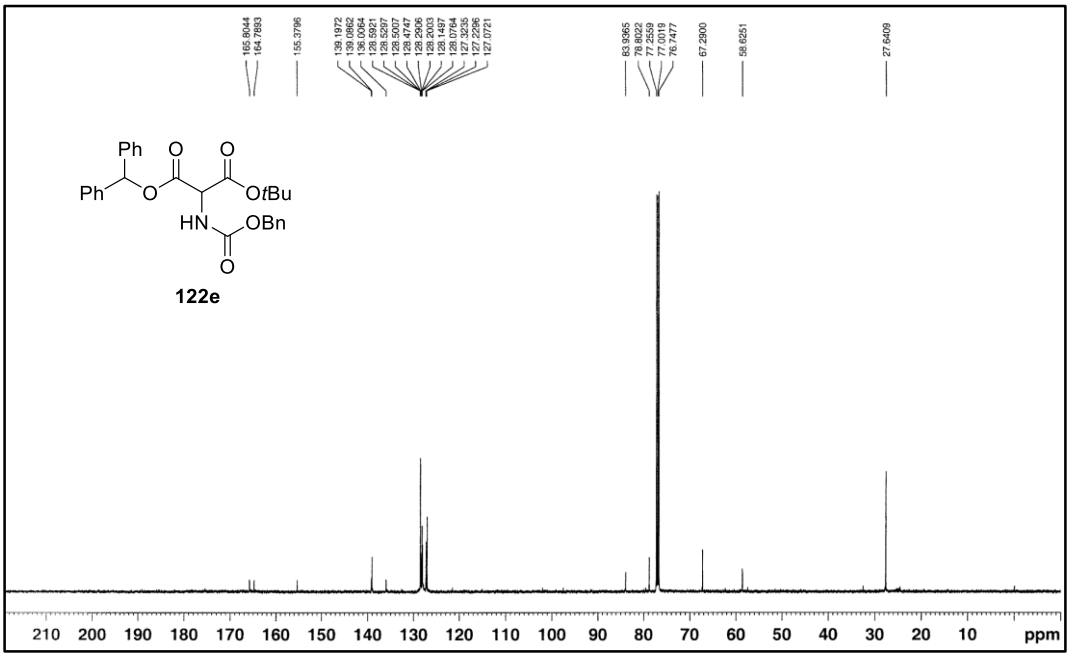
^{13}C-NMR of compound **122d** (125 MHz, $CDCl_3$)



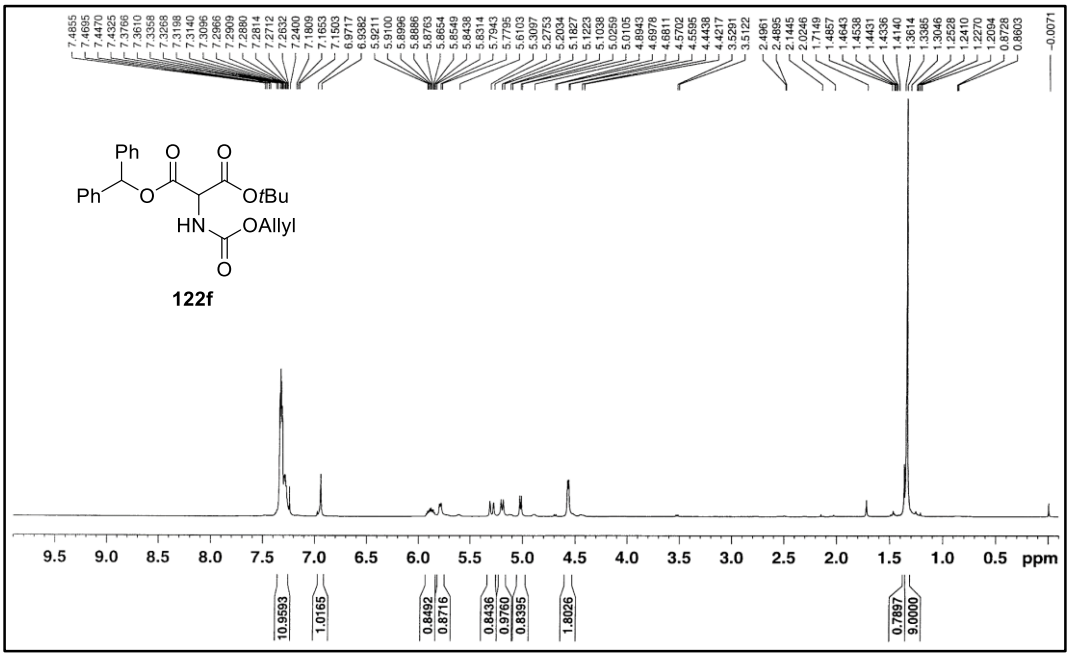
^{1}H-NMR of compound **122e** (300 MHz, $CDCl_3$)



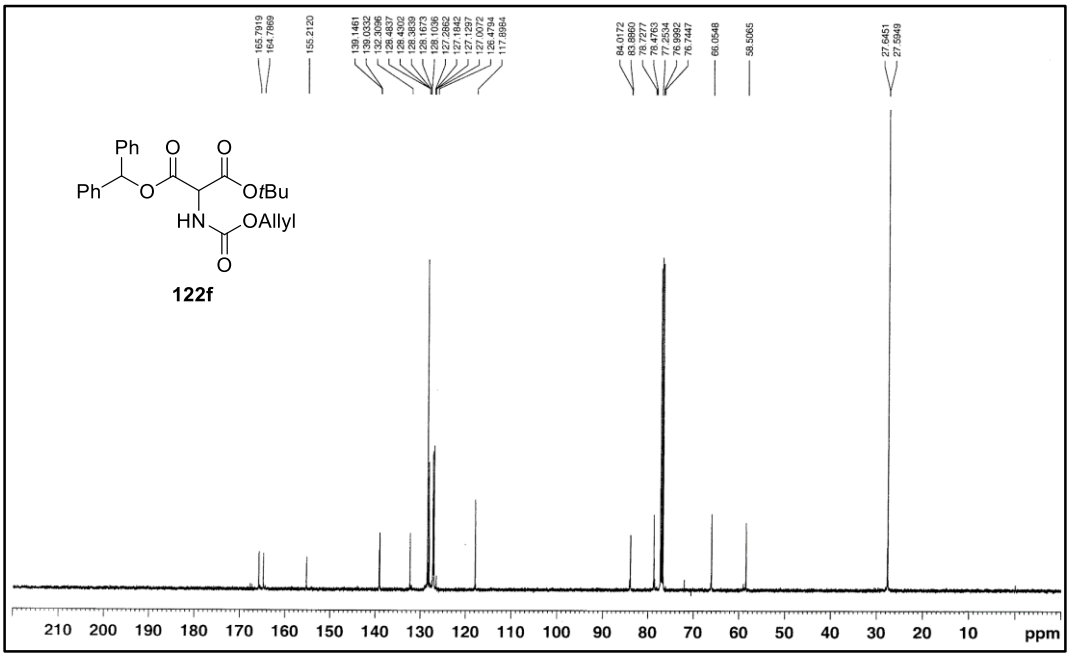
^{13}C-NMR of compound **122e** (125 MHz, $CDCl_3$)



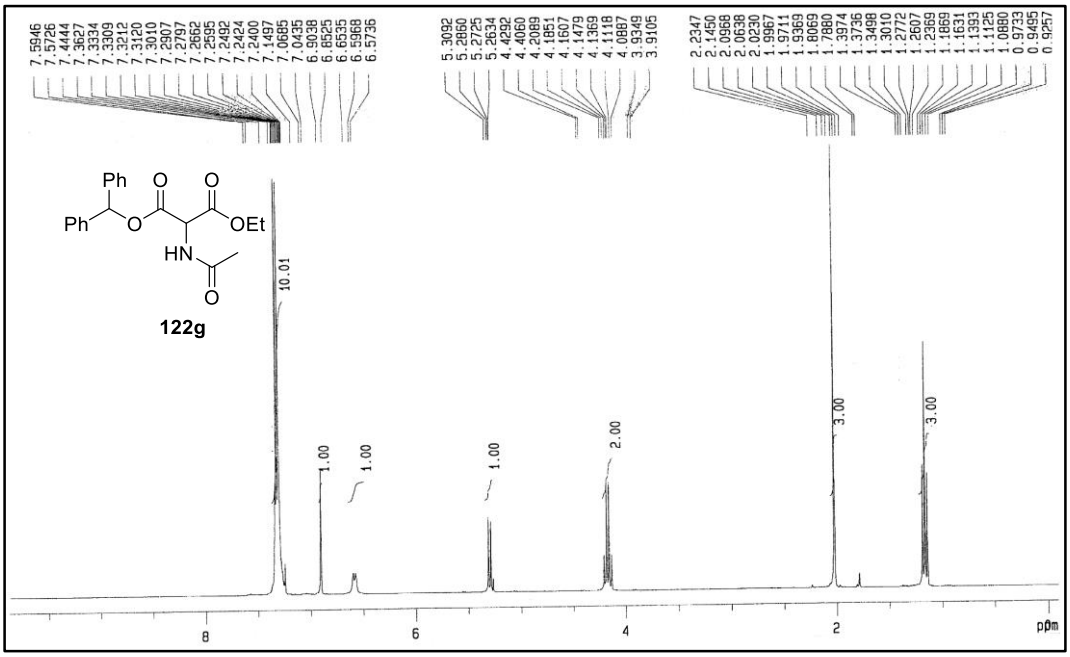
^{1}H-NMR of compound **122f** (500 MHz, $CDCl_3$)



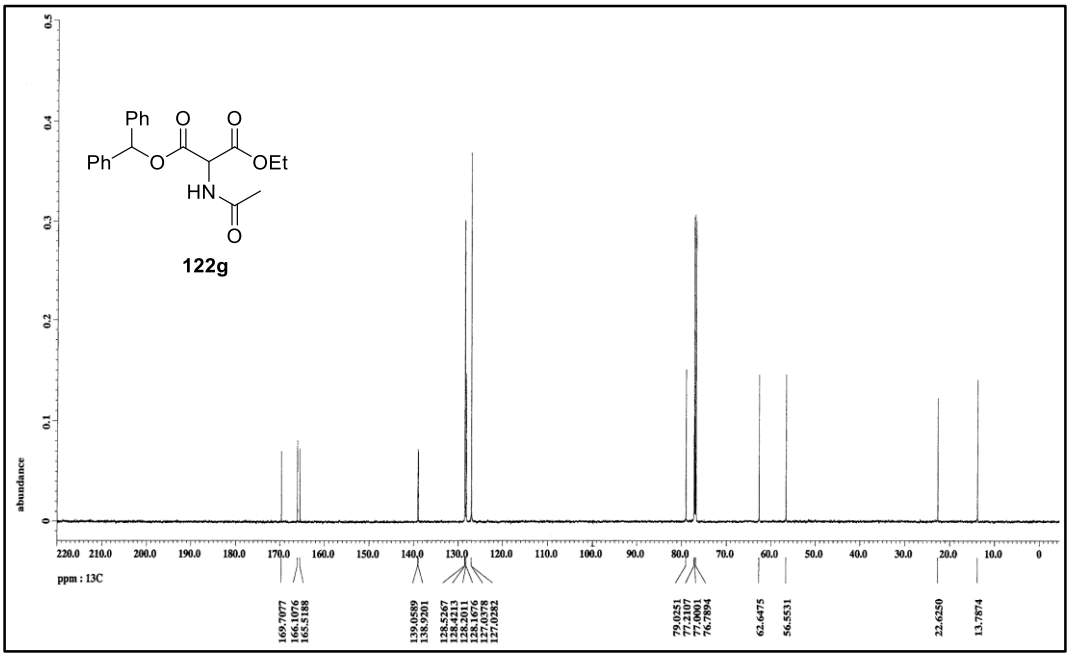
^{13}C-NMR of compound **122f** (125 MHz, $CDCl_3$)



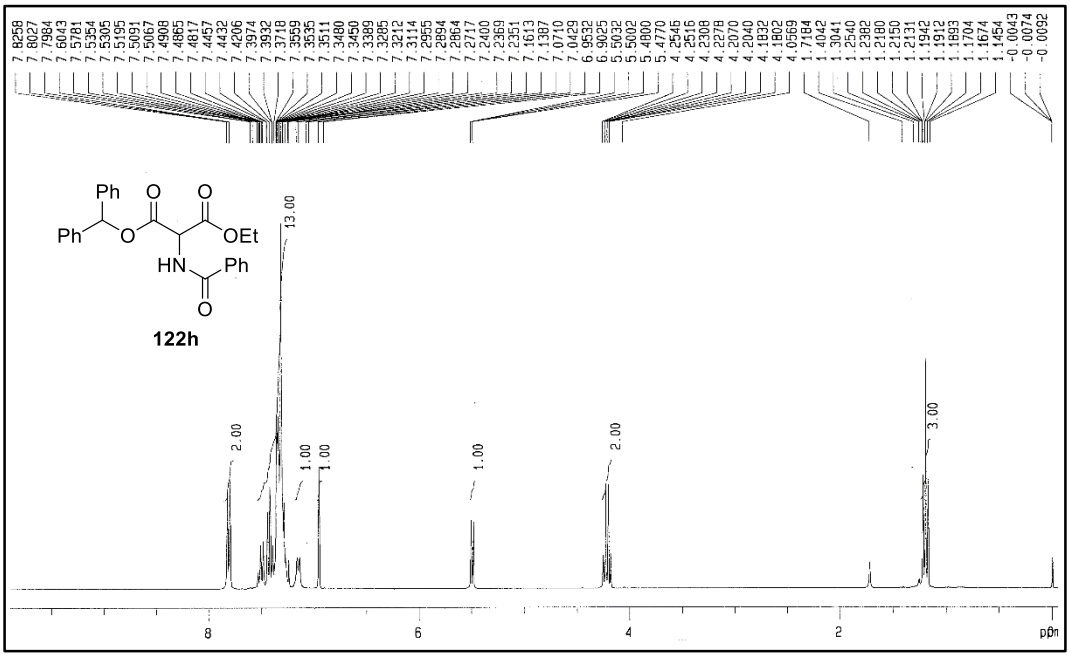
^{1}H-NMR of compound **122g** (300 MHz, $CDCl_3$)



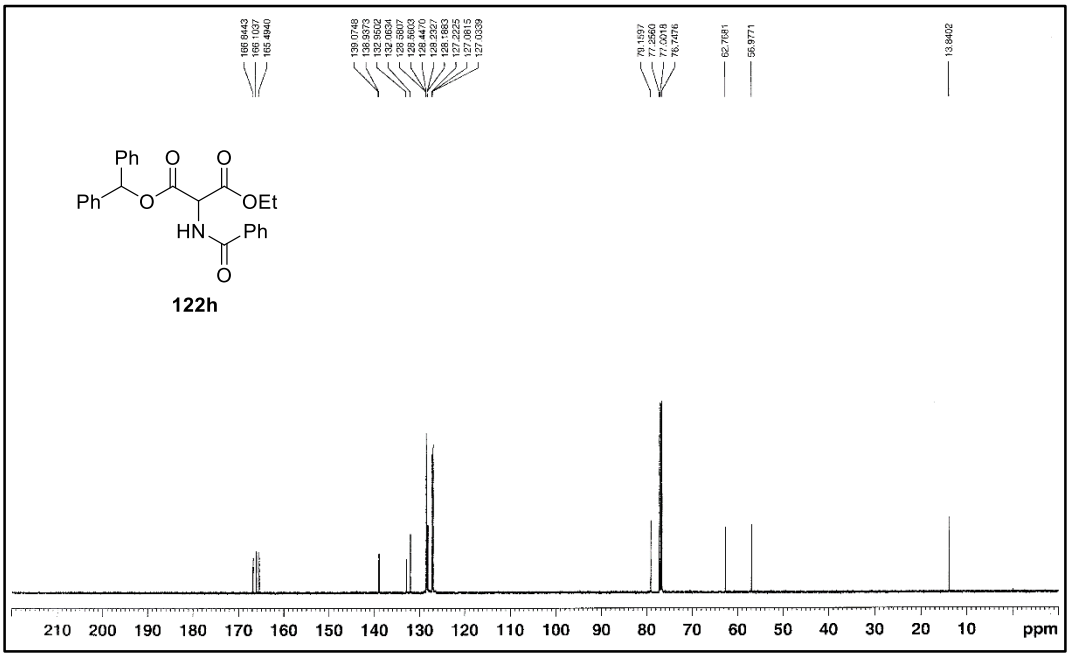
^{13}C-NMR of compound **122g** (150 MHz, $CDCl_3$)



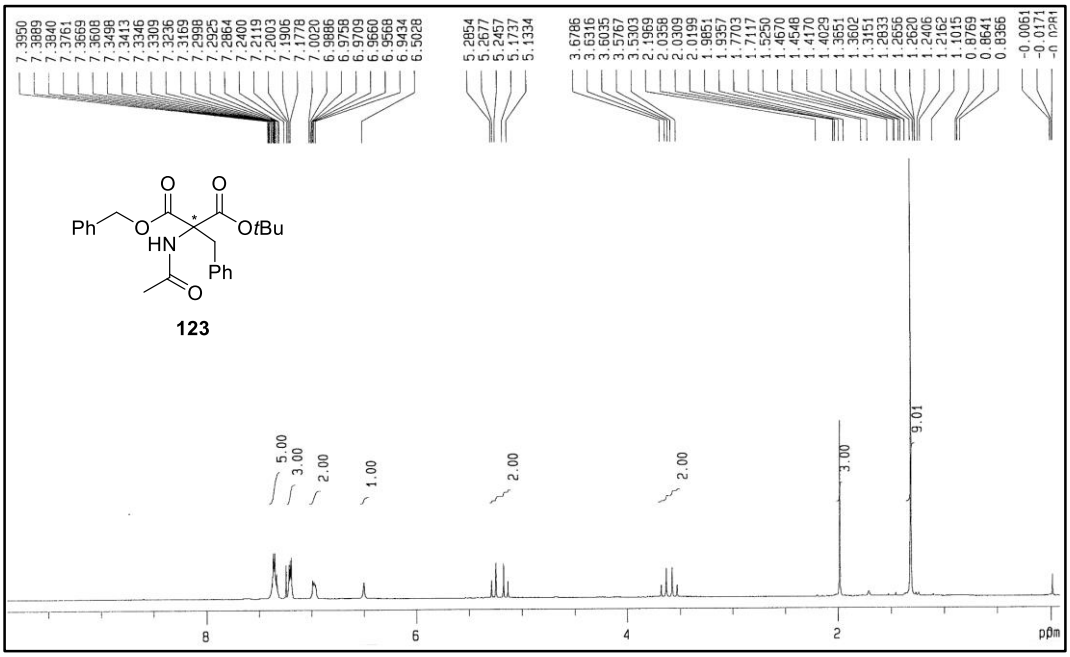
^{1}H-NMR of compound **122h** (300 MHz, $CDCl_3$)



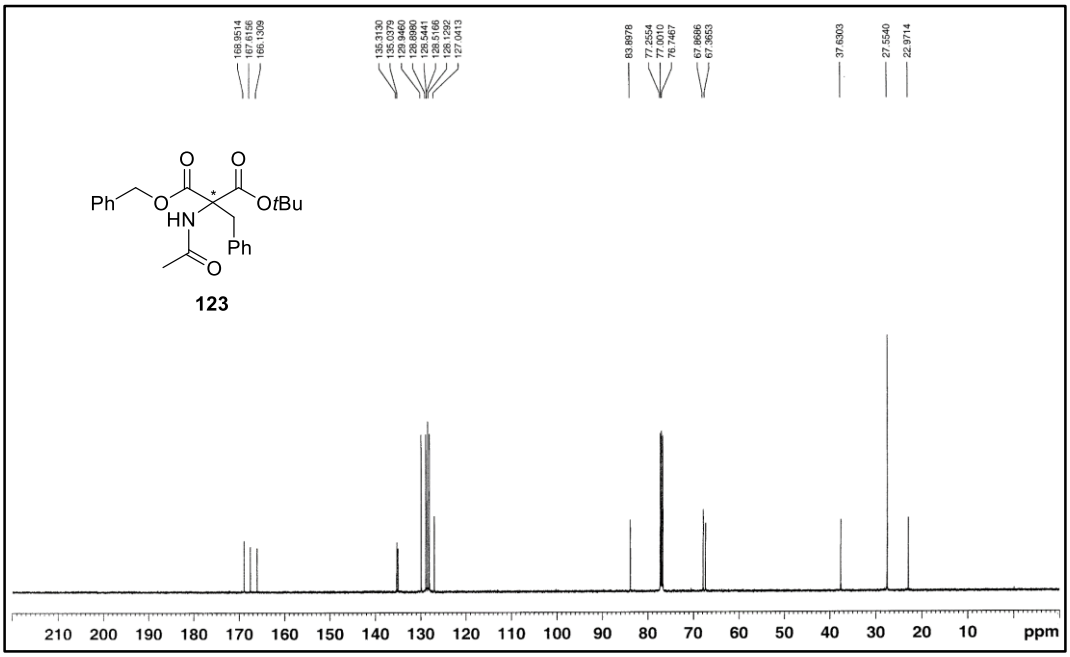
^{13}C-NMR of compound **122h** (125 MHz, $CDCl_3$)



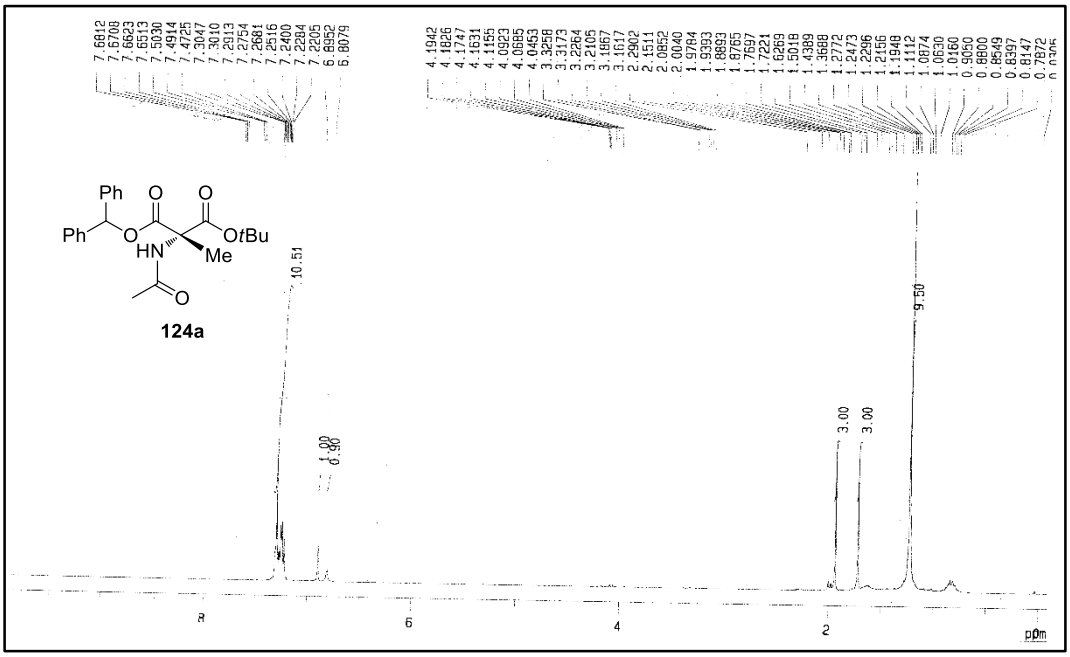
^{1}H-NMR of compound **123** (300 MHz, $CDCl_3$)



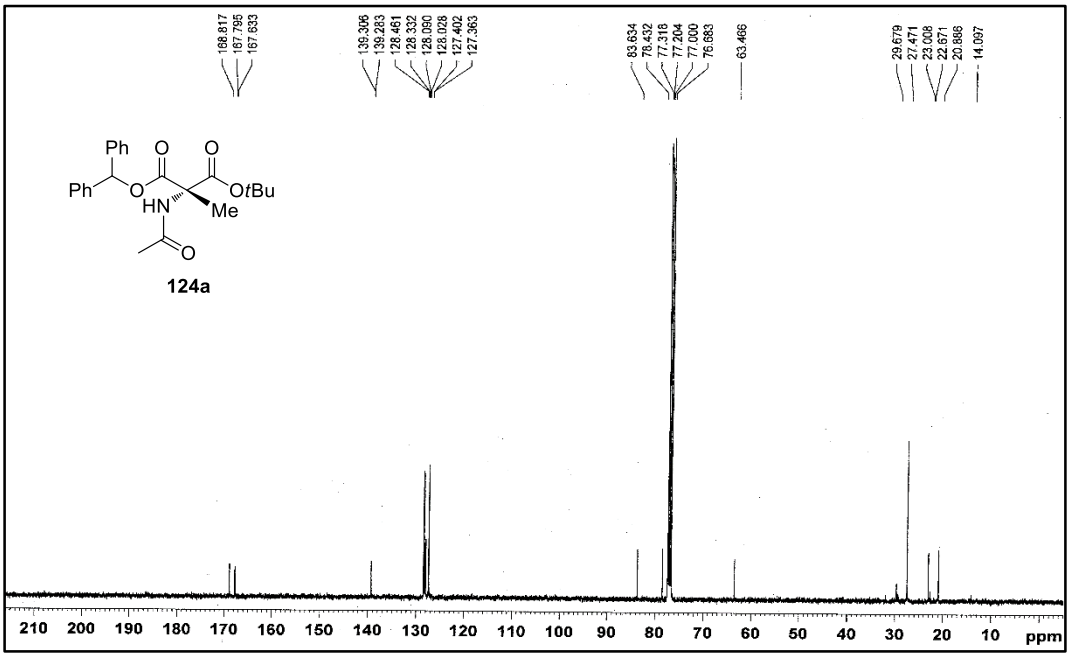
^{13}C-NMR of compound **123** (125 MHz, $CDCl_3$)



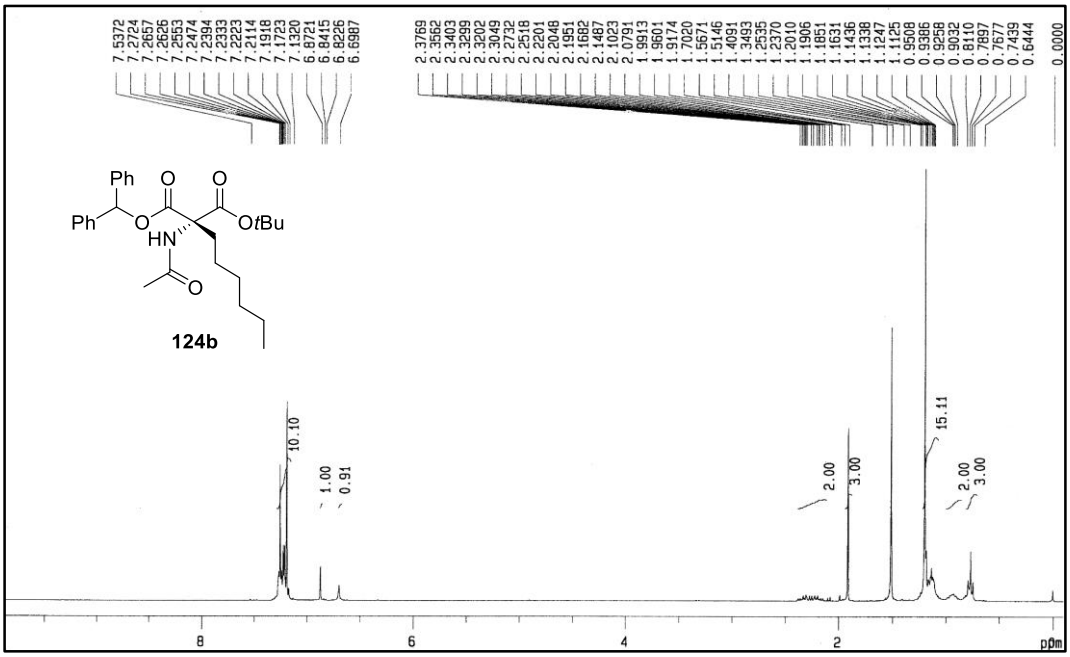
^{1}H-NMR of compound **124a** (300 MHz, $CDCl_3$)



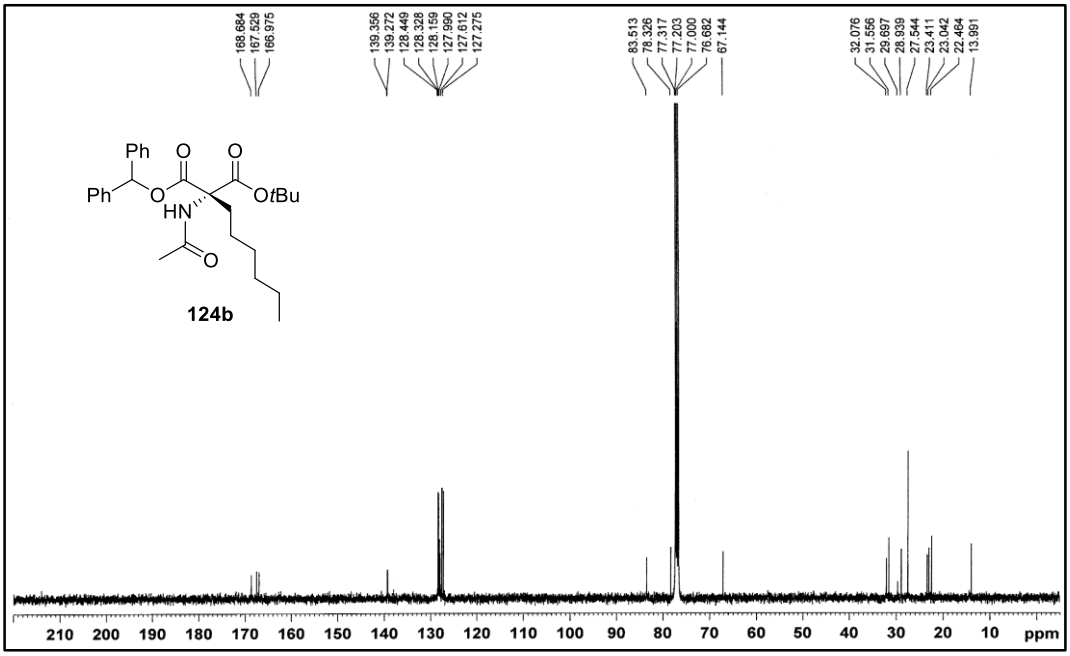
^{13}C-NMR of compound **124a** (125 MHz, $CDCl_3$)



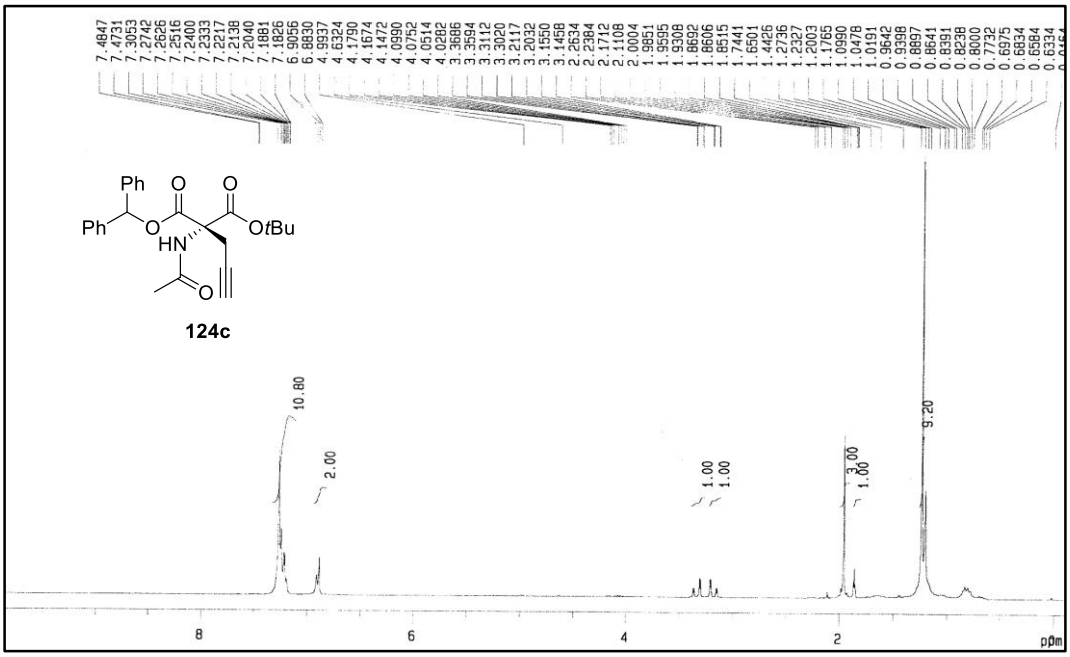
^{1}H-NMR of compound **124b** (300 MHz, $CDCl_3$)



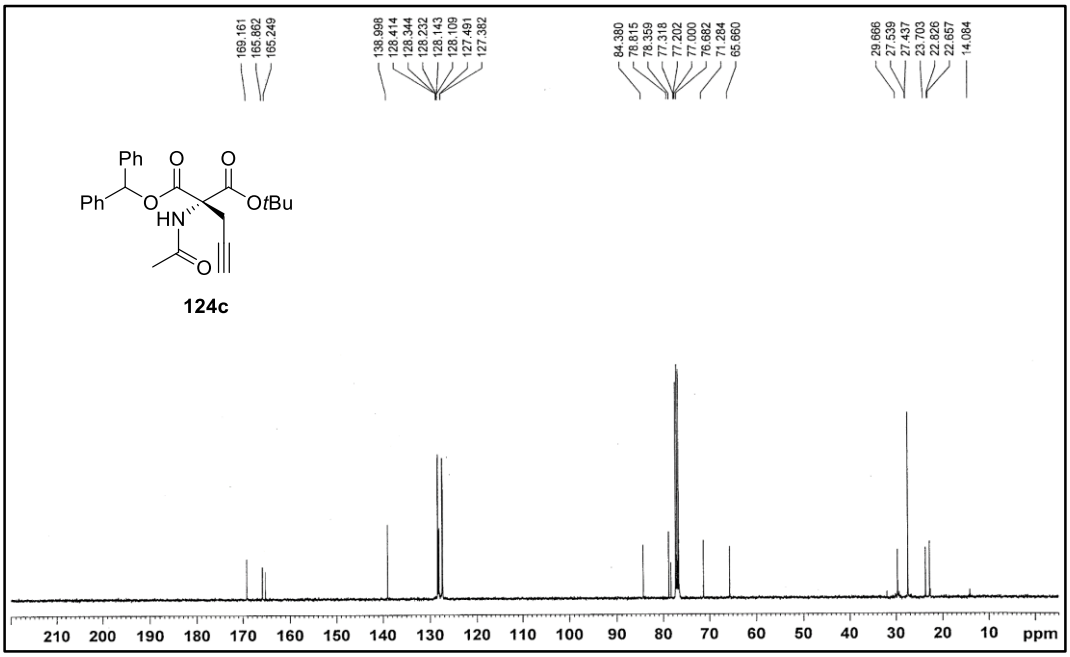
^{13}C-NMR of compound **124b** (125 MHz, $CDCl_3$)



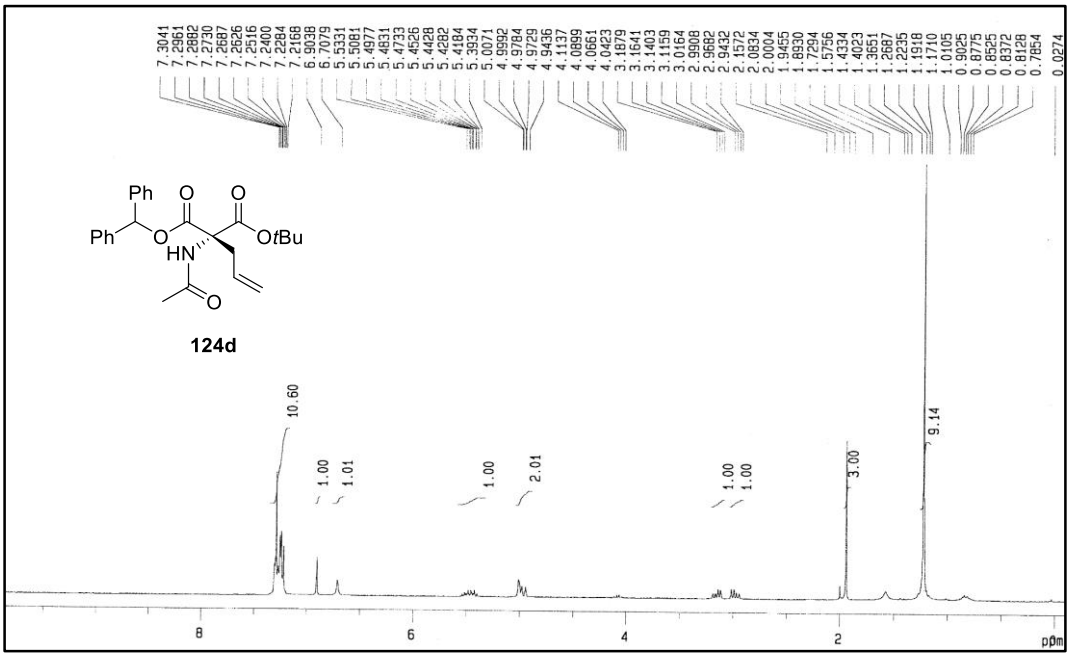
^{1}H-NMR of compound **124c** (300 MHz, $CDCl_3$)



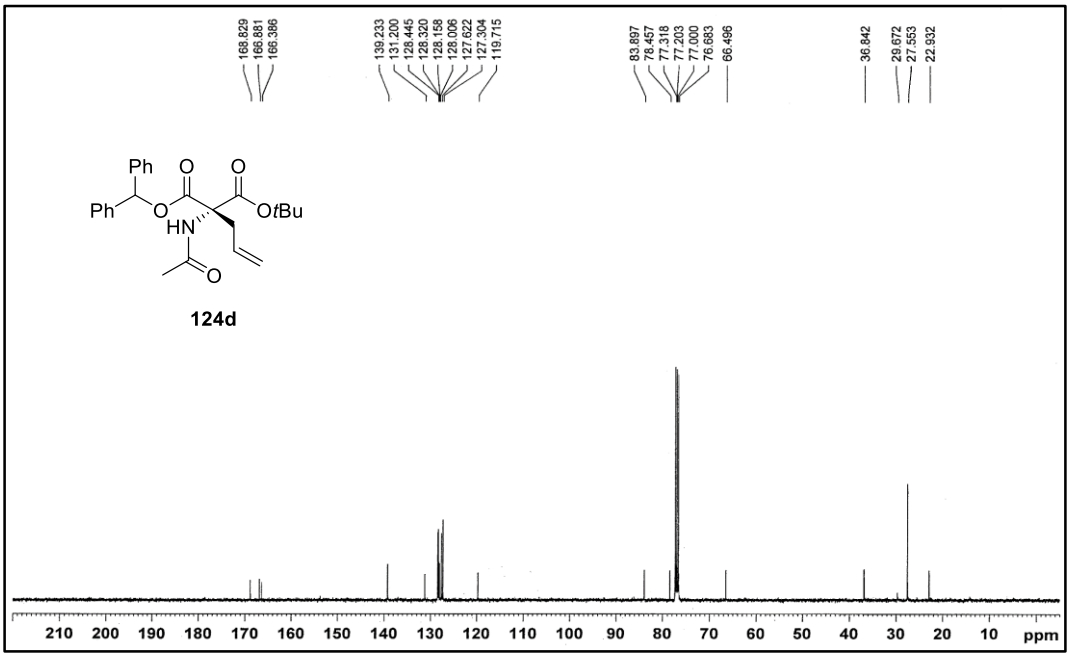
^{13}C-NMR of compound **124c** (125 MHz, $CDCl_3$)



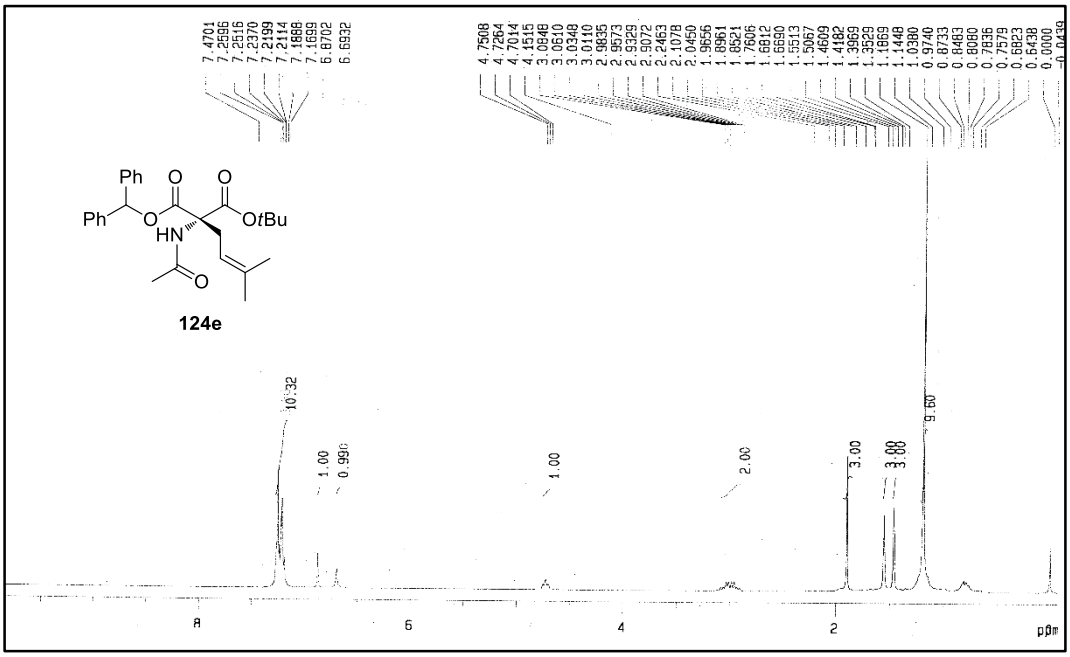
^{1}H-NMR of compound **124d** (300 MHz, $CDCl_3$)



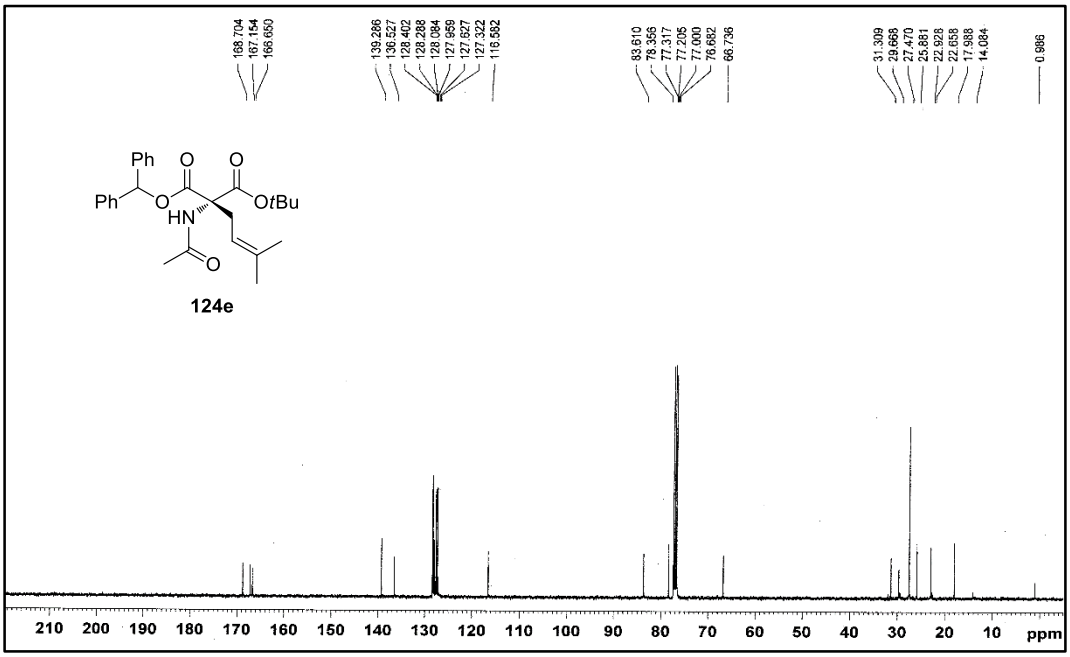
^{13}C-NMR of compound **124d** (125 MHz, $CDCl_3$)



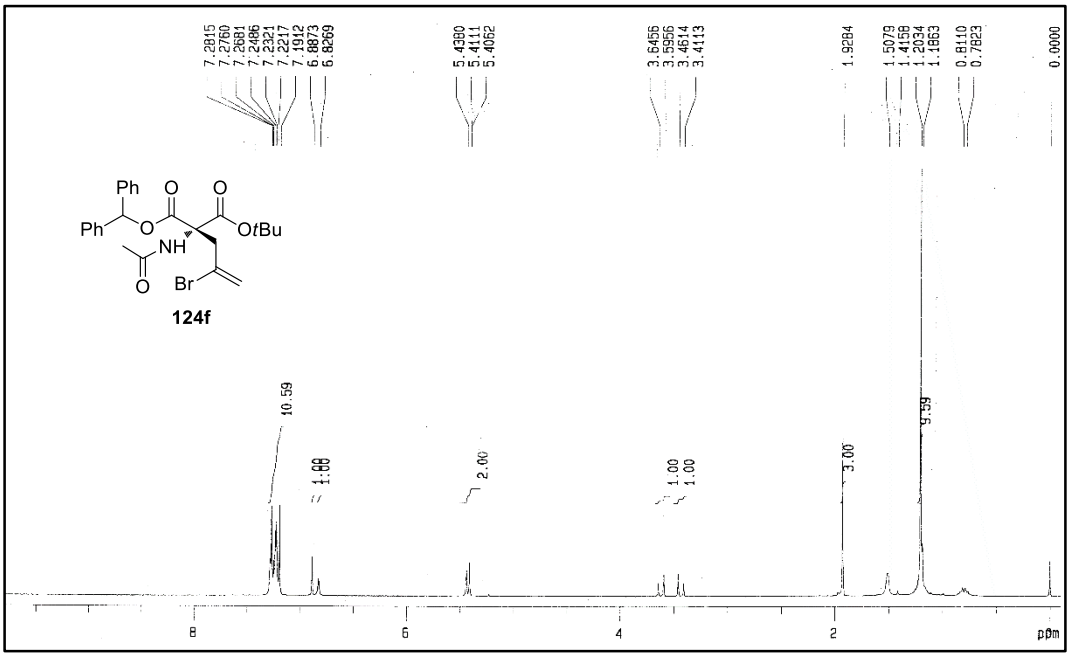
^{1}H-NMR of compound **124e** (300 MHz, $CDCl_3$)



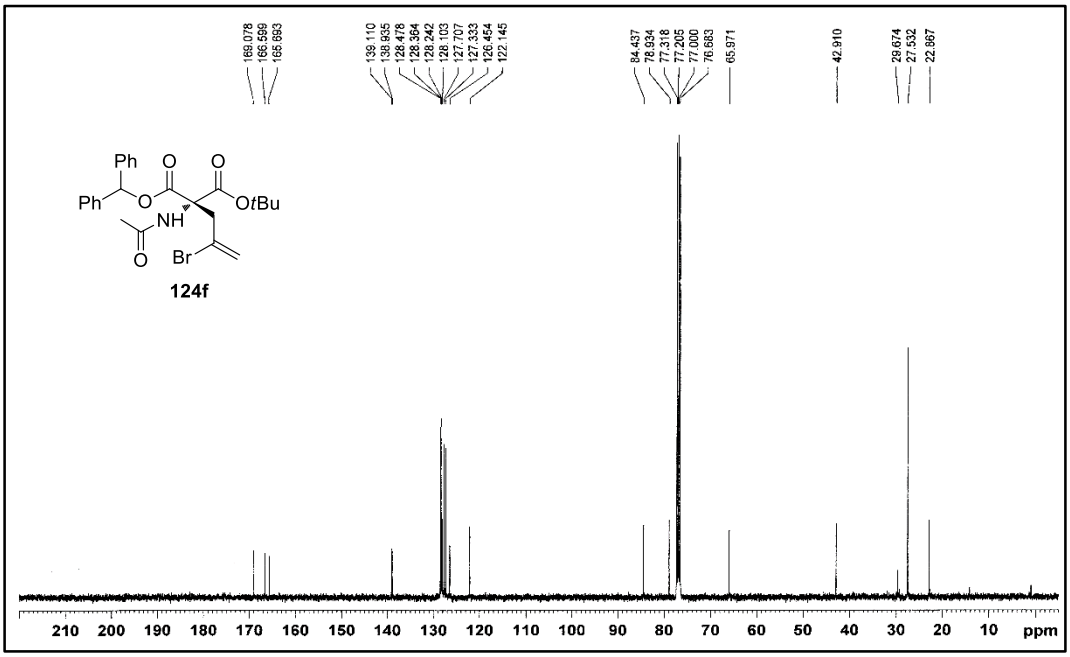
^{13}C-NMR of compound **124e** (125 MHz, $CDCl_3$)



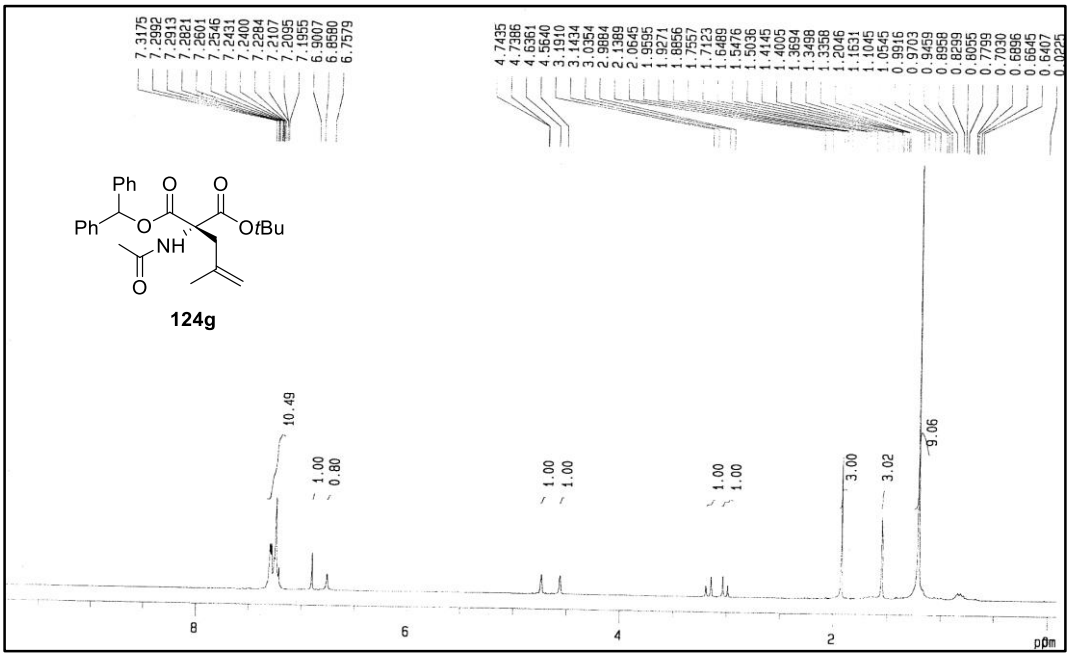
^{1}H-NMR of compound **124f** (300 MHz, $CDCl_3$)



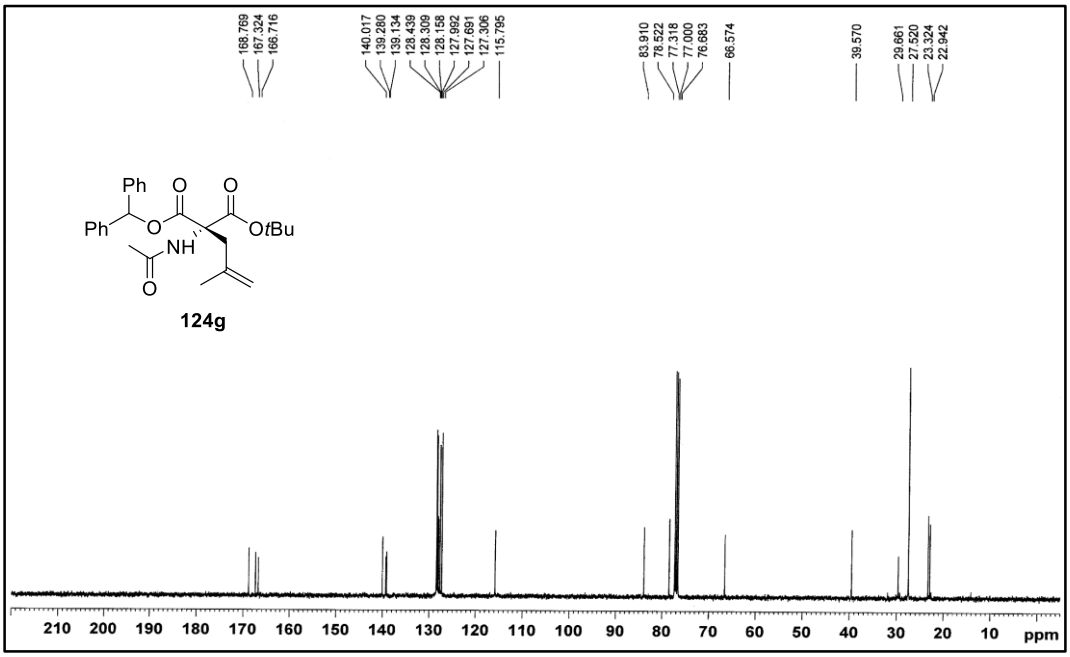
^{13}C-NMR of compound **124f** (125 MHz, $CDCl_3$)



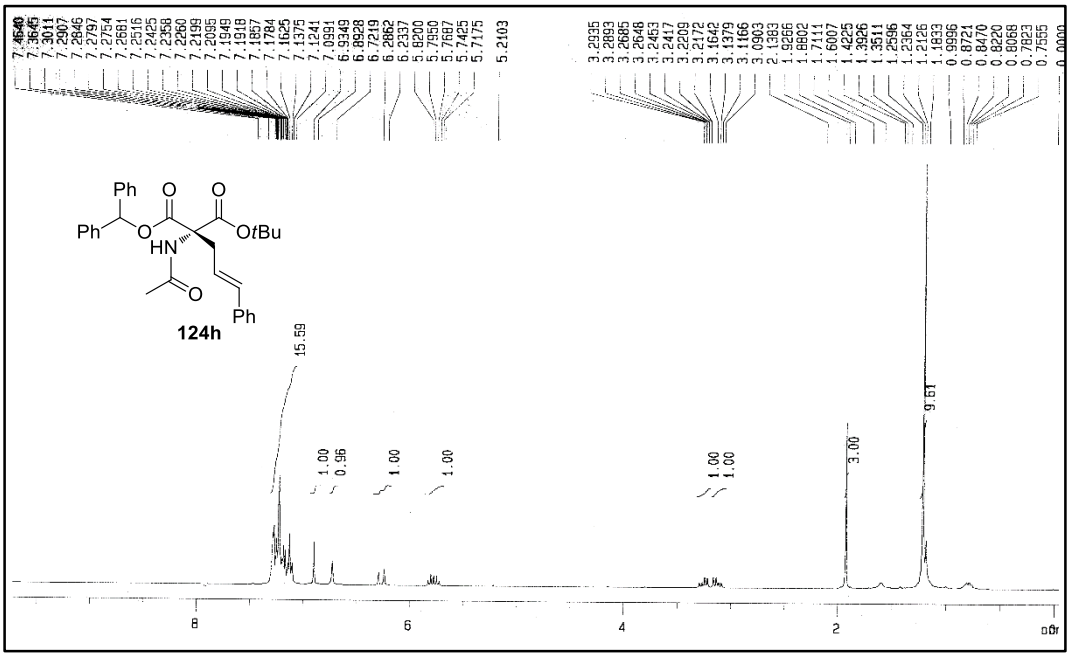
^{1}H-NMR of compound **124g** (300 MHz, $CDCl_3$)



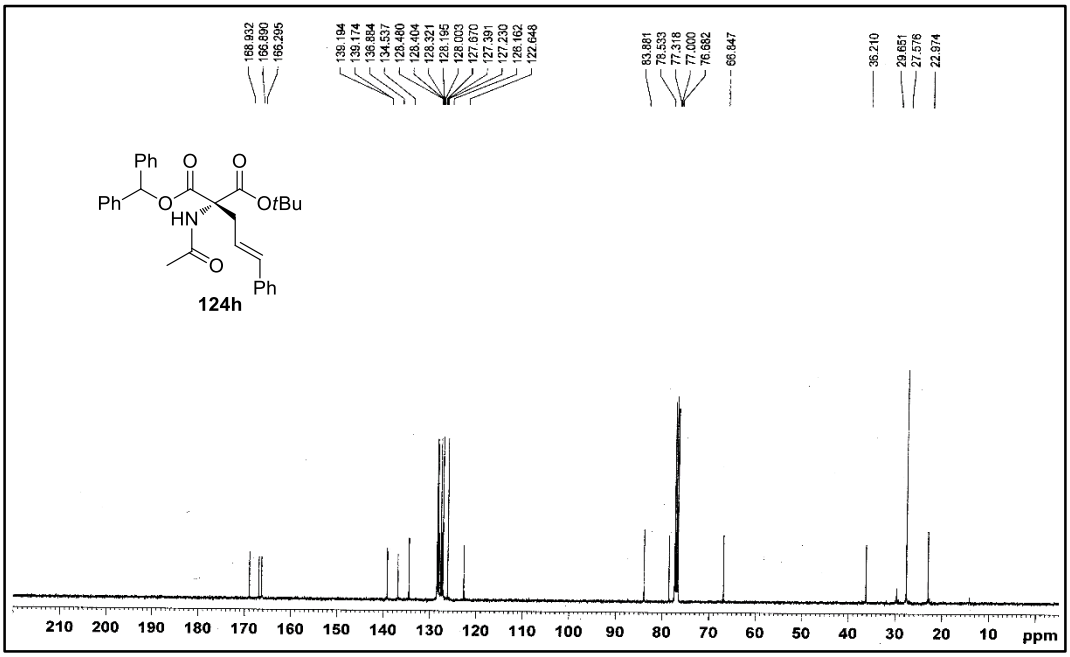
^{13}C-NMR of compound **124g** (125 MHz, $CDCl_3$)



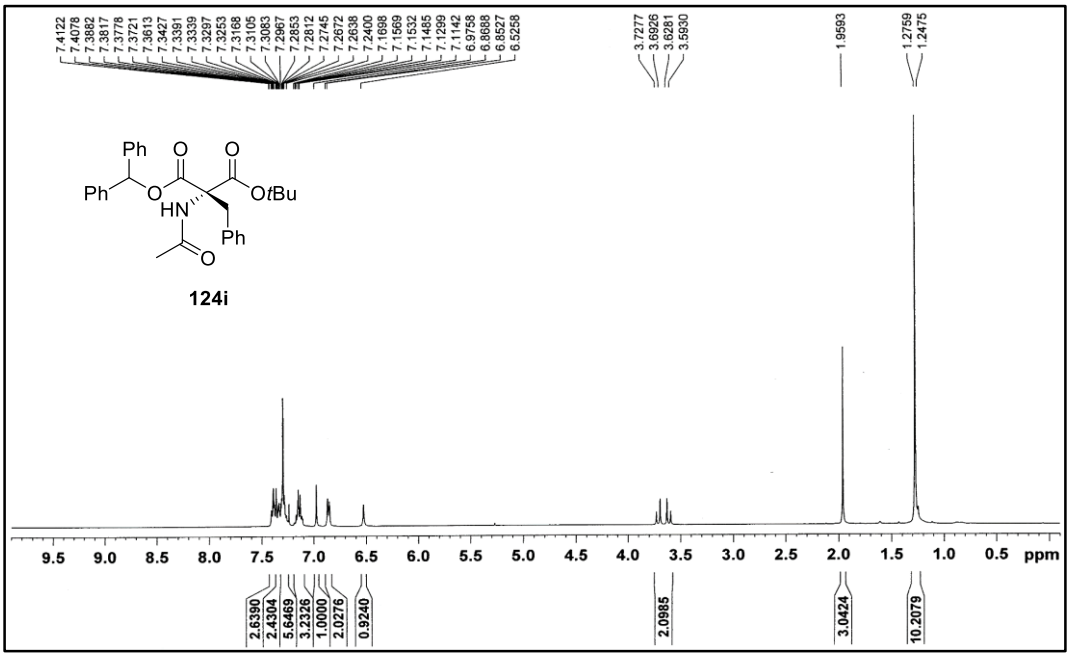
^{1}H-NMR of compound **124h** (300 MHz, $CDCl_3$)



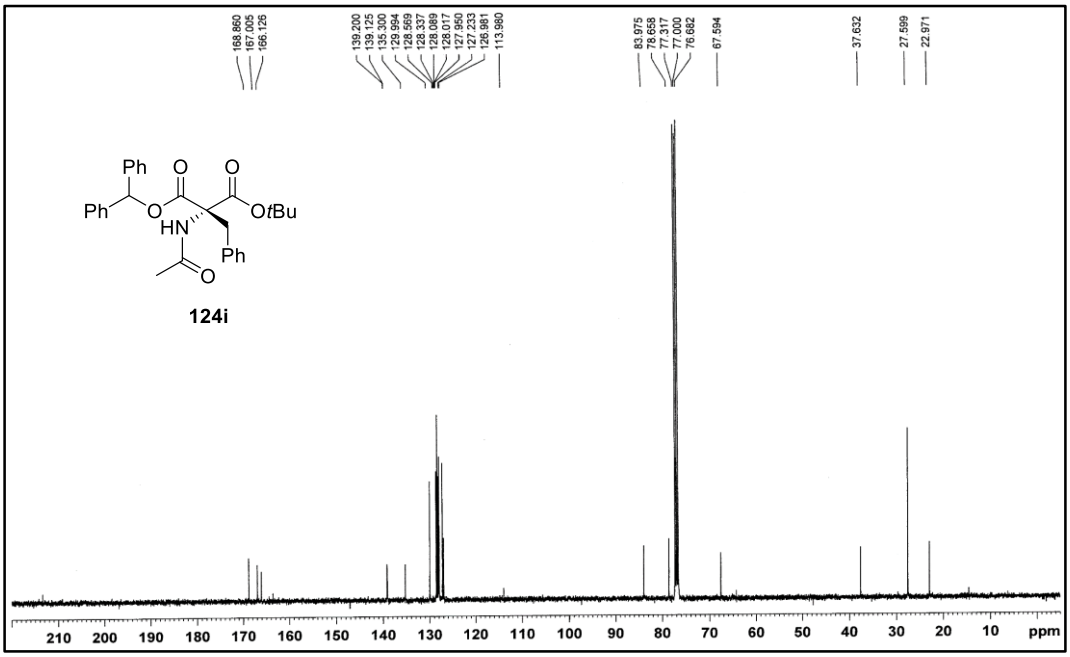
^{13}C-NMR of compound **124h** (125 MHz, $CDCl_3$)



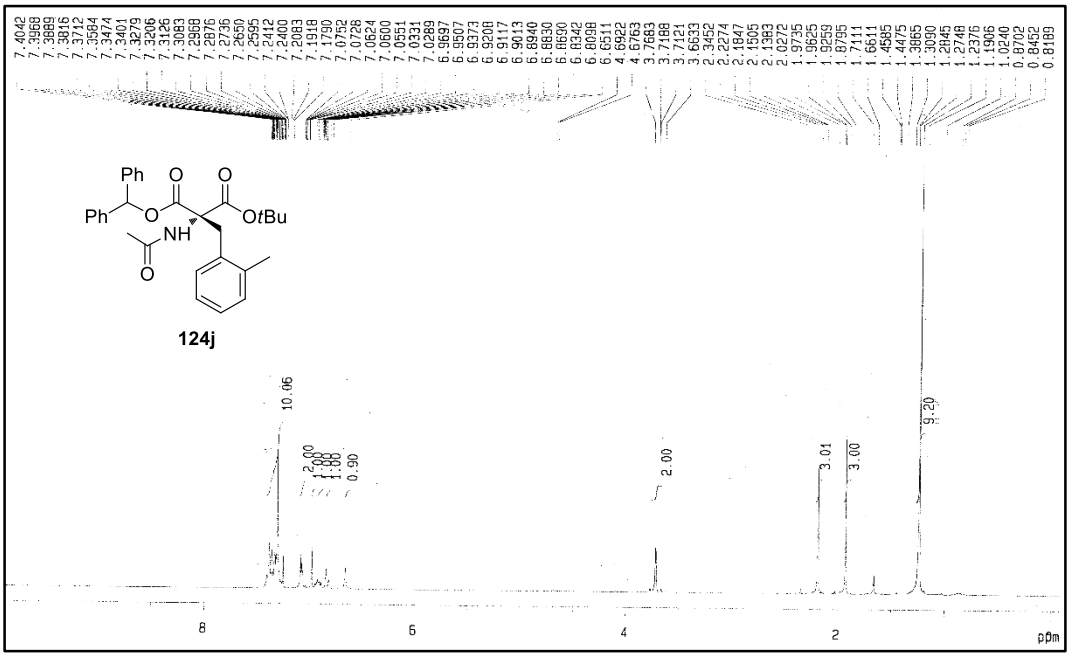
H-NMR of compound **124i** (500 MHz, $CDCl_3$)



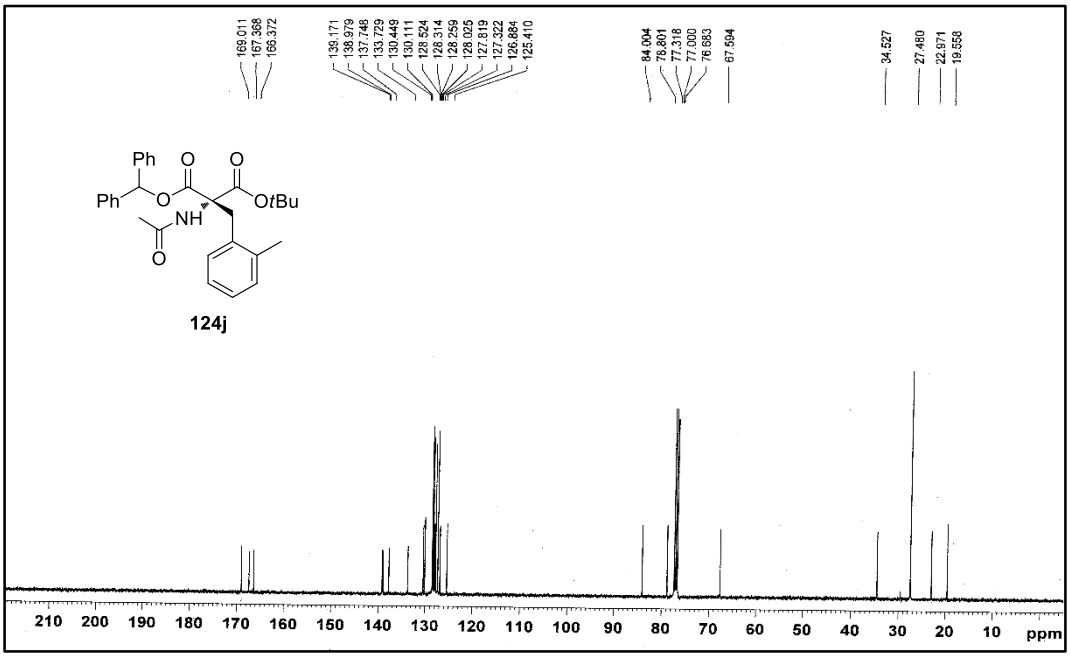
^{13}C-NMR of compound **124i** (125 MHz, $CDCl_3$)



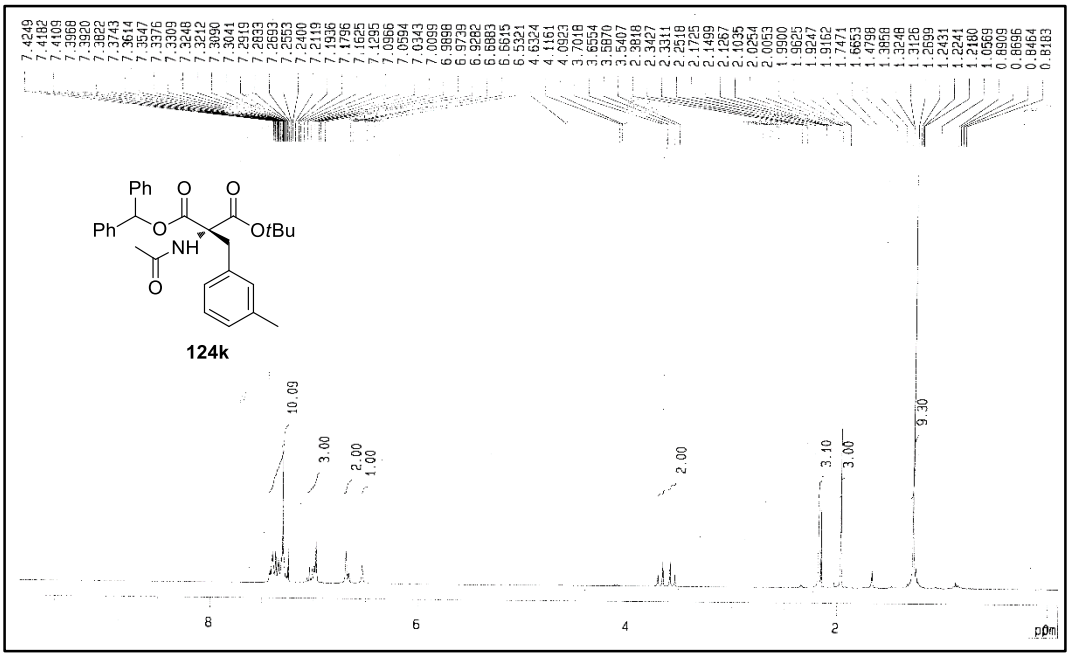
^{1}H-NMR of compound **124j** (300 MHz, $CDCl_3$)



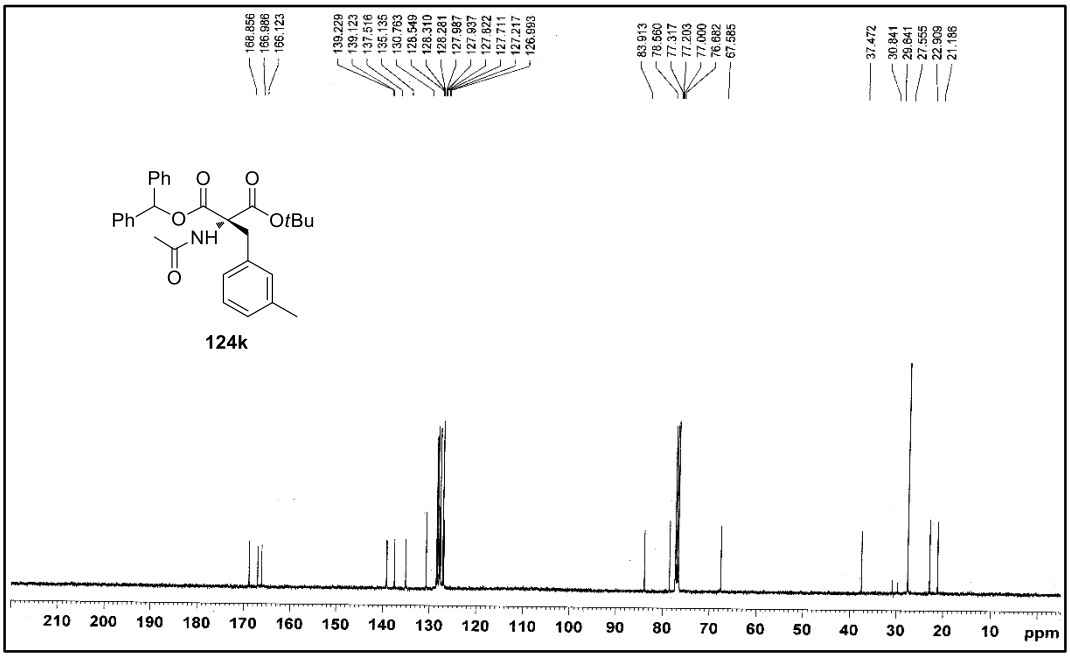
^{13}C-NMR of compound **124j** (125 MHz, $CDCl_3$)



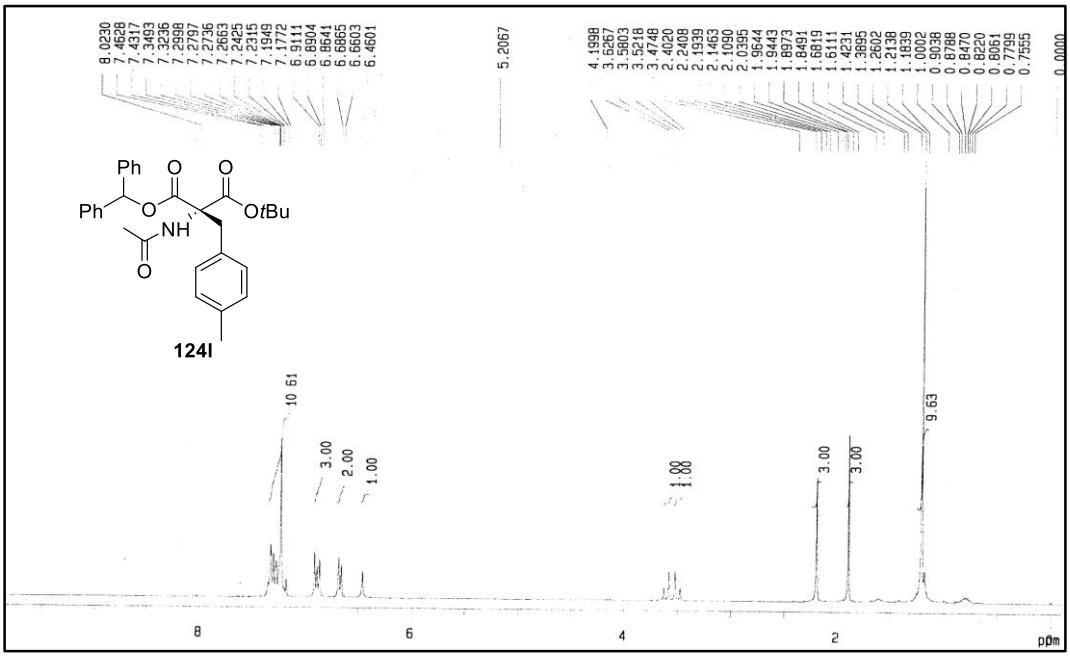
^{1}H-NMR of compound **124k** (300 MHz, $CDCl_3$)



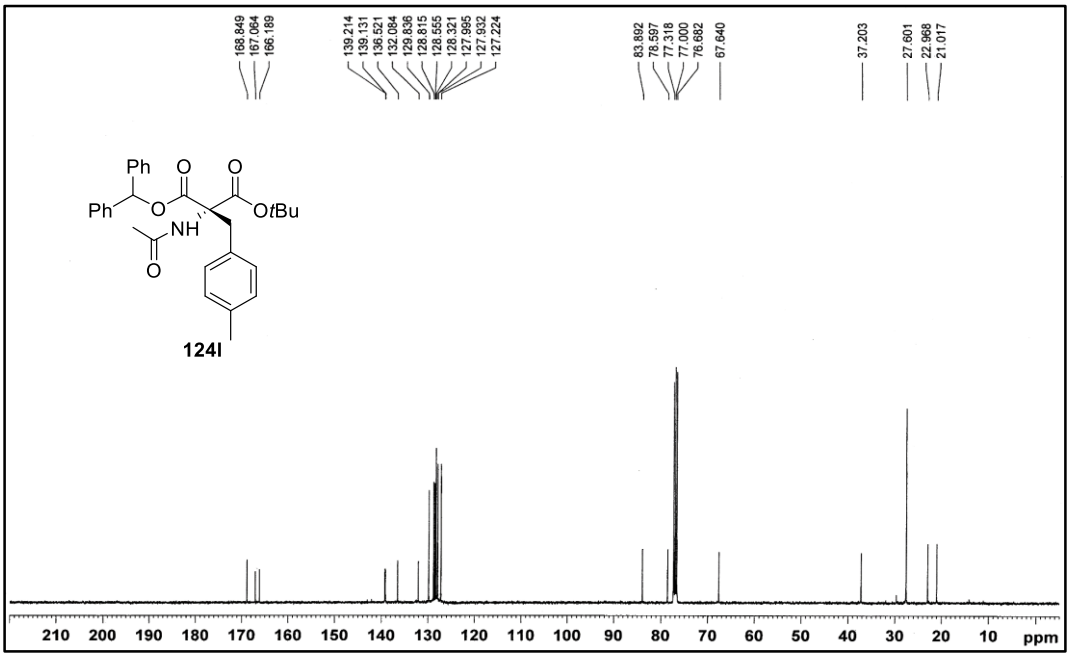
^{13}C-NMR of compound **124k** (125 MHz, $CDCl_3$)



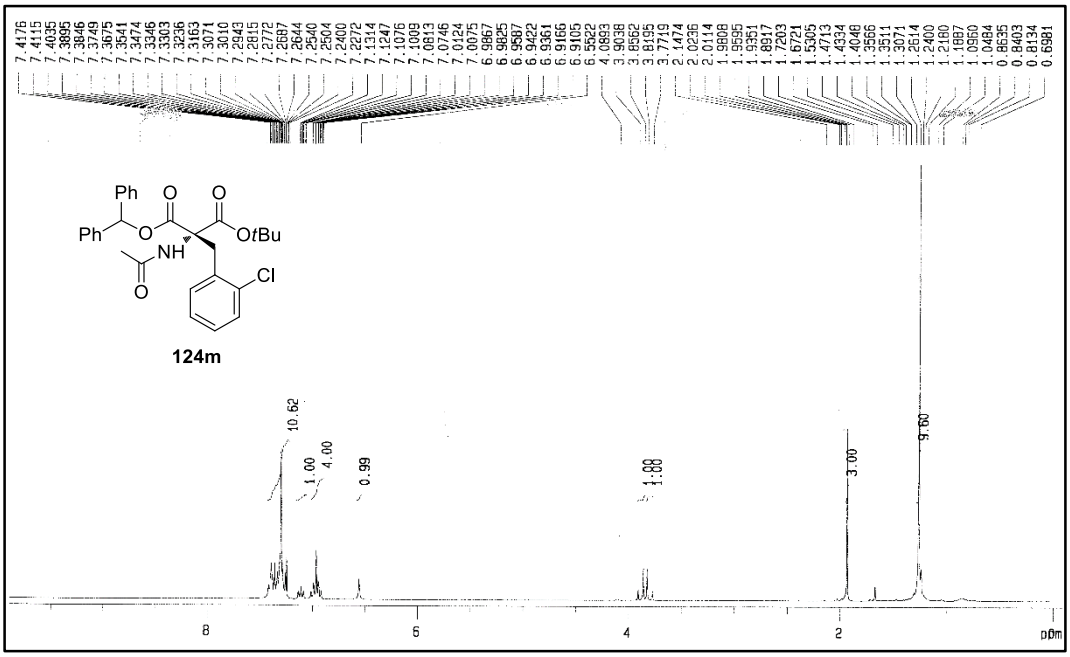
^{1}H-NMR of compound **124l** (300 MHz, $CDCl_3$)



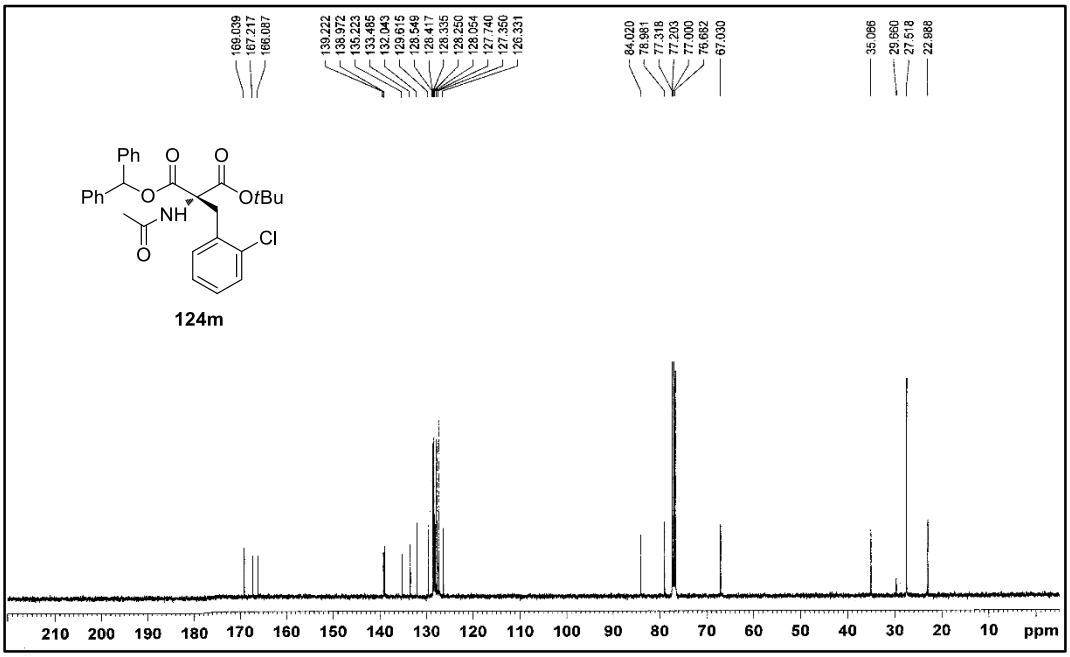
^{13}C-NMR of compound **124l** (125 MHz, $CDCl_3$)



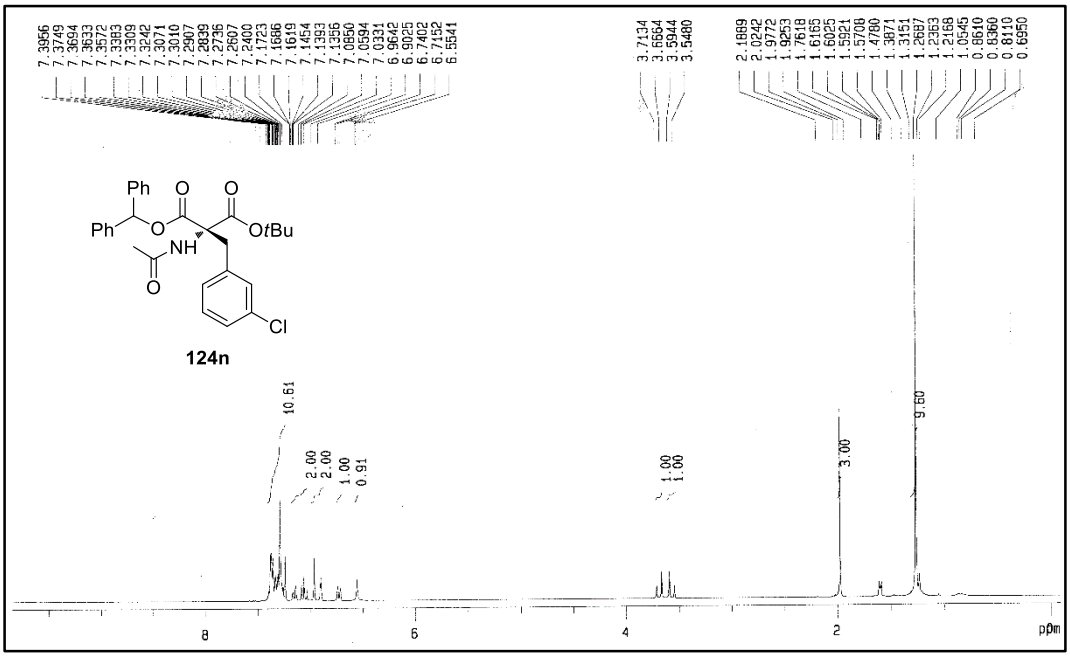
^{1}H-NMR of compound **124m** (300 MHz, $CDCl_3$)



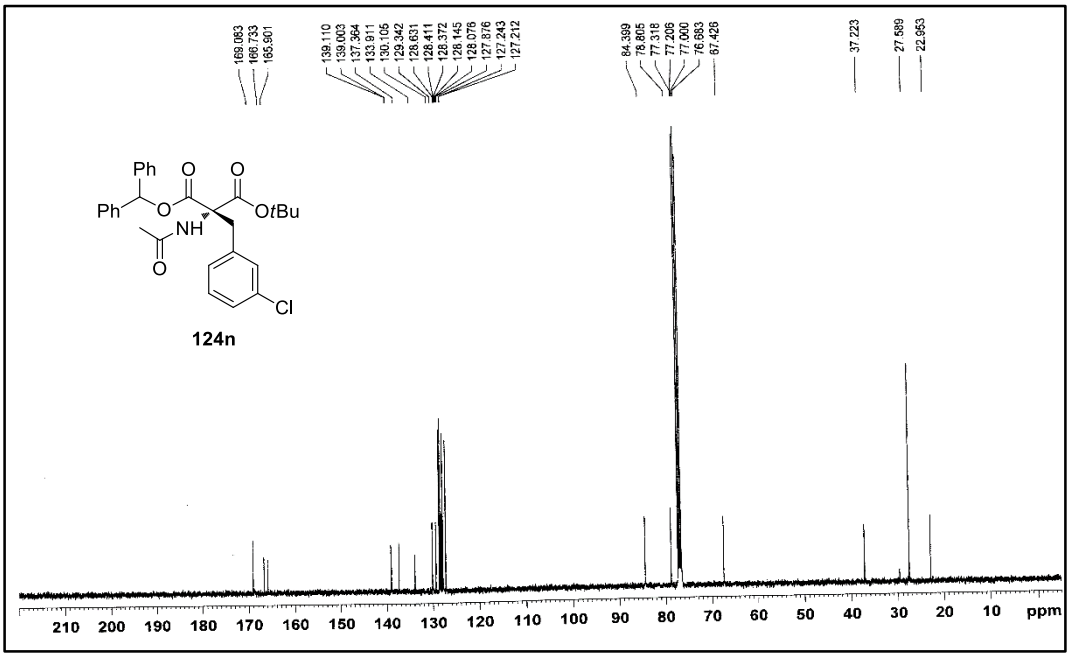
^{13}C-NMR of compound **124m** (125 MHz, $CDCl_3$)



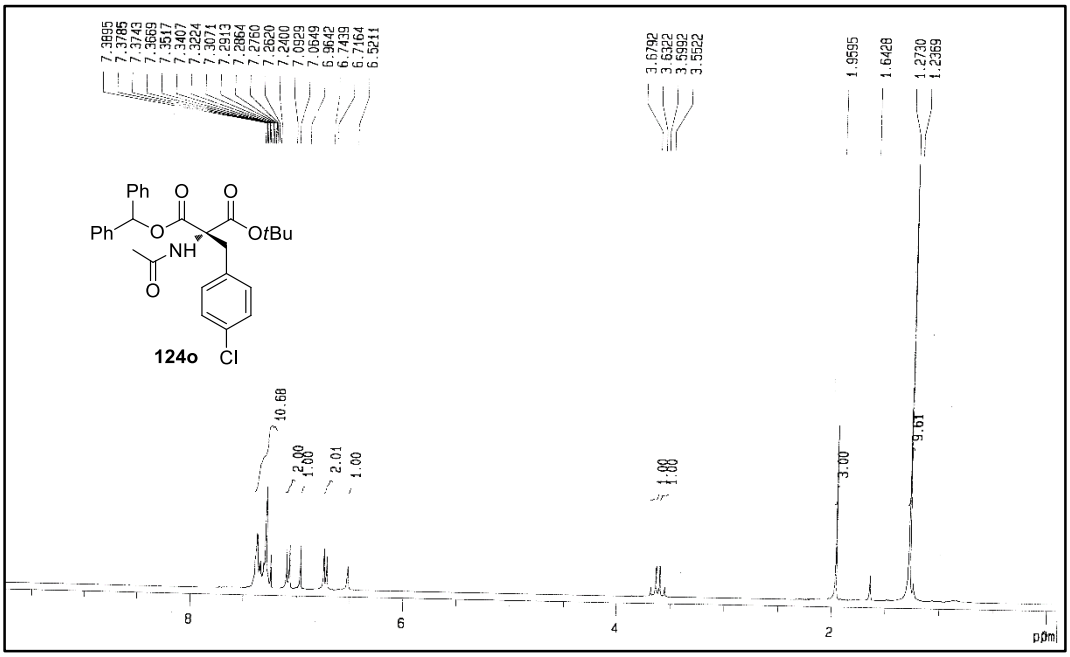
^{1}H-NMR of compound **124n** (300 MHz, $CDCl_3$)



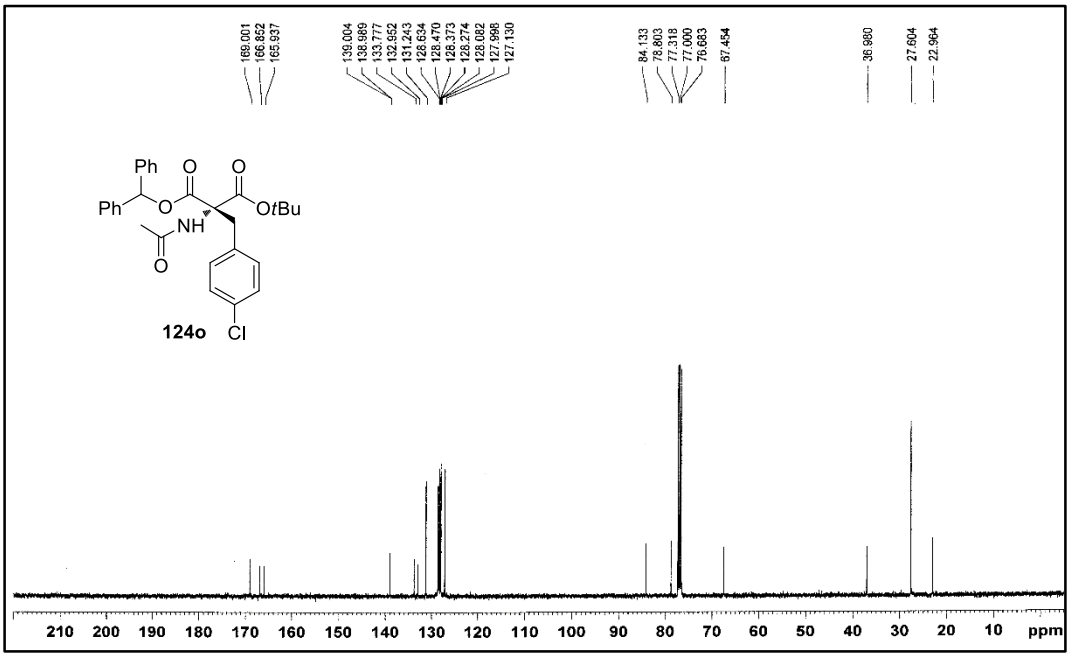
^{13}C-NMR of compound **124n** (125 MHz, $CDCl_3$)



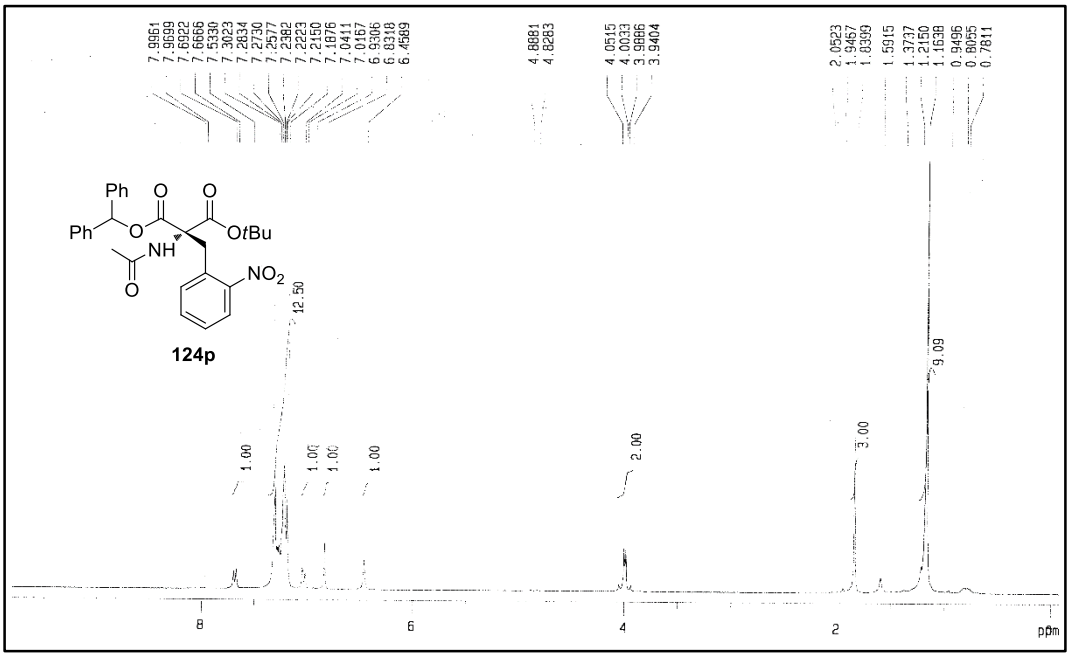
^{1}H-NMR of compound **124o** (300 MHz, $CDCl_3$)



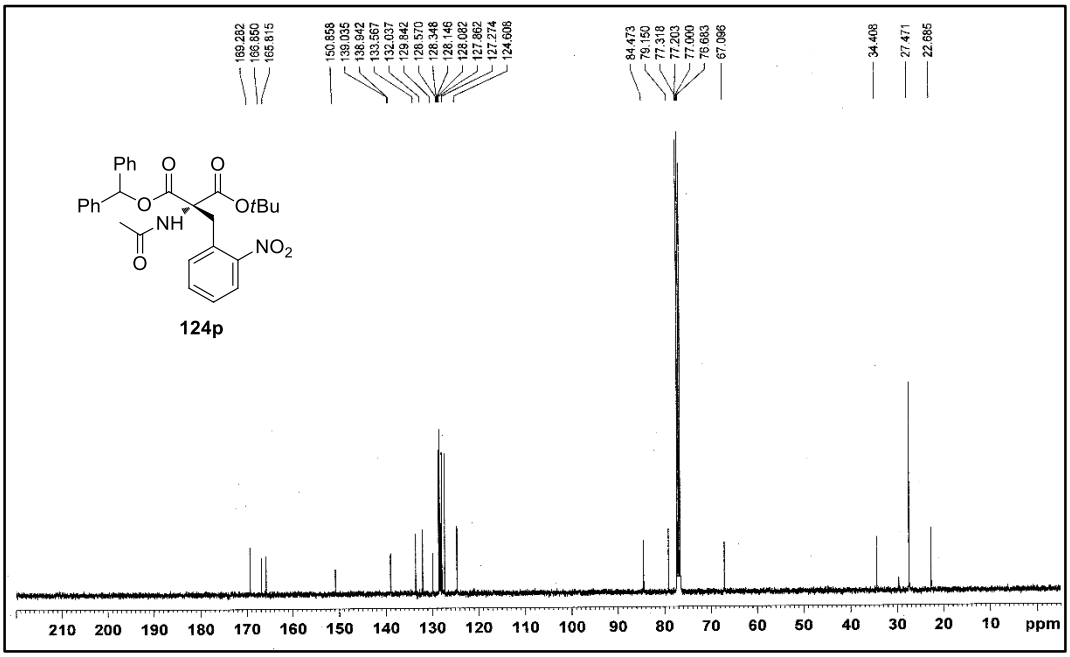
^{13}C-NMR of compound **124o** (125 MHz, $CDCl_3$)



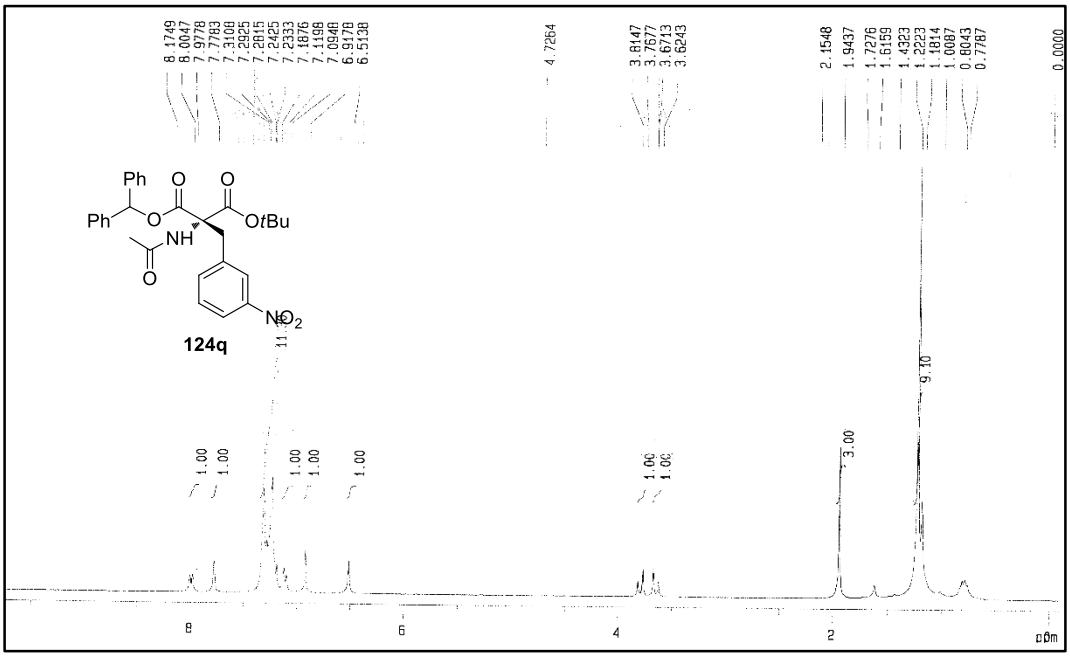
^{1}H-NMR of compound **124p** (300 MHz, $CDCl_3$)



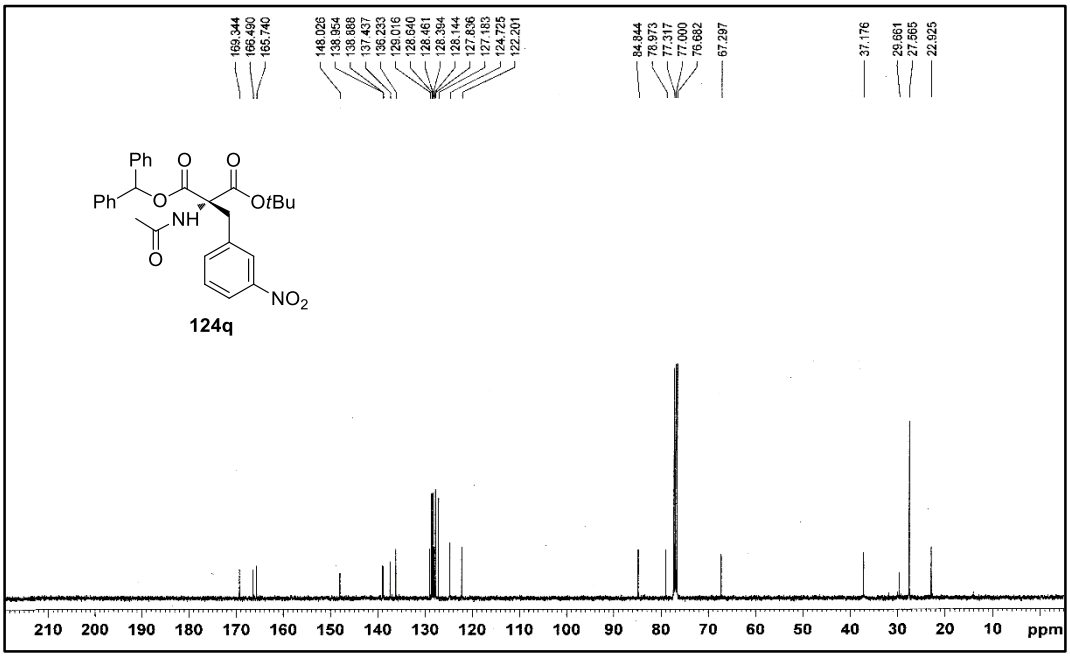
^{13}C-NMR of compound **124p** (125 MHz, $CDCl_3$)



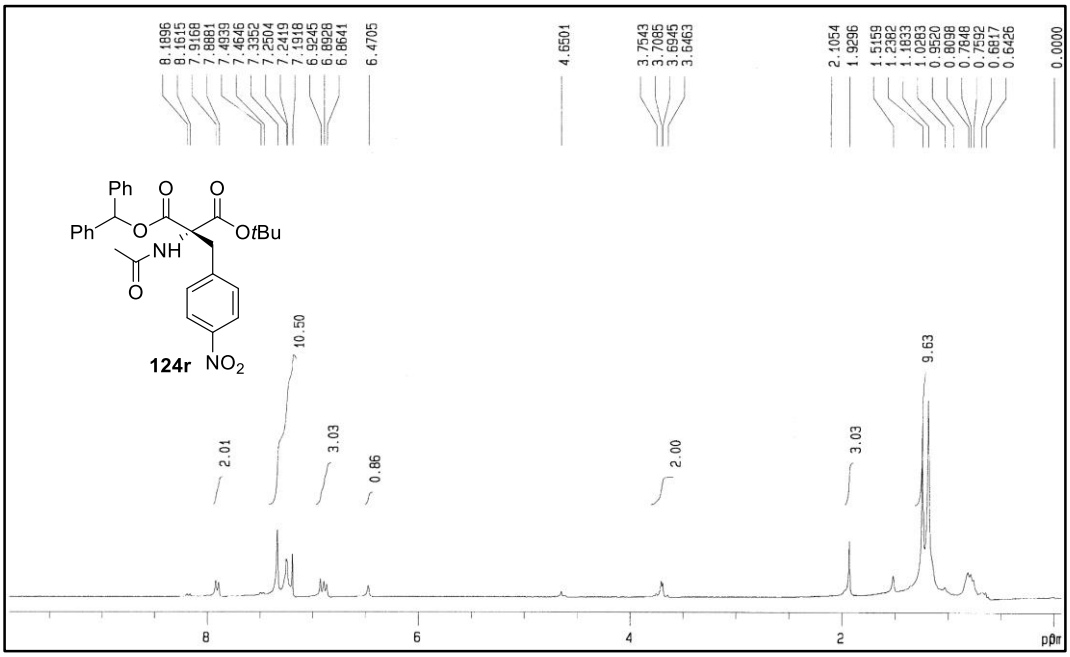
^{1}H-NMR of compound **124q** (300 MHz, $CDCl_3$)



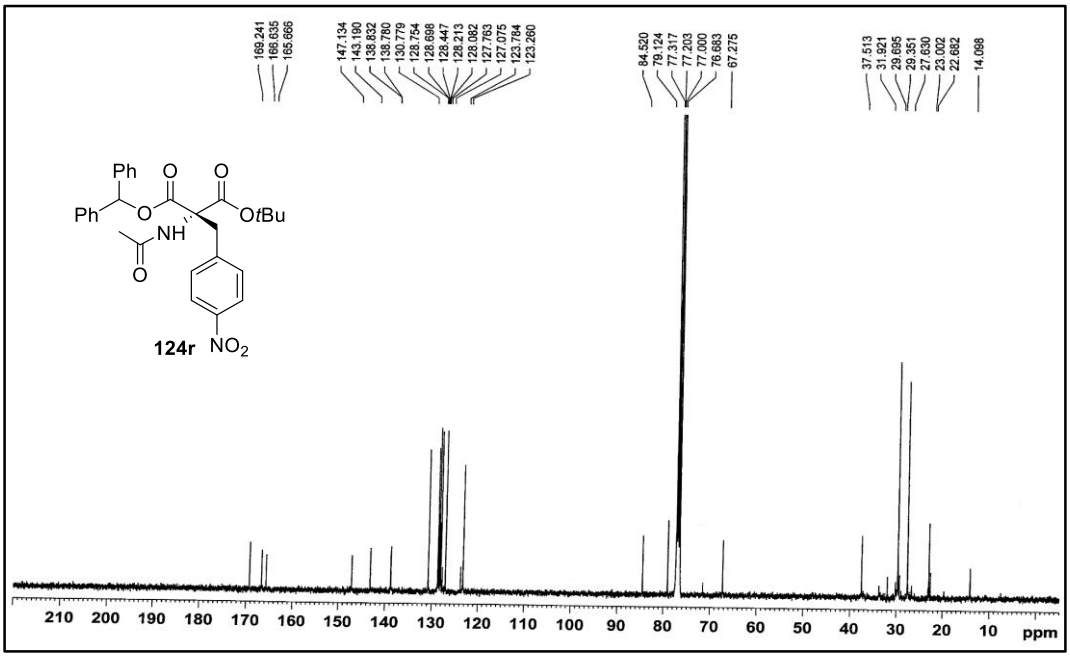
^{13}C-NMR of compound **124q** (125 MHz, $CDCl_3$)



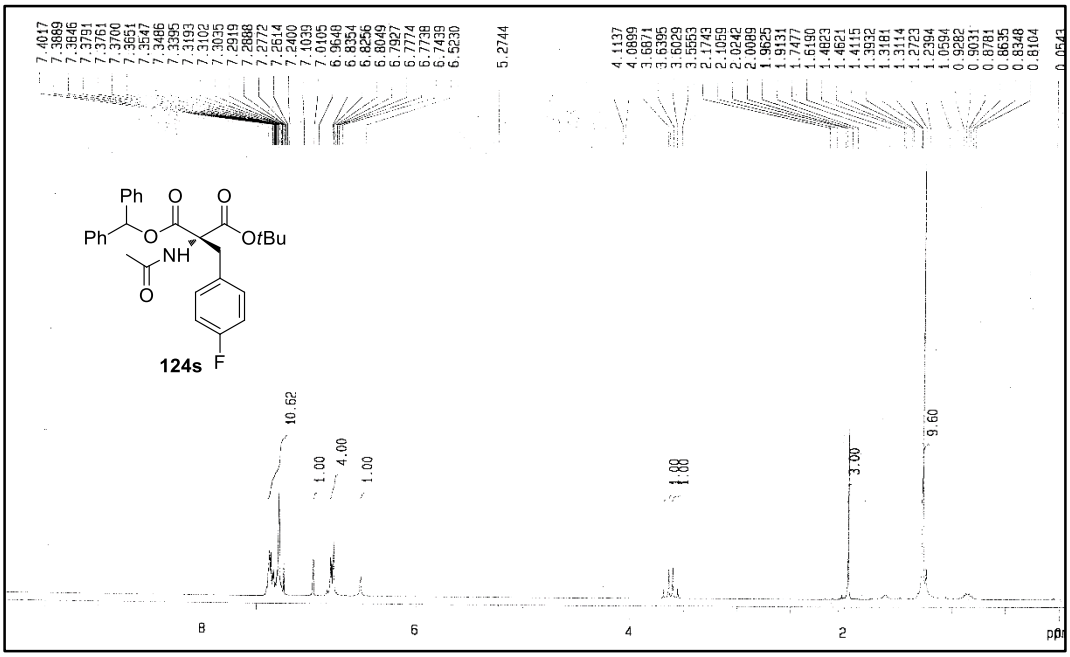
^{1}H-NMR of compound **124r** (300 MHz, $CDCl_3$)



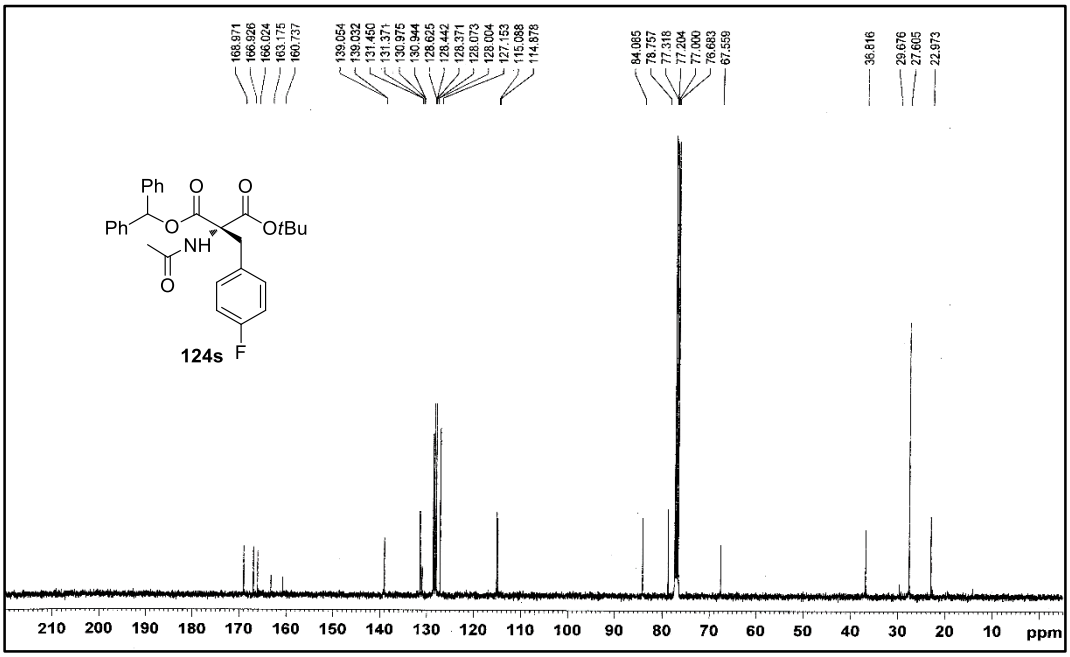
^{13}C-NMR of compound **124r** (125 MHz, $CDCl_3$)



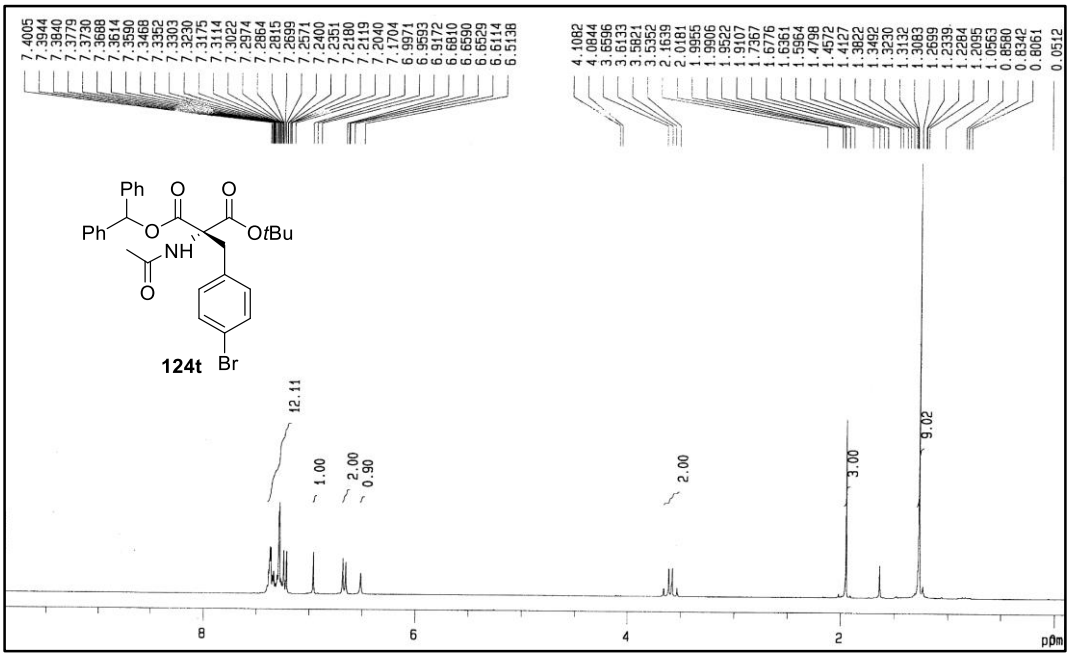
^{1}H-NMR of compound **124s** (300 MHz, $CDCl_3$)



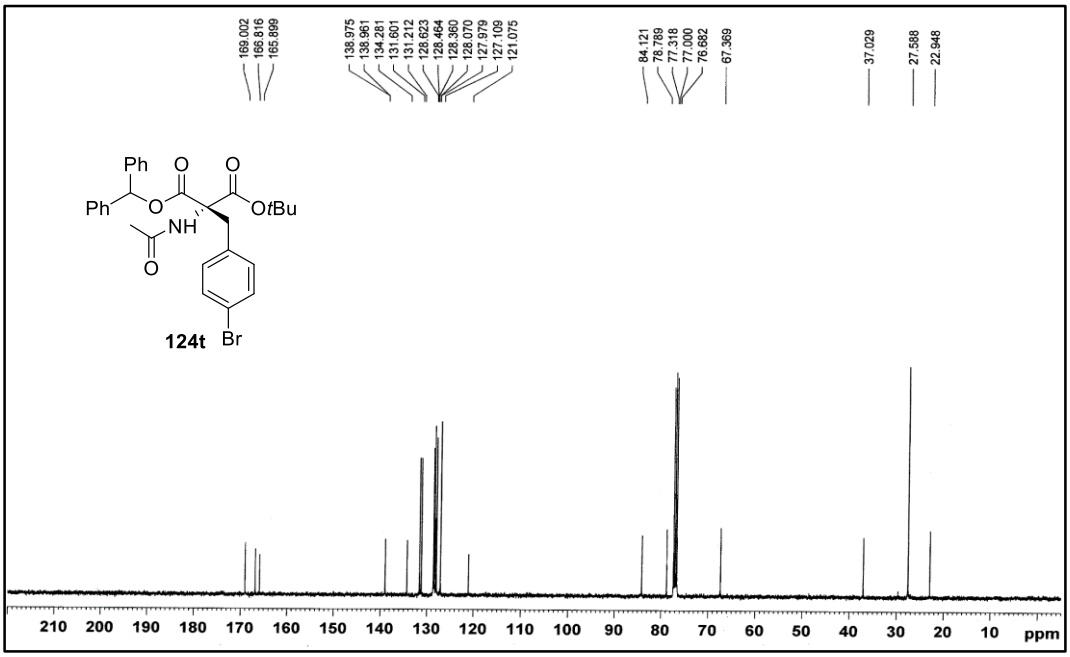
^{13}C-NMR of compound **124s** (100 MHz, $CDCl_3$)



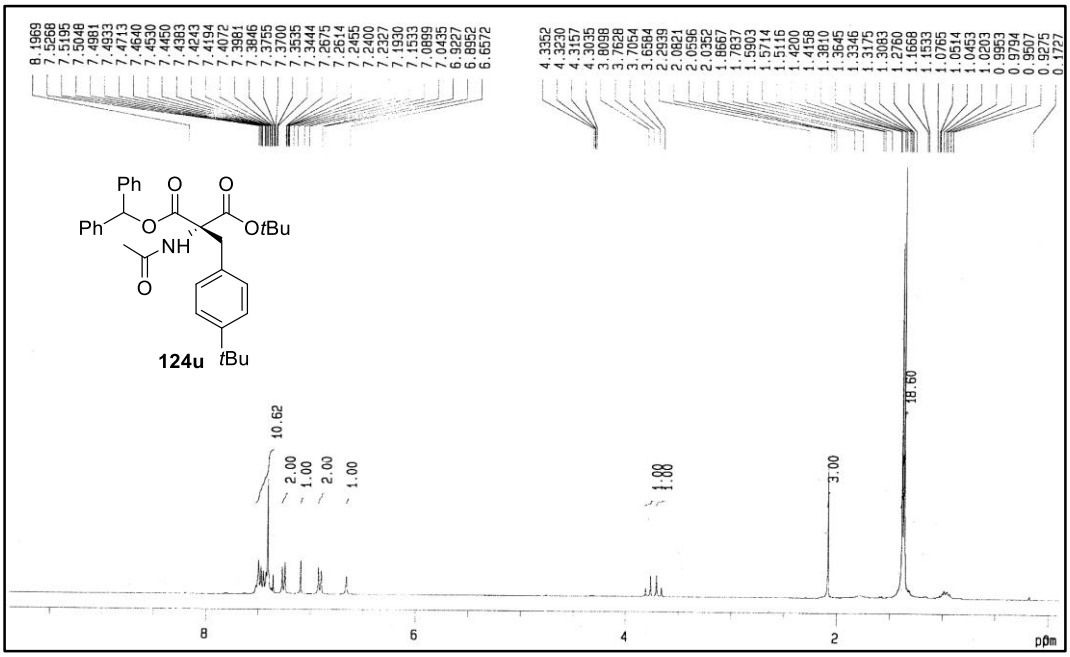
^{1}H-NMR of compound **124t** (300 MHz, $CDCl_3$)



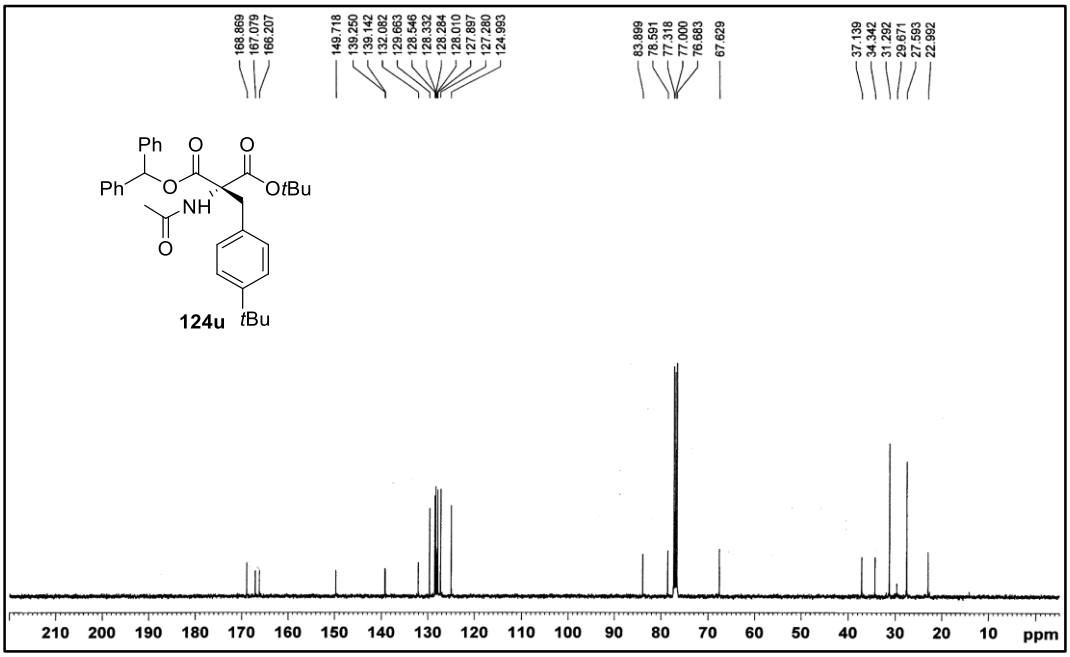
^{13}C-NMR of compound **124t** (125 MHz, $CDCl_3$)



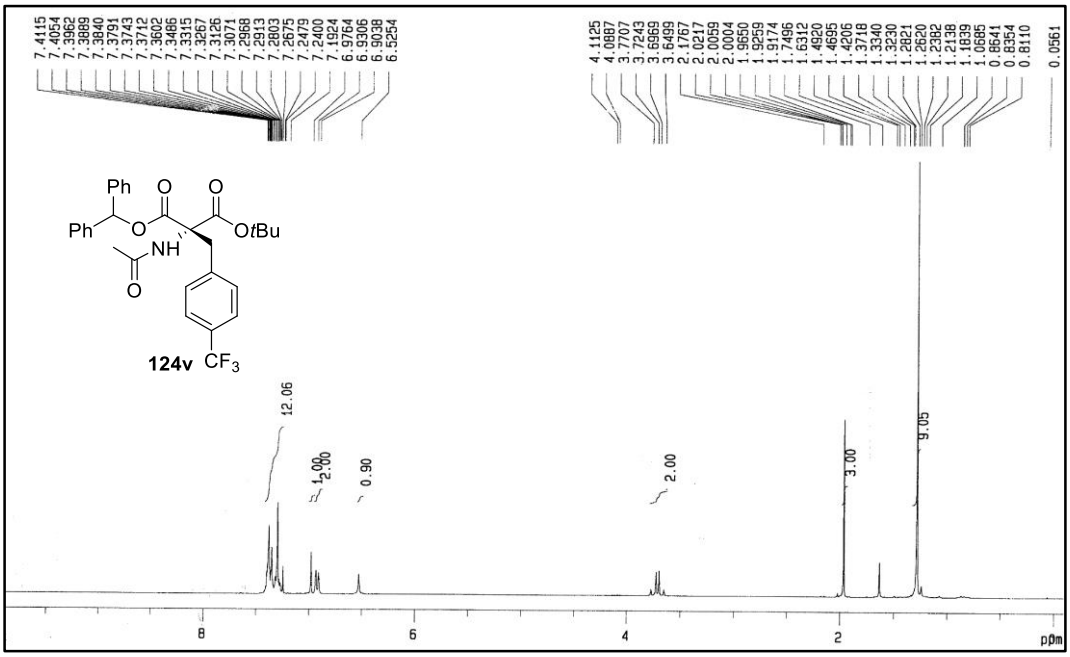
^{1}H-NMR of compound **124u** (300 MHz, $CDCl_3$)



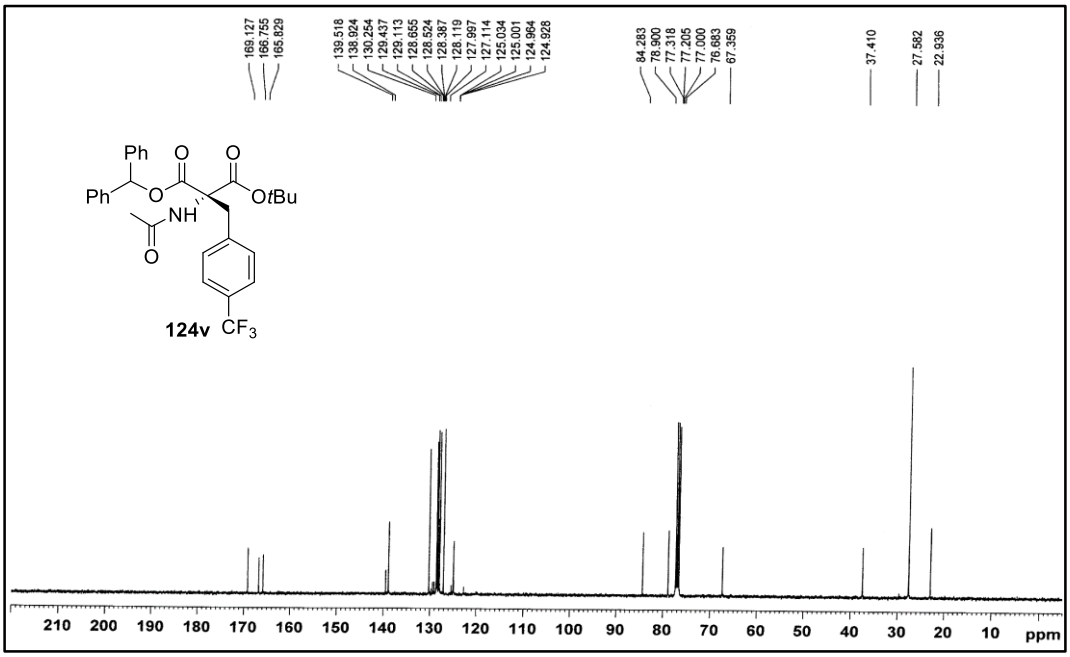
^{13}C-NMR of compound **124u** (125 MHz, $CDCl_3$)



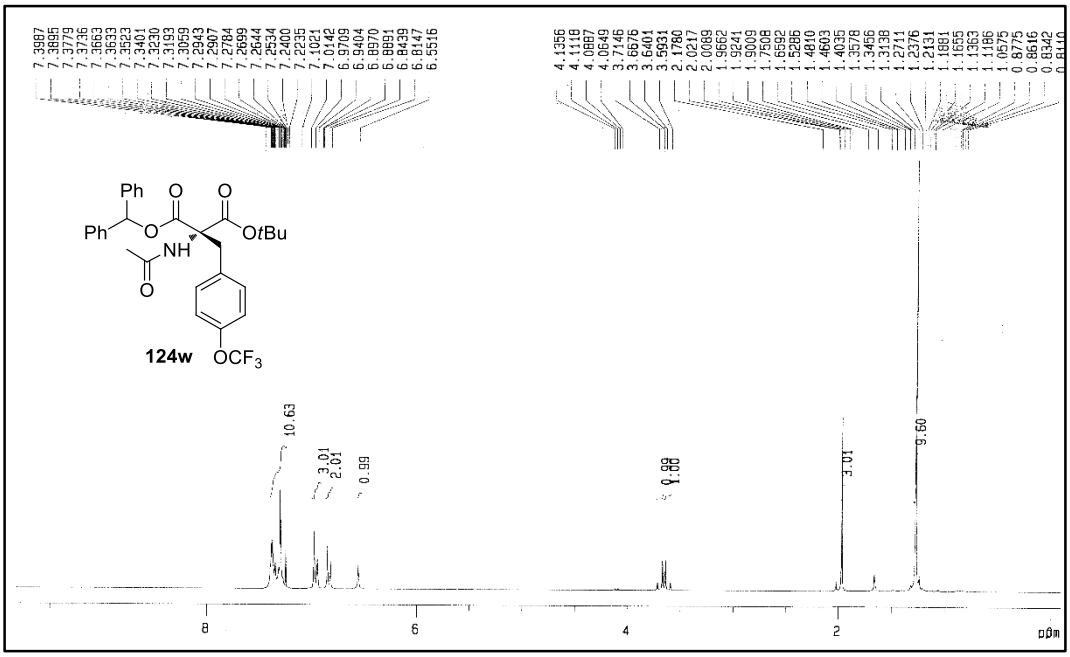
^{1}H-NMR of compound **124v** (300 MHz, $CDCl_3$)



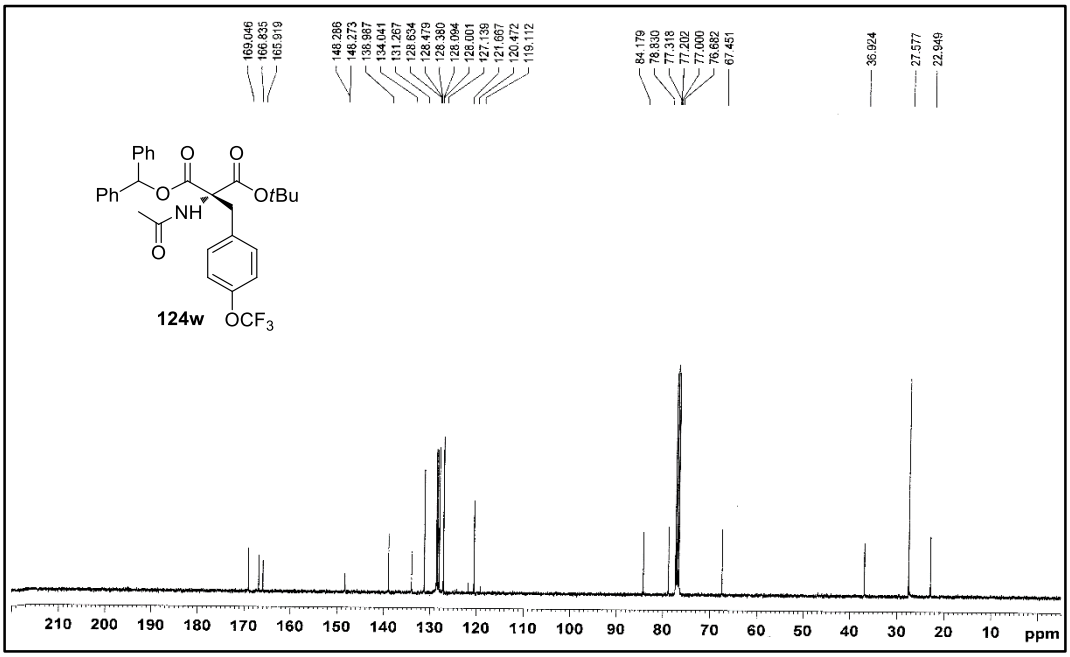
^{13}C-NMR of compound **124v** (125 MHz, $CDCl_3$)



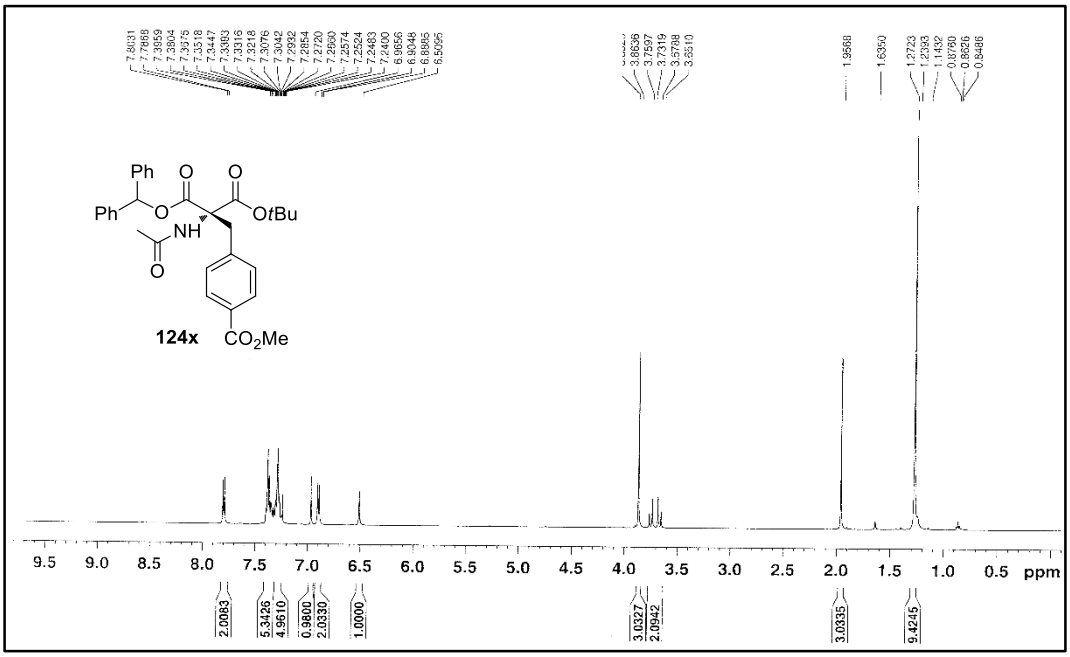
^{1}H-NMR of compound **124w** (300 MHz, $CDCl_3$)



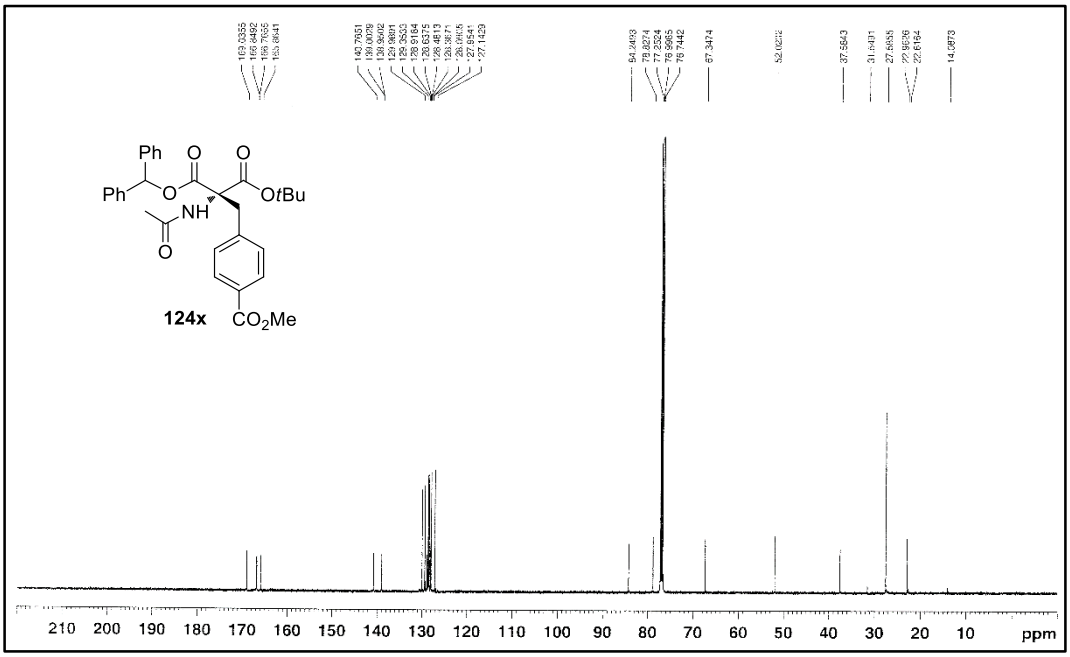
^{13}C-NMR of compound **124w** (125 MHz, $CDCl_3$)



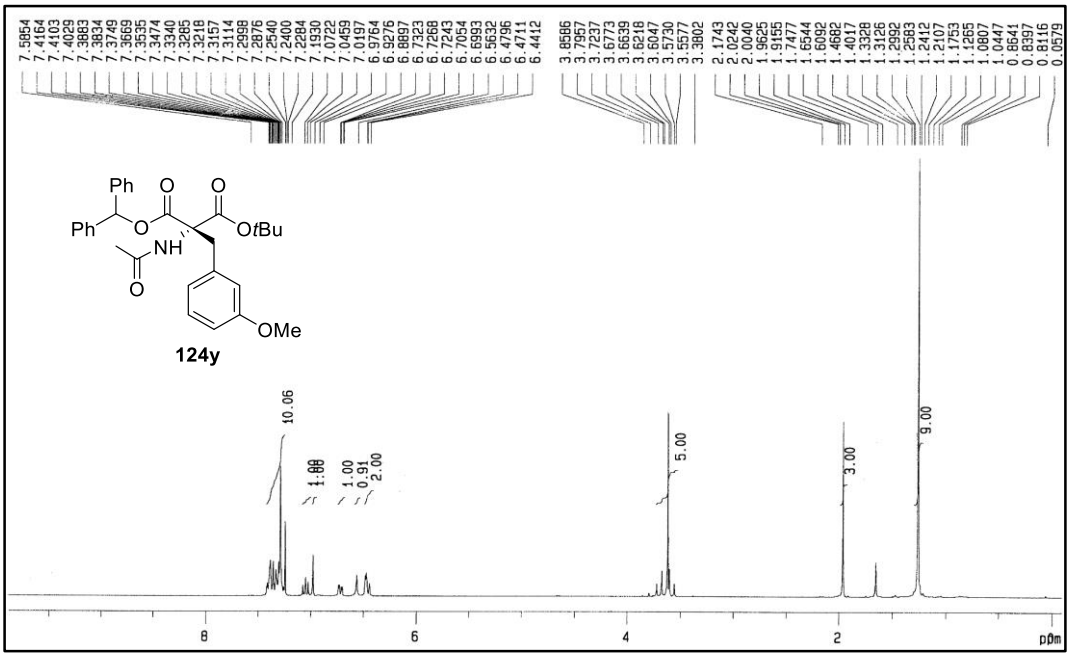
^{1}H-NMR of compound **124x** (500 MHz, $CDCl_3$)



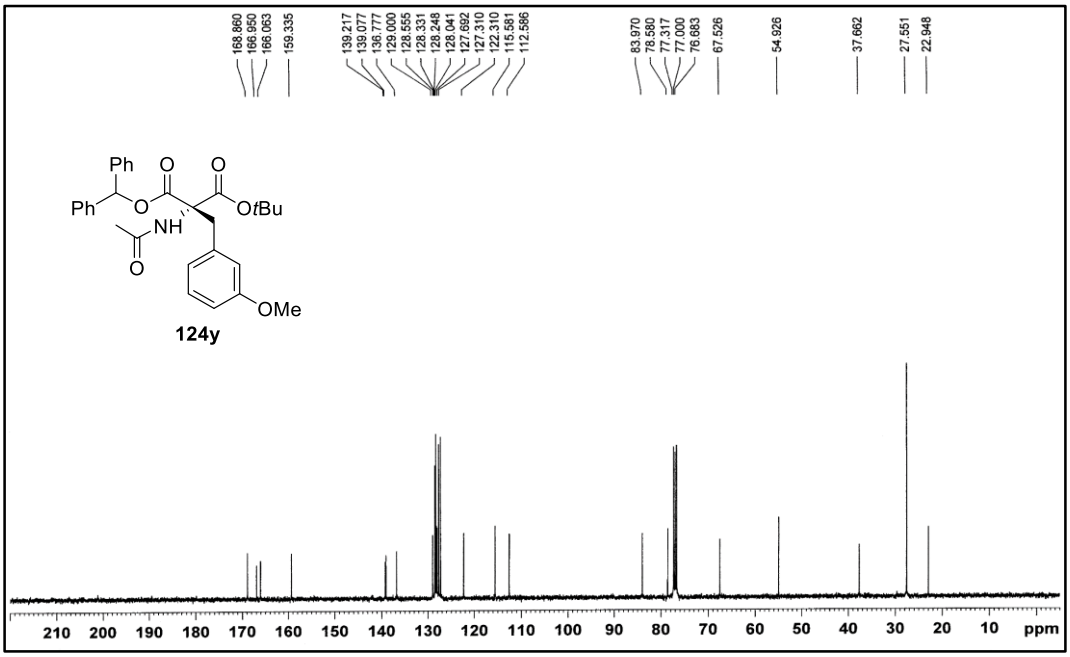
^{13}C-NMR of compound **124x** (100 MHz, $CDCl_3$)



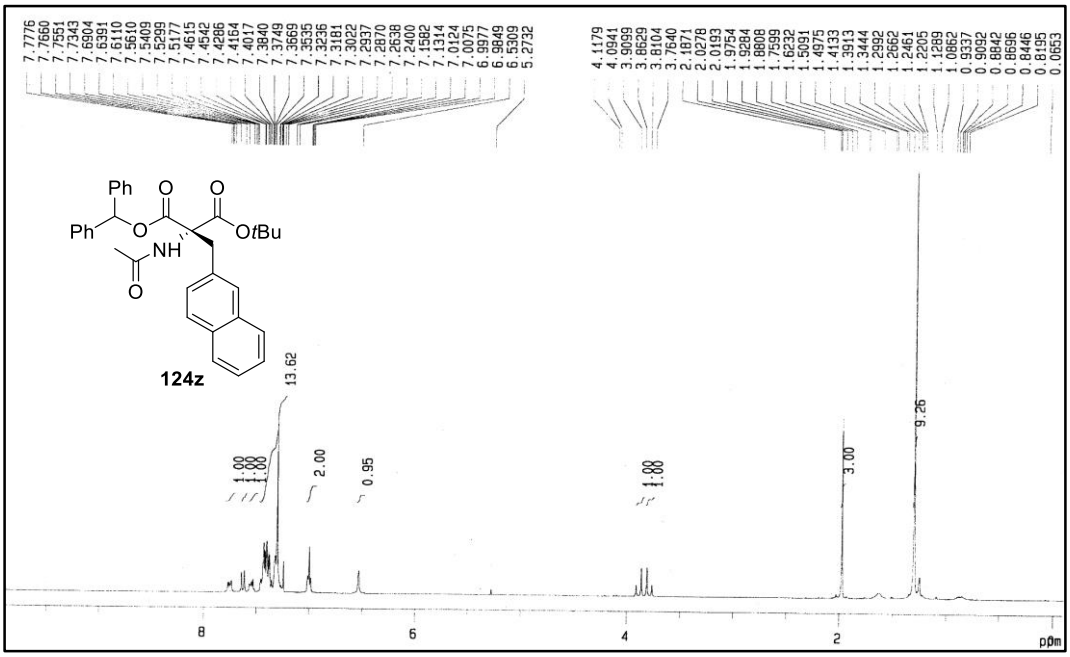
^{1}H-NMR of compound **124y** (300 MHz, $CDCl_3$)



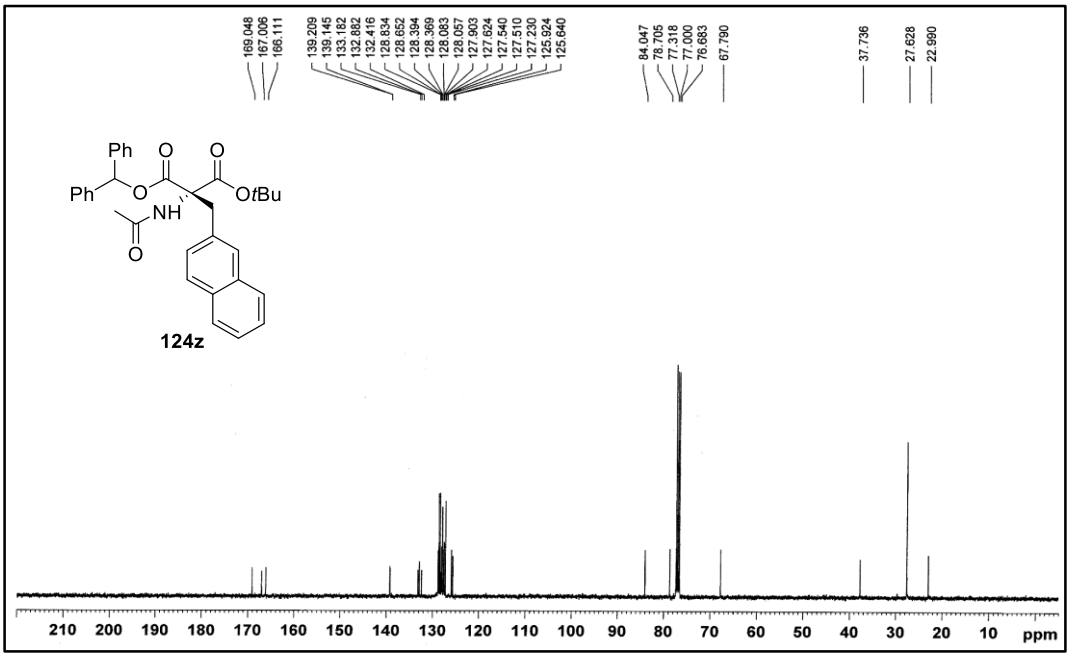
^{13}C-NMR of compound **124y** (125 MHz, $CDCl_3$)



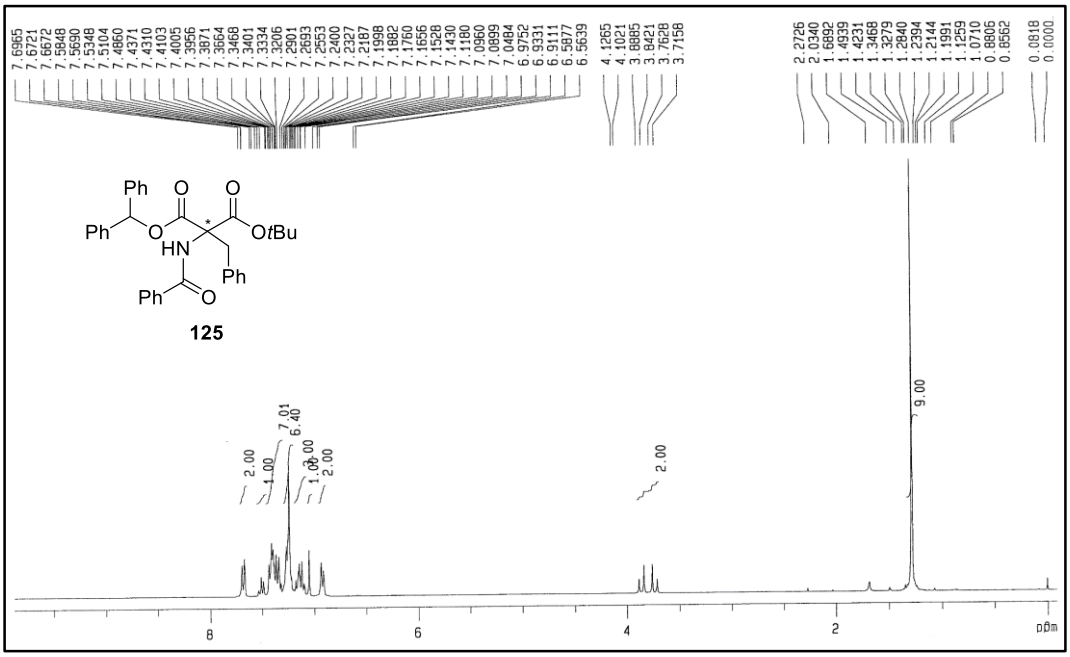
^{1}H-NMR of compound **124z** (300 MHz, $CDCl_3$)



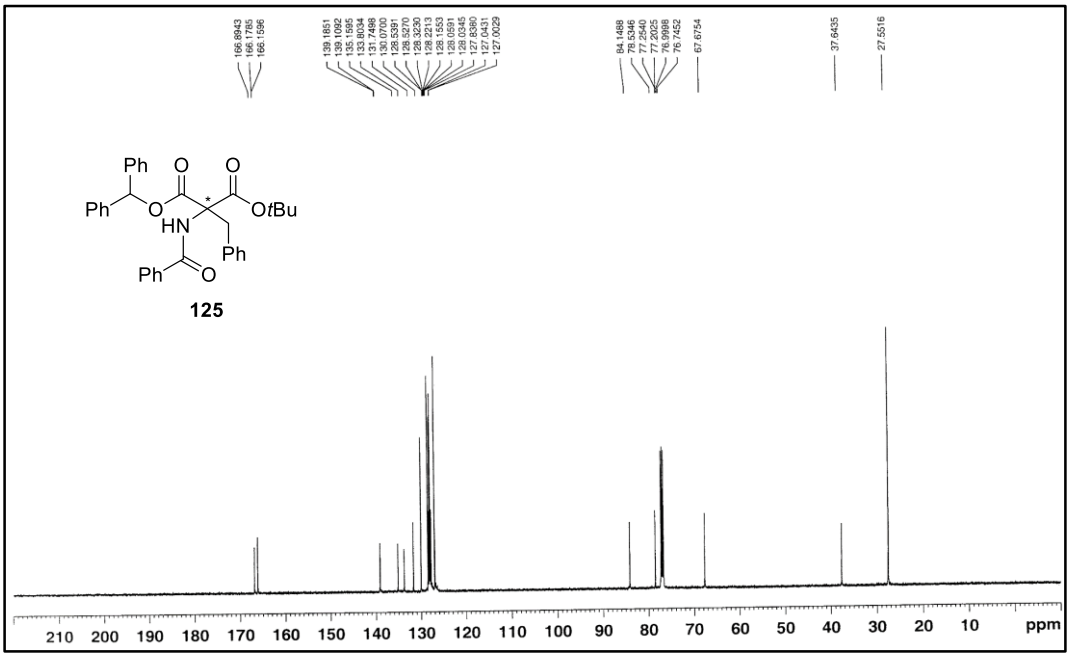
^{13}C-NMR of compound **124z** (125 MHz, $CDCl_3$)



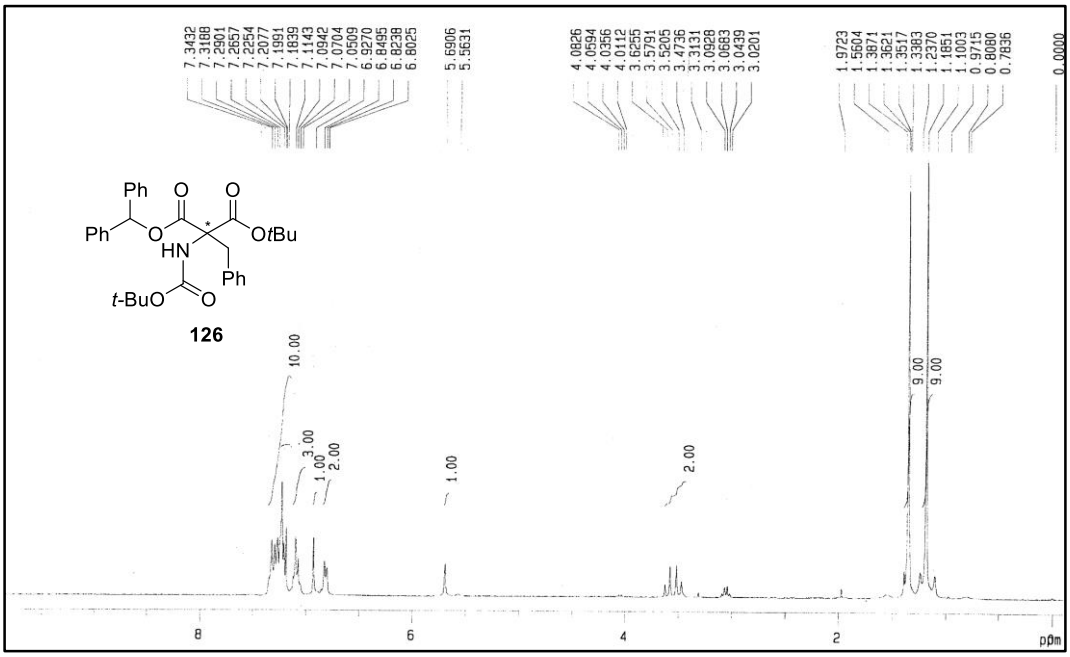
^{1}H-NMR of compound **125** (300 MHz, $CDCl_3$)



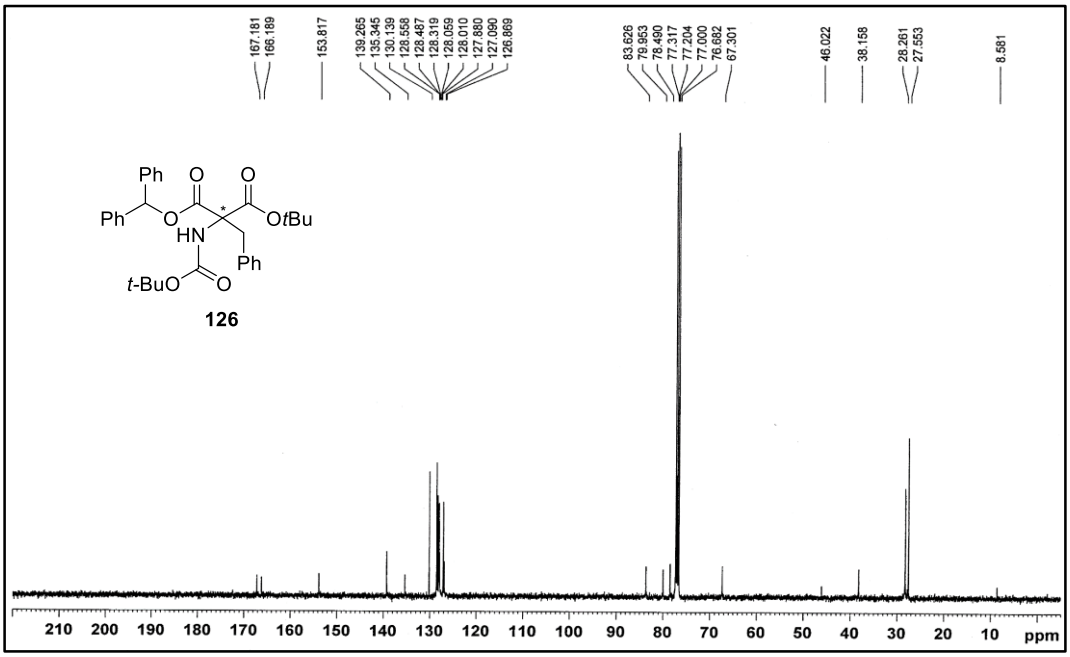
^{13}C-NMR of compound **125** (125 MHz, $CDCl_3$)



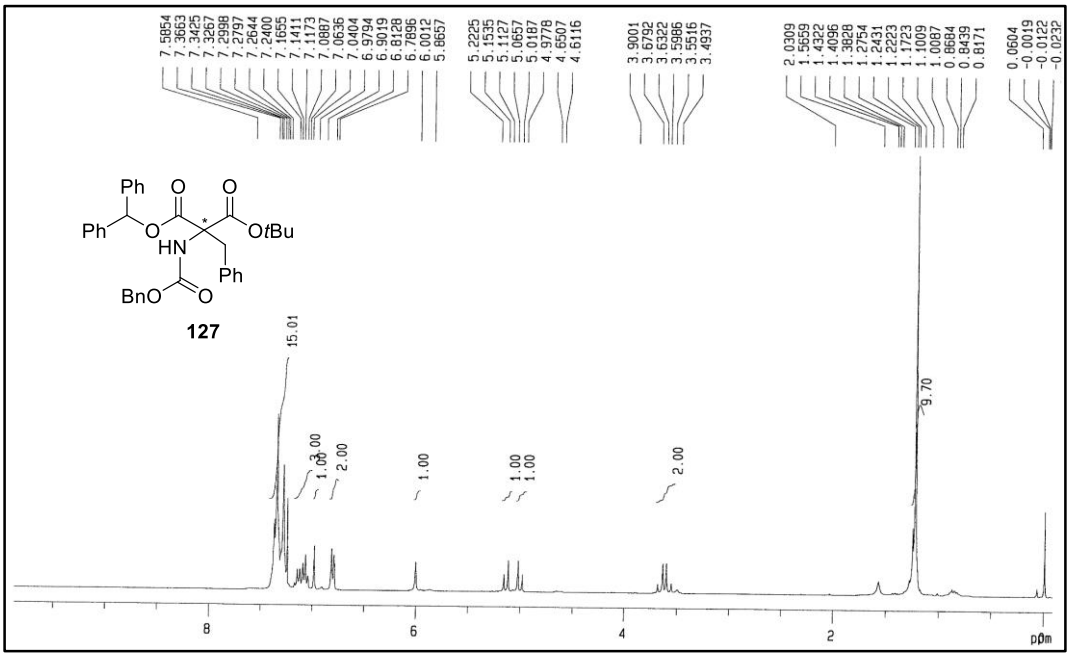
^{1}H-NMR of compound **126** (300 MHz, $CDCl_3$)



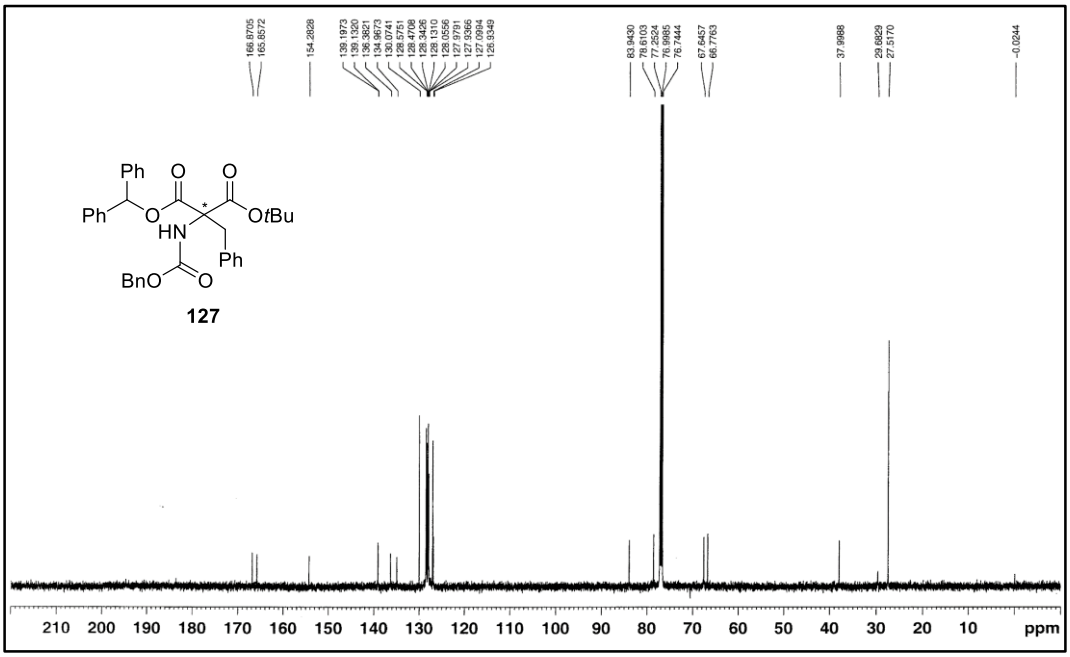
^{13}C-NMR of compound **126** (125 MHz, $CDCl_3$)



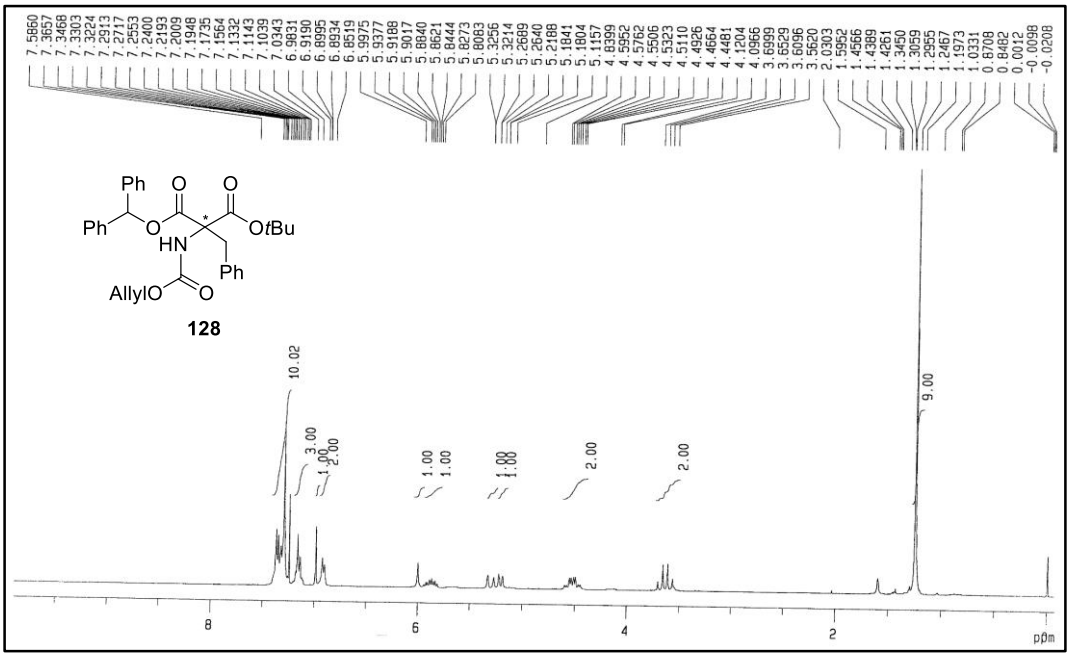
^{1}H-NMR of compound **127** (300 MHz, $CDCl_3$)



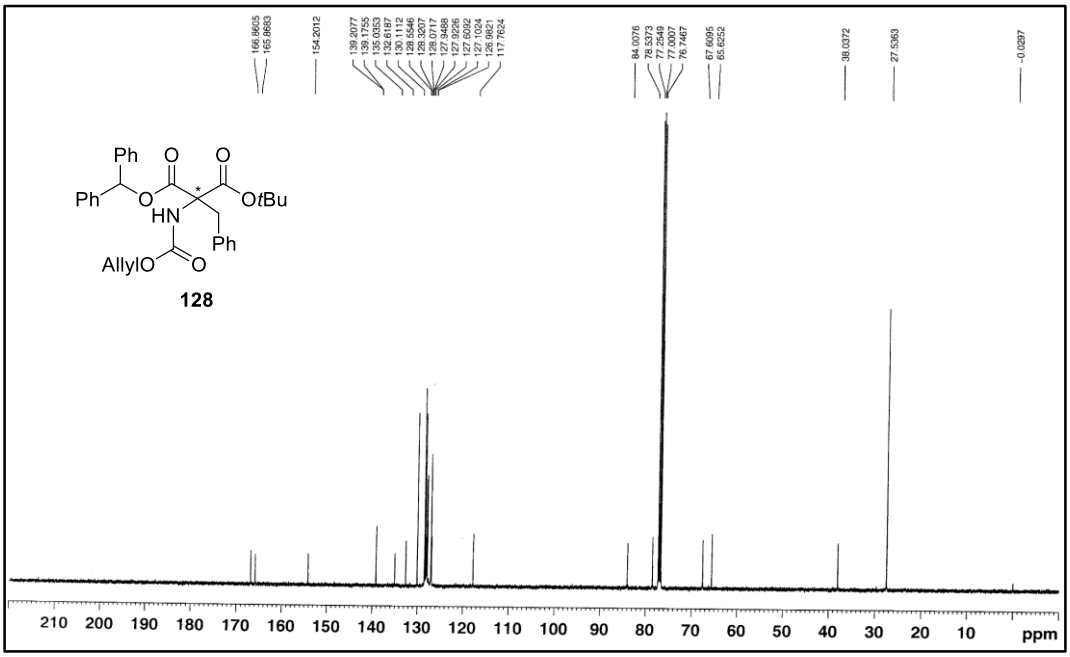
^{13}C-NMR of compound **127** (125 MHz, $CDCl_3$)



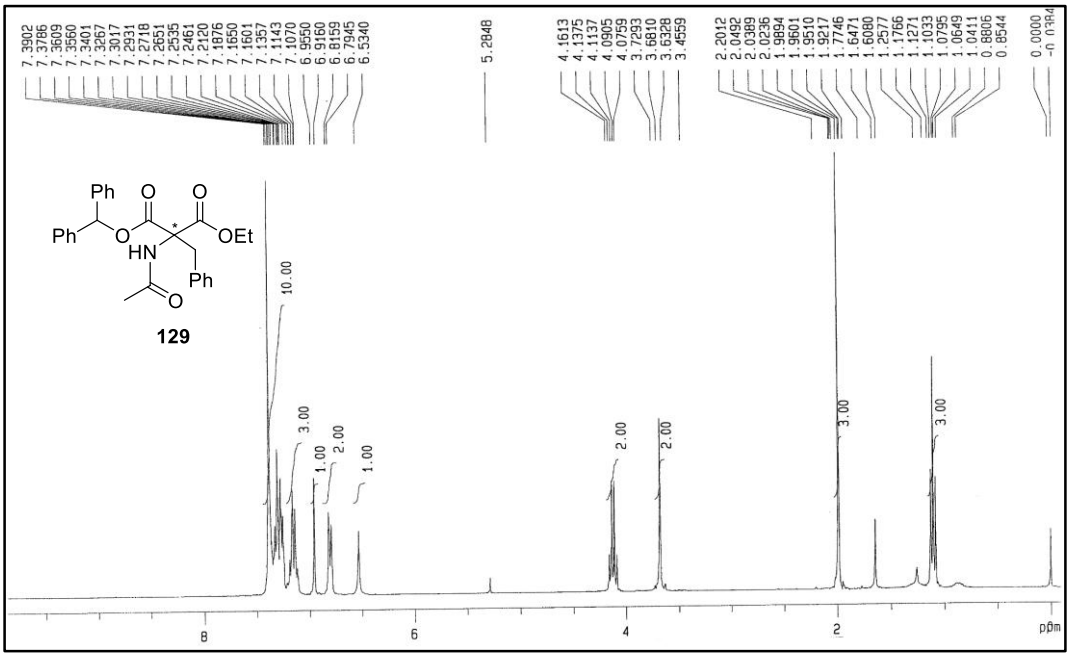
^{1}H-NMR of compound **128** (300 MHz, $CDCl_3$)



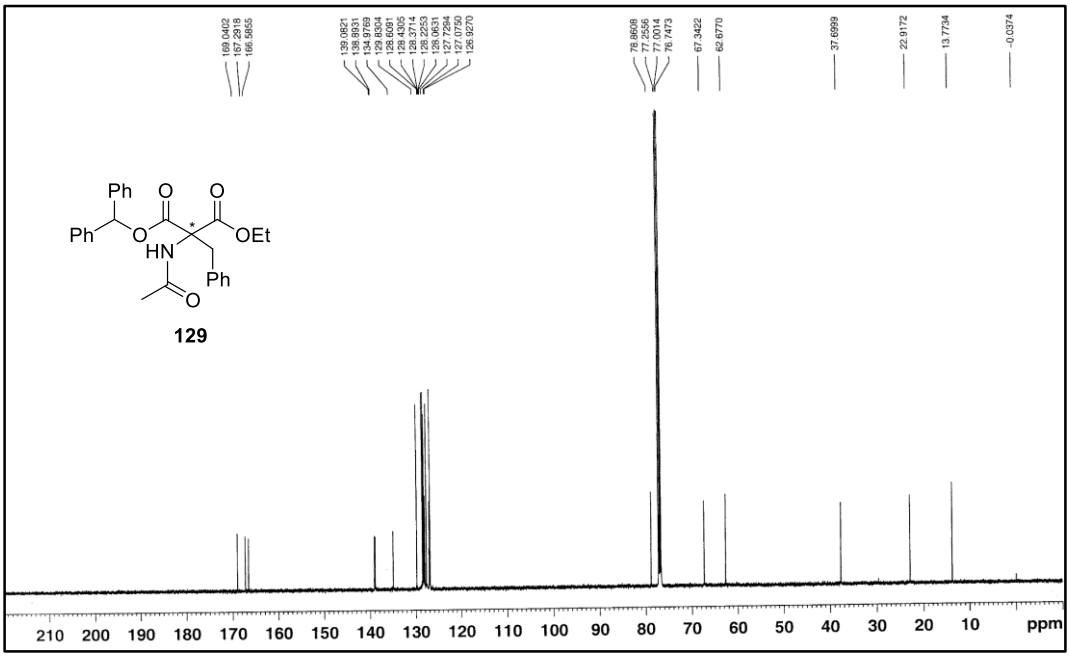
^{13}C-NMR of compound **128** (125 MHz, $CDCl_3$)



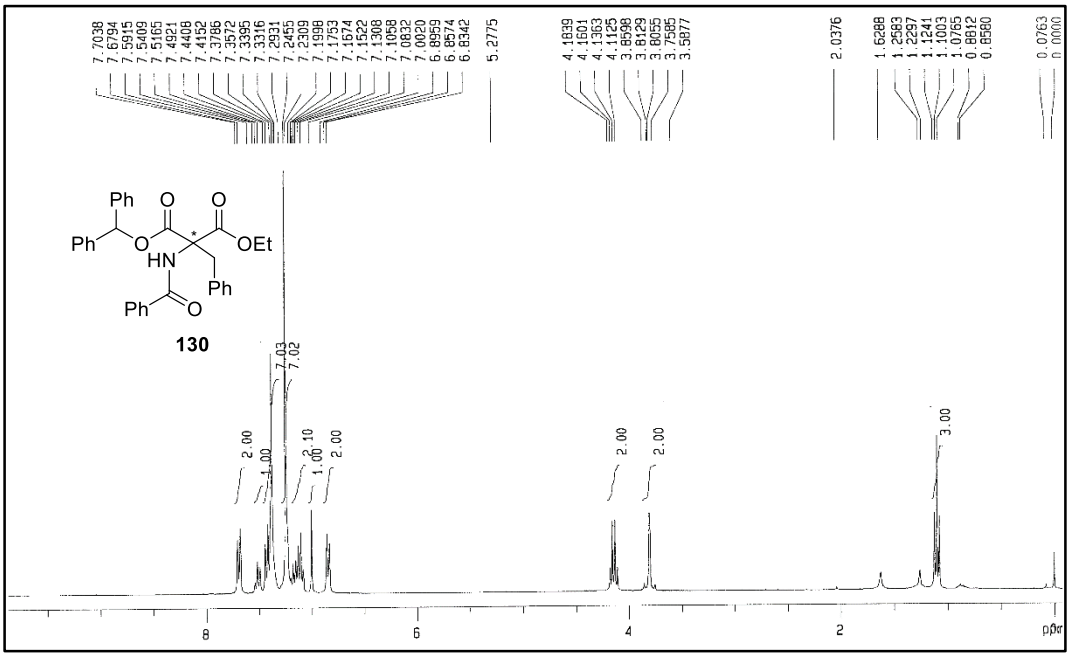
^{1}H-NMR of compound **129** (300 MHz, $CDCl_3$)



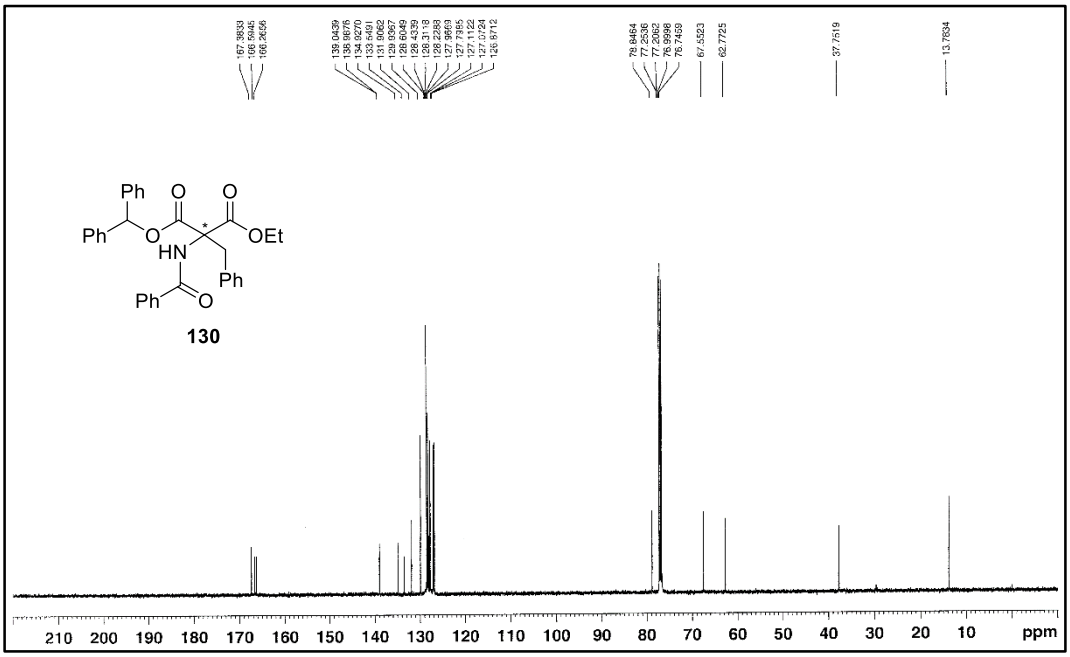
^{13}C-NMR of compound **129** (125 MHz, $CDCl_3$)



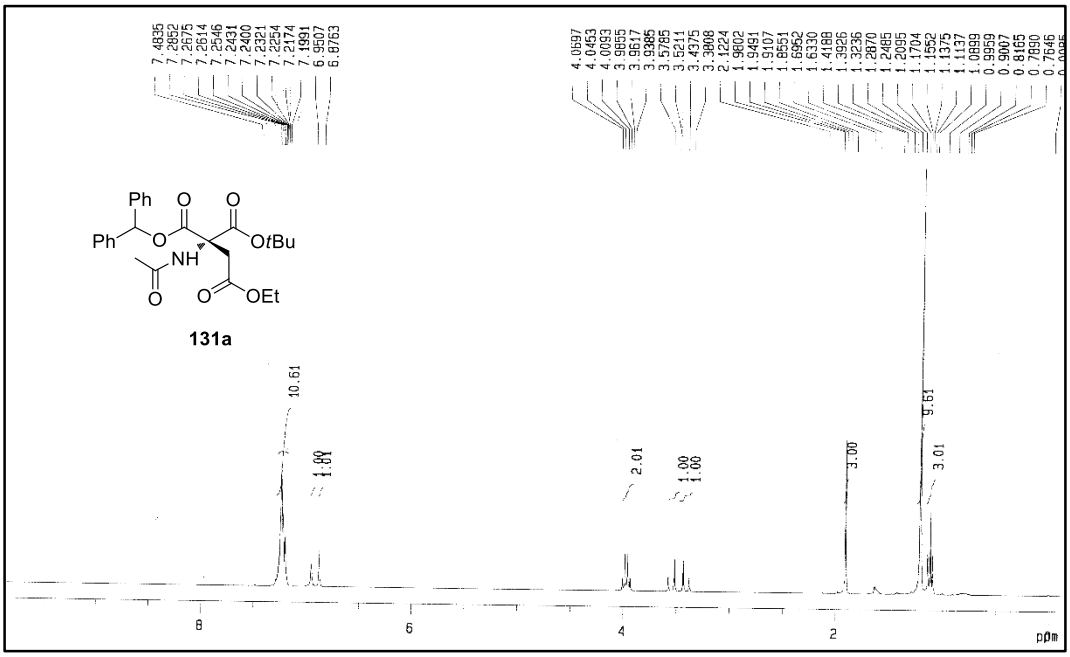
^{1}H-NMR of compound **130** (300 MHz, $CDCl_3$)



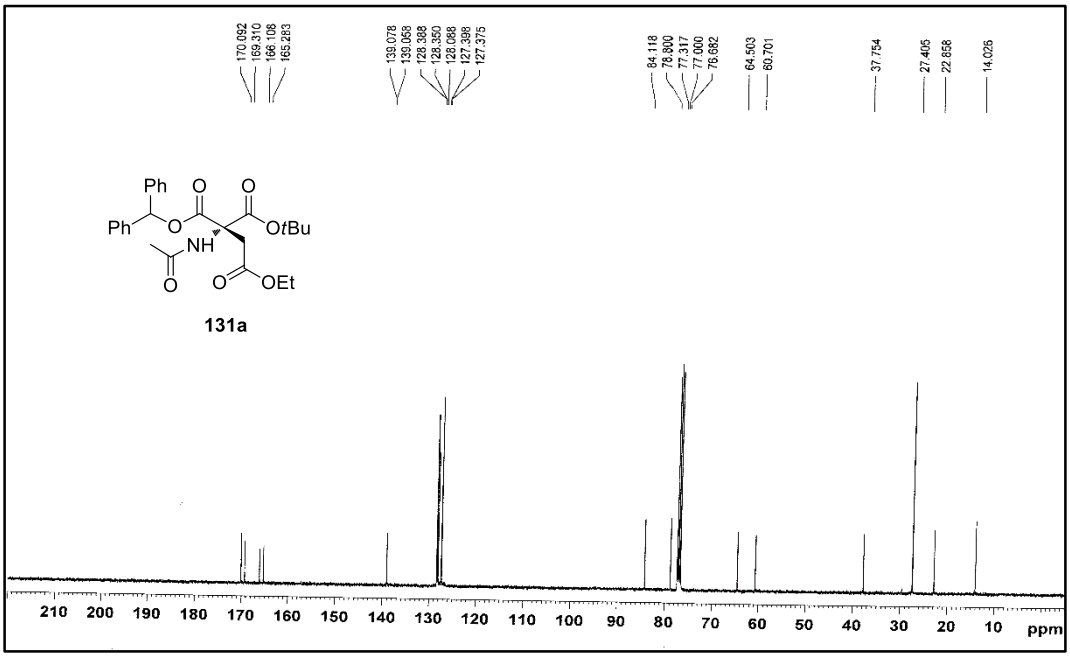
^{13}C-NMR of compound **130** (125 MHz, $CDCl_3$)



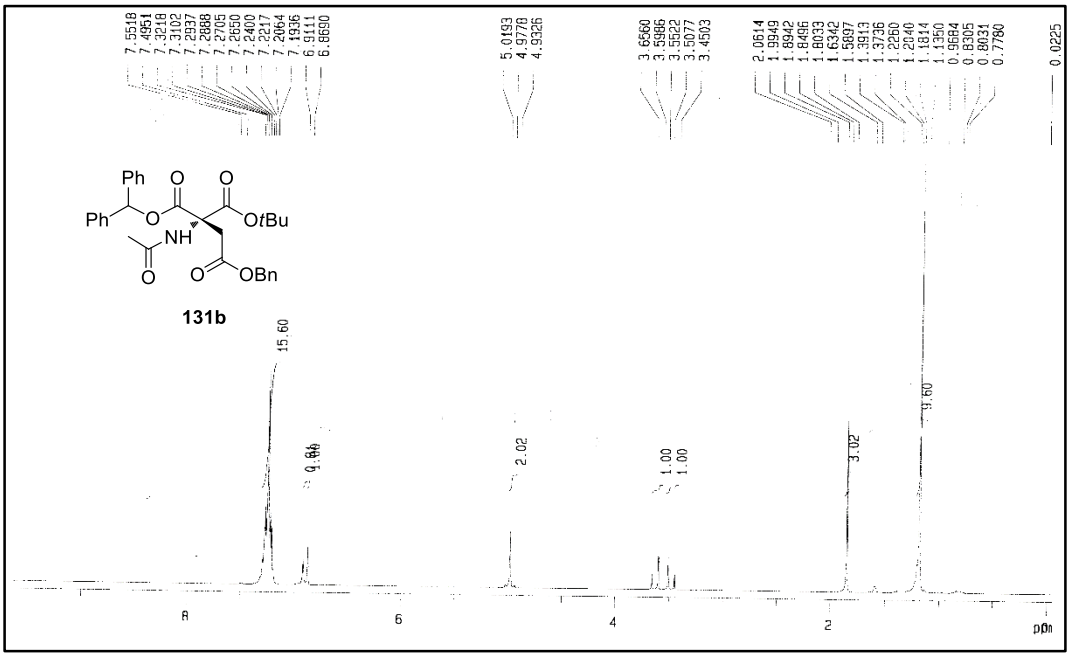
^{1}H-NMR of compound **131a** (300 MHz, $CDCl_3$)



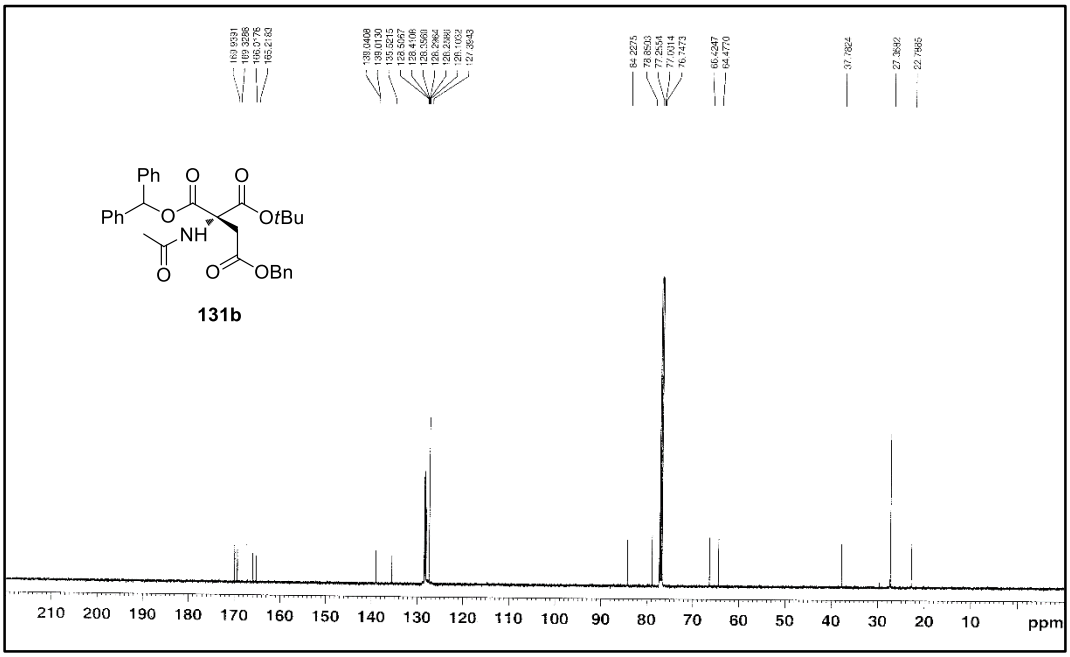
^{13}C-NMR of compound **131a** (125 MHz, $CDCl_3$)



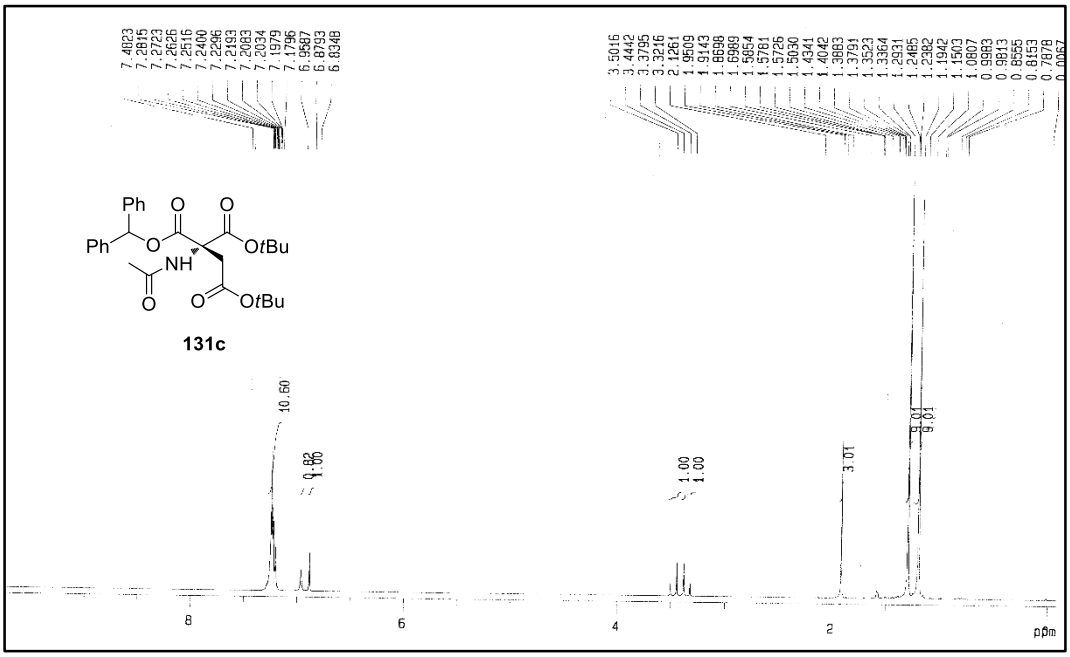
^{1}H-NMR of compound **132b** (300 MHz, $CDCl_3$)



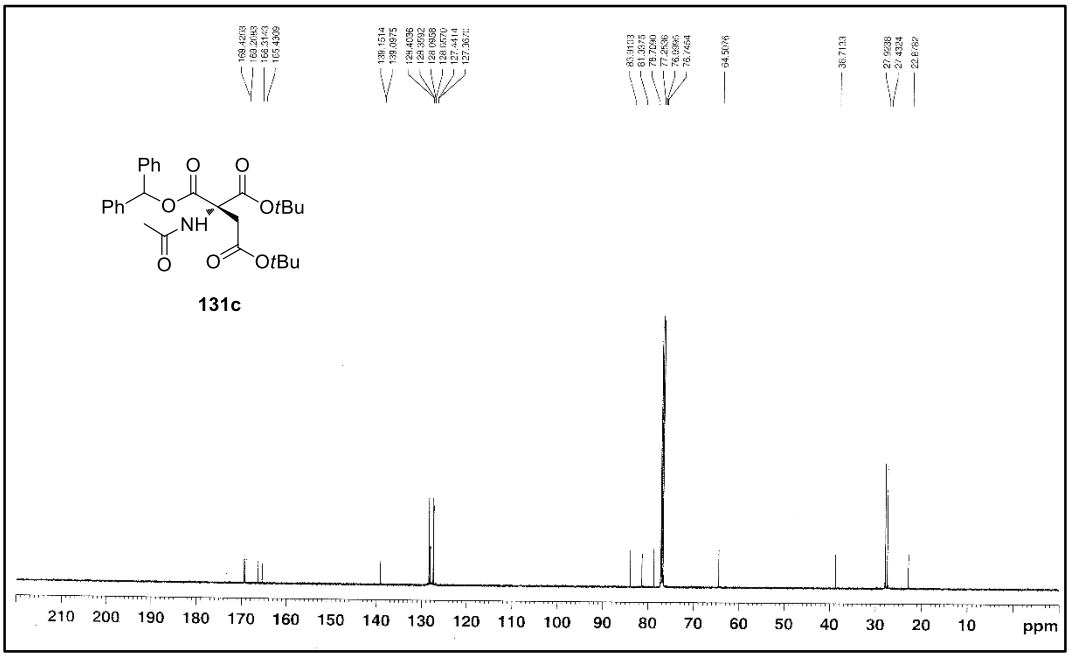
^{13}C-NMR of compound **132b** (125 MHz, $CDCl_3$)



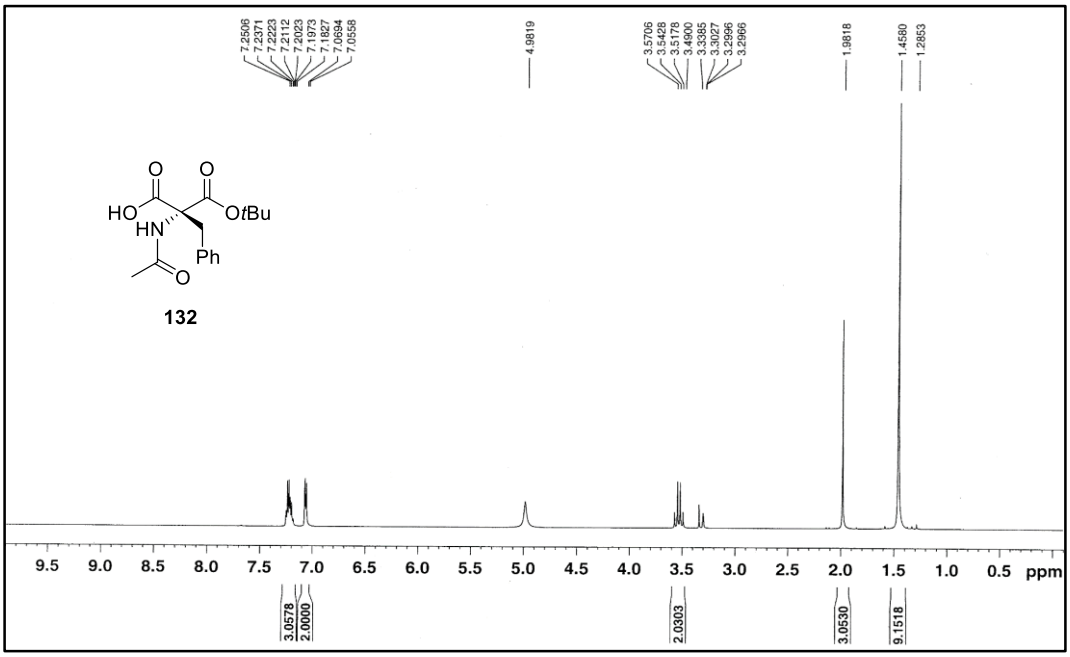
^{1}H-NMR of compound **131c** (300 MHz, $CDCl_3$)



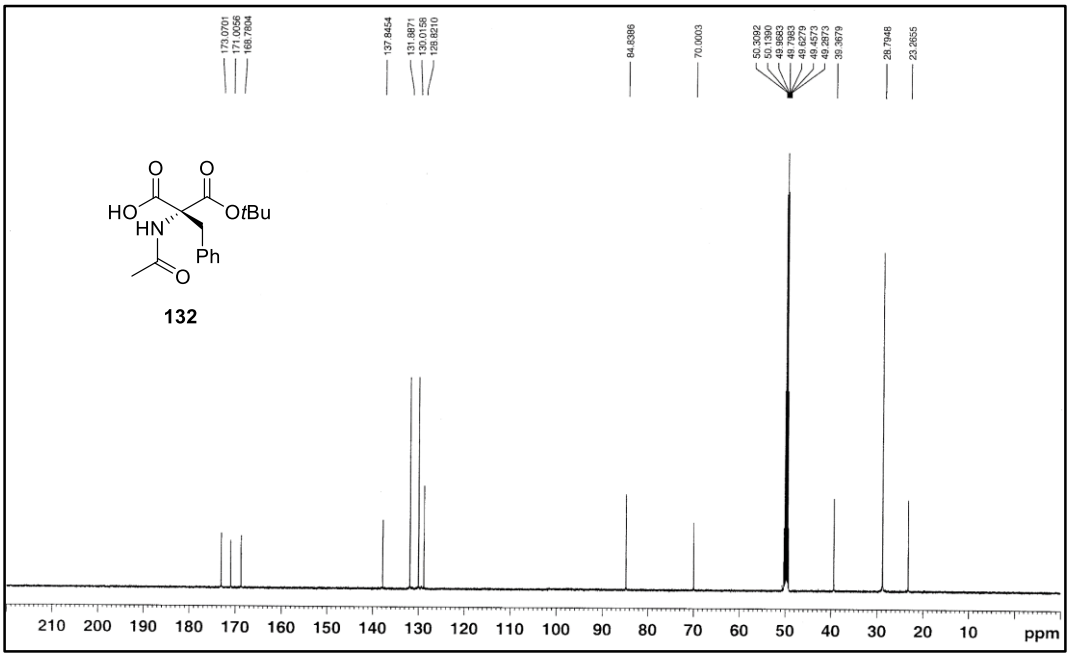
^{13}C-NMR of compound **131c** (125 MHz, $CDCl_3$)



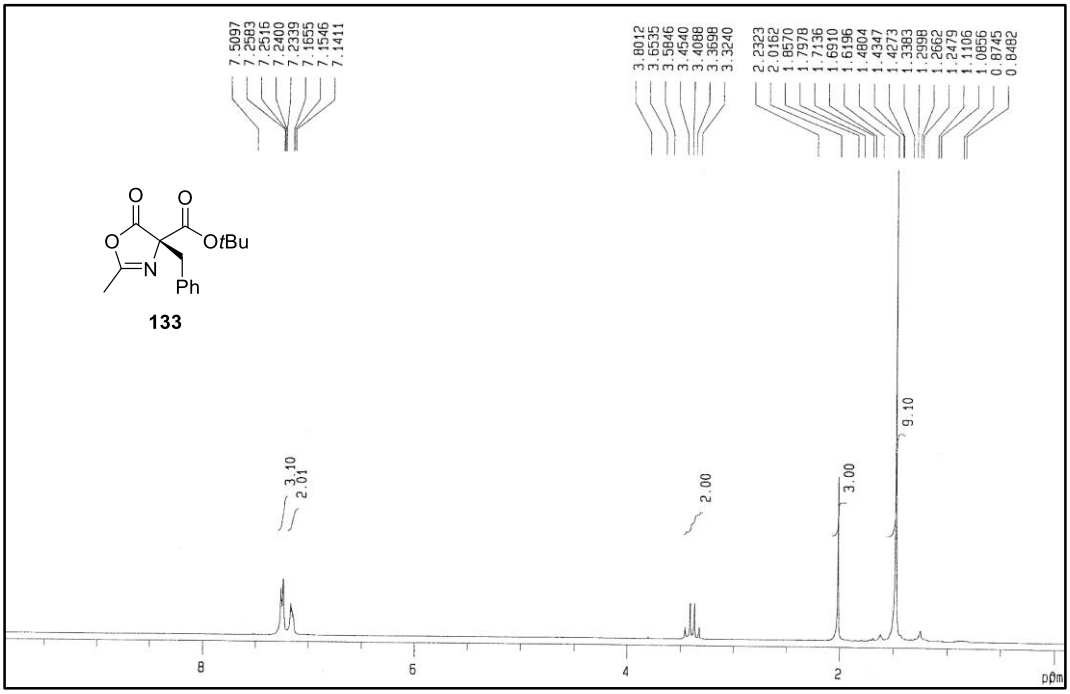
^{1}H-NMR of compound **132** (500 MHz, CD_3OD)



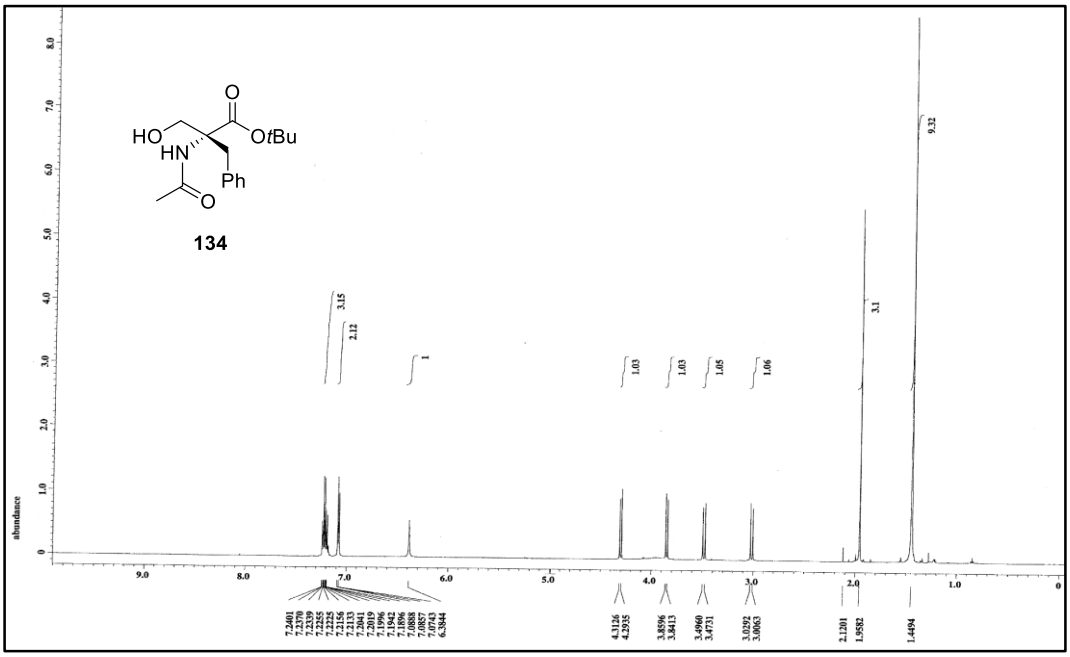
^{13}C-NMR of compound **132** (125 MHz, CD_3OD)



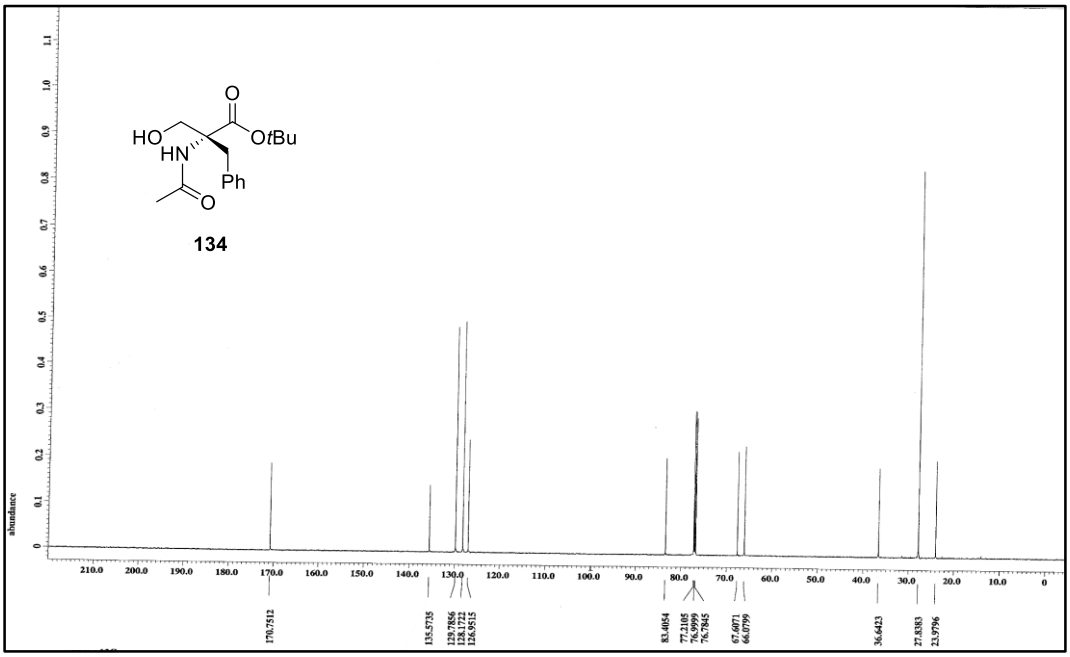
^{1}H-NMR of compound **133** (300 MHz, $CDCl_3$)



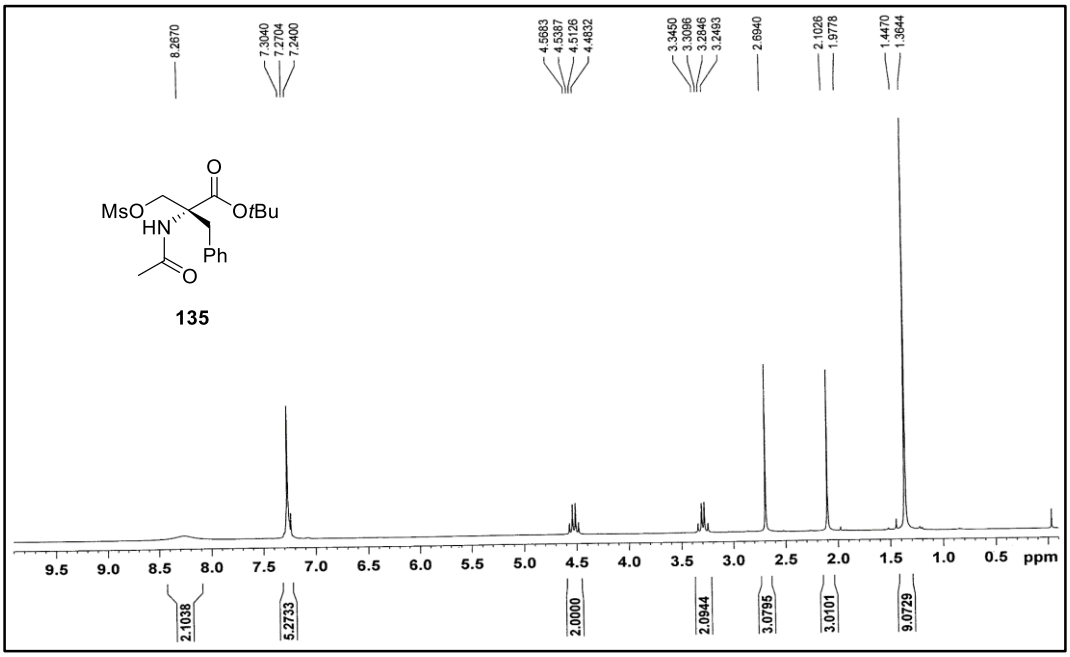
^{1}H-NMR of compound **134** (600 MHz, $CDCl_3$)



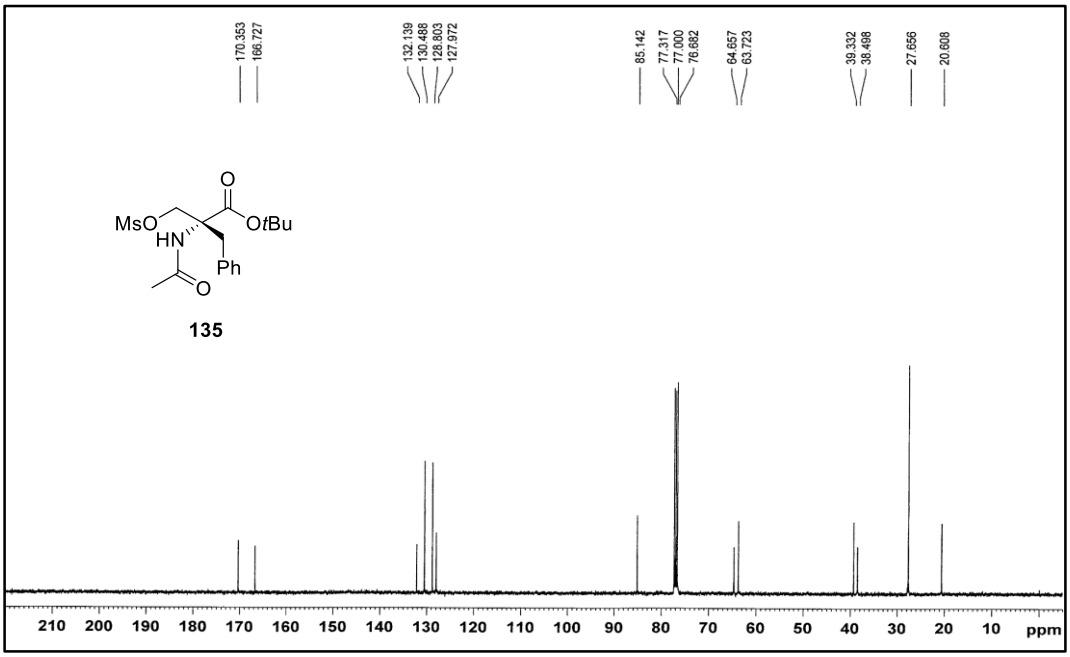
^{13}C-NMR of compound **134** (150 MHz, $CDCl_3$)



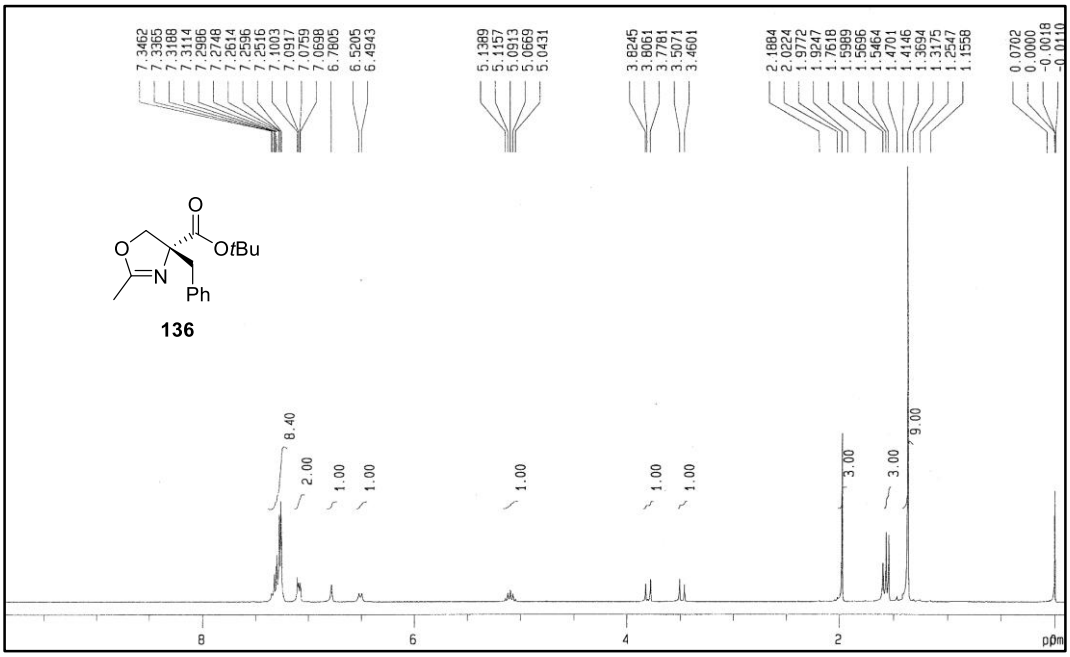
^{1}H-NMR of compound **135** (500 MHz, $CDCl_3$)



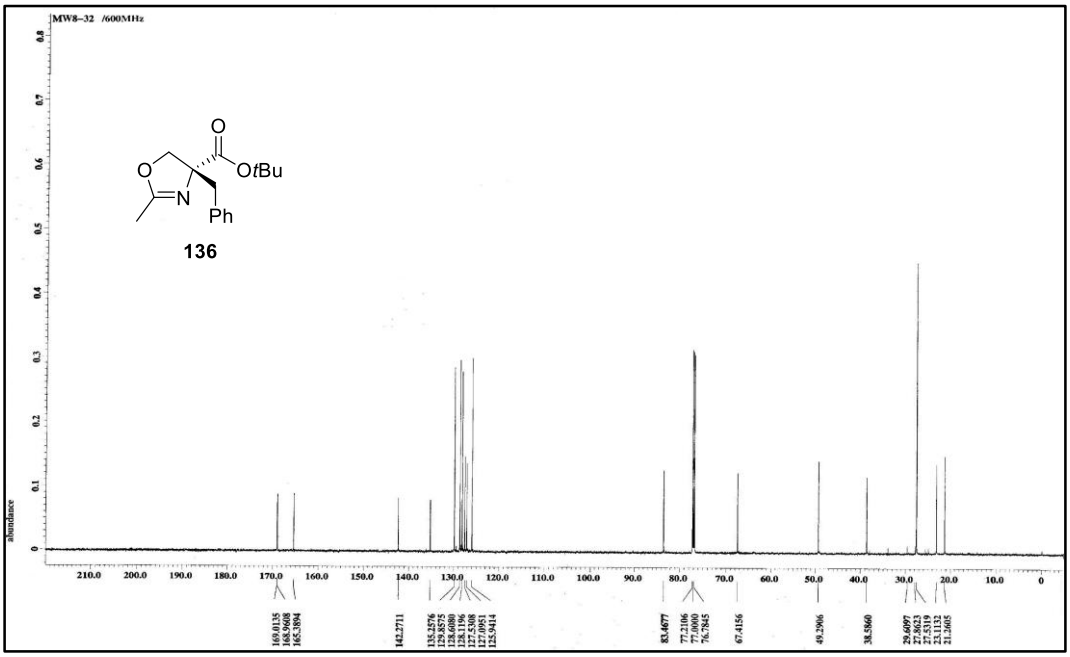
^{13}C-NMR of compound **135** (125 MHz, $CDCl_3$)



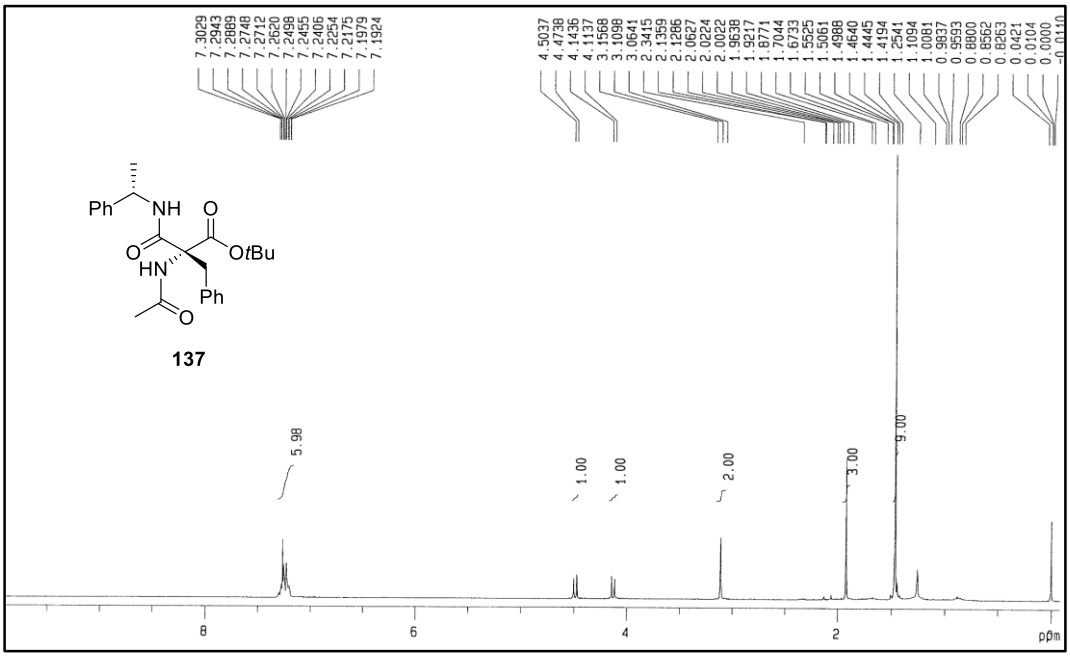
^{1}H-NMR of compound **136** (300 MHz, $CDCl_3$)



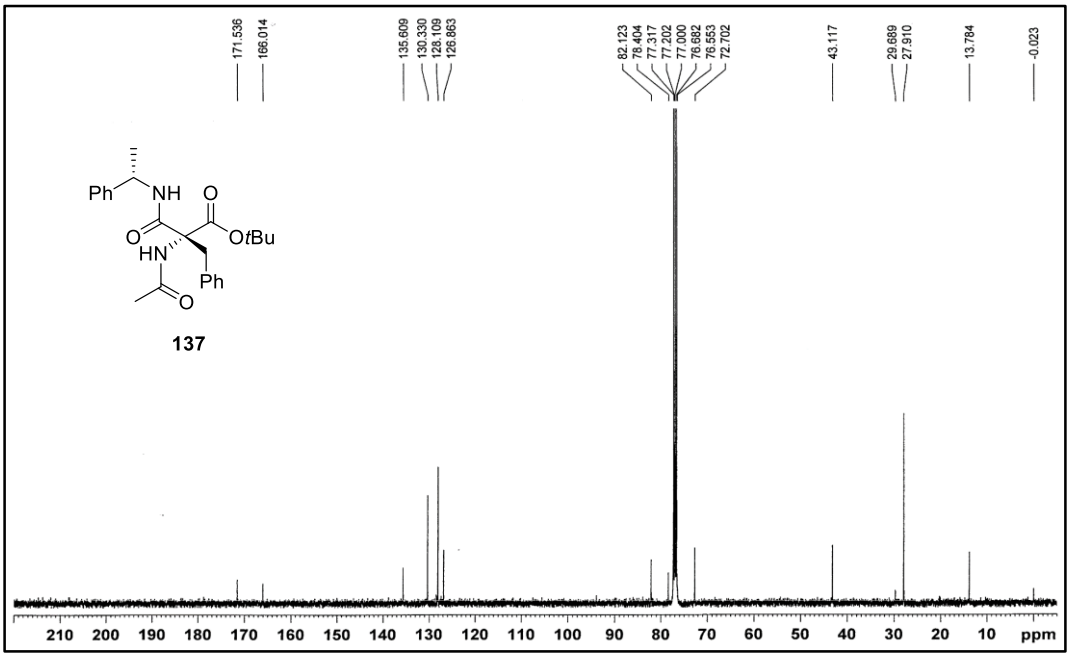
^{13}C-NMR of compound **136** (150 MHz, $CDCl_3$)



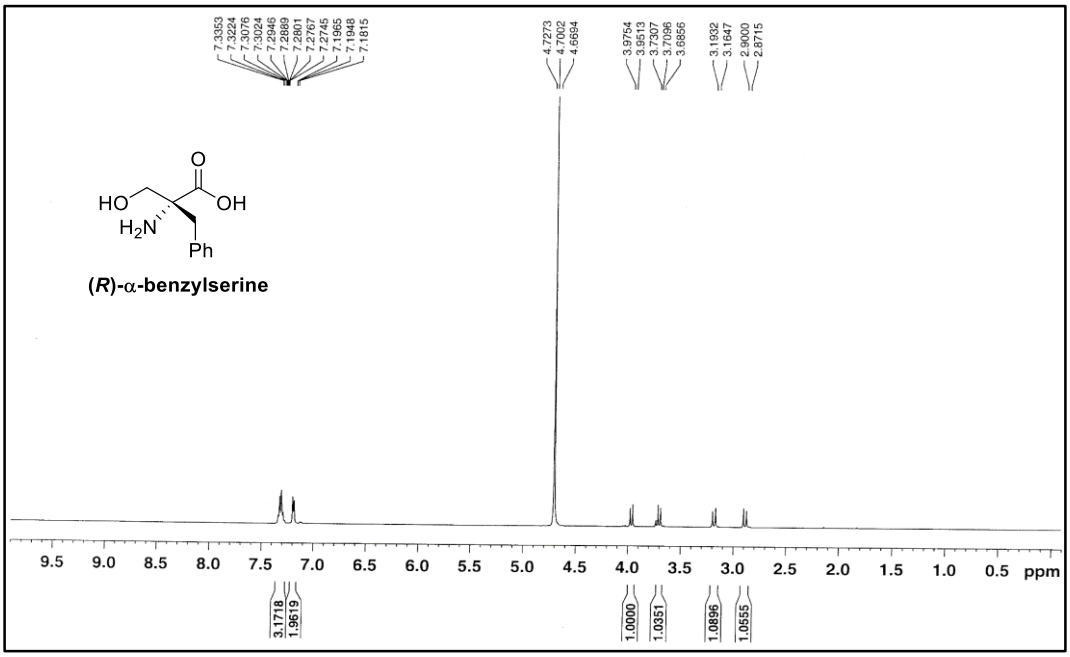
^{1}H-NMR of compound **137** (300 MHz, $CDCl_3$)



^{13}C-NMR of compound **137** (125 MHz, $CDCl_3$)



^{1}H-NMR of compound (*R*)-**α-benzylserine** (500 MHz, D_2O)



^{13}C-NMR of compound (*R*)-**α-benzylserine** (125 MHz, D_2O)