약학박사학위논문

A novel synthetic method for chiral α,α-dialkylmalonate *via* phase-transfer catalytic alkylation and its application to total synthesis of (–)-horsfiline

상전이 촉매 알킬화 반응을 통한 α,α-dialkylmalonate 의 새로운 비대칭 합성법 개발과 그 응용으로서 (–)-horsfiline 의 전합성

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ABSTRACT

Malonates are one of the most fundamental starting material in organic synthesis for C-C bond formation. Notably, chiral α,α-dialkylmalonates have been quite popularly employed in the synthesis of biologically active natural products and pharmaceuticals for the following reasons: the quaternary carbon center of chiral α,α-dialkylmalonates is not racemized, and malonates can be easily modified through chemical conversion of the two esters. In spite of these advantages, chiral malonates can only be obtained by the desymmetrization of (±)-α,α-dialkylmalonates or (±)-α,α-dialkylmalonic acids through enzymatic resolution using the selective hydrolysis of malonates or the selective esterification of malonic acids, respectively. Although the construction of chiral quaternary carbon centers through the asymmetric α-alkylation of carbonyl systems and β-ketoester systems has been extensively studied, to date, the enantioselective direct α-alkylation of malonates has not been reported. Our research team investigated a novel enantioselective synthesis of α,α-dialkylmalonates *via* direct α-alkylation under phase-transfer catalytic condition.

First, our research team attempted the α-benzylation of benzyl *tert*-butyl α-methylmalonate under typical phase-transfer catalytic conditions. This enantioselective phase-transfer catalytic benzylation was performed using representative chiral phase-transfer catalysts. Of them, (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide surprisingly afforded the α-benzylated product with 70% of enantioselectivity. Five additional alkyl *tert*-butyl α-*mono*-methylmalonates were tested in phase-transfer catalytic benzylation and the diphenylmethyl group gave the best enantioselectivity. This substrate was chosen for further investigation of phase-transfer catalytic alkylation with various alkyl halides, and it showed very high chemical yields (up to 99%) and stereoselectivities (up to 97% ee). Additionally, our research team expanded the substrate scope to α-*mono*-aryl and

halo-malonates, and these substrates also showed high enantioselectivities. Notably, the direct, double α-alkylations of diphenylmethyl *tert*-butyl malonate also provided the corresponding α,α-dialkylmalonates without the loss of enantioselectivity.

The high enantioselectivities and the mild reaction conditions could make this method very useful for the synthesis of valuable chiral building blocks. The synthetic potential of this method has been demonstrated by the preparation of α,α-dialkylamino acid and oxyindole systems. The spirooxindole structure is frequently found in biologically active oxyindoles. Their unique spiro structures have challenged many synthetic chemists to develop an efficient synthetic method. Among the various spirooxindole alkaloids, (–)-horsfiline was first isolated in 1991 from the leaves of the *Horsfieldia superba* plant. Our research team attempted to apply our method to the synthesis of the chiral spirooxindole alkaloid (–)-horsfiline. A new and efficient synthetic method for the preparation of (–)-horsfiline *via* the enantioselective phase-transfer catalytic α-allylation of malonate has been developed. (–)-Horsfiline was synthesized in 9 steps (including an in situ step) from diphenylmethyl *tert*-butyl malonate, and enantioselective phase-transfer catalytic alkylation was the key step (32% overall yield, >99% ee). The high enantioselectivity and chemical yield make this approach a practical route for the large-scale synthesis of spirooxindole natural products, thus enabling the systematic investigation of their biological activities.

Key words: asymmetric synthesis, phase-transfer catalysis, chiral malonate, α,α-dialkylmalonates, enantioselective total synthesis, spiro-oxindole, horsfiline

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INTRODUCTION

1. Chiral malonate derivatives

1.1. Outline of chiral malonates

Malonates are one of the most fundamental starting material in organic synthesis for C-C bond formation.[1] These are dicarbonyl compounds with two esters located in the β-positions. Depending on the substituents, the dicarbonyl compounds have either a pro-chiral or chiral α carbon center and the pKa can vary widely.

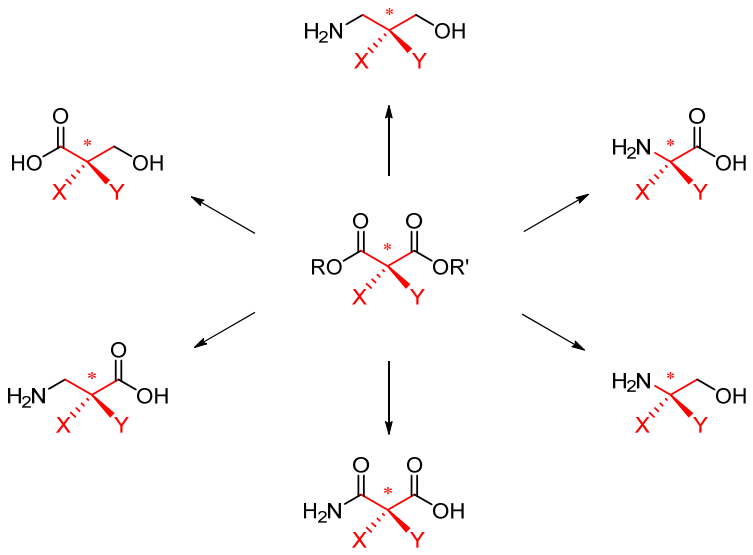


Figure 1. Various modifications of malonates

Among the dicarbonyl compounds, malonates which have two ester substituents at the β-positions, can have a chiral α carbon. Because the ester groups can be converted to various other functional groups, a chiral malonate can be converted into diverse chiral compounds (Figure 1). In addition to chiral malonates, their chiral derivatives can be intermediates in the synthesis of biologically active compounds. Chiral α,α-dialkylmalonates are especially resistant to racemization under normal reaction conditions and can be used in the synthesis of compounds with chiral quaternary carbon centers.

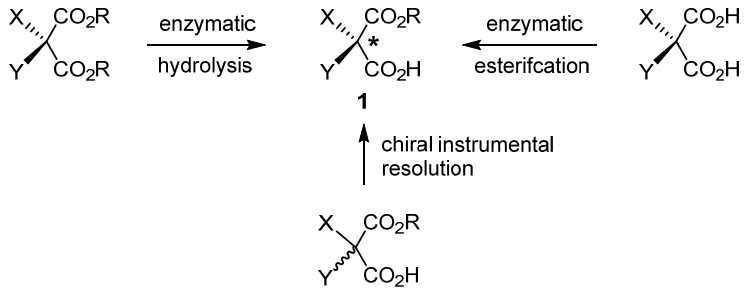


Figure 2. Current methods for obtaining chiral malonates

Therfore, chiral α,α-dialkylmalonates (**1**) have been used quite often for the construction of the chiral quaternary carbon centers of biologically active natural products and pharmaceuticals. At present, chiral malonates can only be obtained by the desymmetrization of (±)-α,α-dialkylmalonates or (±)-α,α-dialkylmalonic acids, which is achieved through enzymatic resolution via selective hydrolysis or selective esterification, respectively (Figure 2).[2] Alternatively, chiral malonates can be obtained from racemic α,α-dialkylmalonates through chiral instrumental resolution.

1.2. Enantioselective synthesis of dicarbonyl compounds

Chiral α-monoalkylmalonates are readily racemized under basic conditions due to the low pKa of the α-proton, which is not a concern for α,α-dialkylmalonates, as they have fully substituted quaternary α-carbon centers. The construction of this quaternary carbon centers is difficult due to steric repulsion between the substituents. In particular, the enantioselective synthesis of chiral quaternary centers has been quite challenging. In this context, the catalytic α-alkylation of dicarbonyl compounds has been extensively studied, and several powerful methods have been developed.[3] Among dicarbonyl compounds, di-ketone and β-ketoester systems have generally been used as substrates for Michael additions or alkylations using metal catalysts or organocatalysts for enantioselective synthesis (Figure 3).

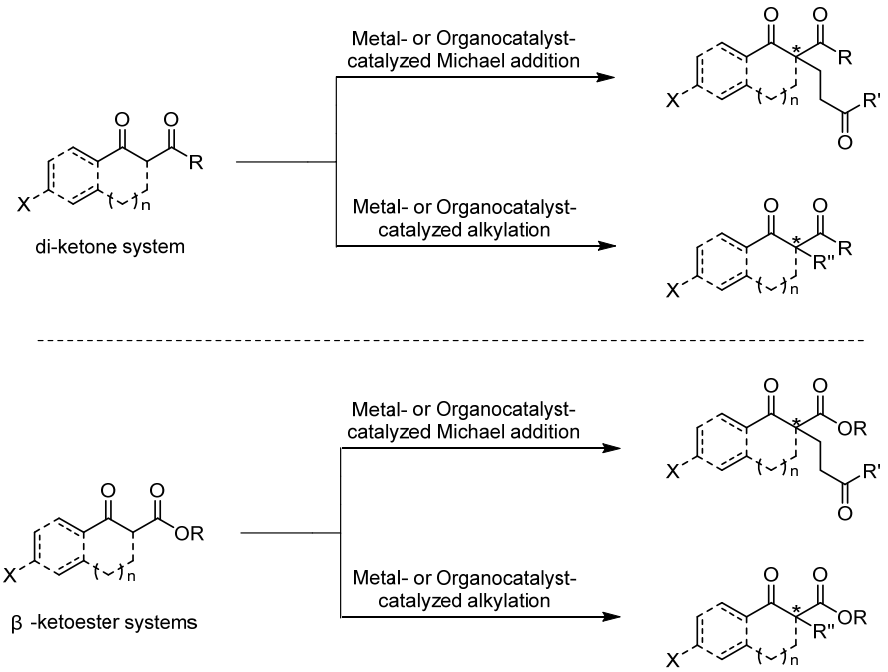
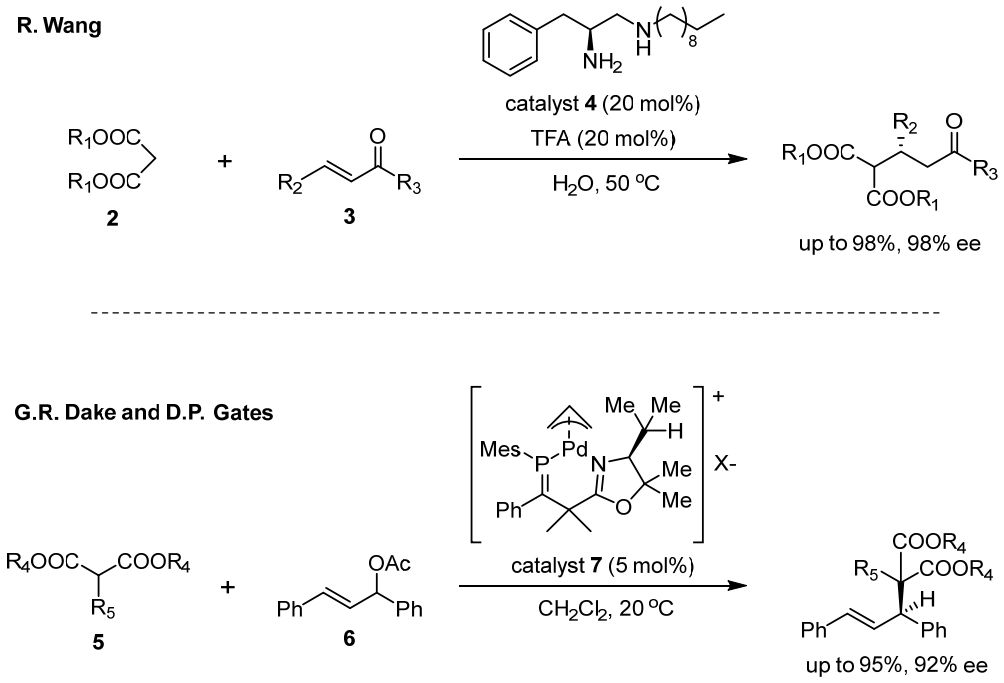


Figure 3. Enantioselective synthesis of dicarbonyl compounds

1.3. Enantioselective synthesis of malonate

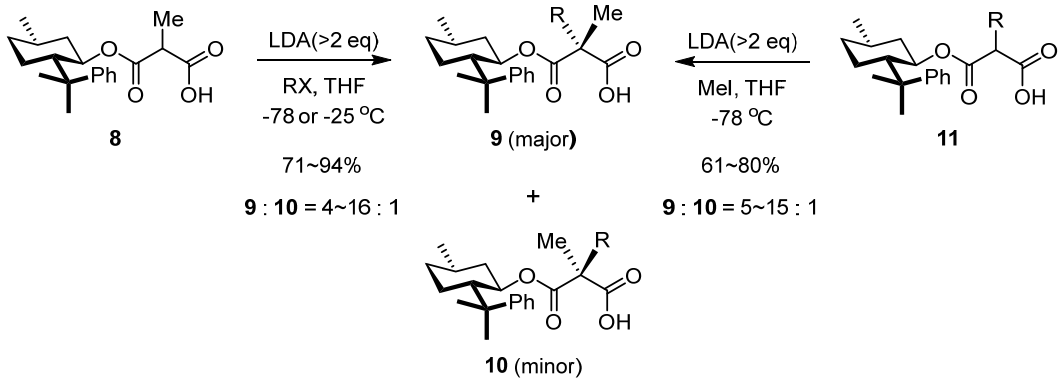
Although the construction of chiral quaternary carbon centers by the asymmetric α-alkylation of dicarbonyl systems has been extensively studied, the enantioselective direct α-alkylation of malonates has not yet been reported. Instead of α-alkylation, several chiral inductions at the β-position of malonate have been reported using asymmetric conjugate addition or palladium-catalyzed allylation.[4] Recently, Wang's group and Dake & Gate's group reported the enantioselective alkylation of the β-position of malonate (Scheme 1).[4m]



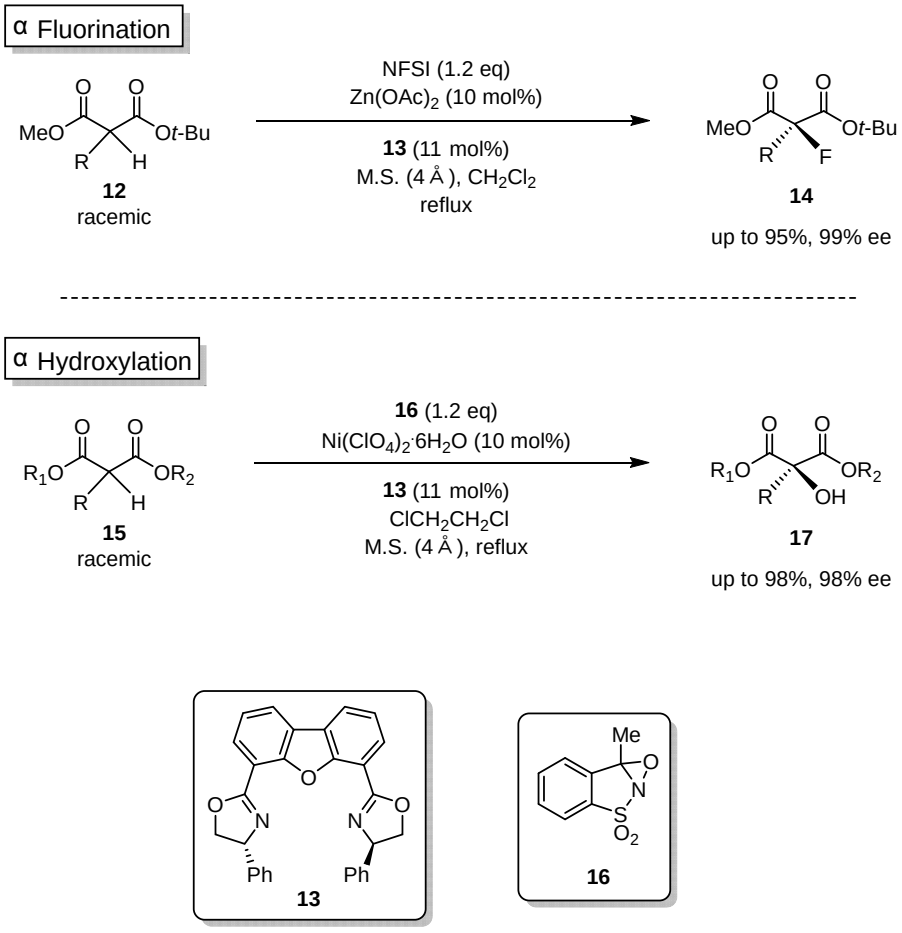
Scheme 1. Representive chiral inductions at the β-position of malonates

R. Wang and co-workers have developed a highly enantioselective Michael addition of malonates (**2**) to α,β-unsaturated ketones (**3**) in water catalyzed by a primary-secondary diamine catalyst (**4**) containing a long alkyl chain.[4h] G.R. Dake and D.P. Gates have developed the palladium-catalyzed allylation of a variety of malonate nucleophiles (**5**) with 1,3-diphenyl-2-propenyl acetate (**6**) using a chiral phospha-alkene-based ligand system with moderate to excellent yields and stereoselectivities (% ee).

Chiral inductions at the β-position of malonates have been studied more often than the chiral α-induction of malonates. In 1989, Fukamoto and co-workers reported the enantioselective construction of a quaternary asymmetric carbon center at the α-position of malonic acid through the reaction of dianions derived from chiral half esters of mono-substituted malonic acids (**8**) with 2 molar equivalents of LDA and alkyl halides (Scheme 2).[5a] Alkylation in the reverse sequence preferentially gave the same diastereoisomer (major **9**, minor **10**). However, this method used a chiral auxiliary, and only showed moderate diastereoselectivity.



Scheme 2. Enantioselective α-alkylaton of malonate using a chiral auxiliary



Scheme 3. Enantioselective α-fluorination and α-hydroxylation of malonates

Recently, Shibata and Toru's group reported the direct α-fluorination and α-hydroxylation of malonates for the synthesis of chiral malonates (Scheme 3).[5b,5c] The chiral α-fluoro-α-alkylmalonates **14** could be obtained in high yields and up to 99% ee through the enantioselective fluorination of racemic malonates **12** using $Zn(OAc)_2$/(*R*,*R*)-DBFOX-Ph (**13**) as a catalyst. Additionally, chiral α-hydroxy malonates **17** can be prepared in high yield and with up to 98% ee from racemic malonates **15** through α-hydroxylation using oxaziridine **16** catalyzed by the Ni^{II}/(*R*,*R*)-DBFOX-Ph (**13**) complex.

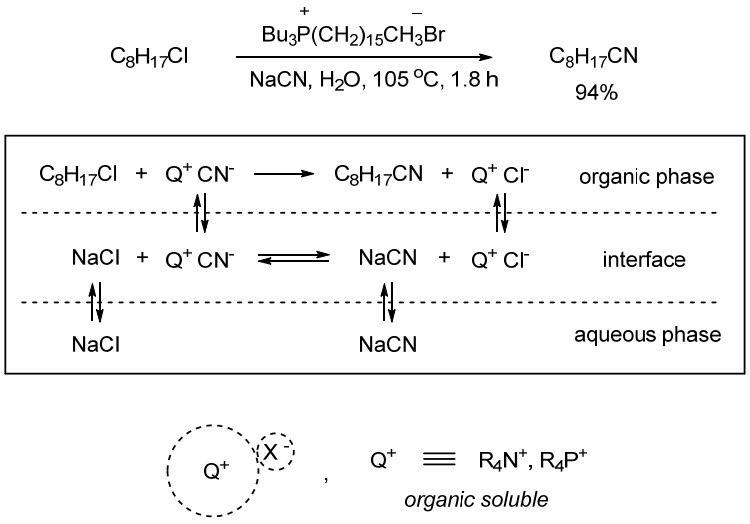
However, these methods are limited to fluorination and hydroxylation, and restricted to small-scale process by the metal catalyst, which can not be applied to an industrial process.

Thus, it is very challenging to develop an efficient and practical synthetic method for the synthesis of chiral malonates. Our research team attempted to develop a method for the enantioselective, direct α-alkylation of malonates using a phase-transfer catalytic (PTC) reaction, a method that is very efficient for practical processes, followed by conversion into various building blocks from the synthesized chiral malonate.

2. Phase-transfer catalysis for asymmetric alkylation

2.1. Phase-transfer catalysis

In 1971, Starks reported that phase-transfer catalysis greatly enhanced the reaction rate between two or more phases through the intervention of a tetra-alkylonium (usually ammonium and phosphonium) salt. This phenomenon was demonstrated by the reaction of 1-chlorooctane with aqueous sodium cyanide that was accelerated by the addition of hexadecyltrobutylphosphonium bromide; without this tetra-alkyl phosphonium salt, the reaction did not proceed (Scheme 4).[6]



Scheme 4. The first report of phase-transfer catalysis

As shown in Scheme 4, the key for phase-transfer catalysis is the generation of tetra-alkylphosphonium cyanide, which makes the cyanide anion soluble in the organic phase and enables reaction with an alkyl halide. Additionally, there are several other advantages

that make phase-transfer catalysis a very useful tool for many organic syntheses:

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

In addition, modification of the catalyst can increase the capacity to catalyze optically active, non-racemic reactions. In particular, the synthesis of optically active α-alkyl-α-amino acids has been intensively developed via phase-transfer catalysis with aqueous alkaline hydroxide base instead of the standard organic bases.

2.2. General mechanism of phase-transfer catalysis

The mechanism of asymmetric phase-transfer catalysis is still being clarified, but it can be generally considered as follows.

2.2.1. Interfacial mechanism by Makosza

Most successful asymmetric transformations using phase-transfer catalysis can be explained by this mechanism. As a representative example, the alkylation of an active methylene group is illustrated in Figure 4. Generally, in this mechanism, a cationic metal salt coordinates with the anionic enolate of the substrate to make the ion pair **20**.

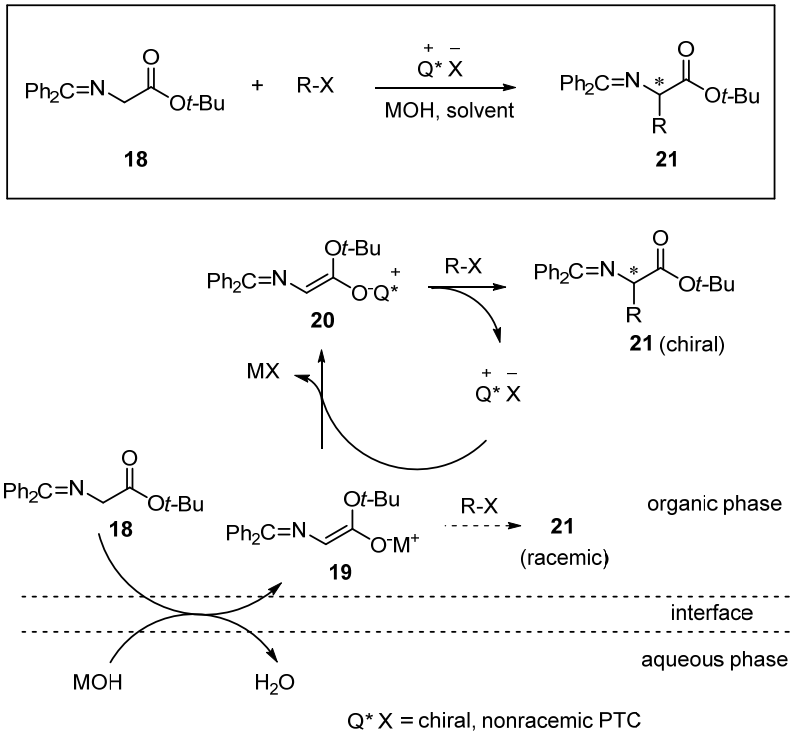


Figure 4. Interfacial mechanism for asymmetric phase-transfer catalysis

As depicted in Figure 4, the reaction was initiated by the abstraction of the α-proton of **18** by aqueous alkaline hydroxide base (MOH), which affords the active methylene anion **19** at the interface of the two phases. Ion exchange with the quaternary onium salt generates the lipophilic salt **20**, and which partitions into the organic phase where it can encounter the alkyl halide (R-X) and form the alkylated product. The catalyst is regenerated during the alkylation step, which enables the use of small quantities of catalyst.

To ensure the high optical purity of chiral **21**, this ion exchange step must occur rapidly enough that undesired racemic alkylation with metal salt **19** does not occur. Additionally, the ion pair between the quaternary onium salt on the catalyst (cation) and the enolate on the substrate (anion) should fit very well together structurally to yield high optical purity. Furthermore, to ensure rapid ion exchange and 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.

2.2.2. Extraction mechanism by Stark

The nucleophilic addition/substitution is explained by the extraction mechanism. The asymmetric epoxidation of α,β-unsaturated ketone is the representative example: this mechanism is shown briefly in Figure 5.

In this mechanism, a chiral liphophilic onium salt, which is generated by anion exchange with a chiral catalyst and a metal salt in the aqueous layer or in the solid state,

is extracted into the organic phase. Then, the nucleophilic anion, which is now in the organic phase supported by the catalyst, attacks prochiral electrophile **22**, and the optically active product **23** is synthesized.

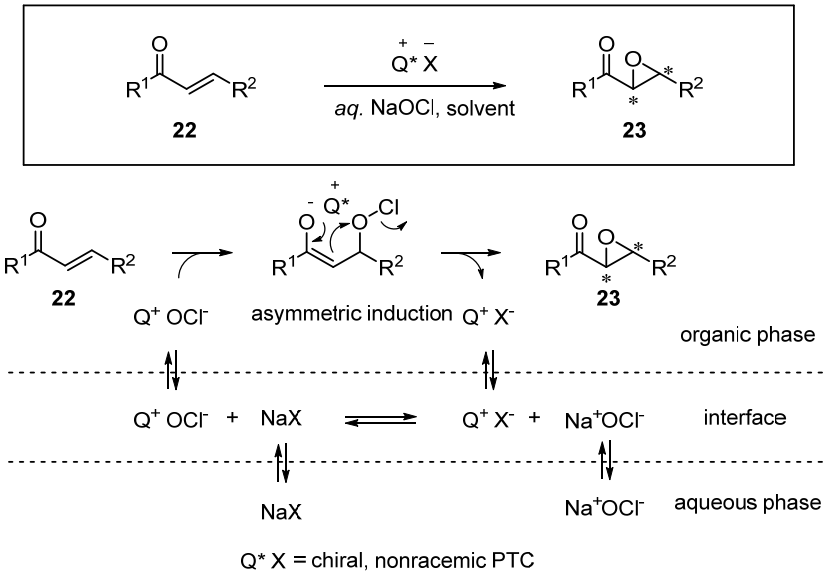
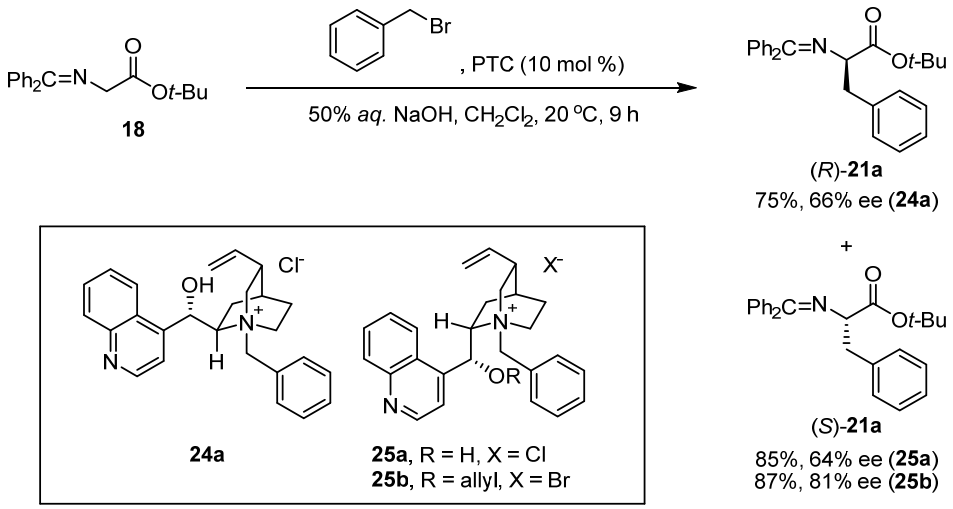


Figure 5. Extraction mechanism for asymmetric phase-transfer catalysis

2.3. Progress of phase-transfer catalytic alkylation

2.3.1. Progress of phase-transfer catalysts

Since M. J. O'Donnell reported his pioneering practical synthetic method for α-alkyl-α-amino acid via phase-transfer catalysis in 1989, this field has been further studied.[7] O'Donnell suggested glycinate Schiff base **18** as a key substrate for the phase-transfer catalytic system.

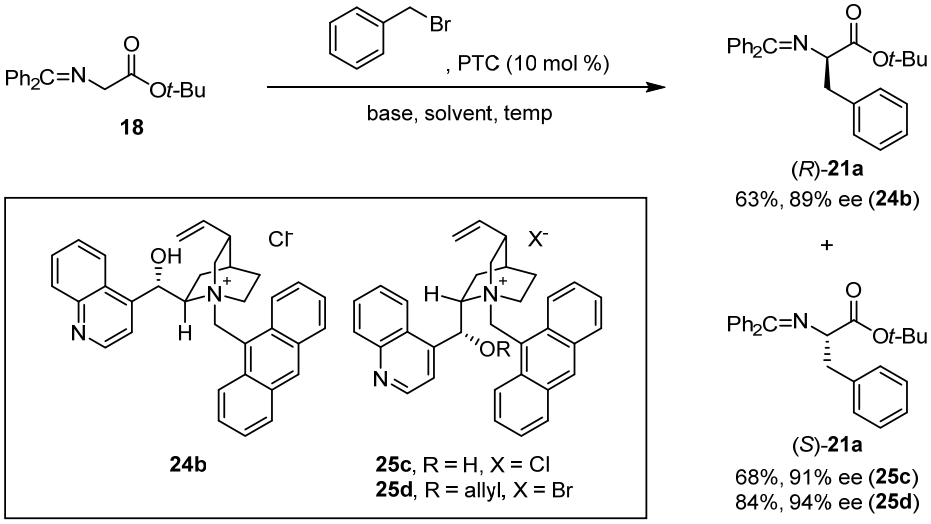


Scheme 5. The first- and second-generation catalysts developed by O'Donnell

The stereoselective alkylation of glycinate Schiff base **18** with benzyl bromide proceeded smoothly under mild basic conditions with the assistance of a chiral catalyst, the cinchonine derivative **24a** (first-generation catalyst reported by Merck group in 1984), in 75% yield and 66% ee. By simply switching the catalyst to cinchonidine derivative **25a**, the pseudo-enantiomer compound of **24a** was obtained in similar chemical and optical yields (85%, 64% ee).[7a] Later, they optimized the catalyst further to enhance the optical

purity of the product. As a result, *O*-allyl protected catalyst **25b** (second generation catalyst) gave a 87% chemical yield and 81% ee (Scheme 5).[7b]

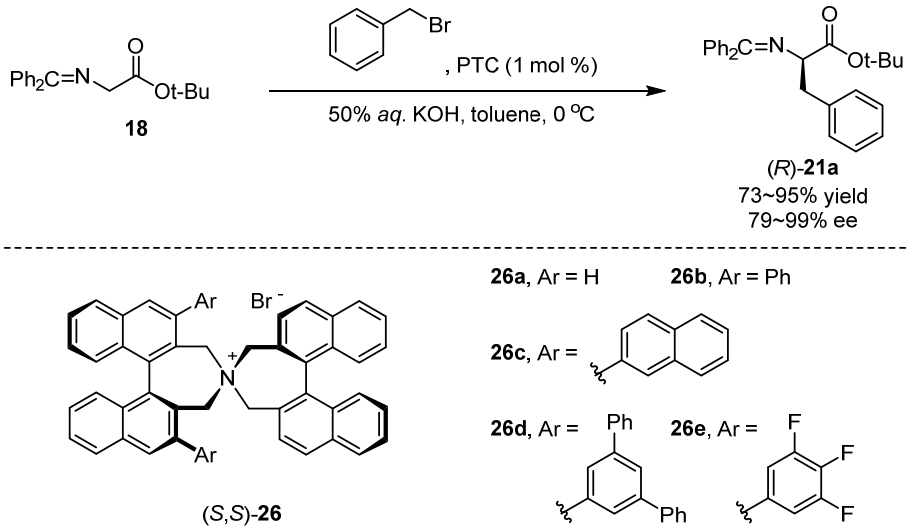
Although asymmetric phase-transfer catalyzed alkylation of an α-alkyl-α-amino acid was accomplished successfully with a commercially available *Cinchona*-derived chiral quaternary ammonium catalyst, further attempts to increase the optical purity were still needed. Meanwhile in 1997, Lygo and Corey independently developed third-generation catalysts bearing *N*-anthracenylmethyl groups, which provided higher stereoselectivities (Scheme 6). [8]



Scheme 6. The third generation catalysts developed by Lygo and Corey

Lygo *et al.* developed cinchonine- and cinchonidine- derived *O*-H-*N*-anthracenylmethyl catalysts (**24b** and **25c**), which provided the product in 89% ee and 91% ee with the opposite absolute configuration (50% aq. KOH as the base, $PhCH_3$ as the solvent at 20 °C). In addition, Corey *et al.* prepared *O*-allyl-*N*-anthracenylmethyl-cinchonidinium bromide **25d** and used it in as the catalyst in the alkylation reaction of glycine Schiff base

with $CsOH \cdot H_2O$ as a base at -78 °C (84%, 94% ee). They also characterized the catalyst through X-ray crystallography of *O*-allyl-*N*-anthracenylmethyl cinchonidinium *p*-nitrophenoxide.

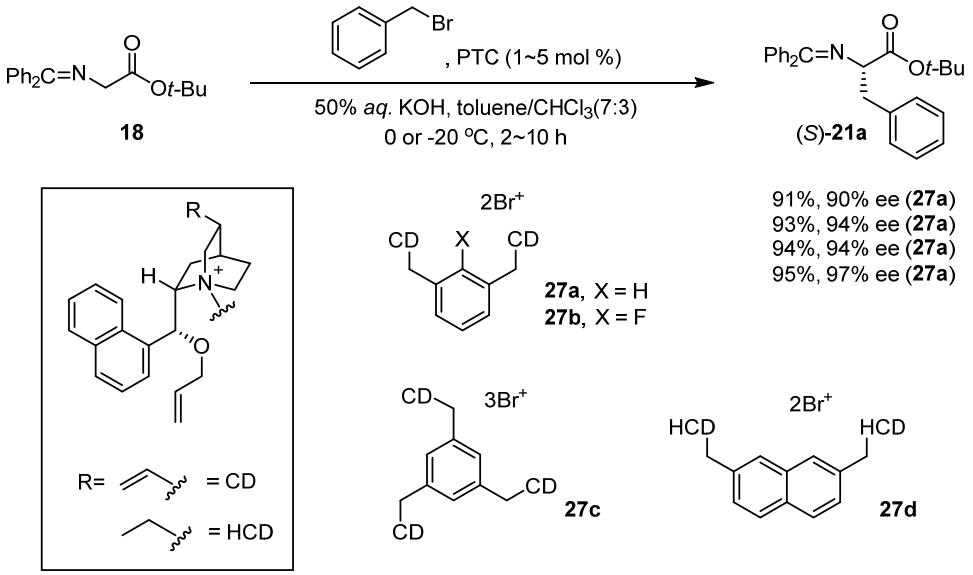


Scheme 7. C-2 symmetric chiral PTCs developed by Maruoka

In 1999, Maruoka *et al.* prepared a new C-2 symmetric chiral catalyst **26** derived from (*S*) or (*R*)-1,1′-binaphthol, which has a structurally rigid spiro ring system (Scheme 7).[9] They successfully used this catalyst in mild phase-transfer catalytic alkylation for the synthesis of optically active α-alkyl-α-amino acids. They succeeded in reducing the amount of catalyst to 1.0 mol % without any loss in the chemical and optical yields.

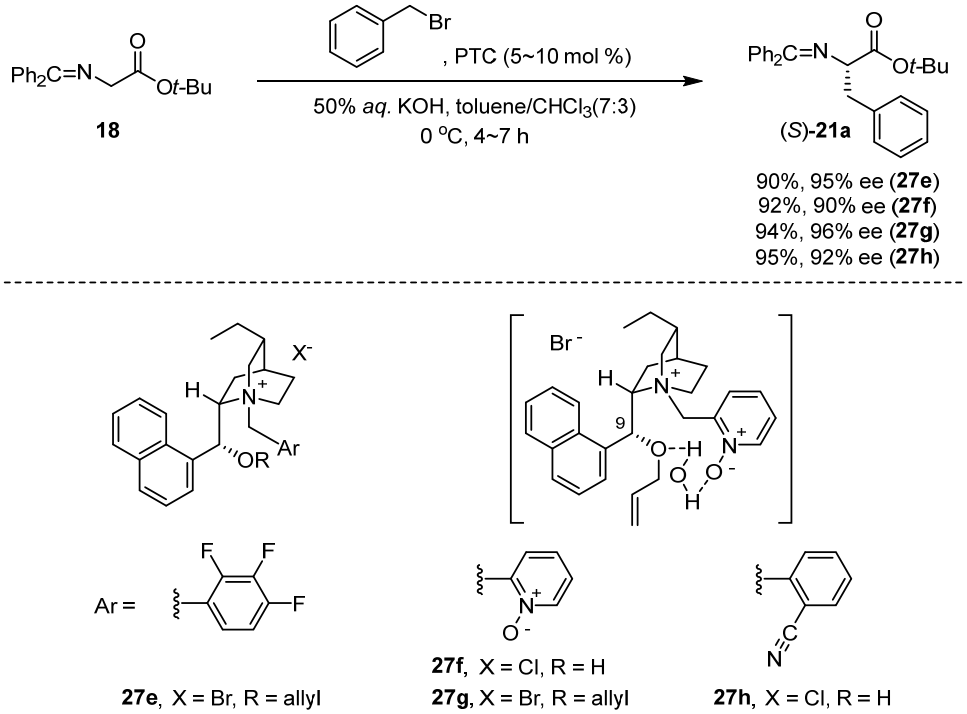
Recently, Jew and Park *et al.* have developed new types of catalysts derived from *Cinchona* alkaloids.[10,11] The first several polymeric catalysts inspired by the Sharpless asymmetric dihydroxylation, were developed and successfully applied to the alkylation of substrate **18**. These catalysts showed higher efficiency than monomeric catalysts, especially the naphthyl dimer catalyst **27d**, which showed the highest enantioselectivity

(97%) with 1.0 mol % at -20 °C (Scheme 8).



Scheme 8. Polymeric PTCs developed by Jew and Park

Jew and Park have also devised different *N*-benzyl substituted *Cinchona* catalysts to examine the electronic effects on stereoselectivity (Scheme 9). Interestingly, an electron-withdrawing *ortho*-substituted group on the *N*-benzyl moiety showed a dramatic enhancement in the enantioselectivity: 2-*N*-oxypyridine showed the best result. This enantioselectivity was explained by the presence of hydrogen-bonding between the *C*-9 oxygen atom and the additional hydrogen bonding acceptor in the *N*-aryl substituent through the intervention of H_2O.[11b] This interaction makes the catalyst rigid, which results in the high enantioselectivity.

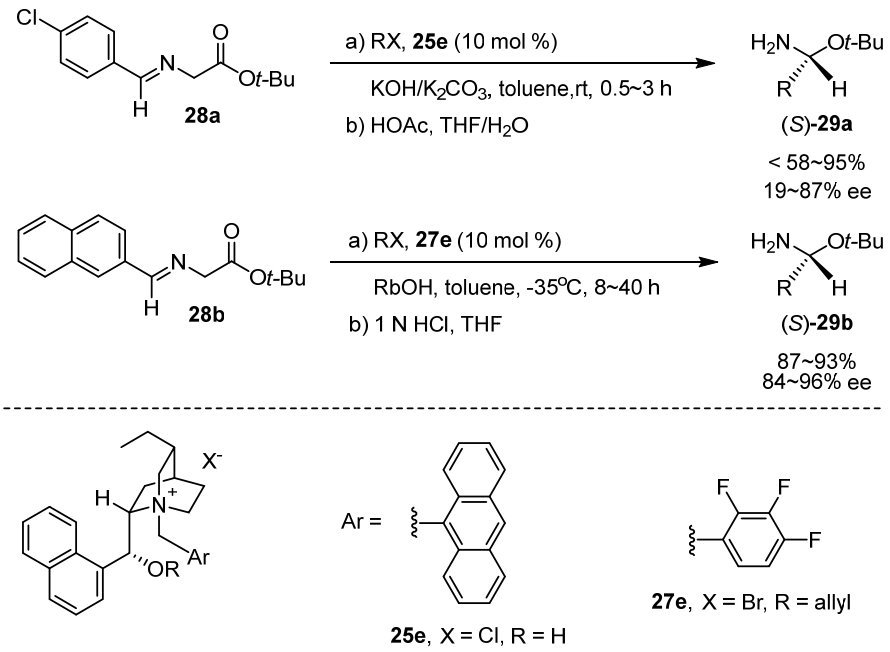


Scheme 9. Electronic effects of chiral PTCs developed by Jew and Park

2.3.2. Progress of the substrates for phase-transfer catalytic alkylation

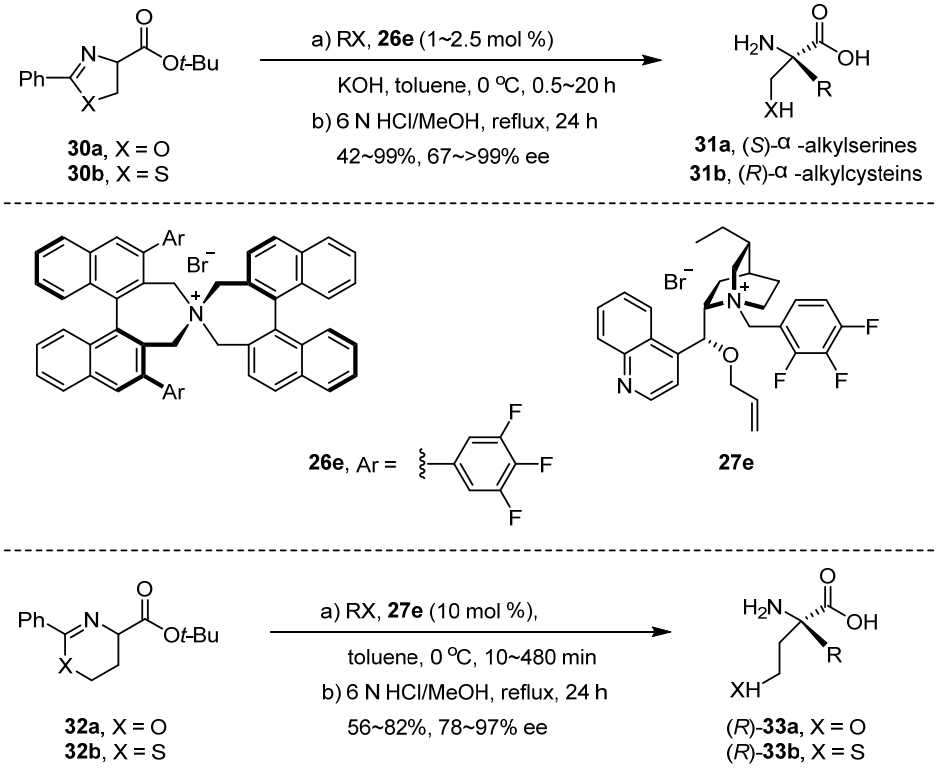
2.3.2.1. Monocarbonyl substrates for phase-transfer catalytic alkylation

As mentioned above, since glycine Schiff base **18** was developed by O'Donnell and co-workers as a substrate for phase-transfer catalytic alkylation, diverse substrates based on **18** have been developed that are appropriate in mono- and di-alkylation for the synthesis of unnatural amino acids. In particular, this type of substrate with a monocarbonyl moiety is used to generate the enolate using a base.



Scheme 10. Monocarbonyl aldimine substrate **28**

In 1992, aldimine Schiff bases **28**, which incorporate a monocarbonyl moiety, were reported by O'Donnell *et al.* for the synthesis of α,α-dialkyl-α-amino acids.[12a] *p*-Chlorophenyl aldimine substrate **28a** was alkylated with phase-transfer catalyst **25e**, which was developed by Lygo.[12b] Bulky aldimine **28b** showed improved enantioselectivity with PTC **27e**, which was developed by Jew and Park.[12c] Aldimine substrates were successfully converted to (*S*)-α-alkylalanine (Scheme 10).

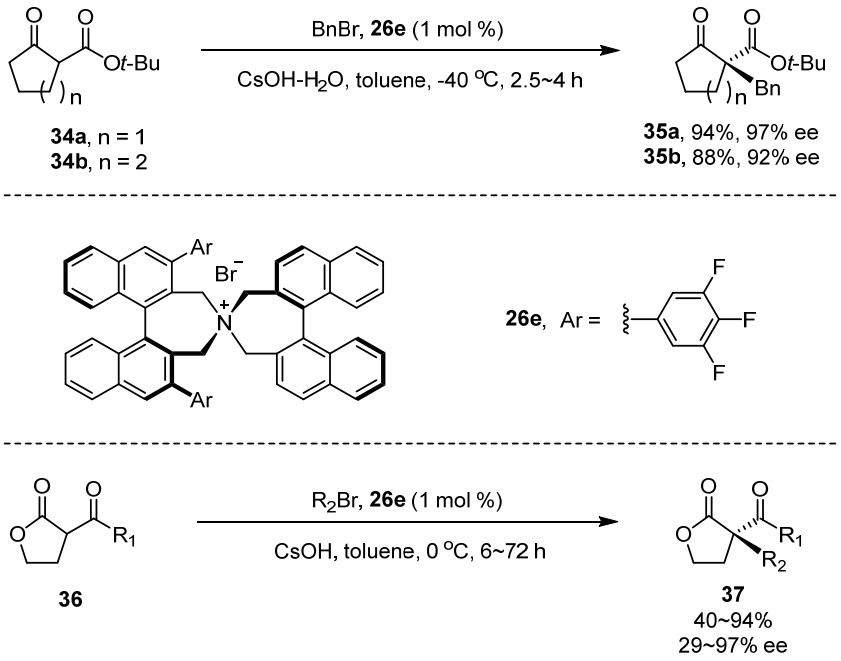


Scheme 11. Monocarbonyl oxazoline and thiazoline substrates **30** and **32**

In 2004, the oxazoline moiety substrate **30a**, which has a monocarbonyl group, was developed by Jew and Park *et al*.[13a] Additionally, in 2006, they developed thiazoline moiety substrate **30b**, which also has a monocarbonyl group.[13b] Furthermore, by ring expansion of **30**, monocarbonyl 6-membered ring substrates **32** were developed for asymmetric phase-transfer catalytic alkylation.[13c] Using these oxazoline and thiazoline moiety substrates, α-alkylserine (**31a**), α-alkylcysteine (**31b**), α-alkylhomoserines (**33a**), and α-alkylhomocysteines (**33b**) were successfully synthesized via phase-transfer catalytic alkylation (Scheme 11).

2.3.2.2. Dicarbonyl substrates for phase-transfer catalytic alkylation

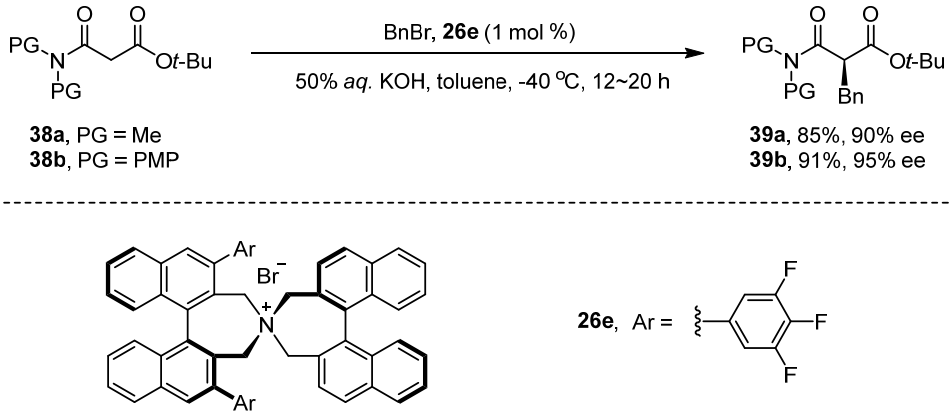
In 2003, Maruoka *et al.* reported the asymmetric alkylation of dicarbonyl β-keto ester substrates **34** via phase-transfer catalytic alkylation.[14a] They also devised α-acyl-γ-butyrolactones **36** as dicarbonyl substrates for phase-transfer catalytic alkylation in 2006.[14b] The enantioselective construction of all-carbon quaternary stereocenters on these substrates was accomplished with good chemical yields and stereoselectivities (Scheme 12).



Scheme 12. Dicarbonyl substrates: β-ketoesters **34** and α-acyl-γ-butyrolactones **36**

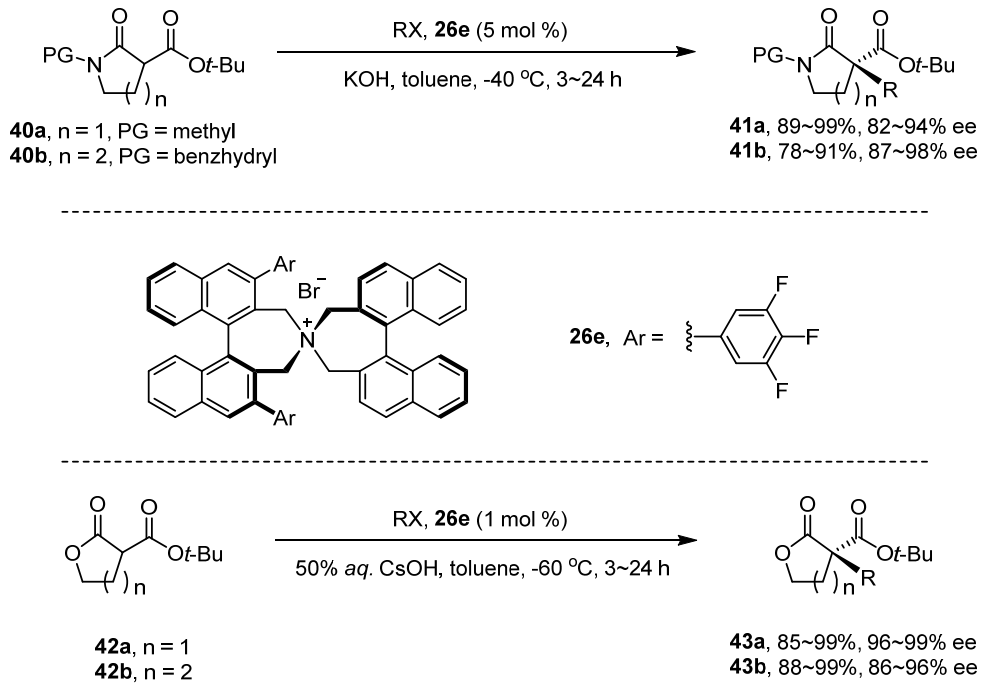
A malonamic ester, dicarbonyl substrate **38**, was designed for monoalkylation and synthesized by Jew and Park *et al.* in 2009.[14c] Because these substrates can be easily converted to versatile synthetic chiral intermediates, malonamic esters **38** are useful

substrates for the generation of a chiral tertiary carbon center. Influenced by the *N*-protecting groups, the enantioselectivities were dramatically changed, and methyl or *p*-methoxyphenyl groups gave high enantioselectivity (Scheme 13).



Scheme 13. Dicarbonyl substrates: malonamic ester **38**

After conducting additional studies on dicarbonyl substrates for phase-transfer catalytic alkylation, Park *et al.* recently developed lactam **40** and lactone **42** substrates.[15] The α-alkylations of N-methyl-α-*tert*-butoxycarbonylbutyrolactam **40a** and N-diphenylmethyl-α-tert-butoxy-carbonylvalerolactam **40b** afforded the corresponding α-alkyl-α-*tert*-butoxycarbonyllactams **41**. Additionally, the α-alkylations of α-*tert*-butoxycarbonyl-butyrolactone **42a** and α-*tert*-butoxycarbonyl-valerolactone **42b** afforded the corresponding α-substituted α-*tert*-butoxycarbonyllactones **43**. The quaternary carbon stereocenters of these substrates were successfully formed under phase-transfer catalytic conditions with high chemical yields and stereoselectivities (Scheme 14).



Scheme 14. Dicarbonyl substrates: lactam **40** and lactone **42**

Regarding the construction of chiral tertiary and quaternary carbon centers, phase-transfer catalytic reaction is one of the most efficient synthetic methods with respect to economic and environmental aspects. Although various carbonyl substrates appropriate for α-alkylation using the asymmetric phase-transfer catalytic reaction have been developed, investigations into new substrates for broadening the reaction scope are still necessary. As one of our research programs for the development of new carbonyl substrates for the phase-transfer catalytic reaction, our research team attempted to develop malonate derivatives and apply them for efficient phase-transfer catalytic reactions.

3. Spiro-oxindole alkaloids

3.1. Synthetic use of α-alkyl-α-(*ortho*-nitro-phenyl)-*tert*-butyl-malonate

Optically active α-alkyl-α-(*ortho*-nitrophenyl)-*tert*-butyl-malonate **44** could be converted to an oxindole structure through a series of processes, e.g., reduction or lactamization. This method can be applied to the synthesis of oxindole based natural products, such as horsfiline, spirotryprostatin B, aspidospermidine, and mersicarpine.

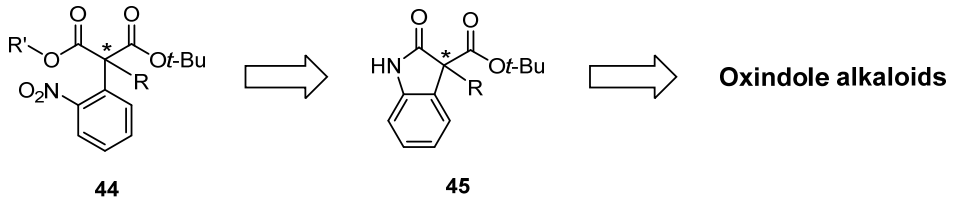


Figure 6. Application of chiral malonates to oxindole derivatives

The first oxindole alkaloids were found in the roots of *Gelsemium sempervirens* (wild yellow jasmine). Additional oxindoles have been isolated from *Aspidosperma*, *Mitragyna*, *Ourouparia*, *Rauwolfia* and *Vinca*.[16] Oxindole natural products have shown diverse biological activity in humans, and have attracted the attention of many scientists. Among the oxindole natural products, a number of products commonly have the chiral quaternary carbon center at the 3-position of the oxindole moiety. Many biological compounds show different activities depending on the stereoisomer, chiral induction of the 3-position of oxindole moiety is very important. Chiral malonates could be crucial precursors of oxindole intermediates for the enantioselective synthesis of oxindole alkaloids.

3.2. The 3,3'-pyrrolidinyl-spirooxindole heterocycle in natural products

Based on a structural core derived from tryptamine, spirooxindole alkaloids belong to a family of natural products first isolated from the plants of the *Apocynaceae* and *Rubiacae* families.[16] The key structural characteristic of these compounds is the spiro ring fusion at the 3-position of the oxindole core, and these have varying degrees of substitution around the pyrrolidine and oxindole rings. In addition to the interesting molecular architecture and densely functionalized core, several natural products possessing this heterocyclic motif exhibit significant bioactivity (Figure 7).

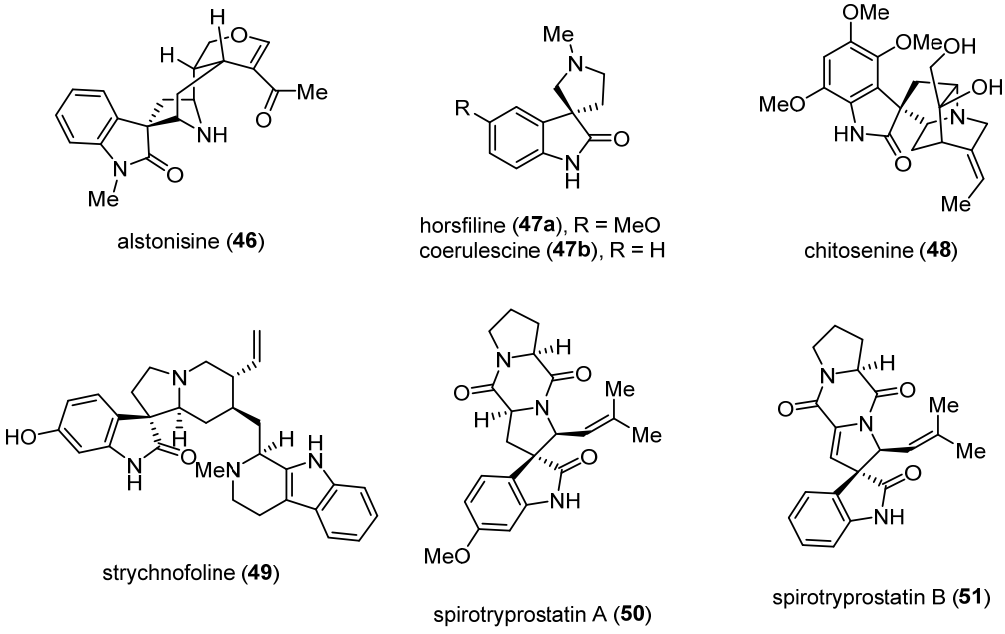


Figure 7. Representative pyrrolidinyl-spirooxindole natural products.

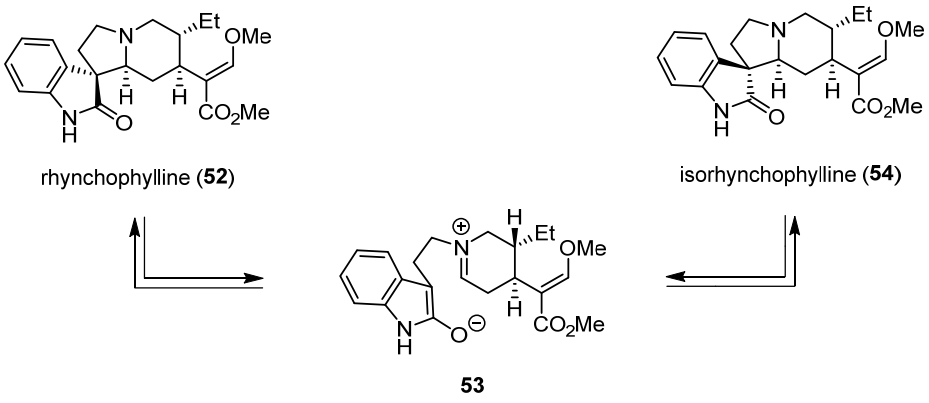
Alstonisine (**46**) was first isolated from *Alstonia muelleriana*,[17] and its biomimetic transformations have been studied by LeQuesne and Garnick.[18] Isolated in 1991,[19] the relatively unsubstituted spirooxindole core of (–)-horsfiline (**47a**) has proven to be a popular target among chemists, and numerous syntheses have been reported. The related compound coerulescine (**47b**), which possesses an even simpler structure, was isolated in 1998; its synthesis is often reported along with that of horsfiline.[20] Chitosenine (**48**) is another structurally interesting natural product and shows short-lived inhibition of ganglionic transmission in vivo in rats and rabbits.[21] Strychnofoline (**49**) inhibits mitosis in a number of cell lines including mouse melanoma B16, Ehrlich, and hepatoma HW165.[22] Spirotryprostatins A and B (**50** and **51**) were isolated from the fermentation broth of *Aspergillus fumigatus* and have been shown to completely inhibit the G2/M progression of mammalian tsFT210 cells at concentrations in excess of 12.5 mg/mL. [23]

3.3. Representative synthetic methods for the 3,3'-pyrrolidinyl-spiro-oxindoles

Most of these oxindole alkaloids possess a common basic framework derived from tryptamine and are characterized by a unique spiro fusion to a pyrrolidine ring at the 3-position of the oxindole core. This appealing spiro architecture is often associated with significant biological activity; thus, the spiro[pyrrolidine-3,3'-oxindole] alkaloids are interesting synthetic targets. Many chemists have reported different strategies for the synthesis of the spiro[pyrrolidine-3,3'-oxindole] ring system in the context of natural product synthesis.

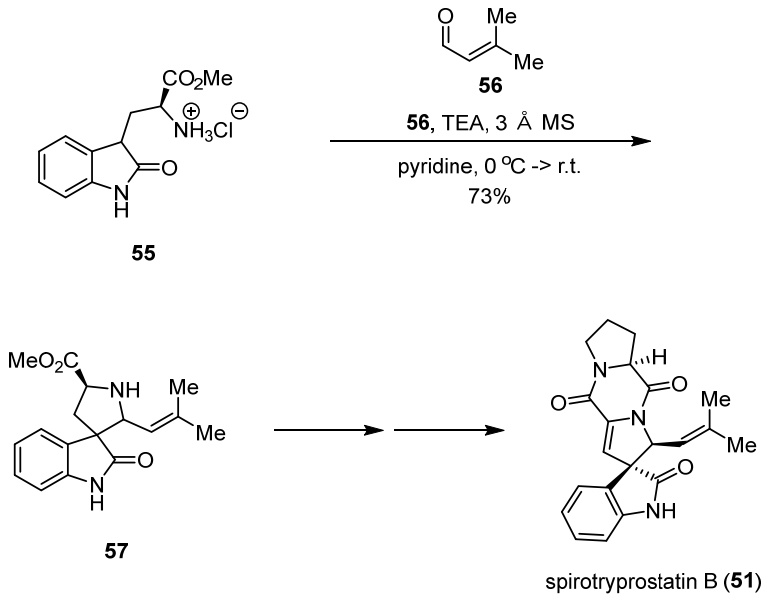
3.3.1. Intramolecular Mannich reactions

In nature, oxindole alkaloids often occur as pairs of interconvertible isomers [e.g., rhynchophylline (**52**) and isorychnophylline (**54**), the (3*S*) epimer of rhynchophylline]. This observation are explained by an isomerization mechanism, wherein both forms can be equilibrated through the ring-opened form **53** accessed by a retro-Mannich reaction (Scheme 15).



Scheme 15. Isomerization of spiro-oxindoles through Mannich/retro-Mannich reaction

One of the most notable recent applications of the Mannich reaction in complex natural product synthesis was documented by Danishefsky in his approach to spirotryprostatin B (**51**).[24] The reaction of oxindole **55** with aldehyde **56** afforded a mixture of diastereoisomeric spiro[pyrrolidine-3,3'-oxindoles] **57**. These compounds were separable at a later stage in the synthesis and afforded spirotryprostatin B (**51**) in a very efficient sequence of reactions (Scheme 16).

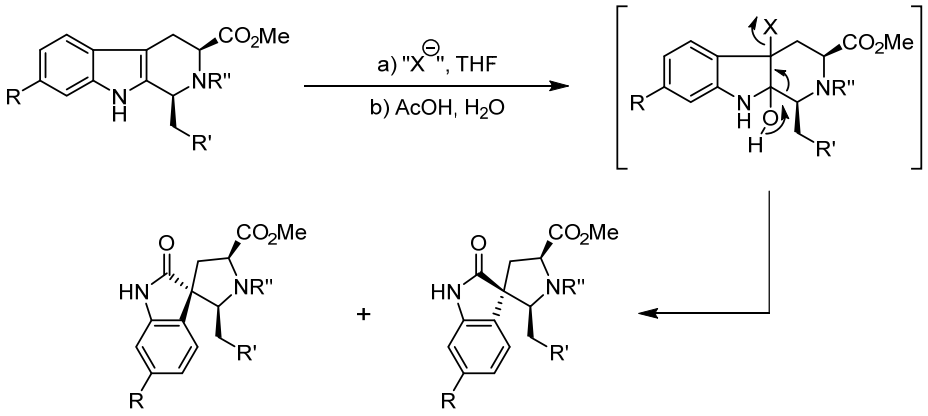


Scheme 16. The Mannich reaction in Danishefsky's synthesis of spirotryprostatin B

3.3.2. Oxidative rearrangement sequences

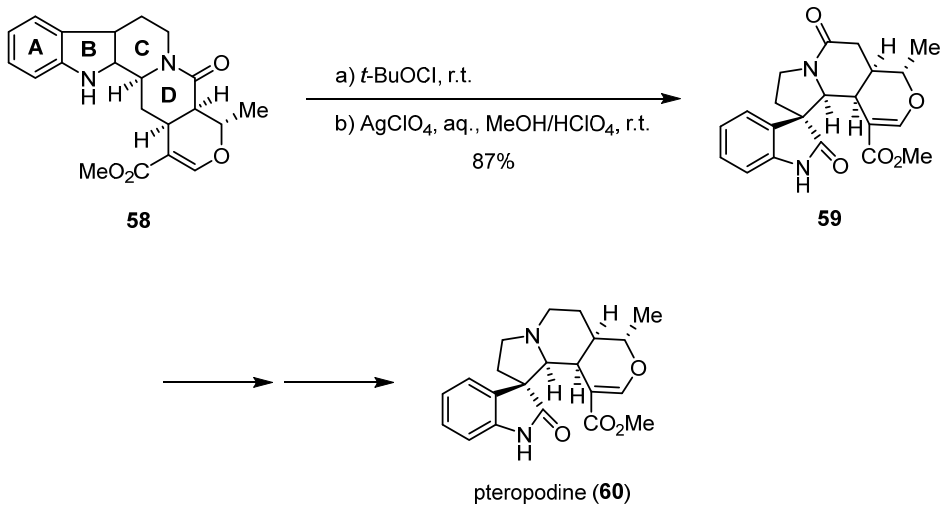
A widely employed method for the construction of the spiro[pyrrolidine-3,3'-oxindole] ring system is the oxidative rearrangement of a tetrahydro-β-carboline. Tetrahydro-β-carbolines are conveniently accessible from derivatives of tryptophan or tryptamine by

the Pictet-Spengler reaction. Alternatively, the tetrahydro-β-carboline can also be prepared from tryptophan through a Bischler-Napieralski reaction followed by reduction. The treatment of tetrahydro-β-carbolines with a suitable oxidant in combination with a hydroxide source results in oxidative rearrangement to the spiro-[pyrrolidine-3,3'-oxindole] ring system (Scheme 17).



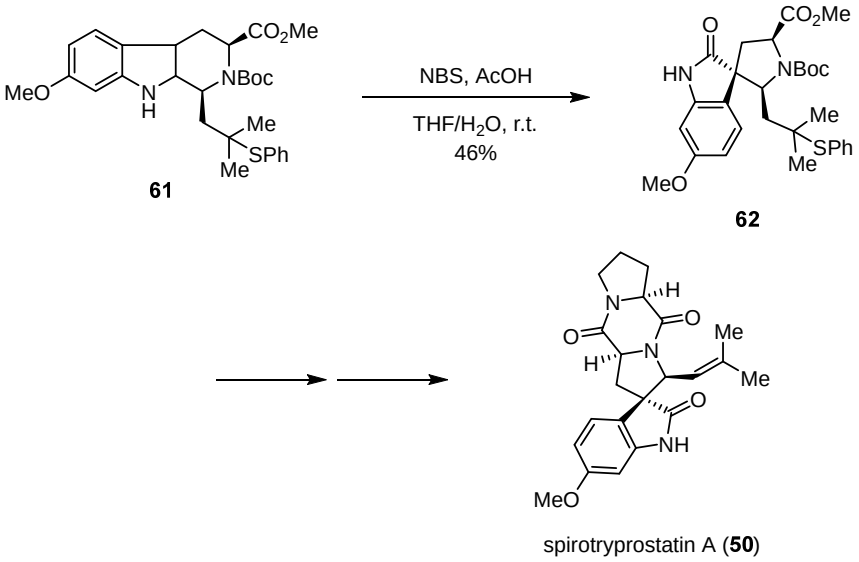
Scheme 17. Mechanism for oxidative spiro rearrangement

An early study by Taylor revealed that rhynchophylline (**52**) can be obtained from dihydro-corynantheine in a three-step procedure by oxidative rearrangement using *tert*-butyl hypochloride, via a chloroindolenine intermediate.[25] Martin used this method for the oxidation of indoles, where N_b is incorporated in a D-ring lactam. The critical rearrangement of **58** to **59** was achieved by the addition of silver perchlorate to initiate the rearrangement of the chloroindolenine, which led ultimately to pteropodine (**60**) (Scheme 18).[26]



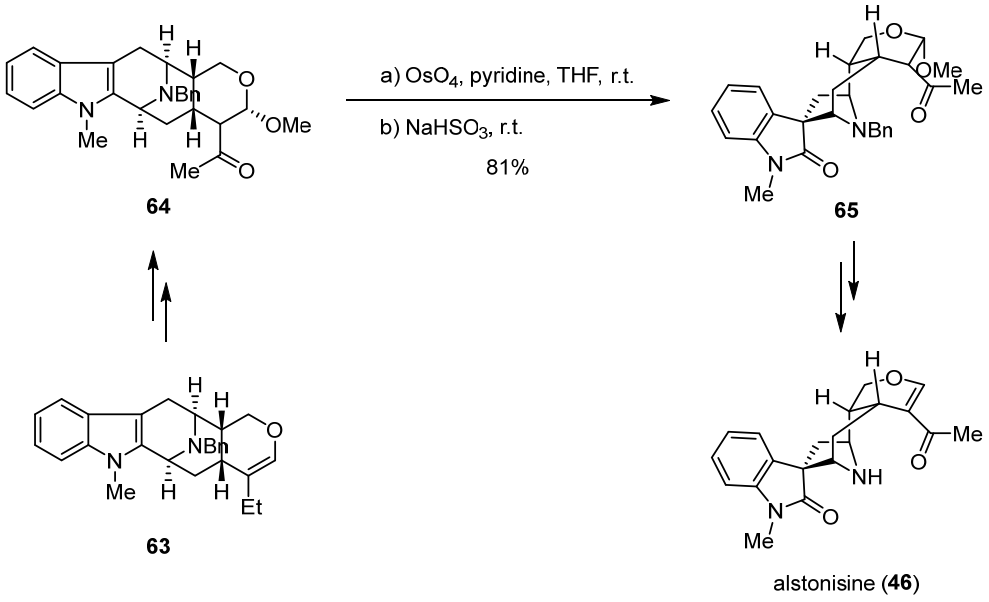
Scheme 18. Oxidative rearrangement in Martin's synthesis of pteropodine

In Danishefsky's synthesis of spirotryprostatin A (**50**), NBoc-protected tetrahydro-β-carboline **61** was used in the oxidative spiro rearrangement to **62**. Spirotryprostatin A (**50**) was obtained by deprotection of the carbamate, installation of the dioxopiperazine by coupling with N-Troc-$_L$-proline and conversion of the tertiary sulfide to the unsaturated prenyl substituent (Scheme 19).[27]



Scheme 19. Oxidative rearrangement in Danishefsky's synthesis of spirotryprostatin A

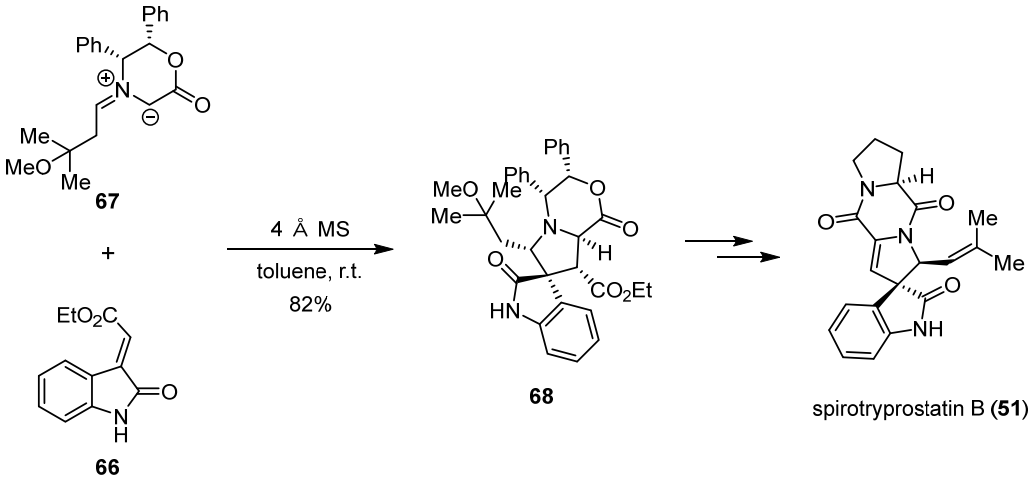
Another method for accessing spiro[pyrrolidine-3,3'-oxindoles] from tetrahydro-β-carbolines employs osmium tetroxide. Cook showed that osmium tetroxide reacts with tetrahydro-β-carbolines selectively to afford a single diastereomer. The osmium atom is most likely complexes with the piperidine nitrogen atom and dihydroxylation then occurs intramolecularly from one face of the substrate. The opposite face of the tetrahydro-β-carbolines undergoes dihydroxylation through the use of bulky ligands, such as the cinchona alkaloid derivatives DHQ-CLB and $(DHQ)_2PHAL$, ultimately leading to the spiro epimers. The key step in the total synthesis of alstonisine (**46**) by Cook uses an oxidative rearrangement of keto acetal **64** obtained from olefin **63**. Spiro[pyrrolidine-3,3'-oxindole] **65** is obtained as the sole diastereomer with 81% yield. The rationale for this selective transformation is the complexation of osmium tetroxide to the piperidine nitrogen atom. The synthesis of alstonisine (**46**) was completed by deprotection of the N_b atom of **65** followed by the base-induced elimination of MeOH (Scheme 20).[28]



Scheme 20. Oxidative rearrangement in Cook's synthesis of alstonisine

3.3.3. Dipolar cycloaddition reactions

Grigg was the first to successfully use 1,3-dipolar cycloadditions for a completely different approach to the synthesis of the spiro[pyrrolidine-3,3'-oxindole] skeleton. He reported that N-substituted and α,α-disubstituted amino acids react with carbonyl compounds to yield azomethine ylides by decarboxylative transamination. Spiro[pyrrolidine-3,3'-oxindoles] are obtained from the reaction of azomethine ylides with oxindolylidene 3-ylidene acetate.[29] Azomethine ylides obtained from different precursors can also react with oxindolin-3-ylidene dipolarophiles leading to the spiro[pyrrolidine-3,3'-oxindole] ring system.

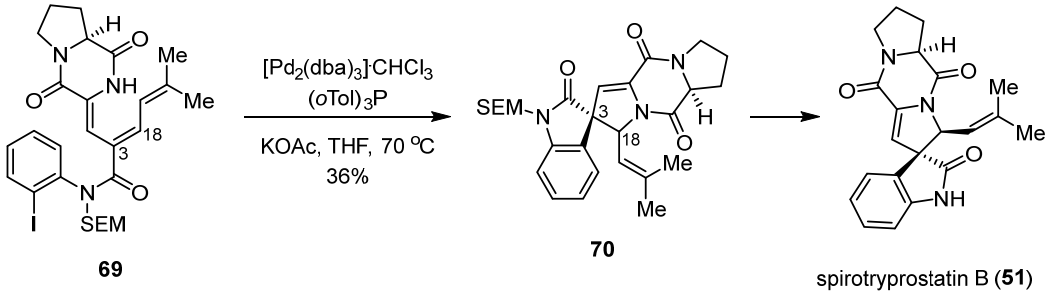


Scheme 21. Key transformation in Williams' synthesis of spirotryprostatin B

A notable recent application of the 1,3-dipolar cycloaddition to the synthesis of spiro[pyrrolidine-3,3'-oxindole] alkaloids is found in the synthesis of spirotryprostatin B (**51**) by Williams. He employed chiral azomethine ylide **67**, which is prepared in situ by the addition of 3-methoxy-3-methyl-1-butanal to 5,6-diphenylmorpholin-2-one. Reaction with oxindole **66** led to cycloadduct **68** in 82% yield (Scheme 21).[30]

3.3.4. Intramolecular Heck Reactions

The use of the Heck reaction was pioneered by Overman, who has applied this reaction to the synthesis of highly complex spiro-oxindole alkaloids.[31] Among syntheses of spiro[pyrrolidine-3,3'-oxindole] alkaloids, Overman's synthesis of spirotryprostatin B (**51**) relies on an asymmetric Heck reaction followed by trapping an η3-allylpalladium species with a tethered nitrogen nucleophile. [32]



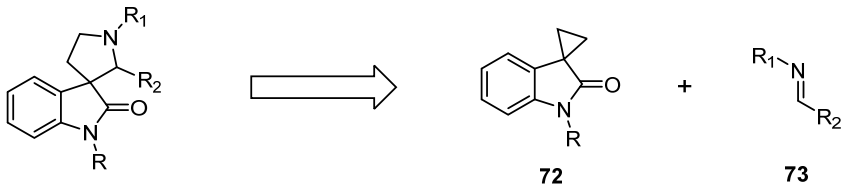
Scheme 22. One-pot Heck reaction/η3-allylpalladium trapping employed for the synthesis of spirotryprostatin B

The key intermediate **69** was accessed from a known allylic alcohol in eight steps. Several conditions for the onepot Heck reaction/η3-allylpalladium trapping were tested, and the best results were obtained with 10% $[Pd_2(dba)_3]\cdot CHCl_3$, 40% tri-*o*-tolylphosphane and excess potassium acetate in THF at 70 °C, giving a 1:1 mixture of **70** and its isomer (inverse configuration at C-3 and C-18) in combined 72% yield. The cleavage of the SEM protecting group from **70** cleanly provided spirotryprostatin B (**51**). In an initial route, in which the Heck reaction was performed with the isomer of **69** bearing the C-3-C-18 (*Z*)-olefin, the stereochemical outcome of the key step could be

tuned in either direction by using Pd/BINAP and excess PMP in DMA at 100 °C and employing either (*R*)- or (*S*)-BINAP in a 6:1 ratio. This was not possible in the reaction with **69** because temperatures over 80 °C in the presence of excess PMP in DMA led to the rapid isomerization of **69** to the isomer bearing the C-3-C-18 (*Z*)-olefin and to the formation of the undesired isomers (Scheme 22).

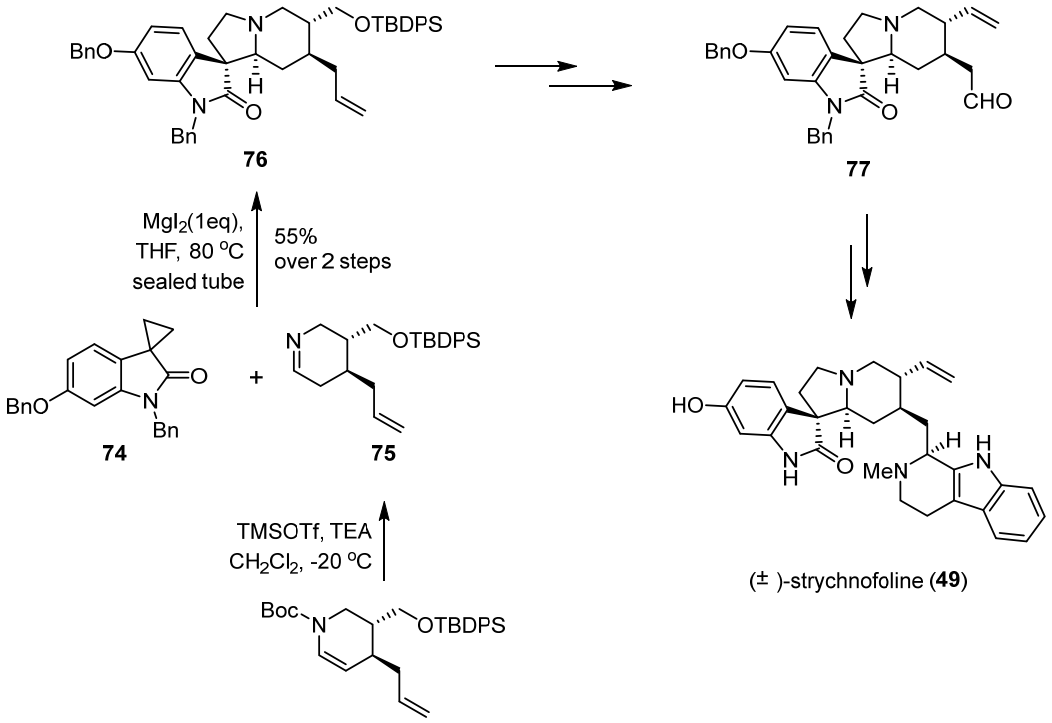
3.3.5. Magnesium iodide-catalyzed ring-expansion reactions

There is a very direct, alternate bond construction strategy to create spiro[pyrrolidine-3,3-oxindole] ring systems **71** that relies on a cyclopropane-opening/ring-expansion reaction of a spiro[cyclopropane-1,3'-oxindole] (**72**) with an aldimine **73** (Scheme 23). This strategy not only presents an alternative to existing methods but also allows for the efficient late-stage coupling of two functionalized fragments in a convergent fashion. The charge-affinity pattern of cyclopropanes, when substituted with electron-withdrawing groups, is manifested in their well-known reactivity as homo-Michael acceptors, and complements that of aldimines.



Scheme 23. Ring-expansion reaction of a spiro[cyclopropane-1,3'-oxindole] (**72**) with an aldimine **73**

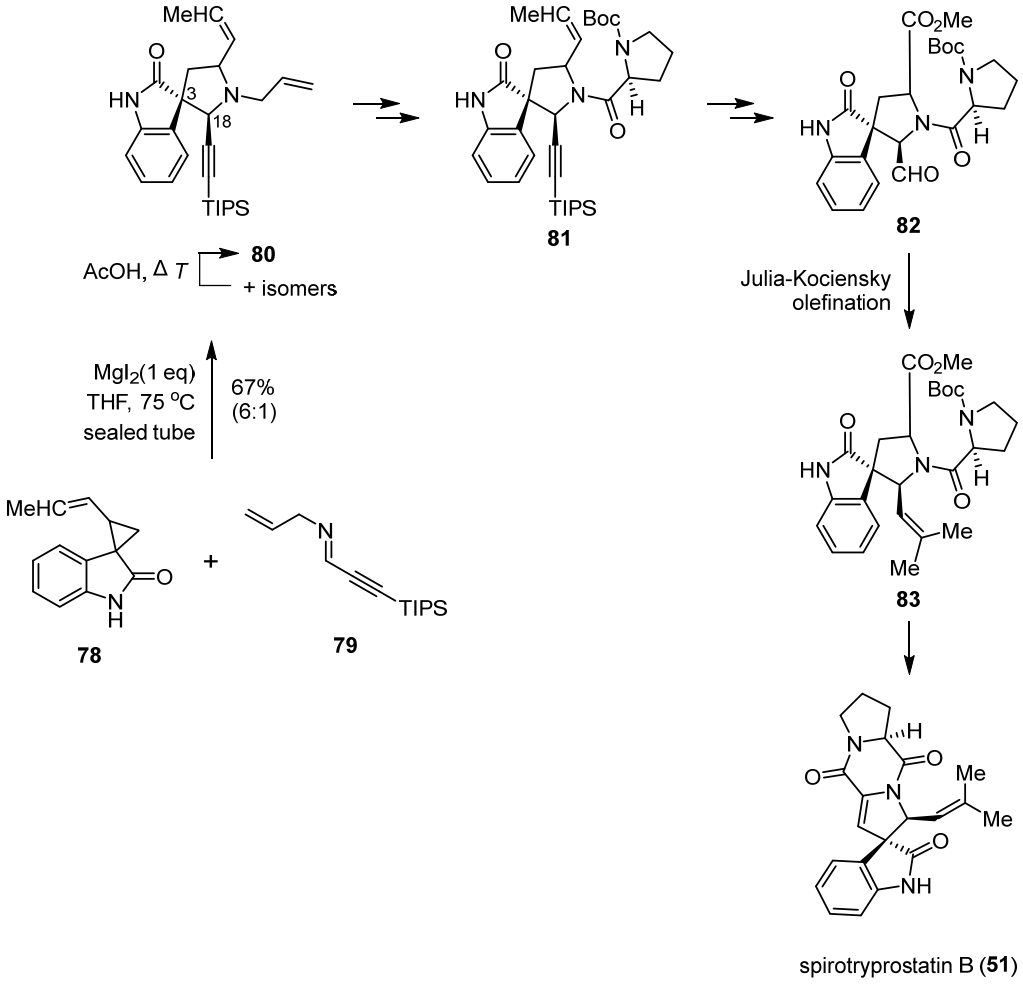
In the first total synthesis of (±)-strychnofoline (**49**), the magnesium iodide-catalyzed coupling of spiro[cyclopropane-1,3'-oxindole] **74** with cyclic imine **75** yielded **76** as a single diastereoisomer. Ring expansion enables the efficient assembly of the key intermediate **76**, which was converted into aldehyde **77** by functional-group interconversions. From **77**, (±)-strychnofoline (**49**) was obtained in two steps through Pictet-Spengler reaction with N-methyltryptamine followed by removal of the benzyl protecting groups (Scheme 24). [33]



Scheme 24. First total synthesis of (±)-strychnofoline employing the ring expansion reaction of oxindole **74** with cyclic imine **75**

The synthetic approach for spirotryprostatin B was driven by interest in the feasibility of using a magnesium iodide catalyzed ring-expansion reaction for the construction of spiro-

[pyrrolidine-3,3'-oxindoles] with a higher degree of substitution on the pyrrolidine ring.



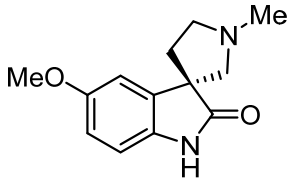
Scheme 25. Use of the ring-expansion reaction of **78** with imine **79** in the synthesis of spirotryprostatin B

Indeed, when spiro[cyclopropane-1,3'-oxindole] **78**, available from diazo-oxindole and piperylene through rhodium-catalyzed cyclopropanation, was used in the cyclopropane-fragmentation/ring-expansion reaction with N-allylimine **79**, pyrrolidine **80** with the required C-3-C-18 *anti* relationship (dr = 6:1) was obtained. The corresponding *syn*

isomers were converted into **80** by refluxing in acetic acid. No products arising from O-alkylation or from 1,7-addition to the cyclopropane could be observed. In the ensuing synthetic sequence, the amide coupling of N-deprotected **80** and N-Boc-$_L$-proline with the concomitant resolution of the racemic material to enantiopure **81** was performed. The transformation to **82** was accomplished using a short synthetic sequence. [34a] Application of the Julia-Kociensky reaction enabled the introduction of the prenyl side chain yielding **83**, from which spirotryprostatin B (**51**) was obtained in a one-pot procedure (Scheme 25). [34b]

3.4. Stereoselective synthesis of (–)-horsfiline

(–)-Horsfiline (**47a**, Figure 8), a representative tricyclic oxindole alkaloid, was first isolated in 1990 by Bodo and co-workers from the leaves of *Horsfieldia superba* Warb.(Myristicaceae), a small tree native to Malaysia and used as a source of intoxicating snuffs.[35] Through synthesis from chiral nonracemic β-carboline precursors, the absolute configuration of (–)-horsfiline was shown to be *R*, as shown in Figure 8.



(-)-Horsfiline (**47a**)

Figure 8. (–)-Horsfiline

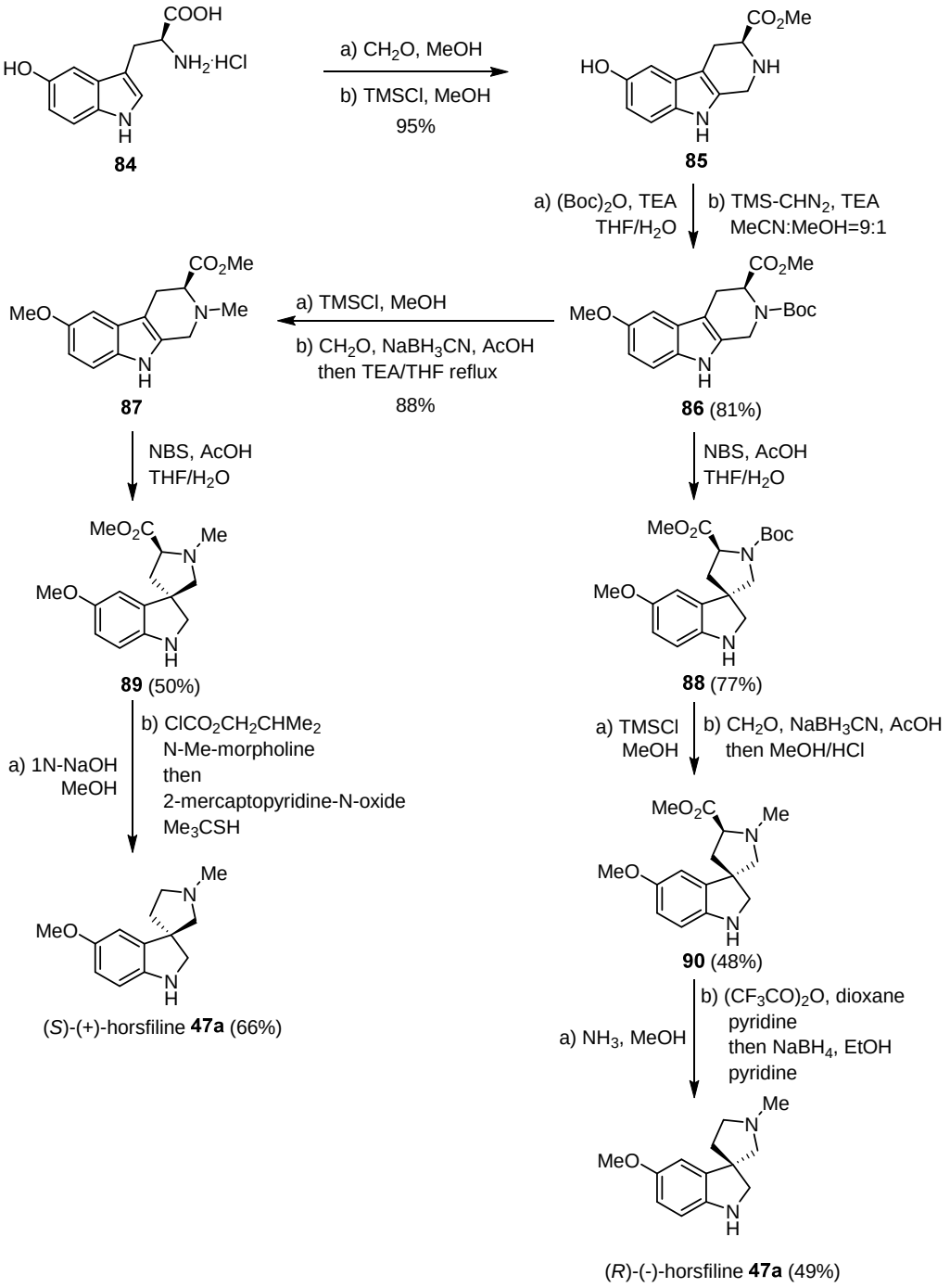
Many synthetic methods have been developed for the synthesis of horsfiline. However, only four syntheses of enantiomerically enriched horsfiline have been reported.[36] In 1994, Borschberg et al. confirmed the absolute configuration of horsfiline by the synthesis of both enantiomers through diastereoselective oxidative rearrangement of chiral tetrahydro-β-carboline precursors, derived from (L)-5-hydroxytryptophan.[36a] In 1999, Fuji et al. employed a chiral reagent for the α-nitroolefination of α-allyloxindole to introduce the quaternary chiral center.[36b] In 1996, Palmisano et al. obtained the pyrrolidine moiety through the cycloaddition of an azomethine ylide with an α,β-unsaturated ester and subsequently separated one isomer by resolution to obtain (–)-horsfiline.[36c] They improved the asymmetric cycloaddition in 2001 using a new chiral alcohol auxiliary substituted α,β-unsaturated ester, which subsequently formed the

oxindole by intramolecular lactamization.[36d] In 2006, Trost et al. employed the first catalytic method in a palladium-catalyzed asymmetric allylation of 3-carboxyoxindoles to establish the spirostereogenic center of (–)-horsfiline.[36e]

3.4.1. Synthesis of (–)-horsfiline using a chiral substrate

Borschberg et al. have synthesized both optical antipodes of horsfiline (**47a**) in approximately 10 steps and with satisfactory overall yields ((–)-horsfiline, 14%; (+)-horsfiline, 22%) from the same enantiomer of the starting tryptophan derivatives.[36a] Because the absolute configuration of (-)-**47a** was not known at that time, they attempted to develop an unambiguous enantioselective synthesis which would furnish both optical antipodes of horsfiline with established absolute configurations.

The key step was the one-pot oxidation-rearrangement of optically pure tetrahydro-β-carboline derivatives (**86**, **87**), which furnished the desired oxindoles with diastereoface selectivity. The relative configuration of the resulting isomers **89** and **90** were analyzed by NOE spectroscopy to deduce the absolute configuration of natural horsfiline in comparison with final products. The required intermediates **86** and **87** were prepared in optically pure form as shown in Scheme 26. Using a modified version of Brossi's protocol, the hydrochloride of the commercially available (*S*)-5-hydroxytryptophan **84** was transformed into **85** in virtually quantitative yield. Then, *N*-Boc-protection and *O*-methylation of **85** and **86** proceeded with very high yield. The *N*-methyl analogue **87** was prepared from **86** through deprotection followed by reductive amination. The diastereoselective oxidative rearrangement of **86** and **87** gave diastereomers **88** and **89**, respectively.



Scheme 26. Synthesis of (+)-horsfiline and (–)-horsfiline by Borschberg et al.

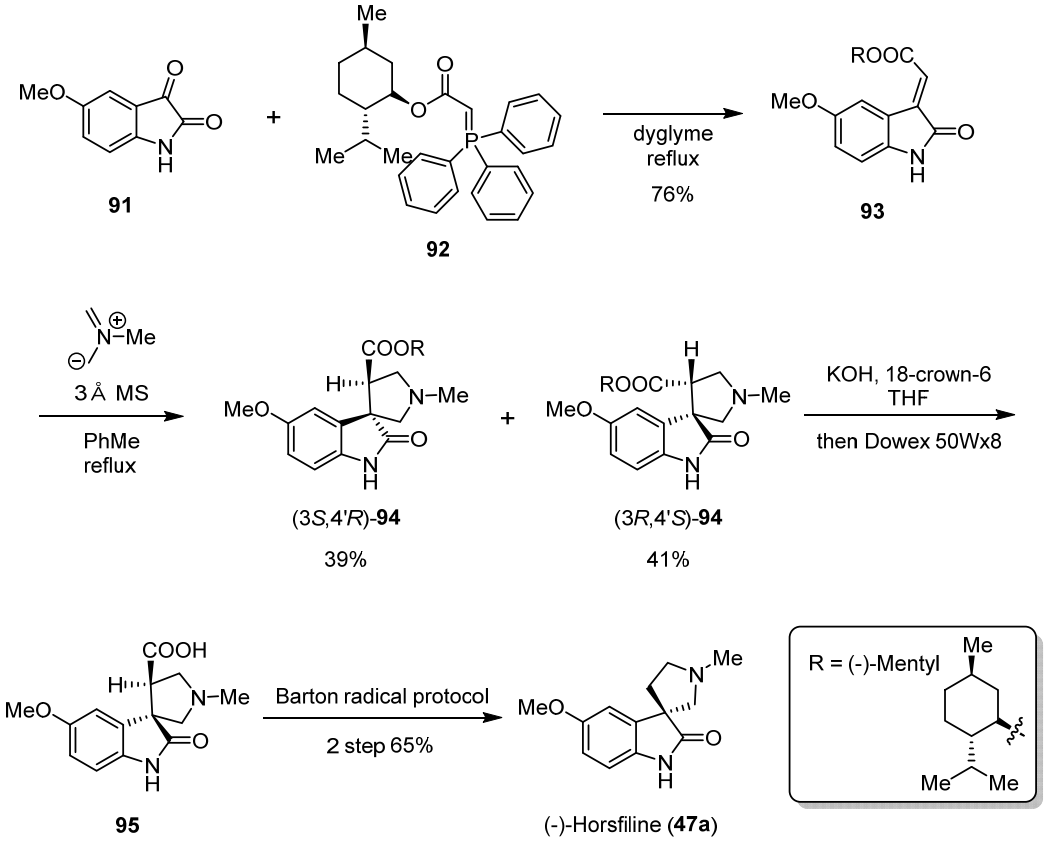
Diastereoisomer **88** was analyzed after deprotection and *N*-methylation, as was **89**. After analyzing **89** and **90** using NOE spectroscopy, the removal of the superfluous carbomethoxy group was performed using a different method. Eventually, the natural (–)-horsfiline was compared with the obtained final products to confirm the optical configuration as *R*.

3.4.2. Synthesis of (–)-horsfiline using a chiral auxiliary

Palmisano et al. have approached the synthesis of horsfiline (**47a**) through the cycloaddition of an azomethine ylide with an α,β-unsaturated ester.[36c] At first, they set the pyrrolidine moiety *via* the cycloaddition of an azomethine ylide with an α,β-unsaturated ester, but the diastereoselectivity of the cycloaddition was disappointingly low. Therefore, they subsequently separated one isomer suitable for (–)-horsfiline through resolution and completed the synthesis of natural (–)-horsfiline. Although it was difficult to classify the asymmetric synthesis of (–)-horsfiline using this method, it was interesting that a 1,3-dipolar cycloaddition was used to construct the pyrrolidine moiety of spiro-oxindole compounds.

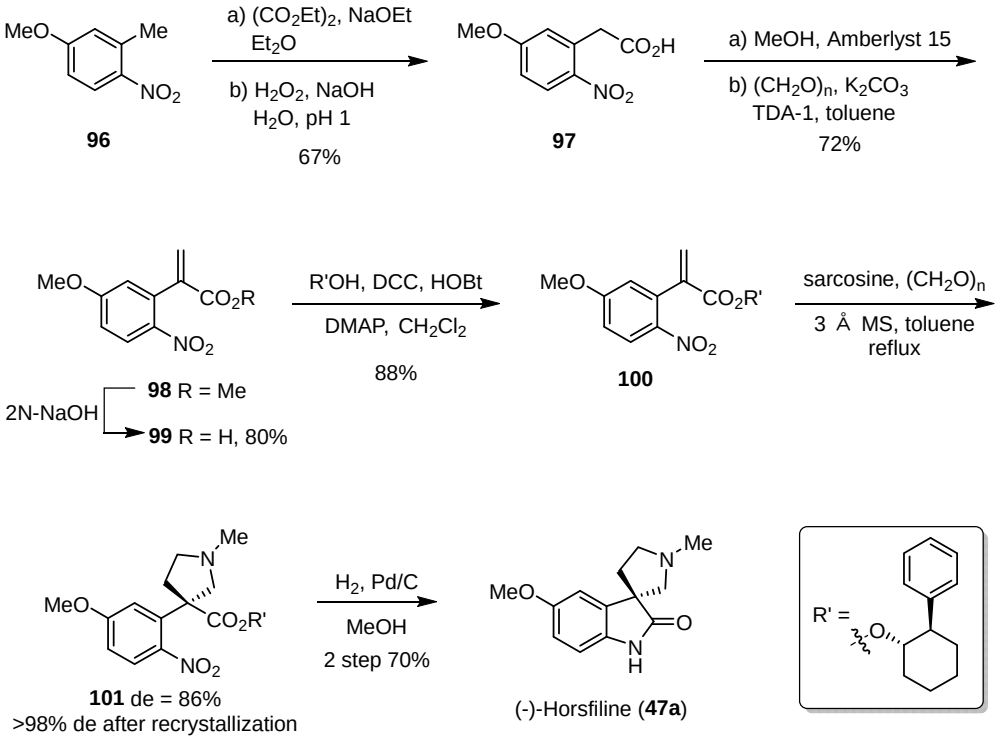
The key step was the cycloaddition of dipolarophile **93** with non-stabilized *N*-methyl-azomethine ylide, which was thermally generated *in situ* from sarcosine and formaldehyde (Scheme 27). The requisite α,β-unsaturated ester **93** was prepared in satisfactory yield by the Wittig homologation of 5-methoxyisatin **91** with (5*R*)- menthyl (triphenylphosphoranylidene)acetate **92** in refluxing diglyme. Although the (-)-menthyl group was selected for generating diastereoselectivity, the result of the cycloaddition was poor (ratio of (-)-(3*S*,4'*R*)-**94**: (-)-(3*R*,4'*S*)-**94** = 39:41). Fortunately, the desired form, (-)-

(3*R*,4'*S*)-**94**, was easily separated by chromatographic separation of the more polar diastereomer. The natural (–)-horsfiline (**47a**) was obtained from (-)-(3*R*,4'*S*)-**94** in 65% overall yield and with good optical purity by cleavage of the chiral auxiliary and subsequent removal of the CO_2H group according to the Barton radical protocol.



Scheme 27. Palmisano's first synthesis of (–)-horsfiline

Since then, Palmisano et al. have improved the intermolecular [3+2] annulation of the azomethine ylide using 2-(2-nitrophenyl)acrylate dienophiles **100** followed by reductive heterocyclization to afford the spiro(indole-pyrrolidine) ring system (Scheme 28).[36d]



Scheme 28. Palmisano's improved asymmetric synthesis of (–)-horsfiline

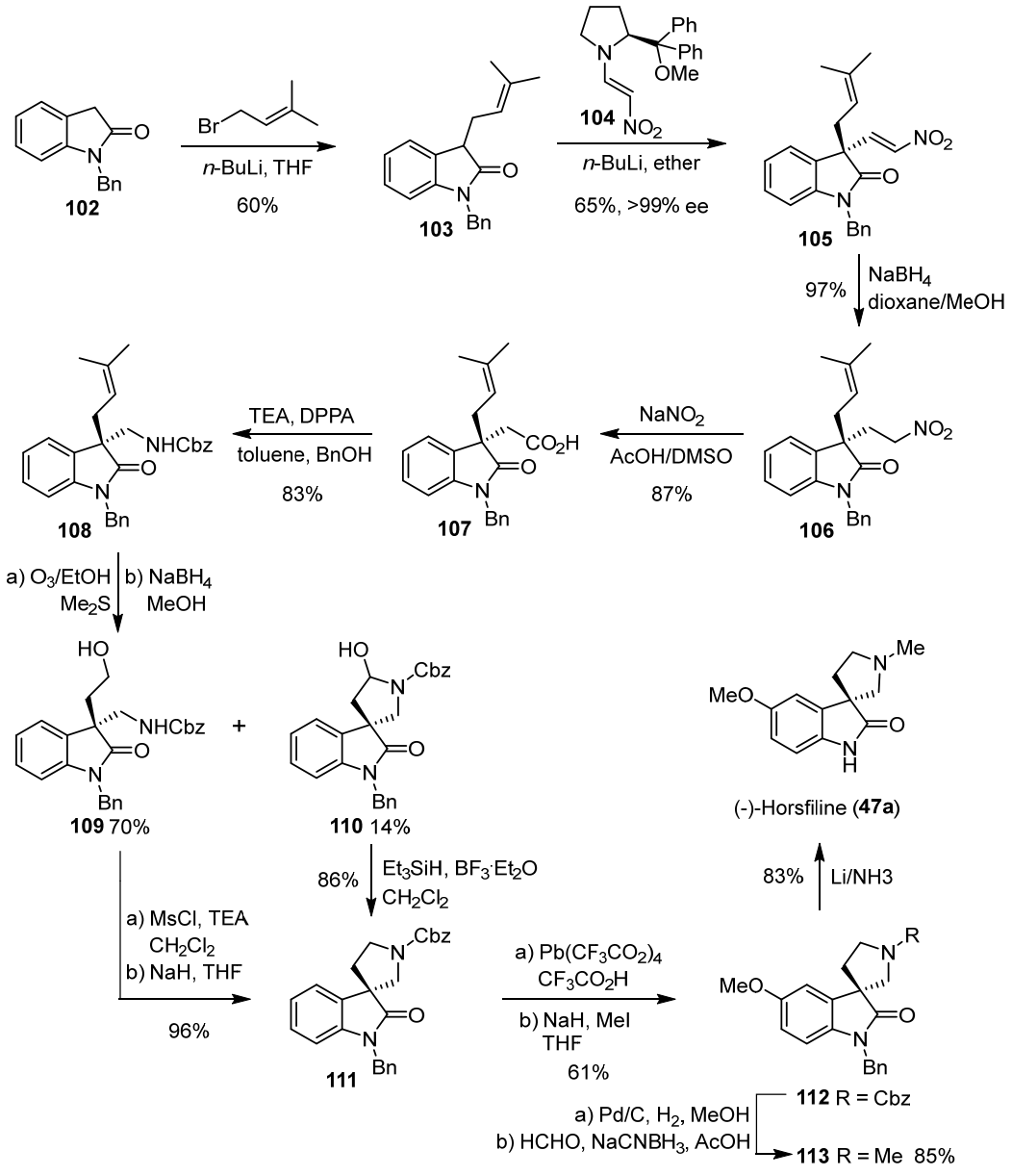
The requisite dienophiles **100** were generated through a series of processes. The Claisen condensation of commercially available 2-nitro-5-methoxytoluene **96** with diethyl oxalate was readily achieved with sodium ethoxide in diethyl ether, without purification, followed by oxidative demolition gave **97** in 67% yield. After esterification, clean methylenation yielded acrylate **98** on treatment with paraformaldehyde in the presence of K_2CO_3 and TDA-1 as a solid-liquid phase-transfer catalyst in toluene. Compound **99** was obtained by general basic hydrolysis, and dienophiles **100** were prepared through a DCC coupling between **99** and auxiliary (R'OH) in 88% yield. Fortunately, the cycloaddition of *N*-methylazomethine ylide with chiral dipolarophiles **100** successfully gave **101** with good diastereoselectivity. Furthermore, recrystallization of the crude mixture of **101**

increased diastereoselectivity to >98% de. Through catalytic hydrogenation, (*R*)-**101** was reduced with the concomitant detachment of the chiral inductor to provide (*R*)-(–)-horsfiline **47a**. Ultimately, Palmisano et al. improved upon a previous approach that showed low stereoselectivity and developed a successful synthetic route to (–)-horsfiline through a highly diastereoselective azomethine ylide cycloaddition followed by reductive lactamization.

3.4.3. Synthesis of (–)-horsfiline using a chiral reagent

Fuji et al. developed synthetic route to (–)-horsfiline using asymmetric nitroolefination as the key step in 1999.[36b] They reported an efficient asymmetric nitroolefination of oxindole derivatives using chiral nitroenamine **104,** and a similar strategy involving the asymmetric nitroolefination of **103** was expected to be well suited to the synthesis of (–)-horsfiline (Scheme29). Oxindole **103** was prepared from **102**, which was readily available from isatin through a known method. A prenyl group was introduced into **102** by treating with 1-bromo-3-methyl-2-butene to furnish **103**, which was followed by asymmetric nitroolefination using chiral nitroenamine **104** to afford **105** in 65% yield with >99% ee. With compound **105** available with high enantiomeric excess, they started to construct the spiropyrrolidine ring system. The nitroolefin was reduced with $NaBH_4$ to give **106** in high yield. The attempted conversion of the nitro group of **106** into a carboxyl group using DMSO/$NaNO_2$/AcOH conditions was successful, affording **107** in 87% yield. Thermal Curtius rearrangement of **107** in benzyl alcohol furnished the corresponding benzoxy carbamate **108** in 83% yield. Ozonolysis of **108** followed by reduction with $NaBH_4$ afforded primary alcohol **109** and cyclic secondary alcohol **110** in 70% and 14% yields,

respectively. The mesylation of **109** followed by base treatment afforded spiropyrrolidine **111**, while reduction of **110** with Et_3SiH in the presence of $BF_3{\cdot}OEt_2$ gave **111**.

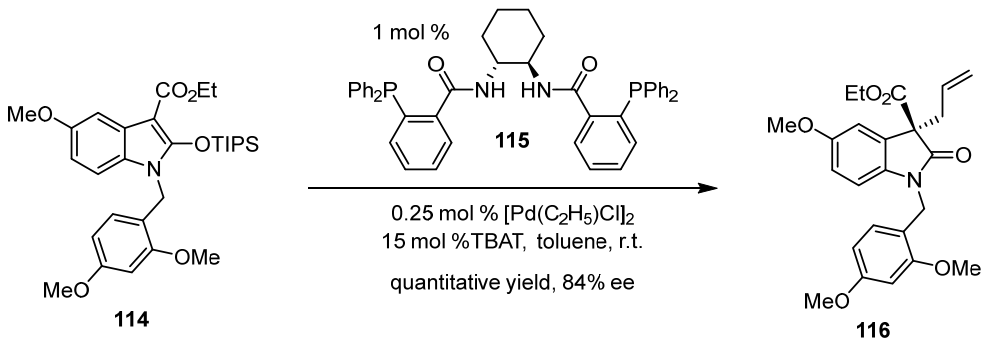


Scheme 29. Synthesis of (–)-horsfiline by Fuji et al.

The regioselective oxidation of **111** at the 5-position was achieved by treatment with $Pb(CF_3CO_2)_4$ in TFA to give a crude phenolic compound which, upon Omethylation, gave **112** in 61% yield. Then, the Cbz group was removed under neutral conditions (Pd-C, H_2, MeOH) at room temperature to yield the free amine. Without purification, the amine was methylated using formaldehyde and $NaCNBH_3$ at room temperature to furnish **113**. Finally, debenzylation was achieved using Li/NH_3 to give **47a,** which had an optical rotation and melting point identical to those of natural (*R*)-(–)-horsfiline.

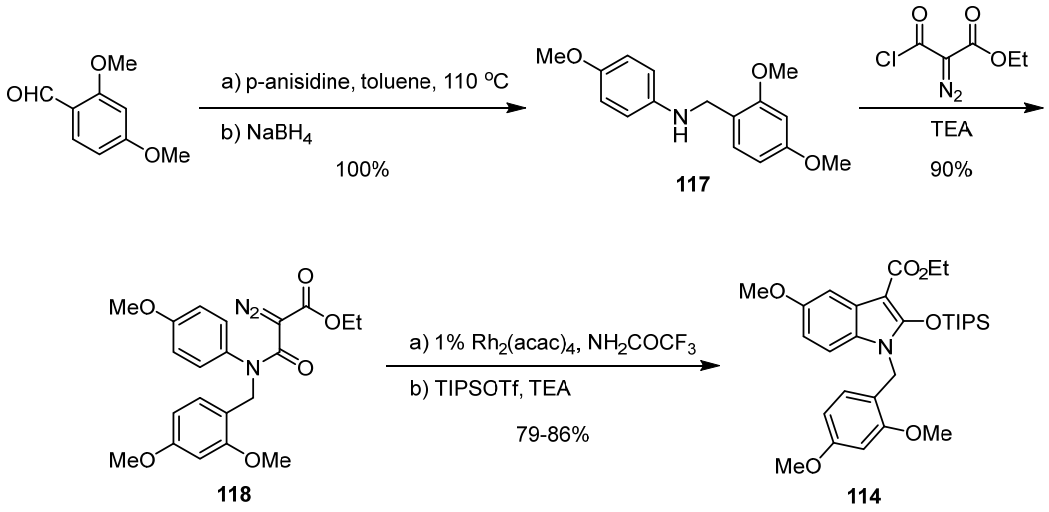
3.4.4. Synthesis of (+)-horsfiline by asymmetric allylic alkylation

In 2006, B. M. Trost and co-workers reported the asymmetric allylic alkylation of the protected oxindole **114** with allyl acetate using chiral ligand **115** in a palladium catalyzed reaction. The enantiomeric excess of **116** was 84% with tetrabutylammonium difluorotriphenylsilicate (TBAT) as a fluoride source in toluene (Scheme 30).[36e] The major enantiomer of **116** could be purified to 98% ee in 69% yield by recrystallizing the minor/major enantiomer pair using heptane or cyclohexane.



Scheme 30. Palladium catalyzed asymmetric allylic alkylation

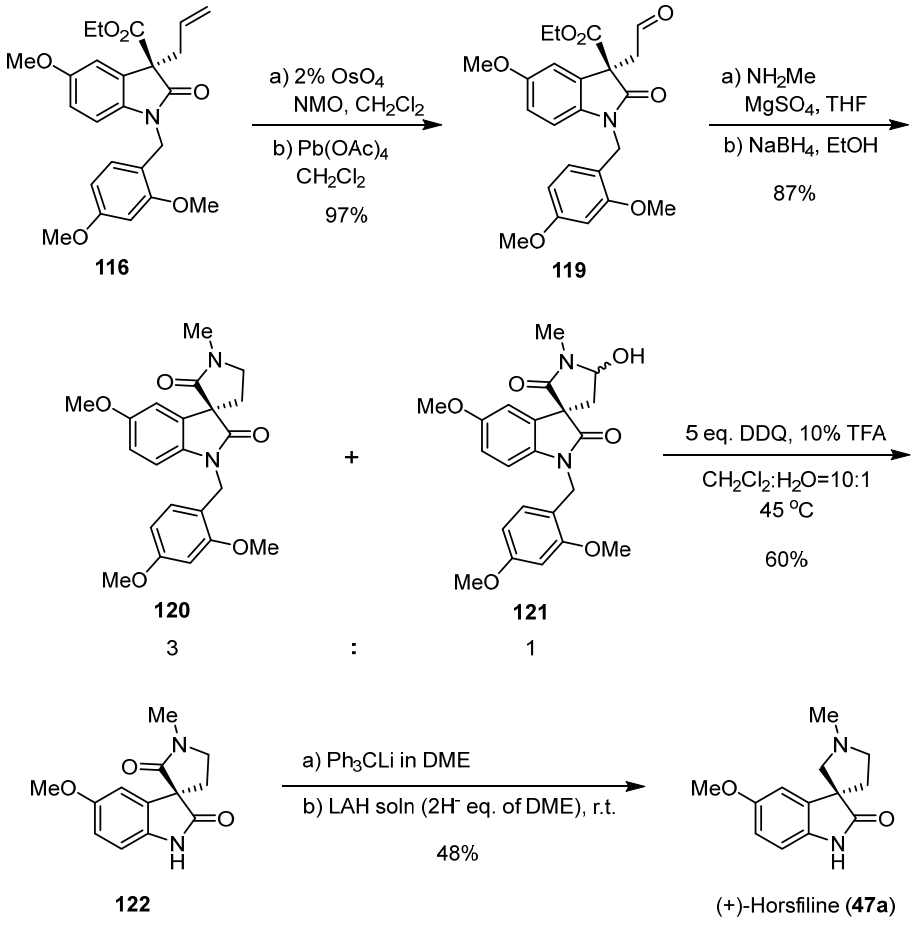
To obtain the protected oxindole **114**, refluxing *p*-anisidine with 2,4-dimethoxybenzaldehyde in toluene followed by the reduction of the imine with sodium borohydride in MeOH resulted in the quantitative yield of the desired amine **117** (Scheme 31). Acylation with the acid chloride derivative of ethyl diazoacetate in the presence of triethylamine led to the formation of amide **118** in 90% yield. Padwa discovered that $Rh_2(acac)_4$ formed the β-lactam with diazoamides containing benzyl protecting groups, whereas the corresponding $Rh_2(CF_3CONH_2)_4$ catalyst led to oxindole formation. Therefore, the Rh C-H insertion of amide **118** followed by protection of the oxindole with TIPSOTf resulted in a 79-86% yield of **114** over two steps when varying the catalyst load from 1 to 3 mol %. Protection of the oxindole was necessary to avoid hydrolysis.



Scheme 31. Synthesis of the protected oxindole core

With the enantiomerically enriched **116** in hand, oxidative cleavage of the allyl group was accomplished using catalytic osmium tetraoxide and *N*-methylmorpholine *N*-oxide (NMO) followed by cleavage of the diol with lead tetraacetate in methylene chloride (Scheme 32). Reductive amination in a two-step procedure, by first forming the imine in

dry THF with $MgSO_4$ and then reducing with $NaBH_4$ in ethanol, provided lactam **120** in 65% yield. The byproduct of the reaction was the lactam alcohol **121**, which presumably forms from cyclization of the hemiaminal onto the ester. Once lactam **120** was formed, only deprotection and a chemoselective reduction remained. Removal of the 2,4-dimethoxybenzyl group from the oxindole nitrogen was accomplished in 60% yield using DDQ in refluxing aqueous methylene chloride.



Scheme 32. Completion of (+)-horsfiline by Trost et al.

The chemoselective reduction of **122** proved to be a difficult challenge. After a lot of challenge, it was finally found that the addition of 2 hydride equivalents of the LAH solution to a prepared solution of **122** and tritylllithium in DME at 0 °C afforded unnatural (+)-horsfiline in 45% yield. With unnatural (+)-horsfiline, a first catalytic total synthesis of the enantiomerically enriched horsfiline was achieved successfully in eight steps and in 11.1% yield.

As one of our research programs for the total synthesis of the natural product, our research team attempted to synthesize enantiomerically enriched (–)-horsfiline using the phase-transfer catalytic α-alkylation of malonates as the key step.

RESULT AND DISCUSSION

1. Chiral malonate derivatives

1.1. Design and synthesis of new malonate substrates for phase-transfer catalytic reactions

Martin O'Donnell's group reported the use of glycine derivatives as substrates in phase-transfer catalytic reactions in 1978.[37a] Since that time, they have measured the pKa values of the conjugate acids of the nucleophiles used in phase-transfer catalytic reactions to determine the suitability of the substrates and concluded that it is appropriate to use substances with pKa values from 16 to 23 in the hydroxide base system used in phase-transfer catalytic reactions.[37b]

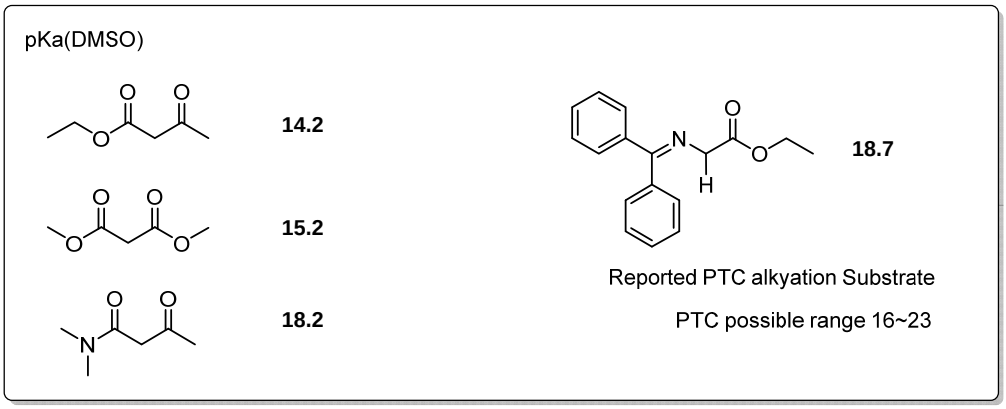
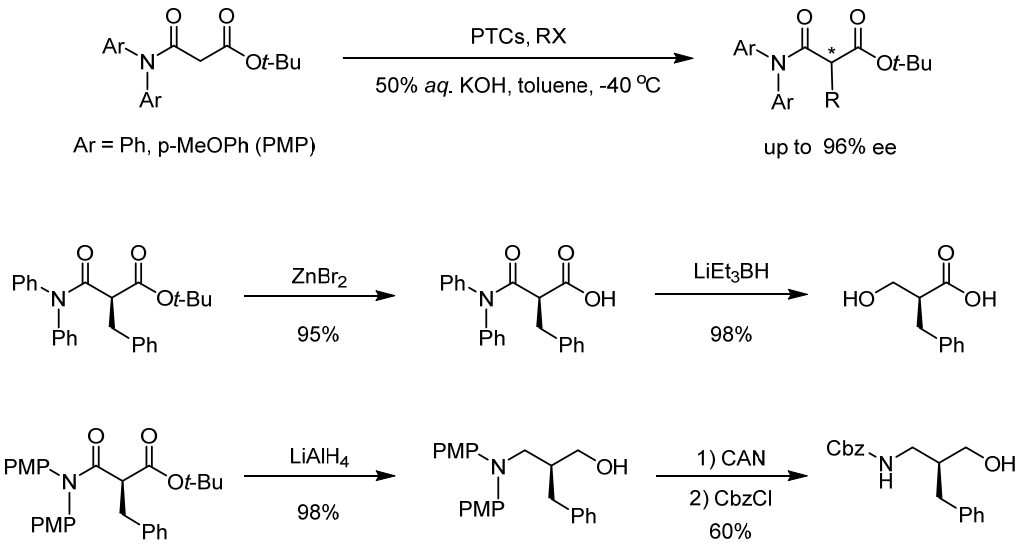


Figure 9. Design of substrates for PTC reactions based on the pKa of the α-proton

Thus, our laboratory group investigated the pKa values of acyclic 1,3-dicarbonyl compounds as substrates for performing the phase-transfer catalytic mono- or di-alkylation.[38] The pKa values of the β-keto esters or malonates were slightly lower than optimal for performing mono-alkylations, and β-keto amides showed values similar to O'Donnell's representative substrates (Figure 9).

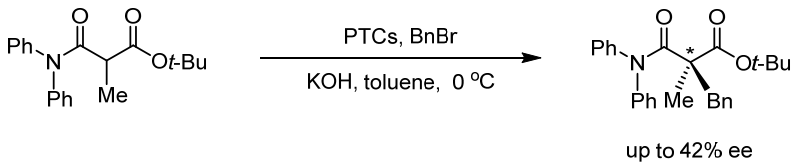
After several studies, our laboratory recently reported a new synthetic method for chiral α-mono-alkylmalonamide esters by the phase-transfer catalytic mono-α-alkylation of *N*,*N*-diarylmalonamide esters and successfully demonstrated its usefulness in the synthesis of various chiral building blocks (Scheme 33).[14c]



Scheme 33. Enantioselective PTC mono-α-alkylation of malonamide esters and their applications

In the malonate substrate system, the α-proton is so acidic that alkaline bases can readily racemize the mono-α-alkylated products of malonate under phase-transfer

catalytic condition. Thus, our research team focused on the phase-transfer catalytic di-alkylation of malonate instead of mono-alkylation. Although PTC alkylation of *N*,*N*-diarylmalonamide esters provided the corresponding mono-alkylated products with high enantioselectivity, dialkylation for the construction of the quaternary carbon center showed both low chemical yields (up to 65%) and poor enantioselectivities (up to 42% ee) due to the low acidity of the second α-proton due to $A_{1,3}$-strain between the *N*-substituents and α-substituents (Scheme 34).[39] In addition, there are some limitations in the derivatization of the chiral malonamide esters to various valuable chiral building blocks due to their relatively low chemical reactivity with respect to amide functionality and the limited chemoselectivity between amide and ester functional groups. In contrast, malonate itself can be easily modified using the the suitable chemical conversion of two different esters. Therefore, our research team attempted to develop a novel enantioselective synthesis of α,α-dialkylmalonates, one of the most fundamental chiral building blocks, via the direct α-alkylation of malonates under phase-transfer catalytic conditions.[40]



Scheme 34. Enantioselective PTC α,α-dialkylation of malonamide esters

First, our research team needed to design enantiotopic asymmetric α-alkylmalonates as substrates for PTC α-alkylation. Because the *tert*-butyl ester group has historically been essential for high enantioselectivity in the previous enantioselective PTC α-alkylations, one of the ester groups in the malonate substrate possessed a *tert*-butyl group (Figure

10).[7a] The other ester group in the malonate substrate contained various alkyl groups, excluding the *tert*-butyl group to maintain asymmetry, that could appropriately interact with phase-transfer catalysts. The substituent at the α-position included alkyl, aryl, halogen and other substituents to expand the scope of substrates.

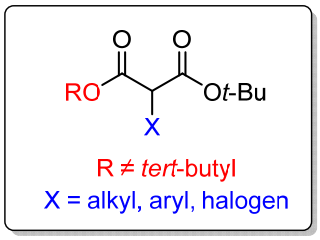
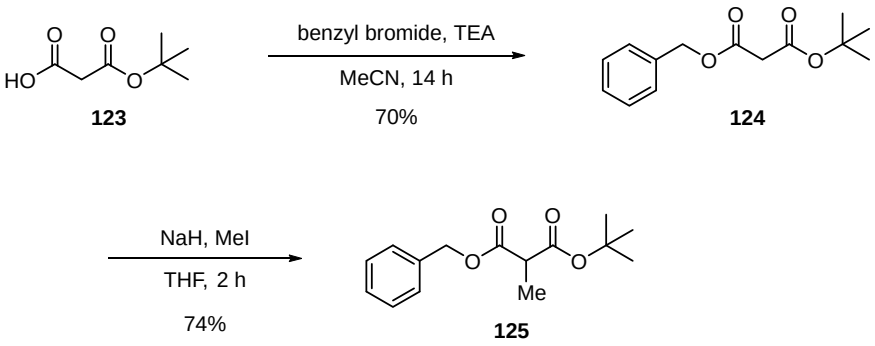


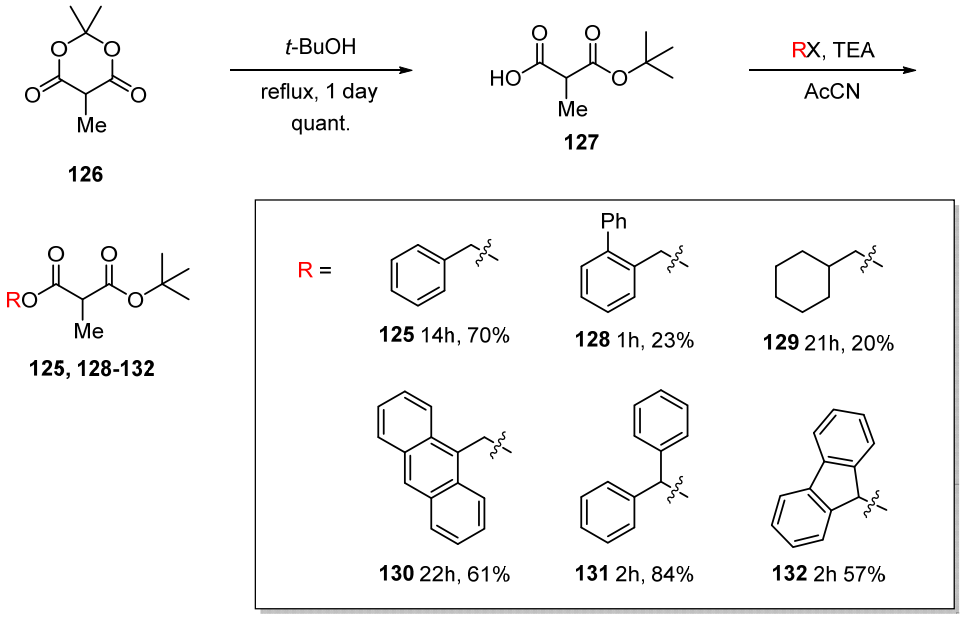
Figure 10. Malonate substrates for PTC reaction

For the preliminary study, benzyl *tert*-butyl α-methylmalonate (**125**), a simple malonate substrate, was prepared in 2 steps from commercially available starting material: benzyl *tert*-butyl malonate (**124**) was synthesized by the esterification of *tert*-butyl hydrogen malonate (**123**) with benzyl bromide, followed by mono-α-methylation with iodomethane to afford the preliminary substrate **125** (Scheme 35).



Scheme 35. Synthesis of preliminary substrate **125**

To optimize the ester group on the opposite side of the *tert*-butyl ester for complexation with phase-transfer catalysts, the benzyl ester had to be changed to various ester groups. However, mono-α-methylation using the above method was too messy and challenging for the synthesis of various substrates because the side products generated during the reaction impeded the isolation of product from the mixture of di-methylation and substrate. Thus, our research team developed a more economic and efficient method for the synthesis of substrates possessing various ester groups, by using esterification as a terminal step. The substrates **125** and **128-132** were prepared in the same 2 steps but were prepared in one step from the key intermediate **127**. Key intermediate **127** was obtained by the tert-butanolysis of commercially available α-methyl Meldrum's acid **126** in quantitative yield, followed by the esterification of intermediate **127** with various alkyl halides to afford six types of substrates, **125** and **128-132** (Scheme 36)



Scheme 36. Synthesis of malonate substrates possessing various ester groups

1.2. Optimization of phase-transfer catalytic reaction with *tert*-butyl-malonates

For the optimization of the phase-transfer catalytic alkylation, our previous reaction conditions were adapted. The enantioselective phase-transfer catalytic benzylation of the preliminary substrate **125** was performed by the representative chiral phase-transfer catalysts (Figure 11 ; **25d**[8b], **26e**[9b], **26f**[9d], **27a'**[10b], **27d**[10c], **27e**[11a] ; 5-10 mol %), along with benzyl bromide (5.0 equiv) and 50% KOH (aq. 5.0 equiv) at 0 °C in toluene. Our research team first thought that the generation of chirality in the direct α-alkylation of α-methylmalonate would be quite challenging due to the variable conformations of the two ester groups.

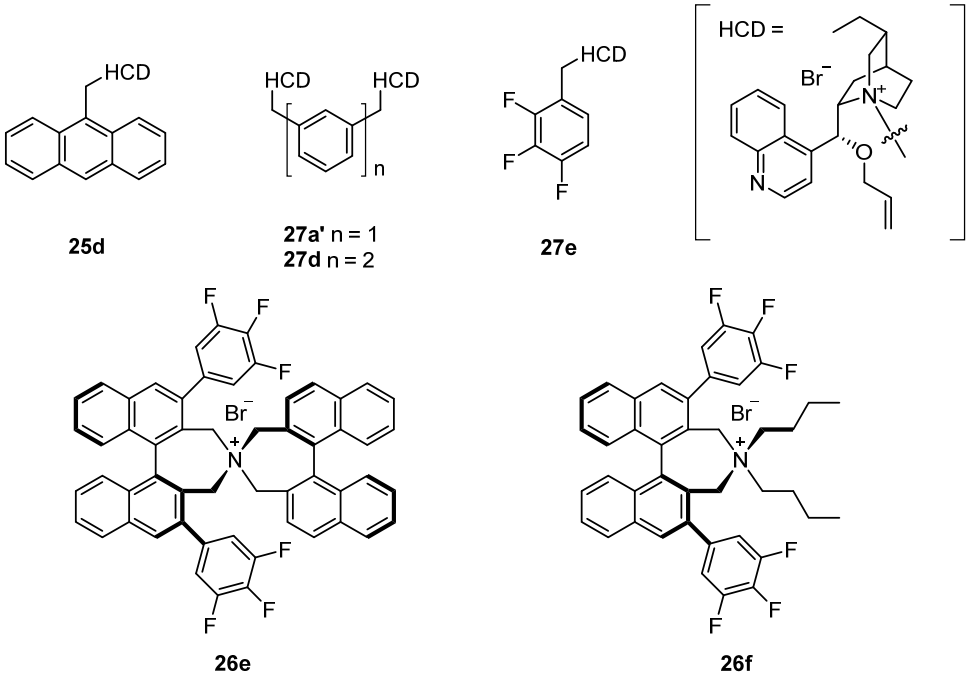
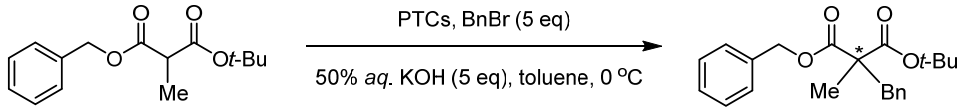


Figure 11. Representative phase-transfer catalysts

However, the result did not match our expectations. As shown in Table 1, catalyst **26e** surprisingly afforded the α-benzylated product (**125d**) with 70% ee and 90% chemical yield (entry 2). Reduced enantioselectivity was observed with **26f** (entry 3, 61%, 49% ee), which had previously showed excellent enantioselective efficiency compared with **26e** in the phase-transfer catalytic alkylation of glycinimine esters **18**.[9d] All of the cinchona-derived catalysts (**25d**, **27a'**, **27d**, **27e**) unfortunately afforded lower enantioselectivities with similar chemical yields similar to those with catalyst **26e**.

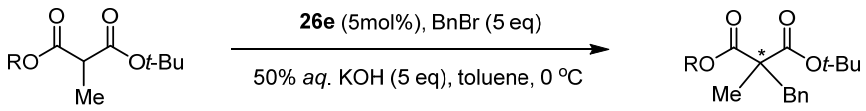
Table 1. Screening of PTCs (**25d**, **26e**, **26f, 27a'**, **27d**, and **27e**)



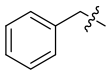
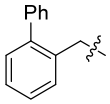
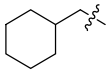
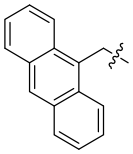
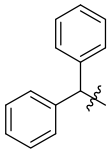
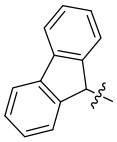
125 **125d**

entry	catalyst (mol%)	time (h)	yield (%)	ee (%)
1	**25d** (10)	17	93	26
2	**26e** (5)	16	90	70
3	**26f** (5)	40	61	49
4	**27a'** (5)	24	84	7
5	**27d** (5)	24	92	70
6	**27e** (10)	15	92	15

Table 2. Screening of substrates **128-132**



125, 128-132 **125d, 128d-132d**

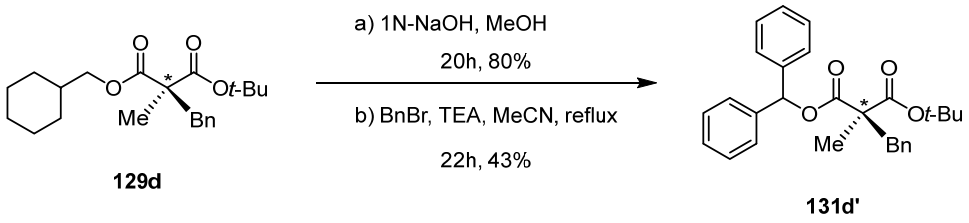
entry	R	substrate	time (h)	yield (%)	ee (%)
1		**125**	16	90	70
2		**128**	13	90	80
3		**129**	60	90	73[a]
4		**130**	19	86	24
5		**131**	13	95	95
6		**132**	16	85	10

[a] Enantiopurity was determined via **131d**, as obtained from **129d**.

The unexpected but promising results prompted us to optimize the structure of malonate substrates to increase enantioselectivity. By varying the ester alkyl groups, five additional alkyl *tert*-butyl α-methylmalonates (**128-132**) were prepared using the above method

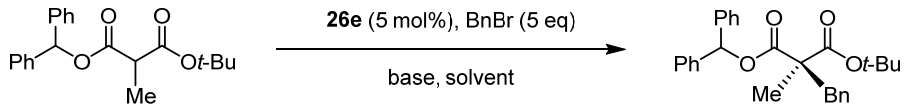
(Scheme 36), and their substrate efficiencies were evaluated by phase-transfer catalytic benzylation in the presence of catalyst **26e** (5 mol%).

As shown in Table 2, the enantioselectivity values differed substantially depending on the alkyl ester group. The 2-biphenyl group (entry 2, **128**, 80% ee) gave a slightly higher enantioselectivity compared to the benzyl group (entry 1, 70% ee), but comparable enantioselectivity was observed with a nonaromatic cyclohexyl group (entry 3, **129**, 73% ee). The 9-anthracenylmethyl group (entry 4, **130**, 24% ee) exhibited quite low enantioselectivity. The best enantioselectivity was achieved with the diphenylmethyl group (entry 5, **131**, 95%ee). It was notable that the fluorenyl group (entry 6, **132**, 10% ee), the cyclized form of the diphenylmethyl group (**131**), showed a loss of enantioselectivity. Its planar geometry might not be suitable for favorable binding to the phase-transfer catalyst **26e**. The benzylated compounds **129d** were not detectable by the UV absorbance used in HPLC analysis; therefore, they needed to be modified to the diphenylmethyl ester forms, which are easily detectable by UV (Scheme 37). The diphenylmethyl ester forms **131d'** were afforded in two steps by hydrolysis and esterification, and the enantiopurities were calculated by HPLC analysis using the same conditions those used with **131d**.



Scheme 37. Modification of cyclohexyl esters to diphenylmethyl esters for HPLC analysis

Table 3. Optimization of reaction conditions with **131** in the presence of **26e**



131 **131d**

entry	solvent	base	temp (°C)	time (h)	yield (%)	ee (%)
1	toluene	50% KOH (5eq)	0	13	95	95
2	CH_2Cl_2	50% KOH (5eq)	0	11	88	82
3	toluene	KOH (5eq)	0	2	90	94
4	toluene	KOH (5eq)	-20	10	90	96
5	toluene	KOH (5eq)	-40	31	95	90
6	toluene	50% CsOH (5eq)	0	30	92	95
7	toluene	CsOH (5eq)	0	24	88	94
8	toluene	50% KOH (2eq)	0	63	83	95
9[a]	toluene	50% KOH (5eq)	0	31	63	78

[a] 2.5 mol % of phase-transfer catalyst **26e** was used.

The reaction conditions were optimized with the best substrate (**131**) by varying the base and the reaction temperature (Table 3). Generally, high enantioselectivities were observed regardless of the base used, but lower enantioselectivity was observed with dichloromethane as a solvent (entry 2, 82% ee). Solid KOH decreased the reaction time compared to 50% aq. KOH, but slightly reduced enantioselectivity and chemical yield

were observed (entry 3, 2 h, 90%, 94% ee). At -20 °C, enantioselectivity was primarily unaffected (entry 4, 96% ee), but a lower temperature of -40 °C slowed the reaction and reduced enantioselectivity (entry 5, 31 h, 90% ee). Comparable enantioselectivities and chemical yields were observed using CsOH as the base, but the reaction was slower (entry 6, 30 h; entry 7, 24 h). Using less base decreased both the chemical yield and the reactivity (entry 8, 63 h, 83%); the use of less catalyst **26e** showed decreased enantioselectivity, chemical yield and reactivity (entry 9, 31 h, 63%, 78% ee). The variation of base, reaction temperature and solvent did not significantly increase both enantioselectivity and chemical yield; thus, our research team selected the initial conditions (entry 1) as optimal.

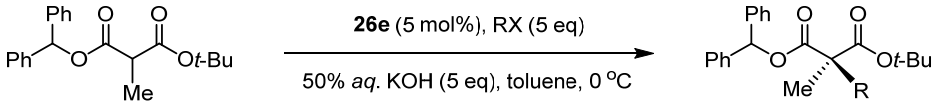
1.3. Scope and limitation of malonate substrates in enantioselective phase-transfer catalytic reaction

1.3.1. Scope of α-methylmalonates in enantioselective phase-transfer catalytic alkylation

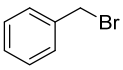
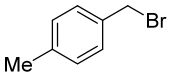
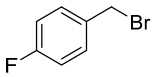
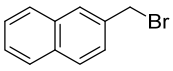
Substrate **131** was chosen for further investigation into the scope and limitations of the enantioselective PTC alkylation with various electrophiles. As shown in Table 4, high chemical yields (87-95%) and enantioselectivities (94-97% ee) were observed for allylic and benzylic halides. The enantiomers of allylated product **131a** were not resolved by HPLC analysis using the chiral columns (entry 1); thus, our research team performed experiments using the alternative allylic bromide (entry 2-3). Various benzylated products **131d-g** showed very high chemical yields and enantioselectivities regardless of the steric and electronic effects of the benzylic bromides.

Absolute configuration was assigned by comparison of the optical rotations of (*R*)-α-methylphenylalanine[41] prepared by acidic hydrolysis of the benzylated product, **131d**; other absolute configurations were tentatively assigned as *R* or *S* based on the absolute configuration (see: Scheme 42).

Table 4. Enantioselective PTC alkylation of **131** with allylic and benzylic halides



131 **131a-g**

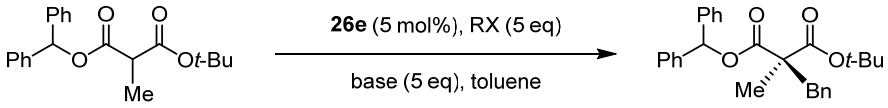
entry	RX	product	time (h)	yield (%)	ee (%)
1		**131a**	14	87	-[a]
2		**131b**	13	87	94 (*S*)
3		**131c**	13	89	94 (*S*)
4		**131d**	13	95	95 (*S*)[b]
5		**131e**	13	95	97 (*S*)
6		**131f**	14	92	95 (*S*)
7		**131g**	13	93	96 (*S*)

[a] Enantiopurity was not determined by HPLC analysis using a chiral columns. [b] Absolute configuration was determined by comparison of the optical rotations of (*R*)-α-methylphenylalanine prepared by acidic hydrolysis of the benzylated product, **131d**.

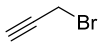
As shown in Table 5, using a propargyl bromide, the desired products were obtained moderate enantioselectivity using the conditions (entry 1). With less reactive aliphatic alkyl halides (ethyl iodide and hexyl iodide), the reaction rates slowed remarkably. Although the enantioselectivities (entry2, 84% ee; entry 3, 87% ee) were good, the desired products were obtained in low chemical yields (30%) even after a few days

stirring under the same conditions. Thus, our research team substituted solid base for aqueous base to accelerate the reaction rates based on the results of the optimization shown in Table 3. Fortunately, our research team obtained satisfactorily fast reaction rates, but slightly reduced enantioselectivities were observed (entry 4, 72% ee; entry 5, 82% ee). Eventually, the best result was obtained at -20 °C using hexyl iodide (entry 6, 80%, 90% ee), but the low temperatures reduced the chemical yield and enantioselectivity (entry 7, 20%, 33% ee).

Table 5. Enantioselective PTC alkylation of **131** with propargyl and aliphatic halides

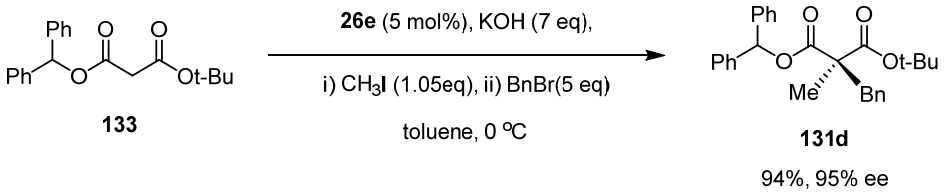


131 **131h-j**

entry	RX	product	base	temp (°C)	time	yield (%)	ee (%)
1		**131h**	50% KOH	0	13h	88	75 (*S*)
2	Ethyl iodide	**131i**	50% KOH	0	4days[a]	30	84 (*S*)
3	Hexyl iodide	**131j**	50% KOH	0	6days[a]	30	87 (*S*)
4	Ethyl iodide	**131i**	KOH	0	1h	99	72 (*S*)
5	Hexyl iodide	**131j**	KOH	0	1h	97	82 (*S*)
6	Hexyl iodide	**131j**	KOH	-20	24h[a]	80	92 (*S*)
7	Hexyl iodide	**131j**	KOH	-40	4days[a]	20	33 (*S*)

[a] Reaction was not completed.

The high enantioselectivities (up to 97% ee) and the broad scope shown in Table 4 and Table 5 indicate that this reaction system is a very efficient enantioselective synthetic method for α,α-dialkylmalonates. In addition, the successive double α-alkylations of α-non-substituted malonate **133** afforded the corresponding α,α-dialkylmalonates without the loss of enantioselectivity and in high chemical yield (Scheme 38). To the best of our knowledge, this is the first report to accomplish enantioselective catalytic direct α-alkylation of malonates.

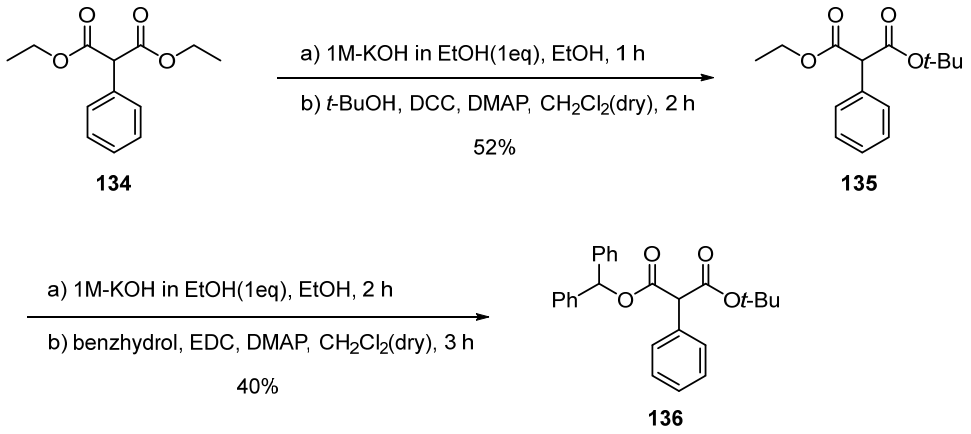


Scheme 38. Double PTC α-alkylations of malonate **133**

1.3.2. Scope of α-arylmalonates in enantioselective phase-transfer catalytic alkylation

Based on the encouraging result with α-methylmalonates, our research team attempted to develop other α-substituted malonate substrates for phase-transfer catalytic alkylation. At first, our research team thought that the aromatic group facilitates the interaction of substrates with phase-transfer catalysts *via* π-π interaction, and our research team tried phase-transfer catalytic alkylation using a simple diphenylmethyl *tert*-butyl α-phenylmalonate **136**. Substrate **136** could be prepared from commercially available diethyl α-phenylmalonate (**134**) in 4 steps (Scheme 39). The partial hydrolysis of diethyl

α-phenylmalonate (**134**) afforded the corresponding mono-acid, which after DCC coupling provided *tert*-butyl ester **135** (52%). Another ethyl ester hydrolysis, followed by EDC coupling gave α-phenylmalonate substrate **136** (31%).

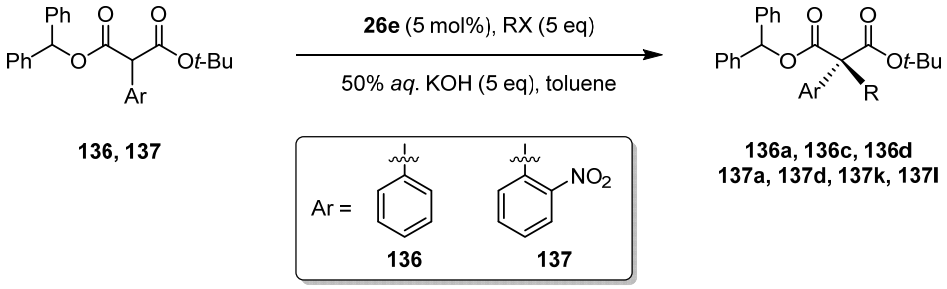


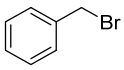
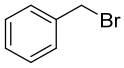
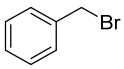
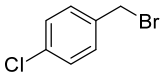
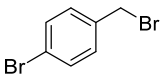
Scheme 39. Synthesis of α-phenylmalonate substrate **136**

As shown in Table 6, α-phenylmalonate showed high enantioselectivity after a short reaction time under the same conditions (entry 1). To further increase the enantioselectivity, the reaction temperature was reduced. The benzylation of **136** at -20 °C gave a very good enantioselectivity (entry 2 98% ee) compared with that at 0 °C. Allylation also showed high chemical yields and enantioselectivities (entry 3, 4). With *ortho*-nitro phenyl substituted substrate **137**, the reaction time was generally longer and the enantioselectivities were lower (entry 5-8) compared with those of **136**.

The absolute configuration was assigned by the X-ray analysis of oxindole derivative **45k**, prepared by the conversion of the *para*-chlorobenzylated product, **137k**; other absolute configurations were tentatively assigned as *R* or *S* based on the absolute configuration (see Figure 12).

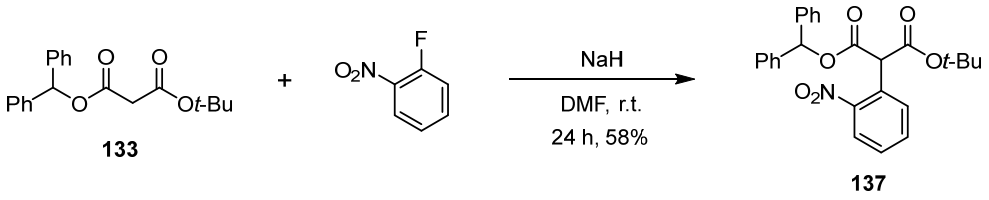
Table 6. Enantioselective PTC alkylation of **136** and **137** with various alkyl halides



entry	substrate	RX	product	temp (°C)	time	yield (%)	ee (%)
1	**136**		**136d**	0	5 h	99	96 (*R*)
2	**136**		**136d**	-20	8 h	90	98 (*R*)
3	**136**		**136a**	-20	14 h	91	95 (*R*)
4	**136**		**136c**	-20	14 h	90	95 (*R*)
5	**137**		**137a**	-20	48 h	96	86 (*R*)
6	**137**		**137d**	-20	20 h	93	95 (*R*)
7	**137**		**137k**	-20	20 h	99	96 (*R*)[a]
8	**137**		**137l**	-20	25 h	98	95 (*R*)

[a] Absolute configuration was assigned as *R* from the X-ray crystal structure of **45k**.

Substrate **137** could be prepared by the nucleophilic aromatic substitution of the α-non-substituted malonate **133** with 2-fluoronitrobenzene in 58% yield (Scheme 40).



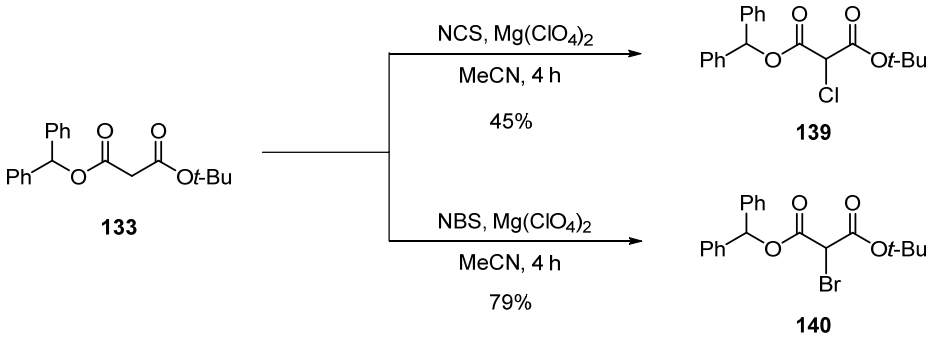
Scheme 40. Synthesis of α-*ortho*-nitrophenylmalonate substrate **137**

1.3.3. Scope of α-halomalonates in enantioselective phase-transfer catalytic alkylation

Malonates possessing an α-halogenated quaternary carbon center have been recognized as privileged elements in organic synthesis for the following reasons. First, a halogenated quaternary carbon center cannot be racemized, although fluorinated quaternary carbon center has a steric environment similar to that of a tertiary carbon center. Second, malonate can be easily modified according to the chemical conversion of the two esters. Third, the high electronegativity of halogens provides molecules with biophysical features such as increased bond energy and lipophilicity, especially in fluorine. Also, because fluorine has the highest electronegativity among all elements and the second smallest van der Waals radius after hydrogen, fluorine can replace hydrogen without changing its steric environment, but it greatly changes the electronic environment through the mimic effect.[42] In spite of these advantages, the enantioselective synthesis of α-fluoromalonate has not been extensively studied; only a few reported studies use an

organometallic catalyst.[5b]

Recently, our laboratory group developed a new enantioselective synthetic method for chiral α-fluoro-α-alkylmalonate under phase-transfer catalytic conditions.[43] Based on the encouraging results with α-alkylmalonates, our research team attempted to expand the phase-transfer catalytic alkylation to the α-halomalonate system for the construction of a quaternary carbon center. Substrate **138** was prepared using a known method[43], and α-chloromalonate **139** and α-bromomalonate **140** were successfully prepared from malonate **133** by direct α-halogenation using *N*-chlorosuccinimide and *N*-bromosuccinimide, respectively, in the presence of magnesium perchlorate (Scheme 41).

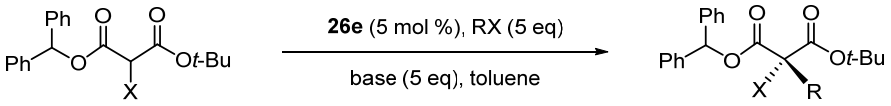


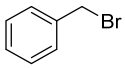
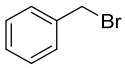
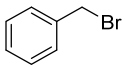
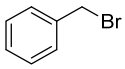
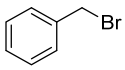
Scheme 41. Preparation of α-halomalonate substrates (**139**, **140**)

As shown in Table 7, the α-benzylated product **138d** could be obtained in 87% ee which is slightly less than that of α-methyl substrate **131** (95% ee in Table 2-4). Our research team speculated that the smaller size of the α-substituent might have less benefit when forming a stable binding conformation with catalyst **26e**. In fact, the α-benzylation of non-substituted diphenylmethyl tert-butylmalonate **133** under PTC conditions in the presence of weak base K_2CO_3 gave the corresponding mono-benzylated product in 65%

ee.[44] In our previous optimization of the base and temperature, the best enantioselectivity was observed with solid CsOH base at -78 ºC (entry 2, 99%, 92% ee); however, the reaction time was quite long (96 h). Thus, our research team finally chose solid KOH at -40 ºC as the optimal reaction conditions (entry 3).

Table 7. Enantioselective phase-transfer alkylation of α-halomalonate



entry	X	RX	base	product	temp	time	yield (%)	ee (%)
1	F(**138**)		50% KOH	**138d**	0°C	13 h	80	87 (*R*)
2	F(**138**)		CsOH	**138d**	-78°C	96 h	99	92 (*R*)
3	F(**138**)		KOH	**138d**	-40°C	20 h	99	90 (*R*)[a]
4	Cl(**139**)		KOH	**139d**	-40°C	5 h	98	93 (*R*)
5	Br(**140**)		KOH	**140d**	-40°C	9 h	99	86 (*R*)
6	Cl(**139**)		KOH	**139a**	-40°C	7 h	99	70 (*R*)
7	Br(**140**)		KOH	**140a**	-40°C	4 h	78	42 (*R*)

[a] Absolute configuration was assigned as *R* by comparison with a reported value. [43]

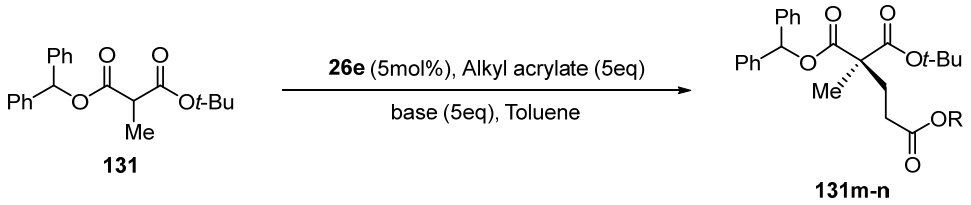
The α-benzylation of **139** and **140** were performed under these optimized reaction conditions. Similar enantioselectivities and chemical yields were observed, as shown in entries 4 and 5. Although the α-allylation of **139** showed moderate enantioselectivity (entry 6), that of **140** showed poor chemical yield and enantioselectivity (entry 7). Our research team speculated that the larger size of the α-substituent might obstruct the approaching electrophile; thus, a suitably sized α-substituent might be crucial for high enantioselectivity.

The absolute configuration was assigned as *R* by the comparison of the optical rotation of the compound derived from benzylated product **138d** with a reported value[43]; other absolute configurations were tentatively assigned as *R* based on the absolute configuration.

1.3.4. Limitation of α-methylmalonates in enantioselective phase-transfer catalytic Michael reaction

Based on the encouraging results from phase-transfer catalytic alkylation, our research team attempted to expand the reaction scope to Michael reactions for the construction of a quaternary carbon center. Our research team expected that the phase-transfer catalytic system could be used in Michael reactions as well as in alkylation if the substrate were the same. For an initial experiment of the phase-transfer catalytic Michael reaction, substrate **131** was chosen as the Michael donor, and ethyl acrylate was chosen as the Michael acceptor. The enantioselective phase-transfer catalytic Michael reaction of substrate **131** was performed using our previous reaction conditions.

Table 8. Enantioselective PTC Michael reaction of α-methylmalonate **131**



entry	R	base	product	temp (°C)	time	yield (%)	ee (%)
1	Ethyl	50% KOH	**131m**	0	<1 h	90	75 (*S*)
2	*t*-Butyl	50% KOH	**131n**	0	<1 h	88	66 (*S*)
3	Ethyl	50% KOH	**131m**	-20	<1 h	85	77 (*S*)
4	Ethyl	50% KOH	**131m**	-40	1 h	60	73 (*S*)
5	Ethyl	KOH	**131m**	-40	<1 h	90	68 (*S*)
6	Ethyl	KOH	**131m**	-78	3 days[a]	50	20 (*S*)
7	Ethyl	$CsCO_3$	**131m**	-78	3 days[b]	-	-
8	Ethyl	CsOH	**131m**	-78	4 days	87	6 (*S*)

[a] Reaction was not completed. [b] Reaction did not proceed.

However, the result defied our expectations; the enantioselectivity was not satisfactory. As shown in Table 8, moderate enantioselectivity was observed under the previous conditions, but the reaction time was very short (entry 1, 90%, 75% ee). Our research team speculated that the reactivity of the Michael reaction was much higher than that of alkylation; thus, the reaction conditions were modified in two ways to improve

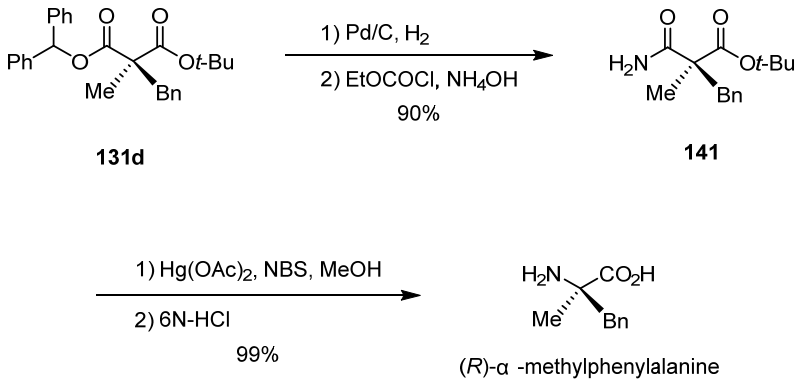
enantioselectivity. First, *tert*-butyl acrylate was used instead of ethyl acrylate as a Michael acceptor for improving the steric hindrance of the electrophile. Unexpectedly, using *tert*-butyl acrylate showed worse results for both chemical yield and enantioselectivity (entry 2, 88%, 66% ee). Second, our research team believed that better enantioselectivity could be achieved at low temperatures based on previous phase-transfer catalytic reactions. Unfortunately, reducing the reaction temperature to -20 °C did not affect the enantioselectivity (entry 3, 77% ee), and further reducing the temperature to -40 °C did not change the reaction time but reduced the chemical yield and enantioselectivity (entry 4, 60%, 73% ee). Additionally, similar enantioselectivities were observed with solid base (entry 5 90%, 68% ee); the worst result was observed at -78 °C regardless of the base utilized (entries 6-8).

The absolute configuration was tentatively assigned by comparison of the above benzylated product **131d** (see Table 4). Although the phase-transfer Michael reaction was limited in enantioselectivity, its high reactivity and chemical yield render this method useful.

1.4. Application and confirmation of absolute configuration

1.4.1. Application to (*R*)-α-methylphenylalanine and absolute configuration of α-methyl-α-alkylmalonates

The synthetic potential of this method has been demonstrated via the synthesis of (*R*)-α-methylphenylalanine from **131d**, as shown in Scheme 42. Optically active α,α-dialkylmalonates could be readily converted to non-natural α-amino acids. The catalytic hydrogenation of **131d** with Pd/C-H_2 followed by acid activation and ammonolysis gave *tert*-butyl malonamide ester **141**. The Hofmann rearrangement of **141**[45] followed by acidic hydrolysis provided α-methylphenylalanine (90%).



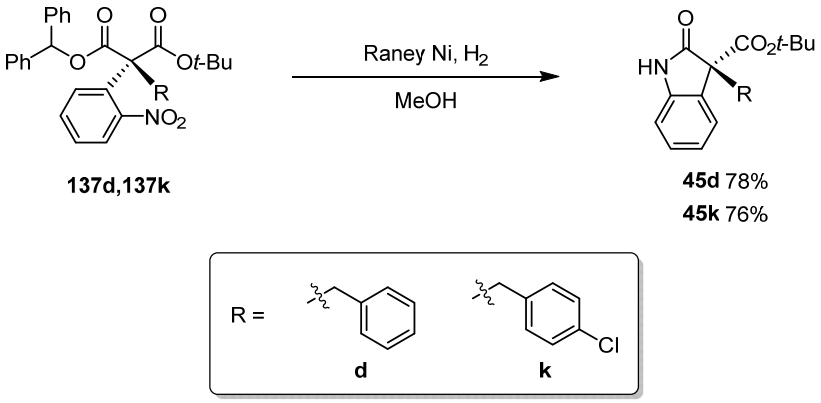
Scheme 42. Synthesis of (*R*)-α-methylphenylalanine

To confirm the absolute configuration of α,α-dialkylmalonates **131b-j** and **131m-n** from α-methyl-malonic acid diphenylmethyl ester *tert*-butyl ester (**131**), the optical rotation of the synthesized (*R*)-α-methylphenylalanine {$[\alpha]_D^{20}$ = +14.1 (*c* 0.5, H_2O)} was compared with the reported value {(*R*)-α-methylphenylalanine, $[\alpha]_D^{20}$ = +6.3 (*c* 1.03, H_2O)}, which

revealed the absolute configuration of **131d** as *S*.[41] The absolute configuration of the benzylated product **131d** was assigned as *S*, and the absolute configurations of the other α,α-dialkylmalonates, **131b-j** and **131m-n,** were tentatively assigned as *S* based on that of **131d**.

1.4.2. Application to oxindole derivatives and absolute configuration of α-aryl-α-alkylmalonates

To expand the applications of this synthetic method, our research team attempted to develop new synthetic methods for representative chiral building blocks. The oxindole derivatives have shown diverse biological activity in humans; thus, these have attracted the attention of many scientists. Therefore, the oxindole moiety was prioritized among the diverse target building blocks.



Scheme 43. Conversion of α-*ortho*-nitrophenyl malonates to oxindole derivatives

Optically active α-alkyl-α-(*ortho*-nitrophenyl)-diphenylmethyl-*tert*-butyl-malonate (**137d**, **137k**) could be readily converted to oxindole derivatives in one step, as shown in Scheme 43. The reduction of **137d** and **137k** by Raney Ni hydrogenation provided α,α-dialkyloxindoles **45d** (78%) and **45k** (76%), respectively. This method can be applied to the synthesis of oxindole-based natural products, including (–)-horsfiline, spirotryprostatin B, aspidospermidine, and mersicarpine.

To confirm the absolute configuration of the alkylated products in Table 6 from α-aryl-malonic acid diphenylmethyl ester *tert*-butyl ester (**136**, **137**), similar organic compounds with previously known absolute configurations were sought and investigated. However, similar optically active organic compounds could not be found. Therefore, to confirm the absolute configuration, one of the alkylated products in Table 6 should be recrystallized for X-ray analysis. However, these alkylated products could not be recrystallized because they are oils. Thus, our research team changed the target compounds from these alkylated products to oxindole derivatives (**45d**, **45k)**; compound **45k**, with a heavy chlorine atom, was chosen for recrystallization and X-ray analysis. Alkylated product **137l**, which has a heavy bromine atom, was excluded from conversion to oxindole derivatives because the bromine atom was removed during hydrogenation.

As shown in Figure 12, the X-ray crystallographic structure of compound **45k** was obtained, showing (*R*)-**45k**. Other absolute configurations of alkylated products in Table 6 were tentatively assigned as *R* based on the absolute configuration of **137k** and the phase-transfer catalytic mechanism.[8]

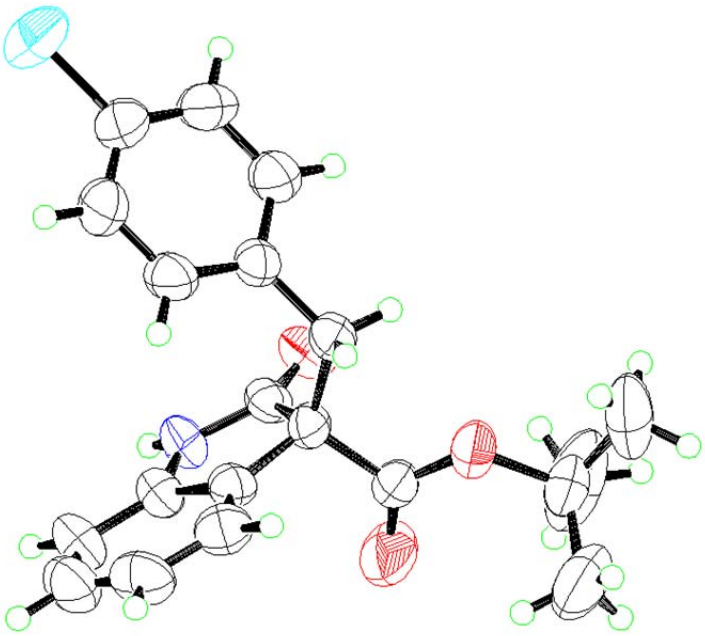


Figure 12. X-ray crystallographic structure of (*R*)-**45k**

This new catalytic system provides an attractive synthetic method for universal chiral building blocks that could be readily converted to versatile chiral target molecules involving quaternary carbon centers.

2. Asymmetric total synthesis of (–)-horsfiline

As mentioned above, our research team developed a new synthetic method for chiral α,α-dialkylmalonates by the enantioselective phase-transfer catalytic α-alkylation of diphenylmethyl *tert*-butyl α-alkylmalonates in the presence of (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide (**26e**) and successfully demonstrated its utility by conversion to versatile chiral intermediates for the construction of the quaternary carbon center including the oxindole skeleton (Scheme 43). Given this set of results, our research team attempted to apply our novel method to the synthesis of a representative spirooxindole alkaloid, (–)-horsfiline, as the first application of our methodology for the total synthesis of a natural product.

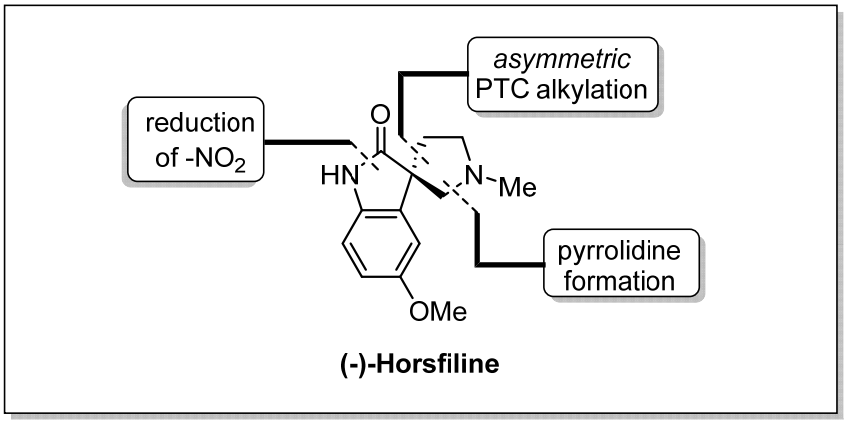


Figure 13. Synthetic approach to (–)-horsfiline

The synthetic approach to (–)-horsfiline is pictured in Figure 13. The oxindole skeleton could be made by reducing the nitro group. The chiral quaternary carbon center could be constructed by asymmetric phase-transfer catalytic alkylation, and the pyrrolidinyl-spiro-skeleton could be obtained through pyrrolidine formation.

2.1. Diverse attempts to synthesize the spiro-oxindole moiety

As mentioned in Scheme 32, the Trost group completed the synthesis of (+)-horsfiline in 2006 using the chemoselective reduction of (*R*)-**122** as the terminal step.[36e] At first, as a formal synthesis of horsfiline, our synthetic target was spirooxindole **122** because our research team considered it easier to synthesize from α,α-dialkylmalonate possessing dicarbonyl group. As shown in the retrosynthetic analysis (Figure 14), the spirooxindole skeleton of (*S*)-**122** can, in principle, be obtained to form the *N*-methyllactam from oxindole **142**, which can be obtained by the chemical conversion of the α,α-disubstituents of oxindole **143**. The oxindole moiety of **143** can be constructed by intramolecular lactamization of (*S*)-**144a** after reduction of the nitro group, and optically active (*S*)-**144a** can be derived from the enantioselective phase-transfer catalytic allylation of **144** in the presence of (*R*,*R*)-**26e**.

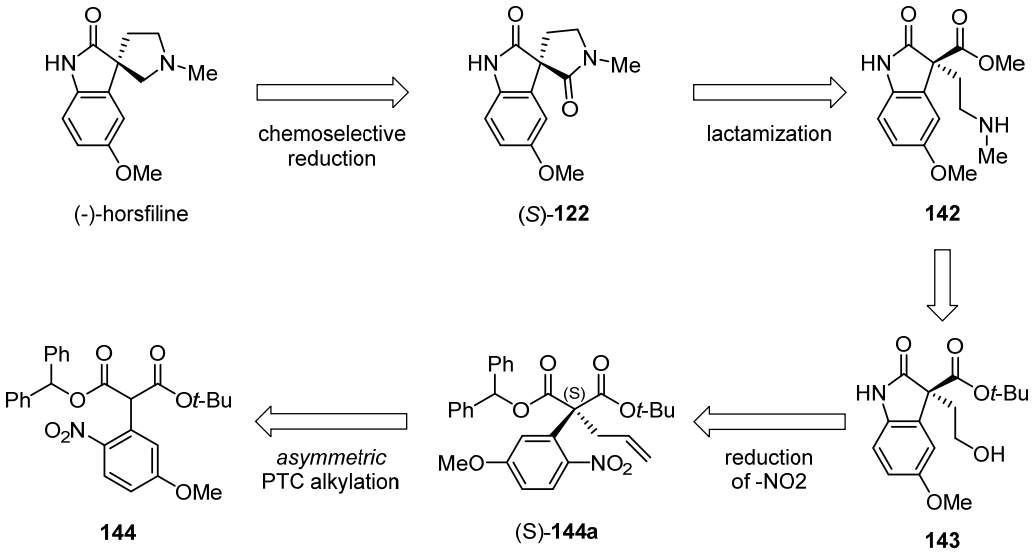
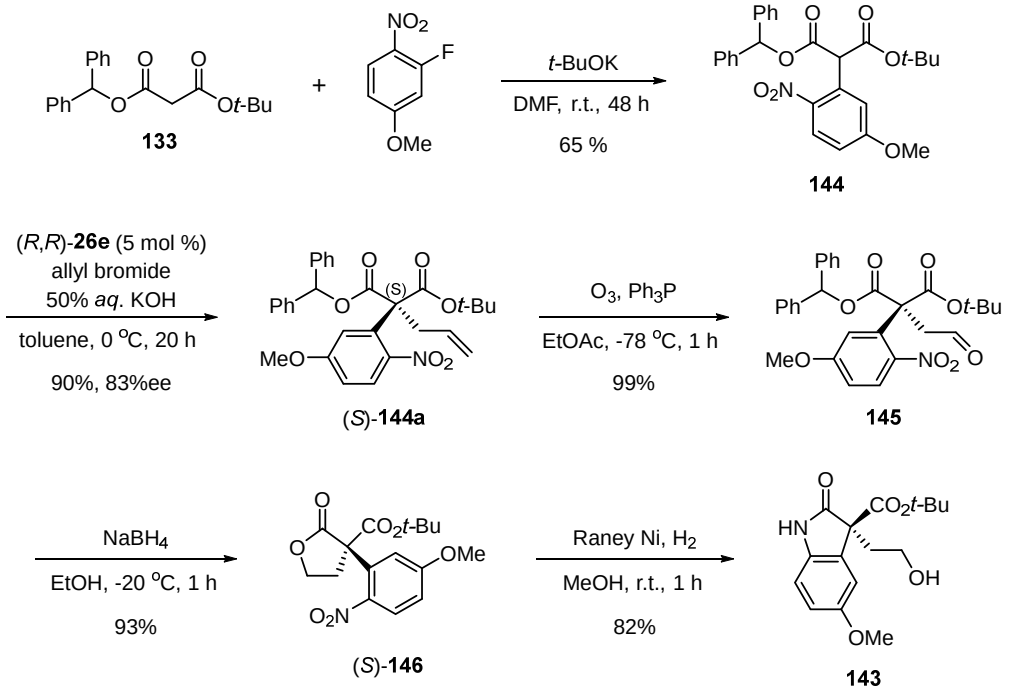


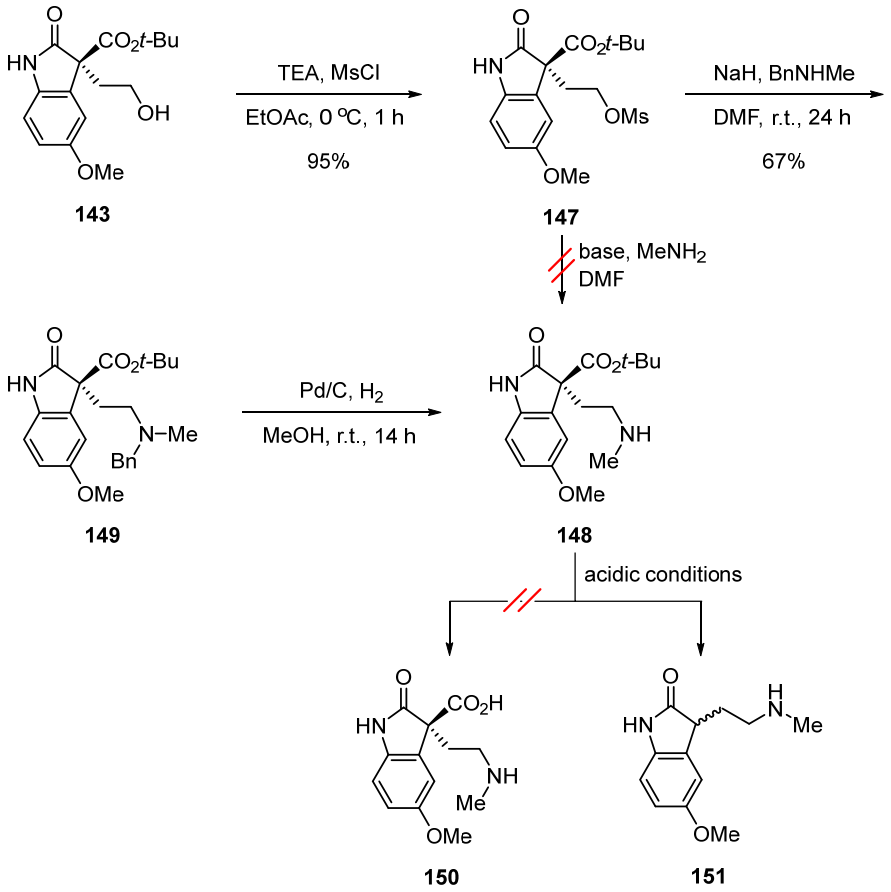
Figure 14. First retrosynthetic analysis of (–)-horsfiline



Scheme 44. Synthesis of oxindole intermediate **143** in the first trial synthesis of (–)-horsfiline

First, substrate **144** for phase-transfer catalytic allylation was prepared from diphenylmethyl *tert*-butyl malonate **133** (Scheme 44). The nucleophilic aromatic substitution of **133** with 2-fluoro-4-methoxy-1-nitro-benzene with *t*-BuOK in dimethylformamide at room temperature afforded α-arylmalonate **144** (65%).[46] As a preliminary study, the enantioselective allylation of **144** was performed under the previously optimized phase-transfer catalysis conditions (see Table 3). The phase-transfer catalytic allylation of **144** in the presence of (*R*,*R*)-**26e** with allyl bromide and 50% KOH at 0 °C in toluene gave the allylated compound (*S*)-**144a** (90%, 83% ee). Before our research team investigated the optimization of phase-transfer catalytic allylation to obtain higher enantioselectivity, our research team first studied the potential of our retrosynthetic

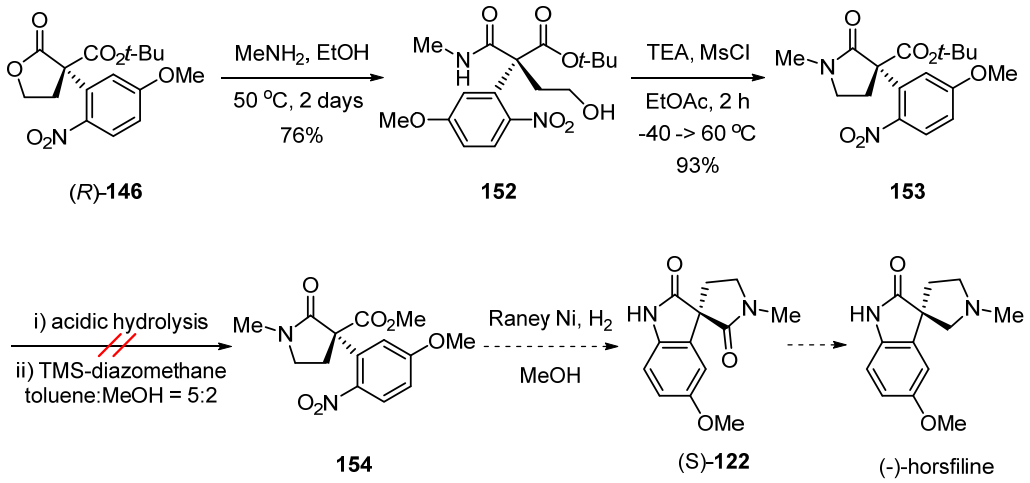
approach. Ozonolysis of (*S*)-**144a**, followed by reductive work up in the presence of triphenylphosphine afforded the corresponding aldehyde **145**. Aldehyde **145** was reduced by sodium borohydride in ethanol at -20 ºC to provide lactone (*S*)-**146** *via* intramolecular lactonization. The reduction of the nitro group of (*S*)-**146** by Raney Ni hydrogenation formed the oxindole moiety of **143** *via* intramolecular lactamization.



Scheme 45. Unsuccessful first trial synthesis of (–)-horsfiline

After obtaining oxindole **143**, the chemical conversion of the α,α-disubstituents of oxindole **143** was attempted. First, the hydroxyl group of **143** must be converted to *N*-

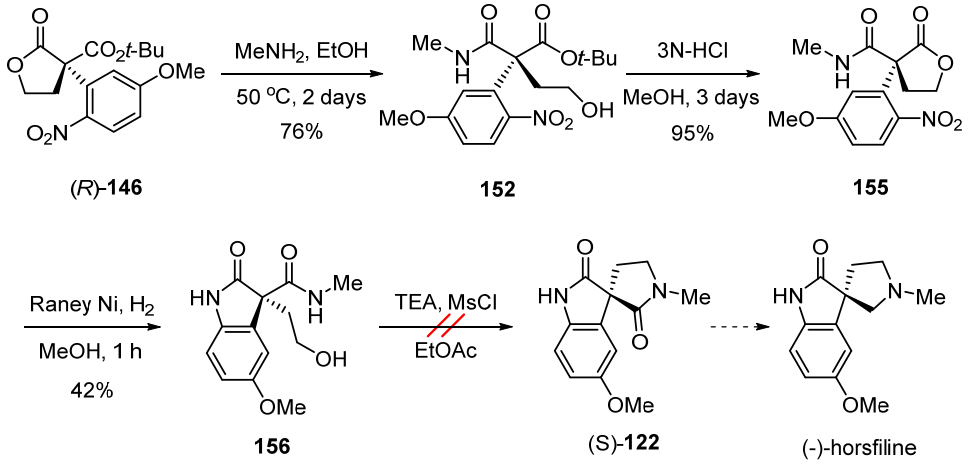
methyl amine, which is fundamental to the composition of horsfiline. Second, the *tert*-butyl ester group of **143** must be modified to methyl ester or ethyl ester, which are more easily attacked by a nucleophile than the *tert*-butyl ester, due to steric hindrance. As shown in Scheme 45, the mesylation of the hydroxyl group of **143** gave **147,** which can be attacked by an amine nucleophile. Unexpectedly, conversion to *N*-methyl amine failed to produce **148** on treatment with *N*-methyl amine under basic conditions. In contrast, conversion to *N*-methyl benzylamine was successful in obtaining **149**, which was followed by cleavage of the benzyl group using hydrogenation to produce compound **148**. Next, our research team attempted the trans-esterification of the *tert*-butyl ester group of **148**, but cleavage of the *tert*-butyl ester group under various acidic conditions, such as HCl or TFA, failed. Instead of the desired product **150**, the side product **151** was observed from decarboxylation.



Scheme 46. Unsuccessful second trial synthesis of (–)-horsfiline

Our research team speculated that the carboxyl group at the α-position of oxindole was more susceptible to decarboxylation under acidic conditions, so our synthetic plan was amended as shown in Scheme 46. At first, our research team performed lactamization

prior to oxindole formation, which was the terminal step. To synthesize (–)-horsfiline, lactone (*R*)-**146** was prepared through the above processes including phase-transfer catalytic allylation using (*S*,*S*)-**26e** (82% ee). The aminolysis of lactone (*R*)-**146** with *N*-methyl amine gave desired compound **152**, and the mesylation of **152** produced lactam **153** through an unusual lactamization with *N-mono*-methyl amide as a nucleophile. Our research team attempted to cleave the *tert*-butyl ester under acidic conditions followed by attempted methylation using TMS-diazomethane, but the desired methyl ester **154** could not be obtained for unknown reasons.



Scheme 47. Unsuccessful third trial synthesis of (–)-horsfiline

At that time, our synthetic plan was modified again by changing the order of the reactions, as shown in Scheme 47. After aminolysis, the addition of 3N HCl solution cleaved the *tert*-butyl group of compound **152**, and a lactone ring was formed with the opposite ester of (*R*)-**146** under acidic conditions. At this stage, the reduction of the nitro group of **155** by Raney Ni hydrogenation gave the oxindole moiety of **156** through an intramolecular lactamization that accompanied lactone ring opening. However,

mesylation of **156** could not produce (*S*)-**122**, which was different from the previous results obtained in the synthesis of **153**. Our research team speculated that the spiro-oxindole moiety could not be formed because of ring strain.

After several failed trial syntheses of (–)-horsfiline, our attention turned from a formal synthesis to a total synthesis for the following reasons. First, cleavage of the *tert*-butyl ester, which is crucial for high enantioselectivity in the phase-transfer alkylation, was very difficult in the dicarbonyl systems of **148** and **153**. Second, lactamization of **156** was difficult due to the weak nucleophilicity of the amide and the ring strain of the spiro-oxindole moiety. To succeed in the total synthesis of (–)-horsfiline from α,α-dialkylmalonate, one of the two carbonyl groups must be reduced. However, because chiral α,α-dialkylmalonate has two different ester groups with similar functionality, the chemoselective reduction of a single ester group was very challenging. Our research team carefully prepared a second retrosynthetic strategy after reflection.

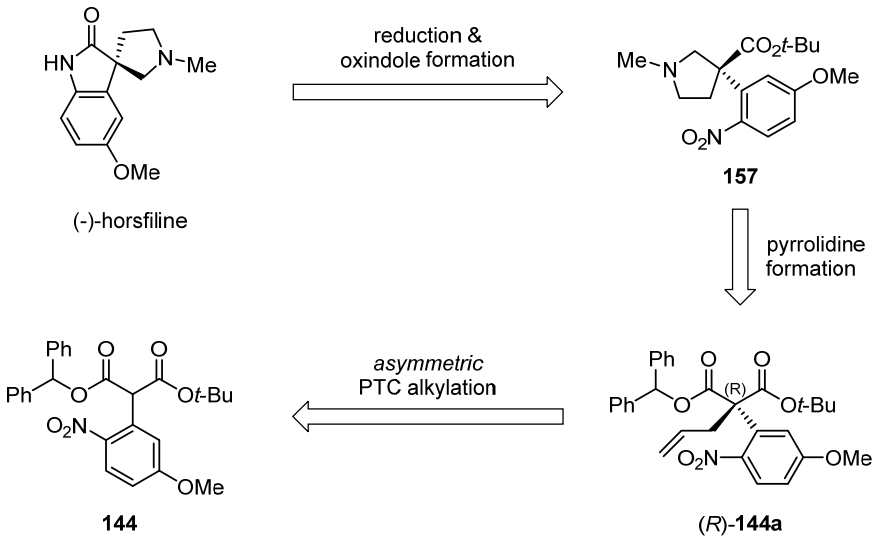
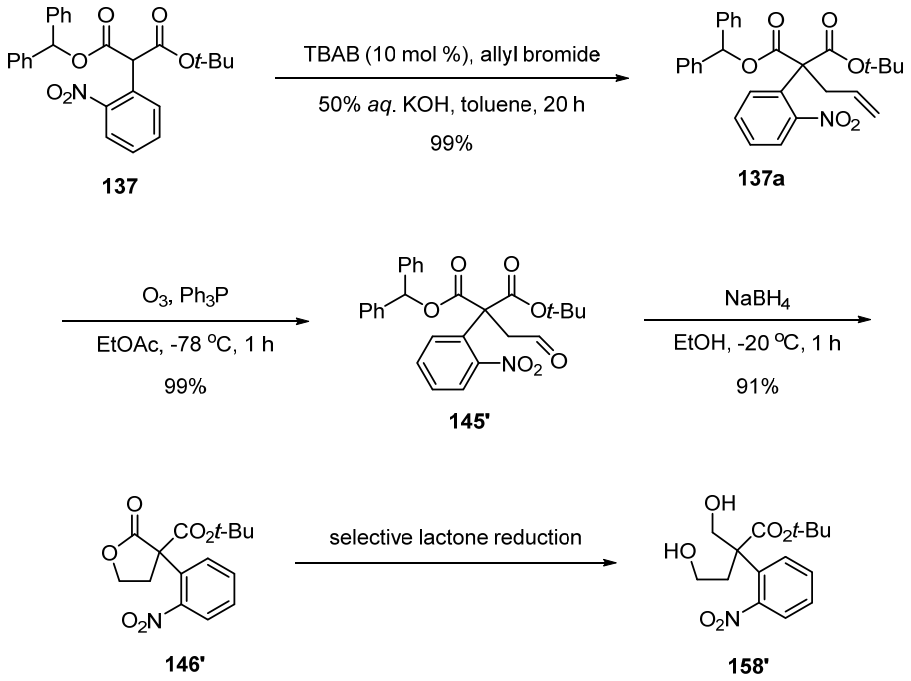


Figure 15. Second retrosynthetic analysis of (–)-horsfiline

The second retrosynthetic analysis is shown in Figure 15. Our research team changed the synthetic route to the construction of the *N*-methylpyrrolidine moiety from (*R*)-**144a** instead of lactamization. The challenging reduction of a single ester group must be accomplished at this stage.

2.2. Total synthesis of (±)-coerulescine

Before our research team initiated the total synthesis of (–)-horsfiline according to our second retrosynthetic analysis, a model study was performed using the more simple compound **137** to decide if this strategy was suitable for the total synthesis of (–)-horsfiline. Compounds **137** and **144** are very similar, but they differ in the presence of a methoxy group attached to a phenyl group. Our model study proceeded with racemic compound, and if our strategy was completed successfully, (±)-coerulescine could be obtained from compound **137**.

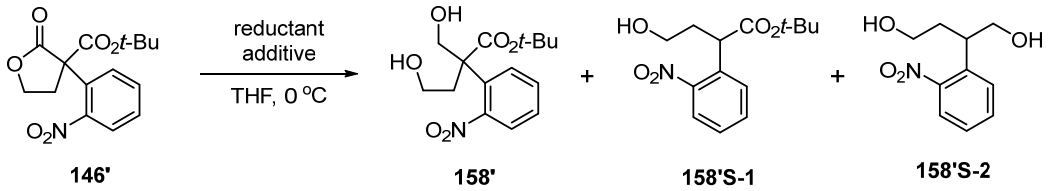


Scheme 48. Beginning of synthesis of (±)-coerulescine as a model study

As shown in Scheme 48, lactone **146'** was prepared from **137** using a procedure similar to that for **146** in Scheme 44. Then, the challenging reduction of a lactone group was

performed. Fortunately, the lactone moiety of **146'** could be reduced to the corresponding diol **158'** by treatment with lithium borohydride in tetrahydrofuran.[47a] Removal of the α-hydroxymethyl group was partially observed as a side reaction by deformylation via the retroaldol reaction of **158'**, which was caused by the α-nitrophenyl group and gave the side-product **158'S-1**. In addition, the *tert*-butyl ester group was also partially reduced by lithium borohydride as a side reaction, resulting in side-product **158'S-2**.

Table 9. Optimization of reaction conditions for the selective reduction of lactone **146'**

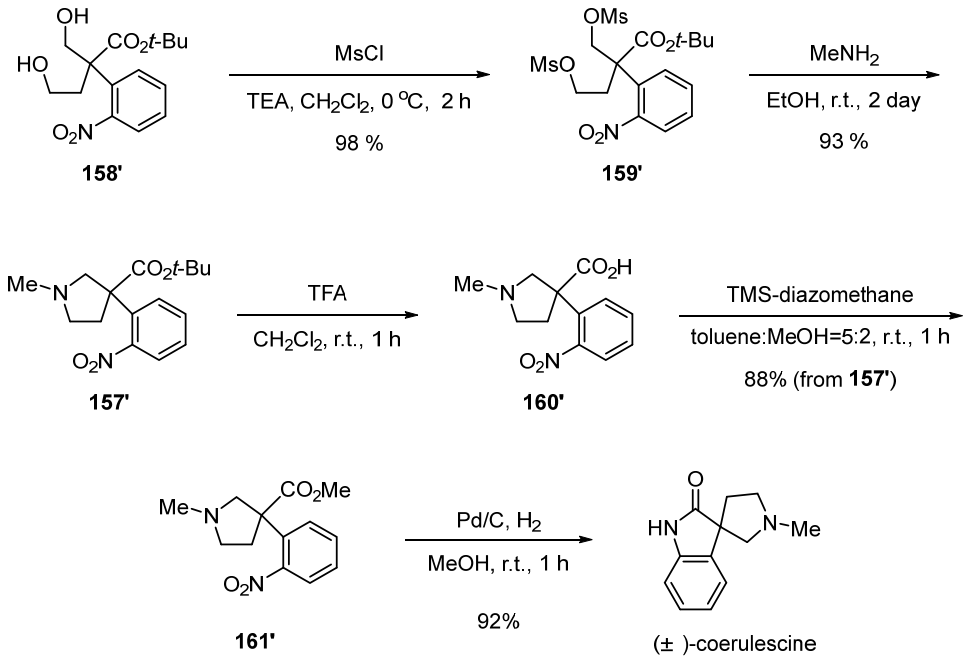


entry	reductant	additive	**158'S-1**	**158'S-2**	time (h)	yield of **158'**
1[a]	$LiBH_4$ (1.2eq)	-	O	O	2	29%
2	$LiBH_4$ (1.5eq)	-	O	O	2	42%
3	$LiBH_4$ (2.5eq)	-	O	O	<1	33%
4[a]	$NaBH_4$ (8eq)	$CeCl_3$•$7H_2O$ (2eq)	O	X	6	17%
5	$NaBH_4$ (12eq)	$CeCl_3$•$7H_2O$ (2eq)	O	X	2	65%
6	$NaBH_4$ (15eq)	$CeCl_3$•$7H_2O$ (2eq)	O	X	2	45%

[a] Starting material **146'** remained at reaction completion.

As shown in Table 9, the yield of **158'** increased to 42% by controlling the equivalents

of lithium borohydride, but accompanying side reactions prevented additional increases in the yield (entry 2-3). To develop a more effective method for the selective reduction of a lactone group, other reductants were investigated. Finally, our research team found a more effective method, which was treatment with sodium borohydride with $CeCl_3 \cdot 7H_2O$ as an additive.[47b] In this method, the partial additional reduction of the *tert*-butyl ester group did not occur; thus, side-product **158'S-2** was not observed. After optimization of the equivalents of sodium borohydride, desired diol **158'** were obtained in 65% (entry 5).



Scheme 49. Completion of synthesis of (±)-coerulescine

After the selective reduction of lactone **146'**, the construction of the *N*-methylpyrrolidine was attempted. Dimesylation of **158'** (99%) followed by double *N*-alkylation using excess methylamine successfully afforded *N*-methylpyrrolidines **157'** (98%). Our research team then performed the final spiro cyclization step. Spirooxindole natural products including

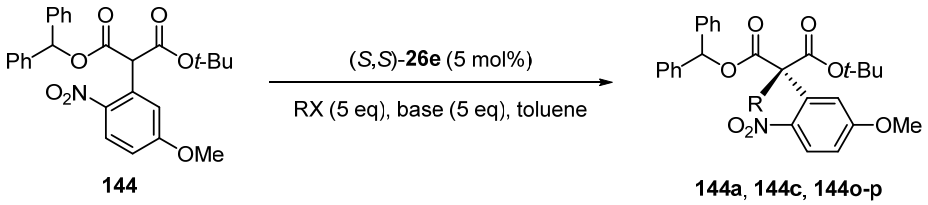
(±)-coerulescine and (–)-horsfiline, are easily racemized via a retro-Mannich reaction in the presence of an acid.[48,36e] Therefore, the last spiro cyclization step from oxindole or pyrrolidine intermediates under acidic conditions should be avoided. For the cyclization to form oxindole from **157'** under neutral conditions, our research team first needed to convert the *tert*-butyl ester group to a smaller methyl ester group. Fortunately, with **157'**, the removal of the *tert*-butyl ester in TFA was readily accomplished and gave **160'**. This was followed by methyl ester formation using excess TMS-diazomethane to afford the corresponding methyl ester **161'**, which readily cyclized to from the final oxindole product, (±)-coerulescine, by catalytic hydrogenation (Scheme 49).

In conclusion, (±)-coerulescine (**47b**) was successfully obtained in 10 steps from diphenylmethyl *tert*-butyl malonate **133** (24.8% overall yield). Our research team was convinced of the suitability of this strategy and attempted to synthesize enantiomerically enriched (–)-horsfiline using the same method.

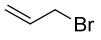
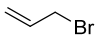
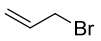
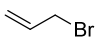
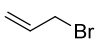
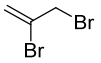
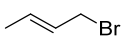
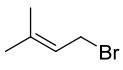
2.3. Improvement of enantioselectivity

Before the synthesis of (–)-horsfiline (**47a**), the phase-transfer catalytic α-allylation of **144** should be optimized because only 82% ee was achieved under the previous conditions with the phase-transfer catalyst (*S*,*S*)-**26e** (Table 10, entry 1).

Table 10. Optimization of PTC α-allylation of **144**.



144 **144a**, **144c**, **144o-p**

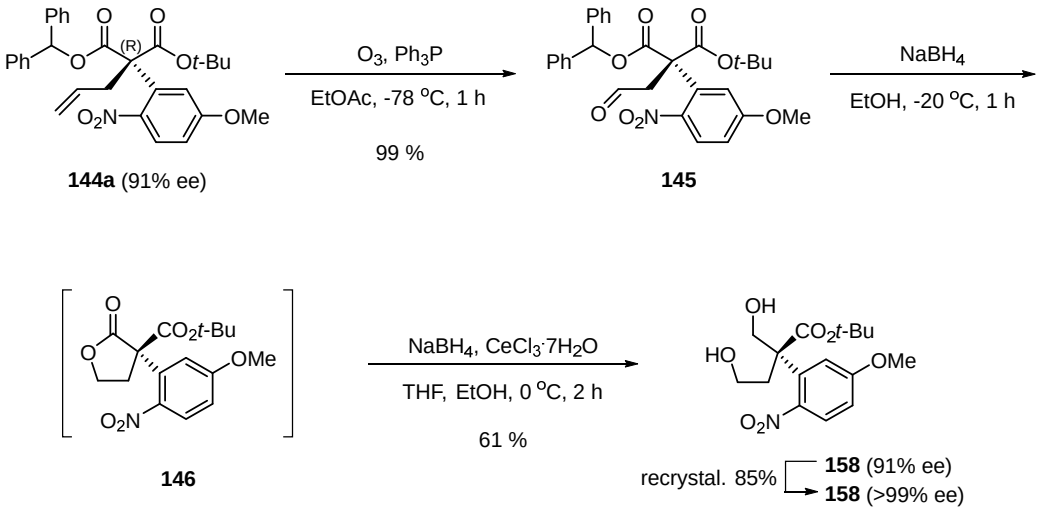
entry	RX	base	temp (ºC)	time (h)	yield (%)	ee (%)
1		50% KOH	0	12	83	82
2		50% KOH	-20	24	97	88
3		50% KOH	-40	72	90	90
4[a]		50% KOH	-40	72	99	91
5		KOH	-40	48	80	81
6		50% KOH	-20	72	85	86
7		50% KOH	-20	5	93	87
8		50% KOH	-20	2	95	71

[a] 10 mole % of catalyst (*S*,*S*)-**26e** was used.

The reaction was performed by varying the base, temperature, and allylating agent in the presence of (*S*,*S*)-**26e**. As shown in Table 10, lower reaction temperatures resulted in higher enantioselectivity with longer reaction times (entries 1 - 3). Increasing the quantity of catalyst afforded higher chemical yields with comparable enantioselectivity (entries 3 and 4). Solid-liquid phase-transfer catalytic conditions using solid KOH base resulted in lower enantioselectivity and lower chemical yield than those with liquid-liquid phase-transfer catalytic conditions using 50% KOH base (entries 3 and 5). With regard to the allylating agent, allyl bromide showed the highest enantioselectivity among the used electrophiles at -20 ºC. Our laboratory group previously improved the enantioselectivity of the phase-transfer catalytic allylation steps during the total synthesis of (-)-paroxetine and (+)-isonitramine by replacing allyl bromide with 2-bromoallyl bromide as an alternative allylating reagent.[49] However, increased enantioselectivity was not observed (entry 6), and the other 2-substituted allylic bromides also showed lower enantioselectivity (entries 7 and 8). Our research team speculates that this lack of improved enantioselectivity is caused by the *ortho*-nitro group of **144**, which might prevent a favorable binding conformation with phase-transfer catalyst (*S*,*S*)-**26e**. The best enantioselectivity was obtained using allyl bromide with 50% KOH at -40 ºC (entry 4, 99%, 91% ee).

To obtain higher enantioselectivity, recrystallization was attempted. However, alkylated product **144a** could not be recrystallized because it was too oily; thus, recrystallization of the major enantiomer was attempted in the following step. As shown in Scheme 50, the ozonolysis of **144a** afforded the corresponding aldehyde **145**, and reduction of **145** with sodium borohydride provided lactone **146** through the procedure used with coerulescine. Without purification, the lactone moiety of **146** could be selectively reduced again to the corresponding diol **158** in situ by additional treatment with sodium borohydride with

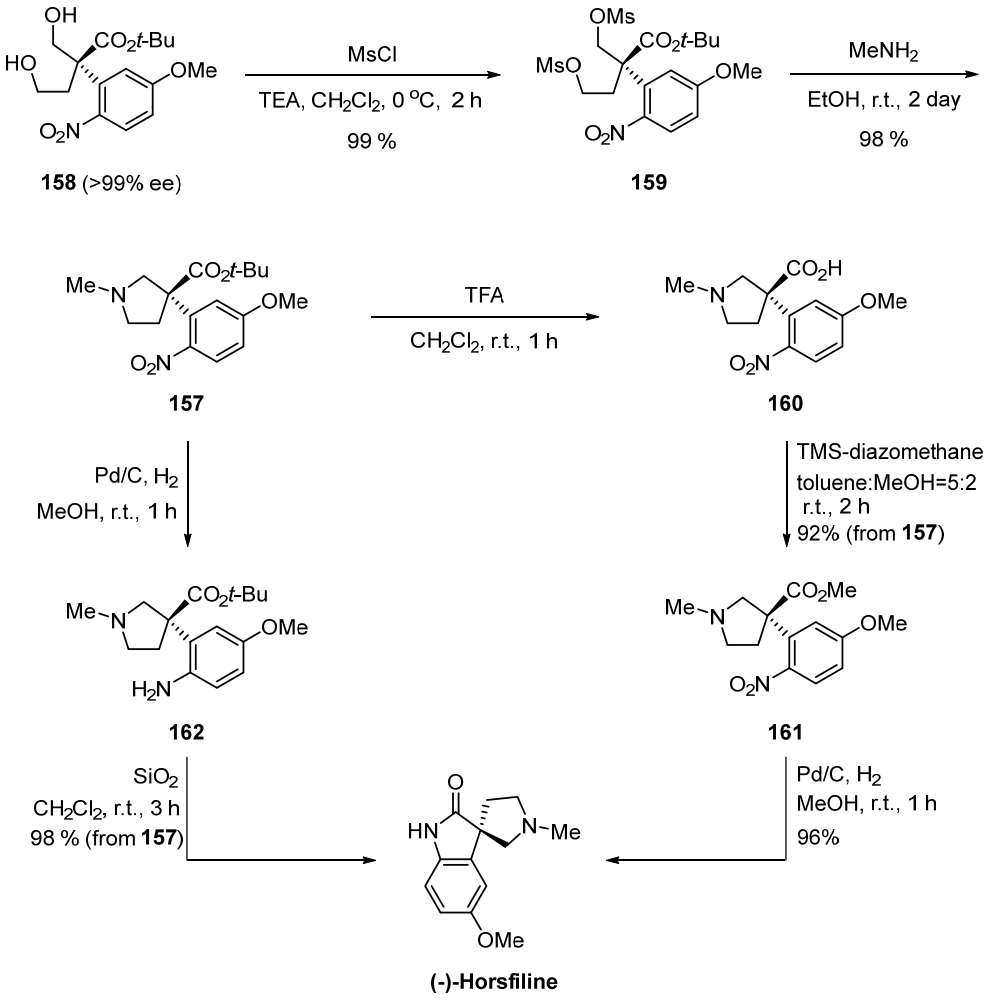
$CeCl_3 \cdot 7H_2O$ and tetrahydrofuran as a co-solvent at 0 ºC (61% from **145**). The obtained diol **158** was suitable for recrystallization. Surprisingly, the major enantiomer of diol **158** could be easily purified as a single stereoisomer (>99% ee) in 85% yield by recrystallizing out the minor/major enantiomer pair (91% ee) using hexane and EtOAc (5:1). Our research team proceeded with the synthesis of (–)-horsfiline using a single enantiomer of **158**.



Scheme 50. Recrystallization of **158** for the synthesis of (–)-horsfiline

2.4. Completion of synthesis of (–)-horsfiline

Following the procedure used for coerulescine, (–)-horsfiline could be synthesized from a single enantiomer of **158**. However, our research team also attempted direct cyclization in the presence of the *tert*-butyl ester group to shorten the overall process.



Scheme 51. Synthetic completion of (–)-horsfiline

The reduction of the nitro group of **157** was performed by catalytic hydrogenation using Pd/C under atmospheric H_2. Unfortunately, the corresponding amine **162** was the only product obtained instead of cyclized spirooxindole (Scheme 51). However, interestingly, during the purification of the obtained amine **162** via column chromatography (SiO_2), the cyclized spirooxindole was partially obtained together with the corresponding amine **162**. Our research team speculates that silicagel (SiO_2) may directly catalyze the spiro cyclization in the presence of the *tert*-butyl ester group. Finally, (–)-horsfiline {$[\alpha]_D^{20}$ = –8.50 (*c* 5, MeOH); $[\alpha]_D^{20}$ = –7.20 (c 1, MeOH)[35]} was successfully obtained by stirring amine **162** with silica gel (SiO_2) in dichloromethane without racemization (98%, >99% ee). As far as we know, this is the first synthetic method for introduction of the *N*-methylpyrrolidine prior to the construction of the oxindole ring among the previously reported enantioselective synthetic methods.

CONCLUSION

A novel enantioselective synthetic method for α,α-dialkylmalonates via phase-transfer catalytic alkylation has been developed. The asymmetric phase-transfer catalytic α-alkylation of diphenylmethyl-*tert*-butyl-α-alkylmalonates afforded the corresponding α,α-dialkylmalonates in high chemical yields (up to 99%) and enantioselectivities (up to 97% ee). Notably, the direct double α-alkylation of diphenylmethyl *tert*-butyl malonate (**133**) also provided the corresponding α,α-dialkylmalonates without the loss of enantioselectivity. Our new catalytic system provides an attractive synthetic method for universal chiral building blocks that can be readily converted to versatile chiral target molecules with quaternary carbon centers. To exemplify this utility, the synthetic potential of this method was successfully demonstrated by the synthesis of (*R*)-α-methylphenylalanine and oxindole structures.

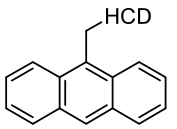
As the first application of the enantioselective phase-transfer catalytic α-alkylation of the malonate system for the total synthesis of a natural product, a new efficient synthetic approach for the synthesis of (–)-horsfiline was developed. (–)-Horsfiline was synthesized in 9 steps (including the in situ step) from diphenylmethyl *tert*-butyl malonate (**133**) via an enantioselective phase-transfer catalytic allylation as the key step (32% overall yield, >99% ee). Both the high enantioselectivity and chemical yield make this approach a practical route for the large scale synthesis of spirooxindole natural products, thus enabling the systematic investigation of their biological activity.

EXPERIMENTAL SECTION

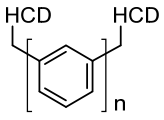
1. General Methods

1.1. Solvents and reagents

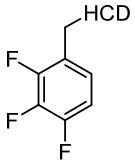
All reagents bought from commercial sources were unpurified. Organic solvents were concentrated under reduced pressure using a Büchi rotary evaporator. As the commercially available KOH was a pellet type, solid KOH should be grinded to the powder form for successful reaction and high enantiopurity. 50% v/w aqueous KOH was used as a stock solution. Phase-transfer catalysts (**25d**[8b], **27a'**[10b], **27d**[10c], **27e**[11a]**)** were prepared according to reported procedures. Phase-transfer catalyst **26e**[9b] (Wako) and **26f**[9d] (Aldrich) was purchased from the commercial source.



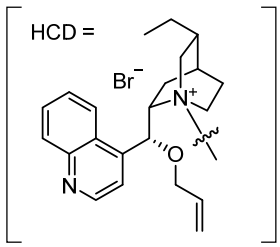
25d

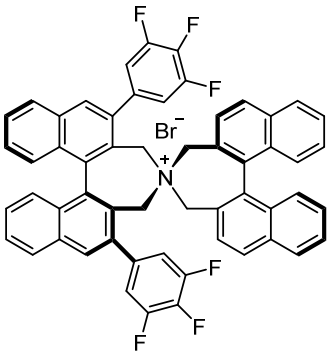


27a' n = 1
27d n = 2

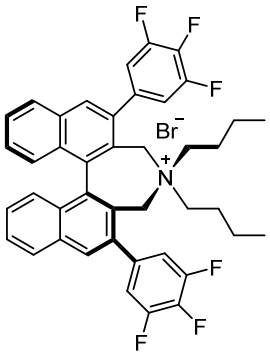


27e





26e



26f

1.2. Chromatography and HPLC

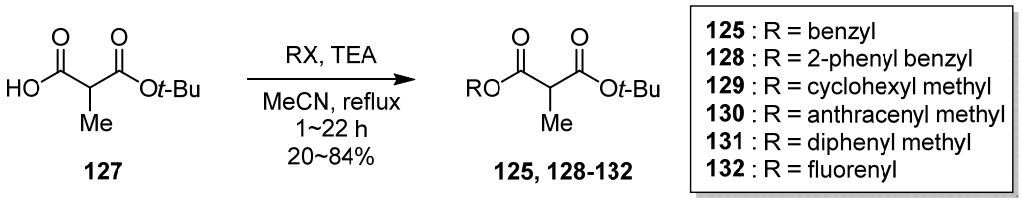
TLC analyses were performed using Merck precoated TLC plate (silica gel 60 GF_{254}, 0.25 mm). Flash column chromatography was carried out using E. Merck Kieselgel 60 (230~400 mesh). Instrument (Hitachi, L-2130) and software (Hitachi, Version LaChrom 8908800-07) were used as HPLC. The enantiomeric excess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

1.3. Spectra

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 (MS) were recorded on a VG Trio-2 GC-MS spectrometer and high-resolution mass spectra (HRMS) were measured on a JEOL JMS 700 or JEOL JMS 600-W (FAB), Agilent 6530 Q-TOF (ESI) spectrometer. Melting points were measured on a Büchi B-540 melting point apparatus and were not corrected. Optical rotations were measured on a JASCO polarimeter P-2000 series or a JASCO DIP-1000 digital polarimeter.

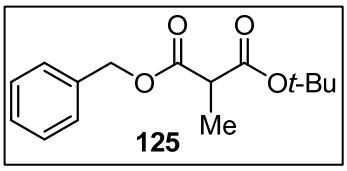
2. Chiral malonate derivatives

2.1. General procedure for α-*mono*-methylmalonates



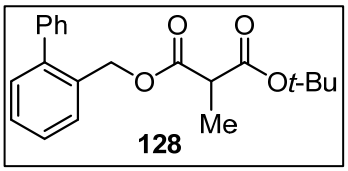
Triethylamine (0.7 ml, 5.02 mmol) was added to a stirred solution of α-methyl-malonate mono-*tert*-butyl ester (**127**, 800 mg, 4.6 mmol) in acetonitrile (15 ml). Alkyl bromide (5.04 mmol) was added to the reaction mixture. After reflux 14 h, the reaction mixture was evaporated and diluted with EtOAc (300 ml), quenched with ammonium chloride (150 ml), washed with brine (150 ml), dried over anhydrous $MgSO_4$, filtered, and concenturated in *vacuo*. The residue was purified by column chromatography (silica gel, hexane: EtOAc = 40:1) to afford desired products.

1-benzyl 3-(*tert*-butyl) 2-methylmalonate (**125**: Scheme 36)



Following the general procedure, the reaction was started with benzyl bromide (0.6 ml, 5.04 mmol). After reflux for 14 h, **125** was obtained as pale yellow oil (850 mg, 70% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.32~7.26 (m, 5H), 5.12 (dd, J_1 = 22 Hz, J_2 = 12.32 Hz, 2H), 3.34 (q, J = 7.25 Hz, 1H), 1.36 (s, 3H), 1.35 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.97, 168.76, 135.47, 128.26, 128.03, 81.31, 66.51, 46.91, 27.53, 13.26 ppm ; IR (KBr) 2980, 2942, 1731, 1498, 1456, 1369, 1331, 1254, 1147, 1094, 1028, 958, 902, 849, 751, 698 cm^{-1} ; HRMS (FAB) : calcd for $[C_{15}H_{21}O_4]^+$: 265.1440, found : 265.1437.

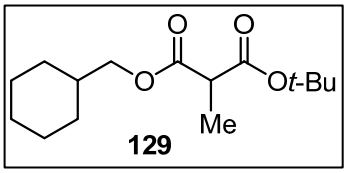
1-([1,1'-biphenyl]-2-ylmethyl) 3-(*tert*-butyl) 2-methylmalonate (**128**: Scheme 36)



128

Following the general procedure, the reaction was started with 2-phenylbenzyl bromide (0.96 ml, 5.04 mmol). After reflux for 1 h, **128** was obtained as yellow oil (360 mg, 23% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.50~7.45 (m, 1H), 7.43~7.27 (m, 8H), 5.08 (dd, J_1 = 13.65 Hz, J_2 = 12.36 Hz, 2H), 3.33 (q, J = 7.26 Hz, 1H), 1.36 (s, 9H), 1.34 (d, J = 7.32 Hz, 3H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.14, 169.06, 142.36, 140.24, 132.88, 130.12, 129.60, 129.15, 128.32, 128.23, 127.51, 127.35, 81.66, 64.91, 47.16, 27.79, 13.51 ppm ; IR (KBr) 2979, 1730, 1456, 1369, 1331, 1250, 1147, 1093, 1029, 849, 754, 704 cm^{-1} ; HRMS (FAB) : calcd for $[C_{21}H_{24}O_4Na]^+$: 363.1572, found : 363.1589.

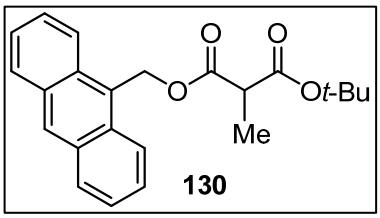
1-(*tert*-butyl) 3-(cyclohexylmethyl) 2-methylmalonate (**129**: Scheme 36)



129

Following the general procedure, the reaction was started with cyclohexylmethyl bromide (0.69 ml, 5.04 mmol). After reflux for 21 h, **129** was obtained as yellow oil (252 mg, 20% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.98~3.85 (m, 2H), 3.31 (q, J = 7.2 Hz, 1H), 1.73~1.57 (m, 6H), 1.43 (s, 9H), 1.35 (d, J = 7.35 Hz, 3H), 1.24~1.11 (m, 3H), 1.00~0.89 (m, 2H) ppm ; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.50, 169.22, 81.44, 70.16, 47.12, 36.98, 29.44, 27.77, 26.20, 25.51, 13.50 ppm ; IR (KBr) 2979, 2928, 2854, 1749, 1732, 1453, 1369, 1332, 1251, 1147, 1081, 1030, 980, 849 cm^{-1} ; HRMS (FAB) : calcd for $[C_{15}H_{27}O_4]^+$: 271.1909, found : 271.1900.

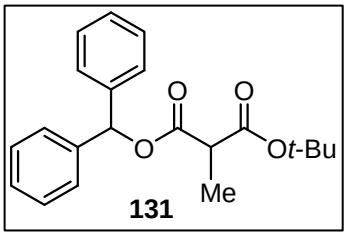
1-(anthracen-9-ylmethyl) 3-(*tert*-butyl) 2-methylmalonate (**130**: Scheme 36)



130

Following the general procedure, the reaction was started with 9-chloromethylanthracene (1144 mg, 5.04 mmol). After reflux for 22 h, **130** was obtained as a yellow solid (1013 mg, 61% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 1H), 8.33 (d, J = 8.88 Hz, 2H), 7.99 (d, J = 8.4 Hz, 2H), 7.57~7.54 (m, 2H), 7.49~7.45 (m, 2H), 6.18 (dd, J_1 = 16.88 Hz, J_2 = 12.6 Hz, 2H), 3.36 (q, J = 7.23 Hz, 1H), 1.38 (d, J = 7.2 Hz, 3H), 1.20 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.68, 168.93, 131.25, 131.02, 129.16, 128.97, 126.58, 125.76, 125.00, 123.87, 81.50, 59.42, 47.07, 27.49, 13.50 ppm ; IR (KBr) 2979, 1745, 1727, 1625, 1454, 1368, 1325, 1252, 1146, 1092, 1024, 957, 888, 847, 786, 734 cm^{-1} ; HRMS (FAB) : calcd for $[C_{23}H_{24}O_4]^+$: 364.1675, found : 364.1667 ; m.p = 71.8 °C.

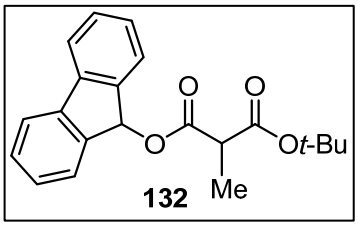
1-benzhydryl 3-(*tert*-butyl) 2-methylmalonate (**131**: Scheme 36)



131

Following the general procedure, the reaction was started with α-bromodiphenylmethane (1248 mg, 5.04 mmol). After reflux for 2 h, **131** was obtained as pale yellow oil (1314 mg, 84% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.32~7.25 (m, 10H), 6.90 (s, 1H), 3.42 (q, J = 7.21 Hz, 1H), 1.38 (d, J = 7.14 Hz, 3H), 1.33 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.10, 168.67, 139.66, 128.28, 128.23, 127.82, 127.72, 127.08, 126.89, 81.44, 77.26, 47.19, 27.55, 13.35 ppm ; IR (KBr) 2980, 1749, 1730, 1496, 1455, 1369, 1248, 1147, 1079, 1026, 966, 849, 744, 699 cm^{-1} ; HRMS (FAB) : calcd for $[C_{21}H_{24}O_4Na]^+$: 363.1572, found : 363.1562.

1-(*tert*-butyl) 3-(9*H*-fluoren-9-yl) 2-methylmalonate (**132**: Scheme 36)

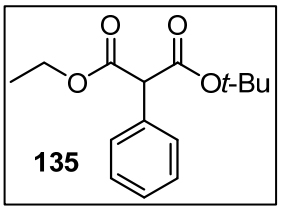


132

Following the general procedure, the reaction was started with 9-bromofluorene (1237 mg, 5.04 mmol). After reflux for 2 h, **132** was obtained as pale yellow oil (894 mg, 57% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.5 Hz, 2H), 7.52 (d, *J* = 7.53 Hz, 2H), 7.39 (t, *J* = 7.53 Hz, 2H), 7.27 (t, *J* = 7.70 Hz, 2H), 6.81 (s, 1H), 3.44 (q, *J* = 7.2 Hz, 1H), 1.43 (d, *J* = 7.14 Hz, 3H), 1.35 (s, 9H) ppm ; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 171.27, 168.76, 141.56, 140.96, 140.87, 129.45, 129.42, 127.69, 125.84, 125.81, 119.93, 119.91, 81.73, 75.52, 47.14, 27.69, 13.53 ppm ; IR (KBr) 2980, 1747, 1729, 1453, 1369, 1313, 1243, 1146, 1097, 1028, 974, 930, 849, 761, 743 cm^{-1} ; HRMS (FAB) : calcd for $[C_{21}H_{22}O_4]^+$: 338.1518, found : 338.1530.

2.2. Preparation of α-*mono*-arylmalonates

1-(*tert*-butyl) 3-ethyl 2-phenylmalonate (**135**: Scheme 39)

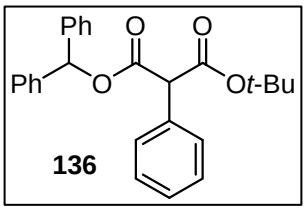


135

KOH (1 M KOH in ethanol, 4.23 ml, 4.23 mmol) was added to a stirred solution of diethyl phenylmalonate (**134**, 1 g, 4.23 mmol) in ethanol (10 ml). After stirring for 1 h, the reaction mixture was evaporated, diluted with EtOAc (50 ml), extracted with 5% $NaHCO_3$ (100 ml) and acidified by 1 M HCl (up to pH 5-6). The residue was extracted with EtOAc (200 ml), dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo* and dissolved with *t*-BuOH (0.52 ml, 5.5 mmol) in dichloromethane (15 ml). 4-Dimethylaminopyridine (51.7 mg, 0.423 mmol) and *N*,*N*′-dicyclohexylcarbodiimide

(1135 mg, 5.5 mmol) was added to a stirred solution. After stirring for 2 h, the reaction mixture was filtered through the Celite 545 by using ether and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane:EtOAc = 30:1) to afford **135** as colorless oil (559 mg, 52% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.39~7.28 (m, 5H), 4.51 (s, 1H), 4.25~4.14 (m, 2H), 1.44 (s, 9H), 1.25 (t, *J* = 7.05 Hz, 3H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.38, 167.13, 133.18, 129.22, 128.41, 127, 93, 82.19, 61.49, 58.98, 27.79, 13.99 ppm ; IR (KBr) 2980, 2935, 1732, 1498, 1455, 1393, 1369, 1345, 1307, 1224, 1141, 1029, 980, 888, 854, 747, 698 cm^{-1} ; HRMS (FAB) : calcd for $[C_{15}H_{21}O_4]^+$: 265.1440, found : 265.1449.

1-benzhydryl 3-(*tert*-butyl) 2-phenylmalonate (**136**: Scheme 39)

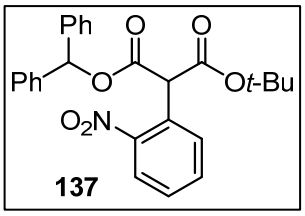


136

KOH (1 M KOH in ethanol, 3.79 ml, 3.79 mmol) was added to a stirred solution of **135** (1 g, 3.79 mmol) in ethanol (10 ml). After stirring for 2 h, the reaction mixture was evaporated, diluted with EtOAc (50 ml), extracted with 5% $NaHCO_3$ (100 ml) and acidified by 1 M HCl (up to pH 5-6). The residue was extracted with EtOAc (200 ml), dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo* and dissolved with benzhydrol (907.8 mg, 4.93 mmol) in dichloromethane (15 ml). 4-Dimethylaminopyridine (648 mg, 5.31 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (945 mg, 4.93 mmol) was added to a stirred solution. After stirring for 4 h, water (15 ml) was added to the reaction mixture. The reaction mixture was extracted with dichloromethane (2×60 ml), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane:EtOAc = 30:1) to afford **136** as a white solid (610.2 mg, 40% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.34~7.19 (m, 15H), 6.85 (s, 1H), 4.59 (s, 1H), 1.31 (s, 9H)

ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.36, 166.81, 139.62, 139.58, 132.92, 129.39, 128.46, 128.40, 128.05, 127.95, 127.14, 127.12, 82.46, 78.01, 59.15, 27.74 ppm ; IR (KBr) 3033, 2979, 1732, 1496, 1454, 1369, 1290, 1221, 1138, 1002, 835, 746, 698 cm^{-1} ; HRMS (FAB) : calcd for $[C_{26}H_{27}O_4]^+$: 403.1909, found : 403.1903 ; m.p = 114.5 °C.

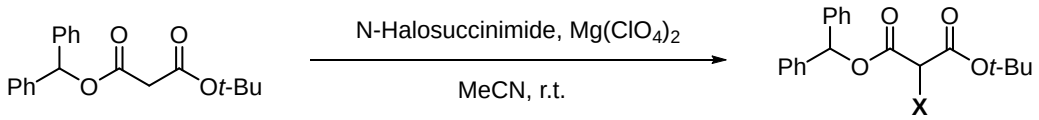
1-benzhydryl 3-(*tert*-butyl) 2-(2-nitrophenyl)malonate (**137**: Scheme 40)



137

Sodium hydride (19.4 mg, 0.81 mmol) was added to a stirred solution of malonate diphenylmethyl ester *tert*-butyl ester (**133**, 202 mg, 0.62 mmol) in DMF (3 ml) at 0°C.[50] After stirring for 30 min, 2-fluoronitrobenzene (0.065 ml, 0.62 mmol) was slowly added to the reaction mixture and stirred for 24 h. The reaction mixture was evaporated and diluted with EtOAc (60 ml), quenched with ammonium chloride (20 ml), washed with brine (20 ml), dried over anhydrous $MgSO_4$, filtered, and concenturated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane: EtOAc=10:1) to afford **137** as a pale yellow solid (160.8 mg, 58% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.03 (dd, J_1 = 7.86 Hz, J_2 = 1.47 Hz, 1H), 7.54~7.43 (m, 3H), 7.37~7.28 (m, 12H), 6.96 (s, 1H), 5.33 (s, 1H), 1.39 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 166.39, 165.59, 148.57, 139.05, 133.05, 130.83, 128.80, 128.32, 128.23, 128.21, 128.10, 127.87, 126.98, 124.76, 82.97, 78.35, 55.28, 27.43 ppm ; IR (KBr) 2980, 1732, 1579, 1529, 1496, 1455, 1394, 1348, 1306, 1228, 1142, 1001, 854, 786, 744, 700 cm^{-1} ; HRMS (FAB) : calcd for $[C_{26}H_{26}O_6N]^+$: 448.1760, found : 448.1753 ; m.p = 111.6 °C.

2.3. General procedure for α-*mono*-halomalonates

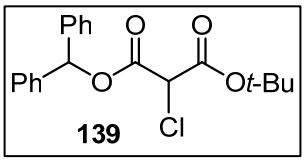


133

X : Cl = **139**, Br = **140**

A solution of **133** (750 mg, 2.298 mmol) in dry acetonitrile (23 ml) was added to the *N*-Halosuccinimide (2.757 mmol) and Magnesium perchlorate (154 mg, 0.689 mmol).[51] The reaction mixture was stirred for 4 h. After solvent was removed on a rotary evaporator, the mixture was diluted with EtOAc (400 ml) and washed with brine (100 ml). The organic layers were dried with MgSO4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane:EtOAc = 40:1~20:1) to afford α-halomalonate substrates as colorless oil.

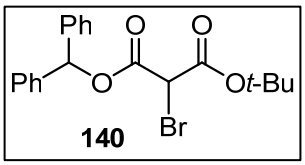
1-benzhydryl 3-(*tert*-butyl) 2-chloromalonate (**139**: Scheme 41)



139

Following the general procedure, the reaction was started using *N*-chlorosuccinimide (368 mg, 2.757 mmol). After purification by column chromatography, **139** was obtained colorless oil (373 mg, 45% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.34~7.25 (m, 10H), 6.96 (s, 1H), 4.84 (s, 1H), 1.36 (s, 9H) ppm ; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 163.79, 162.90, 138.89, 138.86, 128.58, 128.53, 128.35, 128.23, 127.34, 127.08, 84.55, 79.22, 56.70, 27.54 ppm ; IR (KBr) 2921, 2850, 1745, 1598, 1457, 1371, 1299, 1252, 1147, 988, 753, 699 cm^{-1} ; HRMS (CI) : calcd for $[C_{20}H_{20}ClO_4]^+$: 359.1050, found : 359.1046.

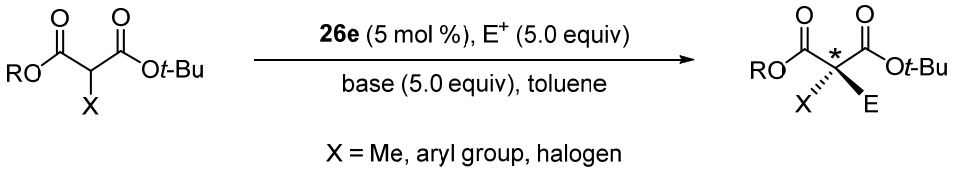
1-benzhydryl 3-(*tert*-butyl) 2-bromomalonate (**140**: Scheme 41)



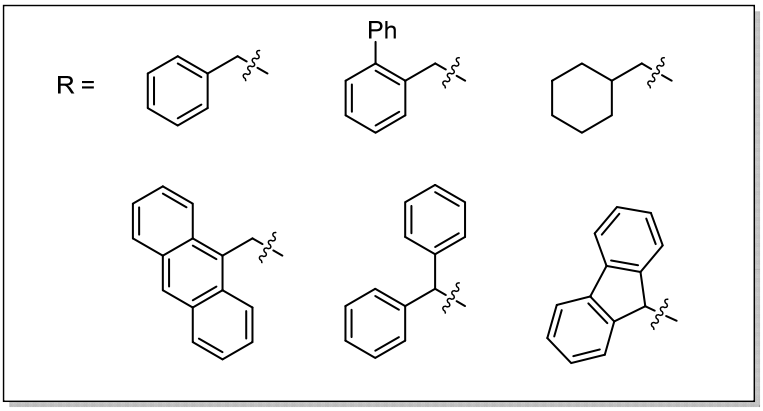
140

Following the general procedure, the reaction was started using *N*-bromosuccinimide (490 mg, 2.757 mmol). After purification by column chromatography, **140** was obtained colorless oil (736 mg, 79% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.35~7.27 (m, 10H), 6.94 (s, 1H), 4.48 (s, 1H), 1.36 (s, 9H) ppm ; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 163.77, 162.90, 138.91, 138.89, 128.52, 128.48, 128.28, 128.17, 127.29, 127.04, 84.40, 79.26, 44.24, 27.47 ppm ; IR (KBr) 2981, 1740, 1496, 1455, 1370, 1294, 1256, 1139, 989, 848, 748, 699 cm^{-1} ; HRMS (CI) : calcd for $[C_{20}H_{20}FO_4]^+$: 403.0545, found : 403.0545.

2.4. General procedure for asymmetric phase-transfer catalytic reactions

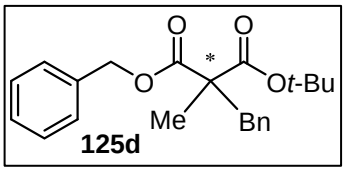


X = Me, aryl group, halogen



Electrophiles (0.5 mmol) was added to a solution of malonate substrates (0.1 mmol) and (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide (**26e**, 4.57 mg, 0.005 mmol) in toluene (0.33 ml). At the designated temperature, base (0.5 mmol) was added to the reaction mixtures and stirred until the substrate was not observed in TLC analysis. EYELA PSL-1400 was used for low temperature stirring and the stirring rate was 7. The reaction mixtures was diluted with EtOAc (10 ml), washed with brine (2×3 ml), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane:EtOAc = 50:1) to afford alkylated malonates.

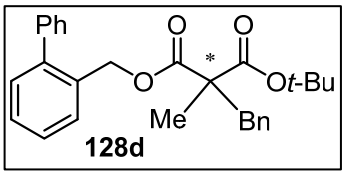
1-benzyl 3-(*tert*-butyl) 2-benzyl-2-methylmalonate (**125d**: Table 2)



125d

Following the general procedure, the reaction was started from **125** (26.4 mg, 0.1 mmol) with benzyl bromide (0.06 ml, 0.5 mmol). At the 0 °C, aq. 50% KOH (0.056 ml, 0.5 mmol) was added to the reaction mixtures. After stirring for 16 h, **125d** was obtained as a white solid (31.9 mg, 90% yield). The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralcel OJ-H, hexane:2-propanol = 95:5), flow rate = 1.0 ml/min, 23 °C, λ = 254 nm, retention time, *S* (major) 7 min, *R* (minor) 8 min, 70% ee. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.38~7.28 (m, 5H), 7.23~7.14 (m, 3H), 7.11~7.06 (m, 2H), 5.15 (s, 2H), 3.19 (dd, J_1 = 28.38 Hz, J_2 = 13.56 Hz, 2H), 1.33 (s, 9H), 1.31 (s, 3H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.94, 170.81, 136.35, 135.55, 130.27, 128.50, 128.30, 128.08, 126.77, 81.73, 66.83, 55.37, 41.03, 27.71, 19.80 ppm ; IR (KBr) 2979, 1730, 1496, 1456, 1369, 1279, 1253, 1156, 1112, 848, 739, 700 cm^{-1} ; HRMS (FAB) : calcd for $[C_{22}H_{26}O_4Na]^+$: 377.1729, found : 377.1721 ; m.p = 67.5 °C ; $[\alpha]^{25}_D$ = +14.6 (*c* 1, $CHCl_3$).

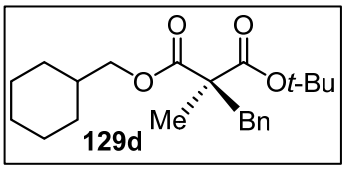
1-([1,1'-biphenyl]-2-ylmethyl) 3-(*tert*-butyl) 2-benzyl-2-methylmalonate (**128d**: Table 2)



128d

Following the general procedure, the reaction was started from **128** (34 mg, 0.1 mmol) with benzyl bromide (0.06 ml, 0.5 mmol). At the 0 °C, aq. 50% KOH (0.056 ml, 0.5 mmol) was added to the reaction mixtures. After stirring for 13 h, **128d** was obtained as colorless oil (38.7 mg, 90% yield). The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralcel OD-H, hexane:2-propanol = 95:5), flow rate = 1.0 ml/min, 23 °C, λ = 254 nm, retention time, *S* (major) 5.3 min, *R* (minor) 4.2 min, 80% ee. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.48~7.29 (m, 9H), 7.19~7.16 (m, 3H), 7.06~7.02 (m, 2H), 5.09 (dd, J_1 = 15.57 Hz, J_2 = 12.27 Hz, 2H), 3.16 (dd, J_1 = 18.3 Hz, J_2 = 13.74 Hz, 2H), 1.32 (s, 9H), 1.27(s, 3H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.85, 170.80, 142.55, 140.28, 136.33, 132.81, 130.28, 130.15, 129.99, 129.21, 128.40, 128.25, 128.07, 127.51, 127.38, 126.74, 81.73, 64.88, 55.39, 41.01, 27.72, 19.76 ppm ; IR (KBr) 3062, 3029, 2978, 2932, 1730, 1480, 1455, 1369, 1279, 1250, 1154, 1111, 969, 848, 748, 702 cm^{-1} ; HRMS (FAB) : calcd for $[C_{28}H_{30}O_4Na]^+$: 453.2042, found : 453.2057 ; $[\alpha]^{25}_D$ = +16.1 (*c* 1, $CHCl_3$).

1-(*tert*-butyl) 3-(cyclohexylmethyl) (*S*)-2-benzyl-2-methylmalonate (**129d**: Table 2)



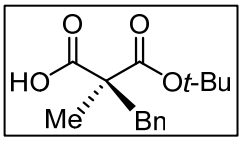
129d

Following the general procedure, the reaction was started from **129** (27 mg, 0.1 mmol) with benzyl bromide (0.06 ml, 0.5 mmol). At the 0 °C, aq. 50% KOH (0.056 ml, 0.5 mmol) was added to the reaction mixtures. After stirring for 60 h, **129d** was obtained as yellow oil (32.4 mg, 90% yield). The enantioselectivity could not be determined by chiral

HPLC analysis because **129d** was not detected well in UV 254 nm. For measurement of enantioselectivity, **129d** was converted into **131d** through two steps. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.29~7.22 (m, 3H), 7.16~7.13 (m, 2H), 4.00~3.87 (m, 2H), 3.21 (dd, J_1 = 23.16 Hz, J_2 = 13.62 Hz, 2H), 1.76~1.59 (m, 6H), 1.46 (s, 9H), 1.31 (s, 3H), 1.27~1.15 (m, 3H), 1.04~0.93 (m, 2H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.19, 170.96, 136.49, 130.24, 128.02, 126.69, 81.57, 70.25, 55.43, 41.06, 37.06, 29.59, 27.81, 26.24, 25.57, 19.83 ppm ; IR (KBr) 2929, 2853, 1730, 1453, 1369, 1277, 1250, 1154, 1114, 987, 849, 739, 701 cm^{-1} ; HRMS (FAB) : calcd for $[C_{22}H_{33}O_4]^+$: 361.2379, found : 361.2371 ; $[\alpha]^{25}_D$ = 9.2 (*c* 1, $CHCl_3$).

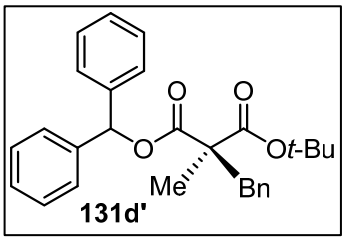
Conversion of **129d** to **131d'** for the determinination of the enantiopurity (Scheme 37)

*Hydrolysis of **129d***



1.0 M NaOH (1.2ml) was added to a solution of α-benzyl-α-methyl-malonate cyclohexylmethyl ester *tert*-butyl ester (**129d**, 36mg, 0.1mmol) in MeOH (1.2 ml). After stirring for 20 h, the reaction mixture was evaporated and diluted with EtOAc (10 ml), extract with water (2×20 mL). Water portion was acidified by 1 M HCl (up to pH 2-3) and extract with EtOAc (50 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 corresponding acid as a white solid (21.1 mg, 80% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.25~7.21 (m, 3H), 7.17~7.14 (m, 2H), 3.20 (dd, J_1 = 45.78 Hz, J_2 = 13.74 Hz, 2H), 1.44 (s, 9H), 1.41 (s, 3H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 177.76, 171.33, 136.05, 130.18, 128.17, 126.96, 82.58, 55.30, 41.29, 27.76, 20.20 ppm ; IR (KBr) 2980, 2936, 1712, 1456, 1370, 1255, 1154, 1119, 847, 735, 702 cm^{-1} ; HRMS (FAB) : calcd for $[C_{15}H_{21}O_4]^+$: 265.1440, found : 265.1441 ; m.p = 126.2 °C ; $[\alpha]^{25}_D$ = 3.3 (*c* 0.5, $CHCl_3$).

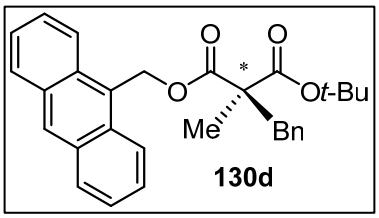
Esterification with diphenylmethanol



131d'

Triethylamine (0.013 ml, 0.093 mmol) was added to a stirred solution of α-benzyl-α-methyl-malonate mono-*tert*-butyl ester (21 mg, 0.08 mmol) in acetonitrile (0.5 ml). α-bromodiphenylmethane (21.8 mg, 0.088 mmol) was added to the reaction mixture. After reflux 22 h, the reaction mixture was evaporated and diluted with EtOAc (10 ml), quenched with ammonium chloride (5 ml), washed with brine (5 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 **131d'** as colorless viscous oil (14.8 mg, 43% yield). The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane:2-propanol = 98:2), flow rate = 1.0 ml/min, 23 °C, λ = 254 nm, retention time, *S* (major) 16 min, *R* (minor) 14 min, 73% ee. The spectra data were exactly same to **131d**.

1-(anthracen-9-ylmethyl) 3-(*tert*-butyl) 2-benzyl-2-methylmalonate (**130d**: Table 2)

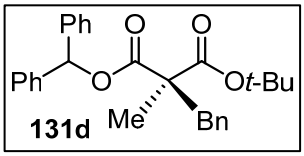


130d

Following the general procedure, the reaction was started from **130** (36.4 mg, 0.1 mmol) with benzyl bromide (0.06 ml, 0.5 mmol). At the 0 °C, aq. 50% KOH (0.056 ml, 0.5 mmol) was added to the reaction mixtures. After stirring for 19 h, **130d** was obtained as yellow viscous oil (39.1 mg, 86% yield). The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralcel OJ-H, hexane:2-propanol = 95:5), flow rate = 1.0 ml/min, 23 °C, λ = 254 nm, retention time, *S* (major) 9.5 min, *R* (minor) 18.6 min, 24% ee. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.50 (s, 1H), 8.30 (d, *J* = 8.79 Hz, 2H), 8.02 (d, *J* = 8.25 Hz, 2H), 7.58~7.45 (m,

4H), 7.18~7.11 (m, 3H), 7.05~7.02 (m, 2H), 6.18 (dd, J_1 = 32.49 Hz, J_2 = 12.54 Hz, 2H), 3.14 (dd, J_1 = 40.74 Hz, J_2 = 13.65 Hz, 2H), 1.29 (s, 3H), 1.12 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.23, 170.83, 136.33, 134.09, 131.33, 131.13, 130.26, 129.21, 129.01, 128.01, 127.20, 126.70, 126.64, 125.88, 125.09, 124.01, 81.63, 59.36, 55.55, 41.02, 27.44, 19.97 ppm ; IR (KBr) 2930, 1729, 1674, 1496, 1455, 1368, 1280, 1253, 1157, 1113, 964, 890, 847, 760, 735, 702 cm^{-1} ; HRMS (FAB) : calcd for $[C_{30}H_{30}O_4]^+$: 454.2144, found : 454.2154 ; $[\alpha]^{25}_D$ = +14.6 (*c* 1, $CHCl_3$).

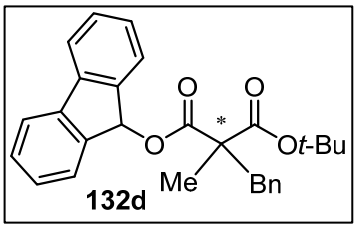
1-benzhydryl 3-(*tert*-butyl) (*S*)-2-benzyl-2-methylmalonate
(**131d**: Table 2, Table 3, Table 4)



131d

Following the general procedure, the reaction was started from **131** (34 mg, 0.1 mmol) with benzyl bromide (0.06 ml, 0.5 mmol). At the 0 °C, aq. 50% KOH (0.056 ml, 0.5 mmol) was added to the reaction mixtures. After stirring for 13 h, **131d** was obtained as colorless viscous oil (40.9 mg, 95% yield). The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane:2-propanol = 98:2), flow rate = 1.0 ml/min, 23 °C, λ = 254 nm, retention time, *S* (major) 16 min, *R* (minor) 14 min, 95% ee. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.39~7.26 (m, 10H), 7.16~7.09 (m, 3H), 6.99~6.96 (m, 2H), 6.94 (s, 1H), 3.22 (dd, J_1 = 18.66 Hz, J_2 = 13.74 Hz, 2H), 1.32 (s, 3H), 1.28 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.15, 170.71, 139.77, 139.68, 136.21, 130.31, 128.49, 128.39, 128.09, 128.04, 127.85, 127.69, 127.08, 126.69, 81.877, 77.57, 55.39, 41.04, 27.66, 19.85 ppm ; IR (KBr) 3032, 2979, 2934, 1729, 1496, 1454, 1369, 1277, 1252, 1154, 1111, 1032, 972, 912, 848, 740, 700 cm^{-1} ; HRMS (FAB) : calcd for $[C_{28}H_{30}O_4Na]^+$: 453.2042, found : 453.2057 ; $[\alpha]^{25}_D$ = +23.9 (*c* 1, $CHCl_3$).

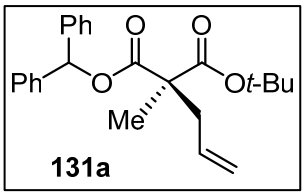
1-(*tert*-butyl) 3-(9*H*-fluoren-9-yl) 2-benzyl-2-methylmalonate (**132d**: Table 2)



132d

Following the general procedure, the reaction was started from **132** (33.8 mg, 0.1 mmol) with benzyl bromide (0.06 ml, 0.5 mmol). At the 0 °C, aq. 50% KOH (0.056 ml, 0.5 mmol) was added to the reaction mixtures. After stirring for 16 h, **132d** was obtained as colorless oil (36.4 mg, 85% yield). The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralcel OD-H, hexane:2-propanol = 99.5:0.5), flow rate = 1.0 ml/min, 23 °C, λ = 254 nm, retention time, *S* (major) 15.6 min, *R* (minor) 19.2 min, 10% ee. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.66~7.63 (m, 2H), 7.52 (d, *J* = 7.14 Hz, 1H), 7.42~7.33 (m, 3H), 7.29~7.22 (m, 5H), 7.18~7.15 (m, 2H), 6.78 (s, 1H), 3.24 (dd, J_1 = 19.77 Hz, J_2 = 13.74 Hz, 2H), 1.34 (s, 3H), 1.28 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.06, 170.59, 141.63, 141.09, 140.99, 136.32, 130.42, 129.52, 129.46, 128.13, 127.74, 127.68, 126.83, 126.39, 125.93, 119.96, 119.95, 81.91, 75.79, 55.49, 41.06, 27.69, 19.91 ppm ; IR (KBr) 2979, 2934, 1730, 1496, 1454, 1369, 1276, 1251, 1154, 1111, 981, 848, 761, 741, 701 cm^{-1} ; HRMS (FAB) : calcd for $[C_{28}H_{28}O_4Na]^+$: 451.1885, found : 451.1880 ; $[\alpha]^{25}_D$ = +2.4 (*c* 1, $CHCl_3$).

1-benzhydryl 3-(*tert*-butyl) (*S*)-2-allyl-2-methylmalonate (**131a**: Table 4)

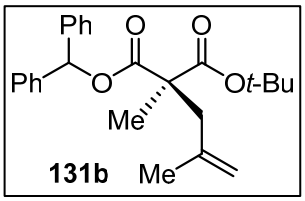


131a

Following the general procedure, the reaction was started from **131** (34 mg, 0.1 mmol) with allyl bromide (0.042 ml, 0.5 mmol). At the 0 °C, aq. 50% KOH (0.056 ml, 0.5 mmol) was added to the reaction mixtures. After stirring for 14 h, **131a** was obtained as yellow oil (33.1 mg, 87% yield). The enantioselectivity was not determined by HPLC analysis using chiral columns. ^{1}H-NMR (300 MHz, $CDCl_3$) δ

7.32~7.23 (m, 10H), 6.90 (s, 1H), 5.68~5.54 (m, 1H), 5.04~4.98 (m, 2H), 2.61 (d, *J* = 7.32 Hz, 2H), 1.37 (s, 3H), 1.27 (s, 9H) ppm ; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 171.15, 170.58, 139.82, 139.77, 132.51, 128.41, 127.98, 127.88, 127.40, 127.07, 119.07, 81.68, 77.42, 53.92, 40.08, 27.65, 19.71 ppm ; IR (KBr) 2980, 2935, 2350, 2309, 1730, 1456, 1369, 1252, 1145, 1110, 921, 846, 741, 699 cm^{-1} ; HRMS (FAB) : calcd for $[C_{24}H_{29}O_4]^+$: 381.2066, found : 381.2066 ; $[\alpha]^{25}_D$ = +10 (*c* 1, $CHCl_3$).

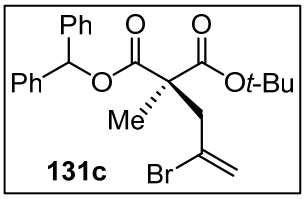
1-benzhydryl 3-(*tert*-butyl) (*S*)-2-methyl-2-(2-methylallyl)malonate (**131b**:Table 4)



131b

Following the general procedure, the reaction was started from **131** (34 mg, 0.1 mmol) with 3-bromo-2-methyl propene (0.05 ml, 0.5 mmol). At the 0 °C, aq. 50% KOH (0.056 ml, 0.5 mmol) was added to the reaction mixtures. After stirring for 13 h, **131b** was obtained as yellow oil (34.3 mg, 87% yield). The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane:2-propanol = 99.5:0.5), flow rate = 1.0 ml/min, 23 °C, λ = 254 nm, retention time, *S* (major) 32.4 min, *R* (minor) 31.5 min, 94% ee. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.34~7.25 (m, 10H), 6.90 (s, 1H), 4.76 (s, 1H), 4.64 (s, 1H), 2.68 (s, 2H), 1.55 (s, 3H), 1.38 (s, 3H), 1.26 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.57, 170.98, 140.89, 139.84, 139.69, 128.40, 127.97, 127.87, 127.49, 127.13, 115.39, 81.73, 77.52, 53.78, 42.93, 27.59, 23.45, 19.82 ppm ; IR (KBr) 2979, 1729, 1455, 1369, 1250, 1157, 1110, 972, 901, 743, 699 cm^{-1} ; HRMS (FAB) : calcd for $[C_{25}H_{30}O_4Na]^+$: 417.2042, found : 417.2022 ; $[\alpha]^{25}_D$ = +7.18 (*c* 1, $CHCl_3$).

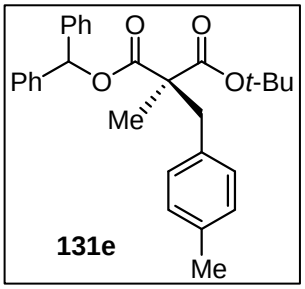
1-benzhydryl 3-(*tert*-butyl) (*S*)-2-(2-bromoallyl)-2-methylmalonate (**131c**: Table 4)



131c

Following the general procedure, the reaction was started from **131** (34 mg, 0.1 mmol) with 2,3-dibromopropene (0.049 ml, 0.5 mmol). At the 0 °C, aq. 50% KOH (0.056 ml, 0.5 mmol) was added to the reaction mixtures. After stirring for 13 h, **131c** was obtained as yellow oil (40.9 mg, 89% yield). The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralcel OD-H, hexane:2-propanol = 98:2), flow rate = 1.0 ml/min, 23 °C, λ = 254 nm, retention time, *S* (major) 4.6 min, *R* (minor) 5.4 min, 94% ee. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.34~7.25 (m, 10H), 6.91 (s, 1H), 5.50 (t, J = 0.84 Hz, 1H), 5.45 (d, J = 1.65 Hz, 1H), 3.15 (dd, J_1 = 18.96 Hz, J_2 = 15.12 Hz, 2H), 1.50 (s, 3H), 1.27 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.50, 169.88, 139.66, 139.51, 128.41, 128.02, 127.94, 127.58, 127.49, 127.20, 121.38, 82.27, 77.89, 54.06, 45.83, 27.59, 19.36 ppm ; IR (KBr) 2979, 1730, 1625, 1496, 1455, 1369, 1293, 1253, 1146, 1112, 961, 900, 845, 741, 699 cm^{-1} ; HRMS (FAB) : calcd for $[C_{24}H_{27}O_4BrNa]^+$: 481.0990, found : 481.1011 ; $[\alpha]^{25}_D$ = +1.79 (*c* 1, $CHCl_3$).

1-benzhydryl 3-(*tert*-butyl) (*S*)-2-methyl-2-(4-methylbenzyl)malonate **(131e**: Table 4)

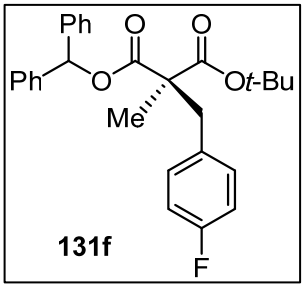


131e

Following the general procedure, the reaction was started from **131** (34 mg, 0.1 mmol) with 4-methylbenzyl bromide (92.5 mg, 0.5 mmol). At the 0 °C, aq. 50% KOH (0.056 ml, 0.5 mmol) was added to the reaction mixtures. After stirring for 13 h, **131e** was obtained as pale yellow oil (42.1 mg, 95% yield). The enantioselectivity was determined by chiral HPLC analysis (DIACEL

Chiralpak AD-H, hexane:2-propanol = 98:2), flow rate = 1.0 ml/min, 23 °C, λ = 254 nm, retention time, *S* (major) 23 min, *R* (minor) 18 min, 97% ee. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.38~7.25 (m, 10H), 6.94~6.92 (m, 3H), 6.86~6.83 (m, 2H), 3.17 (dd, J_1 = 22.71 Hz, J_2 = 13.74 Hz, 2H), 2.25 (s, 3H), 1.31 (s, 3H), 1.28 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.22, 170.84, 139.84, 139.74, 136.21, 133.06, 130.19, 128.78, 128.51, 128.40, 128.10, 127.85, 127.71, 127.13, 81.83, 77.54, 55.46, 40.66, 27.70, 21.02, 19.84 ppm ; IR (KBr) 2979, 2934, 1729, 1515, 1496, 1455, 1369, 1251, 1156, 1112, 973, 846, 743, 699 cm^{-1} ; HRMS (FAB) : calcd for $[C_{29}H_{32}O_4Na]^+$: 467.2198, found : 467.2176 ; $[\alpha]^{25}_D$ = +23.9 (*c* 1, $CHCl_3$).

1-benzhydryl 3-(*tert*-butyl) (*S*)-2-(4-fluorobenzyl)-2-methylmalonate (**131f**: Table 4)

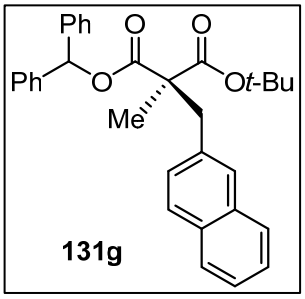


131f

Following the general procedure, the reaction was started from **131** (34 mg, 0.1 mmol) with 4-fluorobenzyl bromide (0.063 ml, 0.5 mmol). At the 0 °C, aq. 50% KOH (0.056 ml, 0.5 mmol) was added to the reaction mixtures. After stirring for 14 h, **131f** was obtained as pale yellow oil (41.1 mg, 92% yield). The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane:2-propanol = 95:5), flow rate = 1.0 ml/min, 23 °C, λ = 254 nm, retention time, *S* (major) 11.3 min, *R* (minor) 10.7 min, 95% ee. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.37~7.26 (m, 10H), 6.93~6.88 (m, 3H), 6.82~6.75 (m, 2H), 3.17 (dd, J_1 = 24.33 Hz, J_2 = 13.71 Hz, 2H), 1.31 (s, 3H), 1.28 (s, 9H) ppm ; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.96, 170.63, 163.40, 160.15, 139.60, 139.55, 131.76, 131.65, 128.51, 128.39, 128.15, 127.89, 127.68, 127.01, 114.98, 114.70, 82.00, 77.56, 55.33, 40.18, 27.62, 19.81 ppm ; IR (KBr) 2979, 2935, 1728, 1604, 1511, 1455, 1369, 1277, 1224, 1158, 1106, 972, 845, 743,

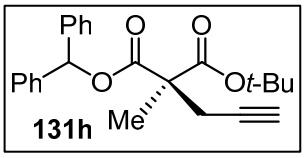
700 cm^{-1} ; HRMS (FAB) : calcd for $[C_{28}H_{29}O_4FNa]^+$: 471.1948, found : 471.1924 ; $[\alpha]^{25}_D$ = +24.5 (*c* 1, $CHCl_3$).

1-benzhydryl 3-(*tert*-butyl) (*S*)-2-methyl-2-(naphthalen-2-ylmethyl)malonate (**131g**: Table 4)



Following the general procedure, the reaction was started from **131** (34 mg, 0.1 mmol) with 2-(bromomethyl)naphthalen (110 mg, 0.5 mmol). At the 0 °C, aq. 50% KOH (0.056 ml, 0.5 mmol) was added to the reaction mixtures. After stirring for 13 h, **131g** was obtained as a white solid (44.6 mg, 93% yield). The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane:2-propanol = 95:5), flow rate = 1.0 ml/min, 23 °C, λ = 254 nm, retention time, *S* (major) 17 min, *R* (minor) 13.3 min, 96% ee. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.76~7.73 (m, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.58~7.54 (m, 1H), 7.46 (s, 1H), 7.41~7.25 (m, 12H), 7.13 (dd, J_1 = 8.43 Hz, J_2 = 1.65 Hz, 2H), 6.96 (s, 1H), 3.40 (dd, J_1 = 20.61 Hz, J_2 = 13.65 Hz, 2H), 1.37 (s, 3H), 1.29 (s, 9H) ppm ; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 171.09, 170.73, 139.70, 139.63, 133.77, 133.17, 132.27, 128.98, 128.56, 128.53, 128.45, 128.37, 128.11, 127.84, 127.61, 127.51, 127.46, 127.03, 125.78, 125.46, 81.94, 77.56, 55.56, 41.09, 27.63, 19.95 ppm ; IR (KBr) 2979, 1728, 1455, 1369, 1254, 1153, 1110, 972, 845, 745, 699 cm^{-1} ; HRMS (FAB) : calcd for $[C_{32}H_{32}O_4]^+$: 480.2301, found : 480.2302 ; m.p = 124.7 °C ; $[\alpha]^{25}_D$ = +28.0 (*c* 1, $CHCl_3$).

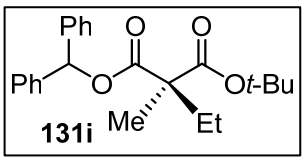
1-benzhydryl 3-(*tert*-butyl) (*S*)-2-methyl-2-(prop-2-yn-1-yl)malonate (**131h**: Table 5)



131h

Following the general procedure, the reaction was started from **131** (34 mg, 0.1 mmol) with propargyl bromide (80% in toluene, 0.074 ml, 0.5 mmol). At the 0 °C, aq. 50% KOH (0.056 ml, 0.5 mmol) was added to the reaction mixtures. After stirring for 13 h, **131h** was obtained as a pale yellow solid (33.3 mg, 88% yield). The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralcel OJ-H, hexane:2-propanol = 98:2), flow rate = 1.0 ml/min, 23 °C, λ = 254 nm, retention time, *S* (major) 9.1 min, *R* (minor) 11.7 min, 75% ee. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.31~7.24 (m, 10H), 6.91 (s, 1H), 2.78 (d, *J* = 2.55 Hz, 2H), 1.95 (t, *J* = 2.76 Hz, 1H), 1.53 (s, 3H), 1.28 (s, 9H) ppm ; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 170.12, 169.42, 139.58, 128.45, 128.37, 128.00, 127.97, 127.30, 127.19, 82.18, 79.27, 77.79, 71.32, 53.65, 27.56, 25.85, 19.70 ppm ; IR (KBr) 3295, 2981, 1732, 1456, 1370, 1293, 1252, 1159, 1117, 970, 845, 742, 699, 651 cm^{-1} ; HRMS (FAB) : calcd for $[C_{24}H_{27}O_4]^+$: 379.1909, found : 379.1906 ; m.p = 45.9 °C ; $[\alpha]^{25}_D$ = +2.34 (*c* 1, $CHCl_3$).

1-benzhydryl 3-(*tert*-butyl) (*S*)-2-ethyl-2-methylmalonate (**131i**: Table 5)

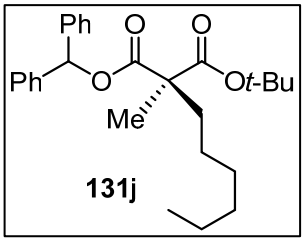


131i

Following the general procedure, the reaction was started from **131** (34 mg, 0.1 mmol) with iodoethane (0.04 ml, 0.5 mmol). At 0 °C, solid KOH (28.1 mg, 0.5 mmol) was quickly added to the reaction mixtures. After stirring for 1 h, **131i** was obtained as a yellow solid (36.5 mg, 99% yield). The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane:2-propanol = 98:2), flow rate = 1.0 ml/min, 23 °C, λ = 254 nm, retention time, *S* (major) 10 min, *R* (minor) 11.3 min, 72% ee. ^{1}H-NMR (300

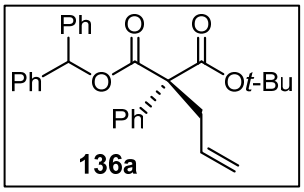
MHz, $CDCl_3$) δ 7.26~7.18 (m, 10H), 6.84 (s, 1H), 1.85 (q, *J* = 7.5 Hz, 2H), 1.31 (s, 3H), 1.21 (s, 9H), 0.74 (t, *J* = 7.35 Hz, 3H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.61, 171.14, 139.93, 128.39, 127.91, 127.84, 127.32, 127.09, 81.36, 77.21, 54.66, 28.50, 27.64, 19.19, 8.44 ppm ; IR (KBr) 2978, 2310, 1729, 1456, 1369, 1254, 1149, 1121, 847, 741, 699 cm^{-1} ; HRMS (FAB) : calcd for $[C_{23}H_{39}O_4]^+$: 369.2066, found : 369.2057 ; m.p = 41.7 °C ; $[\alpha]^{25}_D$ = -30.4 (*c* 1, $CHCl_3$).

1-benzhydryl 3-(*tert*-butyl) (*S*)-2-hexyl-2-methylmalonate (**131j**: Table 5)



Following the general procedure, the reaction was started from **131** (34 mg, 0.1 mmol) with 1-iodohexane (0.074 ml, 0.5 mmol). At -20 °C, solid KOH (28.1 mg, 0.5 mmol) was quickly added to the reaction mixtures. After stirring for 24 h, **131j** was obtained as yellow oil (27.1 mg, 80% yield). The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane:2-propanol = 98:2), flow rate = 1.0 ml/min, 23 °C, λ = 254 nm, retention time, *S* (major) 11.5 min, *R* (minor) 9.8 min, 92% ee. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.31~7.24 (m, 10H), 6.90 (s, 1H), 1.92~1.80 (m, 2H), 1.37 (s, 3H), 1.27 (s, 9H), 1.24~1.03 (m, 8H), 0.83 (t, *J* = 6.78 Hz, 3H) ppm ; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 171.65, 171.32, 139.94, 139.93, 128.39, 127.93, 127.84, 127.38, 127.11, 81.37, 77.21, 54.35, 35.56, 31.53, 29.56, 27.65, 24.00, 22.51, 19.78, 14.00 ppm ; IR (KBr) 2929, 2858, 1729, 1496, 1456, 1369, 1255, 1149, 1125, 1098, 977, 848, 742, 699 cm^{-1} ; HRMS (FAB) : calcd for $[C_{27}H_{37}O_4]^+$: 425.2692, found : 425.2676 ; $[\alpha]^{25}_D$ = +8.1 (*c* 1, $CHCl_3$).

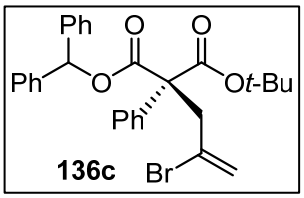
1-benzhydryl 3-(*tert*-butyl) (*R*)-2-allyl-2-phenylmalonate (**136a**: Table 6)



136a

Following the general procedure, the reaction was started from **136** (40.2 mg, 0.1 mmol) with allyl bromide (0.042 ml, 0.5 mmol). At the -20 °C, aq. 50% KOH (0.056 ml, 0.5 mmol) was added to the reaction mixtures. After stirring for 14 h, **136a** was obtained as yellow oil (40.3 mg, 91% yield). The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane:2-propanol = 98:2), flow rate = 1.0 ml/min, 23 °C, λ = 254 nm, retention time, *R* (major) 16 min, *S* (minor) 12.7 min, 95% ee. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.45~7.41 (m, 2H), 7.36~7.23 (m, 11H), 7.18~7.13 (m, 2H), 6.94 (s, 1H), 5.76~5.63 (m, 1H), 4.99 (d, *J* = 6.24 Hz, 1H), 4.95 (s, 1H), 3.11 (d, *J* = 7.14 Hz, 2H), 1.30 (s, 9H) ppm ; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 169.48, 168.85, 139.69, 139.67, 136.73, 132.76, 128.38, 128.27, 127.96, 127.93, 127.77, 127.42, 127.37, 127.01, 118.73, 82.37, 77.84, 62.91, 40.12, 27.62 ppm ; IR (KBr) 3032, 2979, 2349, 1730, 1497, 1456, 1369, 1251, 1153, 1030, 983, 919, 844, 742, 697 cm^{-1} ; HRMS (FAB) : calcd for $[C_{29}H_{31}O_4]^+$: 443.2222, found : 443.2213 ; $[\alpha]^{25}_D$ = -33.7 (*c* 1, $CHCl_3$).

1-benzhydryl 3-(*tert*-butyl) (*R*)-2-(2-bromoallyl)-2-phenylmalonate (**136c**: Table 6)

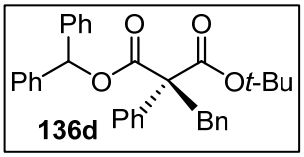


136c

Following the general procedure, the reaction was started from **136** (40.2 mg, 0.1 mmol) with 2,3-dibromopropene (0.049 ml, 0.5 mmol). At the -20 °C, aq. 50% KOH (0.056 ml, 0.5 mmol) was added to the reaction mixtures. After stirring for 14 h, **136c** was obtained as colorless oil (46.9 mg, 90% yield). The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane:2-propanol =

98:2), flow rate = 1.0 ml/min, 23 °C, λ = 254 nm, retention time, *R* (major) 15.8 min, *S* (minor) 17.6 min, 95% ee. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.47~7.43 (m, 2H), 7.29~7.15 (m, 13H), 6.89 (s, 1H), 5.26 (d, J = 2.01 Hz, 2H), 5.13 (d, J = 1.65 Hz, 2H), 3.55 (dd, J_1 = 21.15 Hz, J_2 = 16.83 Hz, 2H), 1.21 (s, 9H) ppm ; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 168.60, 167.83, 139.38, 139.31, 134.89, 128.60, 128.38, 128.33, 128.00, 127.94, 127.85, 127.64, 127.39, 127.31, 127.13, 120.96, 82.96, 78.37, 62.54, 46.10, 27.47 ppm ; IR (KBr) 3032, 2979, 2309, 1731, 1497, 1452, 1370, 1251, 1178, 1148, 1006, 957, 900, 843, 741, 698 cm^{-1} ; HRMS (FAB) : calcd for $[C_{29}H_{30}BrO_4]^+$: 521.1327, found : 521.1324 ; $[\alpha]^{25}_D$ = -10.5 (*c* 1, $CHCl_3$).

1-benzhydryl 3-(*tert*-butyl) (*R*)-2-benzyl-2-phenylmalonate (**136d**: Table 6)

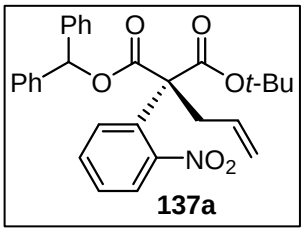


136d

Following the general procedure, the reaction was started from **136** (40.2 mg, 0.1 mmol) with benzyl bromide (0.06 ml, 0.5 mmol). At the 0 °C, aq. 50% KOH (0.056 ml, 0.5 mmol) was added to the reaction mixtures. After stirring for 5 h, **136d** was obtained as pale yellow oil (48.6 mg, 99% yield). The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane:2-propanol = 90:10), flow rate = 1.0 ml/min, 23 °C, λ = 254 nm, retention time, *R* (major) 9 min, *S* (minor) 14 min, 96% ee. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.30~7.16 (m, 15H), 7.10~7.01 (m, 3H), 6.97 (s, 1H), 6.80 (d, J = 7.89 Hz, 2H), 3.65 (dd, J_1 = 18.51 Hz, J_2 = 14.1 Hz, 2H), 1.21 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.40, 168.67, 139.62, 139.50, 137.22, 136.02, 130.45, 128.46, 128.40, 128.27, 127.97, 127.78, 127.68, 127.63, 127.52, 127.19, 127.10, 126.55, 82.44, 77.98, 64.41, 42.68, 27.47 ppm ; IR (KBr) 3031, 2978, 1730, 1496, 1453, 1368, 1249, 1146, 1081, 1032, 845, 741, 698 cm^{-1} ; HRMS (FAB) : calcd for $[C_{33}H_{33}O_4]^+$: 493.2379, found : 493.2392 ; $[\alpha]^{25}_D$ = +1.2 (*c* 1, $CHCl_3$).

1-benzhydryl 3-(*tert*-butyl) (*R*)-2-allyl-2-(2-nitrophenyl)malonate

(**137a**: Table 6)

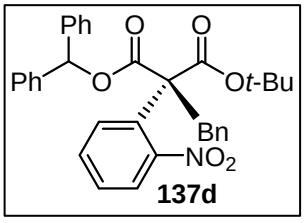


137a

Following the general procedure, the reaction was started from **137** (44.6 mg, 0.1 mmol) with allyl bromide (0.042 ml, 0.5 mmol). At the -20 °C, aq. 50% KOH (0.056 ml, 0.5 mmol) was added to the reaction mixtures. After stirring for 48 h, the residue was purified by column chromatography (silica gel, hexane:EtOAc = 20:1) to afford **137a** as a white solid (46.8 mg, 96% yield). The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane:2-propanol = 95:5), flow rate = 1.0 ml/min, 23 °C, λ = 254 nm, retention time, *R* (major) 9.8 min, *S* (minor) 12.9 min, 86% ee. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.00~7.93 (m, 1H), 7.43~7.36 (m, 2H), 7.30~7.21 (m, 10H), 7.13~7.06 (m, 1H), 6.96 (s, 1H), 5.75~7.61 (m, 1H), 4.97~4.86 (m, 2H), 3.29 (d, *J* = 7.32 Hz, 2H), 1.28 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.39, 167.00, 149.37, 139.33, 139.27, 133.23, 132.35, 132.15, 131.25, 128.33, 128.31, 128.23, 127.98, 127.94, 127.41, 127.20, 125.55, 118.86, 83.53, 78.46, 63.85, 39.57, 27.46 ppm ; IR (KBr) 2980, 1733, 1532, 1454, 1358, 1252, 1205, 1184, 1147, 986, 855, 744, 700 cm^{-1} ; HRMS (FAB) : calcd for $[C_{29}H_{30}O_6N]^+$: 488.2073, found : 488.2091 ; m.p = 88.9 °C ; $[\alpha]^{25}_D$ = +31.8 (*c* 1, $CHCl_3$).

1-benzhydryl 3-(*tert*-butyl) (*R*)-2-benzyl-2-(2-nitrophenyl)malonate

(**137d** (Table 6)

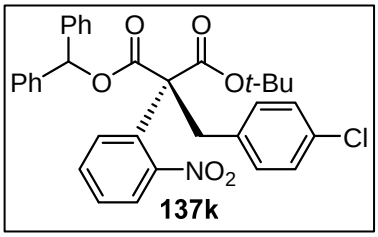


137d

Following the general procedure, the reaction was started from **137** (44.6 mg, 0.1 mmol) with benzyl bromide (0.06 ml, 0.5 mmol). At the -20 °C, aq. 50% KOH (0.056 ml, 0.5 mmol) was added to the reaction mixtures. After stirring for 20 h, the

residue was purified by column chromatography (silica gel, hexane:EtOAc = 20:1) to afford **137d** as colorless viscous oil (50 mg, 93% yield). The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane:2-propanol = 95:5), flow rate = 1.0 ml/min, 23 °C, λ = 254 nm, retention time, *R* (major) 10 min, *S* (minor) 16.8 min, 95% ee. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.13 (dd, J_1 = 8.13 Hz, J_2 = 1.38 Hz, 1H), 7.56~7.43 (m, 12H), 7.22~7.16 (m, 6H), 6.55 (dd, J_1 = 7.98 Hz, J_2 = 1.2 Hz, 1H), 4.23 (dd, J_1 = 24.81 Hz, J_2 = 13.83 Hz, 2H), 1.45 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.54, 167.01, 149.74, 139.30, 139.05, 136.99, 132.76, 131.83, 131.22, 130.90, 128.45, 128.36, 128.10, 128.07, 127.95, 127.56, 127.50, 127.37, 126.29, 124.99, 83.86, 78.67, 66.35, 40.38, 27.40 ppm ; IR (KBr) 2979, 1734, 1533, 1496, 1455, 1359, 1257, 1146, 1080, 953, 854, 758, 701 cm^{-1} ; HRMS (FAB) : calcd for $[C_{33}H_{31}O_6NNa]^+$: 560.2049, found : 560.2060 ; $[\alpha]^{25}_D$ = +80.6 (*c* 1, $CHCl_3$).

1-benzhydryl 3-(*tert*-butyl) (*R*)-2-(4-chlorobenzyl)-2-(2-nitrophenyl)malonate (**137k**: Table 6)

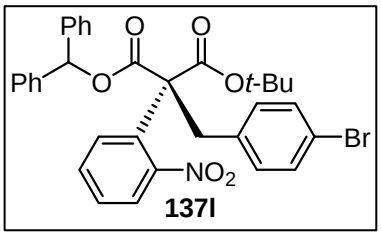


137k

Following the general procedure, the reaction was started from **137** (44.6 mg, 0.1 mmol) with 4-chlorobenzyl bromide (102.7 mg, 0.5 mmol). At the -20 °C, aq. 50% KOH (0.056 ml, 0.5 mmol) was added to the reaction mixtures. After stirring for 20 h, the residue was purified by column chromatography (silica gel, hexane:EtOAc = 20:1) to afford **137k** as pale yellow oil (56.6 mg, 99% yield). The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane:2-propanol = 90:10), flow rate = 1.0 ml/min, 23 °C, λ = 254 nm, retention time, *R* (major) 9 min, *S* (minor) 18.6 min, 96% ee. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.49 Hz, 1H), 7.28~7.15 (m, 10H), 7.00~6.94 (m, 2H), 6.87

(s, 4H), 6.23 (d, J = 7.68 Hz, 1H), 3.91 (dd, J_1 = 23.16 Hz, J_2 = 13.83 Hz, 2H), 1.18 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.42, 166.85, 149.70, 139.12, 138.85, 135.50, 132.57, 132.28, 132.18, 131.44, 128.44, 128.37, 128.17, 128.11, 127.55, 127.30, 125.09, 84.03, 78.78, 66.16, 39.71, 27.36 ppm ; IR (KBr) 2980, 1734, 1577, 1533, 1492, 1455, 1394, 1359, 1257, 1208, 1175, 1146, 1092, 1016, 993, 953, 855, 785, 758, 700 cm^{-1} ; HRMS (FAB) : calcd for $[C_{33}H_{31}ClO_6N]^+$: 572.1840, found : 572.1860 ; $[\alpha]^{25}_D$ = +2.1 (*c* 1, $CHCl_3$).

1-benzhydryl 3-(*tert*-butyl) (*R*)-2-(4-bromobenzyl)-2-(2-nitrophenyl)malonate (**137l**: Table 6)

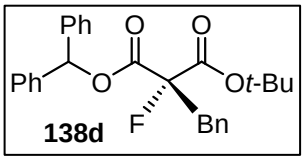


137l

Following the general procedure, the reaction was started from **137** (44.6 mg, 0.1 mmol) with 4-bromobenzyl bromide (125 mg, 0.5 mmol). At the -20 °C, aq. 50% KOH (0.056 ml, 0.5 mmol) was added to the reaction mixtures. After stirring for 25 h, the residue was purified by column chromatography (silica gel, hexane:EtOAc = 20:1) to afford **137l** as pale yellow oil (60.4 mg, 98% yield). The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane:2-propanol = 90:10), flow rate = 1.0 ml/min, 23 °C, λ = 254 nm, retention time, *R* (major) 8.9 min, *S* (minor) 17.8 min, 95% ee. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.86 (dd, J_1 = 8.15 Hz, J_2 = 1.47 Hz, 1H), 7.29~7.15 (m, 11H), 6.99 (dd, J_1 = 7.86 Hz, J_2 = 1.65 Hz, 1H), 6.95 (s, 1H), 6.92 (dd, J_1 = 67.2 Hz, J_2 = 8.43 Hz, 4H), 6.24 (dd, J_1 = 7.97 Hz, J_2 = 1.08 Hz, 1H), 3.88 (dd, J_1 = 27.20 Hz, J_2 = 13.89 Hz, 2H), 1.18 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.41, 166.85, 149.71, 139.11, 138.84, 136.01, 132.69, 132.57, 131.47, 131.44, 130.53, 128.45, 128.38, 128.20, 128.18, 128.12, 127.55, 127.31, 125.11, 120.40, 84.07, 78.80, 66.10, 39.78, 27.36 ppm ; IR (KBr)

2979, 1732, 1533, 1489, 1360, 1257, 1203, 1176, 1146, 1012, 841, 745, 699 cm^{-1} ; HRMS (FAB) : calcd for $[C_{33}H_{31}BrO_6N]^+$: 616.1335, found : 616.1331.

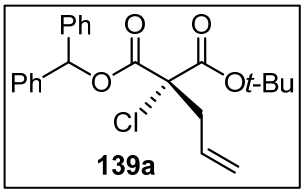
1-benzhydryl 3-(*tert*-butyl) (*R*)-2-benzyl-2-fluoromalonate (**138d**: Table 7)



138d

Following the general procedure, the reaction was started from **138** (34.4 mg, 0.1 mmol) with benzyl bromide (0.06 ml, 0.5 mmol). At -40 °C, solid KOH (28.1 mg, 0.5 mmol) was quickly added to the reaction mixtures. After stirring for 20 h, **138d** was obtained as yellow oil (43 mg, 99% yield). The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane:2-propanol = 96:4), flow rate = 1.0 ml/min, 23 °C, λ = 254 nm, retention time, *R* (major) 13.8 min, *S* (minor) 24.4 min, 90% ee. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.31~7.16 (m, 15H), 6.92 (s, 1H), 3.44 (d, *J* = 15.33 Hz, 2H), 1.28 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.20 (d, *J* = 25.8 Hz), 164.30 (d, *J* = 25.1 Hz), 139.02, 138.92, 133.08, 130.33, 128.54, 128.45, 128.30, 128.24, 128.06, 127.51, 127.32, 126.95, 94.57 (d, *J* = 199.6 Hz), 84.10, 78.67, 39.94 (d, *J* = 20.5 Hz), 27.56 ppm ; IR (KBr) 3033, 2979, 2929, 1752, 1469, 1455, 1370, 1302, 1251, 1156, 1085, 1053, 953, 840, 742, 699 cm^{-1} ; HRMS (CI) : calcd for $[C_{27}H_{26}FO_4]^+$: 433.1815, found : 433.1828 ; $[\alpha]^{25}_D$ = +16.69 (*c* 1, $CHCl_3$)

1-benzhydryl 3-(*tert*-butyl) (*R*)-2-allyl-2-chloromalonate (**139a**: Table 7)

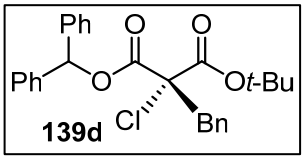


139a

Following the general procedure, the reaction was started from **139** (36.1 mg, 0.1 mmol) with allyl bromide (0.042 ml, 0.5 mmol). At -40 °C, solid KOH (28.1 mg, 0.5 mmol) was quickly added to the reaction mixtures. After stirring for 7 h, **139a** was obtained as colorless oil (39.7 mg, 99% yield). The enantioselectivity was

determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane:2-propanol = 99:1), flow rate = 1.0 ml/min, 23 °C, λ = 254 nm, retention time, *R* (major) 15.8 min, *S* (minor) 18.1 min, 70% ee. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.35~7.26 (m, 10H), 6.93 (s, 1H), 5.81~5.67 (m, 1H), 5.11~5.01 (m, 2H), 2.96 (d, *J* = 6.96 Hz, 2H), 1.28 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.72, 164.71, 139.03, 138.96, 130.28, 128.51, 128.48, 128.34, 128.11, 127.62, 126.97, 120.45, 84.19, 79.07, 70.56, 42.02, 27.46 ppm ; IR (KBr) 2981, 2929, 1744, 1456, 1371, 1278, 1237, 1155, 1029, 972, 839, 742, 699 cm^{-1} ; HRMS (ESI) : calcd for $[C_{23}H_{25}ClO_4Na]^+$: 423.1334, found : 423.1336 ; $[\alpha]^{20}_D$ = +8.97 (*c* 1, $CHCl_3$).

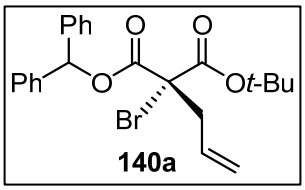
1-benzhydryl 3-(*tert*-butyl) (*R*)-2-benzyl-2-chloromalonate (**139d**: Table 7)



139d

Following the general procedure, the reaction was started from **139** (36.1 mg, 0.1 mmol) with benzyl bromide (0.06 ml, 0.5 mmol). At -40 °C, solid KOH (28.1 mg, 0.5 mmol) was quickly added to the reaction mixtures. After stirring for 5 h, **139d** was obtained as colorless oil (44.2 mg, 98% yield). The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane:2-propanol = 99:1), flow rate = 1.0 ml/min, 23 °C, λ = 254 nm, retention time, *R* (major) 23.4 min, *S* (minor) 21.8 min, 93% ee. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.29~7.04 (m, 15H), 6.87 (s, 1H), 3.48 (s, 2H), 1.21 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.85, 164.88, 138.94, 138.89, 133.74, 130.60, 128.54, 128.42, 128.36, 128.03, 127.74, 127.39, 126.95, 84.25, 79.20, 71.44, 42.89, 27.40 ppm ; IR (KBr) 3032, 2980, 1745, 1496, 1455, 1370, 1272, 1149, 1082, 984, 840, 743, 699 cm^{-1} ; HRMS (CI) : calcd for $[C_{27}H_{26}ClO_4]^+$: 449.1520, found : 449.1518 ; $[\alpha]^{20}_D$ = +20.10 (*c* 1, $CHCl_3$).

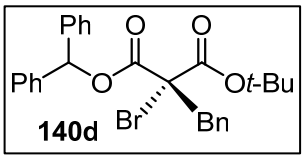
1-benzhydryl 3-(*tert*-butyl) (*R*)-2-allyl-2-bromomalonate (**140a**: Table 7)



140a

Following the general procedure, the reaction was started from **140** (40.5 mg, 0.1 mmol) with allyl bromide (0.042 ml, 0.5 mmol). At -40 °C, solid KOH (28.1 mg, 0.5 mmol) was quickly added to the reaction mixtures. After stirring for 4 h, **140a** was obtained as colorless oil (34.7 mg, 78% yield). The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane:2-propanol = 99:1), flow rate = 1.0 ml/min, 23 °C, λ = 254 nm, retention time, *R* (major) 11.4 min, *S* (minor) 10.1 min, 42% ee. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.37~7.25 (m, 10H), 6.92 (s, 1H), 5.81~5.67 (m, 1H), 5.11~5.02 (m, 2H), 3.02 (d, *J* = 6.6 Hz, 2H), 1.28 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.81, 164.74, 139.09, 138.99, 131.20, 128.49, 128.45, 128.30, 128.09, 127.59, 127.03, 120.25, 84.16, 79.21, 63.35, 42.64, 27.43 ppm ; IR (KBr) 2980, 2929, 1740, 1496, 1455, 1370, 1271, 1234, 1154, 1130, 964, 927, 842, 759, 699, 649 cm^{-1} ; HRMS (CI) : calcd for $[C_{23}H_{26}BrO_4]^+$: 445.1014, found : 445.1008 ; $[\alpha]^{20}_D$ = +0.57 (*c* 1, $CHCl_3$).

1-benzhydryl 3-(*tert*-butyl) (*R*)-2-benzyl-2-bromomalonate (**140d**: Table 7)

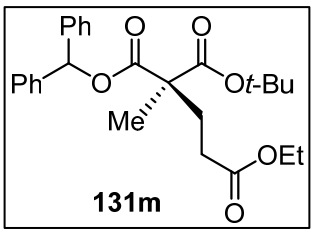


140d

Following the general procedure, the reaction was started from **140** (40.5 mg, 0.1 mmol) with benzyl bromide (0.06 ml, 0.5 mmol). At -40 °C, solid KOH (28.1 mg, 0.5 mmol) was quickly added to the reaction mixtures. After stirring for 9 h, **140d** was obtained as colorless oil (49 mg, 99% yield). The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralcel OJ-H, hexane:2-propanol = 99:1), flow rate = 1.0 ml/min, 23 °C, λ = 254 nm, retention time, *R* (major) 15.5 min, *S* (minor) 11.7 min, 86% ee. ^{1}H-

NMR (300 MHz, $CDCl_3$) δ 7.47~7.36 (m, 10H), 7.32~7.22 (m, 5H), 7.04 (s, 1H), 3.73 (d, *J* = 1.65 Hz, 2H), 1.39 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.95, 165.07, 139.00, 138.92, 134.42, 130.52, 128.54, 128.43, 128.33, 128.05, 128.01, 127.72, 127.41, 127.05, 84.26, 79.41, 64.51, 43.43, 27.38 ppm ; IR (KBr) 3033, 2980, 1745, 1496, 1455, 1370, 1272, 1149, 984, 840, 743, 699 cm^{-1} ; HRMS (ESI) : calcd for $[C_{27}H_{27}BrO_4Na]^+$: 517.0985, found : 517.0889 ; $[\alpha]^{20}_D$ = +6.91 (*c* 1, $CHCl_3$).

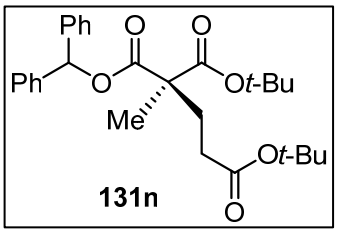
3-benzhydryl 3-(*tert*-butyl) 1-ethyl (*S*)-butane-1,3,3-tricarboxylate (**131m**: Table 8)



131m

Following the general procedure, the reaction was started from **131** (34 mg, 0.1 mmol) with ethyl acrylate (0.054 ml, 0.5 mmol). At the -20 °C, aq. 50% KOH (0.056 ml, 0.5 mmol) was added to the reaction mixtures. After stirring for 1 h, the residue was purified by column chromatography (silica gel, hexane:EtOAc = 10:1) to afford **131m** as colorless oil (37.4 mg, 85% yield). The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane:2-propanol = 95:5), flow rate = 1.0 ml/min, 23 °C, λ = 254 nm, retention time, *S* (major) 21.6 min, *R* (minor) 16.2 min, 77% ee. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.31~7.24 (m, 10H), 6.89 (s, 1H), 4.08 (q, *J* = 7.05 Hz, 2H), 2.25~2.19 (m, 4H), 1.39 (s, 3H), 1.28 (s, 9H), 1.21 (t, *J* = 7.1 Hz, 3H) ppm ; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 172.77, 170.95, 170.51, 139.71, 128.43, 127.99, 127.92, 127.29, 127.04, 81.91, 77.55, 60.40, 53.63, 30.65, 29.58, 27.61, 19.86, 14.14 ppm ; IR (KBr) 2981, 1731, 1496, 1454, 1370, 1256, 1158, 1109, 1026, 976, 847, 743, 700, 648 cm^{-1} ; HRMS (FAB) : calcd for $[C_{26}H_{33}O_6]^+$: 441.2277, found : 441.2280 ; $[\alpha]^{25}_D$ = +2.2 (*c* 1, $CHCl_3$).

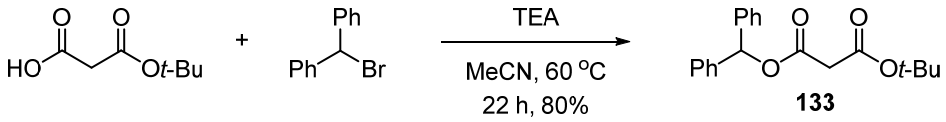
3-benzhydryl 1,3-di-*tert*-butyl (*S*)-butane-1,3,3-tricarboxylate (**131n**: Table 8)



Following the general procedure, the reaction was started from **131** (34 mg, 0.1 mmol) with *tert*-butyl acrylate (0.073 ml, 0.5 mmol). At the 0 °C, aq. 50% KOH (0.056 ml, 0.5 mmol) was added to the reaction mixtures. After stirring for 1 h, the residue was purified by column chromatography (silica gel, hexane:EtOAc = 10:1) to afford **131n** as yellow oil (41.2 mg, 88% yield). The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane:2-propanol = 95:5), flow rate = 1.0 ml/min, 23 °C, λ = 254 nm, retention time, *S* (major) 13.7 min, *R* (minor) 9.8 min, 66% ee. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.31~7.24 (m, 10H), 6.89 (s, 1H), 2.19~2.12 (m, 4H), 1.40 (s, 9H), 1.38 (s, 3H), 1.28 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.09, 171.03, 170.62, 139.75, 128.45, 128.43, 127.98, 127.91, 127.28, 127.06, 81.82, 80.30, 77.50, 53.66, 30.74, 30.70, 28.04, 27.62, 19.79 ppm ; IR (KBr) 2979, 2935, 2350, 1730, 1456, 1369, 1255, 1155, 1108, 848, 742, 700 cm^{-1} ; HRMS (FAB) : calcd for $[C_{28}H_{37}O_6]^+$: 469.2590, found : 469.2592 ; $[\alpha]^{25}_D$ = -0.11 (*c* 1, $CHCl_3$).

2.5. Double asymmetric phase-transfer catalytic α-alkylation

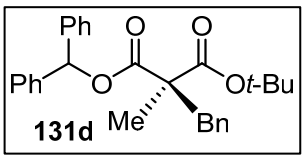
Preparation of malonate **133** (Scheme 38)



Triethylamine (5.44 ml, 39 mmol) was added to a solution of *tert*-butyl hydrogen

malonate (4.62 ml, 30 mmol) and α-Bromodiphenyl methane (9.64 g, 39 mmol) in acetonitrile (60 ml). At 60 °C, reaction mixture was stirred for 22 h. Then reaction mixture was evaporated and diluted with EtOAc (600 ml). Organic layer was washed with saturated aqueous solution of ammonium chloride (200 ml) and brine (200 ml), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane:EtOAc = 40:1~10:1) to afford **133** as pale yellow oil (7.83 g, 80% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.36~7.19 (m, 10H), 6.96 (s, 1H), 3.33 (s, 2H), 1.40 (s, 9H) ppm ; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 165.32, 164.88, 139.41, 128.07, 127.60, 126.80, 81.40, 77.24, 42.77, 27.41 ppm ; IR (KBr) 3033, 2979, 1730, 1496, 1454, 1393, 1369, 1329, 1259, 1144, 1081, 992, 836, 748, 699, 647 cm^{-1} ; HRMS (ESI) : calcd for $[C_{20}H_{22}O_4Na]^+$: 349.1410, found : 349.1422.

Double phase-transfer catalytic α-alkylations of malonate **133** (Scheme 38)



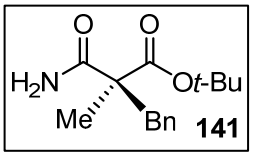
131d

Iodomethane (5.2 μl, 0.084 mmol) was added to a solution of malonate diphenylmethyl ester *tert*-butyl ester (**133**, 26.1 mg, 0.08 mmol) and (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide (**26e**, 3.66 mg, 0.004 mmol) in toluene (0.3 ml). At 0 °C, solid KOH (31.4 mg, 0.56 mmol) was added to the reaction mixtures. After stirring for 4 h, benzyl bromide (0.048 ml, 0.4 mmol) was added to the reaction mixture. EYELA PSL-1400 was used for low temperature stirring and the stirring rate was 7. The reaction mixtures was diluted with EtOAc (10 ml), washed with brine (2×4 ml), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane:EtOAc = 60:1) to afford **131d** as colorless viscous oil (32.4 mg, 94% yield). The enantioselectivity was determined as 95% ee [chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane:2-propanol = 98:2), flow rate = 1.0 ml/min, 23 °C, λ = 254 nm, retention

time, *S* (major) 17 min, *R* (minor) 16 min, 95% ee]. The spectra data were exactly same to above **131d**.

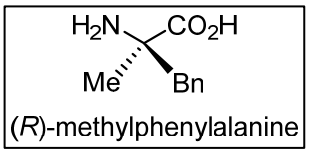
2.6. Application to the synthesis of (*R*)-α-methylphenylalanine

tert-butyl (*S*)-3-amino-2-benzyl-2-methyl-3-oxopropanoate (**141**: Scheme 42)



Palladium carbon (170 mg) was add to a stirred solution of (*S*)-α-benzyl-α-methyl-malonate diphenylmethyl ester *tert*-butyl ester (**131d**, 336 mg, 0.78 mmol) in MeOH (3 ml) under H_2 gas. After sttiring for 3 h, the reaction mixtures was filtered through the Celite 545 and concentrated *in vacuo* and dissolved with dichloromethane (3 ml). Ethyl chloroformate (0.11 ml, 1.17 mmol) and triethylamine (0.33 ml, 2.34 mmol) was added to a stirred solution at 0 °C. After warming (30 °C) and stirring for 1 h, ammonium hydroxide (7.8 ml) was added to reaction mixture and stirred for 5 h. The reaction mixture was evaporated and diluted with EtOAc (50 ml), washed with brine (2×20 ml), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane:EtOAc = 10:1) to afford **141** as a white solid (184.9 mg, 90% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.22~7.18 (m, 5H), 6.92 (s, 1H), 5.38 (s, 1H), 3.31 (dd, J_1 = 87.78 Hz, J_2 = 13.44 Hz, 2H), 1.42 (s, 9H), 1.37 (s, 3H) ppm ; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 174.03, 173.33, 136.82, 130.03, 128.05, 126.78, 82.33, 55.35, 43.20, 27.80, 21.19 ppm ; IR (KBr) 3349, 2979, 2933, 1678, 1604, 1455, 1368, 1255, 1156, 1119, 847, 702 cm^{-1} ; HRMS (FAB) : calcd for $[C_{15}H_{22}O_3N]^+$: 264.1600, found : 264.1610 ; m.p = 90.8 °C ; $[\alpha]^{25}_D$ = +1.8 (*c* 1, $CHCl_3$).

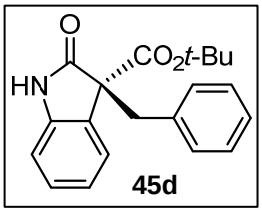
(*R*)-α-methylphenylalanine (Scheme 42)



N-Bromosuccinimide (53.4 mg, 0.3 mmol) was added to a stirred solution of α-benzyl-α-methyl-malonamic acid *tert*-butyl ester (**141**, 26.3 mg, 0.1 mmol) and Mercury (II) acetate (95.6 mg, 0.3 mmol) in DMF (dry, 0.32 ml).[45] After warming (70 °C) and stirring for 2 h, MeOH (for reagent, 2.85 ml) was added to reaction mixture and stirred for 2 h. The reaction mixture was evaporated and diluted with EtOAc (20 ml), washed with brine (2×8 ml), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was dissolved with MeOH (0.5 ml) and 6.0 M HCl (0.5 ml) was added to a stirred solution. After reflux for 1 day, the reaction mixture was evaporated and concentrated *in vacuo*. The residue was purified by ion-exchange column chromatography (DOWEX 50W X8-100 resin, 15% NH_4OH) to afford (*R*)-α-methylphenylalanine as a white solid (17.8 mg, 99% yield). ^{1}H-NMR (300 MHz, D_2O) δ 7.26~7.17 (m, 3H), 7.10~7.08 (m, 2H), 2.97 (dd, J_1 = 96.93 Hz, J_2 = 14.19 Hz, 2H), 1.37 (s, 3H) ppm ; ^{13}C-NMR (100 MHz, D_2O) δ 176.17, 134.27, 130.02, 128.99, 127.86, 62.20, 42.68, 22.38 ppm ; IR (KBr) 3434, 1628, 1404, 1057, 700, 551, 472 cm^{-1} ; HRMS (FAB) : calcd for $[C_{10}H_{14}O_2N]^+$: 180.1025, found : 180.1020 ; m.p = 278.6 °C ; $[\alpha]^{20}_D$ = +14.1 (*c* 0.5, H_2O) [lit. $[\alpha]^{20}_D$ =+6.3 (*c* 1.03, H_2O)].[41]

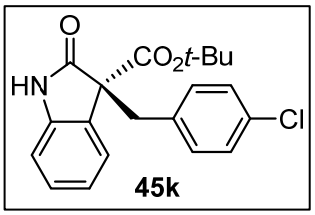
2.7. Application to the synthesis of chiral oxindole derivative

tert-butyl (*R*)-3-benzyl-2-oxoindoline-3-carboxylate (**45d**: Scheme 43)



Raney Nickel (60 mg) was added to a stirred solution of **137d** (107.4 mg, 0.2 mmol) in MeOH (4 ml) under H_2 gas and stirred for 1 h. The reaction mixtures was filtered through the Celite 545 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane:EtOAc = 9:1) to afford **45d** as a white solid (50.4 mg, 78% yield). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.29 (d, *J* = 7.3 Hz, 1H), 7.14 (t, *J* = 7.55 Hz, 1H), 7.03~6.98 (m, 4H), 6.89 (d, *J* = 7 Hz, 2H), 6.59 (d, *J* = 7.65 Hz, 1H), 3.49 (s, 2H), 1.37 (s, 9H) ppm ; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 175.26, 167.93, 141.12, 134.82, 130.10, 128.76, 128.49, 127.71, 126.67, 124.06, 122.33, 109.53, 82.64, 62.08, 39.50, 27.76 ppm ; IR (KBr) 3253, 2927, 1738, 1619, 1473, 1455, 1394, 1369, 1336, 1250, 1154, 1109, 839, 751, 699 cm^{-1} ; HRMS (FAB) : calcd for $[C_{20}H_{21}O_3N]^+$: 323.1521, found : 323.1534 ; m.p = 176.8 °C ; $[\alpha]^{25}_D$ = -148.4 (*c* 0.5, $CHCl_3$).

tert-butyl (*R*)-3-(4-chlorobenzyl)-2-oxoindoline-3-carboxylate (**45k**: Scheme 43)



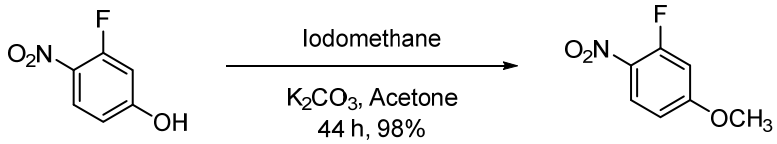
Raney Nickel (60 mg) was added to a stirred solution of **137k** (114.4 mg, 0.2 mmol) in MeOH (4 ml) under H_2 gas and stirred for 1 h. The reaction mixtures was filtered through the Celite 545 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane:EtOAc = 6:1) to afford **45k** as a white solid (54.4 mg, 76% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.28 (d, *J* = 7.32 Hz, 1H), 7.17 (t, *J* = 7.68 Hz, 1H), 7.03 (t, *J* = 7.5 Hz, 1H), 6.88 (dd, J_1 = 44.85 Hz, J_2 = 8.43 Hz, 4H), 6.69 (d, *J* = 7.86 Hz, 1H), 3.44 (t, *J* = 14.1 Hz, 2H), 1.35 (s, 9H) ppm ;

^{13}C-NMR (75 MHz, $CDCl_3$) δ 175.62, 167.74, 141.20, 133.25, 132.63, 131.36, 128.97, 128.08, 127.87, 123.80, 122.45, 109.93, 82.81, 61.96, 38.67, 27.69 ppm ; IR (KBr) 3254, 2979, 1738, 1619, 1473, 1394, 1370, 1337, 1251, 1154, 1094, 1017, 823, 753 cm^{-1} ; HRMS (FAB) : calcd for $[C_{20}H_{20}O_3NCl]^+$: 357.1132, found : 357.1143 ; m.p = 71.6 °C ; $[\alpha]^{25}_D$ = -63.7 (*c* 1, $CHCl_3$).

3. Asymmetric total synthesis of (–)-horsfiline

3.1. Preparation of phase-transfer catalytic substrate

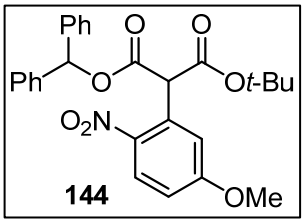
Preparation of 2-fluoro-4-methoxy-1-nitro-benzene (Scheme 44)



Iodomethane (3.74 ml, 60 mmol) was added to a solution of 3-fluoro-4-nitrophenol (4.7 g, 30 mmol) and potassium carbonate (10.37 g, 75 mmol) in acetone (70 ml). The reaction mixture was enveloped in aluminium foil and stirred for 44 h at rt. Reaction mixture was evaporated and diluted with EtOAc (600 ml). Organic layer was washed with brine (2×150 ml), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane:EtOAc = 6:1) to afford 2-fluoro-4-methoxy-1-nitro-benzene as a pale yellow solid (5.03 g, 98% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.09~8.03 (m, 1H), 6.76~6.68 (m, 2H), 3.88 (s, 3H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.28 (d, J = 10.8 Hz), 157.44 (d, J = 263.5 Hz), 127.85(d, J = 0.9 Hz), 110.33(d, J = 3 Hz), 103.13(d, J = 24.2 Hz), 56.30 ppm ; IR (KBr) 3103, 2994, 2952, 2844, 1607, 1511, 1496, 1461, 1442, 1355, 1341, 1295, 1282, 1246, 1200, 1168, 1092, 1019, 956, 866, 849, 828, 749, 683, 636 cm^{-1} ; HRMS (FAB) : calcd for $[C_7H_7FNO_3]^+$: 172.0410, found : 172.0420 ; m.p = 62.1 °C.

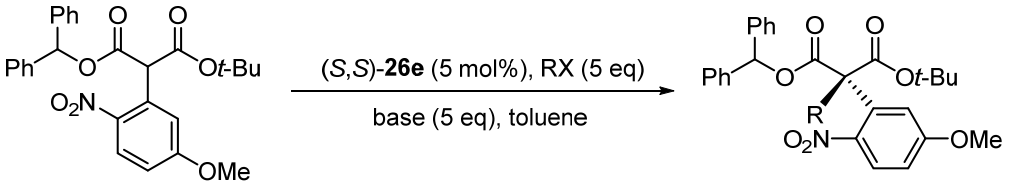
1-benzhydryl 3-(*tert*-butyl) 2-(5-methoxy-2-nitrophenyl)malonate

(**144**: Scheme 44)



Potassium *tert*-butoxide (617 mg, 5.5 mmol) was added to a stirred solution of benzhydryl tert-butyl malonate (**133**, 1.63 g, 5 mmol) in DMF (12 ml) at 0 °C. After stirring for 10 min, a solution of 2-fluoro-4-methoxy-1-nitrobenzene (856 mg, 5 mmol) in DMF (3 ml) was slowly added to the reaction mixture and stirred for 48 h.[50] The reaction mixture was evaporated and diluted with EtOAc (150 ml), quenched with saturated aqueous solution of ammonium chloride (40 ml), washed with brine (40 ml), dried over anhydrous $MgSO_4$, filtered, and concenturated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane: EtOAc=20:1~7:1) to afford **144** as a yellow solid (1.55 g, 65% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.11 (d, J = 9.15 Hz, 1H), 7.37~7.22 (m, 10H), 6.98 (s, 1H), 6.89 (dd, J_1 = 9.15 Hz, J_2 = 2.76 Hz, 1H), 6.77 (d, J = 2.73 Hz, 1H), 5.47 (s, 1H), 3.65 (s, 3H), 1.40 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 166.84, 165.94, 163.28, 141.59, 139.21, 131.33, 128.50, 128.46, 128.13, 128.11, 127.88, 127.30, 127.26, 115.51, 114.18, 83.25, 78.50, 55.91, 55.71, 27.72 ppm ; IR (KBr) 3089, 3064, 3033, 2979, 2936, 2846, 1956, 1890, 1750, 1732, 1608, 1583, 1518, 1496, 1455, 1426, 1394, 1369, 1339, 1297, 1252, 1143, 1084, 1033, 1001, 958, 912, 855, 838, 752, 700, 647, 621 cm^{-1} ; HRMS (FAB) : calcd for $[C_{27}H_{28}NO_7]^+$: 478.1866, found : 478.1862 ; m.p = 68.2 °C.

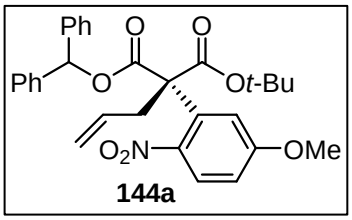
3.2. General procedure for asymmetric phase-transfer catalytic allylation



144 **144a**, **144c**, **144o-p**

Allylic bromides (2 mmol) was added to a solution of 1-benzhydryl 3-*tert*-butyl 2-(5-methoxy-2-nitrophenyl) malonate (**144**, 191 mg, 0.4 mmol) and (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide (**26e**, 18.3 mg, 0.02 mmol) in toluene (1.4 ml). At the designated temperature, base (2 mmol) was added to the reaction mixtures and stirred until the substrate was not observed in TLC analysis. EYELA PSL-1400 was used for low temperature stirring and the stirring rate was 7. The reaction mixtures was diluted with EtOAc (50 ml), washed with brine (2×15 ml), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane:EtOAc = 15:1) to afford allylated malonates.

1-benzhydryl 3-(*tert*-butyl) (*R*)-2-allyl-2-(5-methoxy-2-nitrophenyl)malonate (**144a**: Table 10)

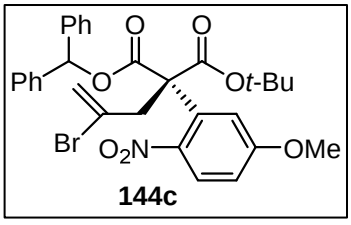


144a

Following the general procedure, the reaction was started with allyl bromide (0.169 ml, 2 mmol), (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide (**26e**, 36.6 mg, 0.04 mmol). At the -40 °C, aq. 50% KOH (0.225 ml, 2 mmol) was added to the reaction mixtures. After stirring for 72 h, **144a** was obtained as yellow oil (204.9 mg, 99% yield). The enantioselectivity was determined by chiral HPLC analysis

(DIACEL Chiralpak AD-H, hexane:2-propanol = 95:5), flow rate = 1.0 ml/min, 20 °C, λ = 254 nm, retention time, *R* (major) 15.9 min, *S* (minor) 21.6 min, 91% ee. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.07 (d, J = 8.97 Hz, 1H), 7.30~7.17 (m, 10H), 6.91 (s, 1H), 6.82 (dd, J_1 = 9.15 Hz, J_2 = 2.73 Hz, 1H), 6.66 (d, J = 2.73 Hz, 1H), 5.73~5.59 (m, 1H), 4.95 (dd, J_1 = 17.13 Hz, J_2 = 1.83 Hz, 1H), 4.88 (dd, J_1 = 10.17 Hz, J_2 = 1.83 Hz, 1H), 3.66 (s, 3H), 3.22 (d, J = 6.96 Hz, 2H), 1.25 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.43, 167.02, 162.48, 142.22, 139.44, 139.39, 135.45, 133.30, 128.36, 128.32, 127.95, 127.93, 127.36, 127.29, 118.82, 117.17, 111.89, 83.36, 78.37, 63.88, 55.63, 39.48, 27.52 ppm ; IR (KBr) 3065, 3031, 3007, 2979, 2937, 2843, 1957, 1732, 1638, 1609, 1580, 1520, 1496, 1455, 1417, 1394, 1369, 1346, 1316, 1252, 1207, 1184, 1152, 1084, 1018, 1002, 957, 923, 843, 756, 700, 647, 620 cm^{-1} ; HRMS (FAB) : calcd for $[C_{30}H_{32}O_7N]^+$: 518.2179, found : 518.2201 ; $[\alpha]^{20}_D$ = +6.62 (91% ee, *c* 1, $CHCl_3$).

1-benzhydryl 3-(*tert*-butyl) (*R*)-2-(2-bromoallyl)-2-(5-methoxy-2-nitrophenyl) malonate (**144c**: Table 10)

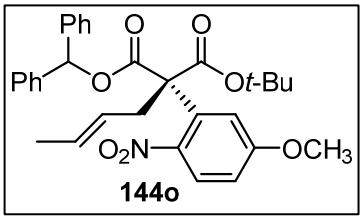


144c

Following the general procedure, the reaction was started with 2,3-dibromopropene (0.196 ml, 2 mmol). At the -20 °C, aq. 50% KOH (0.225 ml, 2 mmol) was added to the reaction mixtures. After stirring for 72 h, **144c** was obtained as yellow oil (202.6 mg, 85% yield). The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane:2-propanol = 95:5), flow rate = 1.0 ml/min, 20 °C, λ = 254 nm, retention time, *R* (major) 10.1 min, *S* (minor) 23.5 min, 86% ee. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.05 (d, J = 8.97 Hz, 1H), 7.31~7.22 (m, 10H), 6.98 (s, 1H), 6.82 (dd, J_1 = 9.06 Hz, J_2 = 2.58 Hz, 1H), 6.58 (d, J = 2.73 Hz, 1H), 5.70 (s, 1H), 5.38 (d, J = 1.65 Hz, 1H), 3.82 (dd, J_1 = 21.975 Hz, J_2 = 15.39 Hz, 2H), 3.59 (s, 3H),

1.22 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.83, 166.15, 162.06, 142.97, 139.11, 138.94, 133.20, 128.43, 128.38, 128.10, 128.06, 128.01, 127.83, 127.47, 127.36, 122.75, 118.41, 112.88, 84.02, 78.88, 64.84, 55.53, 44.83, 27.33 ppm ; IR (KBr) 3088, 3065, 3033, 3006, 2979, 2935, 2850, 1737, 1609, 1580, 1521, 1496, 1456, 1422, 1394, 1370, 1348, 1317, 1252, 1207, 1184, 1147, 1097, 1062, 1018, 1003, 954, 903, 842, 757, 700, 650 cm^{-1} ; HRMS (FAB) : calcd for $[C_{30}H_{31}BrNO_7]^+$: 596.1284, found : 596.1299 ; $[\alpha]^{20}_D$ = +52.92 (86% ee, *c* 1, $CHCl_3$).

1-benzhydryl 3-(*tert*-butyl) (*R*,*E*)-2-(but-2-en-1-yl)-2-(5-methoxy-2-nitrophenyl) malonate (**144o**: Table 10)

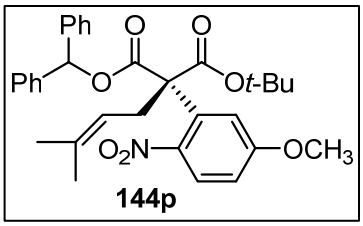


144o

Following the general procedure, the reaction was started with crotyl bromide (0.206 ml, 2 mmol). At the -20 °C, aq. 50% KOH (0.225 ml, 2 mmol) was added to the reaction mixtures. After stirring for 5 h, **144o** was obtained as yellow oil (197.5 mg, 93% yield). The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane:2-propanol = 95:5), flow rate = 1.0 ml/min, 20 °C, λ = 254 nm, retention time, *R* (major) 18.9 min, *S* (minor) 21.5 min, 87% ee. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.11 (d, J = 8.97 Hz, 1H), 7.27~7.24 (m, 10H), 6.92 (s, 1H), 6.86 (dd, J_1 = 9.06 Hz, J_2 = 2.58 Hz, 1H), 6.81 (d, J = 2.4 Hz, 1H), 5.47~5.26 (m, 2H), 3.73 (s, 3H), 3.16 (d, J = 6.24 Hz, 2H), 1.47 (d, J = 5.85 Hz, 3H), 1.29 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.38, 166.99, 162.54, 142.25, 139.56, 135.90, 129.81, 128.28, 128.14, 127.86, 127.78, 127.29, 127.22, 125.29, 117.00, 111.72, 83.01, 78.18, 63.83, 55.61, 38.55, 27.52, 17.78 ppm ; IR (KBr) 3089, 3065, 3033, 3006, 2979, 2936, 2854, 1956, 1732, 1611, 1580, 1520, 1496, 1455, 1393, 1369, 1346, 1316, 1258, 1202, 1184, 1152, 1085, 1031, 1013, 966, 913, 893, 843, 757, 701, 645 cm^{-1} ;

HRMS (FAB) : calcd for $[C_{31}H_{34}NO_7]^+$: 532.2335, found : 532.2317 ; $[\alpha]^{20}_D$ = -12.45 (87% ee, *c* 1, $CHCl_3$).

1-benzhydryl 3-(*tert*-butyl) (*R*)-2-(5-methoxy-2-nitrophenyl)-2-(3-methylbut-2-en-1-yl)malonate (**144p**: Table 10)

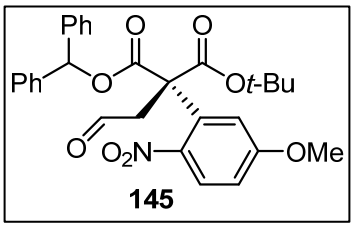


144p

Following the general procedure, the reaction was started with 3,3-dimethylallyl bromide (231 ml, 2 mmol). At the -20 °C, aq. 50% KOH (225 ml, 2 mmol) was added to the reaction mixtures. After stirring for 2 h, **144p** was obtained as yellow oil (207.4 mg, 95% yield). The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane:2-propanol = 95:5), flow rate = 1.0 ml/min, 20 °C, λ = 254 nm, retention time, *R* (major) 18.2 min, *S* (minor) 20.3 min, 71% ee. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.09 (d, *J* = 9.15 Hz, 1H), 7.30~7.17 (m, 10H), 6.89 (s, 1H), 6.83 (dd, J_1 = 9.06 Hz, J_2 = 2.76 Hz, 1H), 6.73 (d, *J* = 2.55 Hz, 1H), 5.01 (t, *J* = 6.39 Hz, 1H), 3.70 (s, 3H), 3.22~3.06 (m, 2H), 1.51 (s, 3H), 1.44 (s, 3H), 1.27 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.53, 167.09, 162.54, 142.33, 139.62, 136.00, 135.27, 128.28, 128.03, 127.86, 127.77, 127.30, 127.21, 118.62, 117.07, 111.78, 82.96, 78.20, 63.74, 55.59, 34.23, 27.50, 25.68, 17.79 ppm ; IR (KBr) 3088, 3064, 3032, 3005, 2978, 2931, 2856, 1956, 1890, 1732, 1672, 1609, 1580, 1520, 1496, 1455, 1393, 1369, 1345, 1316, 1250, 1183, 1150, 1116, 1092, 1058, 1032, 1015, 957, 911, 845, 757, 700, 645 cm^{-1} ; HRMS (FAB) : calcd for $[C_{32}H_{36}NO_7]^+$: 546.2492, found : 546.2476 ; $[\alpha]^{20}_D$ = -11.42 (71% ee, *c* 1, $CHCl_3$).

3.3. Diverse approach to (–)-horsfiline

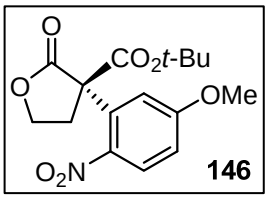
1-benzhydryl 3-(*tert*-butyl) (*R*)-2-(5-methoxy-2-nitrophenyl)-2-(2-oxoethyl) malonate (**145**: Scheme 44, Scheme 50)



145

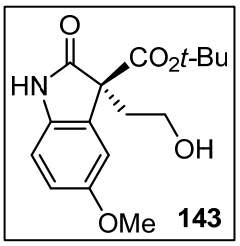
A solution of **144a** (440 mg, 0.85 mmol) in EtOAc (10 ml) was purged with O_3 at -78 ^oC until no more starting material was observed by TLC analysis (20 min). The excess O_3 in the solution was removed by purging of argon at -78^oC for 20 min. To the mixture, four equivalent of triphenyl phosphine (892 mg, 3.4 mmol) was added at -78 ^oC, and then stirred it at -78 ^oC to rt for 20 min. After all solvent was removed on a rotary evaporator, the residue was purified by column chromatography (silica gel, hexane:EtOAc = 5:1) to afford **145** as pale yellow viscous oil (437 mg, 99% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.68 (s, 1H), 8.13 (d, J = 9.08 Hz, 1H), 7.31~7.24 (m, 10H), 7.02 (s, 1H), 6.88 (dd, J_1 = 9.08 Hz, J_2 = 2.52 Hz, 1H), 6.57 (d, J = 2.52 Hz, 1H), 3.60 (s, 3H), 3.45 (ddd, J_1 = 59.23 Hz, J_2 = 17.22 Hz, J_3 = 1.79 Hz, 2H), 1.25 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 198.61, 167.98, 166.29, 162.84, 141.61, 138.71, 138.56, 134.25, 128.93, 128.49, 128.43, 128.38, 128.26, 128.18, 127.45, 127.21, 116.39, 112.91, 84.74, 79.37, 62.43, 55.61, 48.21, 27.29 ppm ; IR (KBr) 3065, 3033, 2979, 2936, 2851, 2754, 1726, 1608, 1580, 1521, 1496, 1456, 1396, 1370, 1346, 1303, 1261, 1212, 1185, 1150, 1081, 1035, 953, 912, 892, 869, 842, 756, 700, 647, 620 cm^{-1} ; HRMS (ESI) : calcd for $[C_{29}H_{29}NO_8Na]^+$: 542.1785, found : 542.1810 ; $[\alpha]^{20}_D$ = +65.18 (91% ee, *c* 1, $CHCl_3$).

tert-butyl (*R*)-3-(5-methoxy-2-nitrophenyl)-2-oxotetrahydrofuran-3-carboxylate (**146**: Scheme 44, Scheme 50)



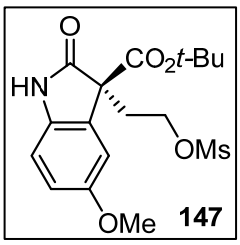
Sodium borohydride (45.4 mg, 1.2 mmol) was added to a solution of **145** (519.5 mg, 1 mmol) in ethanol (6 ml) at -20 °C. The reaction mixture was stirred for 1 h until entire substrate was converted into **146** by TLC analysis. 1N-NaOH (3~4 drop) was added dropwise to the reation mixture for quenching extra sodium borohydride. After all solvent was removed on a rotary evaporator, the mixture was diluted with EtOAc (20 ml) and brine (20 ml). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 20 ml). The combined organic layers were dried with $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane:EtOAc = 5:1~3:1) to afford **146** as white solid (313.5 mg, 93% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.20 (d, J = 9.15 Hz, 1H), 6.91 (dd, J_1 = 9.06 Hz, J_2 = 2.55 Hz, 1H), 6.83 (d, J = 2.76 Hz, 1H), 4.55 (td, J_1 = 8.595 Hz, J_2 = 4.2 Hz, 1H), 4.21 (q, J = 8.4 Hz, 1H), 3.87 (s, 3H), 3.62 (dt, J_1 = 13.71 Hz, J_2 = 8.24 Hz, 1H), 2.50 (dq, J_1 = 13.83 Hz, J_2 = 4.22 Hz, 1H), 1.38 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.82, 165.94, 163.59, 140.86, 135.33, 129.02, 115.99, 112.57, 84.09, 66.42, 61.72, 56.02, 36.02, 27.46 ppm ; IR (KBr) 2979, 1773, 1731, 1612, 1581, 1519, 1371, 1344, 1260, 1155, 1111, 1065, 1032, 841, 756 cm^{-1} ; HRMS (FAB) : calcd for $[C_{16}H_{20}NO_7]^+$: 338.1240 , found : 338.1252 ; m.p = 109.5 °C ; $[\alpha]^{20}_D$ = +8.00 (91% ee, *c* 1, $CHCl_3$).

tert-butyl (*S*)-3-(2-hydroxyethyl)-5-methoxy-2-oxoindoline-3-carboxylate (**143**: Scheme 44)



Raney Nickel (202 mg) was added to a stirred solution of **146** (67.5 mg, 0.2 mmol) in MeOH (3 ml) under H_2 gas and stirred for 1 h. The reaction mixtures was filtered through the Celite 545 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane:EtOAc = 1:1~1:2) to afford **143** as yellow viscous oil (50.4 mg, 82% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 1H), 6.84 (s, 1H), 6.80~6.75 (m, 2H), 3.76 (s, 3H), 3.78~3.72 (m, 1H), 3.66~3.60 (m, 1H), 2.58~2.51 (m, 1H), 2.25~2.19 (m, 1H), 1.37 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 177.00, 167.93, 156.05, 134.06, 130.25, 113.73, 110.57, 110.33, 82.97, 59.88, 59.18, 55.82, 36.81, 27.73 ppm ; IR (KBr) 3322, 2978, 1734, 1605, 1493, 1394, 1370, 1252, 1206, 1155, 1032, 842 cm^{-1} ; HRMS (FAB) : calcd for $[C_{16}H_{21}O_5N]^+$: 307.1420, found : 307.1418.

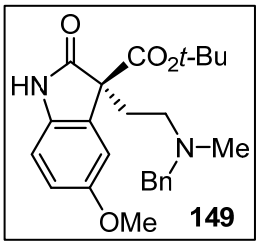
tert-butyl (*S*)-5-methoxy-3-(2-((methylsulfonyl)oxy)ethyl)-2-oxoindoline-3-carboxylate (**147**: Scheme 45)



Methanesulfonyl chloride (0.058 ml, 0.75 mmol) was added to a solution of **143** (153.7 mg, 0.5 mmol) and triethylamine (0.209 ml, 1.5 mmol) in EtOAc (2 ml) at 0 °C. The reaction mixture was allowed to warm to rt. and stirred for 1 h. Saturated aqueous solution of $NaHCO_3$ (10 ml) was added to the reation mixture for quenching and the mixture was diluted with EtOAc (50 ml). The organic layers were separated and washed with brine (20 ml), dried with MgSO4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane:EtOAc = 3:1~1:1)

to afford **147** as yellow oil (183 mg, 95% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.99 (s, 1H), 6.84~6.77 (m, 3H), 4.25~4.09 (m, 2H), 3.76 (s, 3H), 2.85 (s, 3H), 2.78~2.69 (m, 1H), 2.55~2.46 (m, 1H), 1.36 (s, 9H) ppm ; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 175.33, 167.16, 156.09, 134.46, 128.98, 114.07, 110.66, 110.46, 83.28, 65.52, 58.77, 55.84, 37.21, 32.59, 27.67 ppm ; IR (KBr) 3322, 2979, 1737, 1604, 1494, 1441, 1356, 1300, 1253, 1205, 1174, 1030, 937, 826, 753 cm^{-1} ; HRMS (FAB) : calcd for $[C_{17}H_{23}O_7NS]^+$: 385.1195, found : 385.1188.

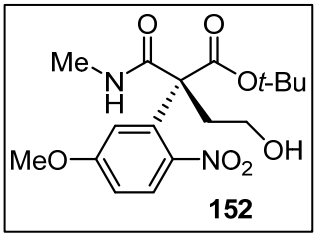
tert-butyl (*S*)-3-(2-(benzyl(methyl)amino)ethyl)-5-methoxy-2-oxoindoline-3-carboxylate (**149**: Scheme 45)



149

Sodium hydride (18 mg, 0.75 mmol) was added to a stirred solution of **147** (192.7 mg, 0.5 mmol) and *N*-methyl benzylamine (0.097 ml, 0.75 mmol) in dry DMF (3 ml) under argon gas. After stirring for 24h, the reaction mixture was diluted with EtOAc (100 ml) and brine (20 ml). The organic layer was separated, washed with brine (2 x 20 ml) again, dried with MgSO4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane: EtOAc=2:1~1:2) to afford **149** as yellow viscous oil (137.5 mg, 67% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.32~7.24 (m, 5H), 7.08 (d, J = 8.43 Hz, 1H), 6.78~6.71 (m, 2H), 4.71 (dd, J_1 = 160.01 Hz, J_2 = 15.18 Hz, 2H), 3.75 (s, 3H), 3.29 (t, J = 6.6 Hz, 2H), 2.96 (s, 3H), 2.58~2.40 (m, 2H), 1.30 (s, 9H) ppm ; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 172.65, 169.65, 155.17, 149.85, 136.80, 136.65, 128.59, 127.83, 127.48, 116.52, 113.80, 107.87, 82.65, 62.86, 58.59, 55.85, 54.57, 36.32, 36.26, 27.63 ppm ; IR (KBr) 2928, 1724, 1607, 1563, 1477, 1369, 1272, 1216, 1155, 1054, 822, 754 cm^{-1} ; HRMS (FAB) : calcd for $[C_{24}H_{31}O_4N_2]^+$: 411.2284, found : 411.2292.

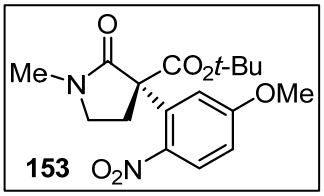
tert-butyl (*R*)-4-hydroxy-2-(5-methoxy-2-nitrophenyl)-2-(methylcarbamoyl) butanoate (**152**: Scheme 46)



152

146 (202.4 mg, 0.6 mmol) was dissolved in methylamine solution 33 wt % in absolute ethanol (5 ml) under argon gas. At the 50 °C, the reaction mixture was stirred for 48 h. After all solvent was removed on a rotary evaporator, the residue was purified by column chromatography (silica gel, hexane:EtOAc = 1:2~only EtOAc) to afford **152** as a yellow solid (168 mg, 76% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.15 (d, J = 8.97 Hz, 2H), 7.07 (d, J = 2.73 Hz, 1H), 6.86 (dd, J_1 = 9.06 Hz, J_2 = 2.73 Hz, 1H), 3.89 (s, 3H), 3.73 (m, 2H), 2.82 (d, J = 4.74 Hz, 3H), 2.74~2.65 (m, 1H), 2.59~2.49 (m, 1H), 2.25 (s, 1H), 1.26 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.72, 170.46, 163.20, 141.26, 137.23, 128.21, 117.08, 111.12, 83.79, 60.71, 59.06, 55.83, 39.12, 27.45, 26.43 ppm ; IR (KBr) 3369, 2976, 2929, 1714, 1654, 1612, 1581, 1514, 1460, 1343, 1256, 1155, 1088, 1038, 843, 757 cm^{-1} ; HRMS (FAB) : calcd for $[C_{17}H_{25}N_2O_7]^+$: 369.1662, found : 369.1668.

tert-butyl (*R*)-3-(5-methoxy-2-nitrophenyl)-1-methyl-2-oxopyrrolidine-3-carboxylate (**153**: Scheme 46)

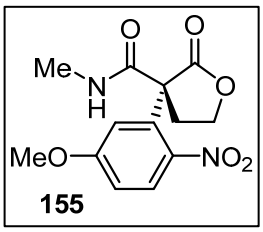


153

Methanesulfonyl chloride (0.093 ml, 1.2 mmol) was added to a solution of **152** (368.4 mg, 1 mmol) and triethylamine (0.347 ml, 2.5 mmol) in EtOAc (4 ml) at 0 °C. The reaction mixture was allowed to warm to 60 °C and stirred for 2 h. Saturated aqueous solution of $NaHCO_3$ (15 ml) was added dropwise to the reation mixture for quenching and the mixture was diluted with EtOAc (20 ml). The organic layers were separated and the aqueous layer was extracted with dichloromethane (20 ml).

The combined organic layers were dried with MgSO4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane:EtOAc = 5:1~3:1) to afford **153** as a pale yellow solid (325.8 mg, 93% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.15 (d, J = 8.79 Hz, 1H), 6.86~6.81 (m, 2H), 4.43 (td, J_1 = 8.43 Hz, J_2 = 3.12 Hz, 1H), 4.05 (dd, J_1 = 15.63 Hz, J_2 = 8.97 Hz, 1H), 3.84 (s, 3H), 3.54~3.44 (m, 1H), 3.06 (s, 3H), 2.44~2.36 (m, 1H), 1.37 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.69, 163.28, 162.47, 141.16, 137.90, 128.69, 116.66, 111.68, 82.89, 67.62, 61.19, 55.76, 37.47, 34.82, 27.50 ppm ; IR (KBr) 2978, 1735, 1705, 1612, 1579, 1519, 1369, 1345, 1317, 1260, 1161, 1066, 1030, 843, 758 cm^{-1} ; HRMS (FAB) : calcd for $[C_{17}H_{23}N_2O_6]^+$: 351.1556, found : 351.1560 ; m.p = 129.7 °C.

(*R*)-3-(5-methoxy-2-nitrophenyl)-N-methyl-2-oxotetrahydrofuran-3-carboxamide (**155**: Scheme 47)

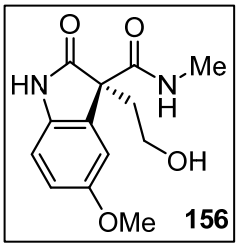


155

3N-HCl (3 ml) was add to a stirred solution of **152** (368.4 mg, 1 mmol) in MeOH (3 ml). After sttiring for 72 h, the reaction mixture was evaporated and diluted with diethyl ether (100 ml), washed with brine (30 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 **155** as a pale yellow solid (279.5 mg, 95% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.05 (d, J = 8.97 Hz, 1H), 6.94~6.86 (m, 2H), 6.21 (s, 1H), 4.55 (td, J_1 = 8.97 Hz, J_2 = 2.58 Hz, 1H), 4.40 (dd, J_1 = 16.67 Hz, J_2 = 9 Hz, 1H), 3.85 (s, 3H), 3.56~3.49 (m, 1H), 2.80 (d, J = 4.77 Hz, 3H), 2.77~2.67 (m, 1H) ppm ; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 175.69, 166.08, 163.29, 140.96, 134.87, 128.82, 116.67, 113.24, 67.73, 60.53, 56.02, 33.10, 27.30 ppm ; IR (KBr) 3395, 2944, 1762, 1680, 1610, 1579, 1519, 1346, 1298, 1260, 1173, 1108, 1021, 870, 830, 755, 708 cm^{-1} ; HRMS (FAB) :

calcd for $[C_{13}H_{15}N_2O_6]^+$: 295.0930, found : 295.0911 ; m.p = 168 °C.

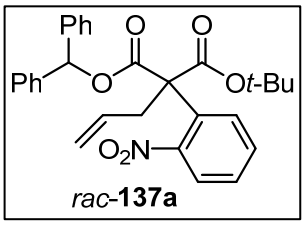
(*R*)-3-(2-hydroxyethyl)-5-methoxy-N-methyl-2-oxoindoline-3-carboxamide (**156**: Scheme 47)



Raney Nickel (196 mg) was added to a stirred solution of **155** (294.3 mg, 1 mmol) in MeOH (10 ml) under H_2 gas and stirred for 1 h. The reaction mixtures was filtered through the Celite 545 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, dichloromethane:MeOH = 20:1~10:1) to afford **156** as a pale yellow solid (111 mg, 42% yield). ^{1}H-NMR (400 MHz, DMSO-*d*) δ 10.50 (bs, 1H), 7.48 (d, *J* = 4.24 Hz, 1H), 6.94 (s, 1H), 6.77 (s, 2H), 4.53 (bs, 1H), 3.70 (s, 3H), 3.18~3.03 (m, 2H), 2.56 (d, *J* = 4.44 Hz, 3H), 2.20 (t, *J* = 7.88 Hz, 2H) ppm ; ^{13}C-NMR (100 MHz, DMSO-*d*) δ 176.69, 168.09, 154.78, 135.44, 130.53, 112.91, 111.55, 109.89, 58.14, 56.76, 55.46, 37.88, 26.36 ppm ; IR (KBr) 3410, 3320, 3212, 2932, 1710, 1626, 1546, 1490, 1441, 1402, 1304, 1271, 1208, 1057, 1031, 819, 707 cm^{-1} ; LRMS (ESI) m/z found : 265.1, 266.1, 287.1 (major), 288.1, 349.1 ; m.p = 160 °C.

3.4. Synthesis of (±)-coerulescine

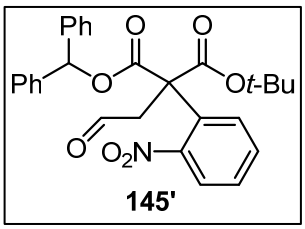
1-benzhydryl 3-(*tert*-butyl) 2-allyl-2-(2-nitrophenyl)malonate
(*rac*-**137a**: Scheme 48)



rac-**137a**

Allylic bromides (2 mmol) was added to a solution of **137** (178.4 mg, 0.4 mmol) and tetrabutylammonium bromide (12.9 mg, 0.04 mmol) in toluene (1.4 ml). At the rt, aq. 50% KOH (0.225 ml, 2 mmol) was added to the reaction mixtures and stirred until the substrate was not observed in TLC analysis. EYELA PSL-1400 was used for low temperature stirring and the stirring rate was 7. After stirring for 20 h, the reaction mixtures was diluted with EtOAc (50 ml), washed with brine (2×15 ml), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane:EtOAc = 15:1) to afford *rac*-**137a** as a white solid (193.1 mg, 99% yield). The spectra data were exactly same to above **137a** except a specific rotation.

1-benzhydryl 3-(*tert*-butyl) 2-(2-nitrophenyl)-2-(2-oxoethyl)malonate
(**145'**: Scheme 48)

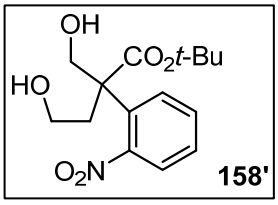


145'

Following the above procedure of **145**, the reaction was started from *rac*-**137a** (414.5 mg, 0.85 mmol). After stirring for 1 h, **145'** was obtained as yellow viscous oil (411.9 mg, 99% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.69 (t, J = 1.68 Hz, 1H), 7.99 (dd, J_1 = 8.06 Hz, J_2 = 1.4 Hz, 1H), 7.44 (td, J_1 = 7.52 Hz, J_2 = 1.16 Hz, 1H), 7.37 (td, J_1 = 7.74 Hz, J_2 = 1.44 Hz, 1H), 7.31~7.23 (m, 10H), 7.04 (dd, J_1 = 7.04 Hz, J_2 = 1.2 Hz, 1H), 7.03 (s, 1H), 3.47 (ddd, J_1 = 74.7 Hz, J_2 = 17.18 Hz, J_3 = 2.44 Hz, 2H),

1.27 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 198.50, 167.86, 166.13, 148.84, 138.56, 138.42, 132.94, 131.49, 130.44, 129.04, 128.38, 128.30, 128.15, 127.53, 127.08, 126.12, 84.89, 79.46, 62.08, 48.44, 27.23 ppm ; IR (KBr) 3033, 2980, 2933, 2755, 1727, 1533, 1455, 1357, 1268, 1212, 1147, 1079, 956, 856, 744, 701 cm^{-1} ; HRMS (ESI) : calcd for $[C_{28}H_{27}NO_7Na]^+$: 512.1680, found : 512.1702.

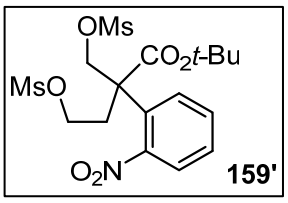
tert-butyl 4-hydroxy-2-(hydroxymethyl)-2-(2-nitrophenyl)butanoate
(**158'**: Scheme 48, Table 9)



Sodium borohydride (45.4 mg, 1.2 mmol) was added to a solution of **145'** (489.5 mg, 1 mmol) in ethanol (6 ml) at -20 °C. The reaction mixture was stirred for 1 h until entire substrate was converted into intermediate **146'** by TLC analysis. The reaction mixture was allowed to warm to 0 °C before tetrahydrofuran (1.5 ml) and cerium (III) trichloride heptahydrate (745.2 mg, 2 mmol) were added. After stirring for 10 min at 0 °C, sodium borohydride (189 mg, 5 mmol) was added and the heterogeneous mixture was stirred for 10 min before a second charge of sodium borohydride (189 mg, 5 mmol) was added.[47b] The reaction mixture was stirred for 2 h until no more intermediate **146'** was observed by TLC analysis, then AcOH (0.5 ml) was added dropwise to the reation mixture for quenching extra sodium borohydride. After all solvent was removed on a rotary evaporator, the mixture was diluted with EtOAc (20 ml) and water (20 ml). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 20 ml). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (20 ml) and brine (20 ml), dried with MgSO4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane:EtOAc = 1:1~only EtOAc) to afford **158'** as white solid (202.4 mg, 65% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.87 (dd,

J_1 = 7.95 Hz, J_2 = 1.29 Hz, 1H), 7.69~7.56 (m, 2H), 7.44~7.39 (m, 1H), 4.14 (dd, J_1 = 120.18 Hz, J_2 = 11.73 Hz, 2H), 3.84~3.75 (m, 1H), 3.63~3.56 (m, 1H), 3.28 (bs, 1H), 2.57~2.37 (m, 3H), 1.40 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.21, 149.90, 134.33, 132.74, 129.99, 128.07, 125.63, 83.53, 67.79, 59.04, 55.05, 37.81, 27.71 ppm ; IR (KBr) 3373, 2979, 1718, 1529, 1357, 1250, 1157, 1038, 853, 841, 787, 748, 712 cm^{-1} ; HRMS (FAB) : calcd for $[C_{15}H_{22}NO_6]^+$: 312.1447, found : 312.1434 ; m.p = 140.8 °C.

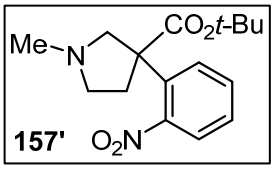
tert-butyl 4-((methylsulfonyl)oxy)-2-(((methylsulfonyl)oxy)methyl)-2-(2-nitrophenyl)butanoate (**159'**: Scheme 49)



Methanesulfonyl chloride (0.116 ml, 1.5 mmol) was added to a solution of **158'** (155.7 mg, 0.5 mmol) and triethylamine (0.209 ml, 1.5 mmol) in dichloromethane (8 ml) at 0 °C. The reaction mixture was allowed to warm to rt and stirred for 2 h. Saturated aqueous solution of $NaHCO_3$ (15 ml) was added dropwise to the reation mixture for quenching and the mixture was diluted with dichloromethane (20 ml). The organic layers were separated and the aqueous layer was extracted with dichloromethane (2 x 20 ml). The combined organic layers were washed with brine (20 ml), dried with MgSO4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane:EtOAc = 1:1) to afford **159'** as colorless oil (229.1 mg, 98% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.94 (dd, J_1 = 7.86 Hz, J_2 = 1.29 Hz, 1H), 7.66 (td, J_1 = 7.05 Hz, J_2 = 1.65 Hz, 1H), 7.51 (d, J = 7.68 Hz, 2H), 4.84 (dd, J_1 = 56.75 Hz, J_2 = 10.23 Hz, 2H), 4.23~4.07 (m, 2H), 2.93 (s, 3H), 2.84 (s, 3H), 2.82~2.59 (m, 2H), 1.43 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.45, 149.77, 132.92, 130.84, 130.25, 129.13, 126.02, 84.85, 71.98, 65.47, 52.83, 37.40, 37.19, 33.67, 31.49, 27.64 ppm ; IR (KBr) 2981, 2940, 1725, 1533, 1461, 1359, 1256, 1176, 961, 836, 789, 748 cm^{-1} ; HRMS (FAB) : calcd for

$[C_{17}H_{26}NO_{10}S_2]^+$: 468.0998, found : 468.0986.

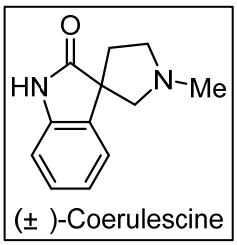
tert-butyl 1-methyl-3-(2-nitrophenyl)pyrrolidine-3-carboxylate (**157'**: Scheme 49)



157'

159' (187 mg, 0.4 mmol) was dissolved in methylamine solution 33 wt % in absolute ethanol (10 ml).[52] At rt, the reaction mixture was stirred for 48 h. After all solvent was removed on a rotary evaporator, the residue was purified by column chromatography (silica gel, hexane:EtOAc:Acetone:MeOH = 10:16:4:1) to afford **157'** as yellow oil (114 mg, 93% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.85 (dd, J_1 = 7.92 Hz, J_2 = 1.26 Hz, 1H), 7.75 (dd, J_1 = 8.06 Hz, J_2 = 0.93 Hz, 1H), 7.54 (dd, J_1 = 7.23 Hz, J_2 = 1.08 Hz, 1H), 7.32 (dd, J_1 = 7.5 Hz, J_2 = 1.08 Hz, 1H), 3.03 (dd, J_1 = 156.33 Hz, J_2 = 10.26 Hz, 2H), 3.00~2.87 (m, 2H), 2.51 (q, J = 7.86 Hz, 1H), 2.37 (s, 3H), 2.17~2.06 (m, 1H), 1.34 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.65, 148.21, 139.93, 133.05, 129.01, 127.17, 124.70, 81.75, 67.17, 57.22, 56.44, 41.84, 38.56, 27.55 ppm ; IR (KBr) 2976, 2939, 2841, 2788, 1731, 1607, 1575, 1528, 1479, 1455, 1357, 1251, 1154, 1085, 1045, 897, 853, 787, 749, 712 cm^{-1} ; HRMS (FAB) : calcd for $[C_{16}H_{23}N_2O_4]^+$: 307.1658, found : 307.1656.

(±)-Coerulescine (**47b**: Scheme 49)



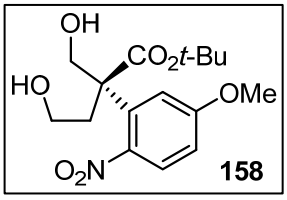
(±)-Coerulescine

Palladium carbon (17 mg) was added to a stirred solution of **157'** (61.3 mg, 0.2 mmol) in MeOH (4 ml) under H_2 gas and stirred for 1 h. The reaction mixtures was filtered through the Celite 545 and concentrated *in vacuo* to afford quantitative aniline intermediate as yellow oil. Silica gel (613 mg) was added to a stirred solution of aniline intermediate (55.3 mg, 0.2 mmol) in dichloromethane (2 ml) and stirred for 3 h. The absorbed residue was purified by column chromatography (silica gel, dichloromethane:MeOH = 20:1~8:1)

to afford **(±)-coerulescine** as a white solid (**47b**, 38.8 mg, 96% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.50 (bs, 1H), 7.35 (d, J = 7.2 Hz, 1H), 7.15 (td, J_1 = 7.62 Hz, J_2 = 0.92 Hz, 1H), 7.00 (td, J_1 = 7.54 Hz, J_2 = 0.64 Hz, 1H), 6.89 (d, J = 7.68 Hz, 1H), 3.01~2.95 (m, 1H), 2.86 (dd, J_1 = 28.4 Hz, J_2 = 9.36 Hz, 2H), 2.84~2.77 (m, 1H), 2.44 (s, 3H), 2.43~2.36 (m, 1H), 2.11~2.05 (m, 1H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 183.47, 140.36, 136.11, 127.67, 123.11, 122.67, 109.70, 66.26, 56.73, 53.70, 41.80, 37.85 ppm ; IR (KBr) 3208, 2925, 2850, 2790, 1712, 1620, 1471, 1337, 1244, 1198, 1153, 1104, 1015, 754, 677 cm^{-1} ; HRMS (FAB) : calcd for $[C_{12}H_{15}N_2O]^+$: 203.1184, found : 203.1178 ; m.p = 122.6 °C.

3.5. Synthesis of (–)-horsfiline

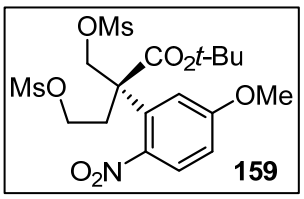
tert-butyl (*R*)-4-hydroxy-2-(hydroxymethyl)-2-(5-methoxy-2-nitrophenyl) butanoate (**158**: Scheme 50)



Following the above procedure of **158'**, the reaction was started from **145** (519.5 mg, 1 mmol). The reaction mixture was stirred until no more intermediate **146** was observed by TLC analysis, and **158** was obtained as a white solid (208.1 mg, 61% yield). The enantioselectivity was determined by chiral HPLC analysis [chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane:2-propanol = 90:10), flow rate = 1.0 ml/min, 20 °C, λ = 254 nm, retention time, *S* (minor) 18.5 min, *R* (major) 21.0 min, 91% ee]. The obtained **158** was dissolved in minimum EtOAc, and then hexane (five-fold volume of EtOAc) was poured to solution of **158**. Immediately, white crystal was formed and only combined organic solution was carefully removed except crystal using Pasteur pipette. Remaining

crystal was dissolved again in minimum EtOAc, and then hexane (five-fold volume of EtOAc) was poured. This procedure was repeated three times to afford single (*R*)-enantiomer **158** (131.2 mg, 63%). All of the removed organic solution was collected and all solvent was removed on a rotary evaporator. Above procedure was repeated six times using obtained residue to afford single (*R*)-enantiomer **158** (45.6 mg, 22%). The enantioselectivity of obtained single (*R*)-enantiomer **158** (total 176.8 mg, 85%) was determined by chiral HPLC analysis [chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane:2-propanol = 90:10), flow rate = 1.0 ml/min, 20 °C, λ = 254 nm, retention time, *R* (only major peak) 21.8 min, >99% ee]. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.00 (d, J = 8.97 Hz, 1H), 7.19 (d, J = 2.58 Hz, 1H), 6.84 (dd, J_1 = 8.97 Hz, J_2 = 2.58 Hz, 1H), 4.13 (dd, J_1 = 125.955 Hz, J_2 = 11.55 Hz, 2H), 3.88 (s, 3H), 3.88~3.79 (m, 1H), 3.67~3.59 (m, 1H), 3.33 (s, 1H), 2.57~2.34 (m, 2H), 2.28 (s, 1H), 1.39 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.08, 162.88, 142.74, 137.57, 128.40, 116.57, 111.31, 83.23, 67.79, 59.09, 55.85, 55.14, 37.79, 27.74 ppm ; IR (KBr) 3403, 2977, 2925, 2851, 1721, 1610, 1578, 1519, 1479, 1460, 1417, 1394, 1369, 1348, 1314, 1291, 1256, 1158, 1097, 1036, 913, 876, 842, 756, 729, 709, 665, 621 cm^{-1} ; HRMS (FAB) : calcd for $[C_{16}H_{24}NO_7]^+$: 342.1553, found : 342.1544 ; m.p = 122.8 °C ; $[\alpha]^{20}_D$ = -87.79 (>99% ee, *c* 1, $CHCl_3$).

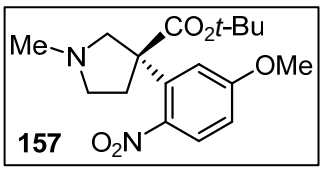
<u>*tert*-butyl (*R*)-2-(5-methoxy-2-nitrophenyl)-4-((methylsulfonyl)oxy)-2-(((methylsulfonyl)oxy)methyl)butanoate (**159**: Scheme 51)</u>



Following the above procedure of **159'**, the reaction was started from **158** (170.7 mg, 0.5 mmol). After stirring for 2 h, **159** was obtained as colorless oil (246 mg, 99% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.05 (d, J = 8.97 Hz, 1H), 6.96 (d, J = 2.55 Hz, 1H), 6.91 (dd, J_1 = 8.97 Hz, J_2 = 2.55 Hz, 1H), 4.85 (dd, J_1 = 45.585 Hz, J_2 =

10.23 Hz, 2H), 4.18 (t, *J* = 7.32 Hz, 2H), 3.90 (s, 3H), 2.96 (s, 3H), 2.88 (s, 3H), 2.78~2.59 (m, 2H), 1.41 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.32, 162.90, 142.45, 13380, 128.72, 116.67, 112.41, 84.46, 71.88, 65.55, 56.01, 52.99, 37.39, 37.26, 33.54, 27.62 ppm ; IR (KBr) 3027, 2981, 2941, 2848, 1726, 1610, 1580, 1522, 1462, 1416, 1395, 1355, 1261, 1175, 1112, 1063, 1031, 960, 894, 840, 785, 755, 671, 621 cm^{-1} ; HRMS (FAB) : calcd for $[C_{18}H_{27}NO_{11}S_2]^+$: 497.1026, found : 497.1034 ; $[\alpha]^{20}_D$ = -116.20 (>99% ee, *c* 1, $CHCl_3$).

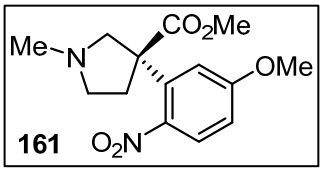
tert-butyl (*R*)-3-(5-methoxy-2-nitrophenyl)-1-methylpyrrolidine-3-carboxylate (**157**: Scheme 51)



157

Following the above procedure of **157'**, the reaction was started from **159** (199 mg, 0.4 mmol). After stirring for 48 h, **157** was obtained as a yellow solid (125.1 mg, 93% yield). The enantioselectivity was determined by chiral HPLC analysis [chiral HPLC analysis (DIACEL Chiralcel OD-H, hexane:2-propanol = 99:1), flow rate = 1.0 ml/min, 20 °C, λ = 254 nm, retention time, *R* (only major peak) 11.9 min, >99% ee]. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.97 Hz, 1H), 7.24 (d, *J* = 2.76 Hz, 1H), 6.76 (dd, J_1 = 8.97 Hz, J_2 = 2.76 Hz, 1H), 3.85 (s, 3H), 3.26 (d, *J* = 10.26 Hz, 1H), 3.01~2.84 (m, 2H), 2.75 (d, *J* = 10.26 Hz, 1H), 2.46 (q, *J* = 8.61 Hz, 1H), 2.35 (s, 3H), 2.15~2.05 (m, 1H), 1.33 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.59, 163.10, 142.75, 141.27, 127.66, 115.53, 110.44, 81.55, 66.92, 57.55, 56.28, 55.66, 41.80, 38.24, 27.57 ppm ; IR (KBr) 2975, 2940, 2841, 2788, 1731, 1612, 1577, 1518, 1479, 1460, 1419, 1392, 1368, 1347, 1315, 1273, 1258, 1155, 1125, 1107, 1074, 1035, 998, 932, 902, 873, 842, 756, 711, 621 cm^{-1} ; HRMS (FAB) : calcd for $[C_{17}H_{25}N_2O_5]^+$: 337.1763, found : 337.1762 ; m.p = 89.7 °C ; $[\alpha]^{20}_D$ = +86.23 (>99% ee, *c* 1, $CHCl_3$).

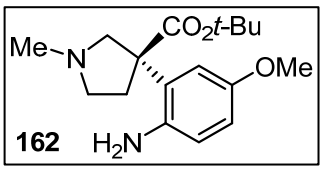
methyl (*R*)-3-(5-methoxy-2-nitrophenyl)-1-methylpyrrolidine-3-carboxylate (**161**: Scheme 51)



161

Trifluoroacetic acid (1.2 ml) was add to a stirred solution of **157** (80 mg, 0.238 mmol) in dichloromethane (2 ml). After sttiring for 1 h, both dichloromethane and trifluoroacetic acid was removed on a rotary evaporator. The crude product (**160**) was concentrated *in vacuo* for 3 h and dissolved with toluene:MeOH=5:2 mixture (3 ml). TMS-diazomethane (0.48 ml, 0.951 mmol) was added to a stirred solution. After stirring for 2 h, the reaction mixture was evaporated and diluted with EtOAc (50 ml), washed with brine (2×20 ml), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, dichloromethane:MeOH = 20:1) to afford **161** as yellow oil (64.4 mg, 92% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.01 (d, J = 9.0 Hz, 1H), 7.25 (s, 1H), 6.80 (dd, J_1 = 9.0 Hz, J_2 = 2.8 Hz, 1H), 3.87 (s, 3H), 3.61 (s, 3H), 3.04 (dd, J_1 = 115.9 Hz, J_2 = 10.1 Hz, 2H), 2.97~2.90 (m, 2H), 2.54 (q, J = 7.3 Hz, 1H), 2.36 (s, 3H), 2.16~2.06 (m, 1H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 174.24, 163.27, 142.11, 141.14, 127.95, 115.64, 110.77, 66.69, 56.81, 56.05, 55.74, 52.30, 41.76, 38.02 ppm ; IR (KBr) 2950, 2841, 2789, 1739, 1577, 1516, 1346, 1257, 1034 cm^{-1} ; HRMS (FAB) : calcd for $[C_{14}H_{19}N_2O_5]^+$: 295.1294, found : 295.1306.

tert-butyl (*R*)-3-(2-amino-5-methoxyphenyl)-1-methylpyrrolidine-3-carboxylate (**162**: Scheme 51)

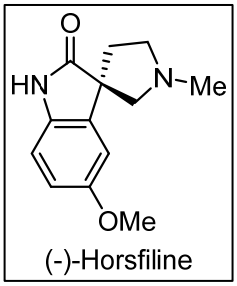


162

^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.65~6.53 (m, 3H), 3.97 (s, 2H), 3.71 (s, 3H), 3.09 (dd, J_1 = 70.68 Hz, J_2 = 9.72 Hz, 2H), 2.94~2.85 (m, 1H), 2.68~2.50 (m, 2H), 2.34 (s, 3H), 2.15~2.06 (m, 1H), 1.36 (s, 9H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ

174.30, 152.05, 138.93, 128.20, 117.77, 113.86, 112.74, 81.07, 64.41, 57.91, 55.76, 55.69, 42.09, 33.81, 27.77 ppm ; IR (KBr) 3438, 3370, 3188, 3063, 2974, 2937, 2833, 2783, 2697, 2656, 1718, 1633, 1613, 1581, 1503, 1455, 1426, 1392, 1368, 1331, 1275, 1252, 1224, 1156, 1124, 1096, 1045, 1002, 902, 847, 812, 754, 709, 640 cm^{-1} ; HRMS (FAB) : calcd for $[C_{17}H_{26}N_2O_3]^+$: 306.1943, found : 306.1947 ; $[\alpha]^{20}_D$ = -25.53 (>99% ee, *c* 1, $CHCl_3$).

(–)-Horsfiline (**47a**: Scheme 51)



(-)-Horsfiline

Following the above procedure of **(±)-coerulescine**, the reaction was started from **157** (67.3 mg, 0.2 mmol). Through aniline intermediate **162**, **(–)-horsfiline** was obtained as a white solid (**47a**, 45.5 mg, 98% yield). The enantioselectivity was determined by chiral HPLC analysis [chiral HPLC analysis (DIACEL Chiralcel OJ-H, hexane:2-propanol = 98:2), flow rate = 1.0 ml/min, 20 °C, λ = 254 nm, retention time, *R* (only major peak) 31.1 min, >99% ee]. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.49 (bs, 1H), 6.97 (d, *J* = 2.04 Hz, 1H), 6.79 (d, *J* = 8.4 Hz, 1H), 6.67 (dd, J_1 = 8.38 Hz, J_2 = 2.2 Hz, 1H), 3.74 (s, 3H), 2.96 (q, *J* = 8.12 Hz, 1H), 2.83 (q, *J* = 9.36 Hz, 2H), 2.76 (q, *J* = 7.92 Hz, 1H), 2.42 (s, 3H), 2.42~2.35 (m, 1H), 2.09~2.01 (m, 1H) ppm ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 183.37, 156.00, 137.53, 133.73, 112.30, 110.11, 110.02, 66.22, 56.65, 55.75, 54.18, 41.72, 37.93 ppm ; IR (KBr) 3222, 2925, 2851, 2788, 1709, 1604, 1490, 1441, 1376, 1349, 1305, 1277, 1205, 1180, 1155, 1049, 1033, 997, 902, 875, 811, 755, 683, 624 cm^{-1} ; HRMS (FAB) : calcd for $[C_{13}H_{17}N_2O_2]^+$: 233.1290, found : 233.1292 ; m.p = 163.8 °C ; $[\alpha]^{20}_D$ = -8.5 (>99% ee, *c* 5, MeOH) [Reported value for natural (–)-horsfiline : $[\alpha]^{20}_D$ = -7.2 (*c* 1, MeOH)].[35]

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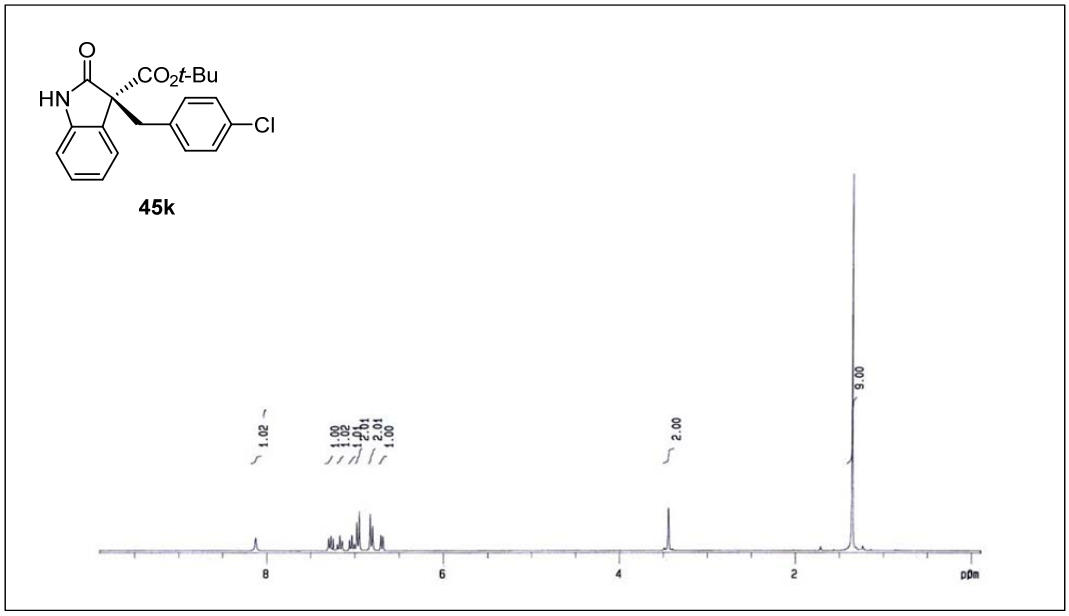
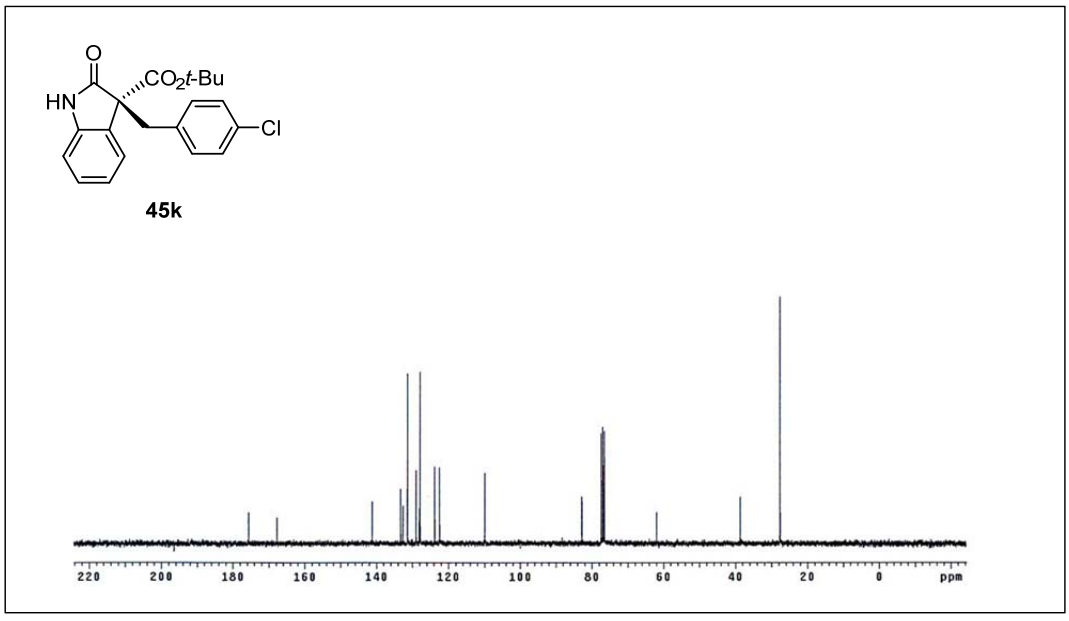
APPENDIX

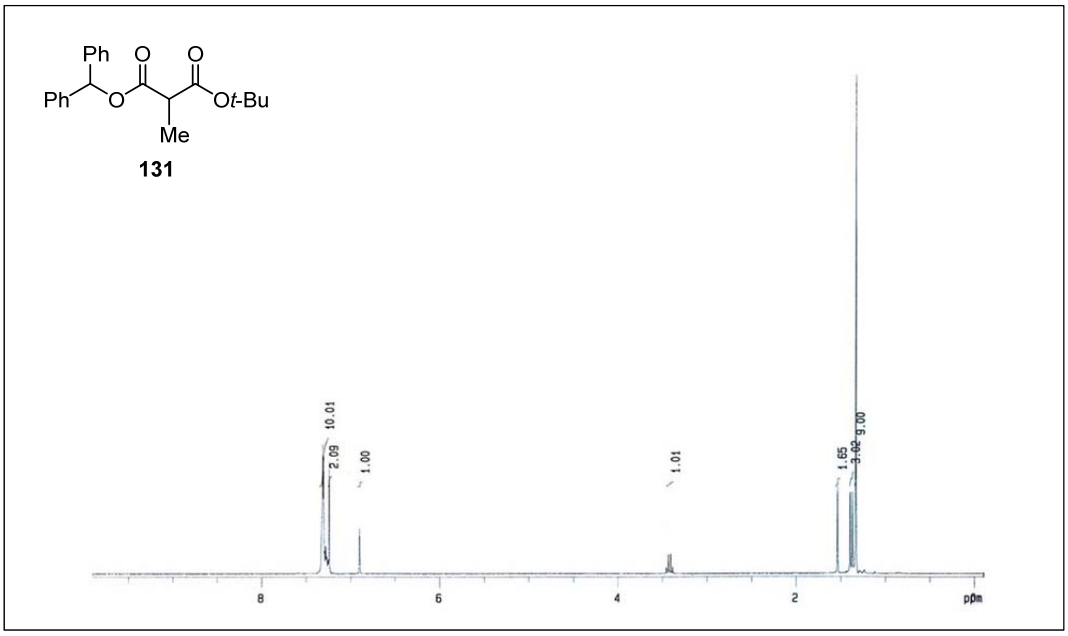
^{1}H-NMR of compound **45k** (300 MHz, $CDCl_3$)



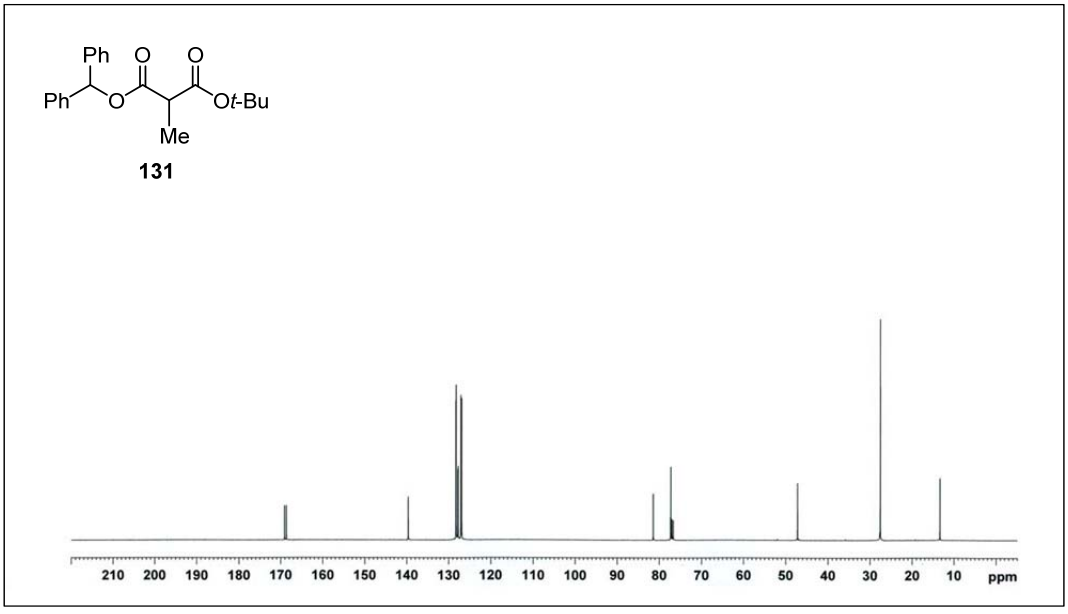
^{13}C-NMR of compound **45k** (75 MHz, $CDCl_3$)



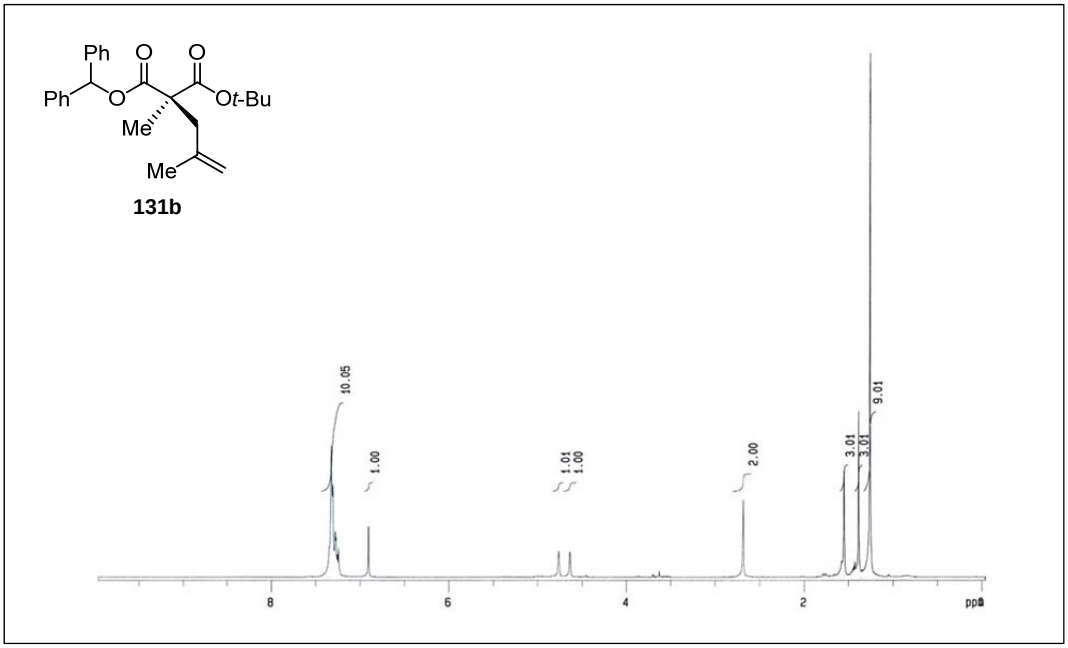
^{1}H-NMR of compound **131** (300 MHz, $CDCl_3$)



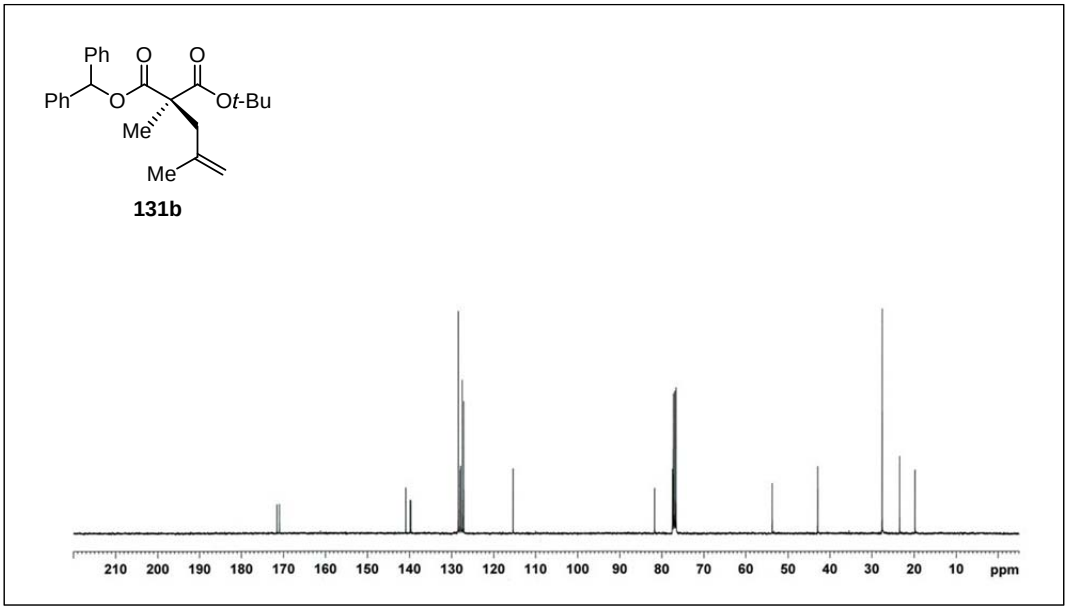
^{13}C-NMR of compound **131** (100 MHz, $CDCl_3$)



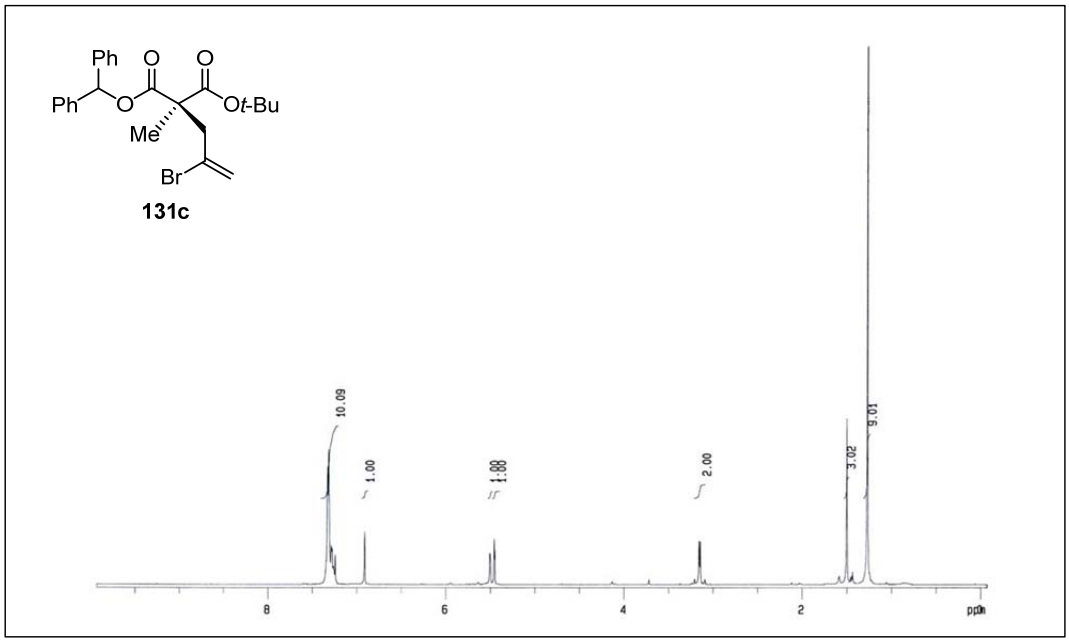
^{1}H-NMR of compound **131b** (300 MHz, $CDCl_3$)



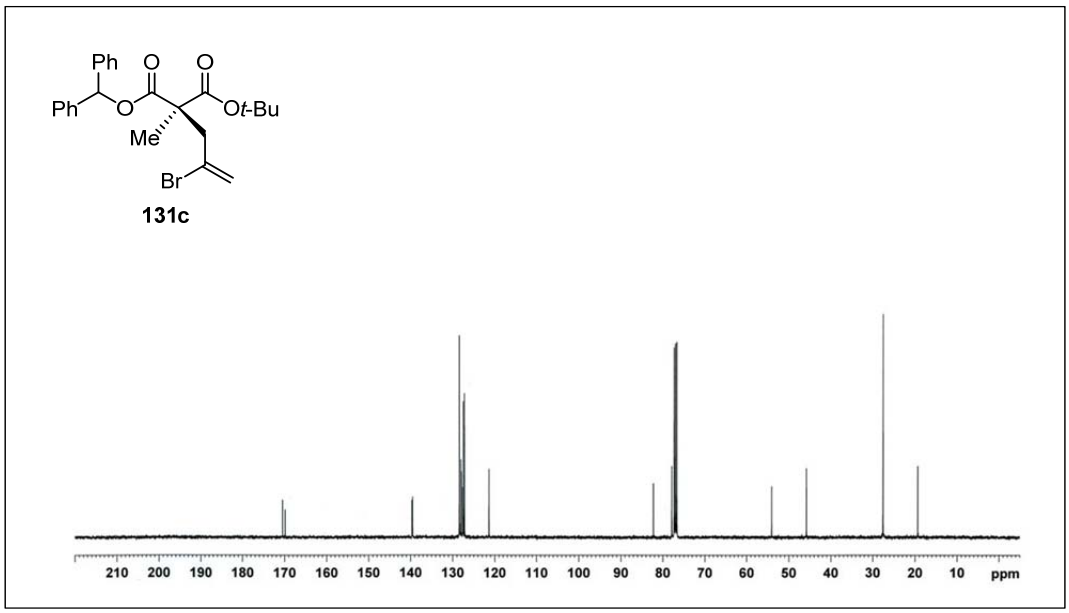
^{13}C-NMR of compound **131b** (100 MHz, $CDCl_3$)



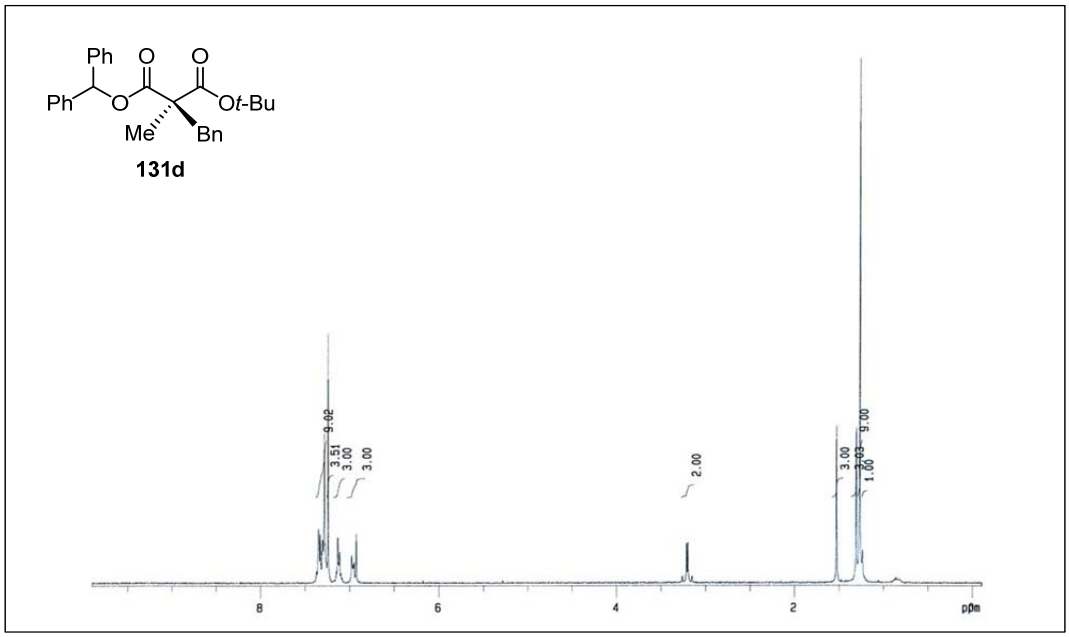
^{1}H-NMR of compound **131c** (300 MHz, $CDCl_3$)



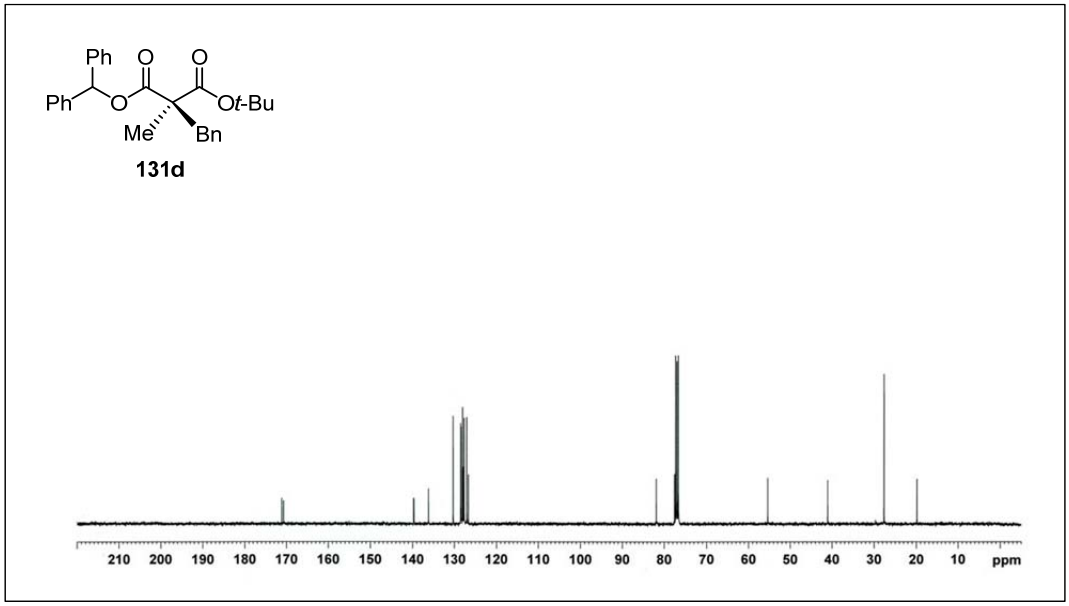
^{13}C-NMR of compound **131c** (100 MHz, $CDCl_3$)



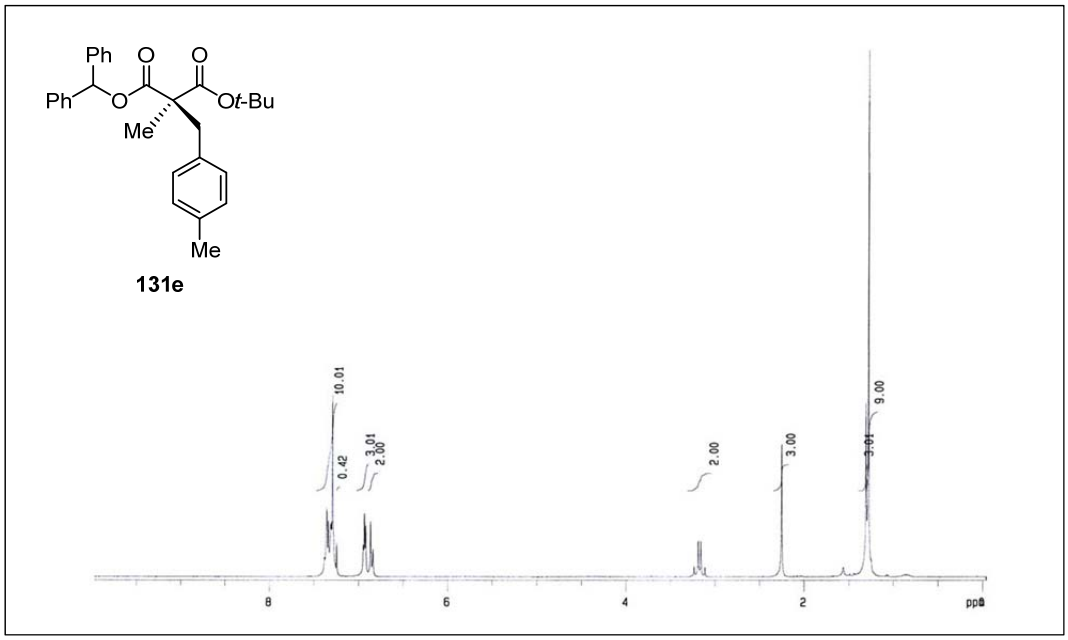
^{1}H-NMR of compound **131d** (300 MHz, $CDCl_3$)



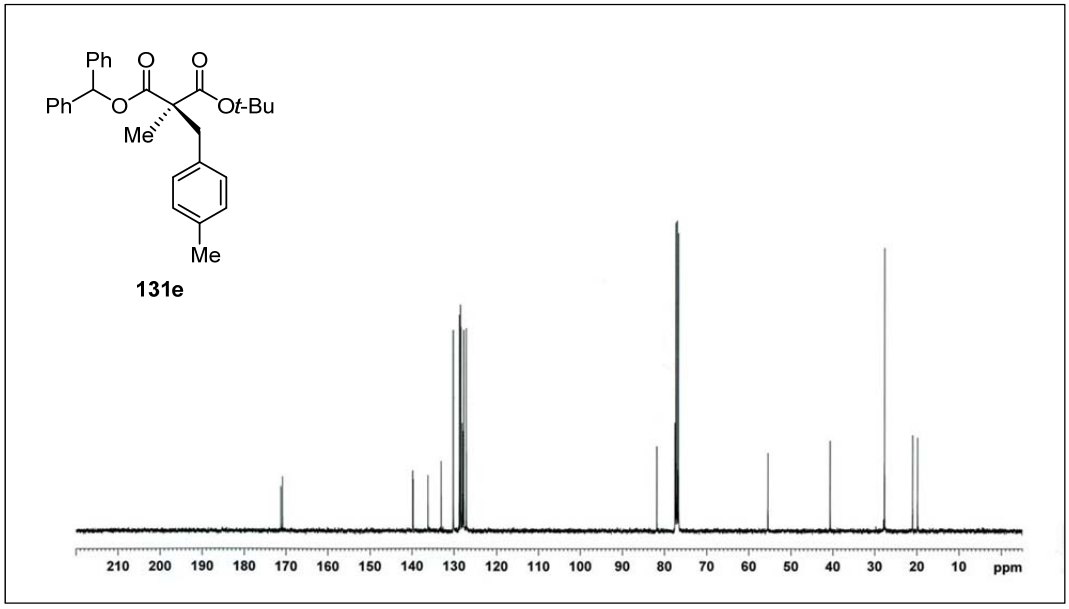
^{13}C-NMR of compound **131d** (100 MHz, $CDCl_3$)



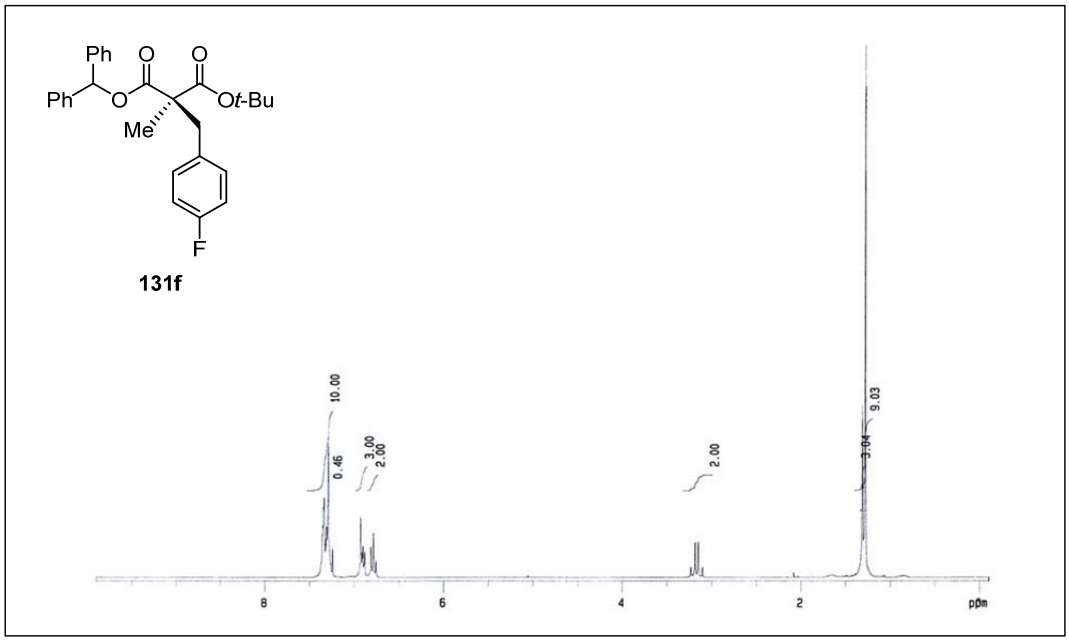
^{1}H-NMR of compound **131e** (300 MHz, $CDCl_3$)



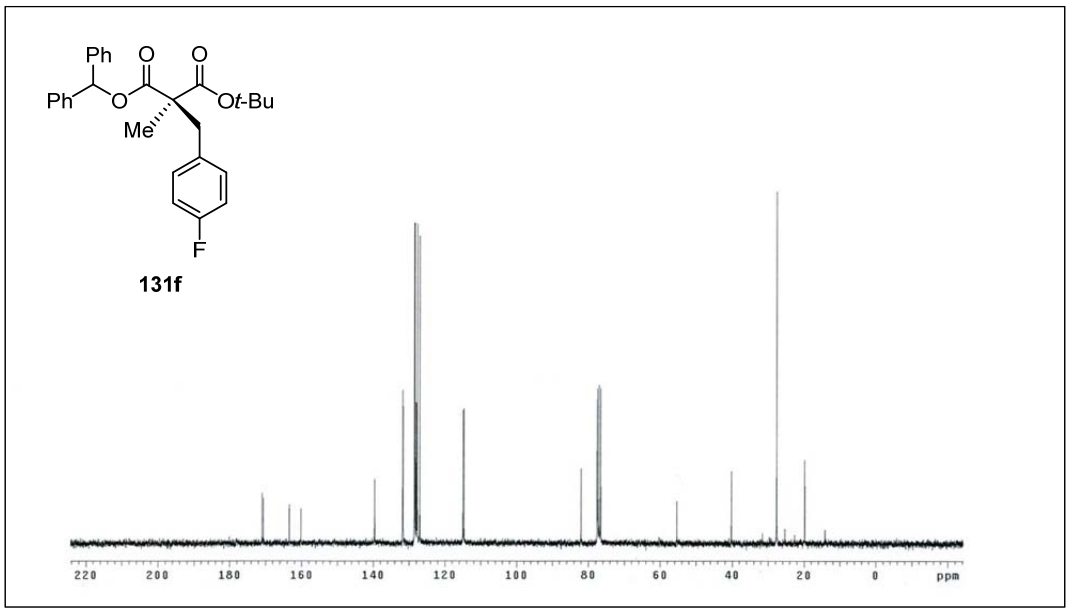
^{13}C-NMR of compound **131e** (100 MHz, $CDCl_3$)



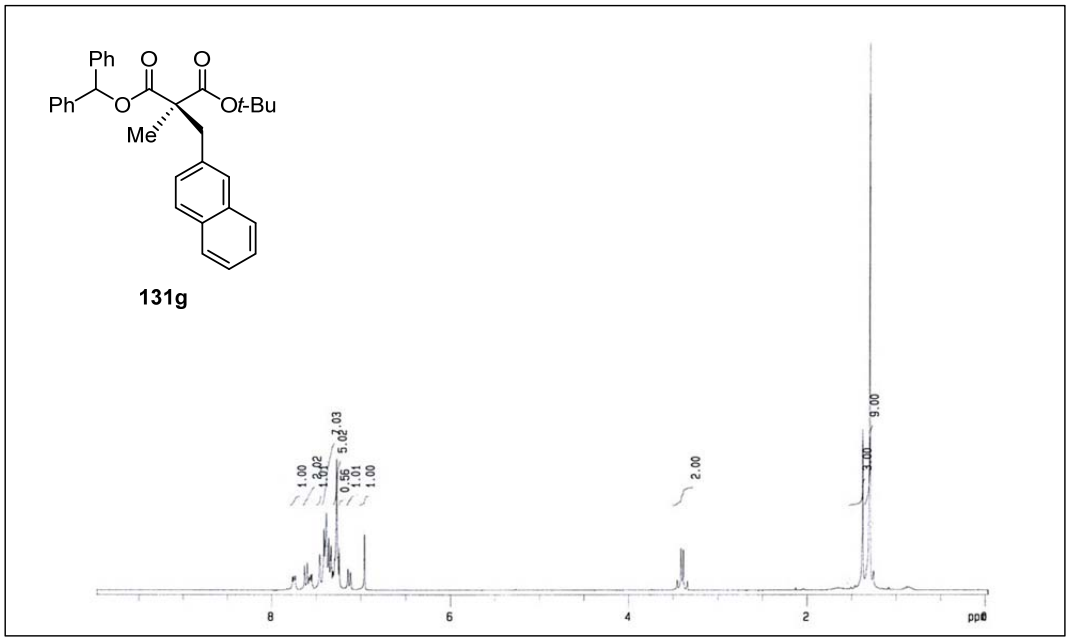
^{1}H-NMR of compound **131f** (300 MHz, $CDCl_3$)



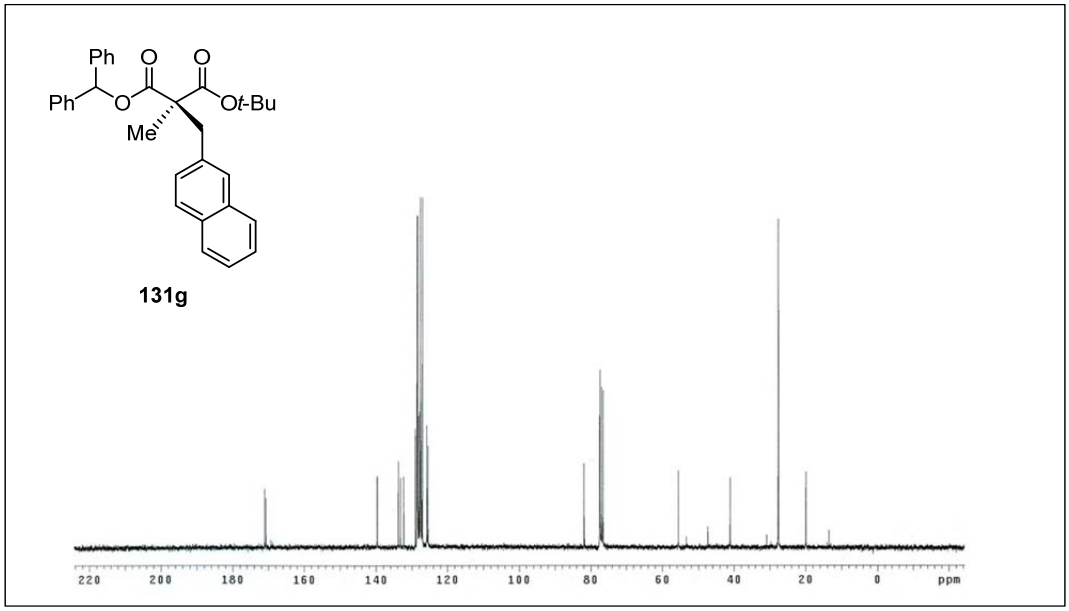
^{13}C-NMR of compound **131f** (75 MHz, $CDCl_3$)



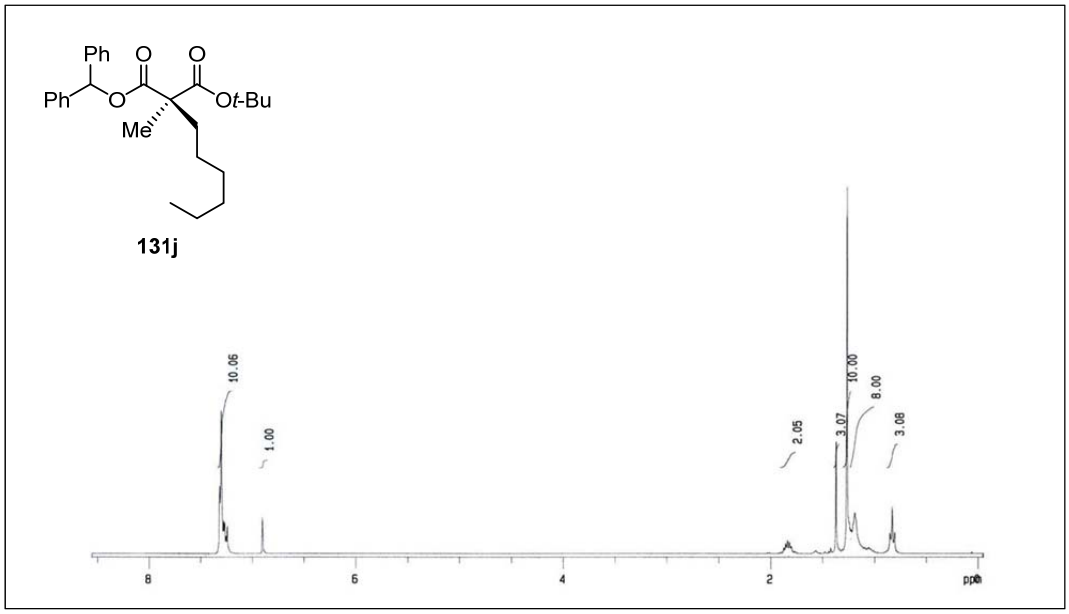
^{1}H-NMR of compound **131g** (300 MHz, $CDCl_3$)



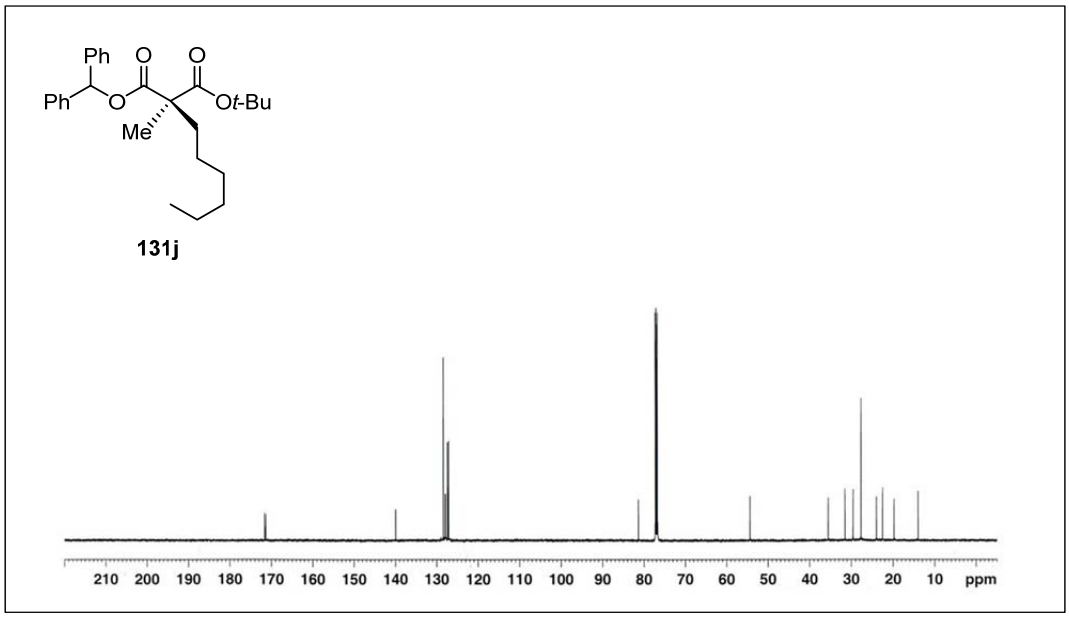
^{13}C-NMR of compound **131g** (75 MHz, $CDCl_3$)



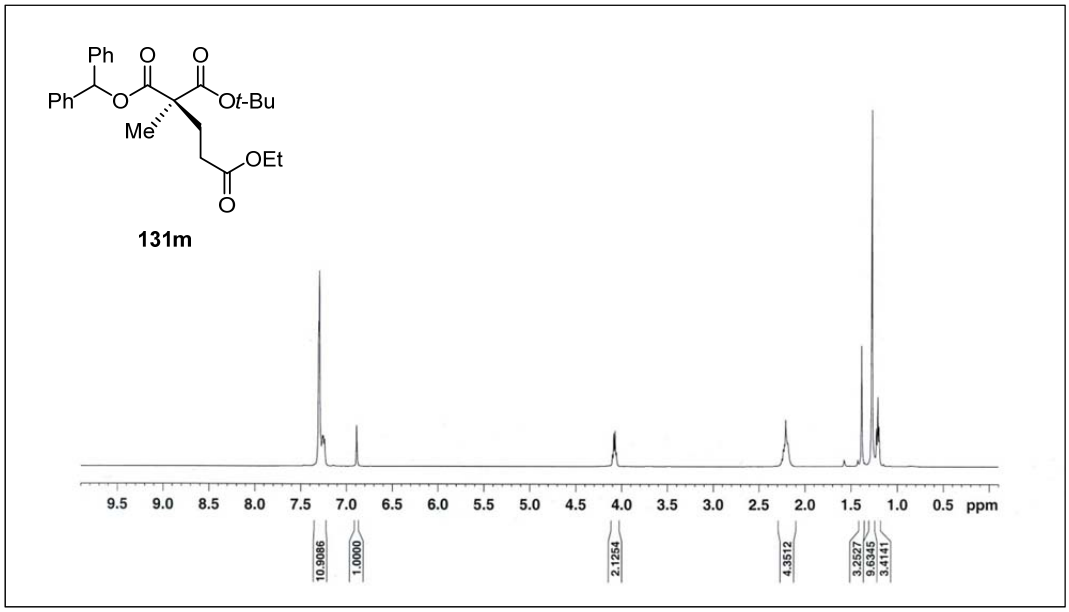
^{1}H-NMR of compound **131j** (300 MHz, $CDCl_3$)



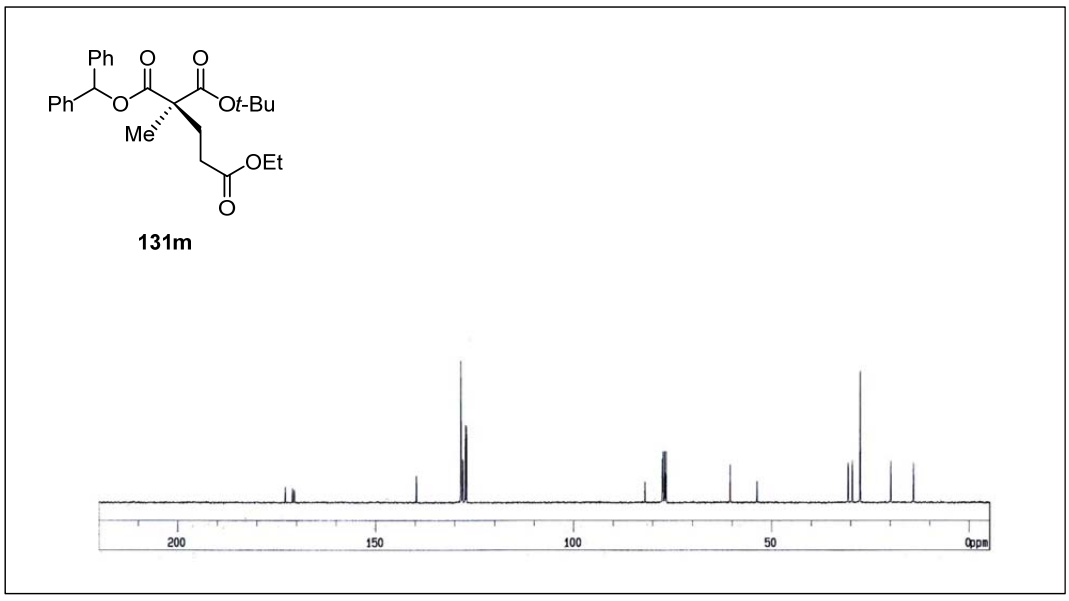
^{13}C-NMR of compound **131j** (125 MHz, $CDCl_3$)



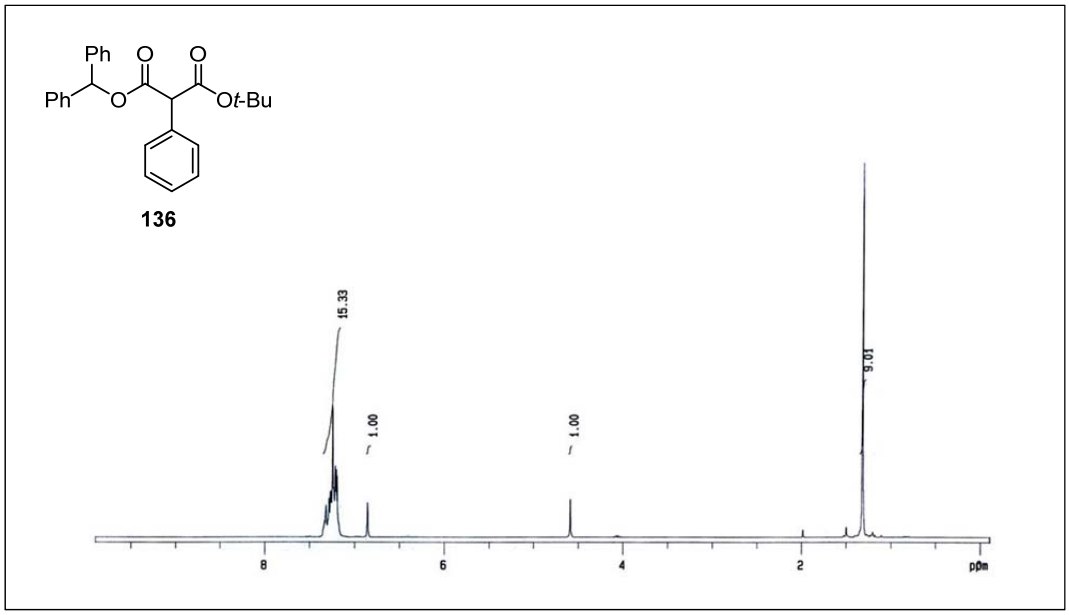
^{1}H-NMR of compound **131m** (500 MHz, $CDCl_3$)



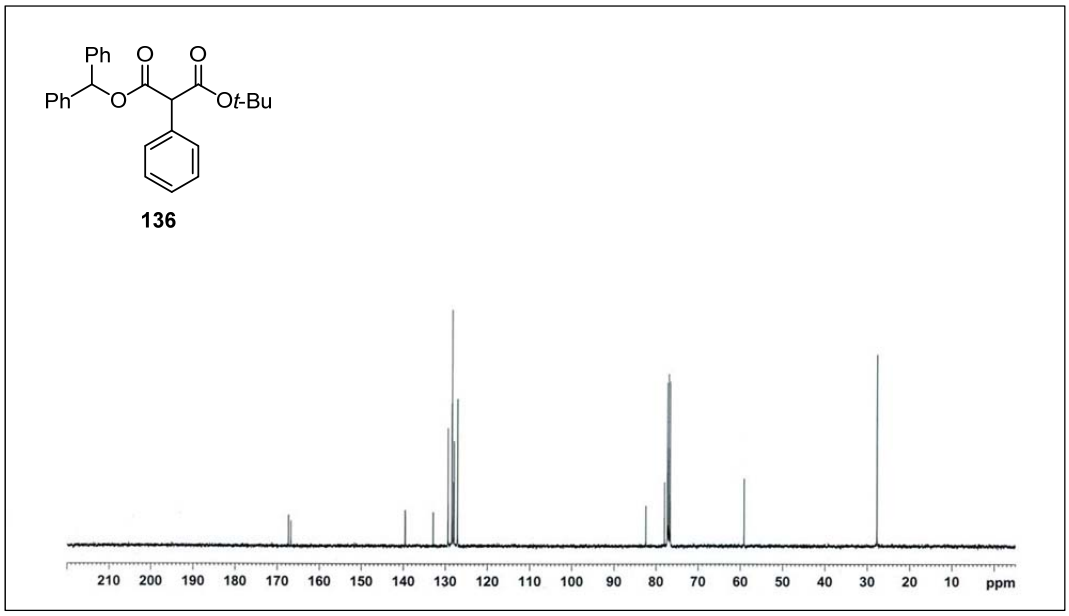
^{13}C-NMR of compound **131m** (75 MHz, $CDCl_3$)



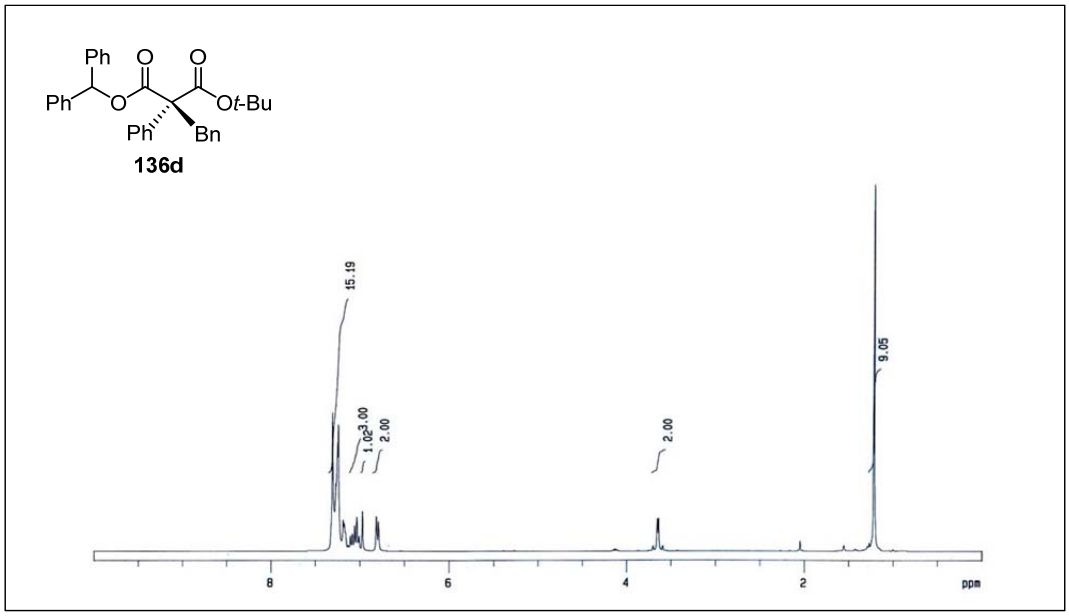
^{1}H-NMR of compound **136** (300 MHz, $CDCl_3$)



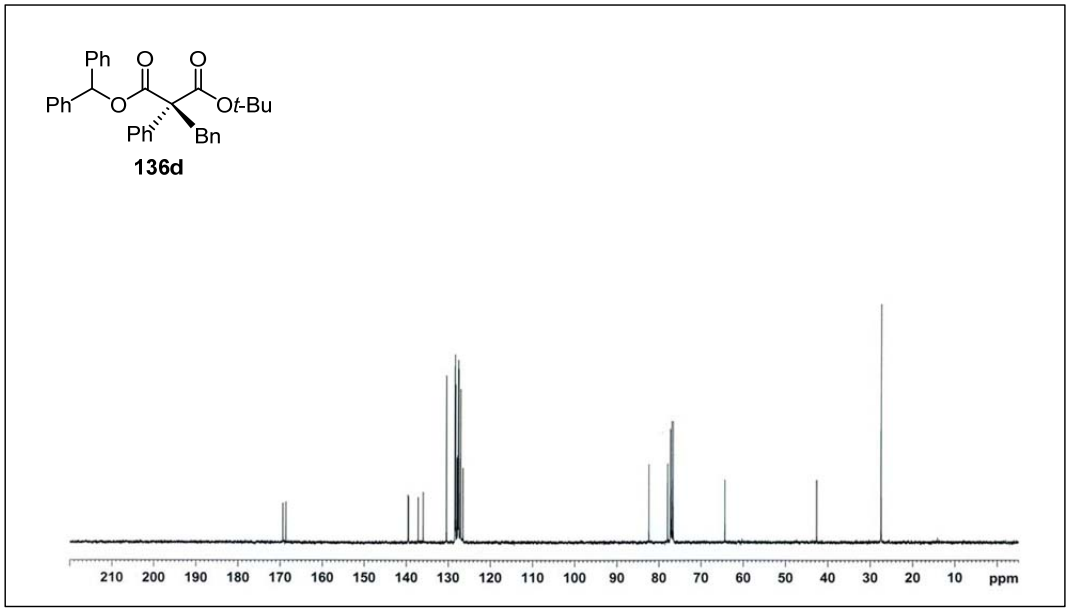
^{13}C-NMR of compound **136** (100 MHz, $CDCl_3$)



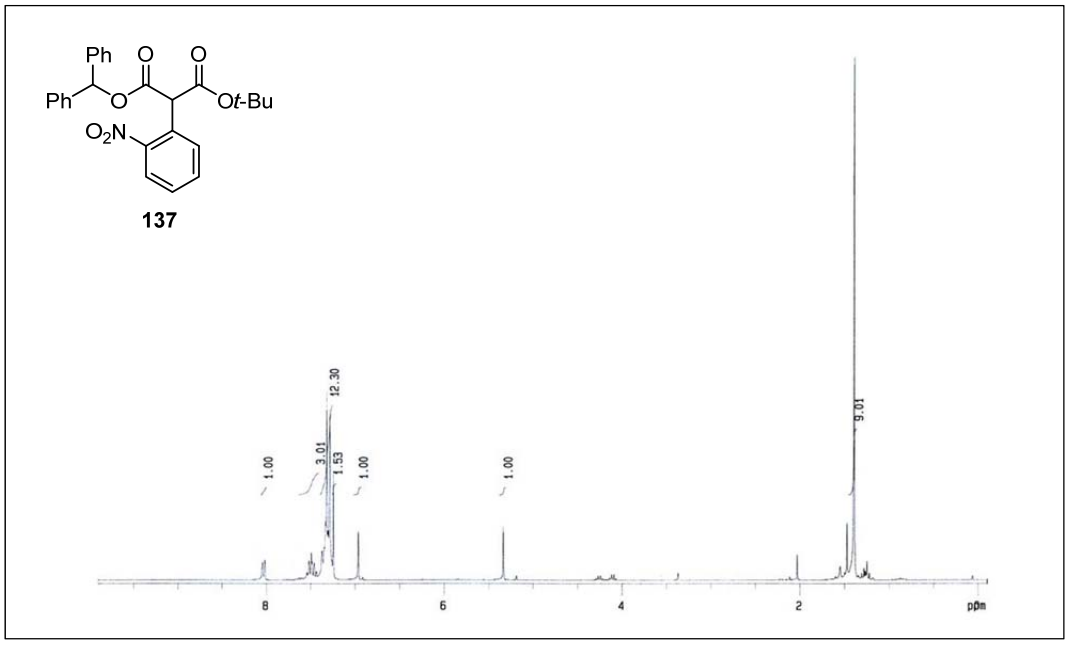
^{1}H-NMR of compound **136d** (300 MHz, $CDCl_3$)



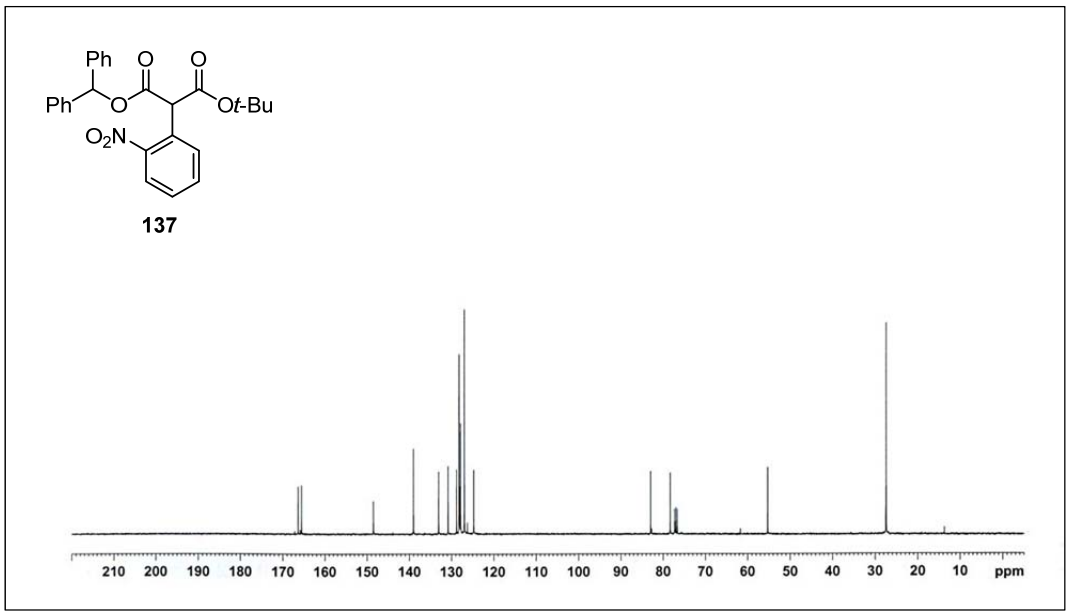
^{13}C-NMR of compound **136d** (100 MHz, $CDCl_3$)



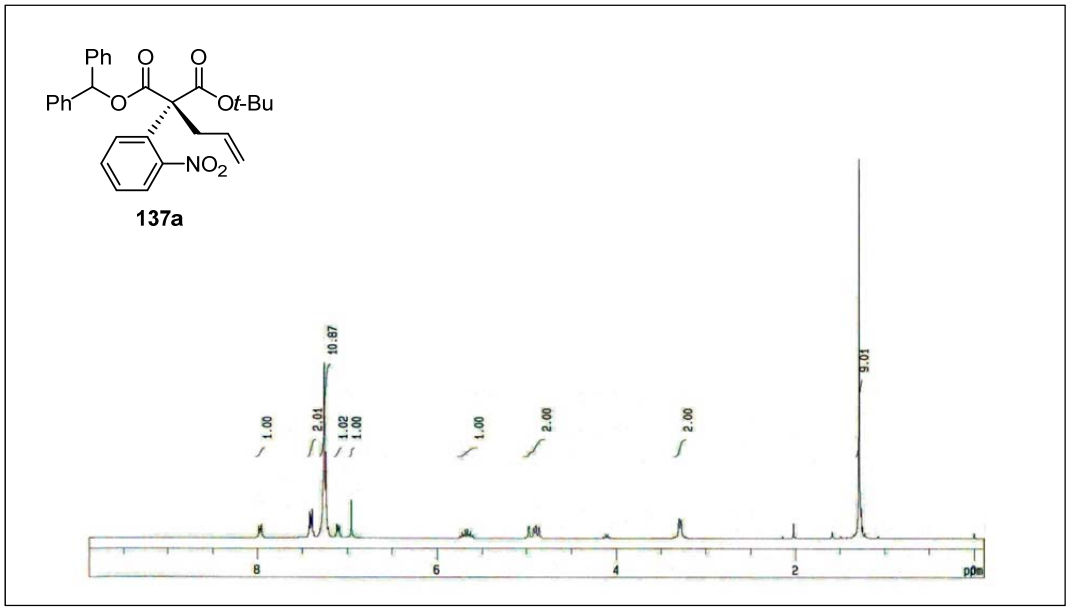
^{1}H-NMR of compound **137** (300 MHz, $CDCl_3$)



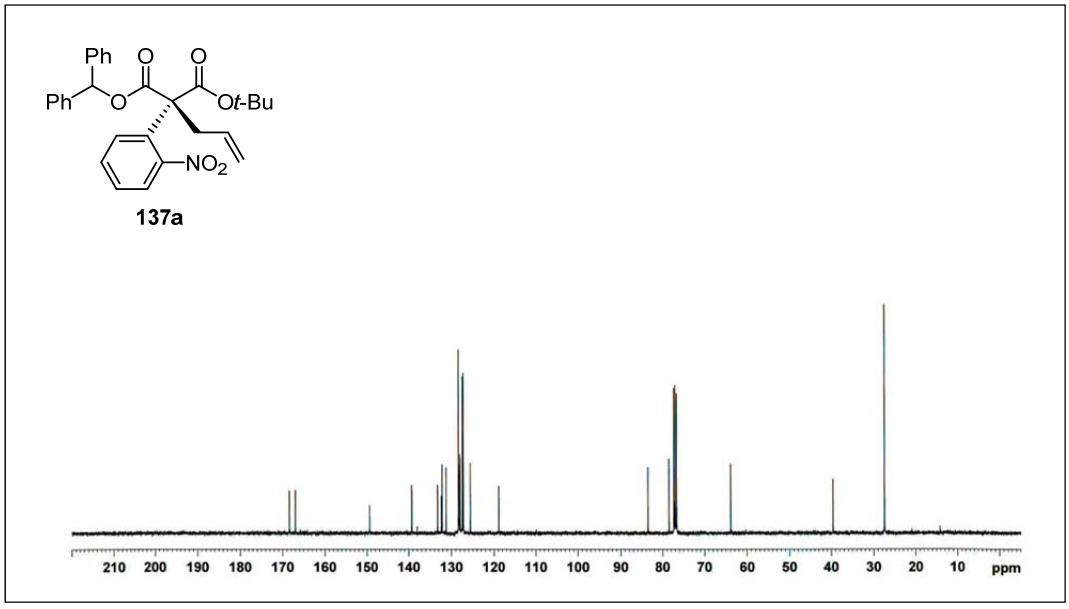
^{13}C-NMR of compound **137** (100 MHz, $CDCl_3$)



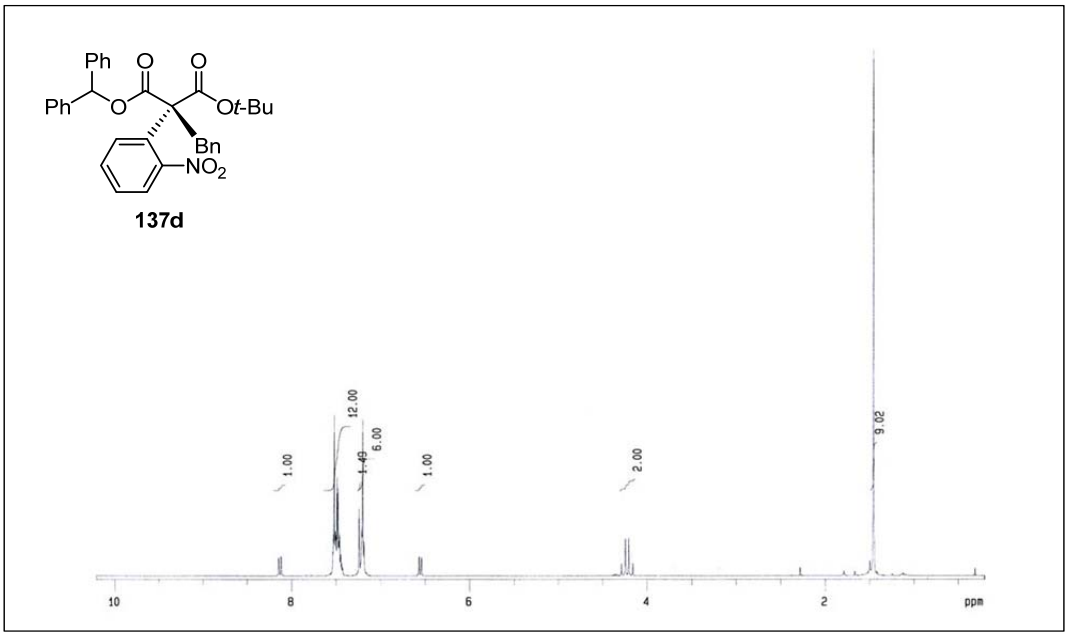
^{1}H-NMR of compound **137a** (300 MHz, $CDCl_3$)



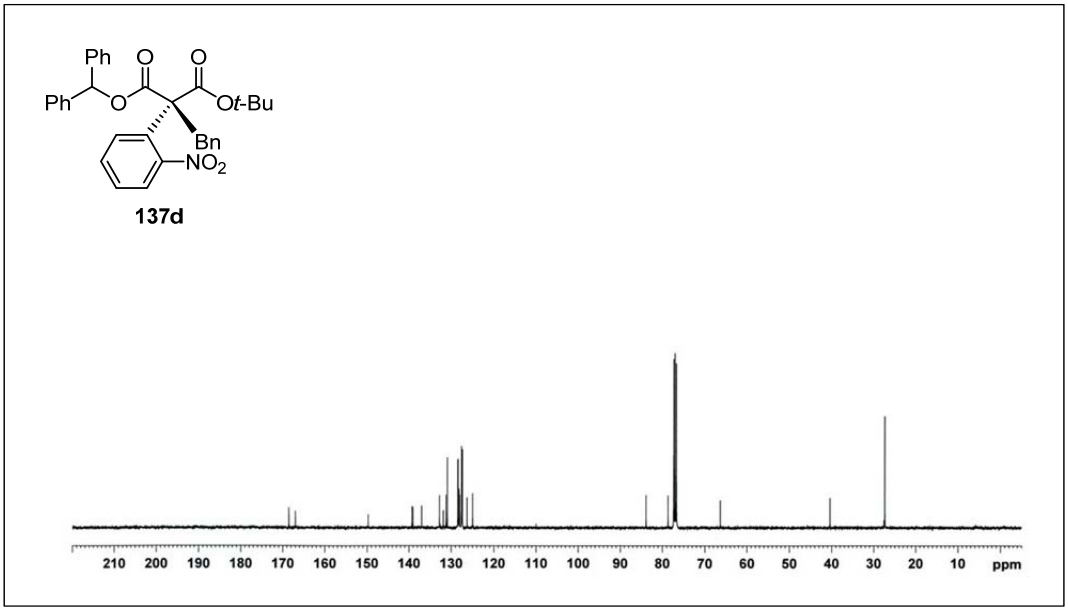
^{13}C-NMR of compound **137a** (100 MHz, $CDCl_3$)



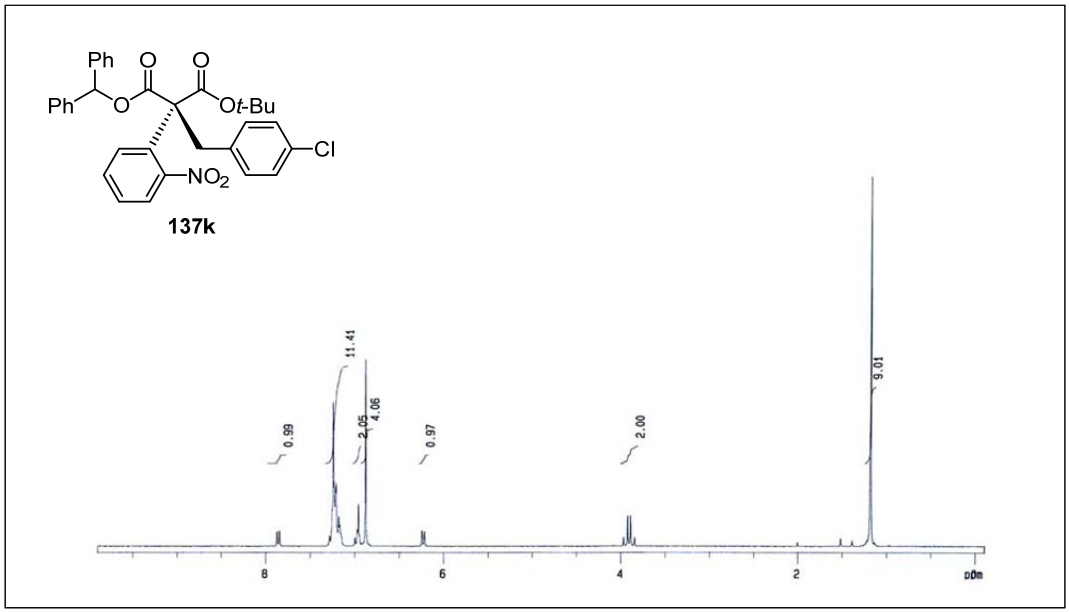
^{1}H-NMR of compound **137d** (300 MHz, $CDCl_3$)



^{13}C-NMR of compound **137d** (100 MHz, $CDCl_3$)



^{1}H-NMR of compound **137k** (300 MHz, $CDCl_3$)



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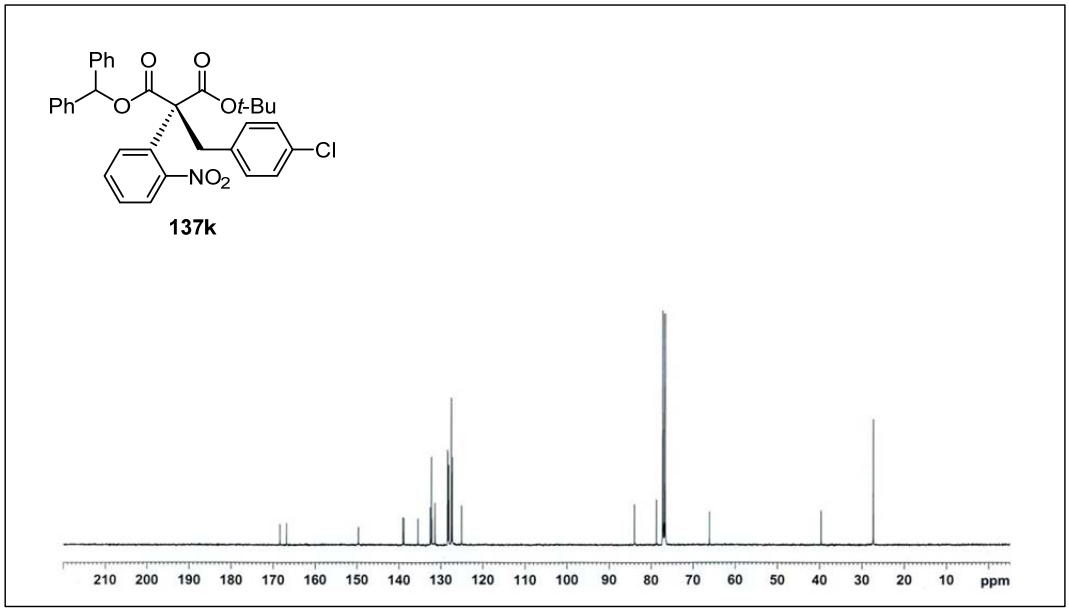
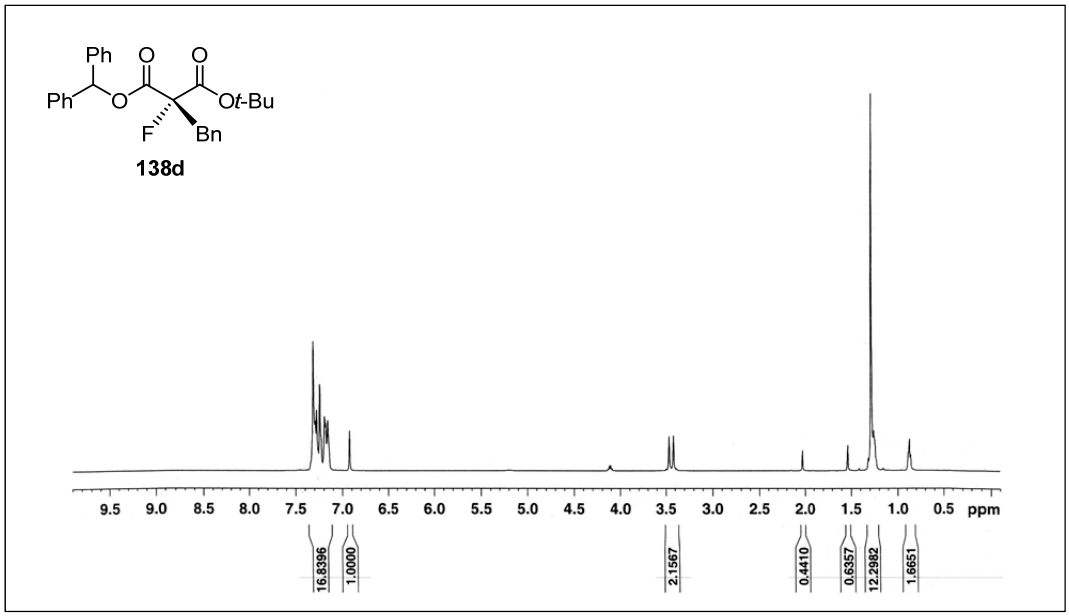
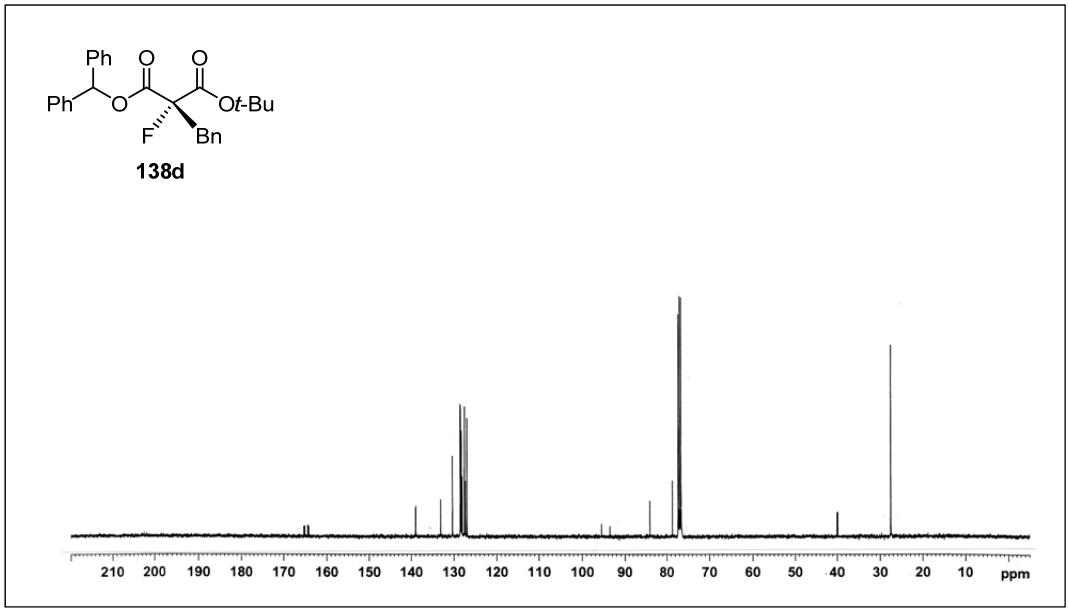


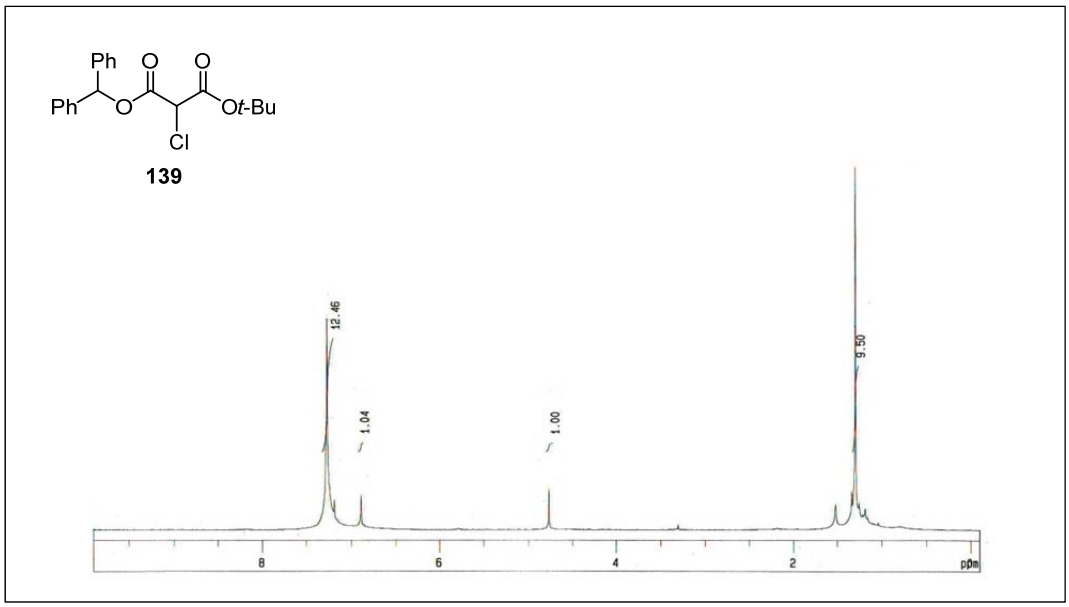
^{1}H-NMR of compound **138d** (400 MHz, $CDCl_3$)



^{13}C-NMR of compound **138d** (100 MHz, $CDCl_3$)



^{1}H-NMR of compound **139** (300 MHz, $CDCl_3$)



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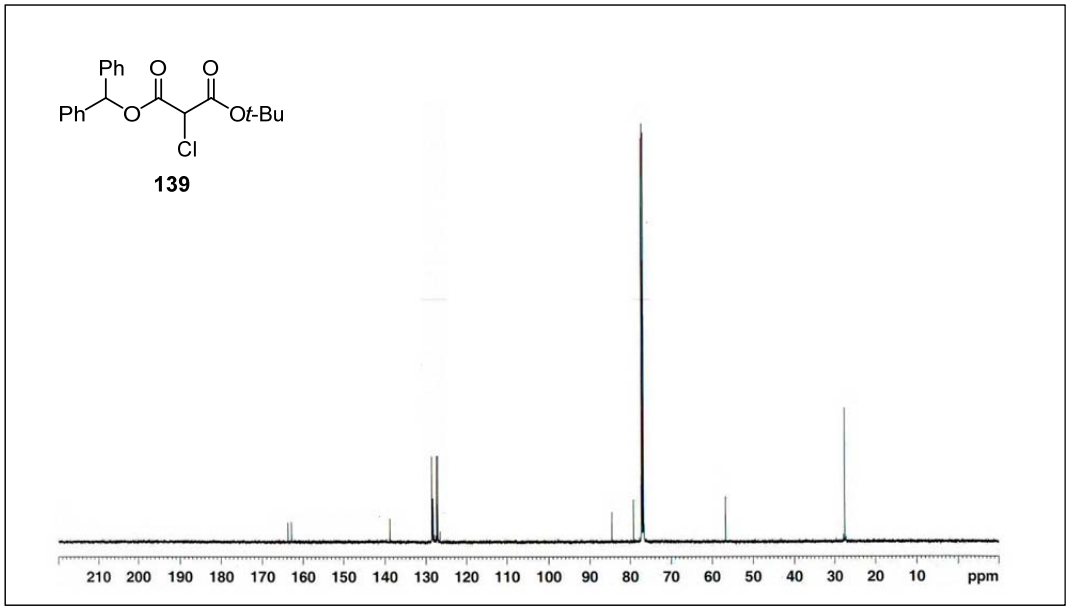
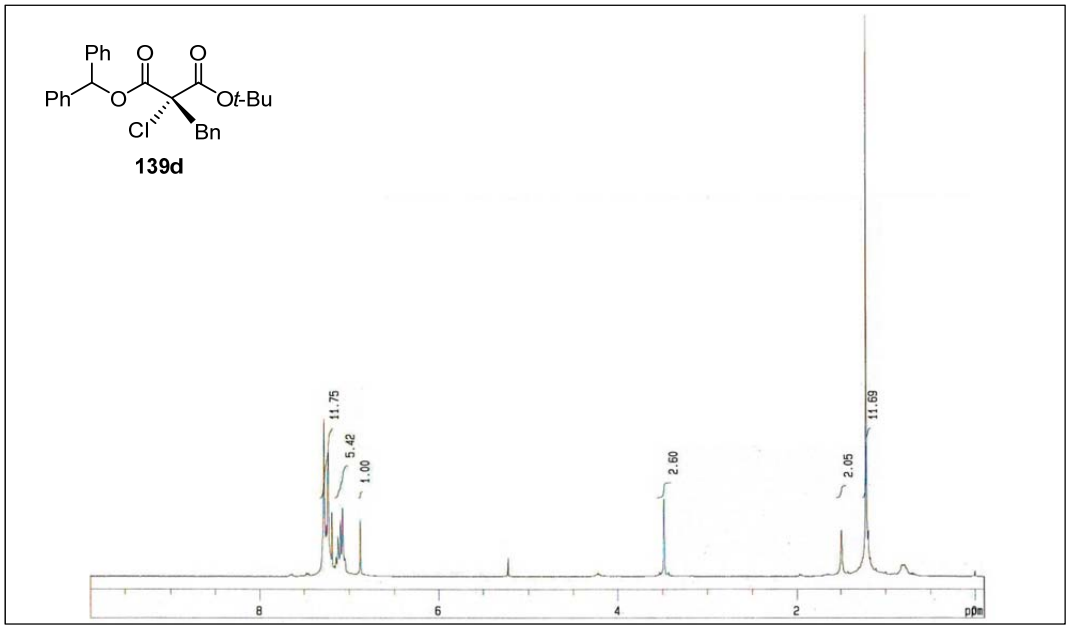
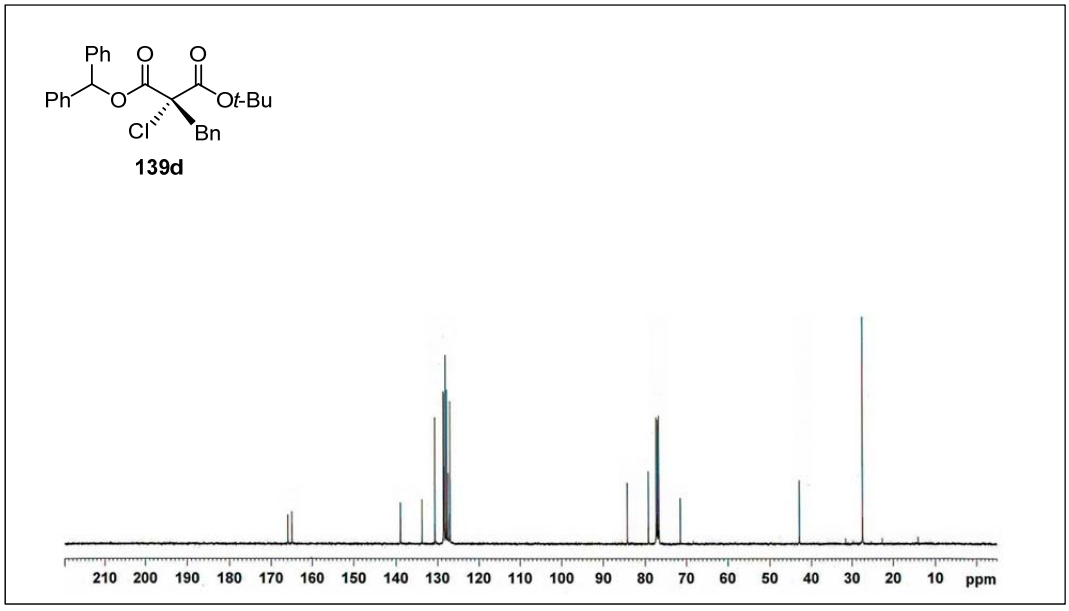


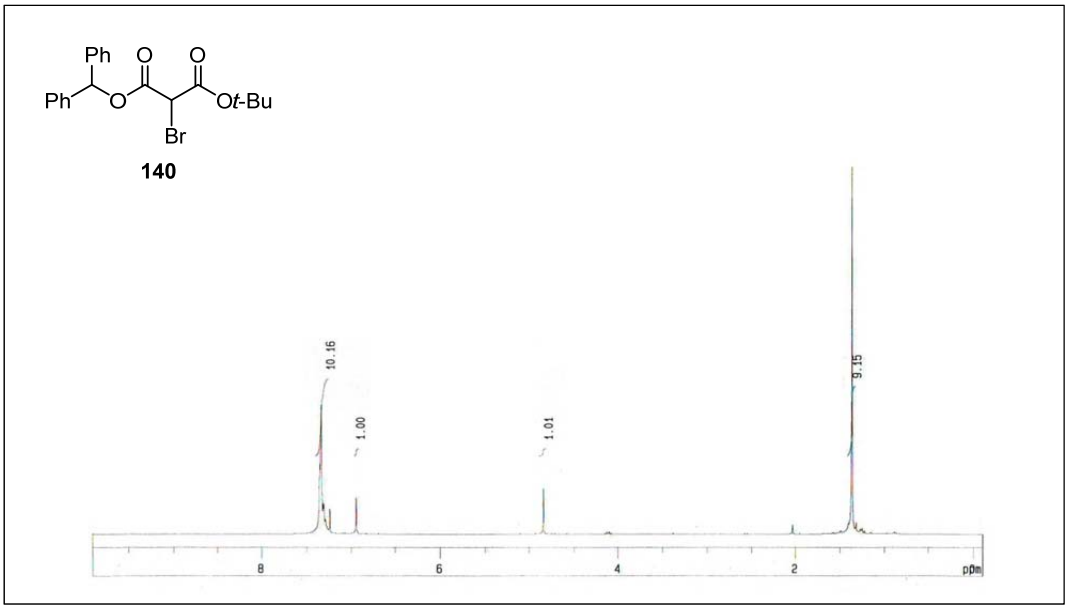
^{1}H-NMR of compound **139d** (300 MHz, $CDCl_3$)



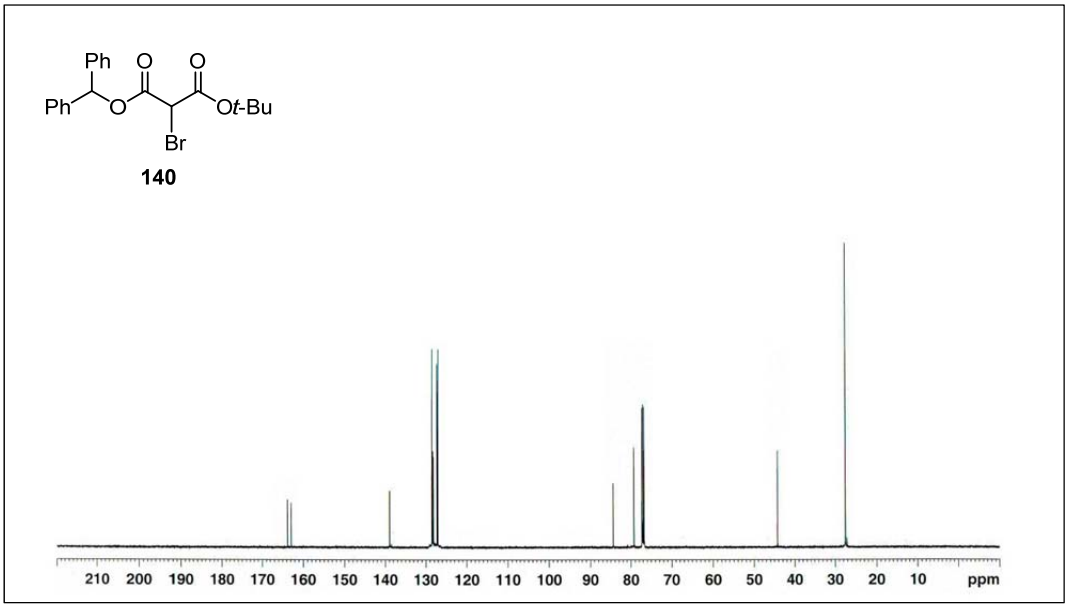
^{13}C-NMR of compound **139d** (100 MHz, $CDCl_3$)



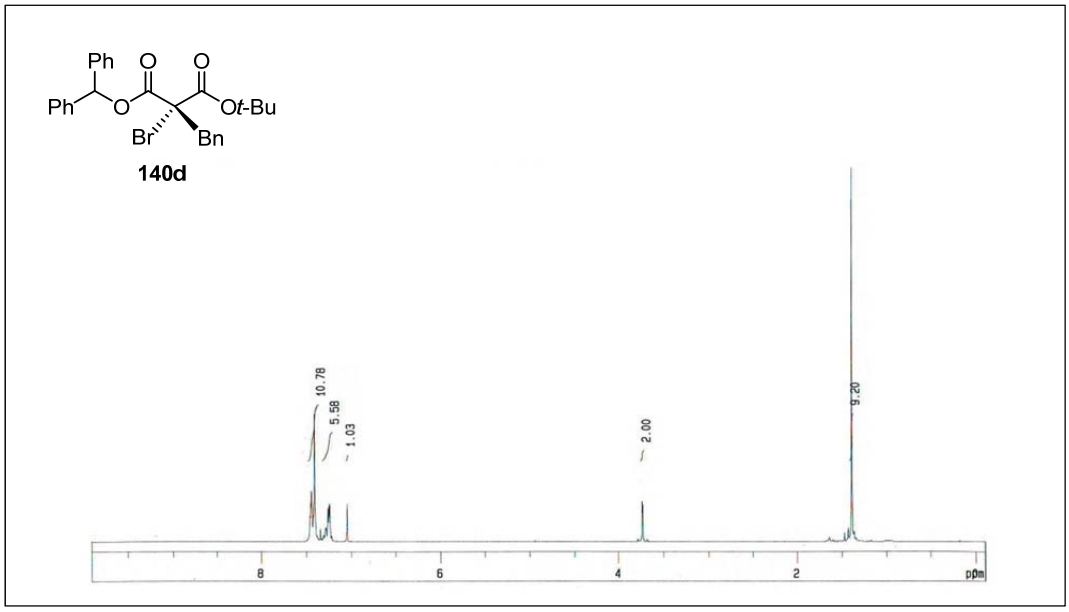
^{1}H-NMR of compound **140** (300 MHz, $CDCl_3$)



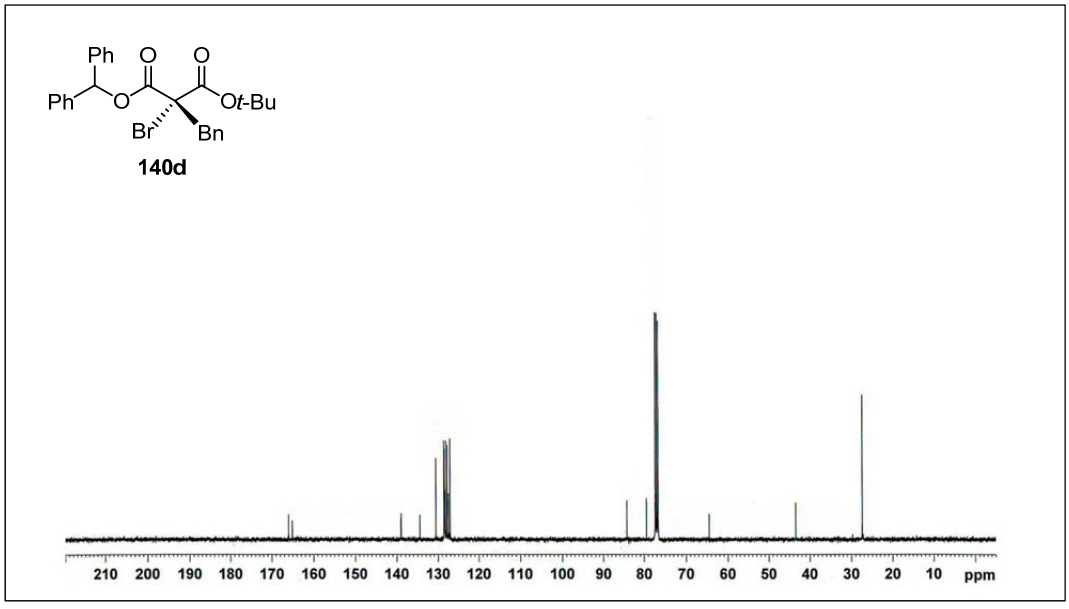
^{13}C-NMR of compound **140** (125 MHz, $CDCl_3$)



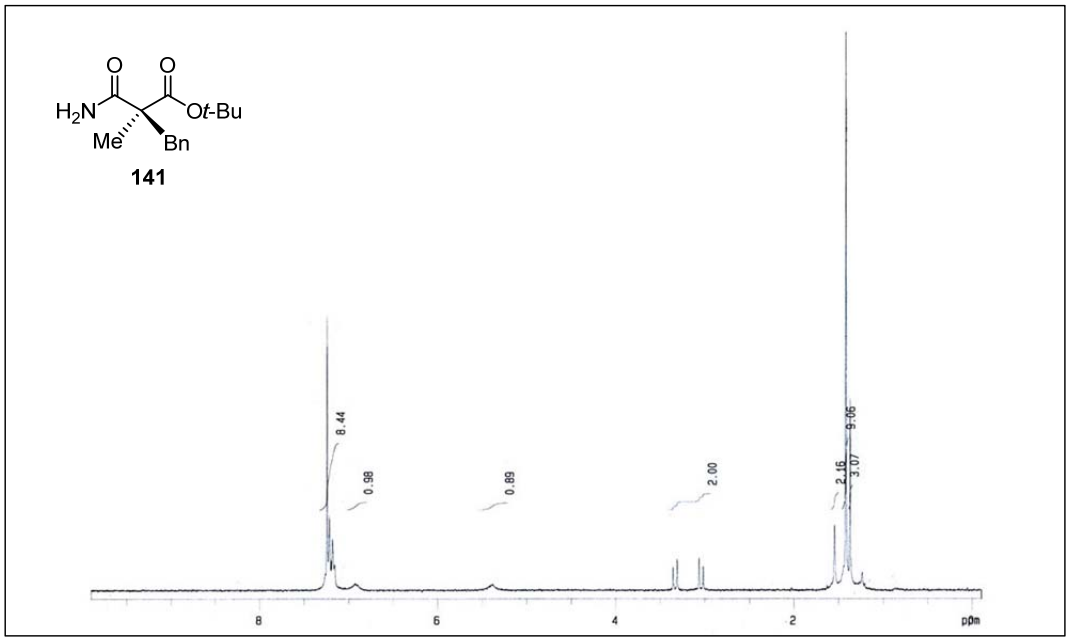
^{1}H-NMR of compound **140d** (300 MHz, $CDCl_3$)



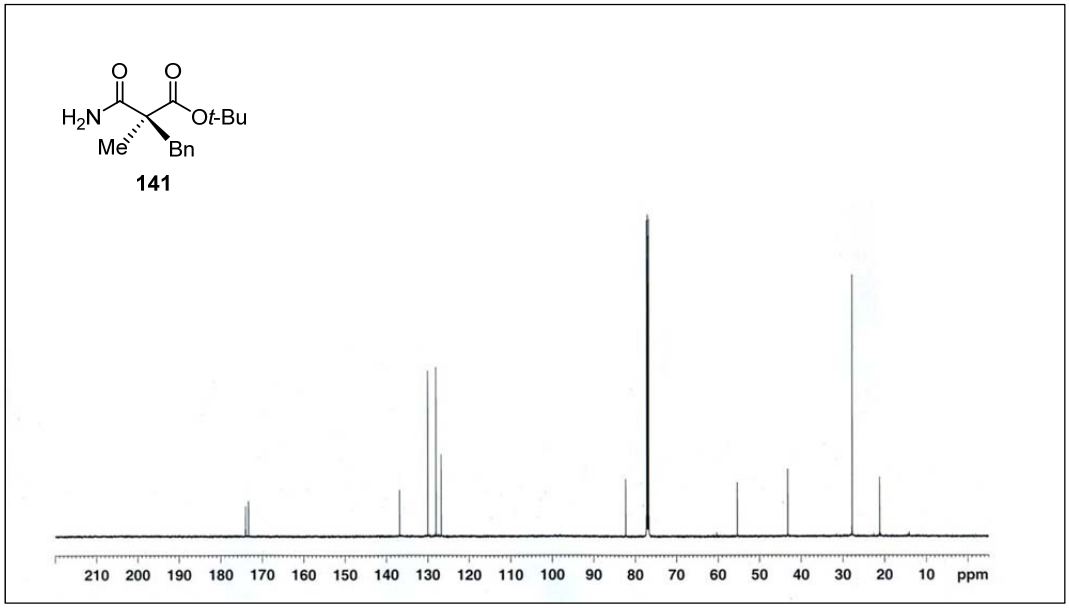
^{13}C-NMR of compound **140d** (100 MHz, $CDCl_3$)



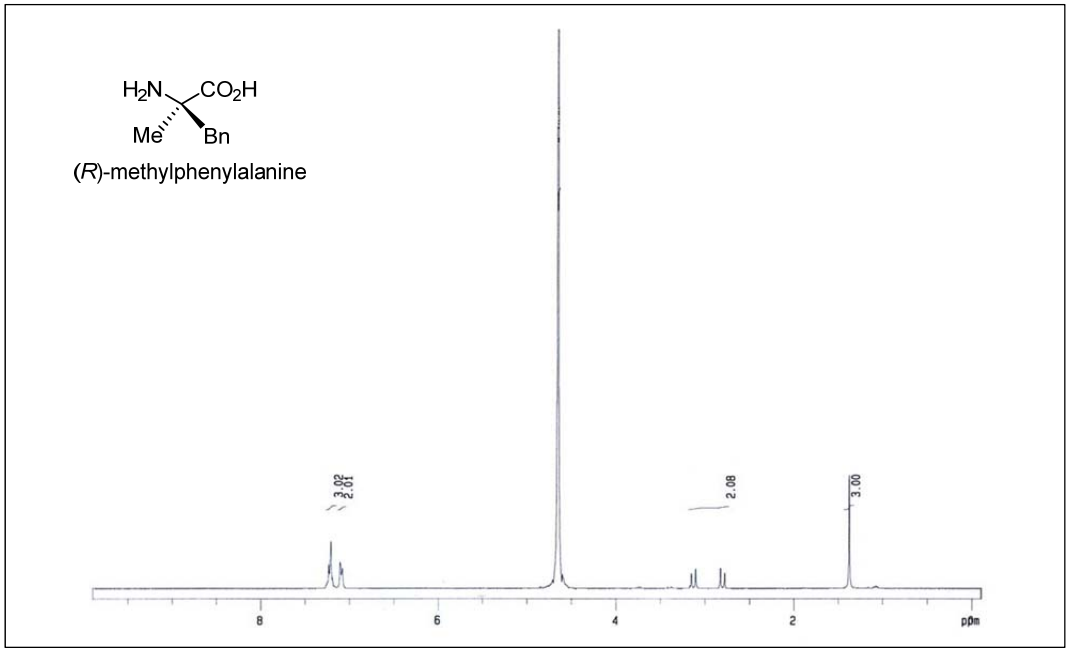
^{1}H-NMR of compound **141** (300 MHz, $CDCl_3$)



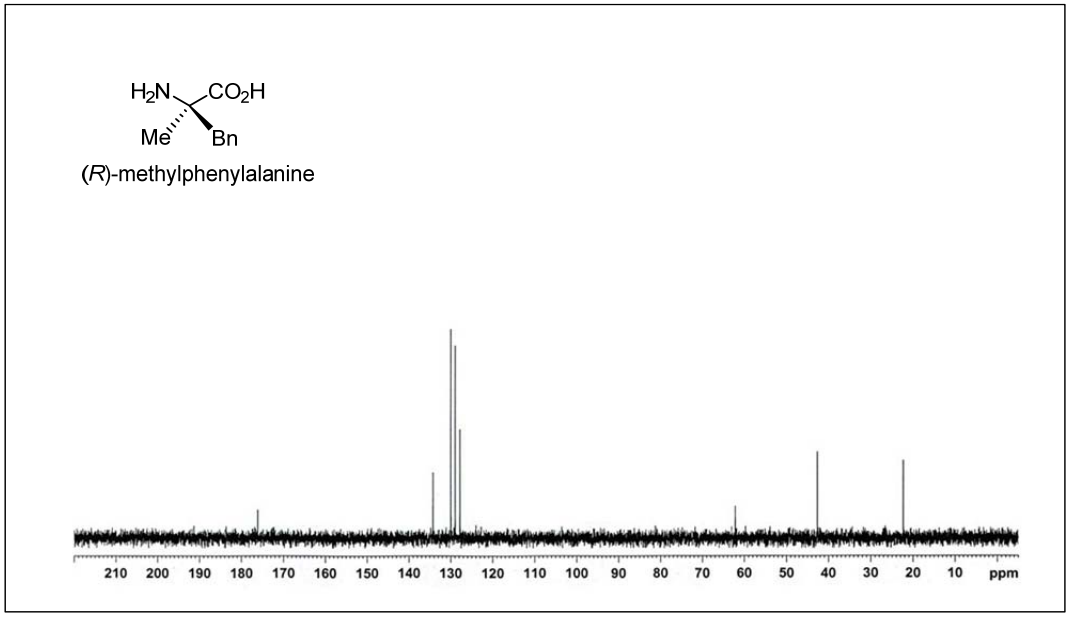
^{13}C-NMR of compound **141** (125 MHz, $CDCl_3$)



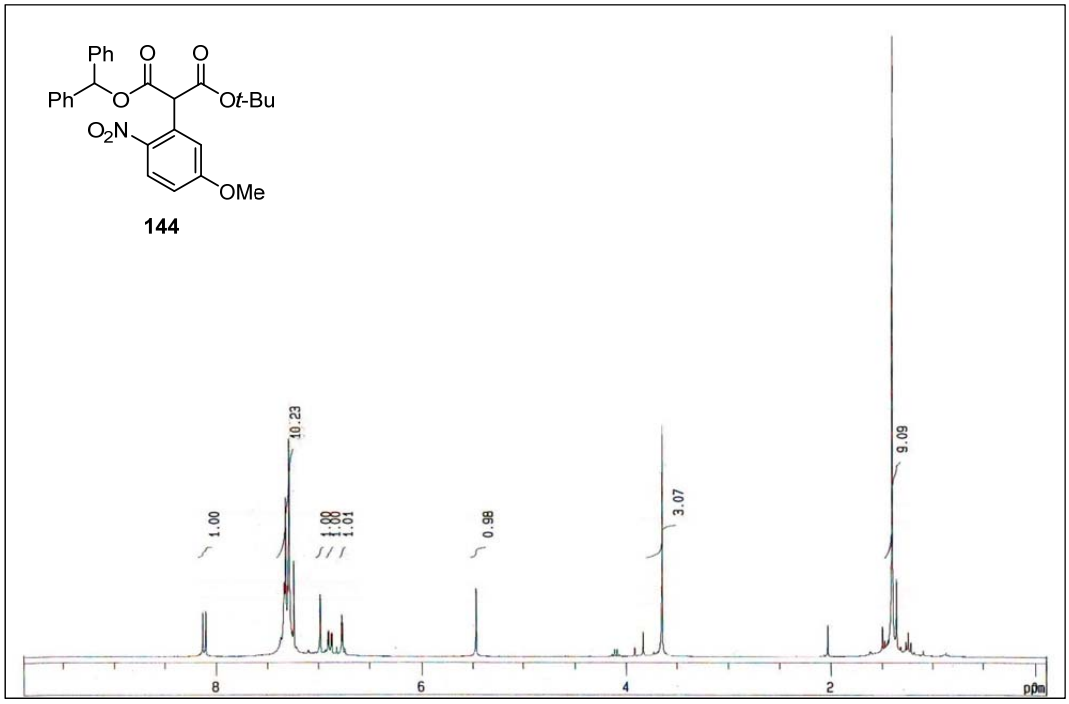
^{1}H-NMR of (*R*)-α-methylphenylalanine (300 MHz, D_2O)



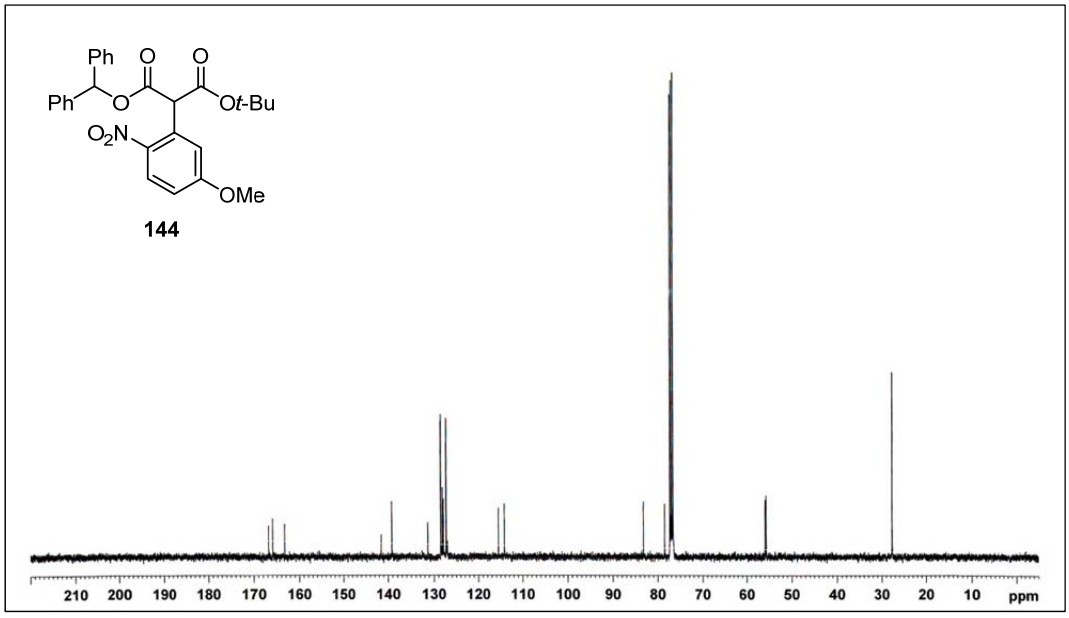
^{13}C-NMR of (*R*)-α-methylphenylalanine (100 MHz, D_2O)



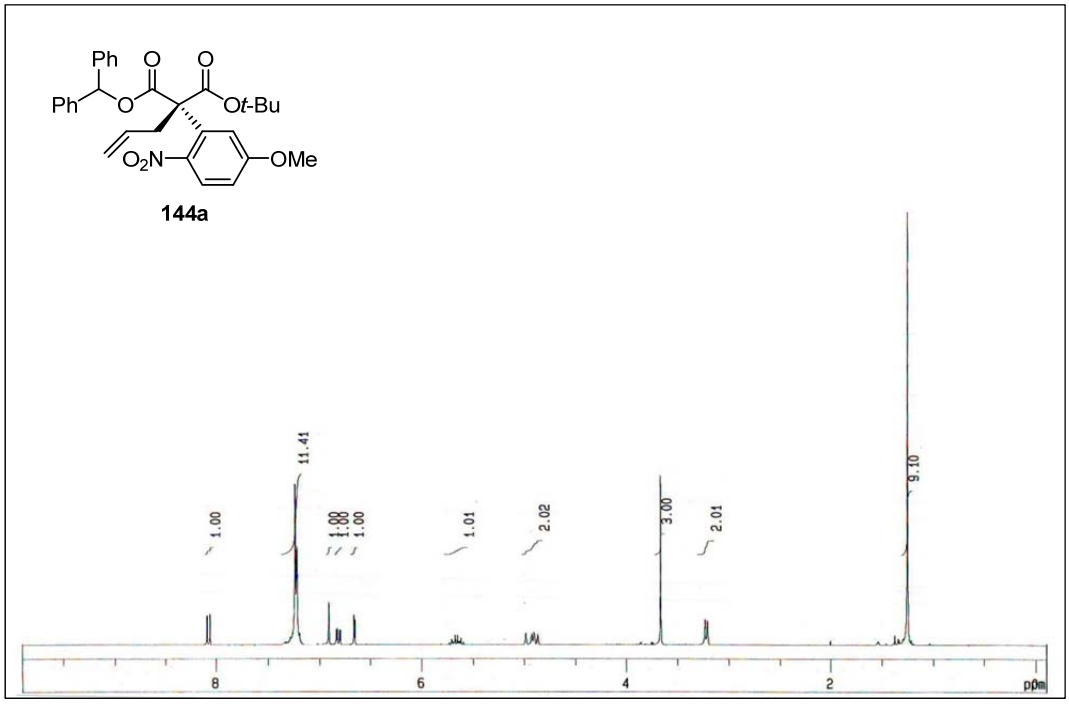
^{1}H-NMR of compound **144** (300 MHz, $CDCl_3$)



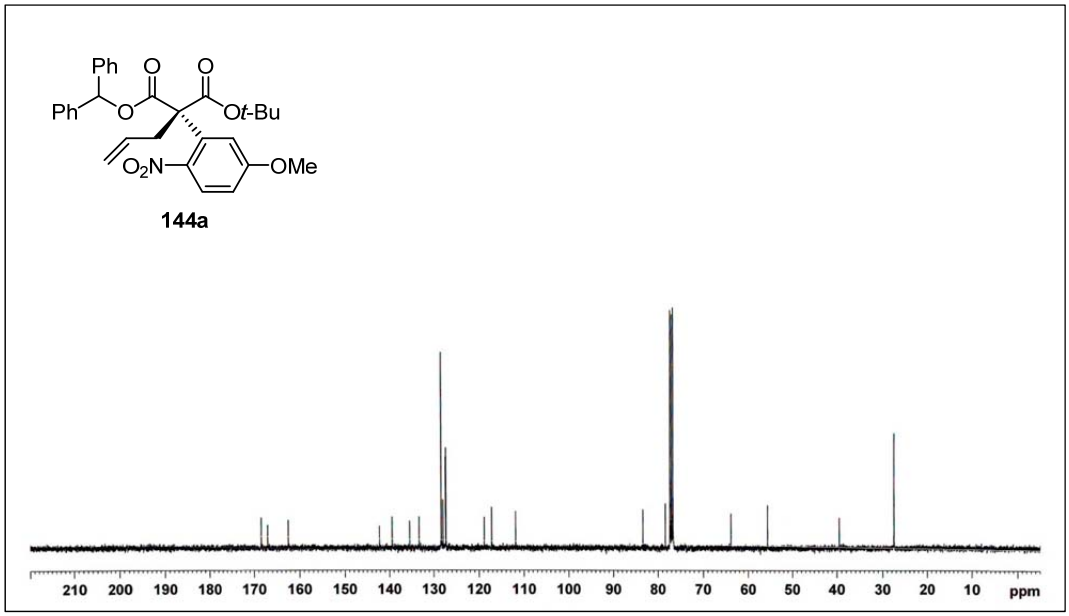
^{13}C-NMR of compound **144** (100 MHz, $CDCl_3$)



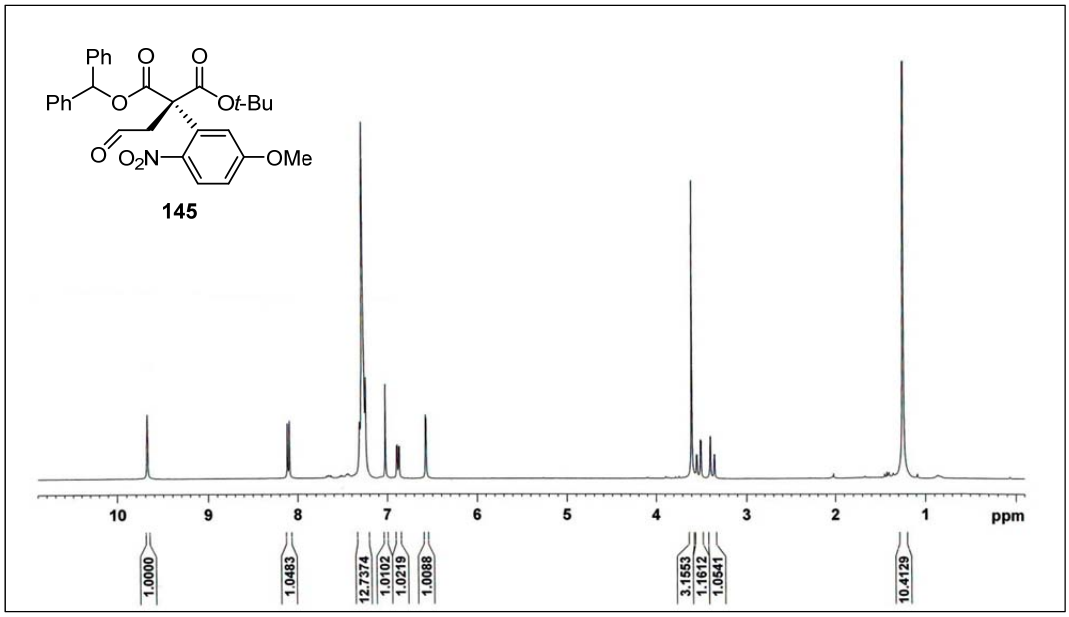
^{1}H-NMR of compound **144a** (300 MHz, $CDCl_3$)



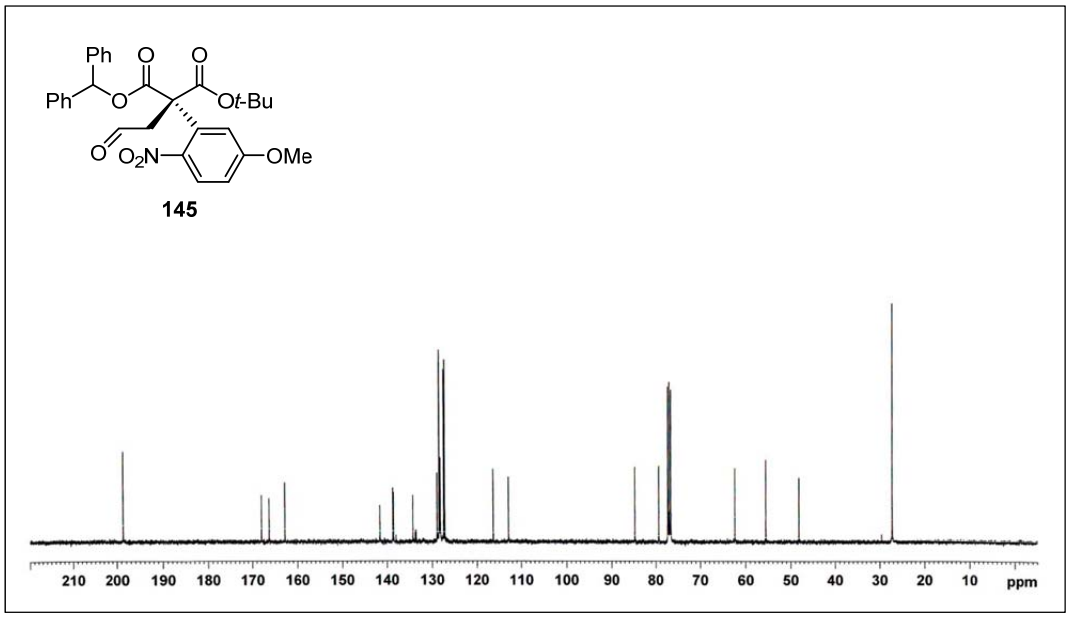
^{13}C-NMR of compound **144a** (100 MHz, $CDCl_3$)



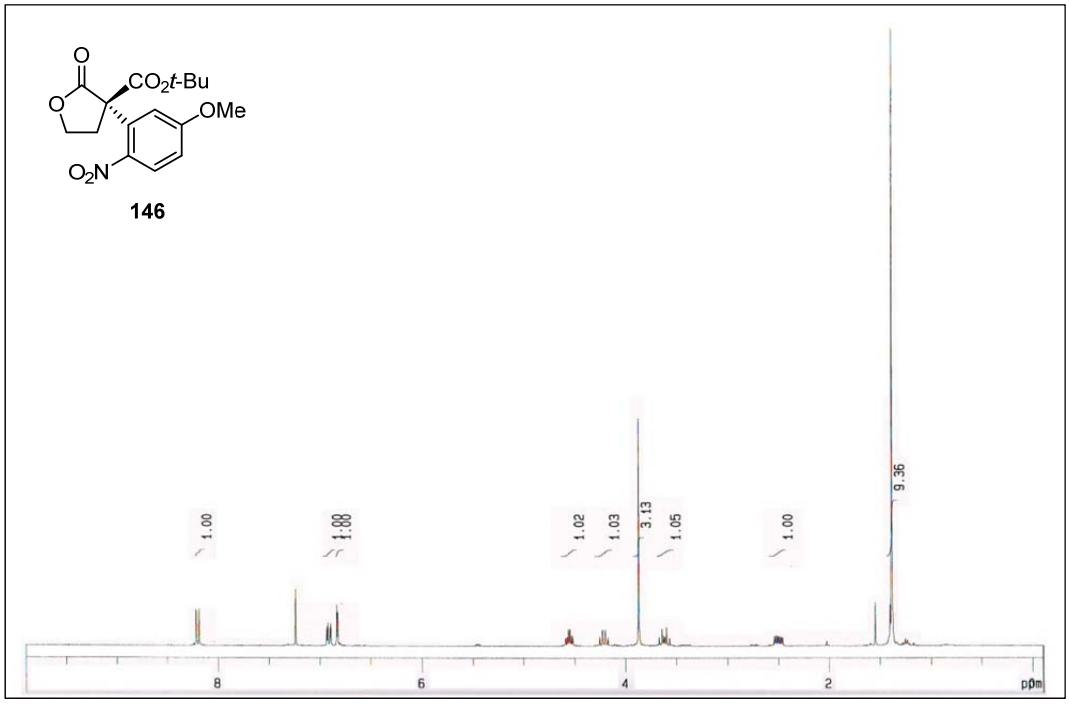
^{1}H-NMR of compound **145** (400 MHz, $CDCl_3$)



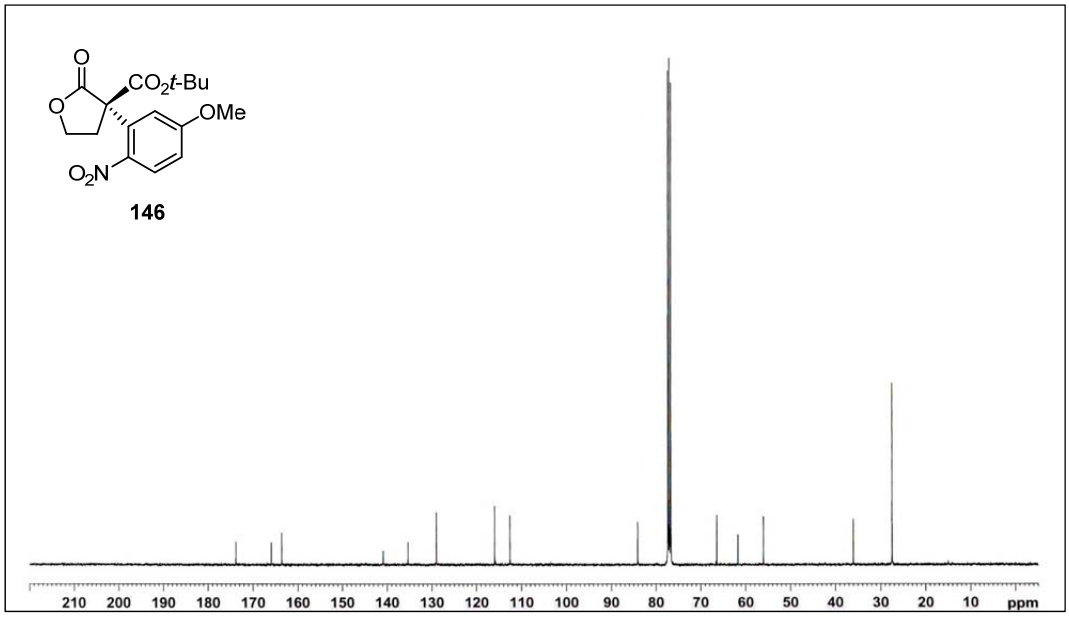
^{13}C-NMR of compound **145** (100 MHz, $CDCl_3$)



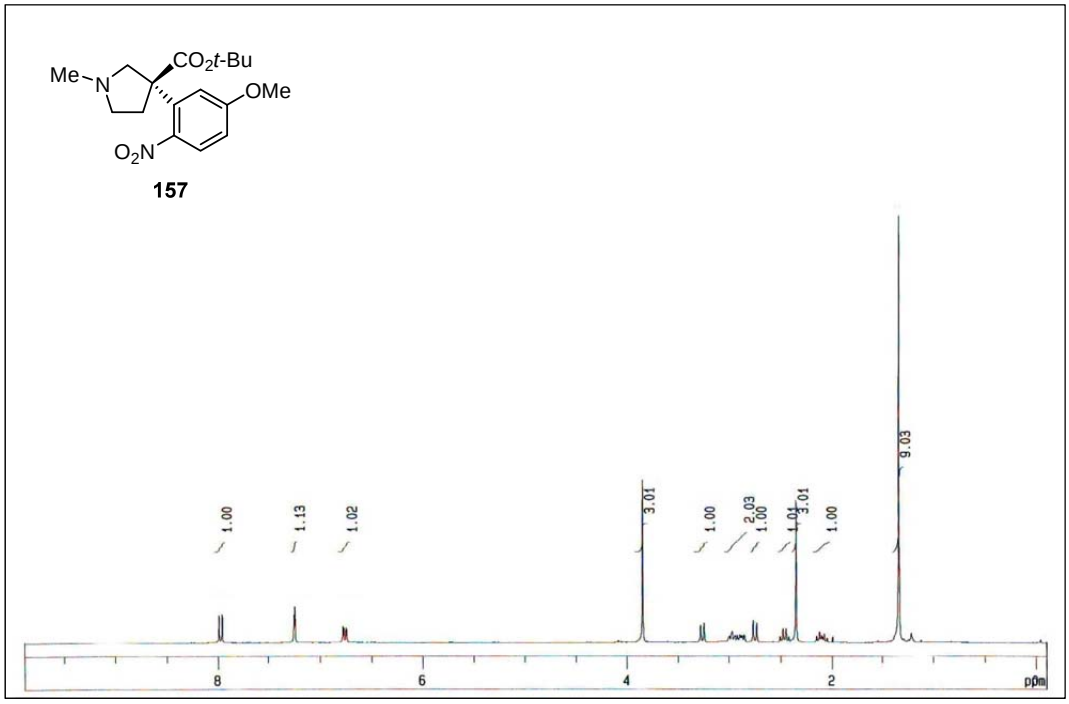
^{1}H-NMR of compound **146** (300 MHz, $CDCl_3$)



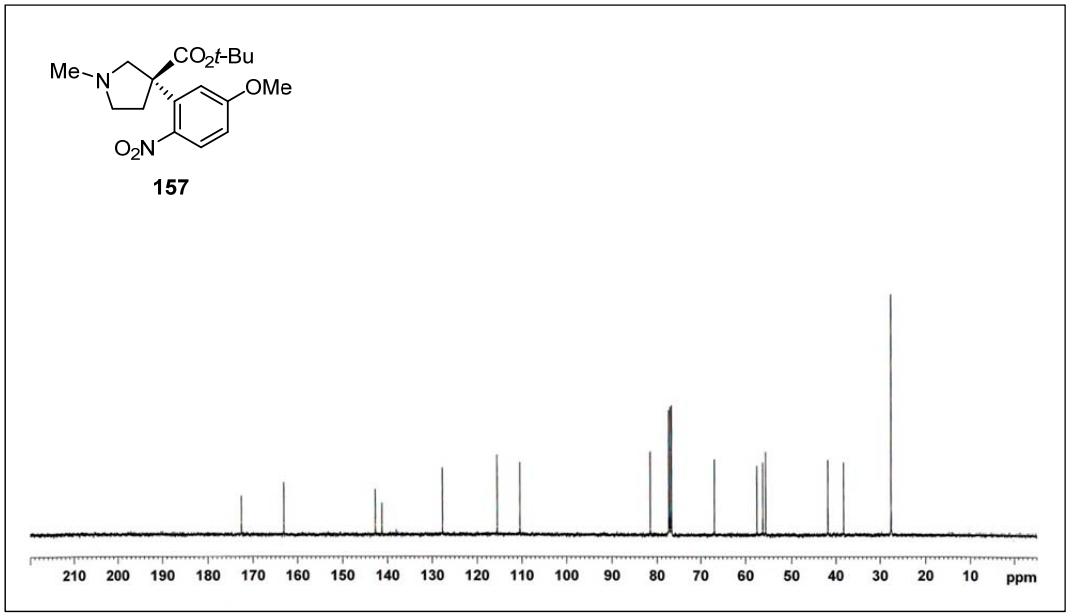
^{13}C-NMR of compound **146** (100 MHz, $CDCl_3$)



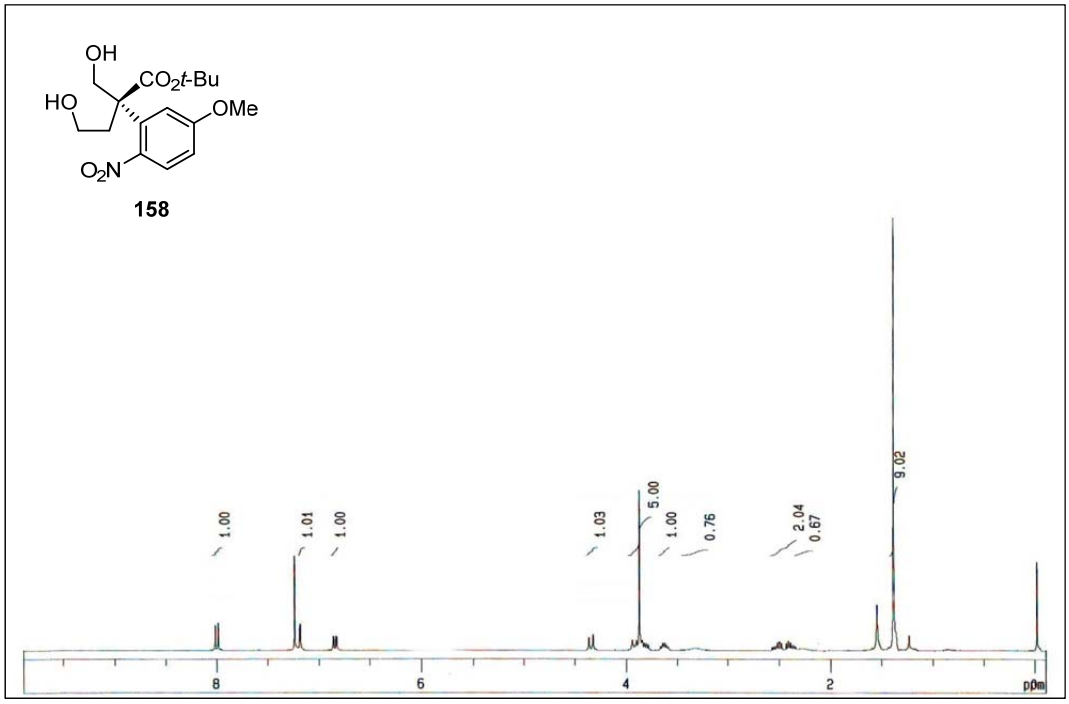
[1]H-NMR of compound **157** (300 MHz, $CDCl_3$)



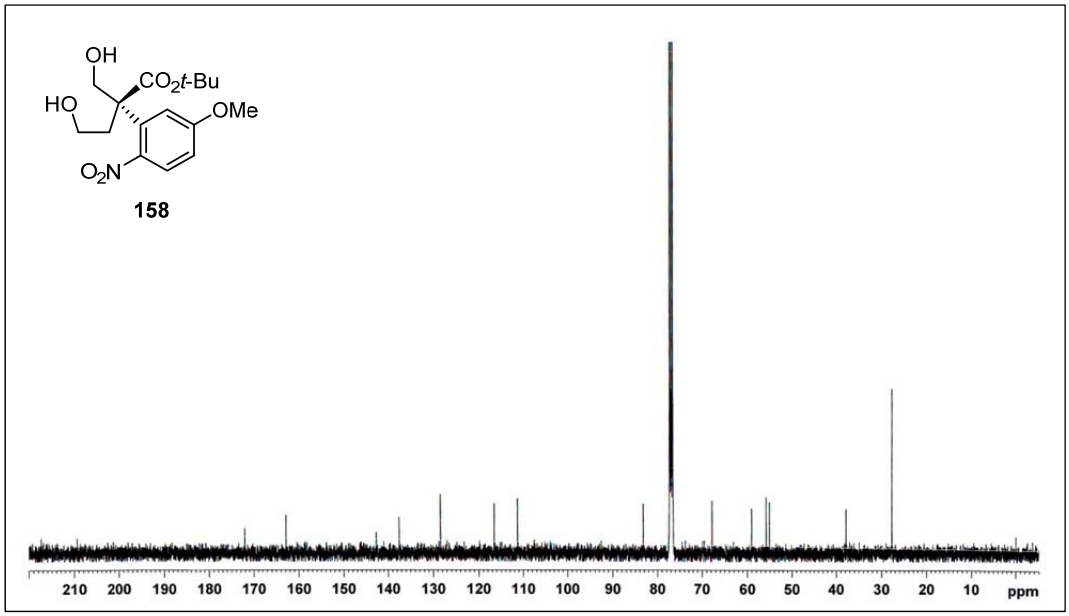
[13]C-NMR of compound **157** (100 MHz, $CDCl_3$)



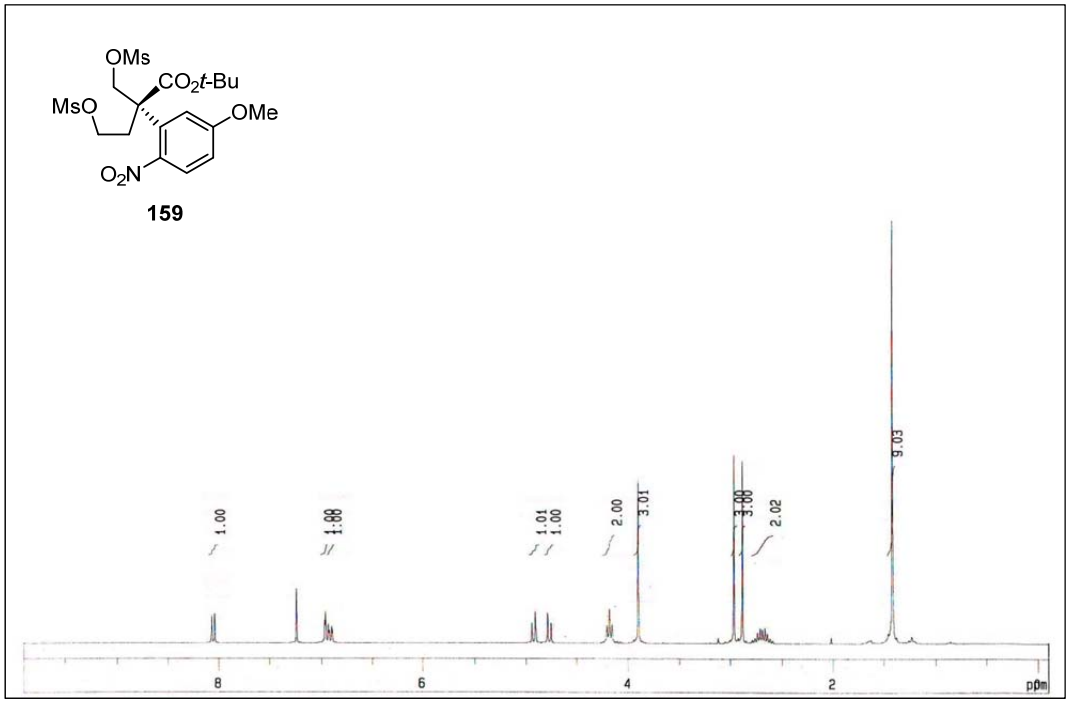
^{1}H-NMR of compound **158** (300 MHz, $CDCl_3$)



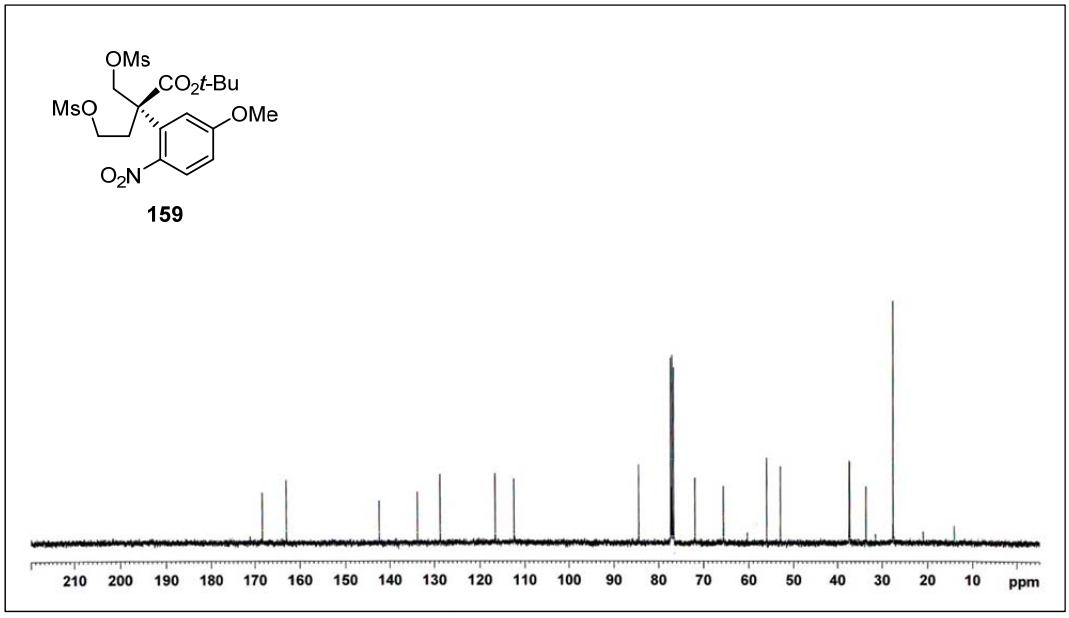
^{13}C-NMR of compound **158** (100 MHz, $CDCl_3$)



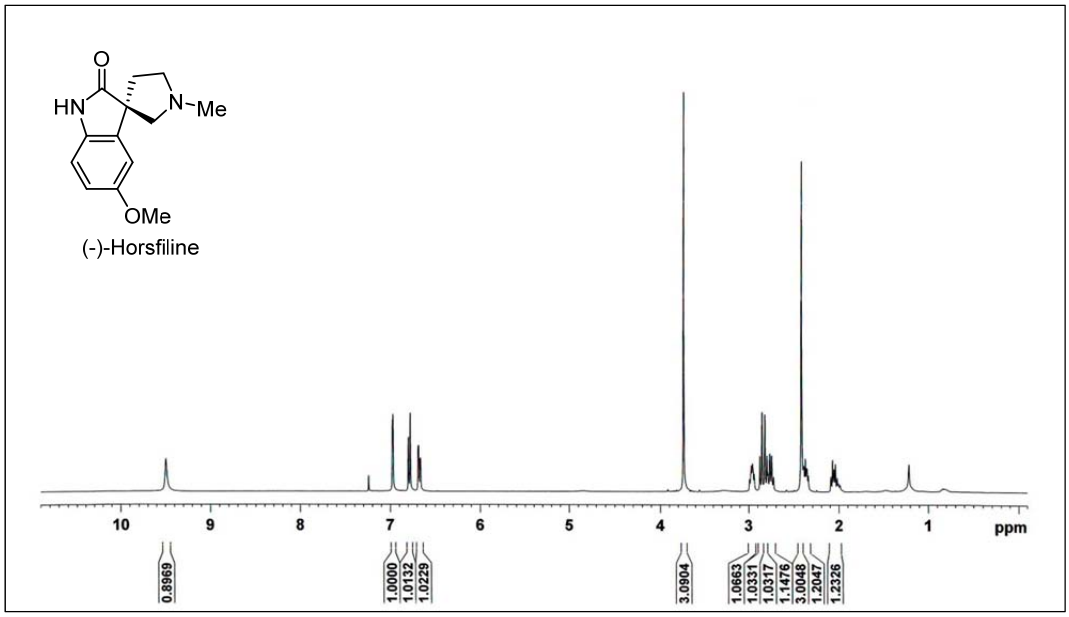
^{1}H-NMR of compound **159** (300 MHz, $CDCl_3$)



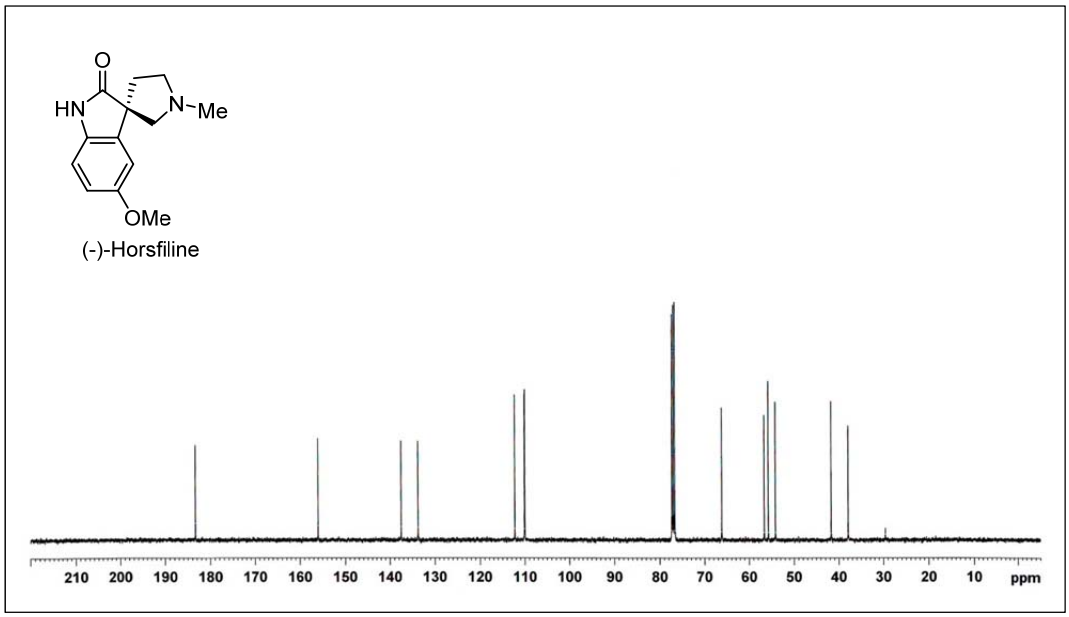
^{13}C-NMR of compound **159** (100 MHz, $CDCl_3$)



^{1}H-NMR of (–)-Horsfiline **47a** (400 MHz, $CDCl_3$)



^{13}C-NMR of (–)-Horsfiline **47a** (100 MHz, $CDCl_3$)



국문초록

유기 합성 분야에서 malonate는 탄소-탄소 결합을 위해 가장 널리 쓰이는 시작 물질 중 하나이다. 특히 키랄성 α,α-dialkylmalonate는 생리 활성 천연물과 의약품의 합성에 꾸준히 이용되어 왔다. 이러한 키랄성 α,α-dialkylmalonate가 갖는 4차 탄소는 라세미화되지 않고 malonate 자체가 갖는 두 에스터 작용기의 변환에 의해 다양한 구조로 바뀔 수 있다. 이러한 이점에도 불구하고 지금까지 α,α-dialkylmalonate는 효소를 이용하거나 키랄성 장비를 이용한 분리 방법을 통해서만 얻을 수 있었다. 비록 카보닐과 β-ketoester 화합물에서는 α위치에 비대칭 알킬화반응을 통해서 입체선택적인 4차 탄소를 합성해왔지만 malonate에서는 아직까지 α위치에 직접적인 비대칭 알킬화반응이 보고된 바가 없다. 상기 이유로 본 연구팀은 상전이촉매화 조건에서 malonate의 α위치에 비대칭 알킬화반응을 수행하여 α,α-dialkylmalonates의 입체선택적인 합성 방법을 개발하고자 하였다.

먼저 일반적인 상전이촉매화 반응조건 하에서 대표적인 상전이 촉매들을 이용하여 benzyl *tert*-butyl α-methylmalonate의 α위치에 벤질화반응을 시도하였다. 이 중에서 (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide 촉매를 사용하였을 때 70%의 입체선택성을 보여주었다. 또한 벤질 에스터를 변환한 5종의 malonate기질을 추가로 합성하여 α위치에 벤질화반응을 수행한 결과 diphenylmethyl 에스터에서 가장 좋은 입체선택성을 얻을 수 있었다. 최적화된 기질과 촉매를 사용하여 다양한 활성, 비활성 알킬 할로젠화물과 반응을 수행한 결과 최대 99%의 화학 수율과 최대 97%의 광학 수율과 다양한 키랄성 알킬화 malonate를 얻을 수 있었다. 추가적으로 α 위치에 메틸이 아닌 아릴이나 할로젠으로 치환된 malonate 기질로 상전이 촉매 반응을 수행한 결과 각각의 기질에서 높은 입체선택성으로 키랄성 알킬화 malonate를 얻을 수 있었다. 또한 diphenylmethyl *tert*-butyl malonate를 기질로 하여 α 위치에 두 번의 알킬화반응을 한 반응계에서 연속적으로 수행한 결과 부합하는 키랄성 α,α-dialkylmalonate를 입체선택성

의 손실 없이 얻을 수 있었다.

새로 개발된 합성 방법은 높은 입체선택성과 온화한 반응 조건을 갖고 있어 다양한 입체선택적인 단위체를 만드는데 아주 유용하게 사용될 수 있다. 얻어진 키랄성 malonate 알킬화물로부터 비천연아미노산과 oxindole 구조를 갖는 단위체로 변환하여 상기 합성방법의 유용성을 나타냈다. 생리활성을 갖는 oxindole 화합물중에 두 개의 환이 한 탄소에 결합되어 있는 spiro-oxindole 구조가 많이 발견된다. 많은 합성학자들이 특이한 spiro-oxindole 구조를 합성하는 효율적인 방법을 개발하고자 하였다. 본 연구팀은 상기 개발된 합성방법을 이용하여 다양한 spiro-oxindole 알칼로이드 중에 (–)-horsfiline의 전합성을 시도하였다. 그리하여 malonate의 α위치에 입체선택적인 상전이 촉매 알킬화반응을 응용한 새로운 (–)-horsfiline의 전합성 방법이 개발되었다. Diphenylmethyl *tert*-butyl malonate를 기질로 하여 총 9단계에 걸쳐 총 32%의 화학 수율과 99% 이상의 광학 수율로 (–)-horsfiline의 전합성을 완료하였다. 높은 광학 수율과 화학 수율은 이 방법이 spiro-oxindole 천연물의 대량공정에 응용될 수 있음을 보여주며, 이는 spiro-oxindole 천연물의 생리활성에 대한 체계적인 조사에 도움이 될 것이다.

주요어: 비대칭 합성, 상전이 촉매화 반응, 키랄성 malonate, α,α-dialkylmalonate, 입체선택적인 전합성, spiro-oxindole, horsfiline

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