Carbon–carbon bond formation reactions via ammonium ylides derived from α-amino acid esters or radical anions of benzoylformates

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Chapter 1.
Introduction

Carbon–carbon bond formations via carbanions are one of the most important methods for the synthesis of natural products and biologically active compounds. Oftentimes, it is necessary to generate carbanions in mild condition, because synthetic chemists yet pose particularly onerous mechanistic challenges owing to complex aggregation phenomena. Accordingly, there has been a substantial effort to develop various novel methods. In this paper, we demonstrated that asymmetric synthesis via ammonium ylides and carbon–carbon bond formation by photoinduced electron-transfer are the new methods of the generated carbanion at mild condition.

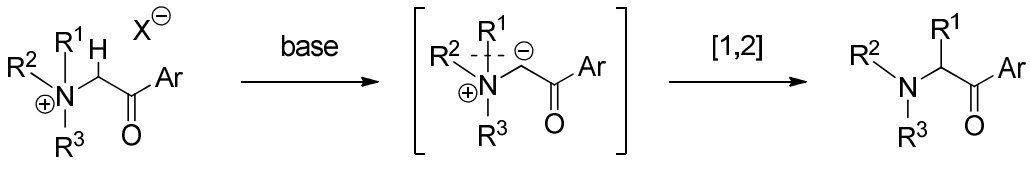
Asymmetric synthesis by rearrangement of carbanion

Asymmetric syntheses by the rearrangements of carbanion are unambiguously an important class of basic methods in organic synthesis. It is synthetically available that carbon–heteroatom is easily transformed to carbon–carbon bond by this rearrangement reaction. One of the famous rearrangements of carbanion is Wittig rearrangement reaction,[1] which carbon–oxygen bond is transformed to carbon–carbon bond, and Stevens rearrangement reaction,[2] which carbon–nitrogen or carbon–sulfur bond is transformed to carbon–carbon bond. The stereoselective carbon–carbon bond formation is important in organic chemistry, and our group has researched the asymmetric synthesis by Stevens rearrangement reaction.

Our group proceeds mainly *N*-ylide type Stevens rearrangement reaction, in which substitute upon nitrogen atom is transferred by treating ammonium salts with bases, and develops stereoselectively the synthetically difficult amines with tertiary and quaternary carbon. This reaction is classified as [1,2], [2,3], and [1,4], in which our group research improvement of regioselectivity.

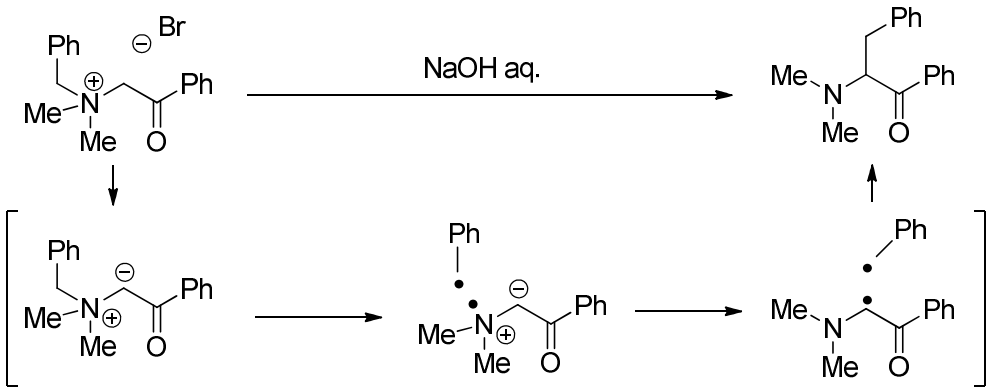
[1,2] Stevens rearrangement reaction is among the most commonly applied transfer of the aliphatic groups upon nitrogen atom (Scheme 1-1).

Scheme 1-1



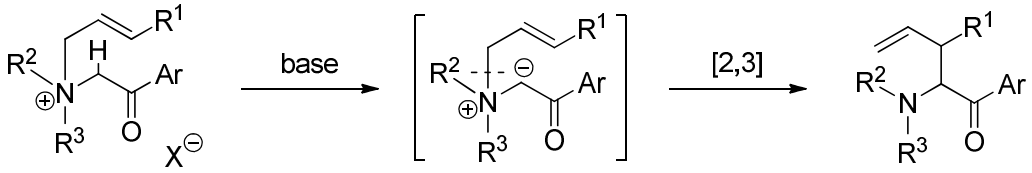
Discovered by Stevens in 1928,[3] a lot of research for this reaction are reported. The mechanisms proposed by Schöllkopf et al. [4] and Ollis et al.[5] are the most leading opinion that the intramolecular radical cleavage and subsequent radical pair recombination proceed (Scheme 1-2).

Scheme 1-2



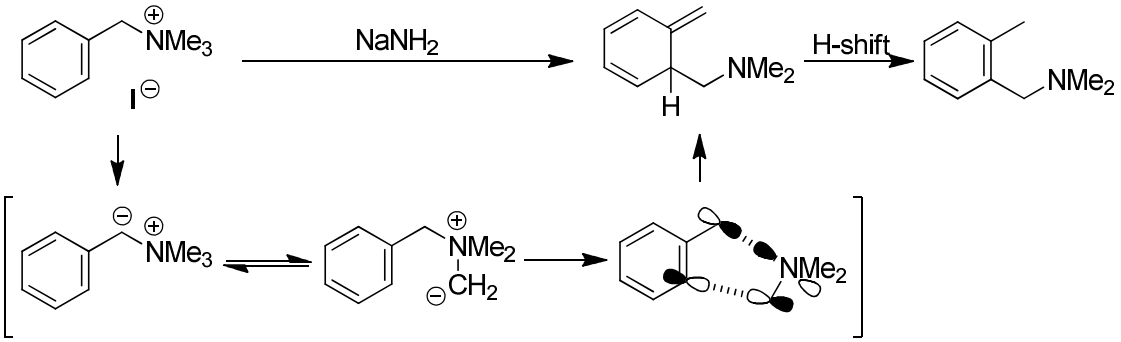
On the other hand, [2,3] Stevens rearrangement reaction, [2,3] sigmatropic rearrangement, occur in substitute allylic groups upon nitrogen atom (Scheme 1-3). And then, Sommelet–Hauser rearrangement reaction, [2,3] sigmatropic rearrangement related to aromatic ring, is realized in substitute benzyl groups upon nitrogen atom.[6]

Scheme 1-3



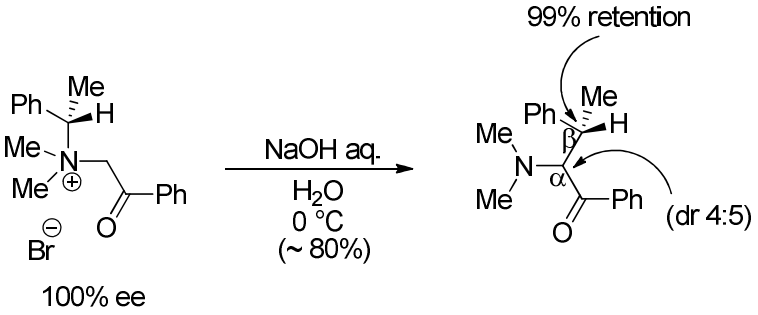
Ingold et al. has developed [2,3] Stevens rearrangement reaction of the sulfur compounds in 1930, [7] and Sommelet et al. has reported that of nitrogen compounds in 1937.[8] Hauser et al. has discovered in 1951 that this reaction is symmetry allowed and sigmatropic rearrangement concertedly via a cyclic transition state (Scheme 1-4).[9]

Scheme 1-4



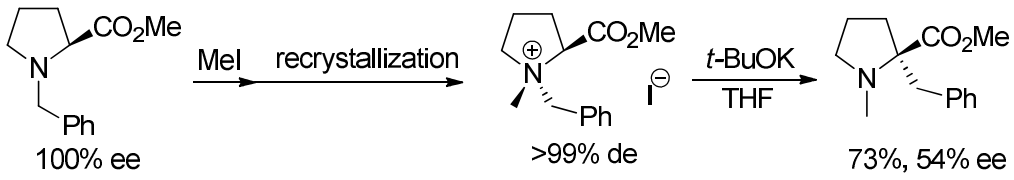
For the asymmetric [1,2] Stevens rearrangement reaction, there are the stereocontrol at the rearrangement group, β position of the rearrangement product, and at the terminal group, α position of it (Scheme 1-5). Ollis et al. has discovered that the stereocontrol at rearrangement group is retention of stereochemistry.[5] It is reasoned that enantioselectivity is improved by the rapidly radical pair recombination, because this rearrangement occur in solvent cage without the rotational degrees of freedom. However, far fewer reports concerning the asymmetric synthesis ascribable to the difficulty of stereocontrol.

Scheme 1-5



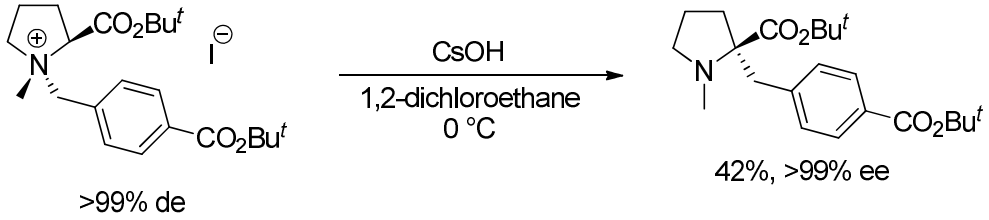
Recently, West et al. has reported that the epimeric mixture of ammonium salts with benzylic group upon nitrogen atom is recrystallized, and [1,2] Stevens rearrangement reaction in one of the epimer proceeds to give the [1,2] rearrangement product in 54% ee (Scheme 1-6).[10]

Scheme 1-6



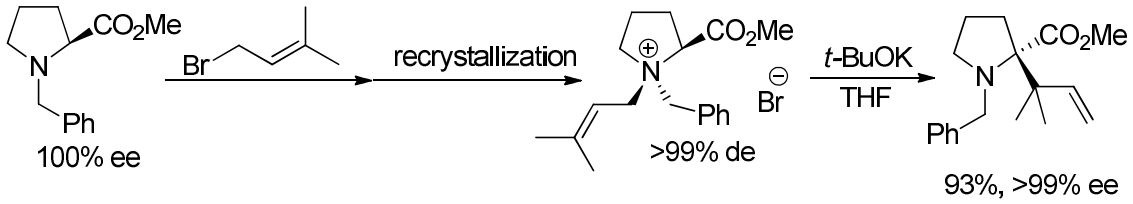
Encouraged by West's results, our group has examined various substitutes and reaction conditions to obtain high enatioselective [1,2] rearrangement products (Scheme 1-7).[11] Although this reaction proceeds in completely chiral transfer from nitrogen atom to carbon atom, high diastereoselective synthesis or resolution of ammonium salts with chiral center upon nitrogen atom is required to giving high enantioselective compounds.

Scheme 1-7



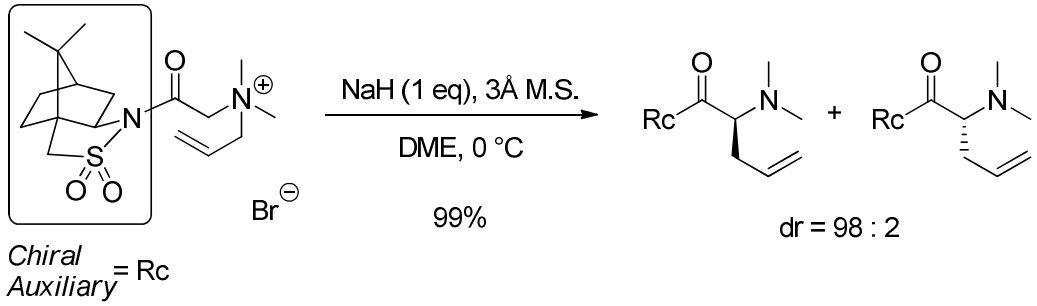
On the other hand, it is expected that the asymmetric [2,3] Stevens rearrangement reaction, which proceeds concertedly in symmetry allowed, is more stereoselective than [1,2] Stevens rearrangement reaction. West et al. has reported that the asymmetric [2,3] Stevens rearrangement reaction proceeds high stereoselectively via chiral transfer from one of the epimeric ammonium salts derived from proline (Scheme 1-8).[10] However, it is necessary to obtain the ammonium salts high diastereoselectively, and the utility at synthesis is restricted.

Scheme 1-8



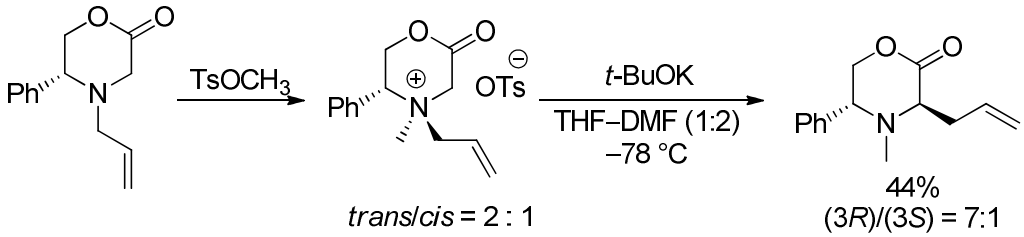
In recent years, Sweeney et al. has reported that [2,3] Stevens rearrangement reaction of the achiral ammonium salts with a chiral auxiliary group proceeds in diastereocontrol to give the α-allylic glycine enantioselectively (Scheme 1-9).[12]

Scheme 1-9



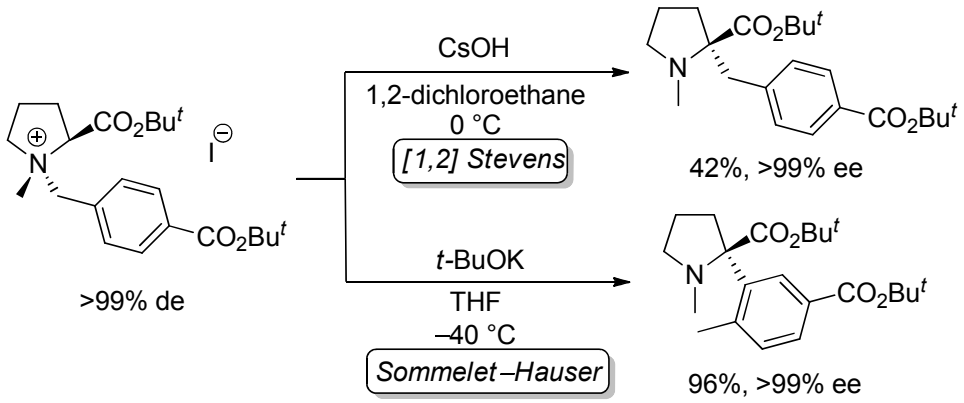
Our group has reported that the asymmetric [2,3] Stevens rearrangement reaction for epimeric mixture of six-membered cyclic ammonium salts proceeds in the kinetic resolution to obtain the rearrangement product high diastereoselectively compared with the substrate (Scheme 1-10).[13] However, in most cases, the substrates are limited to ammonium salts with chiral center upon adjacent carbon atom.

Scheme 1-10



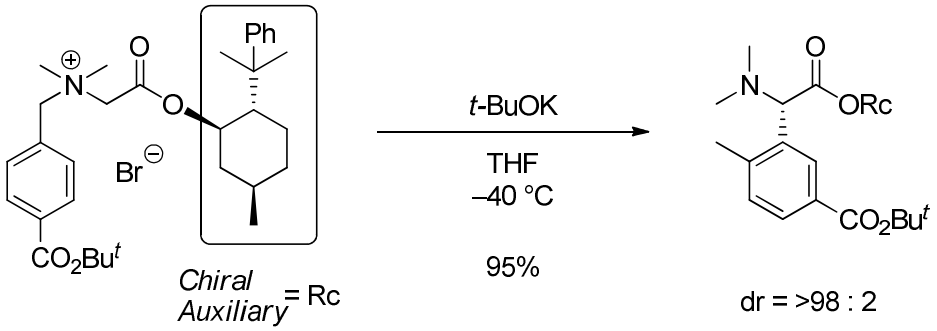
Reported by our group, the asymmetric Sommelet–Hauser rearrangement reaction proceeds in high yield and enantioselectivity with suppressing [1,2] Stevens rearrangement reaction (Scheme 1-11).[14]

Scheme 1-11



Our group has also reported that Sommelet–Hauser rearrangement reaction of achiral ammonium salts with a chiral auxiliary group proceeds in diastereocontrol to give the α-phenylglycine enantioselectively (Scheme 1-12).[14]

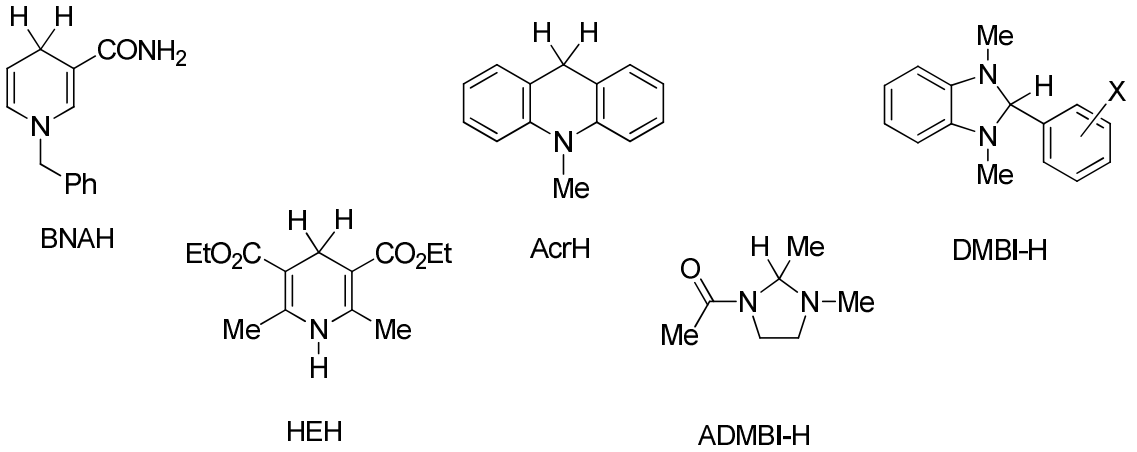
Scheme 1-12



Photoinduced electron-transfer with benzimidazolines

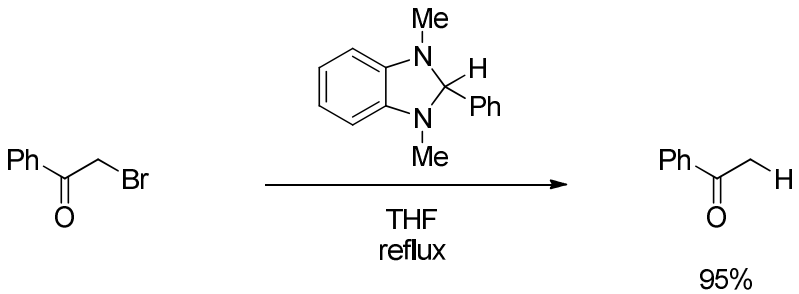
There are various reports for hydride reduction reactions in which direct reductive procedures commonly use active borane[15] and catalysts on In or Ir,[16,17] but these methods have some drawbacks, such as toxic and expensive. Alternatively, Organic hydride donors, such as 1-benzyl-1,4-dihydronicotinamide (BNAH),[18] Hantzsch ester (HEH),[19] 9,10-dihydroacridine (AcrH),[20] 1-acetyl-2,3-dimethylimidazoline (ADMBI-H),[21] and 2-aryl-1,3-dimethylbenzimidazolines (DMBI-H)[22,23,24] are attractive research targets for chemists and biochemists (Figure 1-1). Among organic hydride donors, our group is interested in DMBI-H that X of substitute is transformed to be able to control reductive ability.

Figure 1-1



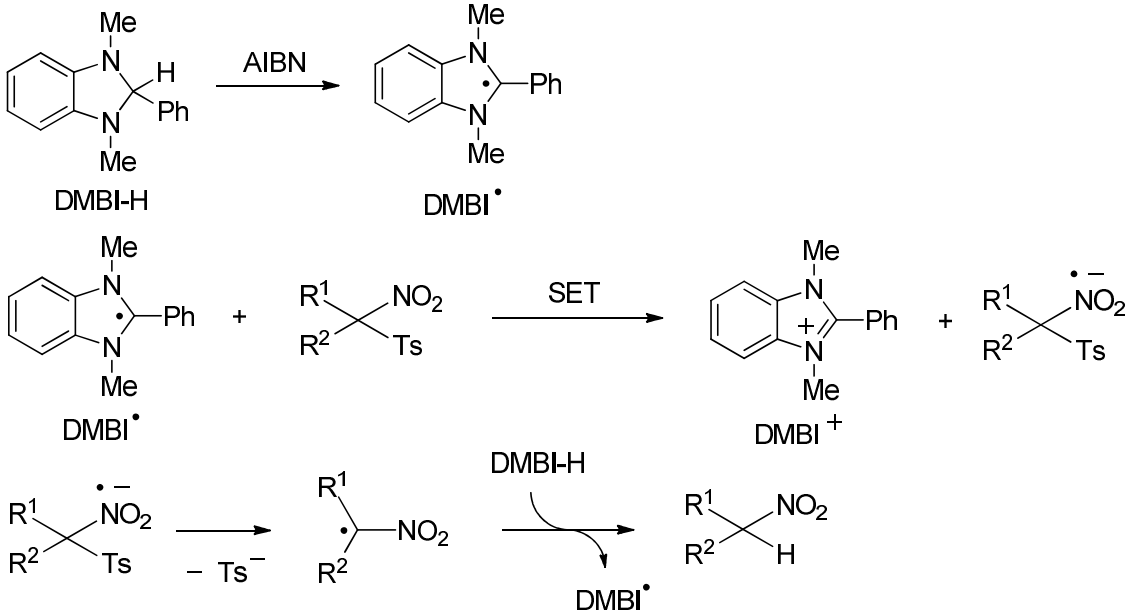
Chikashita et al. has reported that DMBI-H acts as a novel and efficient reagent for mild reductive dehalogenation of α-halo carbonyl compounds (Scheme 1-13).[22a] Further, the utility of DMBI-H as a direct hydride reductive reagent are investigated to apply to several compounds.[22b,c]

Scheme 1-13



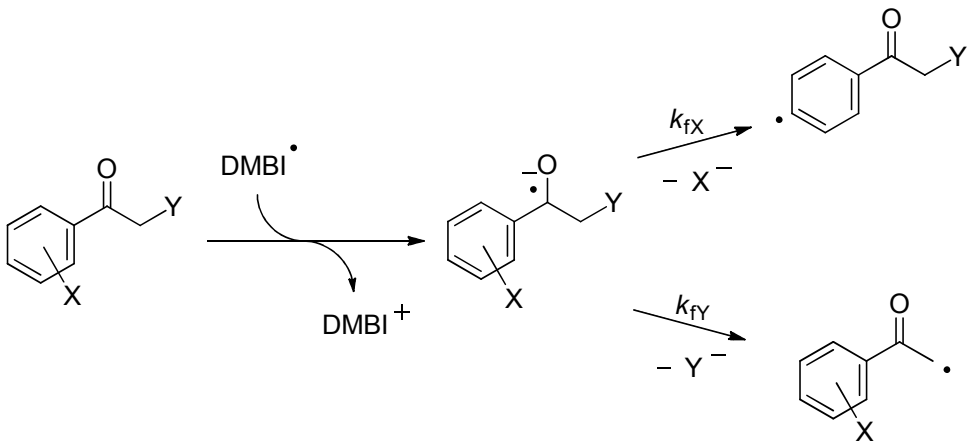
Discovered by Tanner et al., the reductive reaction of α-nitrocyclohexyl *p*-tolylsulfone by DMBI-H proceeds via an electron-transfer and sequence free radical chain (Scheme 1-14).[23a] The reaction pathway begins with initiator (azobisisobutyronitrile, AIBN), in which the single electron-transfer (SET) between α-nitrocyclohexyl *p*-tolylsulfone and initially formed DMBI radical (DMBI$^{\bullet}$) occurs. The subsequent elimination of *p*-toluenesulfonyl group and hydrogen atom abstraction generates the corresponding nitroalkane.

Scheme 1-14



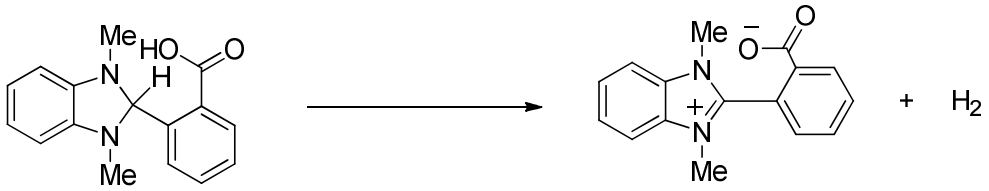
Further, the rate constants for fragmentation of the halide anions from the intermediate ketyls, k_{fX} and k_{fY}, are determined, when they use halogens substituted derivatives as the substrates (Scheme 1-15).[23]

Scheme 1-15



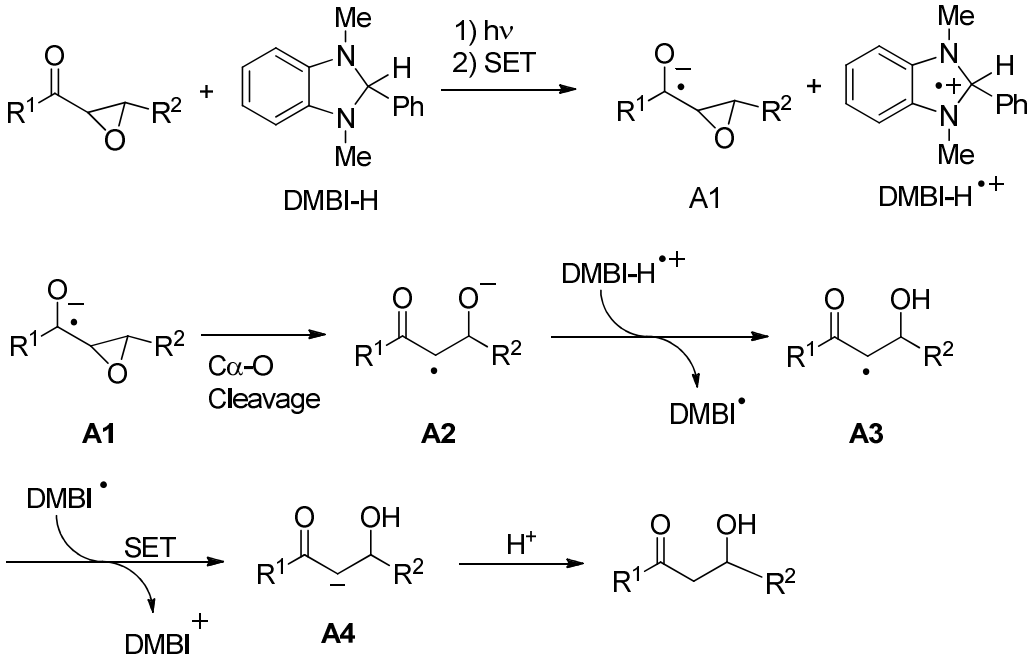
Discovered also by West et al. in 1991,[25] protonolyses of carbon–hydrogen bond can occur under the suitable conditions to produce carbocations and H_2 (Scheme 1-16). On the basis of this results, Thorn et al. has reported that DMBI-H are shown for the first time to eliminate hydrogen by the catalyzed reaction with protic compounds.[26]

Scheme 1-16



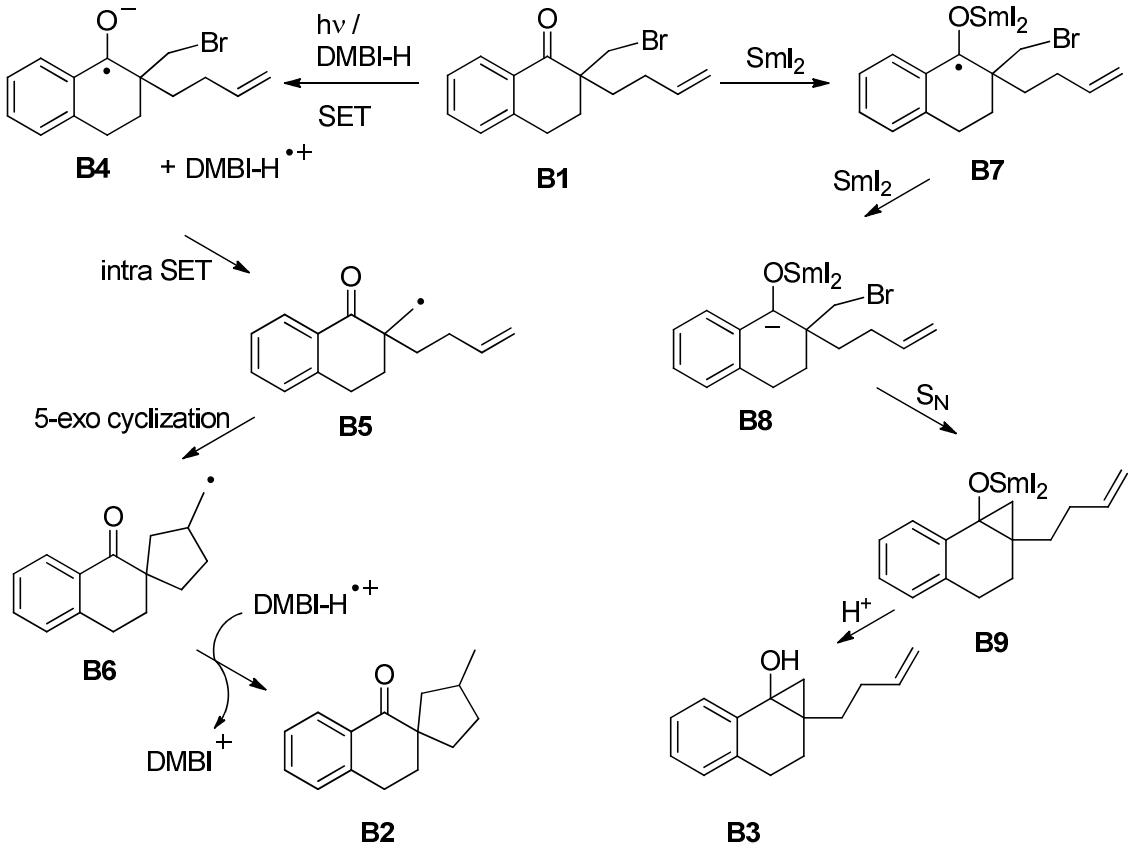
On the other hand, photoinduced electron-transfer processes provide useful methods to generate organic radical ions in solution, and the reaction pathways of radical ions are principally governed by not only their inherent property but also the surrounding medium including solvents and additives.[27] Our group has reported that photoreactions of α,β-epoxy ketones with DMBI-H in aqueous solvent produce β-hydroxy ketones in good yields (Scheme1-17).[24a] A plausible reaction mechanism for this reaction is proposed. The photoexcited state of α,β-epoxy ketones is considered to be efficiently quenched by DMBI-H. The radical anion **A1** undergoes α-carbon–oxygen bond cleavage to give the open radical anion **A2**. The radical anion **A2** abstracts the proton from DMBI radical cation ($DMBI^{\bullet+}$) to give the β-keto radical **A3**, which is reduced by $DMBI^{\bullet}$ to the anion **A4**. Subsequent protonation of **A4** would give β-hydroxy ketones.

Scheme 1-17



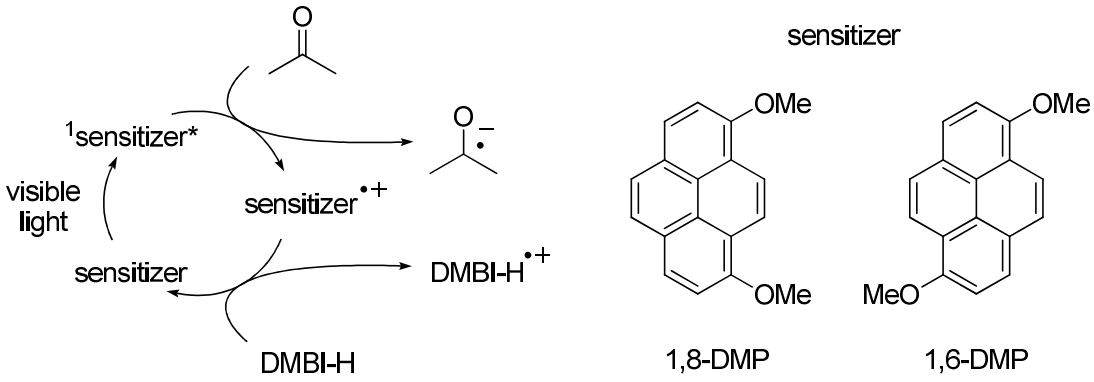
In addition, our group discovers that reactivity of ketyl radicals derived from 2-bromomethyl-2-(3-butenyl)benzocyclic-1-alcanones **B1** changes in dependence on electron-transfer conditions employed (Scheme 1-18).[24e] Photoinduced electron-transfer reaction of **B1** with DMBI-H affords 5-exo radical cyclization product **B2**, while electron-transfer with samarium diiodide produces cyclopropanol **B3**. Photoinduced electron-transfer between **B1** and DMBI-H produces radical anion **B4** and $DMBI^{\bullet+}$. Fast intramolecular single electron-transfer (SET) from the ketyl radical part to the carbon–bromine bond in **B4** occur to give the primary alkyl radical **B5**. The rearrangement of **B5** to **B6** should be much faster than the hydrogen atom transfer from $DMBI\text{-}H^{\bullet+}$ to **B5**. **B6** abstracts hydrogen atom from $DMBI\text{-}H^{\bullet+}$ to give **B2**. On the other hand, reduction of **B1** by SmI_2 produces samarium coordinated ketyl radical **B7**. Intramolecular SET from **B7** to the carbon–bromine bond must be slow, even though such a process exists, because of the extremely low yield of **B2**. **B7** is reduced to become carbanion **B8**, which undergoes S_N against the carbon–bromine bond to give the samarium cyclopropoxide **B9**. The alkoxide **B9** are finally protonated to produce **B3**.

Scheme 1-18



In recent years, our group has investigated photosensitization methods by the sensitizer, such as 1,8- or 1,6-dimethoxypyrene (DMP), owing to several advantageous features which do not exist with direct irradiation (Scheme 1-19).[24i] In the photosensitization cycle followed in the processes, the sensitizer first absorbs light to generate its singlet exited state, from which a single electron is transferred to a carbonyl substrate to generate the carbonyl radical anion (ketyl radical). The simultaneously formed radical cation of sensitizer is subsequently reduced by DMBI-H to regenerate its ground state. Finally, the formed DMBI-H$^{\bullet+}$ reacts with ketyl radical to give a reduction product.

Scheme 1-19

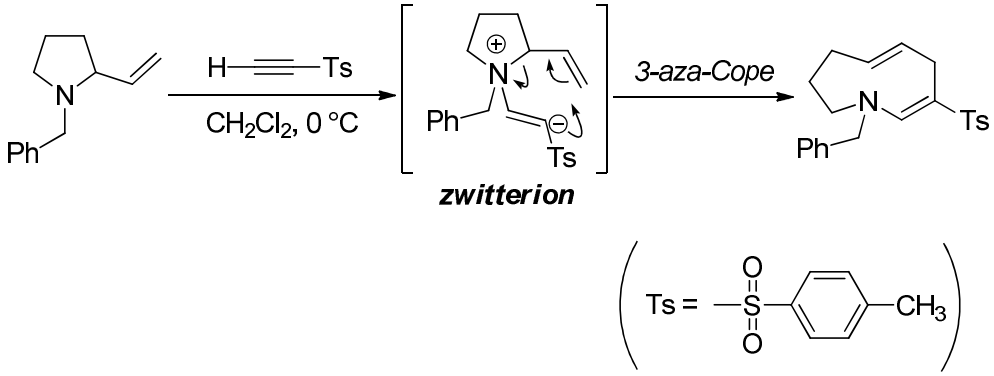


The purpose 1 of this study

N-Ylide type Stevens rearrangement reaction and Sommelet–Hauser rearrangement reaction are useful for the asymmetric synthesis of α-amino ketones and α-amino acid derivatives described above. It is expected that asymmetric [2,3] Stevens rearrangement reaction proceeds concertedly in symmetry allowed and more stereoselectively, while the diversity of substrates and products is restricted because of the difficulty in synthesis of the steric hindered quaternary ammonium salts.

Herein, we are interested in the generated *N*-2-tosylvinyl ammonium zwitterion method using ethynyl tolyl sulfone (tosylacetylene) reported by Back et al. (Scheme 1-20).[28] Ethynyl tolyl sulfone is a highly electrophilic reactivity and reacts with steric hindered amines to give quaternary ammoniums in mild condition.

Scheme 1-20

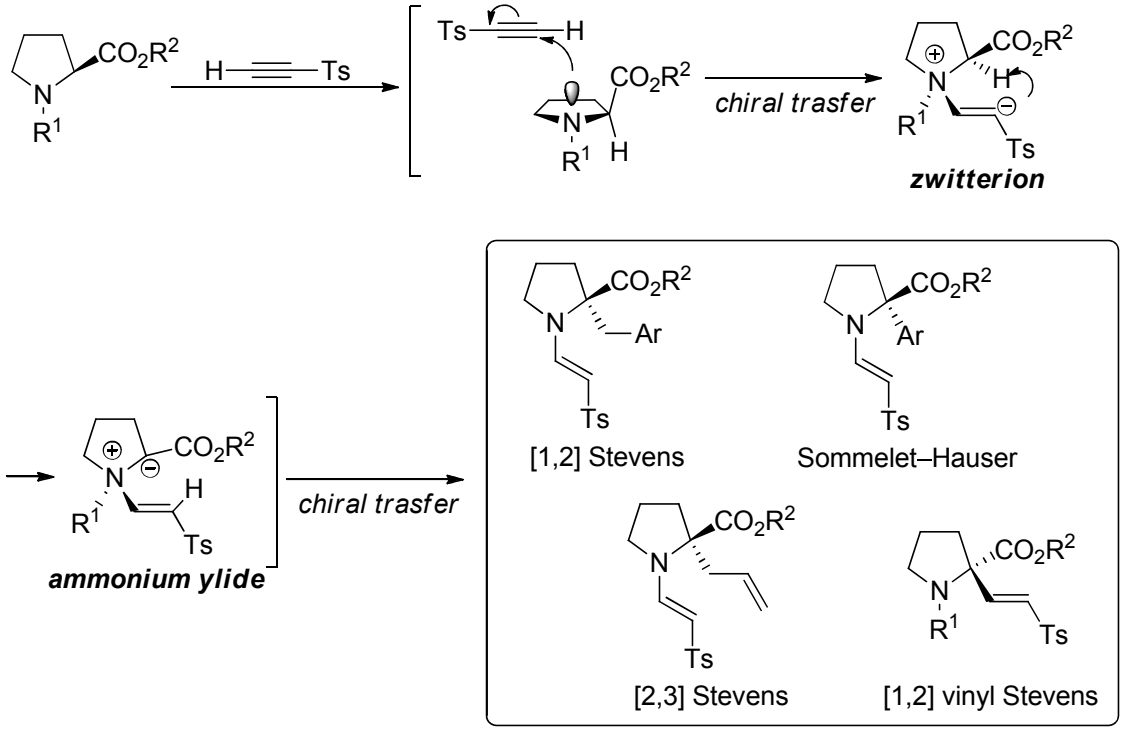


Encouraged by this method, we attempted the asymmetric synthesis of non-natural amino acid derivatives.

In section 2 “Asymmetric α-2-tosylethenylation of proline derivatives via chiral transfer from nitrogen atom to carbon atom”, we conducted synthesis of chiral quaternary proline derivatives on the basis of the following plan (Scheme 1-21).

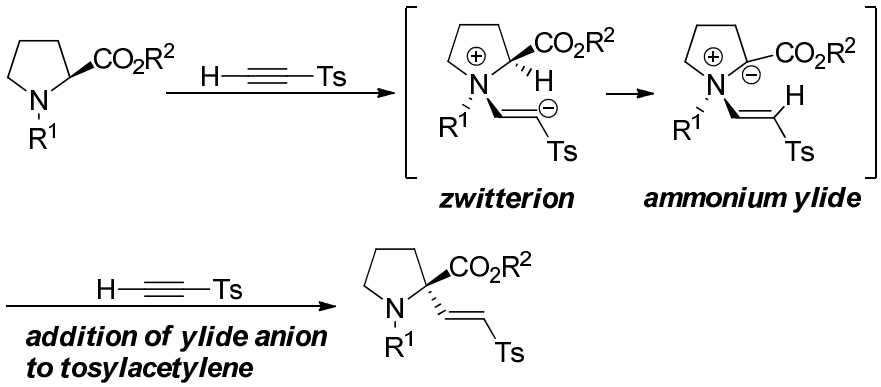
First, the proline derivatives with chiral center upon α-carbon atom are transformed to *N*-2-tosylethenyl ammonium zwitterion diastereoselectively in the reaction of ethynyl tolyl sulfone (chiral transfer from carbon atom to nitrogen atom). The anion part of zwitterion abstracts more acidic proton at α-position of prolines to produce *N*-chiral ammonium ylide. This ylide is an intermediate that Stevens rearrangement reaction and Sommelet–Hauser rearrangement reaction would occur. The [1,2] Stevens rearrangement products and the Sommelet–Hauser rearrangement products would be obtained in introducing benzyl substituents upon nitrogen atom, and using *N*-allylic substrates would give the [2,3] Stevens rearrangement products. Further, [1,2] vinyl Stevens rearrangement reaction would occur in introducing hardly transferred substitutes upon nitrogen atom. In any case, the chiral proline derivatives would be obtained via chiral transfer from nitrogen atom to carbon atom, because the chiral center upon nitrogen atom exists in the generated ylides.

Scheme 1-21

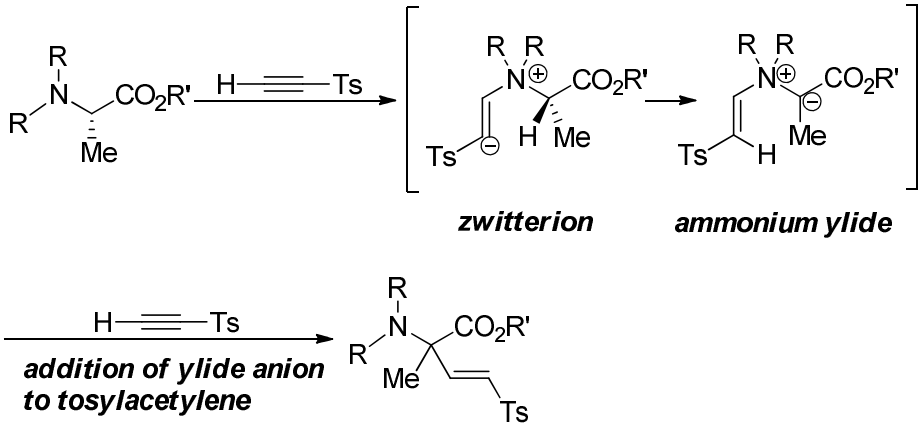


In section 3 "Asymmetric α-2-tosylethenylation of *N*,*N*-dialkyl-L-amino acid esters via the formation of non-racemic ammonium enolates", we applied the method described in section 2 (Scheme 1-22), in which the nucleophilic addition of ammonium ylide to ethynyl tolyl sulfone would occur diastereoselectively, to the acyclic amino acid derivatives (Scheme 1-23).

Scheme 1-22



Scheme 1-23

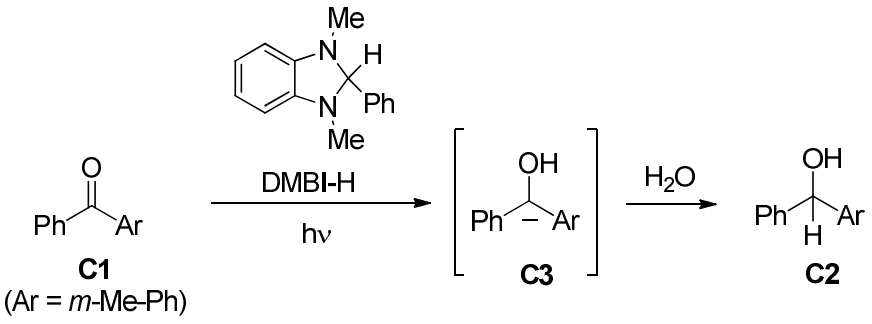


The purpose 2 of this study

Carbon–carbon bond formations promoted by inversion operators are well-established in organic synthesis.[29] However, it is difficult to construct a tertiary alcohol via umpolung reactivity; Fukuzawa et al. has reported that one of the few examples is the SmI_2 promoted carbon–carbon bond formation of α-keto esters/amides.[30]

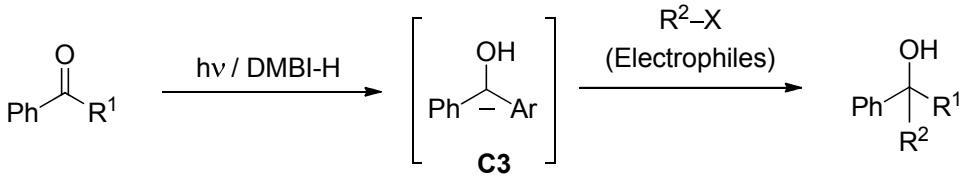
Previously, our group has reported that DMBI-H acts as an effective reagent to promote a photoinduced reduction reaction of ketone **C1** to produce alcohol **C2** (Scheme 1-24).[24g] The reaction is proposed to generate carbanion **C3**, in which the carbonyl carbon becomes nucleophilic (umpolung reactivity) and, finally, **C3** captures a proton from water to give **C2**.

Scheme 1-24



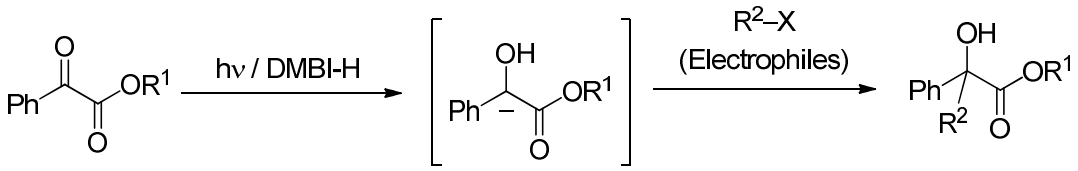
In section 4 “carbon–carbon bond formation via benzoyl umpolung attained by photoinduced electron-transfer with benzimidazolines”, we thought that carbon–carbon bond formation would be possible when the appropriate carbon electrophiles are captured by **C3** in lieu of the protons supplied by water (Scheme 1-25).

Scheme 1-25



Further, we applied this method to benzoylformate derivatives which are reduced to mandelate derivatives (Scheme 1-26). In the reaction of benzoylformate derivatives, the intermediates of carbanion would react with various electrophiles. Mandelate derivatives are useful in various fields of chemistry, such as organic synthesis,[31] biochemistry,[32] and inorganic chemistry,[33] and α-substituted mandelate derivatives are important units in several biologically active natural products and versatile synthetic intermediates.[34] Thus, we decided to examine the photoreaction of benzoylformates in detail.[35]

Scheme 1-26



In section 5 “Conclusion”, the results of this study are summarized.

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Chapter 2.
Asymmetric α-2-tosylethenylation of proline derivatives via chiral transfer from nitrogen atom to carbon atom

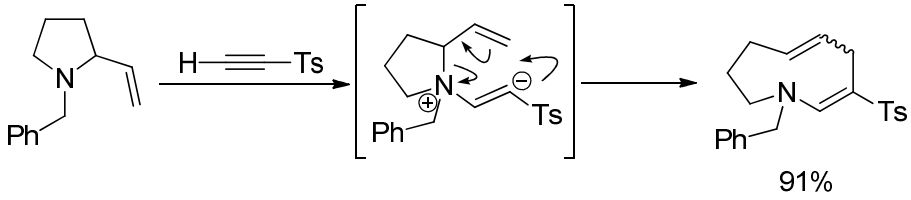
2-1 Background

Stevens rearrangement reaction and Sommelet–Hauser rearrangement reaction by chiral transfer from nitrogen atom to carbon atom are the useful methods which can synthesis the chiral non-natural quaternary amino acids high-enantioselectively, described in section 1 “Introduction”. However, the synthesis of the quaternary ammonium compounds derived from steric hindered tertiary amines is difficult, and more reactive alkyl halides, such as iodomethane and benzylic bromide, are required to obtain quaternary ammonium compounds.

Herein, we are interested in the generated *N*-2-tosylethenyl ammonium zwitterion method using ethynyl tolyl sulfone.[1,2]

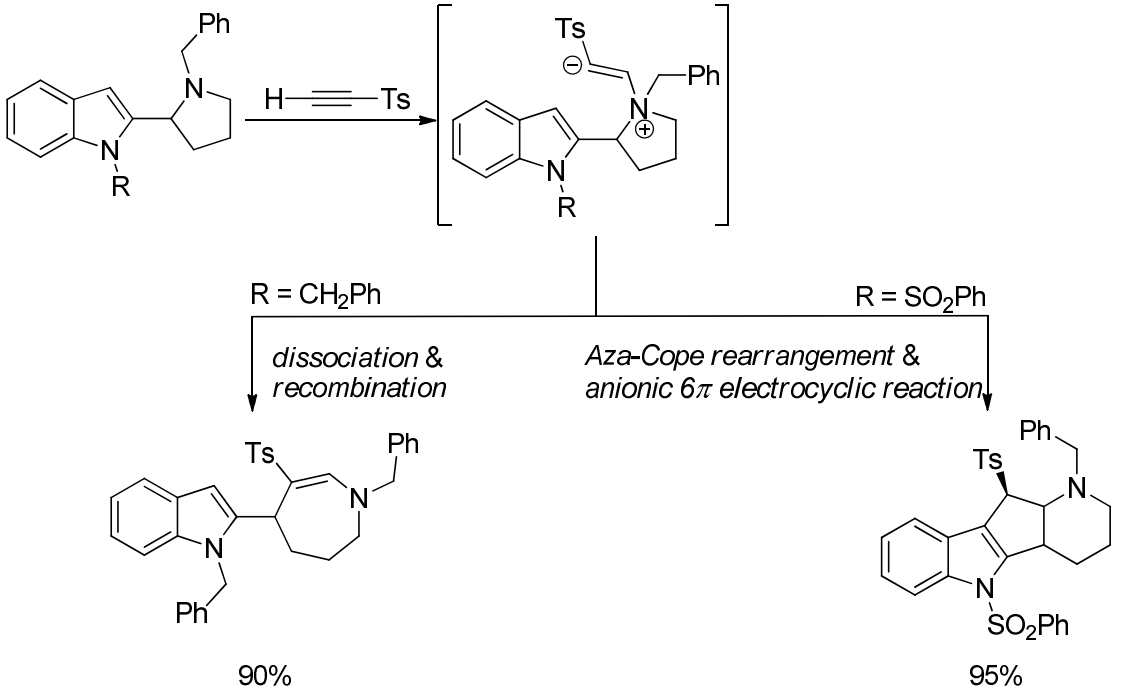
Back et al. has reported that *N*-2-tosylethenyl ammonium zwitterion rearranges to the ring-expansion product via 3-aza Cope rearrangement (Scheme 2-1).[1]

Scheme 2-1



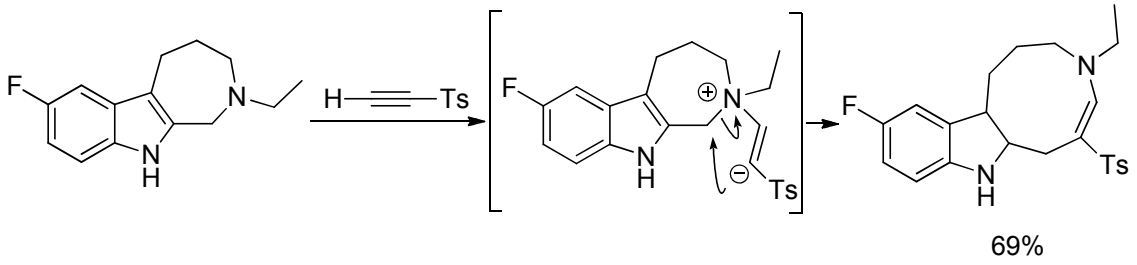
The reactivity of 2-Indolyl piperidine with ethynyl tolyl sulfone changes in dependence on the substitute at nitrogen atom of the indole (Scheme 2-2).[1] The ring-expansion via cleavage–recombination occurs using 2-(*N*-benzyl)indolyl piperidine, while the reaction of 2-(*N*-phenylsulfonyl)indolyl piperidine produces the product derived from the cyclic reaction via Aza–Cope rearrangement reaction and aromatization by 6π electron.

Scheme 2-2



Voskressensky et al. has discovered that the ring-expansion proceeds via cleavage–recombination derived from the occurrence of ammonium zwitterion and affords strategic elements for the construction of complex natural and unnatural products (Scheme 2-3).[2]

Scheme 2-3

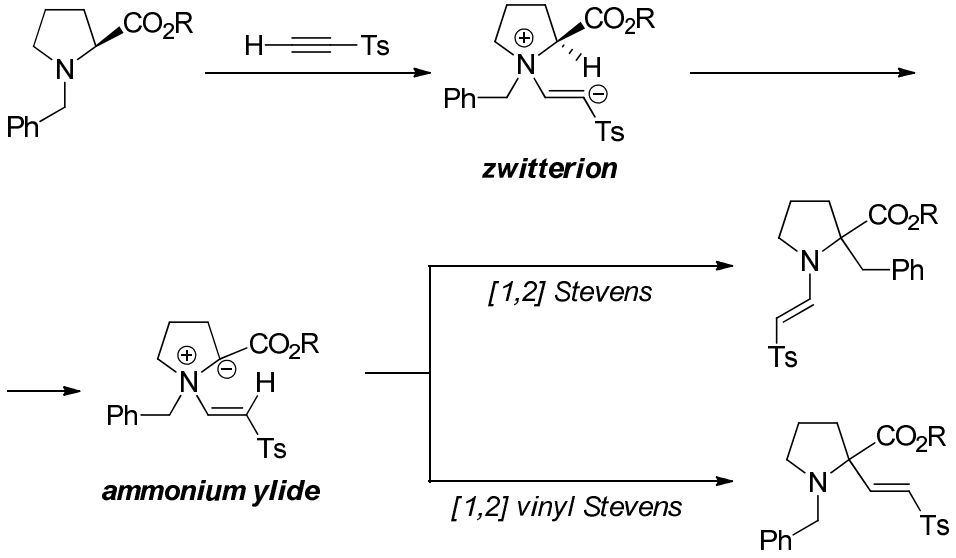


Encouraged by these methods, we attempted the asymmetric synthesis of various non-natural quaternary proline derivatives by the rearrangement reaction of ammonium ylides (Scheme 2-4).

First, the proline derivatives with chiral center upon α-carbon atom are transformed to *N*-chiral ammonium zwitterion in the reaction of ethynyl tolyl sulfone. The anion part of zwitterion abstracts more acidic proton at α-position of prolines to produce the *N*-chiral ammonium ylide. The chiral non-natural quaternary proline derivatives would be obtained, if [1,2] Stevens rearrangement reaction derived from benzylic group or [1,2] vinyl Stevens rearrangement reaction by the transfer of tosylethenyl group occurs.

The reaction of tertiary amines with ethynyl tolyl sulfone would be more simply method, because the ammonium ylides capable of rearrangement reaction occur subsequently.

Scheme 2-4

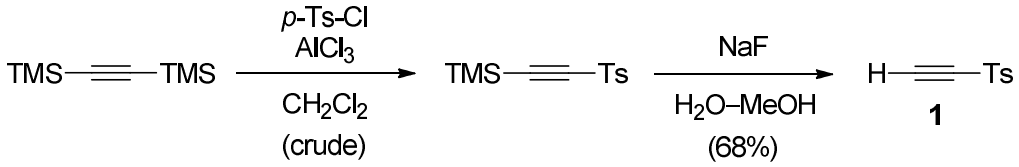


2-2 The assignment of the product structure and configuration at α-position

First, we prepared the substrates and reactants.

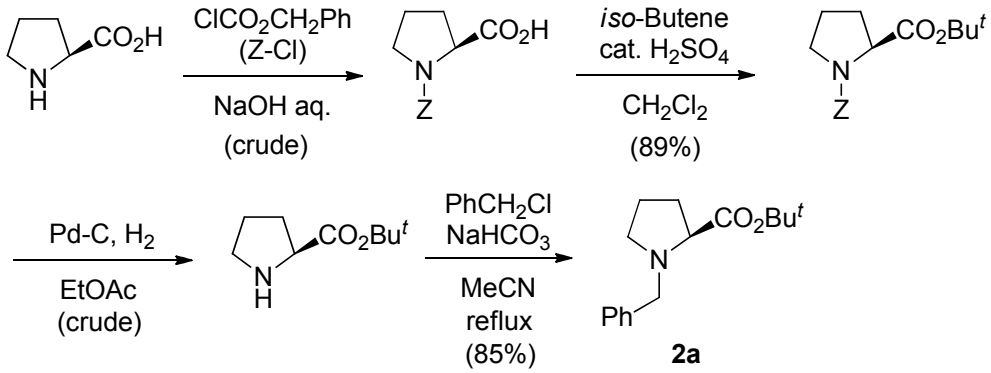
We synthesized ethynyl tolyl sulfone **1** derived from the tosylation of commercial bis(trimethylsilyl)acetylene and subsequently desilylation (Scheme 2-5).

Scheme 2-5



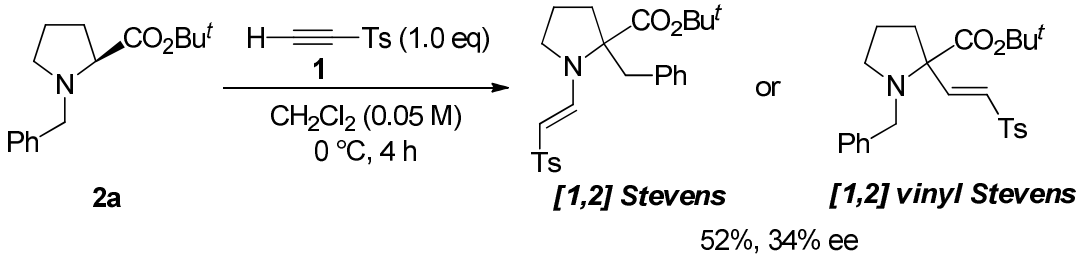
(*S*)-*N*-Benzylproline *tert*-butyl ester **2a** was synthesized (Scheme 2-6). Protection of commercial (*S*)-proline by benzyl chloroformate (Z-Cl) gave Z-proline, of which esterification with isobutene gas afforded Z-proline *tert*-butyl ester. Deprotection of Z group and subsequently benzylation by benzyl chrolide gave **2a**.

Scheme 2-6



On the basis of "2-1 Background", the results of the experiments would be shown (Scheme 2-7). We conducted the reaction of **2a** with 1.0 equiv of **1** in dichloromethane at 0 °C for 4 h. The unreacted **1** was quenched by the addition of methylamine to prevent undesirable reactions, and the α-tosylethenyl adduct **3a** was obtained in 52% yield with 34% ee.

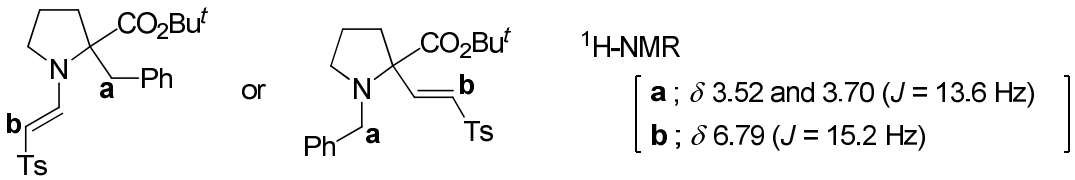
Scheme 2-7



The product structure was assigned by ^{1}H-NMR, while we did not decide which benzyl or tosylethenyl group transferred from the proton of benzyl position **a** and that of double bond site **b** (Scheme 2-8).

Scheme 2-8

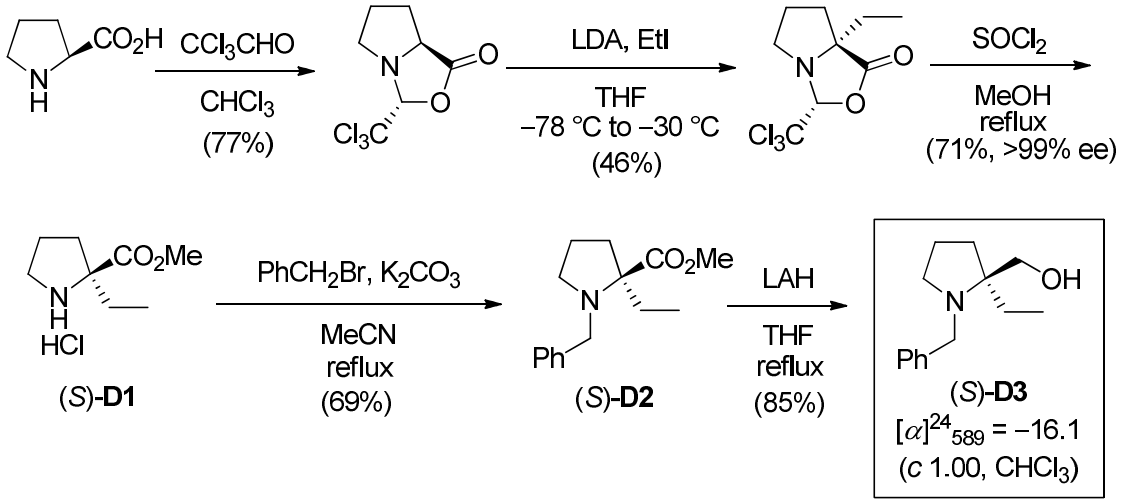
Product



Herein, assignments of the structure and configuration of **3a** were determined by a comparison of the authentic sample (Scheme 2-9). According to the previous report,[3] α-ethylproline derivative (*S*)-**D1** was synthesized. *N*-Benzylation by benzyl bromide

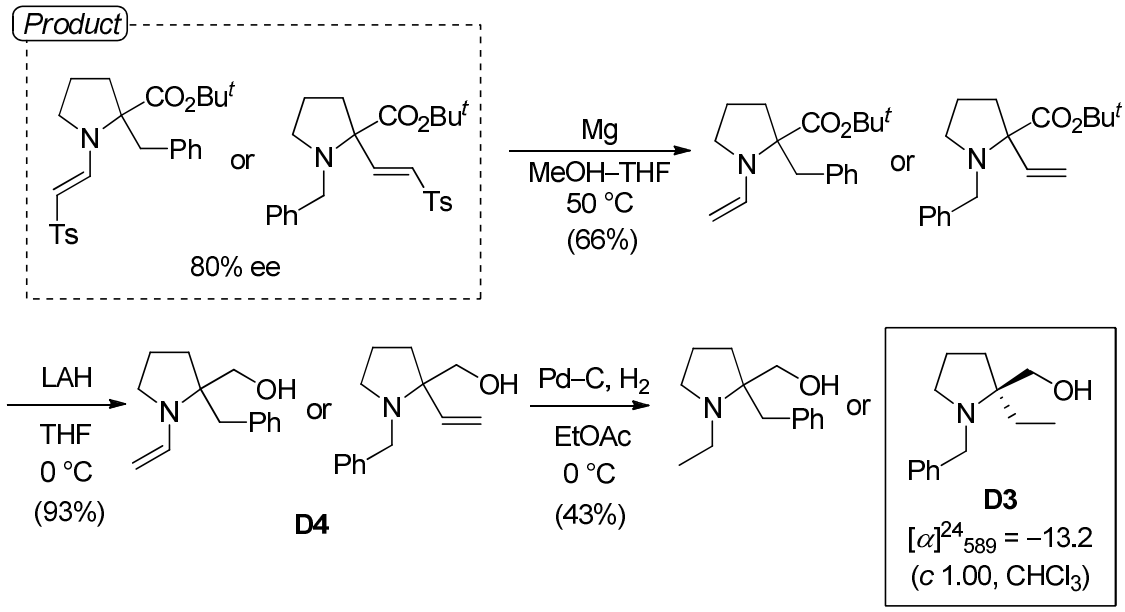
gave (*S*)-**D2**, of which reductive reaction with lithium aluminum hydride afforded *N*-benzyl amino alcohol (*S*)-**D3**. Then, the specific rotation of (*S*)-**D3** was recorded.

Scheme 2-9



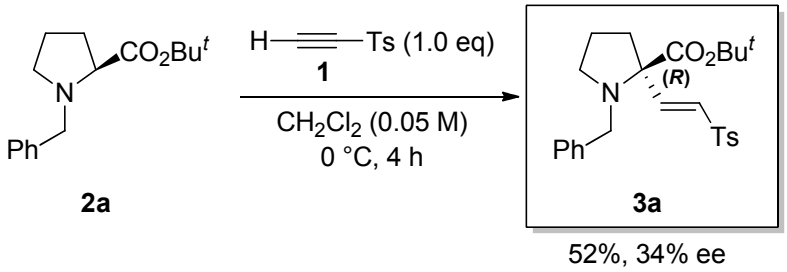
On the other hand, the detosylation of **3a** by the treatment of magnesium and subsequently reductive reaction with lithium aluminum hydride gave **D4** (Scheme 2-10). The hydrogenation of **D4** afforded the same *N*-benzyl amino alcohol (*S*)-**D3**.

Scheme 2-10



As a result, the (*R*)-configuration of **3a**, which was obtained from the proline derivative and ethynyl tolyl sulfone, was determined (Scheme 2-11).

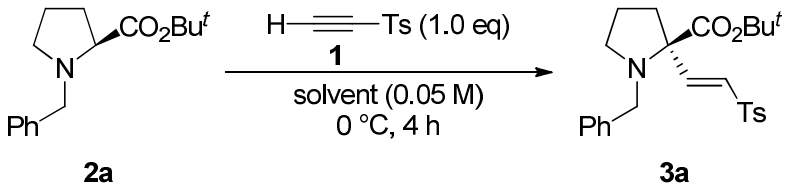
Scheme 2-11



2-3 The investigation of optimal conditions

First, different solvents were explored to discover those suitable for the α-tosylethenylation reaction (Table 2-1). The enantioselectivities of **3a** were increased in toluene, THF and ethyl acetate instead of dichloromethane, while the yields of **3a** were decreased (entries 1-4). Unreacted **2a** and **1** were detected on thin-layer chromatography (TLC). Next, the reaction in *N*,*N*-dimethylformamide (DMF) afforded **3a** in 34% yield with 80% ee (entry 5). However, we detected the disappeared **1** by the observation of TLC. On the results described above, we expected the improvement in yield of **3a** when **1** would be increased. Isopropanol as a protic solvent also was used (entry 6).

Table 2-1

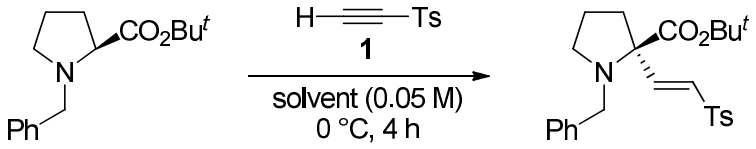


Entry	Solvent	Yield[a] (%)	ee[b] (%)
1	CH_2Cl_2	52	34
2	toluene	34	69
3	THF	17	69
4	EtOAc	22	73
5	DMF	34	80
6	*i*-PrOH	50	42

[a] Isolated yield. [b] Determined by HPLC analysis.

We investigated the dependence on the use of excess amount of **1** (Table 2-2). The yields of **3a** increased in the improvement with amount of **1** (1.0-2.0 equiv), while the enantioselectivity of **3a** decreased to 25% ee in 2.0 equiv of **1** (entries 1-3). When the reaction of **2a** was carried out with 2.0 equiv of **1** in DMF, adduct **3a** was obtained in 59% yield without affecting the enantioselectivity (entries 4-6). Thus, the conditions (amount of **1**: 2.0 equiv, solvent: DMF) was found to be optimal.

Table 2-2



2a **3a**

Entry	Solvent	Equiv of **1**	Yield[a] (%)	ee[b] (%)
1	CH_2Cl_2	1.0	52	34
2	CH_2Cl_2	1.5	85	27
3	CH_2Cl_2	2.0	89	25
4	DMF	1.0	34	80
5	DMF	1.5	44	79
6	DMF	2.0	59	80

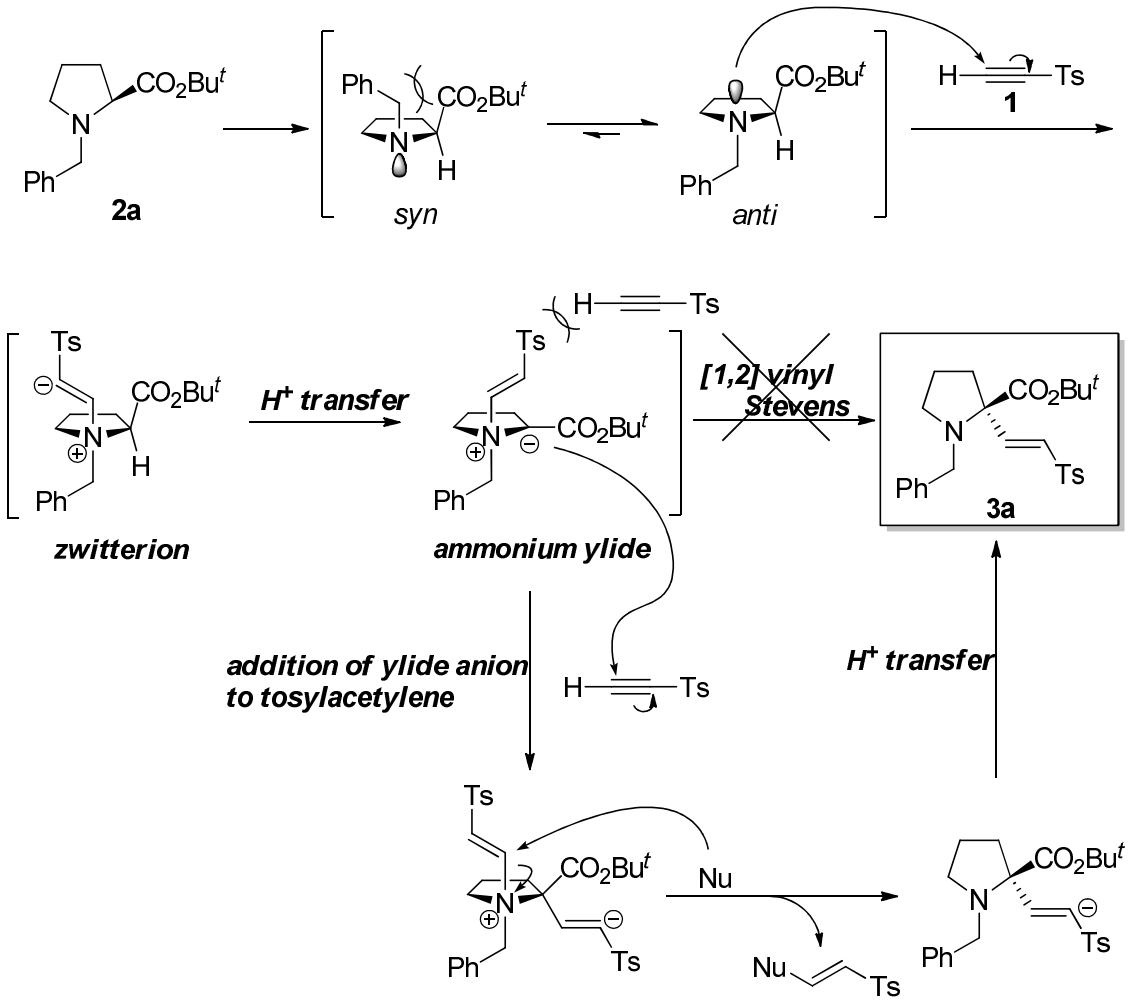
[a] Isolated yield. [b] Determined by HPLC analysis.

2-4 A proposed mechanism

We propose a plausible mechanism for the reaction of **1** and **2a** on the basis of the observations that (*R*)-configuration of **3a** was obtained and **2a** is favorite of the more stable conformation (Scheme 2-12).[4] The reaction of **2a**, which forms the anti-conformation by steric effects, with **1** affords *N*-tosylethenyl ammonium zwitterion diastereoselectively. The anion part of zwitterion abstracts more acidic proton at α-position of proline to produce *N*-chiral ammonium ylide. [1,2] Vinyl Stevens rearrangement reaction would not occur, because the reaction via the chiral transfer from nitrogen atom to carbon atom would produce (*S*)-configuration of **3a**. Thus, we thought that the anion part of ammonium ylide would attack to **1**. The addition of ammonium ylide to **1** would give zwitterion diastereoselectively because of the steric

repulsion of the *N*-2-tosylethenyl substituent. Finally, the *N*-2-tosylethenyl substituent is eliminated by the reaction with nucleophiles to form (*R*)-configuration of **3a**.

Scheme 2-12



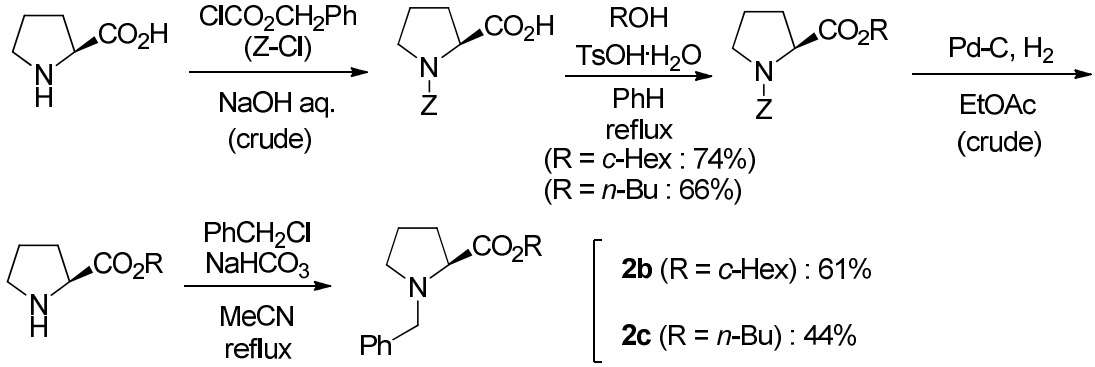
2-5 The effects of the ester site and the substituent upon nitrogen atom

On the basis of a proposed mechanism, it would be important factor for the enantioselectivity of the attained product that the quaternarization would occur diastereoselectively and the anion part of ammonium ylide would attack to **1** diastereoselectively. We explored the effects of the ester site and the substituent upon nitrogen atom to improve the enantioselectivity of products.

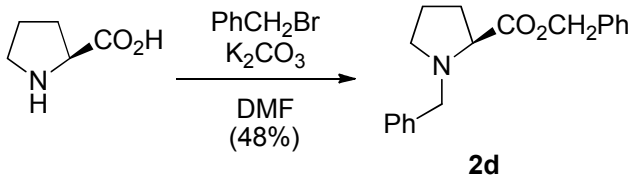
(*S*)-*N*-Benzylproline cyclohexyl ester **2b** was synthesized (Scheme 2-13). Protection

of commercial (*S*)-proline by benzyl chloroformate (Z-Cl) gave Z-proline, of which esterification with cyclohexanol afforded Z-proline cyclohexyl ester. Deprotection of Z group and subsequently benzylation by benzyl chrolide gave **2b**. (*S*)-*N*-Benzylproline *n*-butyl ester **2c** was synthesized by the same procedure with **2b** using *n*-butanol instead of cyclohexanol. (*S*)-*N*-Benzylproline benzyl ester **2d** was synthesized from (*S*)-proline and benzyl bromide (Scheme 2-14).

Scheme 2-13



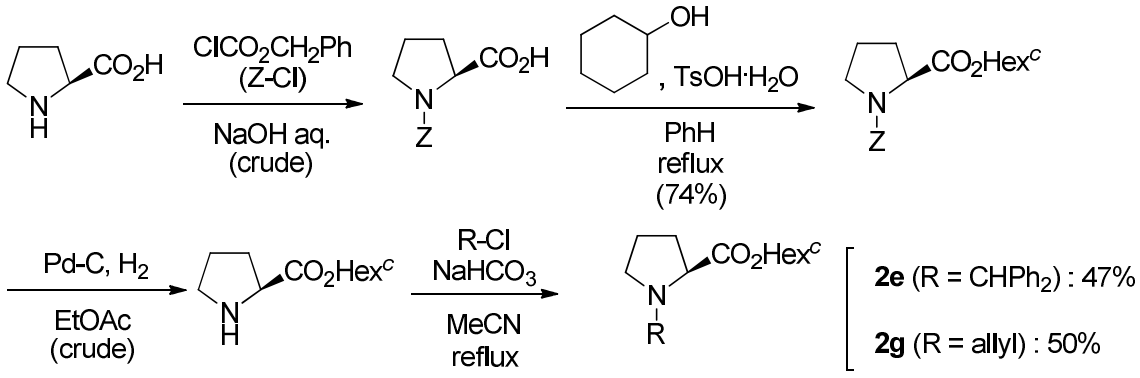
Scheme 2-14



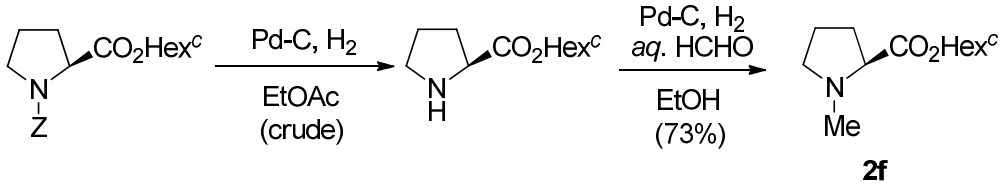
2d

(*S*)-*N*-(Diphenylmethyl)proline cyclohexyl ester **2e** and (*S*)-*N*-allylproline cyclohexyl ester **2g** was synthesized by the same procedure with **2b** using benzhydryl chloride and allyl chloride instead of benzyl chloride (Scheme 2-15). (*S*)-*N*-Methylproline cyclohexyl ester **2f** was synthesized (Scheme 2-16). Deprotection of Z group and subsequently methylation by formalin gave **2f**.

Scheme 2-15



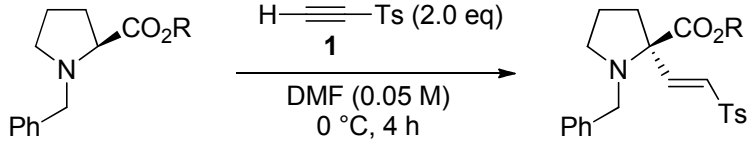
Scheme 2-16



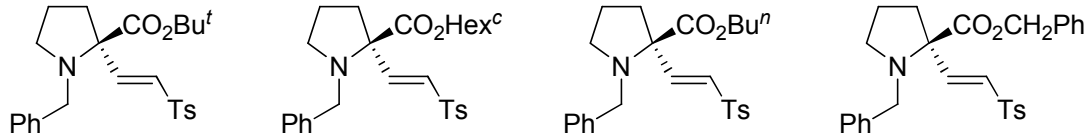
2f

When the reaction of (*S*)-*N*-benzylproline cyclohexyl ester **2b** was carried out under the same conditions, the enantioselectivity was slightly improved (Scheme 2-17). Reactions of primary esters, such as *n*-butyl **2c** and benzyl **2d**, gave **3c** and **3d** excellent enantioselectively, while the yields were lower.

Scheme 2-17



2a-d **3a-d**



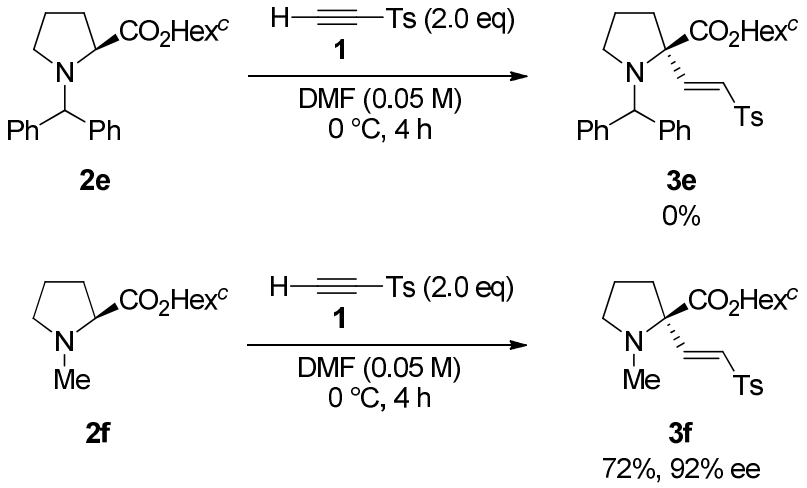
3a	**3b**	**3c**	**3d**
62%, 79% ee	45%, 89% ee	39%, 96% ee	39%, 99% ee

The enantioselectivities of **3** improved with less steric hindrance of the ester sites. We thought that the steric repulsion between the ester site and **1** decrease in the quaternarization (Scheme 2-12) to improve the enantioselectivities of **3**. On the other hand, the yields of **3** decreased with a series of the ester sites. We reasoned that the side reaction of secondary and primary esters which are intolerable of the nucleophiles would occur, because the anion part of zwitterion and ylide would act as nucleophiles.

Next, we examined the effects of the substituent upon nitrogen atom (Scheme 2-18). Sterically hindered *N*-diphenylmethyl derivative **2e** did not react at all. The initial formation of the zwitterion might have been inhibited in this case. In contrast, the reaction of less sterically hindered *N*-methyl derivative **2f** afforded **3f** in moderate yield with good enantioselectivity. While we anticipated that the substituents upon nitrogen atom infect the diastereoselectivites in the addition of the anion part of ylide to **1**, the

effect of that to diastereoselectivities of **3** did not appear because of more bulky tosyl ethenyl group than methyl and benzyl groups.

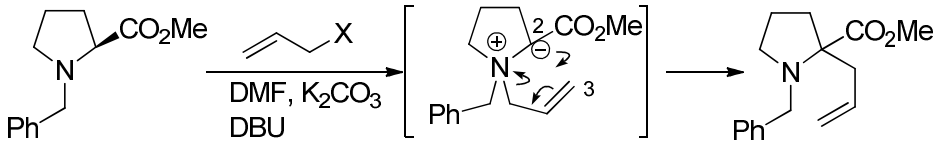
Scheme 2-18



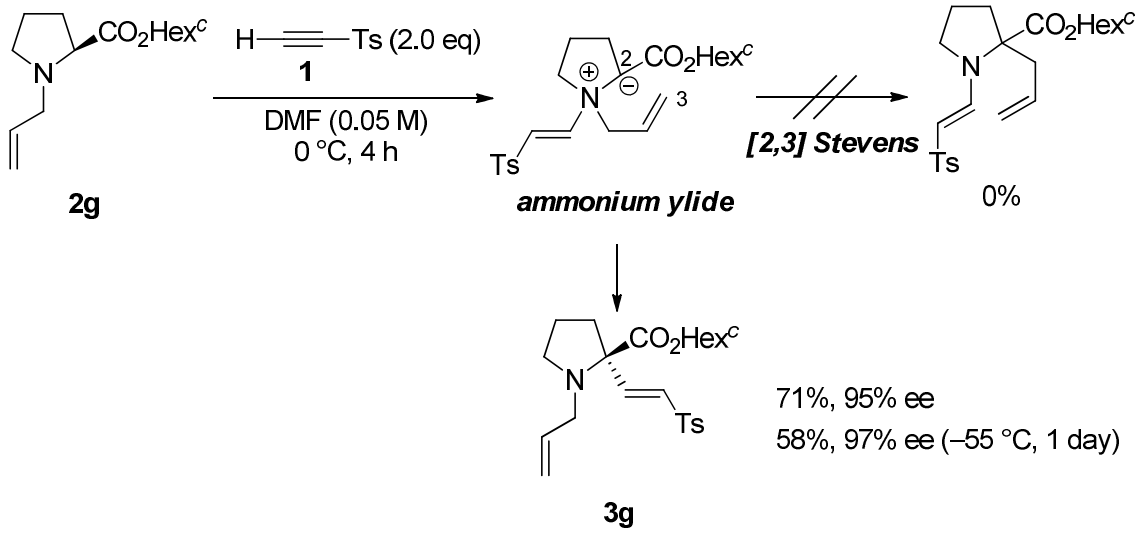
On the basis of these results, we understood that the ester site infected the enantioselectivities of **3** and the substituents upon nitrogen atom implicated the improvement of yields.

When allyl group is introduced upon nitrogen atom, [2,3] Stevens rearrangement reaction can proceed via the generated ammonium ylide (Scheme 2-19).[5] In order to elucidate the mechanism for the reaction, we conducted the reaction of *N*-allyl derivative **2g** (Scheme 2-20). The reaction of **2g** and **1** gave α-tosylethenylated product **3g**, while [2,3] Stevens rearrangement product was not obtained at all. We also examined that [2,3] Stevens rearrangement reaction would occur at lower reaction temperature (−55 °C), but the reaction gave the α-tosylethenylated product **3g** only. Because concertedly [2,3] Stevens rearrangement reaction would be restricted, we reasoned that the anion part of ammonium ylide would attack to **1** too fast.

Scheme 2-19



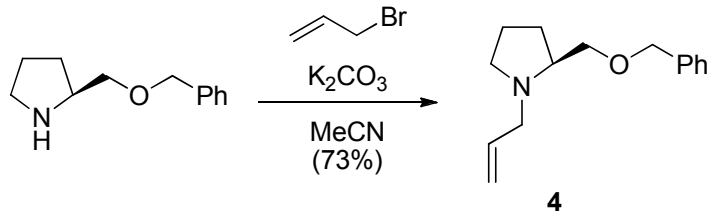
Scheme 2-20



Next, we conducted the reaction of (*S*)-1-allyl-2-(benzyloxymethyl)pyrrolidine **4**, of which the proton at α-position is no more acidic in occurrence of ammonium zwitterion, with **1** to explore the possibility of [3,3] sigmatropic rearrangement reaction between ammonium zwitterion and allyl group.

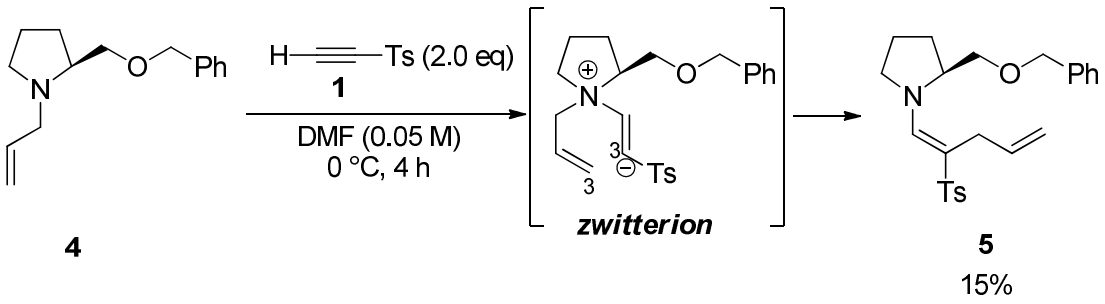
The substrate **4** was synthesized from (*S*)-2-(benzyloxymethyl)pyrrolidine and allyl bromide (Scheme 2-21).

Scheme 2-21



The reaction of **4** with **1** gave [3,3] sigmatropic rearrangement product in low yield (Scheme 2-22). On the basis of this result, we reasoned that [3,3] sigmatropic rearrangement reaction of **2g** hardly occurs, and the transform of ammonium zwitterion to ammonium ylide proceed smoothly.

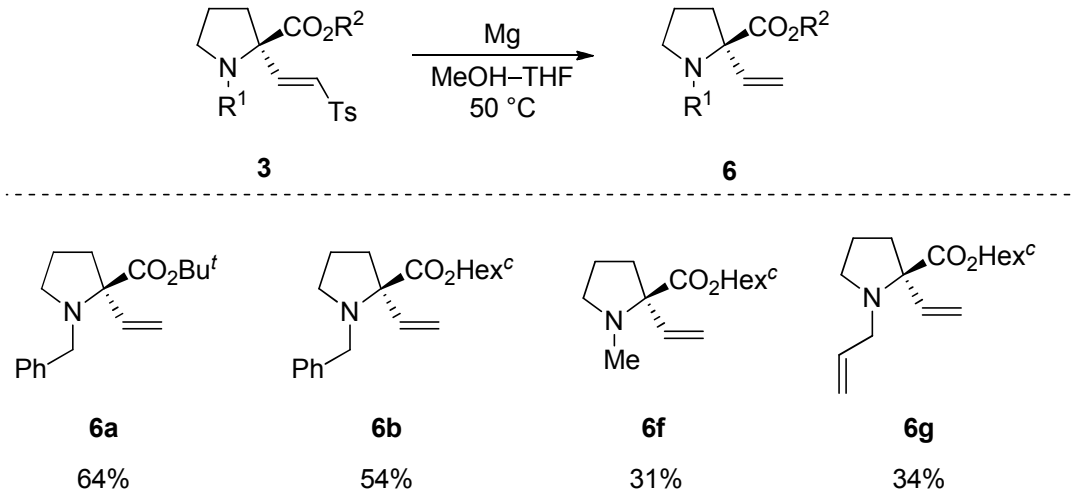
Scheme 2-22



2-6 The transform to vinyl group via the reductive desulfonylation

In order to induce useful amino acid derivatives, it is necessary to transform tosylethenyl group of the product obtained by the α-tosylethenylated reaction with **1**. The reductive desulfonylation reaction was attempted by treatment with magnesium (Scheme 2-23). We conducted that a solution of **3** in THF was added to a suspension of magnesium powder in dry methanol at 50 °C under an argon atmosphere to produce α-vinylated product **6**.

Scheme 2-23

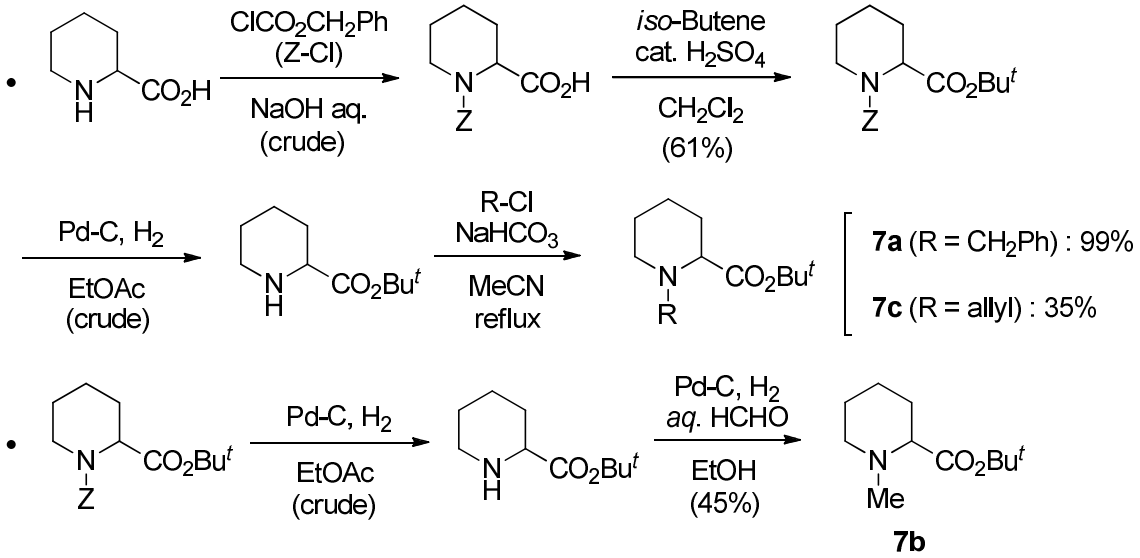


2-7 The reaction of the other cyclic amino acid derivatives and ethynyl tolyl sulfone

We explored the reaction of pipecolinic acid derivatives which have six-membered ring, because the reaction of five-membered ring substrates proceeded smoothly.

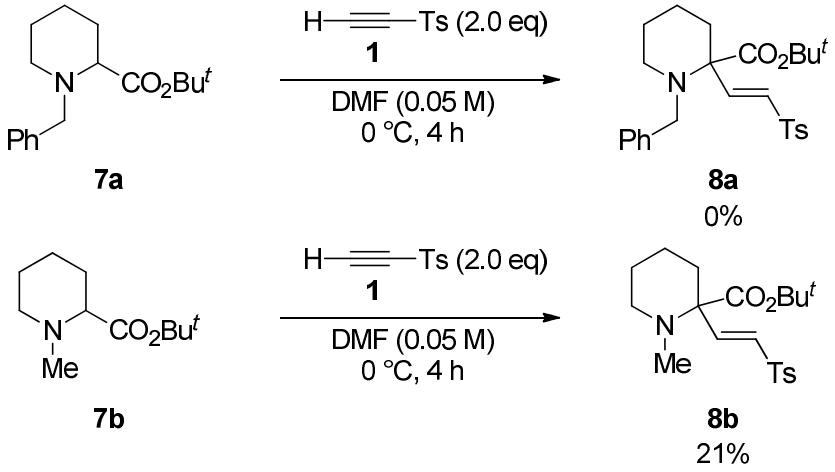
(*rac*)-*N*-Benzylpipecolinic acid *tert*-butyl ester **7a** was synthesized by the same procedure with **2a** using (*rac*)-pipecolinic acid instead of (*S*)-proline (Scheme 2-24). (*rac*)-*N*-Methylpipecolinic acid *tert*-butyl ester **7b** and (*rac*)-*N*-allylpipecolinic acid *tert*-butyl ester **7c** was synthesized by the same procedure.

Scheme 2-24



While we conducted the reaction of **7a**, α-tosylethenylated product **8a** was not obtained at all (Scheme 2-25). It was reasoned that quaternarization of **7a** is restricted by steric repulsion upon nitrogen atom. The reaction of less steric hindered **7b** with **1** gave α-tosylethenylated product **8b** in low yield. We understood that the quaternarization of substrates with the six-membered ring hardly occurred.

Scheme 2-25

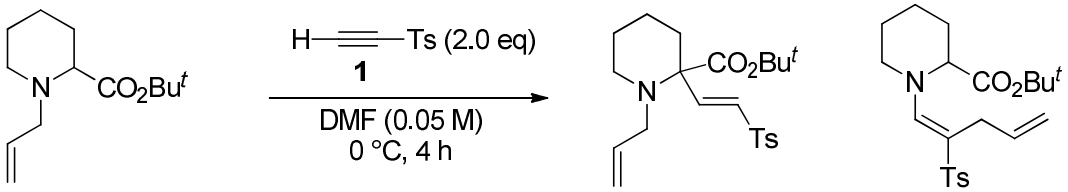


7a → **8a** 0%

7b → **8b** 21%

Next, we conducted the reaction of *N*-allyl substrate **7c** with **1** to obtain [3,3] sigmatropic rearrangement product **9** (Scheme 2-26). In the reaction of six-membered ring pipecolinic acid derivatives, we understood that not only [2,3] Stevens rearrangement reaction was restricted, but also the ammonium ylide hardly occurred.

Scheme 2-26

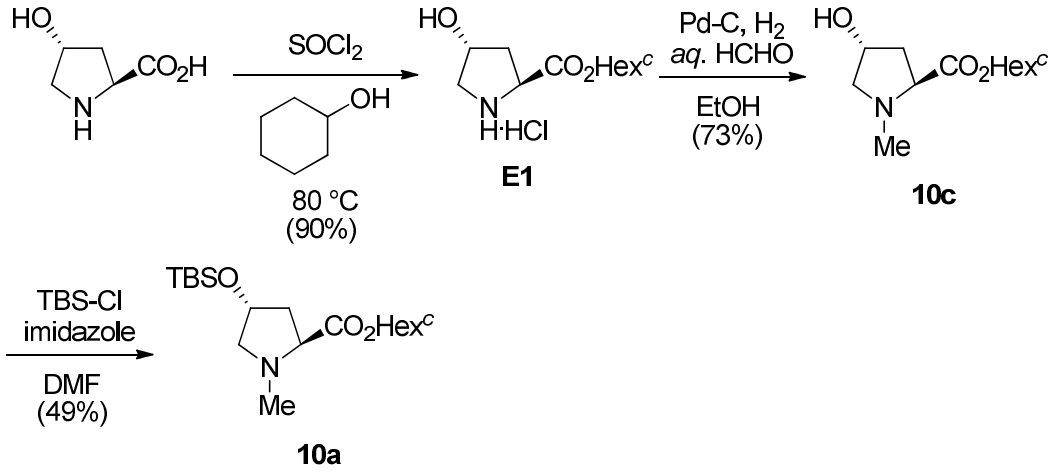


7c → **8c** 0%; **9** 50%

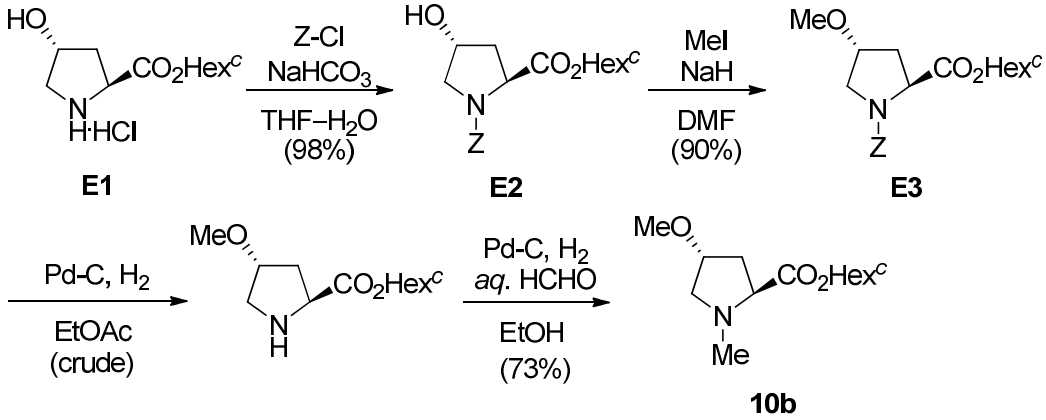
Further, we explored the reaction of proline derivatives with the substituent on the cyclic skeleton.

(2*S,*4*R*)-4-(*tert*-Butyldimethylsilyloxy)-*N*-methylproline cyclohexyl ester **10a** was synthesized (Scheme 2-27). A solution of commercial (2*S,*4*R*)-4-hydroxyproline and thionyl chloride in cyclohexanol was heated to afford (2*S,*4*R*)-4-hydroxyproline cyclohexyl ester **E1**, of which *N*-methylation produce (2*S,*4*R*)-4-hydroxy-*N*-methylproline cyclohexyl ester **10c**. The reaction of **10c** with *tert*-butyldimethylsilyl chloride (TBS-Cl) gave **10a**. (2*S,*4*R*)-4-methoxy-*N*-methylproline cyclohexyl ester **10b** was synthesized (Scheme 2-28). Protection of **E1** by benzyl chloroformate (Z-Cl) gave **E2**, of which methoxylation with iodomethane afforded **E3**. Deprotection of Z group and subsequently *N*-methylation by formalin gave **10b**.

Scheme 2-27

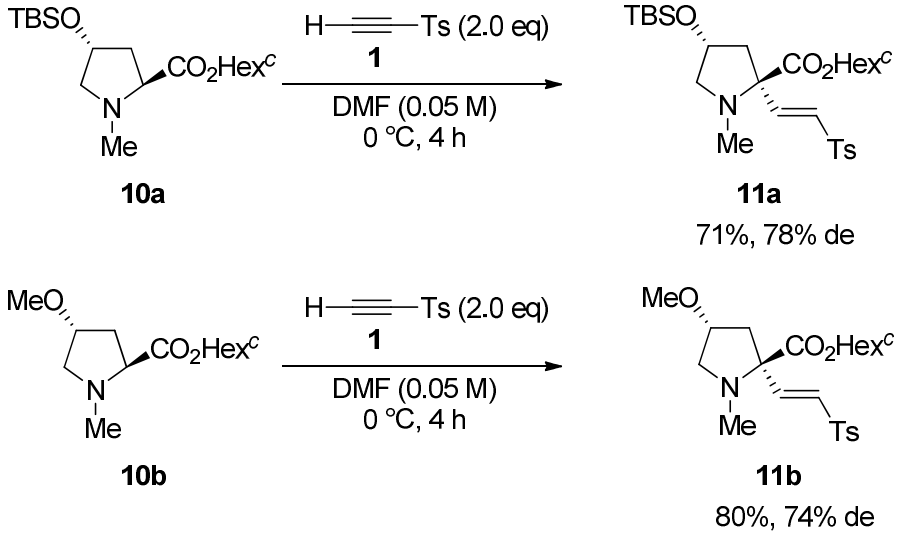


Scheme 2-28



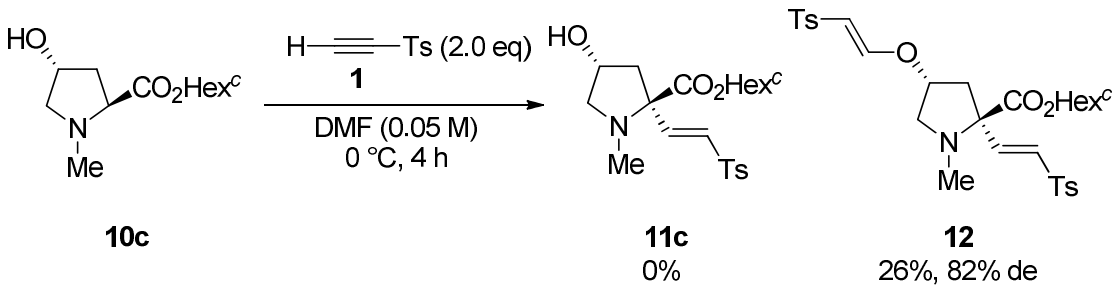
We conducted the reaction of **10a** protected by *tert*-butyldimethylsilyl group or **10b** protected by methyl group to obtain α-tosylethenylated product **11a** in 78% de or **11b** in 74% de, respectively (Scheme 2-29). Because the stereoselectivity decreased compared to the result of the reaction with **3f**, we reasoned that the diastereoselectivity in the nucleophilic addition of ammonium ylide to **1** (Scheme 2-12) would was affected. It was thought that the 4-substituent, which is located on the same face as *N*-methyl group, would inhibit the diastereoselective addition due to steric repulsion.

Scheme 2-29



The reaction of the 4-hydroxy derivative **10c** did not give the expected product **11c**, while bistosylethenyl product with α-position and *O*-substituent **12** was obtained (Scheme 2-30).

Scheme 2-30



2-8 Summary

We demonstrated that *tert*-amines derived from amino acids reacted with ethynyl tolyl sulfone to produce steric hindered quaternary ammonium, and the enantioselective α-tosylethenylation proceeded by subsequent transformation reaction. This reaction is a simply method for the asymmetric synthesis of the non-natural proline derivatives because of in situ-generated quaternary ammonium ylide.

Experimental Section

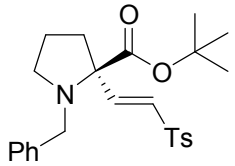
General

Infrared spectra were recorded on a Perkin Elmer Spectrum GX FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were measured on a Varian 400 MHz (^{1}H: 400 MHz, ^{13}C: 100 MHz) spectrometer. Splitting patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. Specific rotations were recorded on a JASCO Polarimeter P–1010. High-resolution mass spectra were measured on a Thermo Fisher Scientific LC/FT-MS spectrometer. Reactions were conducted in appropriate round-bottomed flask with a magnetic stirring bar under an argon atmosphere. *N*,*N*-Dimethylformamide (DMF) was dried over molecular sieves 4Å. For thin layer chromatography (TLC) analysis throughout this work, Merck TLC plates (silica gel 60 F_{254}) were used. The products were purified by preparative column chromatography on silica gel (silica gel 60N, spherical neutral, KANTO Chemical Co., Inc., Japan).

Representative procedure for the asymmetric α-2-tosylvinylation of *N*-substituted proline ester 2a

A solution of tosylacetylene (**1**) (74.7 mg, 0.414 mmol) in DMF (1.3 mL) was added to a solution of **2a** (53.8 mg, 0.206 mmol) in DMF (2.7 mL) at 0 °C under an argon atmosphere. After stirring for 4 h at the same temperature, the excess amount of **1** was quenched by addition of 40% methylamine solution in methanol (46 μL, 0.45 mmol). The resulting mixture was stirred for 15 min at room temperature, diluted with water, and extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate, and concentrated. Purification of the residue by chromatography on silica gel (hexane/ethyl acetate = 20/1 to 10/1 as eluent) gave **3a** (55.0 mg, 60% yield) as a colorless oil.

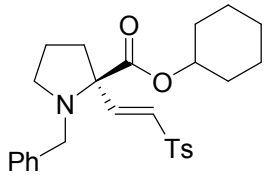
(*E*)-*tert*-Butyl 1-benzyl-2-(2'-tosylvinyl)pyrrolidine-2-carboxylate (3a)



Colorless oil; 80% ee [determined by HPLC analysis: Daicel Chiralpak AD–H column, *n*-hexane/isopropanol = 98/2 as eluent, flow rate = 0.50 mL/min, t_R = 38.5 min for (*S*)-**3a** and 47.3 min for (*R*)-**3a**]; $[\alpha]^{28}_{589}$ +14.5 (*c* 1.00 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (2H, d, *J* = 8.4 Hz, ArH), 7.32-7.13 (8H, m, ArH and TsCH=C*H*), 6.79 (1H, d, *J* = 15.2 Hz, TsC*H*=CH), 3.70 (1H, d, *J* = 13.6 Hz, CH_2Ph), 3.52 (1H, d, *J* = 13.6 Hz, CH_2Ph), 2.98 (1H, ddd, *J* = 8.4, 8.4, 3.2 Hz, pyrrolidine-NCH_2), 2.79-2.70 (1H, m, pyrrolidine-NCH_2), 2.42 (3H, s, ArCH_3), 2.39-2.30 (1H, m, pyrrolidine-CH_2), 1.95-1.71 (3H, m, pyrrolidine-CH_2), 1.51 (9H, s,

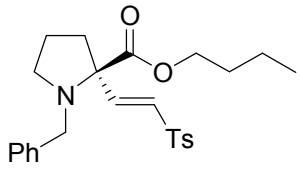
t-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 147.1, 144.1, 139.1, 137.6, 130.2, 129.8, 128.3, 128.1, 127.5, 126.9, 82.4, 72.2, 54.0, 51.4, 38.3, 28.2, 22.2, 21.5; IR (film) 3061, 2978, 2873, 2838, 1720, 1627, 1597, 1494, 1454, 1394, 1369, 1318, 1266, 1148, 1107, 1086, 1028, 973, 842, 812, 738, 703 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{25}H_{32}NO_4S$: 442.2047. Found: 442.2041.

(*E*)-Cyclohexyl 1-benzyl-2-(2'-tosylvinyl)pyrrolidine-2-carboxylate (3b)



Colorless oil; 89% ee [determined by HPLC analysis: Daicel Chiralpak AD–H column, *n*-hexane/isopropanol = 90/10 as eluent, flow rate = 0.50 mL/min, t_R = 18.9 min for (*S*)-**3b** and 25.1 min for (*R*)-**3b**]; $[\alpha]^{23}_{589}$ +18.2 (*c* 1.00 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (2H, d, *J* = 8.0 Hz, ArH), 7.34-7.13 (8H, m, ArH and TsCH=C*H*), 6.81 (1H, d, *J* = 15.2 Hz, TsC*H*=CH), 4.91 (1H, tt, *J* = 8.4, 3.8 Hz, OCH), 3.69 (1H, d, *J* = 13.4 Hz, CH_2Ph), 3.49 (1H, d, *J* = 13.4 Hz, CH_2Ph), 3.00 (1H, ddd, *J* = 8.4, 8.4, 3.2 Hz, pyrrolidine-NCH_2), 2.76 (1H, ddd, *J* = 8.4, 8.0, 8.0 Hz, pyrrolidine-NCH_2), 2.45-2.32 (1H, m, pyrrolidine-CH_2), 2.42 (3H, s, ArCH_3), 1.97-1.64 (7H, m, pyrrolidine-CH_2 and *c*-Hex), 1.58-1.24 (6H, m, *c*-Hex); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 146.8, 144.2, 139.0, 137.6, 130.6, 129.8, 128.3, 128.1, 127.6, 127.0, 73.7, 71.8, 54.0, 51.4, 38.3, 31.6, 31.5, 25.2, 23.42, 23.39, 22.2, 21.6; IR (film) 3061, 3029, 2937, 2858, 1721, 1632, 1597, 1494, 1452, 1368, 1320, 1253, 1192, 1145, 1086, 1031, 1013, 973, 812, 739, 700 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{27}H_{34}NO_4S$: 468.2203. Found: 468.2197.

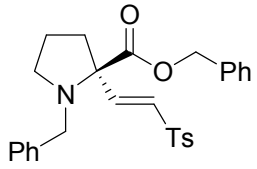
(*R*,*E*)-*n*-Butyl 1-benzyl-2-(2'-tosylvinyl)pyrrolidine-2-carboxylate (3c)



Colorless oil; 96% ee [determined by HPLC analysis: Daicel Chiralpak AD–H column, *n*-hexane/isopropanol = 92/8 as eluent, flow rate = 0.50 mL/min, t_R = 23.8 min for (*S*)-**3c** and 29.3 min for (*R*)-**3c**]; $[\alpha]^{25}_{589}$ +19.6 (*c* 1.00 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (2H, ddd, *J* = 8.0, 2.0, 2.0 Hz, ArH), 7.34-7.19 (6H, m, ArH and TsCH=C*H*), 7.15 (2H, dd, *J* = 7.8, 1.4 Hz, ArH), 6.80 (1H, d, *J* = 15.2 Hz, TsC*H*=CH), 4.19 (2H, t, *J* = 6.6 Hz, CH_2CH$_2$CH$_2$CH$_3$), 3.67 (1H, d, *J* = 13.6 Hz, CH_2Ph), 3.47 (1H, d, *J* = 13.6 Hz, CH_2Ph), 3.00 (1H, ddd, *J* = 8.6, 8.0, 3.2 Hz, pyrrolidine-NCH_2), 2.75 (1H, ddd, *J* = 8.6, 7.6, 7.6 Hz, pyrrolidine-NCH_2), 2.43-2.34 (1H, m, pyrrolidine-CH_2), 2.42 (3H, s, ArCH_3), 1.97-1.74 (3H, m, pyrrolidine-CH_2), 1.70-1.63 (2H, m, CH$_2$CH_2CH$_2$CH$_3$), 1.45-1.34 (2H, m,

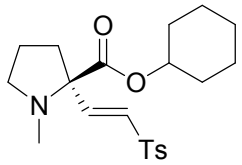
$CH_2CH_2CH_2CH_3$), 0.95 (3H, t, J = 7.6 Hz, $CH_2CH_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 146.5, 144.2, 139.0, 137.5, 130.6, 129.9, 128.3, 128.1, 127.6, 127.0, 71.9, 65.1, 54.0, 51.4, 38.3, 30.6, 22.2, 21.6, 19.2, 13.6; IR (film) 3061, 2961, 2873, 1726, 1629, 1597, 1494, 1455, 1370, 1319, 1266, 1188, 1146, 1106, 1086, 1020, 973, 812, 737, 702 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{25}H_{32}NO_4S$: 442.2047. Found: 442.2038.

(*R*,*E*)-Benzyl 1-benzyl-2-(2'-tosylvinyl)pyrrolidine-2-carboxylate (3d)



Colorless oil; 99% ee [determined by HPLC analysis: Daicel Chiralpak AD–H column, *n*-hexane/isopropanol = 85/15 as eluent, flow rate = 0.50 mL/min, t_R = 24.6 min for (*S*)-**3d** and 32.5 min for (*R*)-**3d**]; $[\alpha]^{26}_{589}$ +15.8 (*c* 1.00 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (2H, ddd, J = 8.0, 1.8, 1.8 Hz, ArH), 7.41-7.32 (5H, m, ArH), 7.31 (1H, d, J = 15.0 Hz, TsCH=C*H*), 7.30-7.18 (5H, m, ArH), 7.10 (2H, dd, J = 7.6, 1.6 Hz, ArH), 6.77 (1H, d, J = 15.0 Hz, TsC*H*=CH), 5.24 (1H, d, J = 12.2 Hz, OCH_2Ph), 5.20 (1H, d, J = 12.2 Hz, OCH_2Ph), 3.64 (1H, d, J = 13.4 Hz, NCH_2Ph), 3.41 (1H, d, J = 13.4 Hz, NCH_2Ph), 2.97 (1H, ddd, J = 8.6, 8.0, 3.2 Hz, pyrrolidine-NCH_2), 2.72 (1H, ddd, J = 8.6, 7.8, 7.8 Hz, pyrrolidine-NCH_2), 2.43-2.34 (1H, m, pyrrolidine-CH_2), 2.41 (3H, s, $ArCH_3$), 1.97-1.72 (3H, m, pyrrolidine-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 146.2, 144.2, 138.9, 137.4, 135.3, 130.8, 129.9, 128.6, 128.5, 128.4, 128.3, 128.1, 127.6, 127.0, 71.8, 66.9, 53.9, 51.3, 38.2, 22.2, 21.6; IR (film) 3062, 3033, 2956, 2839, 1729, 1634, 1597, 1495, 1454, 1371, 1318, 1266, 1145, 1086, 1027, 975, 813, 737, 700 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{28}H_{30}NO_4S$: $[MH^+]$ 476.1890. Found: 476.1887.

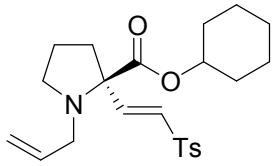
(*R*,*E*)-Cyclohexyl 1-methyl-2-(2'-tosylvinyl)pyrrolidine-2-carboxylate (3f)



Colorless oil; 93% ee [determined by HPLC analysis: Daicel Chiralpak AD–H column, *n*-hexane/ethanol = 92/8 as eluent, flow rate = 0.50 mL/min, t_R = 22.6 min for (*R*)-**3f** and 29.1 min for (*S*)-**3f**]; $[\alpha]^{22}_{589}$ +84.5 (*c* 1.00 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (2H, d, J = 8.0 Hz, ArH), 7.33 (2H, d, J = 8.0 Hz, ArH), 7.21 (1H, d, J = 15.2 Hz, TsCH=C*H*), 6.64 (1H, d, J = 15.2 Hz, TsC*H*=CH), 4.85 (1H, tt, J = 8.4, 4.0 Hz, OCH), 3.08-3.02 (1H, m, NCH_2), 2.88 (1H, ddd, J = 8.4, 7.8, 7.8 Hz, NCH_2), 2.43 (3H, s, $ArCH_3$), 2.37-2.27 (1H, m, pyrrolidine-CH_2), 2.25 (3H, s, NCH_3), 1.93-1.61 (7H, m, pyrrolidine-CH_2 and *c*-Hex), 1.57-1.24 (6H, m, *c*-Hex);

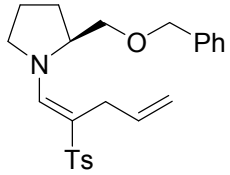
^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 146.4, 144.1, 137.6, 130.1, 129.8, 127.6, 73.4, 71.4, 54.6, 38.1, 35.6, 31.6, 31.5, 25.2, 23.4, 23.3, 22.2, 21.5; IR (film) 3059, 2938, 2859, 1721, 1633, 1597, 1450, 1319, 1256, 1228, 1191, 1145, 1087, 1035, 1012, 970, 951, 909, 788, 707 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{21}H_{30}NO_4S$: 392.1890. Found: 392.1876.

(*R*,*E*)-Cyclohexyl 1-allyl-2-(2'-tosylvinyl)pyrrolidine-2-carboxylate (3g)



Colorless oil; 95% ee [determined by HPLC analysis: Daicel Chiralpak AD–H column, *n*-hexane/isopropanol = 94/6 as eluent, flow rate = 0.50 mL/min, t_R = 22.3 min for (*S*)-**3g** and 27.1 min for (*R*)-**3g**]; $[\alpha]^{24}_{589}$ +72.6 (*c* 1.00 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (2H, d, *J* = 7.8 Hz, ArH), 7.32 (2H, d, *J* = 7.8 Hz, ArH), 7.24 (1H, d, *J* = 15.0 Hz, TsCH=C*H*), 6.67 (1H, d, *J* = 15.0 Hz, TsC*H*=CH), 5.71 (1H, dddd, *J* = 17.0, 10.2, 6.8, 5.2 Hz, CH_2CH=CH_2), 5.09 (1H, dd, *J* = 17.0, 1.2 Hz, CH_2CH=CH_2), 5.01 (1H, dd, *J* = 10.2, 1.2 Hz, CH_2CH=CH_2), 4.85 (1H, tt, *J* = 8.4, 4.0 Hz, OCH), 3.20-3.09 (2H, m, CH_2CH=CH_2 and pyrrolidine-NCH_2), 2.99 (1H, dd, *J* = 14.2, 6.8 Hz, CH_2CH=CH_2), 2.76 (1H, ddd, *J* = 8.8, 7.6, 7.6 Hz, pyrrolidine-NCH_2), 2.43 (3H, s, $ArCH_3$), 2.36-2.27 (1H, m, pyrrolidine-CH_2), 1.95-1.61 (7H, m, pyrrolidine-CH_2 and *c*-Hex), 1.57-1.23 (6H, m, *c*-Hex); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 146.9, 144.1, 137.6, 135.9, 130.0, 129.8, 127.5, 116.2, 73.6, 71.7, 52.7, 51.7, 38.3, 31.54, 31.46, 25.2, 23.40, 23.36, 22.2, 21.5; IR (film) 3058, 2939, 2860, 1720, 1642, 1597, 1450, 1317, 1266, 1192, 1145, 1086, 1036, 1012, 973, 925, 837, 812, 738, 705 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{23}H_{32}NO_4S$: 418.2047. Found: 418.2036.

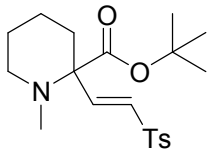
(*R*,*E*)-2-Benzyloxymethyl-1-(2'-tosylpent-1',4'-dien-1'-yl)pyrrolidine (5)



Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (1H, s, NCH=C), 7.66 (2H, d, *J* = 7.8 Hz, ArH), 7.40-7.26 (5H, m, ArH), 7.17 (2H, d, *J* = 7.8 Hz, ArH), 5.78-5.66 (1H, m, CH_2CH=CH_2), 4.91-4.84 (2H, m, CH_2CH=CH_2), 4.55 (2H, s, CH_2Ph), 3.87-3.79 (1H, m, NC*H*CH_2O or NCH_2), 3.57-3.46 (2H, m, NC*H*CH_2O or NCH_2), 3.44 (1H, dd, *J* = 9.6, 5.6 Hz, CH_2OCH_2Ph), 3.41 (1H, dd, *J* = 9.6, 6.0 Hz, CH_2OCH_2Ph), 3.14-3.01 (2H, m, CH_2CH=CH_2), 2.37 (3H, s, $ArCH_3$), 2.01-1.81 (3H, m, pyrrolidine-CH_2), 1.77-1.68 (1H, m, pyrrolidine-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7, 142.0, 140.3, 137.9, 137.5, 129.2, 128.4, 127.7, 127.5, 127.3, 115.0, 101.8,

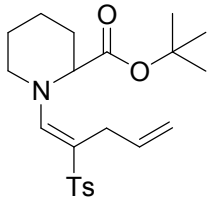
73.4, 72.8, 63.3, 48.3, 29.1, 27.3, 24.5, 21.4; IR (film) 3060, 3028, 2976, 2922, 2871, 1616, 1493, 1453, 1400, 1349, 1328, 1277, 1134, 1085, 1034, 1015, 914, 815, 737, 698 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{24}H_{30}NO_3S$: 412.1941. Found: 412.1924.

(*E*)-*tert*-Butyl 1-methyl-2-(2'-tosylvinyl)piperidine-2-carboxylate (8b)



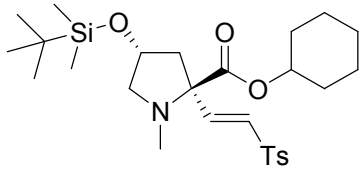
Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (2H, d, *J* = 8.2 Hz, ArH), 7.33 (2H, d, *J* = 8.2 Hz, ArH), 7.08 (1H, d, *J* = 15.4 Hz, TsCH=C*H*), 6.56 (1H, d, *J* = 15.4 Hz, TsC*H*=CH), 2.84 (1H, ddd, *J* = 11.4, 11.4, 3.6 Hz, NCH_2), 2.65 (1H, ddd, *J* = 11.4, 4.0, 4.0 Hz, NCH_2), 2.43 (3H, s, $ArCH_3$), 2.32 (3H, s, NCH_3), 2.08-1.97 (1H, m, piperidine-CH_2), 1.73-1.38 (5H, m, piperidine-CH_2), 1.46 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 147.5, 144.2, 137.5, 131.2, 129.8, 127.6, 82.3, 67.8, 50.5, 40.6, 36.3, 28.1, 25.1, 21.5, 20.4; IR (film) 3059, 2976, 2937, 2861, 2814, 1720, 1599, 1452, 1394, 1369, 1320, 1303, 1248, 1147, 1086, 1033, 980, 912, 843, 814, 775, 735, 705 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{20}H_{30}NO_4S$: 380.1890. Found: 380.1878.

(*E*)-*tert*-Butyl 1-(2'-tosylpent-1',4'-dien-1'-yl)piperidine-2-carboxylate (9)



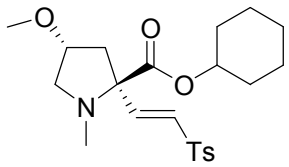
Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (2H, d, *J* = 8.0 Hz, ArH), 7.38 (1H, s, NCH=C), 7.20 (2H, d, *J* = 8.0 Hz, ArH), 5.68 (1H, dddd, *J* = 17.2, 10.4, 5.4, 4.9 Hz, CH_2CH=CH_2), 4.94 (1H, dddd, *J* = 10.4, 1.9, 1.7, 1.6 Hz, CH_2CH=CH_2), 4.89 (1H, dddd, *J* = 17.2, 1.9, 1.7, 1.6 Hz, CH_2CH=CH_2), 4.24 (1H, d, *J* = 5.2 Hz, NCHCO), 3.50 (1H, ddd, *J* = 12.8, 1.6, 1.6 Hz, piperidine-NCH_2), 3.35 (1H, ddd, *J* = 12.8, 12.8, 3.2 Hz, piperidine-NCH_2), 3.03 (1H, dddd, *J* = 18.6, 4.9, 1.9, 1.9 Hz, CH_2CH=CH_2), 2.92 (1H, dddd, *J* = 18.6, 5.4, 1.7, 1.7 Hz, CH_2CH=CH_2), 2.36 (3H, s, $ArCH_3$), 2.12 (1H, ddd, *J* = 14.0, 2.0, 2.0 Hz, piperidine-CH_2), 1.70-1.57 (3H, m, piperidine-CH_2), 1.53-1.36 (1H, m, piperidine-CH_2), 1.42 (9H, s, *t*-Bu), 1.36-1.22 (1H, m, piperidine-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 147.9, 142.3, 139.7, 136.1, 129.2, 127.3, 115.8, 101.4, 82.0, 60.5, 48.6, 29.4, 28.0, 27.3, 25.3, 21.4, 20.1.

(4*R*,*E*)-Cyclohexyl 4-(*tert*-butyldimethylsilyloxy)-1-methyl-2-(2'-tosylvinyl)pyrrolidine-2-carboxylate (11a)



Colorless crystals; (2*R*,4*R*)/(2*S*,4*R*) = 89:11 mixture; ^{1}H NMR (400 MHz, C_6D_6) δ 7.87 (0.22H, d, *J* = 8.4 Hz, ArH), 7.85 (1.78H, d, *J* = 8.4 Hz, ArH), 7.60 (0.89H, d, *J* = 14.8 Hz, TsCH=C*H*), 7.55 (0.11H, d, *J* = 15.0 Hz, TsCH=C*H*), 7.03 (0.89H, d, *J* = 14.8 Hz, TsC*H*=CH), 6.86 (0.11H, d, *J* = 15.0 Hz, TsC*H*=CH), 6.75 (2H, d, *J* = 8.4 Hz, ArH), 4.86-4.76 (0.11H, m, CO_2CH), 4.80 (0.89H, tt, *J* = 8.4, 4.2 Hz, CO_2CH), 4.45-4.39 (0.89H, m, 4-CH), 4.16-4.08 (0.11H, m, 4-CH), 3.08-2.92 (0.22H, m, 5-CH_2), 3.04 (0.89H, dd, *J* = 9.4, 6.4 Hz, 5-CH_2), 2.95 (0.89H, dd, *J* = 9.4, 2.0 Hz, 5-CH_2), 2.46 (0.89H, dd, *J* = 13.6, 6.8 Hz, 3-CH_2), 2.26 (0.11H, dd, *J* = 13.4, 5.6 Hz, 3-CH_2), 2.17 (0.33H, s, NCH_3 or $ArCH_3$), 2.12 (2.67H, s, NCH_3 or $ArCH_3$), 1.91 (0.11H, dd, *J* = 13.4, 8.0 Hz, 3-CH_2), 1.86 (2.67H, s, NCH_3 or $ArCH_3$), 1.84 (0.33H, s, NCH_3 or $ArCH_3$), 1.80 (0.89H, dd, *J* = 13.6, 4.0 Hz, 3-CH_2), 1.63-1.38 (4H, m, *c*-Hex), 1.38-1.02 (6H, m, *c*-Hex), 0.89 (0.99H, s, *t*-Bu), 0.87 (8.01H, s, *t*-Bu), –0.04 (2.67H, s, $SiCH_3$), –0.05 (2.67H, s, $SiCH_3$), –0.06 (0.33H, s, $SiCH_3$), –0.07 (0.33H, s, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 144.9, 144.1, 137.6, 131.1, 129.8, 127.7, 73.7, 71.7, 70.1, 63.4, 47.6, 35.8, 31.54, 31.53, 25.8, 25.2, 23.4, 21.6, 18.0, –4.9; IR (film) 3058, 2933, 2857, 2795, 1723, 1633, 1597, 1465, 1451, 1384, 1321, 1255, 1193, 1146, 1088, 1038, 1007, 911, 836, 778, 708 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{27}H_{44}NO_5SSi$: 522.2704. Found: 522.2688.

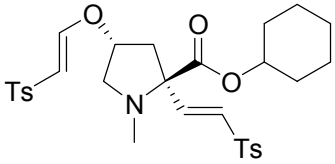
(4*R*,*E*)-Cyclohexyl 4-methoxy-1-methyl-2-(2'-tosylvinyl)pyrrolidine-2-carboxylate (11b)



Colorless oil; (2*R*,4*R*)/(2*S*,4*R*) = 87:13 mixture; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (2H, d, *J* = 8.0 Hz, ArH), 7.35-7.29 (0.26H, m, ArH), 7.32 (1.74H, d, *J* = 8.0 Hz, ArH), 7.18 (0.87H, d, *J* = 15.2 Hz, TsCH=C*H*), 7.12 (0.13H, d, *J* = 15.0 Hz, TsCH=C*H*), 6.72 (0.87H, d, *J* = 15.2 Hz, TsC*H*=CH), 6.58 (0.13H, d, *J* = 15.0 Hz, TsC*H*=CH), 4.85 (1H, tt, *J* = 8.6, 4.0 Hz, CO_2CH), 4.05-3.99 (0.87H, m, 4-CH), 3.94-3.87 (0.13H, m, 4-CH), 3.29 (0.13H, dd, *J* = 9.1, 6.8 Hz, 5-CH_2), 3.25 (0.39H, s, OCH_3), 3.21 (2.61H, s, OCH_3), 3.09 (0.87H, dd, *J* = 10.2, 1.8 Hz, 5-CH_2), 3.04 (0.87H, dd, *J* = 10.2, 6.2 Hz, 5-CH_2), 2.94 (0.13H, dd, *J* = 9.1, 5.4 Hz, 5-CH_2), 2.62 (0.87H, dd, *J* = 13.7, 7.4 Hz, 3-CH_2), 2.44 (0.39H, s, NCH_3 or $ArCH_3$), 2.43 (2.61H,

s, NCH_3 or $ArCH_3$), 2.40 (0.13H, dd, J = 13.4, 4.8 Hz, 3-CH_2), 2.33 (0.39H, s, NCH_3 or $ArCH_3$), 2.23 (2.61H, s, NCH_3 or $ArCH_3$), 2.10 (0.13H, dd, J = 13.4, 7.6 Hz, 3-CH_2), 1.87-1.76 (2H, m, *c*-Hex), 1.83 (0.87H, dd, J = 13.7, 3.6 Hz, 3-CH_2), 1.75-1.62 (2H, m, *c*-Hex), 1.59-1.23 (6H, m, *c*-Hex); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 144.9, 144.2, 137.5, 130.8, 129.8, 127.6, 78.6, 73.8, 71.6, 60.0, 56.6, 44.2, 35.7, 31.57, 31.55, 25.2, 23.39, 23.38, 21.5; IR (film) 3059, 2936, 2859, 1719, 1617, 1597, 1450, 1375, 1319, 1302, 1287, 1260, 1232, 1188, 1146, 1101, 1086, 1036, 1012, 949, 909, 837, 814, 732, 708 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{22}H_{32}NO_5S$: 422.1996. Found: 422.1983.

(4*R*,1'*E*,1"*E*)-Cyclohexyl 1-methyl-2-(2'-tosylvinyl)-4-(2"-tosylvinyloxy)pyrrolidine-2-carboxylate (12)



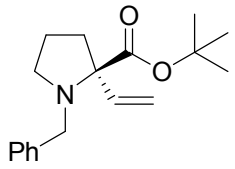
White solid; (2*R*,4*R*)/(2*S*,4*R*) = 91:9 mixture; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (2H, d, J = 8.4 Hz, ArH), 7.73 (2H, d, J = 8.4 Hz, ArH), 7.44 (0.09H, d, J = 12.4 Hz, TsCH=C*H*O), 7.40 (0.91H, d, J = 12.4 Hz, TsCH=C*H*O), 7.33 (2H, d, J = 8.4 Hz, ArH), 7.32 (2H, d, J = 8.4 Hz, ArH), 7.12 (0.91H, d, J = 15.0 Hz, TsCH=C*H*C), 7.06 (0.09H, d, J = 15.0 Hz, TsCH=C*H*C), 6.71 (0.91H, d, J = 15.0 Hz, TsC*H*=CHC), 6.57 (0.09H, d, J = 15.0 Hz, TsC*H*=CHC), 5.61 (0.09H, d, J = 12.4 Hz, TsC*H*=CHO), 5.54 (0.91H, d, J = 12.4 Hz, TsC*H*=CHO), 4.84 (1H, tt, J = 8.6, 3.6 Hz, CO_2CH), 4.66-4.59 (0.91H, m, 4-CH), 4.56-4.50 (0.09H, m, 4-CH), 3.16 (0.91H, d, J = 11.0 Hz, 5-CH_2), 3.12 (0.91H, dd, J = 11.0, 5.0 Hz, 5-CH_2), 3.05 (0.09H, d, J = 4.4 Hz, 5-CH_2), 3.03 (0.09H, dd, J = 7.2, 4.4 Hz, 5-CH_2), 2.76 (0.91H, dd, J = 14.3, 7.2 Hz, 3-CH_2), 2.64 (0.27H, s, NCH_3 or $ArCH_3$), 2.63 (0.27H, s, NCH_3 or $ArCH_3$), 2.50 (0.09H, dd, J = 14.2, 3.2 Hz, 3-CH_2), 2.44 (2.73H, s, NCH_3 or $ArCH_3$), 2.43 (2.73H, s, NCH_3 or $ArCH_3$), 2.33 (0.27H, s, NCH_3 or $ArCH_3$), 2.22 (2.73H, s, NCH_3 or $ArCH_3$), 2.18 (0.09H, dd, J = 14.2, 8.0 Hz, 3-CH_2), 1.93 (0.91H, dd, J = 14.3, 2.6 Hz, 3-CH_2), 1.85-1.61 (4H, m, *c*-Hex), 1.57-1.22 (6H, m, *c*-Hex); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 158.5, 144.5, 143.9, 143.8, 139.2, 137.2, 131.3, 129.9, 129.8, 127.6, 126.9, 108.3, 79.8, 74.4, 71.3, 59.8, 44.0, 35.4, 31.6, 31.5, 25.1, 23.41, 23.39, 21.6, 21.5; IR (KBr) 3067, 2936, 2858, 1722, 1626, 1606, 1494, 1450, 1400, 1380, 1315, 1302, 1261, 1208, 1142, 1084, 1036, 1017, 968, 892, 814, 778, 706 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{30}H_{38}NO_7S_2$: 588.2084. Found: 588.2077.

Representative procedure for the reductive desulfonylation of 3a with Mg

A solution of **3a** (61.9 mg, 0.140 mmol) in THF (1.4 mL) was added to a suspention of magnesium powder (34.1 mg, 1.40 mmol) in dry methanol (1.4 mL) at

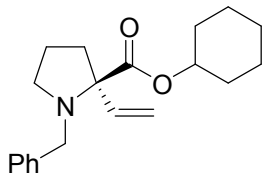
50 °C. After stirring for 5 h at the same temperature, the resulting mixture was quenched with saturated aqueous ammonium chloride at 0 °C and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over sodium sulfate and concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 10/1 as eluent) to give **6a** (25.9 mg, 64% yield) as a colorless oil.

***tert*-Butyl 1-benzyl-2-vinylpyrrolidine-2-carboxylate (6a)**



Colorless oil; $[\alpha]^{25}_{589}$ +17.8 (*c* 1.00 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (2H, d, *J* = 7.4 Hz, Ph), 7.30 (2H, dd, *J* = 7.4, 7.4 Hz, Ph), 7.21 (1H, t, *J* = 7.4 Hz, Ph), 6.11 (1H, dd, *J* = 17.5, 10.8 Hz, C*H*=CH_2), 5.41 (1H, dd, *J* = 17.5, 1.2 Hz, CH=CH_2), 5.20 (1H, dd, *J* = 10.8, 1.2 Hz, CH=CH_2), 3.95 (1H, d, *J* = 13.8 Hz, CH_2Ph), 3.68 (1H, d, *J* = 13.8 Hz, CH_2Ph), 2.95 (1H, ddd, *J* = 8.2, 8.2, 5.0 Hz, pyrrolidine-NCH_2), 2.69 (1H, ddd, *J* = 8.2, 8.2, 7.2 Hz, pyrrolidine-NCH_2), 2.38-2.29 (1H, m, pyrrolidine-CH_2), 1.91-1.76 (3H, m, pyrrolidine-CH_2), 1.52 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 140.7, 139.3, 128.1, 126.5, 114.6, 81.1, 73.2, 53.8, 50.7, 37.9, 28.3, 21.8; IR (film) 3086, 3063, 3027, 2977, 2935, 2878, 2834, 1720, 1687, 1494, 1455, 1394, 1368, 1253, 1156, 1072, 1028, 994, 920, 844, 829, 799, 734, 700 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{18}H_{26}NO_2$: 288.1958. Found: 288.1953.

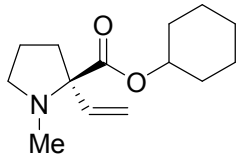
Cyclohexyl 1-benzyl-2-vinylpyrrolidine-2-carboxylate (6b)



Colorless oil; $[\alpha]^{25}_{589}$ +25.0 (*c* 1.00 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (2H, d, *J* = 7.2 Hz, Ph), 7.30 (2H, dd, *J* = 7.2, 7.2 Hz, Ph), 7.22 (1H, t, *J* = 7.2 Hz, Ph), 6.13 (1H, dd, *J* = 17.5, 10.7 Hz, C*H*=CH_2), 5.42 (1H, dd, *J* = 17.5, 1.4 Hz, CH=CH_2), 5.22 (1H, dd, *J* = 10.7, 1.4 Hz, CH=CH_2), 4.91 (1H, tt, *J* = 8.6, 4.4 Hz, OCH), 3.94 (1H, d, *J* = 14.0 Hz, CH_2Ph), 3.65 (1H, d, *J* = 14.0 Hz, CH_2Ph), 2.96 (1H, ddd, *J* = 8.4, 8.4, 5.2 Hz, pyrrolidine-NCH_2), 2.70 (1H, ddd, *J* = 8.4, 8.4, 6.8 Hz, pyrrolidine-NCH_2), 2.41-2.33 (1H, m, pyrrolidine-CH_2), 1.95-1.69 (7H, m, pyrrolidine-CH_2 and *c*-Hex), 1.59-1.21 (6H, m, *c*-Hex); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 140.6, 139.0, 128.1, 126.6, 114.8, 72.84, 72.76, 53.8, 50.6, 38.0, 31.75, 31.69, 25.4, 23.6, 21.8; IR (film) 3086, 3062, 3027, 2938, 2859, 1719, 1638, 1604, 1494, 1452, 1364, 1315, 1248, 1179, 1106, 1035, 1014, 914, 826, 734, 699 cm^{-1};

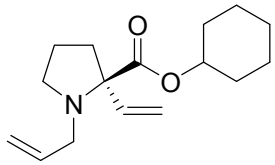
HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{20}H_{28}NO_2$: 314.2115. Found: 314.2105.

(*R*)-Cyclohexyl 1-methyl-2-vinylpyrrolidine-2-carboxylate (6f)



Colorless oil; $[\alpha]^{26}_{589}$ +13.0 (*c* 1.00 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.99 (1H, dd, *J* = 17.5, 10.8 Hz, C*H*=CH_2), 5.22 (1H, dd, *J* = 17.5, 1.2 Hz, CH=C*H*$_2$), 5.16 (1H, dd, *J* = 10.8, 1.2 Hz, CH=C*H*$_2$), 4.82 (1H, tt, *J* = 8.6, 4.0 Hz, OCH), 3.00-2.93 (1H, m, NCH_2), 2.83 (1H, ddd, *J* = 8.4, 8.0, 7.2 Hz, NCH_2), 2.37 (3H, s, NCH_3), 2.31-2.23 (1H, m, pyrrolidine-CH_2), 1.90-1.75 (5H, m, pyrrolidine-CH_2 and *c*-Hex), 1.72-1.63 (2H, m, *c*-Hex), 1.53-1.21 (6H, m, *c*-Hex); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 137.8, 114.7, 72.6, 72.0, 53.9, 37.1, 35.7, 31.7, 31.6, 25.4, 23.5, 21.7; IR (film) 2985, 2860, 2795, 1721, 1639, 1451, 1350, 1304, 1248, 1224, 1181, 1121, 1099, 1072, 1036, 1015, 993, 922, 816, 734 cm^{-1}.

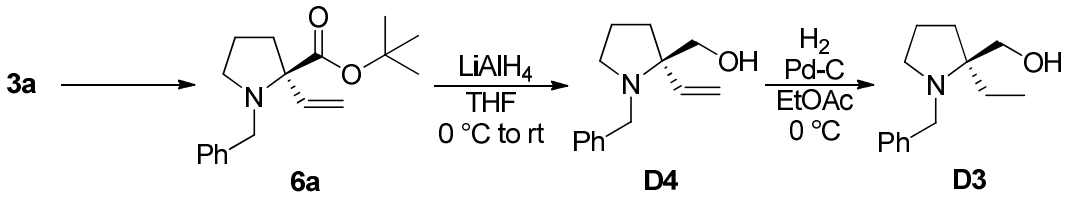
(*R*)-Cyclohexyl 1-allyl-2-vinylpyrrolidine-2-carboxylate (6g)



Colorless oil; $[\alpha]^{26}_{589}$ +31.3 (*c* 1.00 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.03 (1H, dd, *J* = 17.4, 10.8 Hz, 2-C*H*=CH_2), 5.84 (1H, dddd, *J* = 17.2, 10.0, 7.2, 5.2 Hz, CH_2C*H*=CH_2), 5.28 (1H, dd, *J* = 17.4, 1.6 Hz, 2-CH=C*H*$_2$), 5.16 (1H, dd, *J* = 17.2, 1.4 Hz, CH_2CH=C*H*$_2$), 5.15 (1H, dd, *J* = 10.8, 1.4 Hz, 2-CH=C*H*$_2$), 5.03 (1H, d, *J* = 10.0 Hz, CH_2CH=C*H*$_2$), 4.83 (1H, tt, *J* = 8.6, 4.1 Hz, OCH), 3.32 (1H, dddd, *J* = 14.0, 5.2, 1.6, 1.4 Hz, C*H*$_2$CH=CH_2), 3.15-3.05 (2H, m, C*H*$_2$CH=CH_2 and pyrrolidine-NCH_2), 2.73 (1H, ddd, *J* = 8.8, 8.4, 6.8 Hz, pyrrolidine-NCH_2), 2.34-2.22 (1H, m, pyrrolidine-CH_2), 1.90-1.76 (5H, m, pyrrolidine-CH_2 and *c*-Hex), 1.73-1.64 (2H, m, *c*-Hex), 1.54-1.22 (6H, m, *c*-Hex); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 138.4, 137.0, 115.7, 114.5, 72.7, 72.6, 31.7, 31.6, 25.4, 23.5, 21.6; IR (film) 3082, 2938, 2860, 2816, 1722, 1641, 1451, 1416, 1358, 1247, 1222, 1179, 1106, 1037, 1015, 993, 958, 918, 865, 825, 785, 734 cm^{-1}.

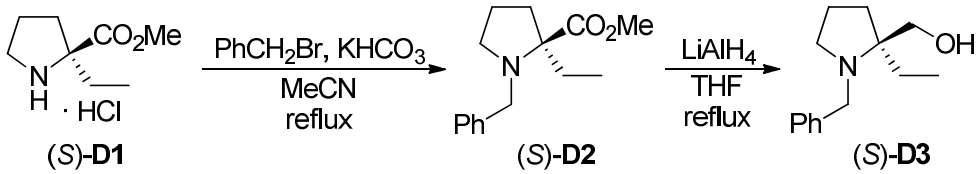
Determination of the absolute configuration of 3a

Preparation of (1-benzyl-2-ethylpyrrolidin-2-yl)methanol



(Step 1) A solution of **6a** (138 mg, 0.478 mmol) in THF (4.8 mL) was added to a suspension of lithium aluminium hydride (45 mg, 1.2 mmol) in THF (4.8 mL) at 0 °C and stirred for 1 h at room temperature. The resulting mixture was diluted with diethyl ether and quenched with water (45 μL), 15% aqueous sodium hydroxide solution (45 μL), and water (135 μL) at 0 °C. The mixture was stirred for 3 h at room temperature and filtered through a pad of Celite. The filtrate was concentrated and the residue was purified by chromatography on silica gel (hexane/ethyl acetate = 4/1 to 2/1 as eluent) to give (1-benzyl-2-vinylpyrrolidin-2-yl)methanol (**D4**) (96 mg, 93% yield) as a colorless oil. (Step 2) A mixture of **D4** (78 mg, 0.36 mmol) and palladium on activated carbon (loading: 10 wt.%, 7 mg) in ethyl acetate (3.6 mL) was stirred for 3 h at 0 °C under a hydrogen atmosphere. The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated. Purification of the residue by chromatography on silica gel (dichloromethane/methanol = 10/1 as eluent) afforded (1-benzyl-2-ethylpyrrolidin-2-yl)methanol (**D3**) (34 mg, 43% yield) as a colorless oil. 81% ee [determined by HPLC analysis: Daicel Chiralpak AD–H column, *n*-hexane/isopropanol = 99.2/0.8 as eluent, flow rate = 0.50 mL/min, t_R = 21.7 min for (*S*)-**D3** and 29.1 min for (*R*)-**D3**]; $[\alpha]^{24}_{589}$ −13.2 (*c* 1.00 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.22 (5H, m, Ph), 3.83 (1H, d, *J* = 13.0 Hz, C*H*$_2$Ph), 3.46 (1H, d, *J* = 10.4 Hz, CH_2O), 3.37 (1H, d, *J* = 10.4 Hz, CH_2O), 3.34 (1H, d, *J* = 13.0 Hz, C*H*$_2$Ph), 2.91 (1H, ddd, *J* = 9.1, 7.6, 2.8 Hz, pyrrolidine-NCH_2), 2.51 (1H, ddd, *J* = 9.1, 9.1, 7.6 Hz, pyrrolidine-NCH_2), 1.93 (1H, ddd, *J* = 12.8, 10.0, 5.6 Hz, pyrrolidine-CH_2), 1.81 (1H, ddd, *J* = 12.8, 8.6, 7.4 Hz, pyrrolidine-CH_2), 1.75-1.60 (2H, m, pyrrolidine-CH_2), 1.60-1.40 (3H, m, C*H*$_2$$CH_3$ and OH), 0.91 (3H, t, *J* = 7.6 Hz, CH_2C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.0, 128.5, 128.3, 126.9, 66.4, 63.6, 51.8, 51.3, 31.4, 24.4, 22.2, 8.7; IR (film) 3420, 3085, 3062, 3028, 2965, 2878, 2806, 1603, 1494, 1455, 1413, 1365, 1309, 1252, 1206, 1149, 1058, 973, 945, 923, 861, 827, 699 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{14}H_{22}NO$: 220.1696. Found: 220.1694.

Preparation of the authentic sample (*S*)-19



(*S*)-**D1** (*S*)-**D2** (*S*)-**D3**

(Step 1) A mixture of (*S*)-methyl 2-ethylpyrrolidine-2-carboxylate hydrochloride [(*S*)- **D1**] (109 mg, 0.56 mmol), benzyl bromide (74 μL, 0.62 mmol), and potassium hydrogen carbonate (0.17 g, 1.7 mmol) in acetonitrile (2.8 mL) was stirred for 0.5 h at room temperature and refluxed for 2 h. The resulting mixture was concentrated and the residue was purified by chromatography on silica gel (hexane/ethyl acetate = 20/1 as eluent) to obtain (*S*)-methyl 1-benzyl-2-ethylpyrrolidine-2-carboxylate [(*S*)-**D2**] (96.2 mg, 69% yield) as a colorless oil. (Step 2) A solution of (*S*)-**D2** (96.2 mg, 0.39 mmol) in THF (2 mL) was added to a suspension of lithium aluminium hydride (22 mg, 0.59 mmol) in THF (2 mL) at 0 °C and the mixture was refluxed for 30 min. The resulting mixture was cooled at 0 °C, diluted with diethyl ether (4 mL), and quenched with water (22 μL), 15% aqueous sodium hydroxide solution (22 μL), and water (66 μL) at 0 °C. The mixture was stirred for 1 h at room temperature and filtered through a pad of Celite. The filtrate was concentrated and the residue was purified by chromatography on silica gel (hexane/ethyl acetate = 3/1 as eluent) to give (*S*)-**D3** (72.6 mg, 85% yield) as a colorless oil; >99% ee [determined by HPLC analysis: Daicel Chiralpak AD–H column, *n*-hexane/isopropanol = 99.2/0.8 as eluent, flow rate = 0.50 mL/min, t_R = 20.8 min for (*S*)-**D3** and 26.4 min for (*R*)-**D3**]; $[\alpha]^{24}_{589}$ –16.1 (*c* 1.00 in $CHCl_3$).

Assignments of the stereochemistry of 11

The (2*R*,4*R*) and (2*S*,4*R*) stereochemistry of **11a** and **11b** were assigned by ^{1}H NMR assay. The data were summarized in Figure 2-1.

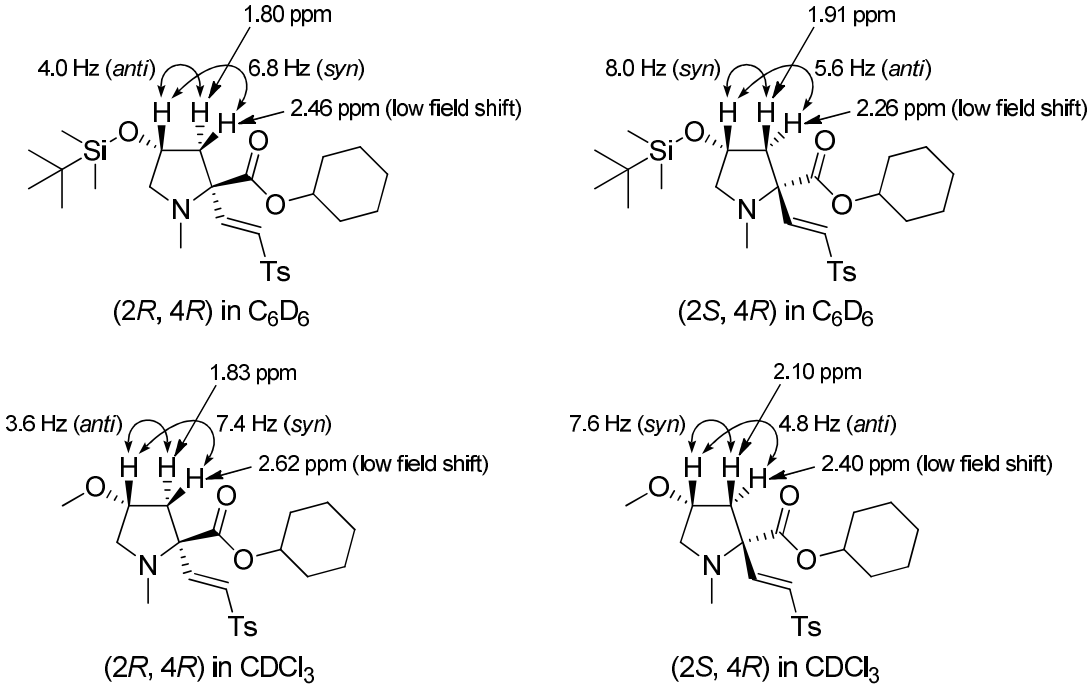
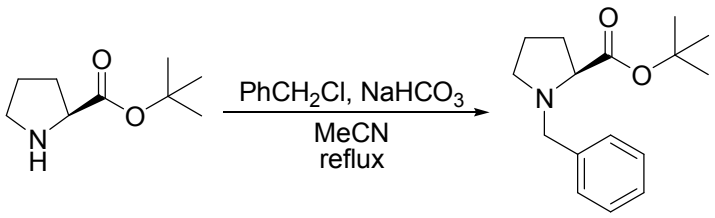


Figure 2-1

Preparation of substrates

(*S*)-*N*-Benzylproline *tert*-butyl ester (2a)

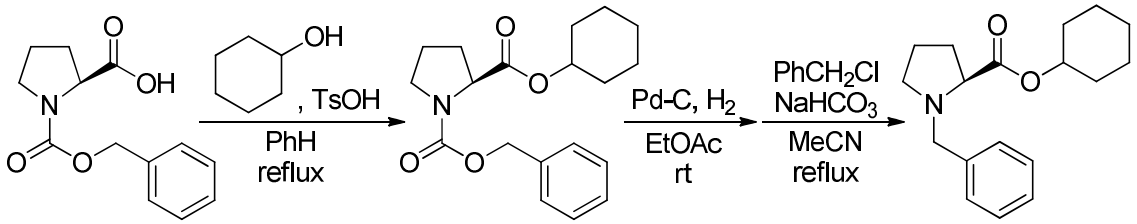


2a

A mixture of (*S*)-proline *tert*-butyl ester (0.53 g, 3.0 mmol), benzyl chloride (0.39 mL, 3.4 mmol), and sodium hydrogen carbonate (0.77 g, 9.2 mmol) in acetonitrile (15 mL) was refluxed for 6 h. The resulting mixture was cooled to room temperature and filtered. The filtrate was concentrated and the residue was purified by chromatography on silica gel (hexane/ethyl acetate = 5:1 as eluent) to obtain **2a** (0.70 g, 85% yield) as a colorless oil. $[\alpha]^{24}_{589}$ –68.8 (*c* 1.00 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.27 (4H, m, Ph), 7.23 (1H, tt, *J* = 7.0, 1.6 Hz, Ph), 3.99 (1H, d, *J* = 12.8 Hz, C*H*$_2$Ph), 3.50 (1H, d, *J* = 12.8 Hz, C*H*$_2$Ph), 3.14 (1H, dd, *J* = 8.8, 6.0 Hz, NCHCO), 2.99 (1H, ddd, *J* = 8.8, 7.8, 3.2 Hz, pyrrolidine-NCH$_2$), 2.36 (1H, ddd, *J* = 8.8, 8.0, 8.0 Hz, pyrrolidine-NCH$_2$),

2.14-2.02 (1H, m, pyrrolidine-CH_2), 1.98-1.68 (3H, m, pyrrolidine-CH_2), 1.46 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 138.9, 129.0, 128.1, 126.9, 80.4, 65.8, 58.4, 53.0, 29.1, 28.1, 22.9; IR (film) 3063, 3028, 2976, 2876, 2797, 1738, 1723, 1494, 1478, 1454, 1391, 1367, 1292, 1253, 1213, 1153, 1076, 1029, 966, 914, 846, 737, 699 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{16}H_{24}NO_2$: 262.1802. Found: 262.1800.

(*S*)-*N*-Benzylproline cyclohexyl ester (2b)



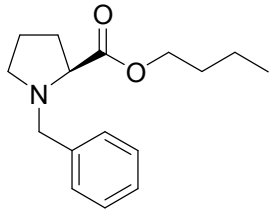
2b

(Step 1) A solution of (*S*)-Cbz-proline (0.87 g, 3.5 mmol), cyclohexanol (0.41 mL, 3.9 mmol) and *p*-toluenesulfonic acid, monohydrate (76 mg, 0.40 mmol) in benzene (7 mL) was refluxed for 26 h with azeotropic removal of water by a Dean-Stark trap. The resulting mixture was cooled to room temperature and quenched with saturated aqueous sodium hydrogen carbonate. The mixture was extracted with ethyl acetate and the combined extracts were washed with brine. The solution was dried over sodium sulfate and concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 2:1 as eluent) to obtain (*S*)-Cbz-proline cyclohexyl ester (0.86 g, 74% yield) as a colorless oil.

(Step 2) A mixture of (*S*)-Cbz-proline cyclohexyl ester (0.86 g, 2.6 mmol) and palladium on activated carbon (loading: 10 wt.%, 58 mg) in ethyl acetate (5 mL) was stirred for 4 h at room temperature under a hydrogen atmosphere. The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated. A mixture of the residual oil, benzyl chloride (0.33 mL, 2.9 mmol), and sodium hydrogen carbonate (0.65 g, 7.8 mmol) in acetonitrile (13 mL) was refluxed for 16 h. The resulting mixture was cooled to room temperature and filtered. The filtrate was concentrated and the residue was purified by chromatography on silica gel (hexane/ethyl acetate = 4/1 as eluent) to give **2b** (0.45 g, 61% yield) as a colorless oil. $[\alpha]^{24}_{589}$ –60.4 (*c* 1.00 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.27 (4H, m, Ph), 7.23 (1H, tt, *J* = 7.0, 1.6 Hz, Ph), 4.80 (1H, tt, *J* = 9.2, 3.6 Hz, OCH), 3.96 (1H, d, *J* = 13.0 Hz, C*H*$_2$Ph), 3.52 (1H, d, *J* = 13.0 Hz, C*H*$_2$Ph), 3.23 (1H, dd, *J* = 8.8, 6.0 Hz, NCHCO), 3.01 (1H, ddd, *J* = 8.8, 7.6, 3.6 Hz, pyrrolidine-NCH_2), 2.38 (1H, ddd, *J* = 8.8, 8.0, 8.0 Hz, pyrrolidine-NCH_2), 2.17-2.06 (1H, m, pyrrolidine-CH_2), 2.00-1.67 (7H, m, pyrrolidine-CH_2 and *c*-Hex), 1.58-1.20 (6H, m, *c*-Hex); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 138.6, 129.1, 128.1, 126.9, 72.6, 65.3, 58.3, 52.9, 31.6, 31.5, 29.2, 25.3, 23.68, 23.66, 22.8; IR (film) 3062, 3028, 2937, 2859, 2797, 1726, 1494, 1453, 1358, 1276, 1178, 1076, 1039, 1016, 969, 930, 911, 892, 743, 699 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{18}H_{26}NO_2$: 288.1958. Found:

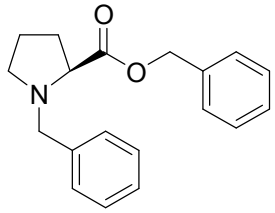
288.1955.

(*S*)-*N*-Benzylproline *n*-butyl ester (2c)



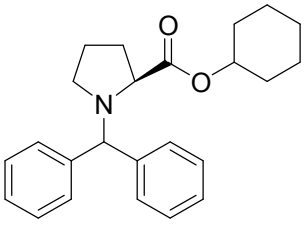
Prepared in 44% yield from (*S*)-Cbz-proline by the same procedure with **2b** using *n*-butanol instead of cyclohexanol. Colorless oil; $[\alpha]^{24}_{589}$ –62.4 (*c* 1.00 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.27 (4H, m, Ph), 7.23 (1H, tt, *J* = 7.0, 1.6 Hz, Ph), 4.09 (1H, dt, *J* = 10.8, 6.8 Hz, C*H*$_2$CH$_2$CH$_2$CH$_3$), 4.06 (1H, dt, *J* = 10.8, 6.8 Hz, C*H*$_2$CH$_2$CH$_2$CH$_3$), 3.93 (1H, d, *J* = 12.8 Hz, C*H*$_2$Ph), 3.55 (1H, d, *J* =12.8 Hz, C*H*$_2$Ph), 3.25 (1H, dd, *J* = 8.8, 6.4 Hz, NCHCO), 3.02 (1H, ddd, *J* = 8.8, 7.6, 3.2 Hz, pyrrolidine-NCH$_2$), 2.39 (1H, ddd, *J* = 8.8, 7.6, 7.6 Hz, pyrrolidine-NCH$_2$), 2.18-2.07 (1H, m, pyrrolidine-CH$_2$), 2.01-1.71 (3H, m, pyrrolidine-CH$_2$), 1.65-1.57 (2H, m, CH$_2$C*H*$_2$CH$_2$CH$_3$), 1.42-1.32 (2H, m, CH$_2$CH$_2$C*H*$_2$CH$_3$), 0.93 (3H, t, *J* = 7.4 Hz, CH$_2$CH$_2$CH$_2$C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 138.4, 129.1, 128.1, 126.9, 65.2, 64.3, 58.5, 53.0, 30.6, 29.2, 22.9, 19.0, 13.6; IR (film) 3062, 3028, 2960, 2874, 2799, 1744, 1730, 1494, 1454, 1375, 1355, 1274, 1176, 1074, 1029, 999, 969, 912, 840, 741, 700 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{16}H_{24}NO_2$: 262.1802. Found: 262.1800.

(*S*)-*N*-Benzylproline benzyl ester (2d)



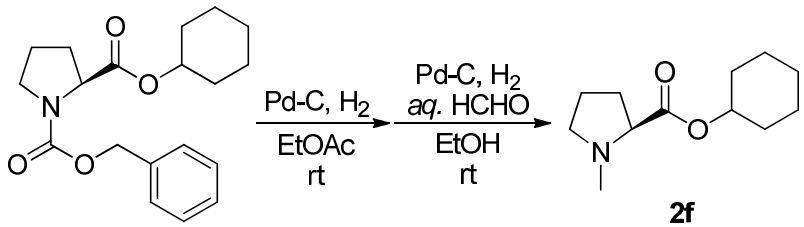
Prepared in 48% yield according to the literature. Colorless oil; $[\alpha]^{24}_{589}$ –58.3 (*c* 1.00 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.20 (10H, m, ArH), 5.13 (1H, d, *J* = 12.4 Hz, OC*H*$_2$Ph), 5.08 (1H, d, *J* = 12.4 Hz, OC*H*$_2$Ph), 3.92 (1H, d, *J* = 12.6 Hz, NC*H*$_2$Ph), 3.55 (1H, d, *J* = 12.6 Hz, NC*H*$_2$Ph), 3.31 (1H, dd, *J* = 8.8, 6.0 Hz, NCHCO), 3.03 (1H, ddd, *J* = 8.8, 8.0, 3.2 Hz, pyrrolidine-NCH$_2$), 2.40 (1H, ddd, *J* = 8.8, 8.0, 8.0 Hz, pyrrolidine-NCH$_2$), 2.18-2.07 (1H, m, pyrrolidine-CH$_2$), 2.04-1.71 (3H, m, pyrrolidine-CH$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 138.4, 136.0, 129.1, 128.5, 128.2, 128.14, 128.12, 127.0, 66.2, 65.1, 58.5, 53.1, 29.3, 23.0; IR (film) 3063, 3031, 2955, 2877, 2800, 1741, 1731, 1495, 1454, 1374, 1354, 1270, 1167, 1077, 1029, 1001, 911, 824, 750, 698 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{19}H_{22}NO_2$: 296.1645. Found: 296.1641.

(*S*)-*N*-Diphenylmethylproline cyclohexyl ester (2e)



Prepared in 47% yield from (*S*)-Cbz-proline by the same procedure with **2b** using benzhydryl chloride instead of benzyl chloride. White solid; $[\alpha]^{26}_{589}$ –76.4 (*c* 1.00 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.40 (4H, m, Ph), 7.28-7.21 (4H, m, Ph), 7.19-7.12 (2H, m, Ph), 4.90-4.86 (1H, m, C*H*Ph_2), 4.68-4.59 (1H, m, OCH), 3.52-3.46 (1H, m, NCHCO), 3.01-2.93 (1H, m, NCH_2), 2.73-2.65 (1H, m, NCH_2), 2.20-2.07 (1H, m, pyrrolidine-CH_2), 1.99-1.73 (4H, m, pyrrolidine-CH_2 and *c*-Hex), 1.73-1.45 (4H, m, *c*-Hex), 1.42-1.15 (5H, m, *c*-Hex); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 143.7, 143.0, 128.3, 128.2, 128.0, 127.8, 126.93, 126.87, 72.0, 71.7, 63.0, 51.4, 31.53, 31.46, 30.1, 25.4, 23.7, 23.6, 23.4; IR (KBr) 3070, 3025, 2939, 2857, 1712, 1487, 1451, 1357, 1343, 1303, 1193, 1140, 1076, 1015, 986, 949, 928, 898, 858, 838, 766, 748, 707 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{24}H_{30}NO_2$: 364.2271. Found: 364.2253.

(*S*)-*N*-Methylproline cyclohexyl ester (2f)

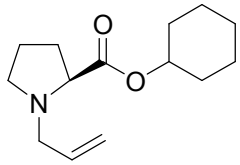


2f

A mixture of (*S*)-Cbz-proline cyclohexyl ester (0.97 g, 2.9 mmol) and palladium on activated carbon (loading: 10 wt.%, 75 mg) in ethyl acetate (6 mL) was stirred for 1.5 h at room temperature under a hydrogen atmosphere. The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated. A mixture of the residual oil, palladium on activated carbon (loading: 10 wt.%, 85 mg), and formaldehyde solution (37 wt.% in water, 2.2 mL, 29 mmol) in ethanol (6 mL) was stirred for 24 h at room temperature under a hydrogen atmosphere. The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated. The mixture was diluted with water and extracted with hexane. The combined extracts were washed with brine, dried over sodium sulfate and concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 1/1 as eluent) to obtain **2f** (0.45 g, 73% yield) as a colorless oil. $[\alpha]^{23}_{589}$ –76.1 (*c* 1.00 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.83 (1H, tt, *J* = 9.2, 3.8 Hz, OCH), 3.17-3.09 (1H, m, NCHCO), 2.93 (1H, dd, *J* = 8.6, 7.0 Hz, NCH_2), 2.41

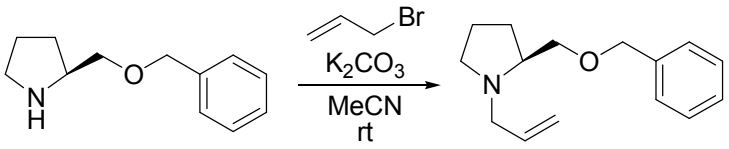
(3H, s, NCH_3), 2.31 (1H, ddd, *J* = 8.6, 8.6, 8.6 Hz, NCH_2), 2.19-2.07 (1H, m, pyrrolidine-CH_2), 1.99-1.67 (7H, m, pyrrolidine-CH_2 and *c*-Hex), 1.60-1.20 (6H, m, *c*-Hex); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 72.6, 67.5, 56.2, 40.6, 31.54, 31.47, 29.5, 25.3, 23.70, 23.67, 22.9; IR (film) 2938, 2859, 2780, 1739, 1727, 1451, 1360, 1344, 1315, 1278, 1177, 1123, 1078, 1054, 1040, 1016, 986, 930, 893, 865, 842, 827, 801, 756 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{12}H_{22}NO_2$: 212.1645. Found: 212.1643.

(*S*)-*N*-Allylproline cyclohexyl ester (2g)



Prepared in 50% yield from (*S*)-Cbz-proline by the same procedure with **2b** using allyl chloride instead of benzyl chloride. Colorless oil; $[\alpha]^{24}_{589}$ –76.6 (*c* 1.00 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.93 (1H, dddd, *J* = 17.1, 10.0, 6.4, 6.4 Hz, CH_2CH=CH_2), 5.18 (1H, dddd, *J* = 17.1, 1.8, 1.2, 1.2 Hz, CH_2CH=CH_2), 5.08 (1H, dddd, *J* = 10.0, 1.8, 1.2, 1.2 Hz, CH_2CH=CH_2), 4.81 (1H, tt, *J* = 9.0, 3.8 Hz, OCH), 3.33 (1H, dddd, *J* = 13.0, 6.4, 1.2, 1.2 Hz, CH_2CH=CH_2), 3.17-3.09 (3H, m, CH_2CH=CH_2, NCHCO, and pyrrolidine-NCH_2), 2.40 (1H, ddd, *J* = 8.8, 8.0, 8.0 Hz, pyrrolidine-NCH_2), 2.19-2.05 (1H, m, pyrrolidine-CH_2), 1.98-1.67 (7H, m, pyrrolidine-CH_2 and *c*-Hex), 1.59-1.20 (6H, m, *c*-Hex); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 135.5, 117.3, 72.6, 65.2, 57.5, 53.4, 31.53, 31.51, 29.4, 25.3, 23.7, 22.9; IR (film) 3077, 2937, 2859, 2798, 1727, 1644, 1451, 1419, 1358, 1262, 1179, 1124, 1086, 1039, 1016, 994, 964, 918, 864, 842, 801, 762 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{14}H_{24}NO_2$: 238.1802. Found: 238.1798.

(*S*)-1-Allyl-2-(benzyloxymethyl)pyrrolidine (4)

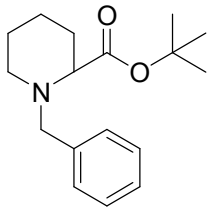


4

A mixture of 2-(benzyloxymethyl)pyrrolidine (429 mg, 2.24 mmol), allyl bromide (194 μL, 2.24 mmol), and potassium carbonate (0.47 g, 3.4 mmol) in acetonitrile (11 mL) was stirred for 12 h at room temperature. The resulting mixture was filtered and the filtrate was concentrated. The residue was purified by chromatography on silica gel (ethyl acetate as eluent) to give **4** (376 mg, 73% yield) as a colorless oil. $[\alpha]^{22}_{589}$ –50.6 (*c* 1.00 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.23 (5H, m, Ph), 5.97-5.86 (1H, m, CH_2CH=CH_2), 5.19-5.13 (1H, m, CH_2CH=CH_2), 5.09-5.04 (1H, m, CH_2CH=CH_2), 4.52 (2H, s, CH_2Ph), 3.54 (1H, dddd, *J* = 13.4, 5.8, 1.6, 1.6 Hz, CH_2CH=CH_2), 3.51 (1H, dd, *J* = 9.2, 5.2 Hz, NCHCH_2O), 3.37 (1H, dd, *J* = 9.2, 6.0 Hz, NCHCH_2O), 3.07 (1H, ddd, *J* = 9.2, 6.8, 2.4 Hz, pyrrolidine-NCH_2), 2.94 (1H, dddd, *J* = 13.4, 7.4, 1.0, 1.0 Hz,

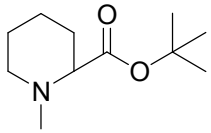
C*H*$_2$CH=CH$_2$), 2.70-2.63 (1H, m, NC*H*CH$_2$O), 2.22 (1H, ddd, *J* = 9.2, 9.2, 7.4 Hz, pyrrolidine-NCH$_2$), 1.96-1.86 (1H, m, pyrrolidine-CH$_2$), 1.81-1.59 (3H, m, pyrrolidine-CH$_2$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 138.4, 136.2, 128.2, 127.5, 127.4, 116.6, 73.7, 73.2, 62.7, 58.3, 54.4, 28.6, 22.8; IR (film) 3067, 3030, 2963, 2910, 2856, 2792, 1642, 1496, 1453, 1418, 1362, 1260, 1205, 1101, 1027, 995, 917, 736, 697 cm^{-1}; HRMS–ESI (*m*/*z*): [M+H]$^+$ calcd for C$_{15}$H$_{22}$NO: 232.1696. Found: 232.1688.

***N*-Benzylpipecolinic acid *tert*-butyl ester (7a)**



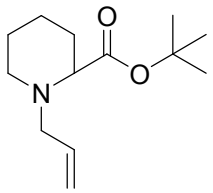
Prepared in quantitative yield from (*rac*)-Cbz-pipecolinic acid *tert*-butyl ester by the same procedure with **2b**. Colorless oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.37-7.33 (2H, m, Ph), 7.32-7.27 (2H, m, Ph), 7.23 (1H, tt, *J* = 7.0, 1.6 Hz, Ph), 3.83 (1H, d, *J* = 13.2 Hz, C*H*$_2$Ph), 3.38 (1H, d, *J* = 13.2 Hz, C*H*$_2$Ph), 3.01 (1H, dd, *J* = 7.6, 4.4 Hz, NCHCO), 2.91 (1H, ddd, *J* = 11.2, 6.1, 4.8 Hz, piperidine-NCH$_2$), 2.11 (1H, ddd, *J* = 11.2, 7.6, 4.4 Hz, piperidine-NCH$_2$), 1.87-1.73 (2H, m, piperidine-CH$_2$), 1.66-1.44 (3H, m, piperidine-CH$_2$), 1.49 (9H, s, *t*-Bu), 1.41-1.30 (1H, m, piperidine-CH$_2$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 173.3, 138.7, 129.1, 128.0, 126.8, 80.5, 65.0, 60.3, 50.0, 29.6, 28.1, 25.3, 22.6; IR (film) 3028, 2976, 2935, 2856, 2807, 1726, 1493, 1452, 1391, 1367, 1289, 1253, 1205, 1148, 1056, 1002, 939, 910, 886, 850, 832, 803, 774, 732, 698 cm^{-1}; HRMS–ESI (*m*/*z*): [M+H]$^+$ calcd for C$_{17}$H$_{26}$NO$_2$: 276.1958. Found: 276.1953.

***N*-Methylpipecolinic acid *tert*-butyl ester (7b)**



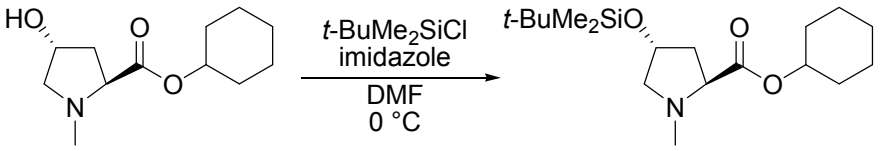
Prepared in 45% yield from (*rac*)-Cbz-pipecolinic acid *tert*-butyl ester by the same procedure with **2f**. Colorless oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.94 (1H, ddd, *J* = 11.6, 3.8, 3.8 Hz, NCH$_2$), 2.60 (1H, dd, *J* = 9.8, 3.4 Hz, NCHCO), 2.27 (3H, s, NCH$_3$), 2.10-2.02 (1H, m, NCH$_2$), 1.84-1.77 (1H, m, piperidine-CH$_2$), 1.75-1.55 (4H, m, piperidine-CH$_2$), 1.47 (9H, s, *t*-Bu), 1.34-1.23 (1H, m, piperidine-CH$_2$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 172.8, 80.6, 68.4, 54.9, 44.1, 29.6, 28.0, 25.3, 22.8; IR (film) 2976, 2937, 2857, 2781, 2715, 1739, 1727, 1455, 1391, 1367, 1293, 1255, 1207, 1152, 1104, 1056, 1035, 1003, 948, 882, 850, 833, 793, 769, 735 cm^{-1}; HRMS–ESI (*m*/*z*): [M+H]$^+$ calcd for C$_{11}$H$_{22}$NO$_2$: 200.1645. Found: 200.1642.

_N_-Allylpipecolinic acid _tert_-butyl ester (7c)



Prepared in quantitative yield from (*rac*)-Cbz-pipecolinic acid *tert*-butyl ester by the same procedure with **2g**. Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87 (1H, dddd, *J* = 17.3, 10.0, 8.0, 5.4 Hz, CH_2CH=CH_2), 5.13 (1H, dddd, *J* = 17.3, 1.7, 1.6, 1.6 Hz, CH_2CH=CH_2), 5.10 (1H, dddd, *J* = 10.0, 1.7, 1.4, 1.0 Hz, CH_2CH=CH_2), 3.26 (1H, dddd, *J* = 13.4, 5.4, 1.6, 1.4 Hz, CH_2CH=CH_2), 3.00 (1H, ddd, *J* = 11.7, 6.1, 3.6 Hz, piperidine-NCH_2), 2.95 (1H, dd, *J* = 8.0, 2.0 Hz, NCHCO), 2.94 (1H, dddd, *J* = 13.4, 8.0, 1.6, 1.0 Hz, CH_2CH=CH_2), 2.15 (1H, ddd, *J* = 11.7, 7.9, 4.0 Hz, piperidine-NCH_2), 1.89-1.65 (3H, m, piperidine-CH_2), 1.65-1.38 (2H, m, piperidine-CH_2), 1.44 (9H, s, *t*-Bu), 1.38-1.26 (1H, m, piperidine-CH_2).

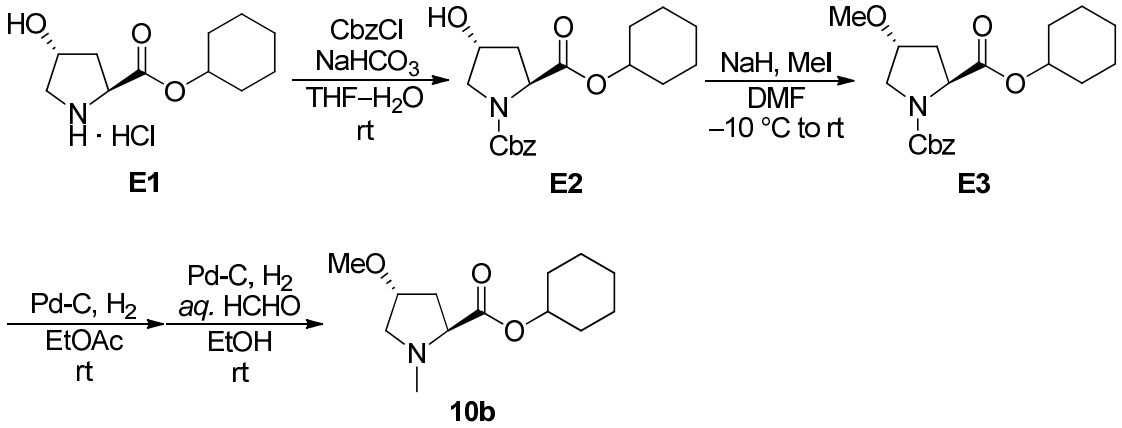
(2_S_,4_R_)-4-(_tert_-Butyldimethylsilyloxy)-_N_-methylproline cyclohexyl ester (10a)



10c **10a**

To a solution of **10c** (0.59 g, 2.6 mmol) and imidazole (0.38 g, 5.6 mmol) in DMF (5 mL) was added *tert*-butyldimethylsilyl chloride (0.43 g, 2.8 mmol) at 0 °C and the mixture was stirred for 3.5 h at the same temperature. The resulting mixture was diluted with water and extracted with ethyl acetate. The combined extracts were washed with water and brine, dried over sodium sulfate and concentrated. Purification of the residue by chromatography on silica gel (hexane/ethyl acetate = 5/1 as eluent) gave **10a** (0.44 g, 49% yield) as a colorless oil. $[\alpha]^{27}_{589}$ –34.3 (*c* 1.00 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.82 (1H, tt, *J* = 9.0, 4.0 Hz, CO_2CH), 4.46-4.38 (1H, m, 4-CH), 3.36 (1H, dd, *J* = 9.3, 6.0 Hz, 5-CH_2), 3.20 (1H, dd, *J* = 8.4, 8.0 Hz, 2-CH), 2.40 (3H, s, NCH_3), 2.29 (1H, dd, *J* = 9.3, 5.4 Hz, 5-CH_2), 2.17 (1H, ddd, *J* = 13.2, 8.0, 8.0 Hz, 3-CH_2), 2.00 (1H, ddd, *J* = 13.2, 8.4, 3.6 Hz, 3-CH_2), 1.90-1.81 (2H, m, *c*-Hex), 1.77-1.65 (2H, m, *c*-Hex), 1.59-1.20 (6H, m, *c*-Hex), 0.88 (9H, s, *t*-Bu), 0.05 (3H, s, $SiCH_3$), 0.04 (3H, s, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 72.9, 70.4, 66.4, 64.9, 41.1, 40.0, 31.6, 31.5, 25.8, 25.3, 23.8, 23.7, 18.0, –4.9; IR (film) 2935, 2858, 2785, 1744, 1731, 1453, 1381, 1361, 1320, 1255, 1191, 1128, 1101, 1018, 909, 836, 777 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{18}H_{36}NO_3Si$: 342.2459. Found: 342.2449.

(2*S*,4*R*)-4-Methoxy-*N*-methylproline cyclohexyl ester (10b)



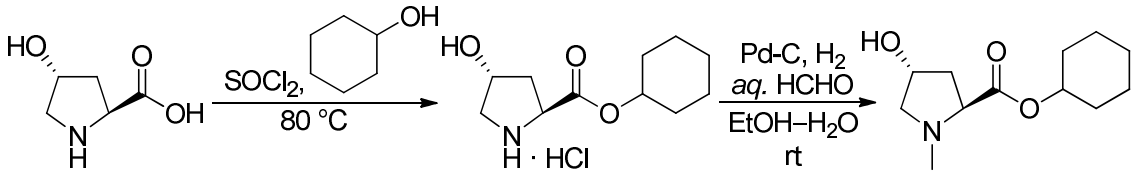
(Step 1) A mixture of **E1** (1.13 g, 4.52 mmol) and sodium hydrogen carbonate (1.93 g, 23 mmol) in THF (9 mL) and water (4.5 mL) was treated with benzyl chloroformate (CbzCl) (0.67 mL, 4.7 mmol) at room temperature and stirred for 2.5 h at the same temperature. The resulting mixture was diluted with water and extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate, and concentrated to obtain *trans*-*N*-benzyloxycarbonyl-4-hydroxy-L-proline cyclohexyl ester (**E2**) (1.54 g, 98% yield) as a colorless oil.

(Step 2) Sodium hydride (55 wt.% in oil, 0.33g, 7.6 mmol) was added slowly to a solution of **E2** (1.32 g, 3.80 mmol) and iodomethane (0.57 mL, 9.1 mmol) in DMF (7.6 mL) at –10 °C. The reactant was stirred for 30 min at room temperature and quenched with saturated aqueous ammonium chloride at 0 °C. The mixture was extracted with ethyl acetate and the combined extracts were washed with water and brine. The solution was dried over sodium sulfate and concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 4/1 to 2/1 as eluent) to obtain *trans*-*N*-benzyloxycarbonyl-4-methoxy-L-proline cyclohexyl ester (**E3**) (1.23 g, 90% yield) as a colorless oil.

(Step 3) A mixture of **E3** (127 mg, 0.35 mmol) and palladium on activated carbon (loading: 10 wt.%, 7 mg) in ethyl acetate (1.8 mL) was stirred for 15 h at room temperature under a hydrogen atmosphere. The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated. A mixture of the residual oil, palladium on activated carbon (loading: 10 wt.%, 19 mg), and formaldehyde solution (37 wt.% in water, 0.28 mL, 3.5 mmol) in ethanol (1.4 mL) was stirred for 24 h at room temperature under a hydrogen atmosphere. The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated. The residue was treated with saturated aqueous sodium hydrogen carbonate and extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate and concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 1/1 to 1/2 as eluent) to obtain **10b** (68.0 mg, 81% yield) as a colorless oil. $[\alpha]^{22}_{589}$ –67.6 (*c* 1.00 in EtOH); ^{1}H

NMR (400 MHz, $CDCl_3$) δ 4.83 (1H, tt, *J* = 9.2, 3.6 Hz, CO_2CH), 4.03-3.95 (1H, m, 4-CH), 3.45 (1H, dd, *J* = 9.9, 6.2 Hz, 5-CH_2), 3.29 (3H, s, OCH_3), 3.19 (1H, dd, *J* = 8.2, 8.2 Hz, 2-CH), 2.41 (3H, s, NCH_3), 2.37 (1H, dd, *J* = 9.9, 4.8 Hz, 5-CH_2), 2.132 (1H, dd, *J* = 8.2, 5.8 Hz, 3-CH_2), 2.131 (1H, dd, *J* = 8.2, 4.8 Hz, 3-CH_2), 1.90-1.80 (2H, m, *c*-Hex), 1.77-1.67 (2H, m, *c*-Hex), 1.59-1.21 (6H, m, *c*-Hex); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 78.9, 72.9, 66.1, 61.8, 56.7, 40.6, 36.6, 31.6, 31.5, 25.3, 23.71, 23.69; IR (film) 2937, 2859, 2785, 1739, 1731, 1454, 1362, 1321, 1263, 1230, 1186, 1106, 1040, 1017, 956, 916, 828, 800, 763, 732 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{13}H_{24}NO_3$: 242.1751. Found: 242.1747.

(2*S*,4*R*)-4-Hydroxy-*N*-methylproline cyclohexyl ester (10c)



E1 **10c**

(Step 1) Thionyl chloride (0.40 mL, 5.5 mmol) was added to a mixture of *trans*-4-hydroxy-L-proline (656 mg, 5.00 mmol) in cyclohexanol (5 mL) at room temperature and the mixture was stirred for 12 h at 80 °C. The resulting mixture was cooled to room temperature and diluted with cyclohexane to precipitate. The solid was isolated by filtration and washed with cyclohexane to afford *trans*-4-hydroxy-L-proline cyclohexyl ester hydrochloride (**E1**) (1.13 g, 90% yield) as a white solid.

(Step 2) A mixture of **E1** (0.27 g, 1.1 mmol), palladium on activated carbon (loading: 5 wt.%, 53 mg), and formaldehyde solution (37 wt.% in water, 0.80 mL, 11 mmol) in ethanol (2 mL) was stirred for 15 h at room temperature under a hydrogen atmosphere. The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated. The residue was treated with saturated aqueous sodium hydrogen carbonate and extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate and concentrated. The residue was purified by chromatography on silica gel (dichloromethane/methanol = 10/1 as eluent) to obtain **10c** (0.18 g, 73% yield) as a colorless oil. $[\alpha]^{27}_{589}$ –63.7 (*c* 1.00 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.82 (1H, tt, *J* = 9.0, 4.2 Hz, CO_2CH), 4.50-4.43 (1H, m, 4-CH), 3.43 (1H, dd, *J* = 10.0, 6.0 Hz, 5-CH_2), 3.32 (1H, dd, *J* = 7.8, 7.6 Hz, 2-CH), 2.76 (1H, br, OH), 2.42 (3H, s, NCH_3), 2.38 (1H, dd, *J* = 10.0, 4.0 Hz, 5-CH_2), 2.24 (1H, ddd, *J* = 13.5, 7.6, 7.6 Hz, 3-CH_2), 2.05 (1H, ddd, *J* = 13.5, 7.8, 3.0 Hz, 3-CH_2), 1.90-1.80 (2H, m, *c*-Hex), 1.77-1.67 (2H, m, *c*-Hex), 1.59-1.20 (6H, m, *c*-Hex); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 72.9, 69.9, 65.8, 64.1, 40.3, 39.9, 31.5, 31.4, 25.2, 23.61, 23.59; IR (film) 3402, 2938, 2859, 2789, 1731, 1452, 1384, 1359, 1264, 1198, 1124, 1089, 1065, 1038, 1016, 911, 842, 800, 762 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{12}H_{22}NO_3$: 228.1594. Found: 228.1588.

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2) (a) Waykole, L.; Paquett, L. A. *Org. Syn.* **1987**, *67*, 149-156. (b) Drouillat, B.; Couty, F.; Razafimahaléo, V. *Synlett* **2009**, 3182-3186. (c) Voskressensky, L. G.; Listratova, A. V.; Borisova, T. N.; Kovaleva, S. A.; Borisov, R. S.; Varlamov, A. V. *Tetrahedron* **2008**, *64*, 10443-10452. (d) Voskressensky, L. G.; Listratova, A. V.; Borisova, T. N.; Alexandrov, G. G.; Varlamov, A. V. *Eur. J. Org. Chem.* **2007**, 6106–6117. (e) Voskressensky, L. G.; Akbulatov, S. V.; Borisova, T. N.; Kleimenov, A. V.; Varlamov, A. V. *Russ. Chem. Bull., Int. Ed.* **2007**, *56*, 2323–2329. (f) Voskressensky, L. G.; Borisova, T. N.; Listratova, A. V.; Kulikova, L. N.; Titov, A. A.; Varlamov, A. V. *Tetrahedron Lett.* **2006**, *47*, 4585–4589.
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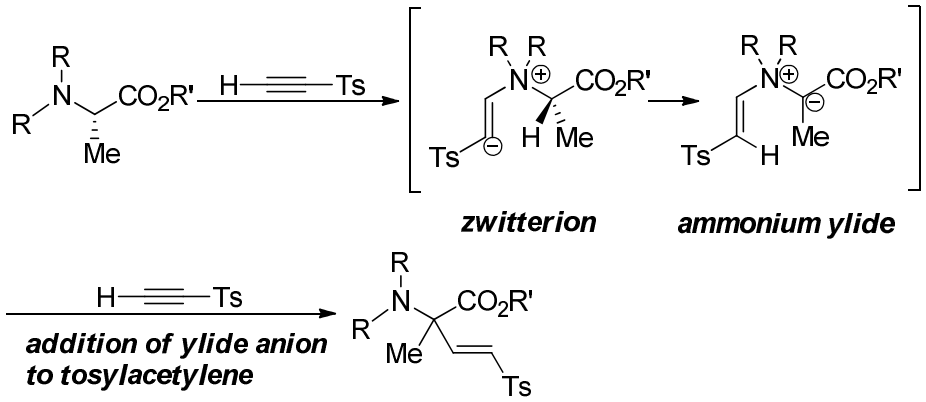
Chapter 3.
Asymmetric α-2-tosylethenylation of *N*,*N*-dialkyl-L-amino acid esters via the formation of non-racemic ammonium enolates

3-1 Background

In section 2, we explained that the α-tosylethenylation of the cyclic amino acid derivatives proceeded enantioselectively via chiral transfer from nitrogen atom to carbon atom.

In this section, we attempted the reaction of acyclic amino acid derivatives with ethynyl tolyl sulfone to conduct the asymmetric synthesis of α-tosylethenylated non-natural acyclic amino acid derivatives (Scheme 3-1).

Scheme 3-1



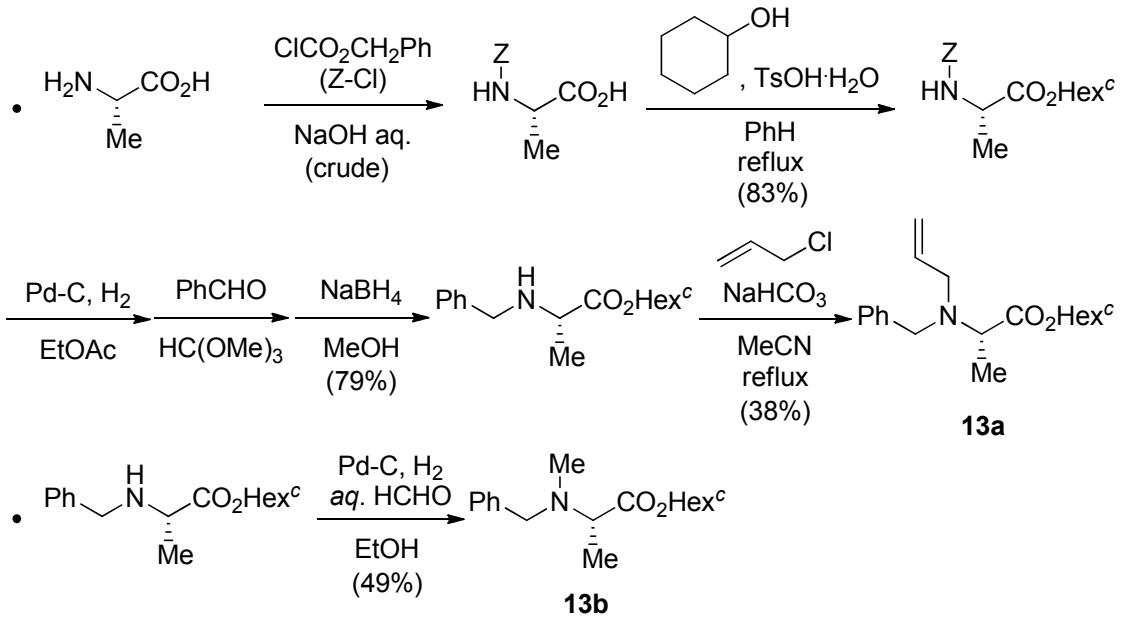
3-2 α-Tosylethenylation by chiral transfer from nitrogen atom to carbon atom

First, we prepared the substrates and reactants.

(*S*)-*N*-Allyl-*N*-benzylalanine cyclohexyl ester **13a** was synthesized (Scheme 3-2). Protection of commercial (*S*)-alanine by benzyl chloroformate (Z-Cl) gave Z-alanine, of which esterification with cyclohexanol afforded Z-alanine cyclohexyl ester. Deprotection of Z group, imination by benzaldehyde and subsequently reduction by sodium borohydride gave *N*-benzyl alanine cyclohexyl ester, which reacted with allyl

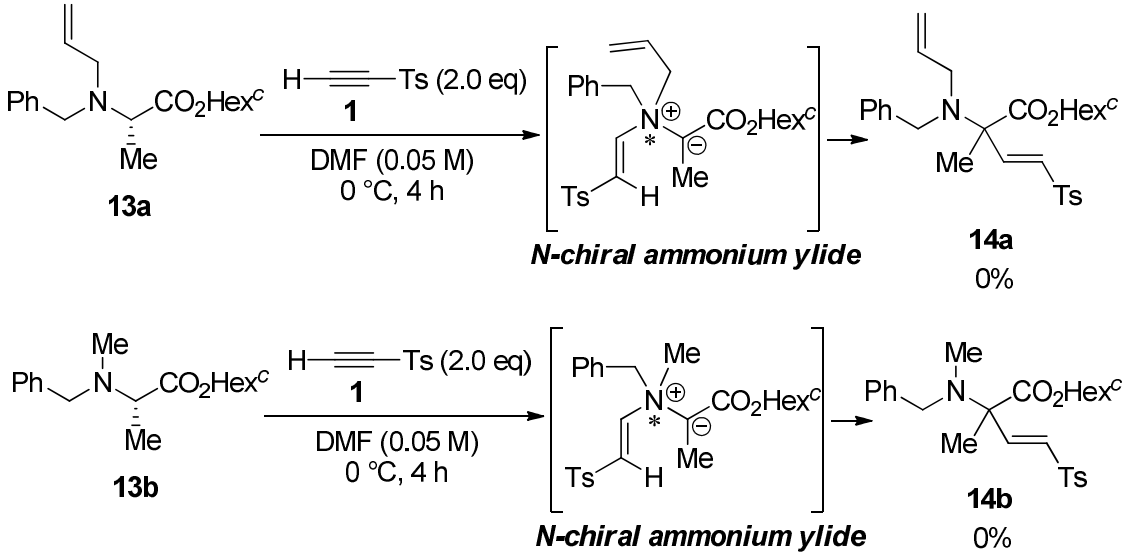
chloride to produce **13a**. *N*-Methyl substrate **13b** was synthesized from *N*-benzyl alanine cyclohexyl ester and formalin.

Scheme 3-2



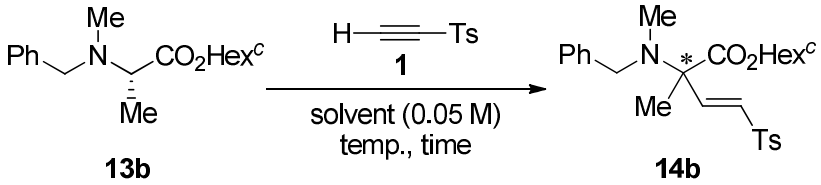
On the basis of "3-1 Background", the results of the experiments would be shown. We explored the asymmetric reaction of **13a** or **13b**, of which chiral center generates upon nitrogen atom in occurrence of ammonium ylides, via chiral transfer from nitrogen atom to carbon atom. We conducted the reaction of **13a** or **13b** with 2.0 equiv of **1** in DMF at 0 °C for 4 h (Scheme 3-3). **13a** did not react at all, while we confirmed the slightly quaternarization of **13b**.

Scheme 3-3



Herein, different solvents were explored to obtain α-tosylethenylated product **14b** (Table 3-1). The expected product **14b** was obtained in toluene and THF instead of DMF in low yields with low ee (entries 1,2). When the reaction of **13b** carried out in dichloromethane at 0 °C for 23 h, adduct **14b** was obtained in 46% yield without affecting the enantioselectivity (entry 3). In order to improve the yield of **14b**, we conducted the reaction of **13b** with 1.5 equiv of **1** in dichloromethane (0.1 M) at room temperature to afford **14b** in moderate yield with lower ee (entry 4). On the basis of this result, the addition of DMF to dichloromethane did affect the reaction negatively (entry 5). Described above, there was a limit to the asymmetric α-tosylethenylation via chiral transfer from nitrogen atom to carbon atom for obtaining the target products in high yield and enantioselectivity.

Table 3-1



Entry	Solvent	Equiv of **1**	Temp.	Time	Yield[a] (%)	ee[b] (%)
1	toluene	1.0	r.t.	1 day	27	31
2	THF	1.0	r.t.	2 days	19	28
3	CH_2Cl_2	1.0	0 °C	23 h	46	35
4	CH_2Cl_2 (0.1 M)	1.5	r.t.	10 h	69	9
5	CH_2Cl_2–DMF	1.0	0 °C	4 h	trace	–
	(1 : 1)		↓	↓		
			r.t.	22 h		

[a] Isolated yield. [b] Determined by HPLC analysis.

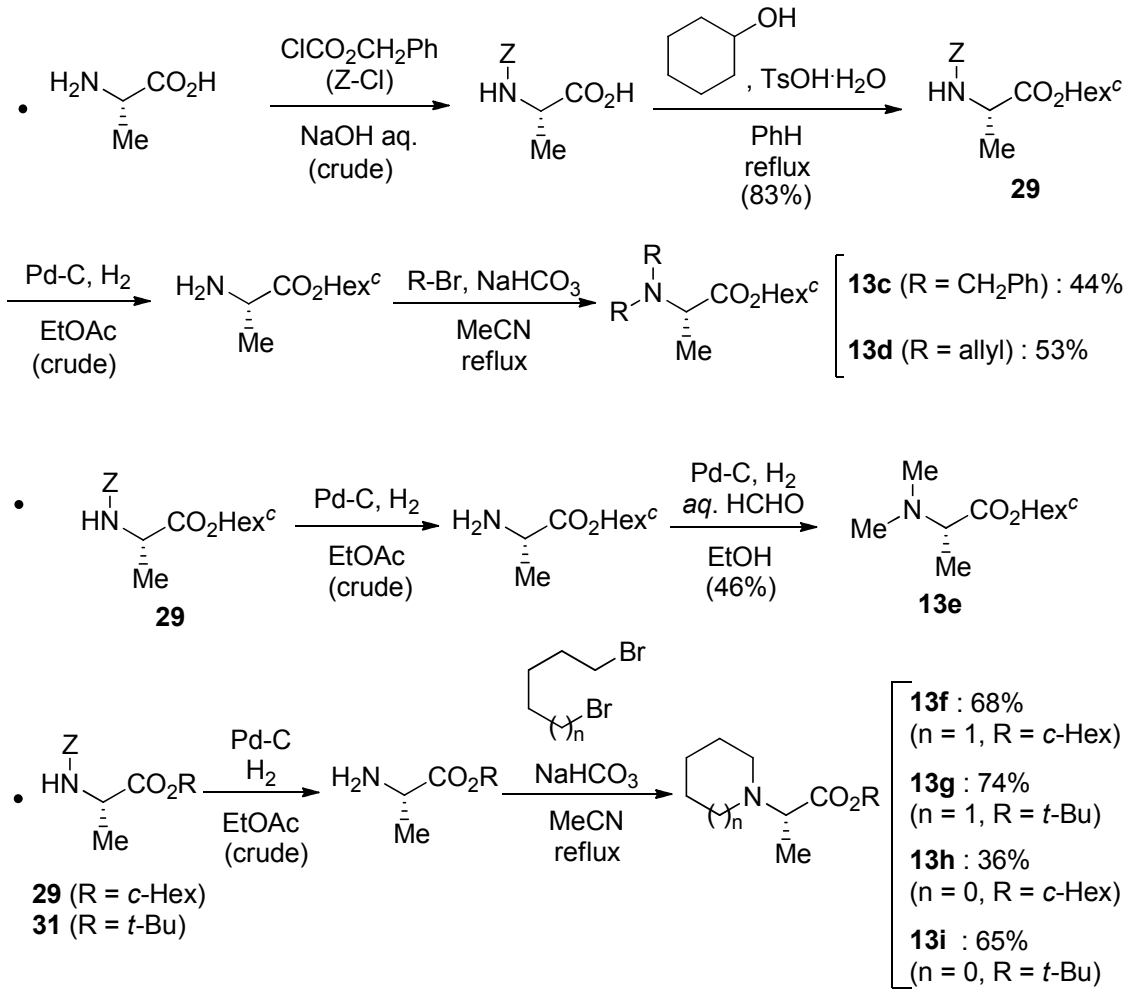
3-3 α-Tosylethenylation via non-racemic ammonium enolates

While we attempted "enantioselective α-tosylethenylation by chiral transfer from nitrogen atom to carbon atom", the expected results were not obtained. Herein, we applied to various *N*,*N*-dialkylalanine esters to investigate the reaction of acyclic amino acid derivatives with ethynyl tolyl sulfone.

First, we prepared the substrates.

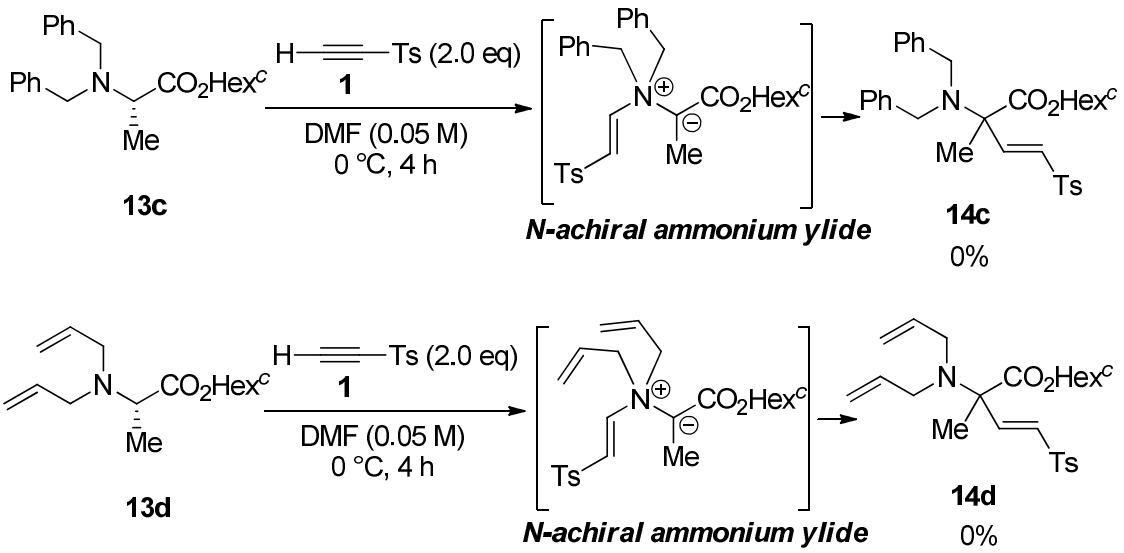
The (*S*)-*N*,*N*-dibenzylalanine cyclohexyl ester **13c** was synthesized (Scheme 3-4). Protection of commercial (*S*)-alanine by benzyl chloroformate (Z-Cl) gave Z-alanine, of which esterification with cyclohexanol afforded Z-alanine cyclohexyl ester. Deprotection of Z group and subsequently benzylation by benzyl bromide gave the *N*,*N*-dibenzyl alanine cyclohexyl ester **13c**. The (*S*)-*N*,*N*-diallylalanine cyclohexyl ester **13d** was synthesized by the same procedure with **13c** using allyl bromide instead of benzyl bromide. The 2-piperidinyl substrate **13f** and the 2-pyrrolidinyl substrate **13h** was synthesized by the same procedure with **13c** using 1,5-dibromopentane and 1,4-dibromobutane instead of benzyl bromide. The *tert*-butyl ester **13g** and **13i** was synthesized by the same procedure with **13f** and **13h** using isobutene gas instead of cyclohexanol. The *N*,*N*-dimethyl substrate **13e** was synthesized from alanine cyclohexyl ester and formalin.

Scheme 3-4



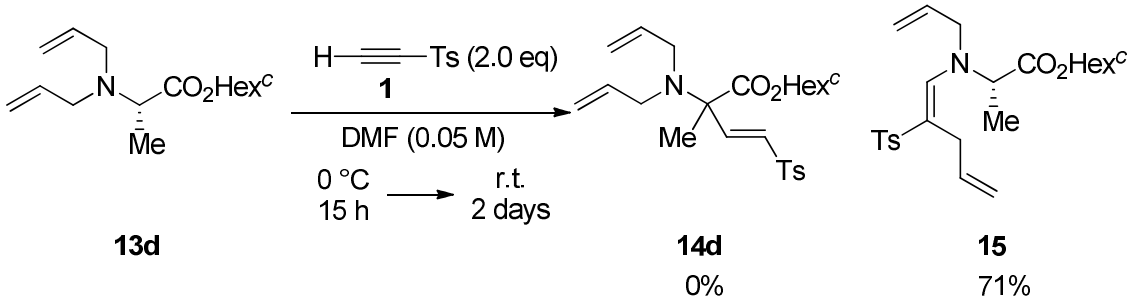
We conducted the reaction of *N*,*N*-dibenzyl **13c** and *N*,*N*-dialkyl **13d**, while the expected product **14c** and **14d** were not obtained at all (Scheme 3-5). It was reasoned that quaternarization of **13** is restricted by steric repulsion upon nitrogen atom.

Scheme 3-5



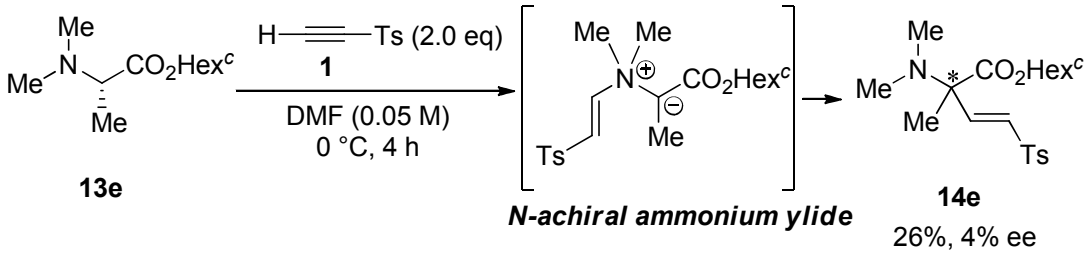
We extended the reaction time not to be able to obtain α-tosylethenylated product **14d**, while [3,3] sigmatropic rearrangement reaction, which is thought to be later than α-tosylethenylation in the reaction of proline derivatives, proceeded to give **15** (Scheme 3-6).

Scheme 3-6



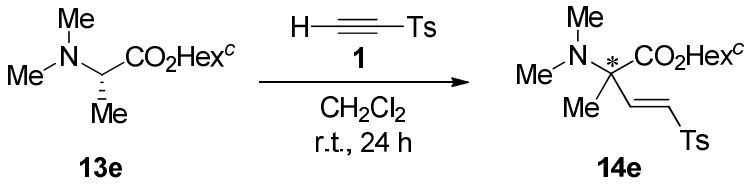
We conducted the reaction of *N*,*N*-dimethyl substrate **13e** to afford the expected α-tosylethenyl product **14e** in low yield (Scheme 3-7). Unexpectedly, **14e** was obtained in an enantio-enriched form, even though the expected reaction intermediate is the achiral ammonium ylide.

Scheme 3-7



Herein, dichloromethane instead of DMF were explored to improve the yield of **14e** without affecting the enantioselectivity (Table 3-2). Prompted by this unexpected observation, we investigated the reaction using other types of *N*,*N*-dialkyl amino acid esters.

Table 3-2

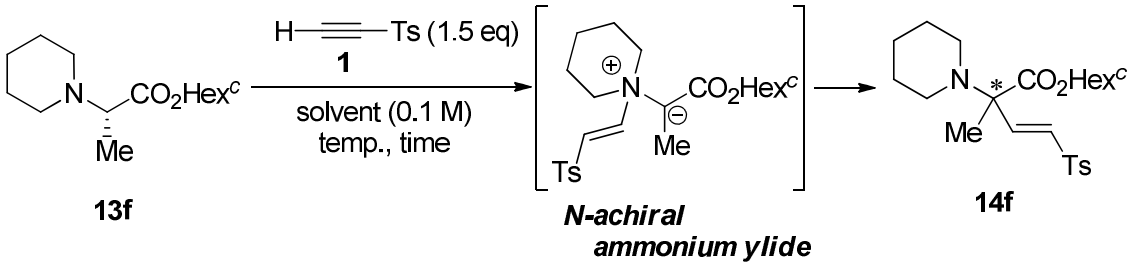


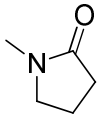
Entry	Conc. (M)	Equiv of **1**	Yield[a] (%)	ee[b] (%)
1	0.05	1.0	37	9
2	0.1	1.5	57	4

[a] Isolated yield. [b] Determined by HPLC analysis.

We conducted the reaction of the alanine derivative **13f**, which have six-membered ring on nitrogen atom (Table 3-3). The α-tosylethenylated product **14f** was obtained in good yield with 30% ee (entry 1). The reaction of **13f** with **1** proceeded in lower reaction temperature in order to improve the enantioselectivity, while the yield and enantioselectivity of **14f** decreased (entries 2,3). DMF instead of dichloromethane were explored to improve the enantioselectivity of **14f** (entry 4). We expected the improvement in the enantioselectivity when polar solvents would be used. Because the reaction in methanol gave **14f** in good yield with low ee, we thought that the enantioselectivity did not concern in polarity of solvents (entry 5). The yields and enantioselectivities were not affected in amides solvent, such as *N*,*N*-dimethylacetamide (DMA) and *N*-methyl-2-pyrrolidinone (entries 6,7). On the basis of this result, the addition of dichloromethane to DMF did affect the reaction negatively (entry 8).

Table 3-3

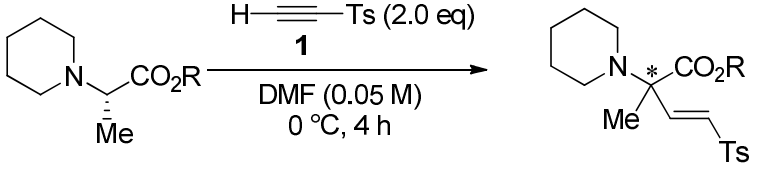


Entry	Solvent	Temp.	Time (h)	Yield[a] (%)	ee[b] (%)
1	CH_2Cl_2	r.t.	0.5	79	30
2	CH_2Cl_2	−20 °C	15	75	16
3	CH_2Cl_2	−40 °C	15	39	21
4	DMF	r.t.	3	23	77
5	MeOH	r.t.	3	78	45
6	DMA	r.t.	3	28	83
7		r.t.	3	27	81
8	CH_2Cl_2–DMA (1 : 1)	r.t.	3	43	68

[a] Isolated yield. [b] Determined by HPLC analysis. [c] DMA = *N*,*N*-dimethylacetamide

When the reaction of **13f** was carried out with 2.0 equiv of **1** in DMF, adduct **14f** was obtained in 17% yield with 75% ee (Scheme 3-8). In order to improve the yield of **14**, we conducted the reaction of *tert*-butyl ester **13g** to afford α-tosylethenylated product **14g** in 39% without affecting the enantioselectivity.

Scheme 3-8

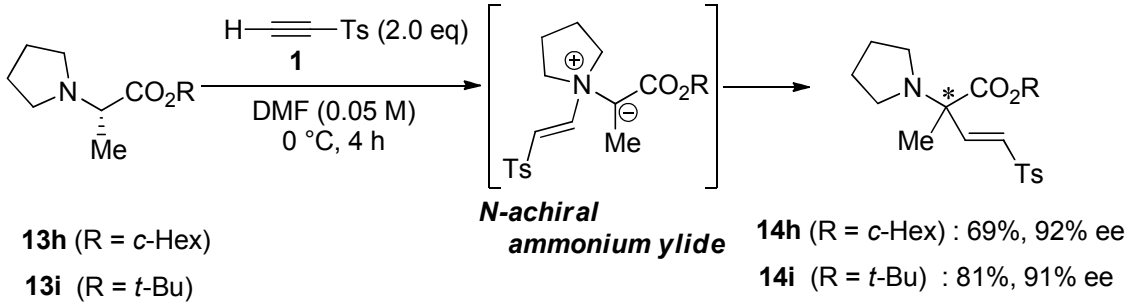


13f (R = *c*-Hex)
13g (R = *t*-Bu)

14f (R = *c*-Hex) : 17%, 75% ee
14g (R = *t*-Bu) : 39%, 78% ee

When the reaction of the alanine derivative **13h**, which have five-membered ring on nitrogen atom, was carried out under the optimal conditions, the yield and enantioselectivity were improved (Scheme 3-9). Further, we conducted the reaction of the *tert*-butyl ester **13i** to afford the α-tosylethenylated product **14i** in good yield with excellent enantioselectivity. We thought that the initially quaternarization proceeded smoothly, because the steric repulsion upon nitrogen atom would be reduced.

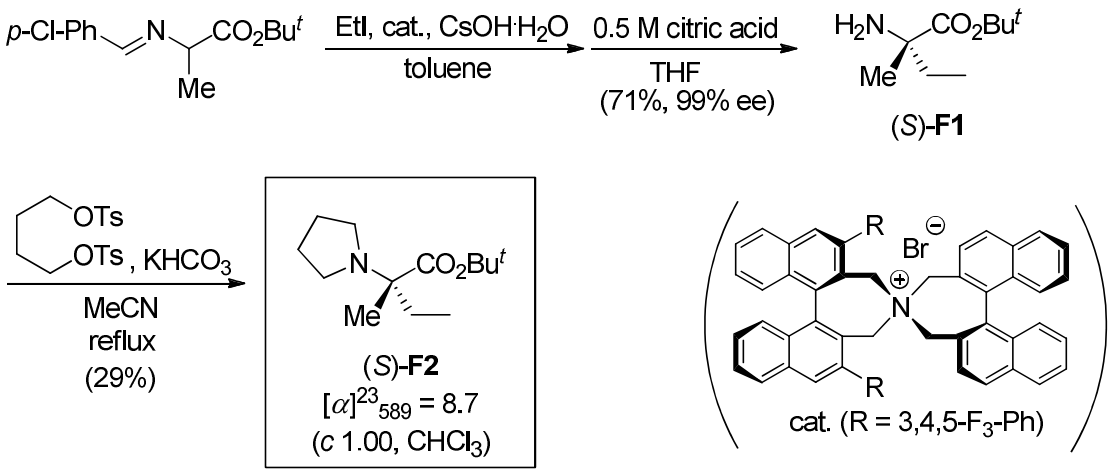
Scheme 3-9



3-4 The assignment of the configuration at α-position

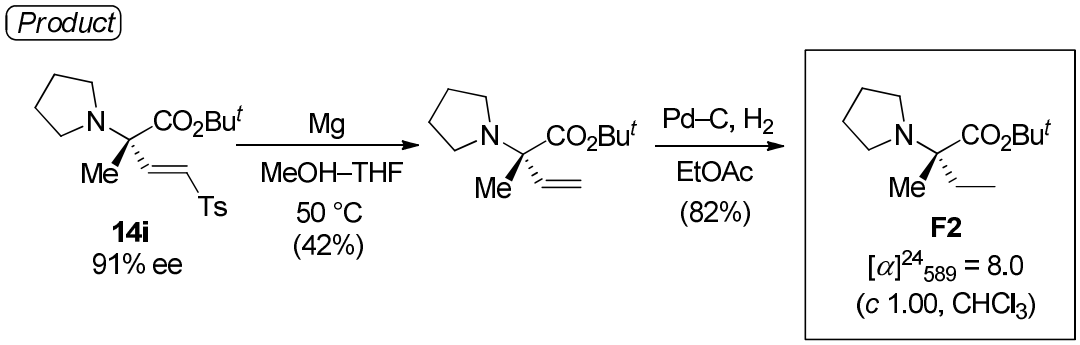
The assignment of the configuration of **14i** was determined by a comparison of the authentic sample (Scheme 3-10). According to the previous report,[1] (*S*)-α-ethylalanine derivative **F1** was synthesized from the corresponding schiff base. Cyclization of nitrogen atom on (*S*)-**F1** gave (*S*)-**F2**, of which the specific rotation was recorded.

Scheme 3-10



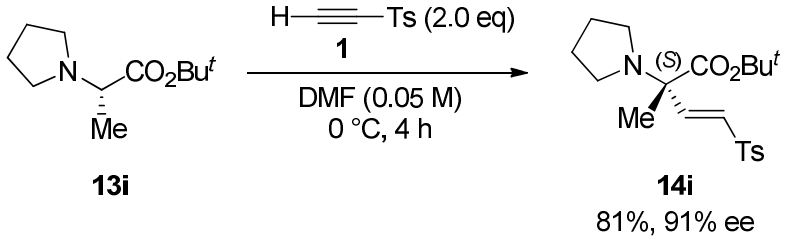
On the other hand, the detosylation of **14i** by the treatment of magnesium and subsequently hydrogenation reaction gave (*S*)-**F2**, which was the same (*S*)-α-ethylalanine derivative described above (Scheme 3-11).

Scheme 3-11



As a result, the (*S*)-configuration of **14i**, which was obtained from the *N*,*N*-dialkylalanine derivative and ethynyl tolyl sulfone, was determined (Scheme 3-12).

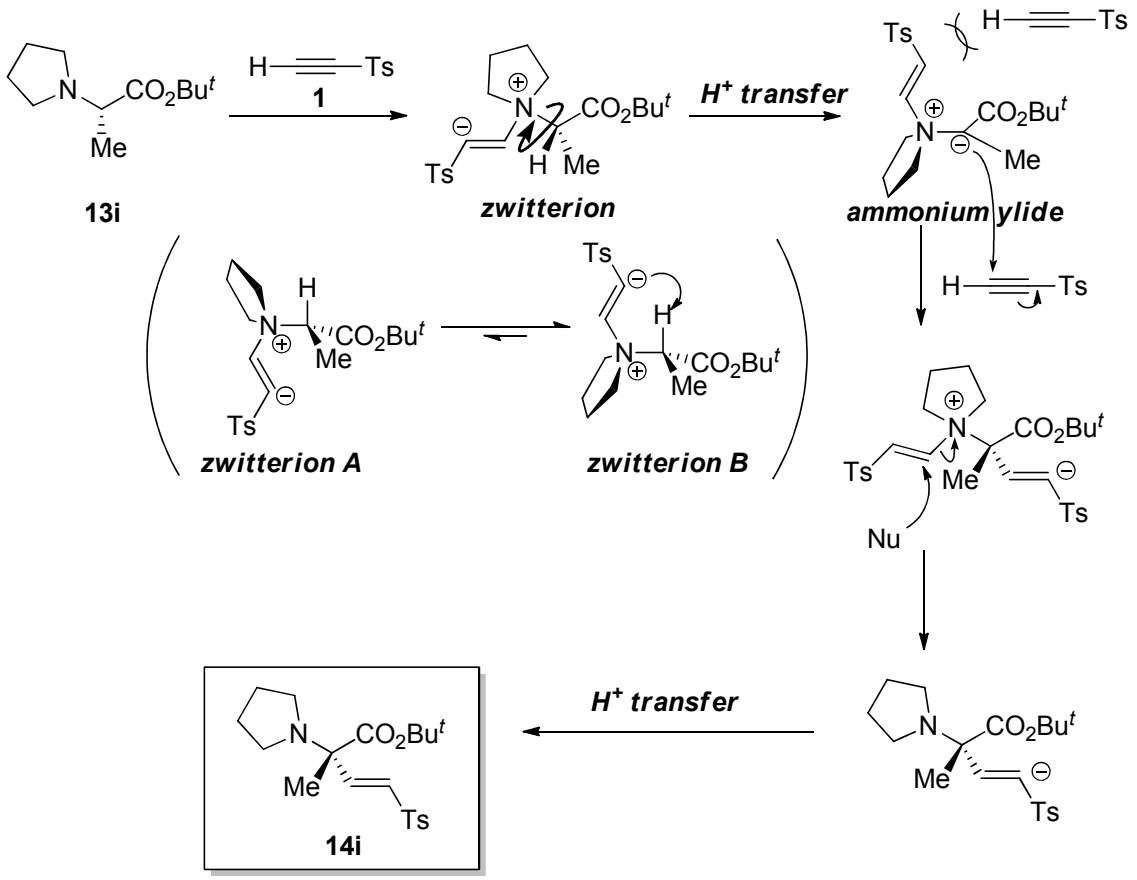
Scheme 3-12



3-5 A proposed mechanism

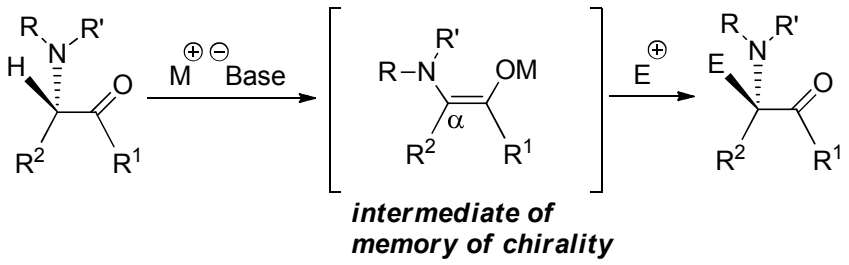
We thought that the reaction of the alanine derivatives proceeded in the same way as the proline derivatives (Scheme 3-13). The reaction of **13i** with **1** affords *N*-tosylethenyl ammonium zwitterion, of which nitrogen–α-carbon bond would rotate freely to become ***zwitterion A*** or ***zwitterion B***. We expected the conformation of ***zwitterion B*** because the anion part would move near more acidic proton at α-position of alanine. The anion part of ***zwitterion B*** abstracts α-proton to produce ammonium ylide, of which the anion part would attack to **1** quickly. In the nucleophilic addition of ammonium ylide, the intermediate was obtained in an enantio-enriched form because of the steric repulsion of the *N*-2-tosylethenyl substituent. Finally, the *N*-2-tosylethenyl substituent is eliminated by the reaction with nucleophiles to form (*S*)-configuration of **14i**.

Scheme 3-13



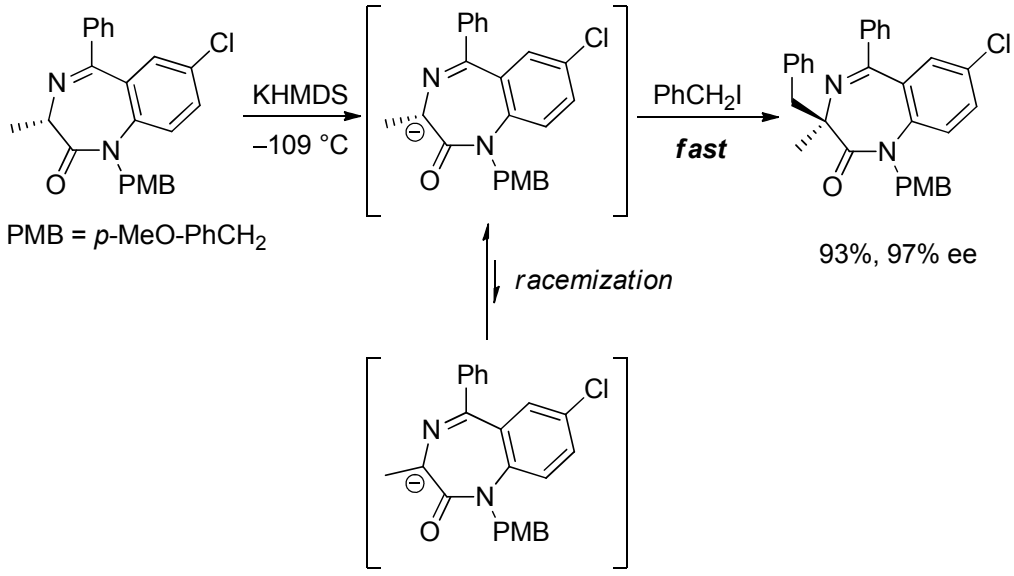
Although its exact origin is unclear, the high stereoselectivity might be rationalized as a result of the formation of the non-racemic ammonium enolate (memory of chirality). Carlier et al.,[2] Kouklovsky et al.,[3] and Kawabata et al.[4] reported memory of chirality of α-amino ketone or α-amino acid derivatives (Scheme 3-14). The addition of electrophiles to achiral enolates, which was treated with properly basic reagents, gave the corresponding chiral product.

Scheme 3-14



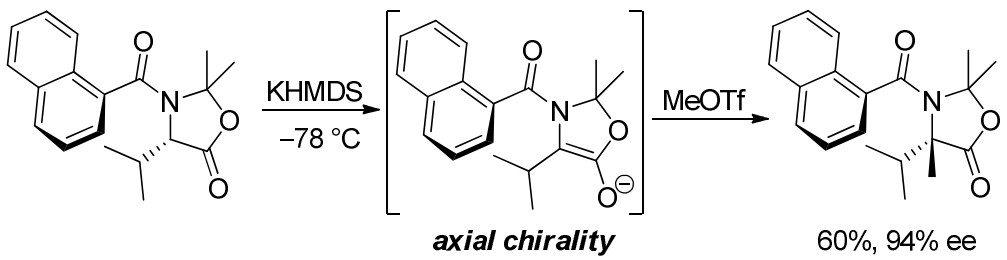
Carlier et al. has reported that potassium bis(trimethylsilyl)amide (KHMDS) was added to 1,4-benzodiazepine-2-one at －109 °C, and the generated enolate reacted with benzyl iodide to afford the chiral product with 97% ee (Scheme 3-15).[2] It was explained that the reaction conditions in low temperature and high reactive reagent, such as benzyl iodide, resulted in a significantly enantioselectivity, because memory of chirality was attributed to the competition between the racemization and alkylation.

Scheme 3-15



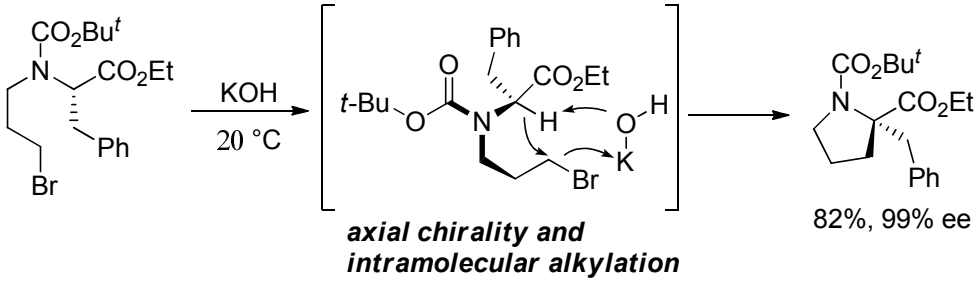
Kouklovsky et al. has discovered that KHMDS was added to oxazoline with cyclic α-amino acid skeleton at －78 °C, and the generated enolate reacted with methyl triflate to afford the chiral product with 94% ee (Scheme 3-16).[3] It was reported that memory of chirality was observed due to axial chirality which was concerned with rotation of Ar–CO bond and N–CO bond.

Scheme 3-16



Kawabata et al. has reported that the reaction of acyclic amino acid derivatives with memory of chirality proceeded at room temperature (Scheme 3-17).[4] The deprotonation and electrophilic addition would proceed concertedly to restrict the racemization, because the intramolecular reaction would occur via the barrier of rotation by bulky substituent upon nitrogen atom to prevent rotation of nitrogen–α-carbon bond.

Scheme 3-17

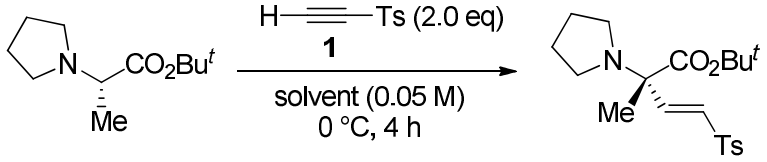


These reactions described above have in common with retention of stereochemistry in inducing substituents, while α-tosylethenylation proceeded with inversion of stereochemistry. This type reaction with memory of chirality was rarely known, and extremely interested academically.

3-6 The effects of solvents in the α-tosylethenylation reaction

First, different solvents were explored to discover those suitable for the α-tosylethenylation reaction (Table 3-4). The yields of **13i** were increased in dichloromethane, toluene, THF and ethyl acetate instead of DMF without affecting the enantioselectivity (entries 1-5). Next, the reaction in methanol afforded **14i** in 81% yield with lower ee (entry 6). When isopropanol as aprotic solvent also was used, the yield and enantioselectivity of **14i** were similar to the results in nonpolar solvents (entry 7).

Table 3-4



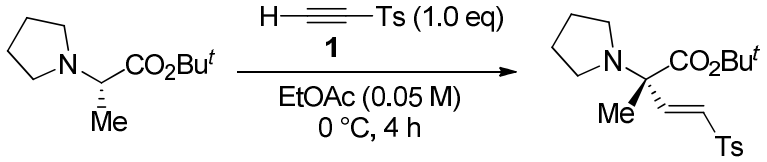
13i **14i**

Entry	Solvent	Yield[a] (%)	ee[b] (%)
1	DMF	81	91
2	CH_2Cl_2	97	90
3	toluene	92	88
4	THF	91	94
5	EtOAc	99	90
6	MeOH	81	78
7	*i*-PrOH	92	93

[a] Isolated yield. [b] Determined by HPLC analysis.

We conducted the reaction of **13i** with 1.0 equiv of **1** to decrease the yield of **14i** (Scheme 3-18). It was reasoned that initially quaternarization proceeded slowly due to decreasing amount of **1**. However, tosylethenyl group upon nitrogen atom after the addition of ammonium ylide to **1** was used as subsequent quaternarization of **13i**, because this reaction proceeded smoothly despite of 1.0 equiv of **1**.

Scheme 3-18



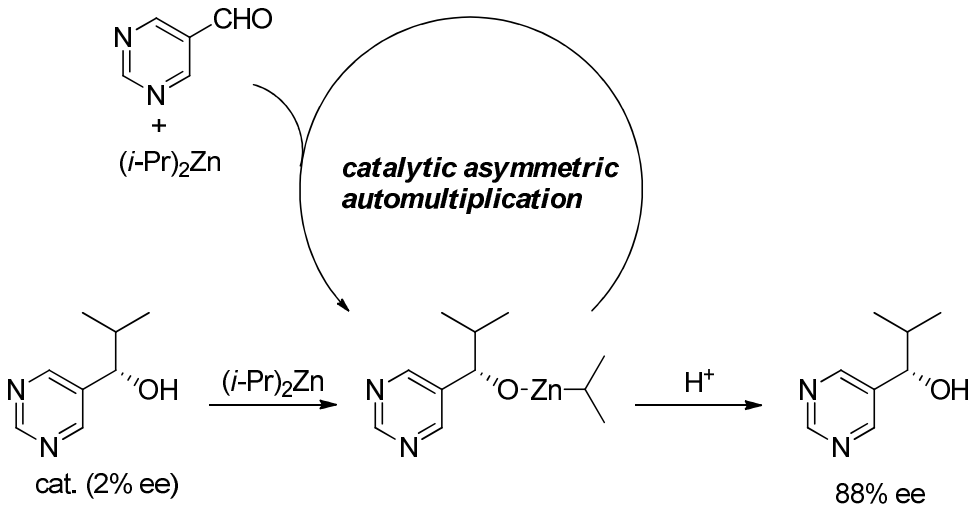
13i **14i**

86%, 91% ee

We explored the asymmetric autocatalysis by the substrates to attempt the reaction with non-racemic substrates at different % ee.

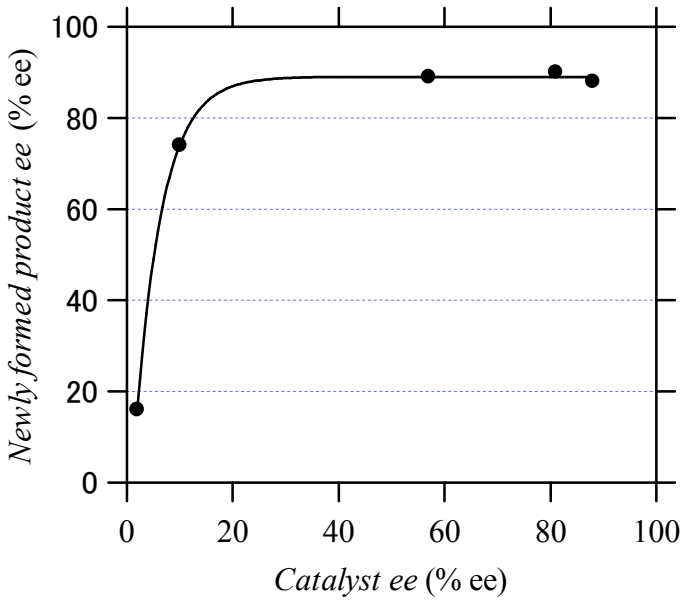
Soai et al. has reported that the addition of diisopropyl zinc and 5-formyl pyridine to 5-pyrimidylalkanol with 2% ee promoted asymmetric automultiplication to give alkanol with 10% ee (Table 3-5, Figure 3-1). Further, high enantioselective alkanol was obtained by the repetition of this reaction.[5]

Table 3-5



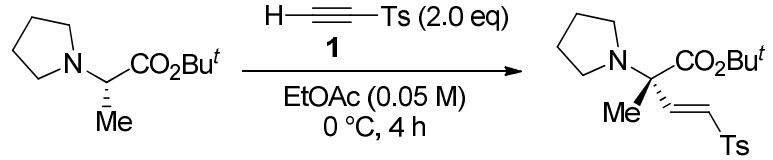
Run	Catalyst ee (%)	Newly formed product ee (%)
1	2	10
2	10	57
3	57	81
4	81	88
5	88	88

Figure 3-1



We conducted the reaction of non-racemic substrate (*S*)-**13i** at different% ee (25% ee, 51% ee, and 75% ee) and obtained the results against the % ee of the product **14i**. The non-linear effects were not observed (Table 3-6, Figure 3-2). The asymmetric automultiplication did not occur in α-tosylethenylation reaction.

Table 3-6



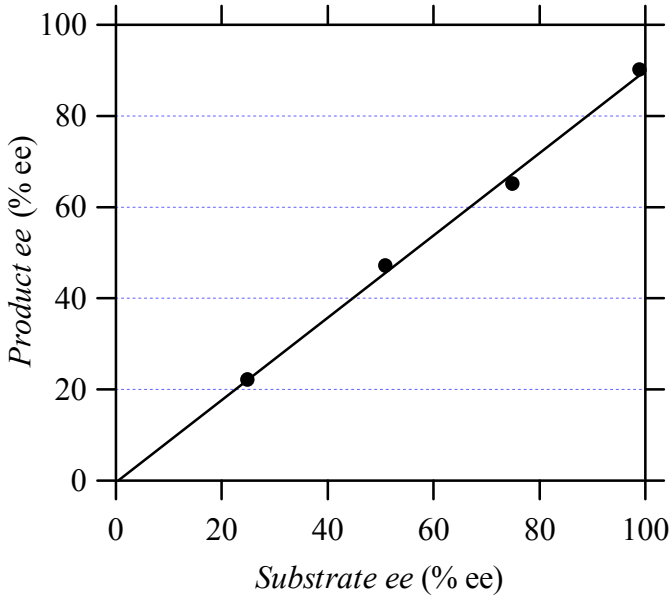
13i
(25% ee to 99% ee)

14i
99%

Entry	Substrate ee (%)	Product ee (%)[a]
1	25	22
2	51	47
3	75	65
4	99	90

[a] Determined by HPLC analysis.

Figure 3-2

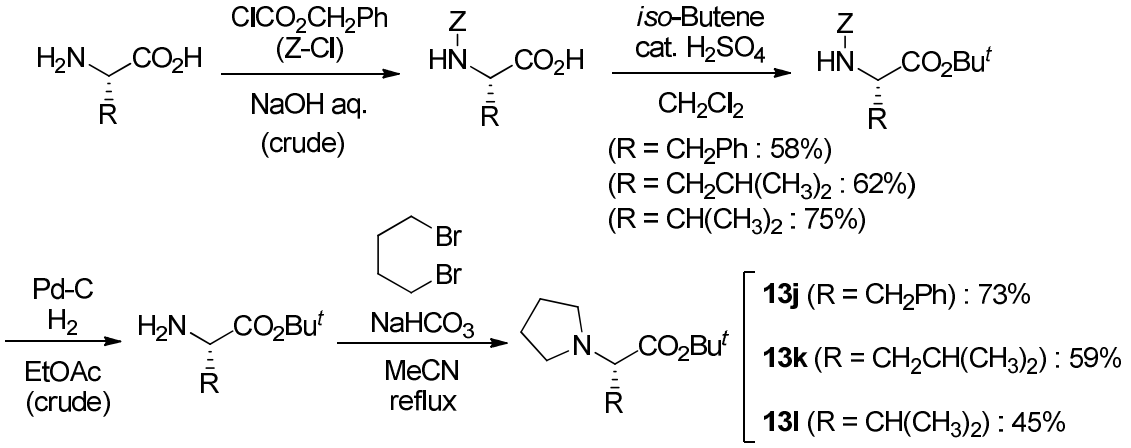


3-7 The application to the other amino acid derivatives

First, we prepared the substrates.

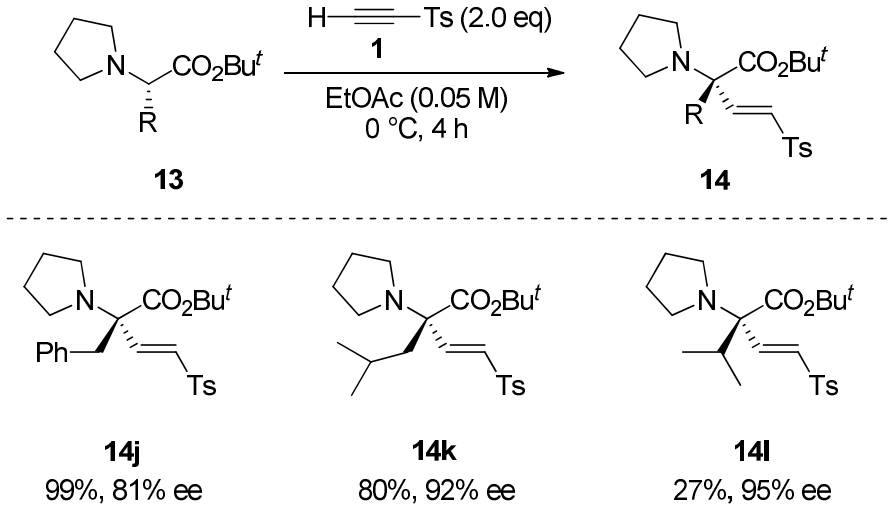
The various 2-pyrrolidinyl substrate **13j**, **13k** and **13l** was synthesized by the same procedure with **13i** using the corresponding amino acid instead of alanine (Scheme 3-19).

Scheme 3-19

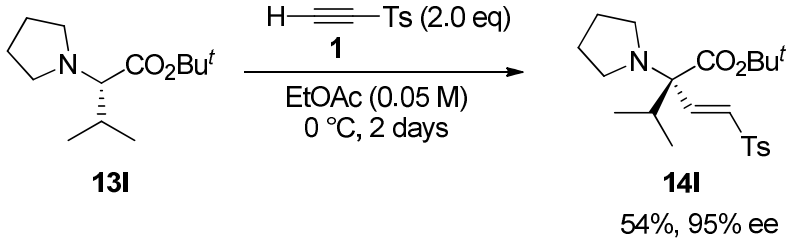


Other α-amino acid derivatives prepared from phenylalanine **13j** or leucine **13k** reacted smoothly with the same levels of enantioselectivity, while the valine derivative **13l** was less reactive (Scheme 3-20). The corresponding α-adduct **14l** was obtained in only 27% yield with 95% ee. The yield was improved to 54% after 48 h of stirring (Scheme 3-21).

Scheme 3-20



Scheme 3-21



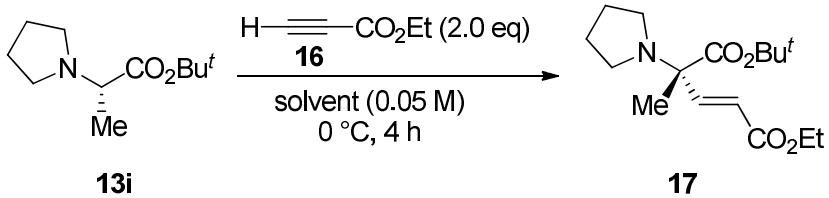
13l **14l**

54%, 95% ee

3-8 The reaction of the *N*-cyclic alanine derivative with ethyl propynoate

We conducted less reactive acetylene instead of ethynyl tolyl sulfone (Table 3-7). The reaction of **13i** with ethyl propynoate **16** in DMF gave **17** in low yield with moderate ee (entry 1). Different solvents were explored to discover those suitable for this reaction. The yields of **17** were decreased in dichloromethane, toluene, THF and ethyl acetate instead of DMF (entries 2-5). The satisfied results were not obtained compared to the reaction with ethynyl tolyl sulfone. We thought that the enantioselectivity was decreased, because the anion part of ammonium ylide would slowly attack to **16**, which is less reactive than ethynyl tolyl sulfone, and competed with the rotation of nitrogen–α-carbon bond.

Table 3-7



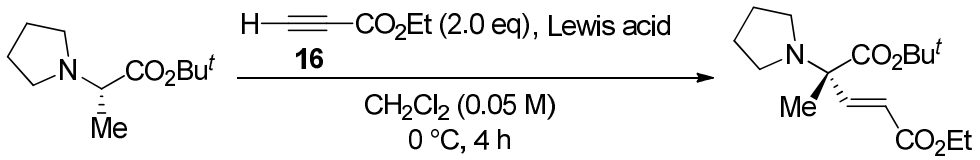
13i **17**

Entry	Solvent	Yield[a] (%)	ee[b] (%)
1	DMF	27	49
2	CH_2Cl_2	11	67
3	toluene	trace	–
4	THF	17	67
5	EtOAc	11	78

[a] Isolated yield. [b] Determined by HPLC analysis.

We conducted the reaction with addition of lewis acid in order to improve the reactivity of **16** (Table 3-8). Unexpectedly, the improvement of yields and enantioselectivities were not observed, and the substrate **13i** and **16** were decomposed (entries 1-5).

Table 3-8



Entry	Lewis acid (equiv)	Yield[a] (%)	ee[b] (%)
1	BF_3·Et_2O (1.0)	9	65
2	$FeCl_3$ (0.9)	4	70
3	$SnCl_4$ (1.0)	0	–
4	$ZnCl_2$ (1.2)	0	–
5	$AlCl_3$ (1.0)	trace	–

[a] Isolated yield. [b] Determined by HPLC analysis.

3-9 Summary

The asymmetric α-tosylethenylation reaction of cyclic amino acid derivatives could not proceed via chiral transfer from nitrogen atom to carbon atom. However, α-tosylethenylated products were obtained in an enantio-enriched form, even though the expected reaction intermediate is the achiral ammonium ylide. When we also applied this reaction to the various amino acid derivatives, α-tosylethenylation reaction proceeded enantioselectively.

Experimental Section

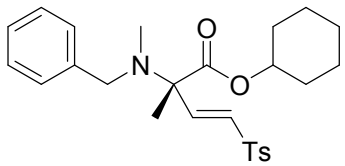
General

^{1}H and ^{13}C NMR spectra were measured on a Varian 400 MHz (^{1}H: 400 MHz, ^{13}C: 100 MHz) spectrometer. Splitting patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. Infrared spectra were recorded on a Perkin Elmer Spectrum GX FT-IR spectrometer. High-resolution mass spectra were measured on a Thermofisher Scientific LC/FT-MS spectrometer. Specific rotations were recorded on a JASCO Polarimeter P–1010. Reactions were conducted in round-bottomed flask with a magnetic stirring bar under a argon atmosphere. *N*,*N*-Dimethylformamide (DMF) was dried over molecular sieves 4Å prior to use. For thin layer chromatography (TLC) analysis throughout this work, Merck TLC plates (silica gel 60 F_{254}) were used. The products were purified by preparative column chromatography on silica gel (silica gel 60N, spherical neutral, KANTO Chemical Co., Inc., Japan).

Representative procedure for the asymmetric α-2-tosylvinylation of *N*-benzyl-*N*-methyl α-alanine ester 13b

A solution of tosylacetylene (**1**) (36.2 mg, 0.201 mmol) in CH_2Cl_2 (1.3 mL) was added to a solution of **13b** (55.2 mg, 0.200 mmol) in CH_2Cl_2 (2.7 mL) at 0 °C under an argon atmosphere. After stirring for 23 h at the same temperature, the excess amount of **1** was quenched by addition of 40% methylamine solution in methanol (46 μL, 0.45 mmol). The resulting mixture was stirred for 15 min at room temperature, diluted with water, and extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate, and concentrated. Purification of the residue by chromatography on silica gel (hexane/dichloromethane = 1/3 to 1/8 as eluent) gave **14b** (41.6 mg, 46% yield) as a colorless oil.

(*E*)-Cyclohexyl 2-(*N*-benzyl-*N*-methylamino)-2-methyl-4-tosylbut-3-enoate (14b)



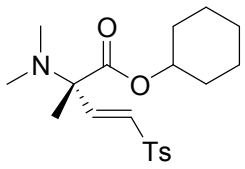
Colorless oil; 35% ee [determined by HPLC analysis: Daicel Chirapak AD–H column, *n*-hexane/isopropanol = 91.5/8.5 as eluent, flow rate = 0.50 mL/min, t_R = 24.4 min for the minor enantiomer and 27.7 min for the major enantiomer]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (2H, d, *J* = 8.1 Hz, ArH), 7.34-7.19 (8H, ArH, Ph and TsCH=C*H*), 6.68 (1H, d, *J* = 15.4 Hz, TsC*H*=CH), 4.87 (1H, tt, *J* = 8.1, 4.1 Hz, OCH), 3.61 (1H, d, *J* = 13.9 Hz, CH_2Ph), 3.53 (1H, d, *J* = 13.9 Hz, CH_2Ph), 2.41 (3H, s, ArCH_3), 2.14 (3H, s, NCH_3), 1.89-1.59 (4H, m, *c*-Hex), 1.59-1.22 (6H, m, *c*-Hex),

1.49 (3H, s, 2-CH_3).

Representative procedure for the asymmetric α-tosylvinylation of *N*,*N*-dialkyl α-amino acid esters

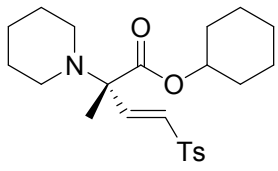
A solution of tosylacetylene (**1**) (75.9 mg, 0.421 mmol) in DMF (1.3 mL) was added to a solution of **13e** (42.1 mg, 0.211 mmol) in DMF (2.7 mL) at 0 °C under an argon atmosphere. After stirring for 4 h at the same temperature, the excess amount of **1** was quenched by addition of 40% methylamine solution in methanol (46 μL, 0.45 mmol). The resulting mixture was stirred for 15 min at room temperature, diluted with water, and extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate, and concentrated. Purification of the residue by chromatography on silica gel (hexane/ethyl acetate = 1/1 to ethyl acetate as eluent) gave **14e** (21.1 mg, 26% yield) as a colorless oil.

(*E*)-Cyclohexyl 2-(*N*,*N*-dimethylamino)-2-methyl-4-tosylbut-3-enoate (14e)



Colorless oil; 4% ee [determined by HPLC analysis: Daicel Chirapak AD–H column, *n*-hexane/ethanol = 92/8 as eluent, flow rate = 0.50 mL/min, t_R = 24.7 min for the (*S*)-**14e** and 29.0 min for the (*R*)-**14e**]; $[\alpha]^{24}_{589}$ –1.5 (*c* 1.00 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (2H, d, *J* = 8.2 Hz, ArH), 7.33 (2H, d, *J* = 8.2 Hz, ArH), 7.13 (1H, d, *J* = 15.2 Hz, TsCH=C*H*), 6.58 (1H, d, *J* = 15.2 Hz, TsC*H*=CH), 4.83 (1H, tt, *J* = 8.8, 4.0 Hz, OCH), 2.43 (3H, s, $ArCH_3$), 2.28 (6H, s, $N(CH_3)_2$), 1.93-1.64 (4H, m, *c*-Hex), 1.58-1.22 (6H, m, *c*-Hex), 1.38 (3H, s, 2-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 146.9, 144.3, 137.4, 131.6, 129.9, 127.7, 73.9, 67.2, 39.7, 31.48, 31.46, 25.2, 23.51, 23.50, 21.6, 20.6; IR (film) 3059, 2938, 2861, 2793, 1721, 1634, 1597, 1452, 1369, 1320, 1235, 1147, 1086, 1037, 1013, 972, 912, 813, 736, 683 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{20}H_{30}NO_4S$: 380.1890. found: 380.1876.

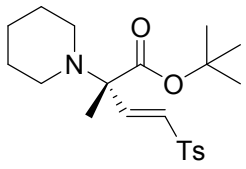
(*E*)-Cyclohexyl 2-methyl-2-(piperidin-1-yl)-4-tosylbut-3-enoate (14f)



Colorless oil; 75% ee [determined by HPLC analysis: Daicel Chiralpak AD–H column, *n*-hexane/ethanol = 95/5 as eluent, flow rate = 0.50 mL/min, t_R = 17.0 min for the (*S*)-**14f** and 20.8 min for the (*R*)-**14f**]; $[\alpha]^{25}_{589}$ –16.2 (*c* 1.00 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (2H, d, *J* = 8.2 Hz, ArH), 7.33 (2H, d, *J* = 8.2 Hz, ArH), 7.16 (1H, d, *J* = 15.2 Hz, TsCH=C*H*), 6.61 (1H, d, *J* = 15.2 Hz, TsC*H*=CH),

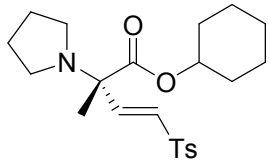
4.82 (1H, tt, J = 8.6, 3.6 Hz, OCH), 2.48 (4H, t, J = 5.0 Hz, NCH_2), 2.43 (3H, s, $ArCH_3$), 1.83-1.63 (4H, m, *c*-Hex), 1.56-1.24 (12H, m, piperidine-CH_2 and *c*-Hex), 1.35 (3H, s, 2-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 148.3, 144.2, 137.5, 130.9, 129.8, 127.5, 73.5, 67.7, 48.4, 31.5, 31.4, 26.6, 25.2, 24.6, 23.4, 23.3, 22.6, 21.5, 20.7; IR (film) 3058, 2937, 2858, 1723, 1632, 1597, 1452, 1371, 1320, 1240, 1179, 1147, 1120, 1087, 1034, 1013, 961, 908, 835, 812, 737, 704, 685 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{23}H_{34}NO_4S$: 420.2203. found: 420.2188.

(*E*)-*tert*-Butyl 2-methyl-2-(piperidin-1-yl)-4-tosylbut-3-enoate (14g)



Colorless oil; 77% ee [determined by HPLC analysis: Daicel Chiralcel OJ–H column, *n*-hexane/ethanol = 99/1 as eluent, flow rate = 0.50 mL/min, t_R = 34.1 min for the (*R*)-**14g** and 37.8 min for the (*S*)-**14g**]; $[\alpha]^{24}_{589}$ –21.1 (*c* 1.00 in EtOH); ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (2H, d, J = 8.2 Hz, ArH), 7.32 (2H, d, J = 8.2 Hz, ArH), 7.14 (1H, d, J = 15.4 Hz, TsCH=C*H*), 6.59 (1H, d, J = 15.4 Hz, TsC*H*=CH), 2.49 (4H, t, J = 4.8 Hz, NCH_2), 2.43 (3H, s, $ArCH_3$), 1.54-1.38 (6H, m, piperidine-CH_2), 1.44 (9H, s, *t*-Bu), 1.31 (3H, s, 2-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 148.8, 144.2, 137.6, 130.6, 129.8, 127.6, 82.1, 68.1, 48.5, 28.1, 26.7, 24.7, 21.6, 20.8; IR (film) 2975, 2935, 2854, 2816, 1723, 1628, 1597, 1455, 1393, 1369, 1319, 1286, 1253, 1148, 1123, 1087, 1049, 961, 885, 840, 812, 770, 675 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{21}H_{32}NO_4S$: 394.2047. found: 394.2032.

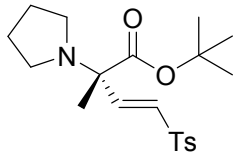
(*S*,*E*)-Cyclohexyl 2-methyl-2-(pyrrolidin-1-yl)-4-tosylbut-3-enoate (14h)



Colorless oil; 92% ee [determined by HPLC analysis: Daicel Chiralpak AD–H column, *n*-hexane/ethanol = 95/5 as eluent, flow rate = 0.50 mL/min, t_R = 21.5 min for (*S*)-**14h** and 25.5 min for (*R*)-**14h**]; $[\alpha]^{25}_{589}$ –27.2 (*c* 1.00 in EtOH); ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (2H, d, J = 8.2 Hz, ArH), 7.33 (2H, d, J = 8.2 Hz, ArH), 7.18 (1H, d, J = 15.4 Hz, TsCH=C*H*), 6.56 (1H, d, J = 15.4 Hz, TsC*H*=CH), 4.83 (1H, tt, J = 8.6, 3.8 Hz, OCH), 2.82-2.74 (2H, m, NCH_2), 2.71-2.62 (2H, m, NCH_2), 2.44 (3H, s, $ArCH_3$), 1.84-1.63 (4H, m, *c*-Hex), 1.73 (4H, tt, J = 3.2 Hz, NCH_2CH_2) 1.56-1.24 (6H, m, *c*-Hex), 1.45 (3H, s, 2-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 146.6, 144.2, 137.4, 131.1, 129.8, 127.6, 73.6, 65.4, 47.3, 31.4, 25.2, 24.1, 23.4, 23.1, 21.5; IR (film) 3059, 2938, 2860, 1722, 1631, 1597, 1452, 1370, 1320, 1302, 1289, 1250, 1193, 1147, 1085, 1035, 1013, 973, 912, 835, 812, 736, 706 cm^{-1}; HRMS–ESI

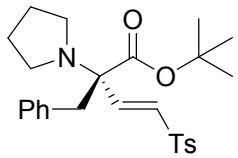
(*m*/*z*): $[M+H]^+$ calcd for $C_{22}H_{32}NO_4S$: 406.2047. found: 406.2033.

(*S*,*E*)-*tert*-Butyl 2-methyl-2-(pyrrolidin-1-yl)-4-tosylbut-3-enoate (14i)



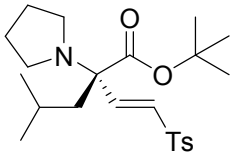
Colorless oil; 91% ee [determined by HPLC analysis: Daicel Chiralpak AS–H column, *n*-hexane/isopropanol = 90/10 as eluent, flow rate = 0.50 mL/min, t_R = 22.7 min for the (*R*)-**14i** and 31.0 min for (*S*)-**14i**]; $[\alpha]^{25}_{589}$ –30.5 (*c* 1.00 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (2H, d, *J* = 8.0 Hz, ArH), 7.33 (2H, d, *J* = 8.0 Hz, ArH), 7.16 (1H, d, *J* = 15.2 Hz, TsCH=C*H*), 6.53 (1H, d, *J* = 15.2 Hz, TsC*H*=CH), 2.81-2.73 (2H, m, NCH_2), 2.71-2.63 (2H, m, NCH_2), 2.43 (3H, s, $ArCH_3$), 1.72 (4H, tt, *J* = 3.0, 3.0 Hz, NCH_2CH_2), 1.45 (9H, s, *t*-Bu), 1.42 (3H, s, 2-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 147.0, 144.2, 137.5, 130.8, 129.8, 127.5, 82.1, 65.6, 47.2, 28.0, 24.1, 23.1, 21.5; IR (film) 3062, 2972, 2875, 2828, 1729, 1596, 1475, 1456, 1392, 1368, 1303, 1269, 1146, 1088, 990, 877, 844, 815, 740, 699 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{20}H_{30}NO_4S$: 380.1890. found: 380.1878.

(*S*,*E*)-*tert*-Butyl 2-benzyl-2-(pyrrolidin-1-yl)-4-tosylbut-3-enoate (14j)



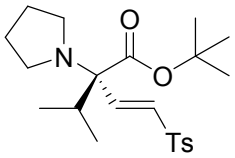
Colorless oil; 89% ee [determined by HPLC analysis: Daicel Chiralcel OD–H column, *n*-hexane/isopropanol = 98.2/1.8 as eluent, flow rate = 0.50 mL/min, t_R = 20.2 min for (*R*)-**14j** and 22.7 min for (*S*)-**14j**]; $[\alpha]^{22}_{589}$ +17.9 (*c* 1.00 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (2H, d, *J* = 8.0 Hz, ArH), 7.29 (2H, d, *J* = 8.0 Hz, ArH), 7.18-7.12 (3H, m, Ph), 6.98-6.94 (2H, m, Ph), 6.77 (1H, d, *J* = 15.2 Hz, TsCH=C*H*), 6.60 (1H, d, *J* = 15.2 Hz, TsC*H*=CH), 3.47 (1H, d, *J* = 12.8 Hz, CH_2Ph), 2.88 (2H, ddd, *J* = 12.6, 3.6, 2.6 Hz, pyrrolidine-NCH_2), 2.77 (1H, d, *J* = 12.8 Hz, CH_2Ph), 2.67 (2H, ddd, *J* = 12.6, 3.6, 2.6 Hz, pyrrolidine-NCH_2), 2.42 (3H, s, $ArCH_3$), 1.72 (2H, ddd, *J* = 7.0, 3.6, 2.6 Hz, pyrrolidine-CH_2), 1.69 (2H, ddd, *J* = 7.0, 3.6, 2.6 Hz, pyrrolidine-CH_2), 1.41 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 147.3, 144.1, 137.6, 135.0, 131.4, 130.4, 129.7, 128.1, 127.7, 127.0, 82.6, 69.6, 47.2, 44.8, 28.2, 23.7, 21.6; IR (film) 3062, 3032, 2974, 2934, 2873, 1718, 1597, 1495, 1454, 1393, 1369, 1319, 1302, 1264, 1147, 1086, 1021, 973, 841, 813, 737, 702 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{26}H_{34}NO_4S$: 456.2203. found: 456.2186.

(*S*,*E*)-*tert*-Butyl 2-isobutyl-2-(pyrrolidin-1-yl)-4-tosylbut-3-enoate (14k)



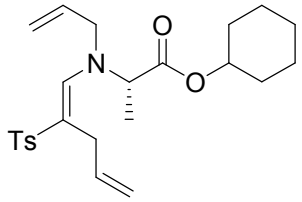
Colorless oil; 93% ee [determined by HPLC analysis: Daicel Chiralpak AS–H column, *n*-hexane/isopropanol = 95/5 as eluent, flow rate = 0.50 mL/min, t_R = 24.8 min for (*R*)-**14k** and 33.2 min for (*S*)-**14k**]; $[\alpha]^{22}_{589}$ −38.5 (*c* 1.00 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (2H, d, *J* = 8.2 Hz, ArH), 7.29 (2H, d, *J* = 8.2 Hz, ArH), 7.17 (1H, d, *J* = 15.4 Hz, TsCH=C*H*), 6.62 (1H, d, *J* = 15.4 Hz, TsC*H*=CH), 2.72 (2H, ddd, *J* = 12.8, 4.4, 2.8, pyrrolidine-NCH_2), 2.54 (2H, ddd, *J* = 12.8, 4.4, 2.8, pyrrolidine-NCH_2), 2.40 (3H, s, $ArCH_3$), 1.98-1.87 (1H, m, $CH_2CH(CH_3)_2$), 1.69-1.53 (6H, m, $CH_2CH(CH_3)_2$ and pyrrolidine-CH_2), 1.44 (9H, s, *t*-Bu), 0.824 (3H, d, *J* = 6.6 Hz, $CH_2CH(CH_3)_2$), 0.821 (3H, d, *J* = 6.6 Hz, $CH_2CH(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 147.2, 144.1, 137.8, 131.0, 129.8, 127.6, 82.2, 68.6, 47.4, 46.8, 28.2, 24.5, 24.3, 23.7, 23.5, 21.6; IR (film) 3059, 2964, 2872, 1717, 1628, 1597, 1457, 1392, 1368, 1320, 1300, 1241, 1146, 1087, 1039, 1017, 977, 921, 841, 811, 707, 686 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{23}H_{36}NO_4S$: 422.2360. found: 422.2344.

(*S*,*E*)-*tert*-Butyl 2-isopropyl-2-(pyrrolidin-1-yl)-4-tosylbut-3-enoate (14l)



Colorless oil; 97% ee [determined by HPLC analysis: Daicel Chiralpak AS–H column, *n*-hexane/isopropanol = 97/3 as eluent, flow rate = 0.50 mL/min, t_R = 40.9 min for (*R*)-**14l** and 46.8 min for (*S*)-**14l**]; $[\alpha]^{23}_{589}$ −47.9 (*c* 1.00 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (2H, d, *J* = 8.2 Hz, ArH), 7.30 (2H, d, *J* = 8.2 Hz, ArH), 7.04 (1H, d, *J* = 15.2 Hz, TsCH=C*H*), 6.56 (1H, d, *J* = 15.2 Hz, TsC*H*=CH), 2.81-2.71 (2H, m, NCH_2), 2.51-2.42 (2H, m, NCH_2), 2.41 (3H, s, $ArCH_3$), 2.35 (1H, septet, *J* = 6.8 Hz, $CH(CH_3)_2$), 1.66-1.57 (4H, m, pyrrolidine-CH_2), 1.46 (9H, s, *t*-Bu), 0.82 (3H, d, *J* = 6.8 Hz, $CH(CH_3)_2$), 0.72 (3H, d, *J* = 6.8 Hz, $CH(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 144.1, 144.0, 138.0, 132.9, 129.8, 127.5, 82.1, 72.5, 46.6, 33.5, 28.3, 23.6, 21.6, 18.4, 16.4; IR (film) 3059, 2971, 2930, 2875, 1716, 1633, 1597, 1456, 1392, 1369, 1320, 1297, 1289, 1252, 1147, 1087, 1017, 976, 928, 878, 841, 815, 734, 709 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{22}H_{34}NO_4S$: 408.2203. found: 408.2189.

(*S*,*E*)-Cyclohexyl 2-[*N*-(prop-2-en-1-yl)-*N*-(2'-tosylpent-1',4'-dien-1'-yl)amino]propanoate (15)

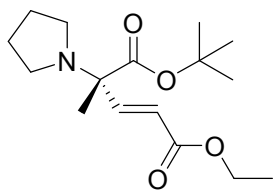


Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (2H, d, *J* = 8.2 Hz, ArH), 7.60 (1H, s, NCH=C), 7.21 (2H, d, *J* = 8.2 Hz, ArH), 5.76 (1H, dddd, *J* = 17.0, 10.0, 5.2, 4.4 Hz, CCH_2CH=CH_2), 5.68 (1H, dddd, *J* = 17.6, 10.0, 5.2, 4.6 Hz, NCH_2CH=CH_2), 5.15 (1H, dddd, *J* = 10.0, 1.8, 1.6, 1.0 Hz, NCH_2CH=CH_2), 5.14 (1H, dddd, *J* = 17.6, 1.8, 1.6, 1.0 Hz, NCH_2CH=CH_2), 4.90 (1H, dd, *J* = 10.0, 1.6 Hz, CCH_2CH=CH_2), 4.87 (1H, dd, *J* = 17.0, 1.6 Hz, CCH_2CH=CH_2), 4.78 (1H, tt, *J* = 7.8, 3.6 Hz, OCH), 4.06 (1H, q, *J* = 7.2 Hz, NCHCO), 3.84 (1H, dddd, *J* = 17.6, 5.2, 1.6, 1.6 Hz, NCH_2CH=CH_2), 3.78 (1H, dddd, *J* = 17.6, 4.6, 1.6, 1.6 Hz, NCH_2CH=CH_2), 3.06-2.91 (2H, m, CCH_2CH=CH_2), 2.37 (3H, s, $ArCH_3$), 1.85-1.64 (4H, m, *c*-Hex), 1.56-1.20 (6H, m, *c*-Hex), 1.46 (3H, d, *J* = 7.2, 2-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 145.5, 142.4, 139.7, 136.7, 134.4, 129.3, 127.4, 117.0, 115.6, 103.0, 73.9, 61.2, 51.6, 31.4, 29.1, 25.2, 23.5, 21.4, 16.7.

Representative procedure for the asymmetric α-2-ethoxycarbonylethenylation of (*S*)-*tert*-butyl 2-(pirrolidin-1-yl)propanoate (13i)

Ethyl propionate (**16**) (42.1 μL, 0.415 mmol) was added to a solution of **13i** (41.4 mg, 0.208 mmol) in ethyl acetate (4.0 mL) at 0 °C under an argon atmosphere. After stirring for 4 h at the same temperature, the excess amount of **16** was quenched by addition of 40% methylamine solution in methanol (46 μL, 0.45 mmol). The resulting mixture was stirred for 15 min at room temperature, diluted with water, and extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate, and concentrated. Purification of the residue by chromatography on silica gel (hexane/ethyl acetate = 4/1 to 2/1 as eluent) gave **17** (6.9 mg, 11% yield) as a colorless oil.

(*E*)-*tert*-Butyl 2-methyl-2-(pyrrolidin-1-yl)-4-ethoxycarbonylbut-3-enoate (17)

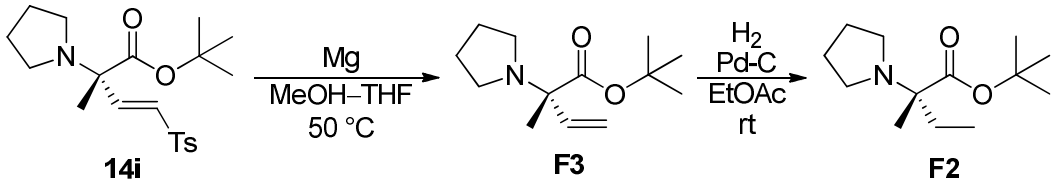


Colorless oil; 78% ee [determined by HPLC analysis: Daicel Chiralcel OD–H column, *n*-hexane/isopropanol = 99.3/0.7 as eluent, flow rate = 0.50 mL/min, t_R = 13.0 min for

(*R*)-**17** and 15.8 min for (*S*)-**17**]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (1H, d, *J* = 16.0 Hz, C*H*=CHCO), 5.97 (1H, d, *J* = 16.0 Hz, CH=C*H*CO), 4.18 (2H, q, *J* = 7.2 Hz, OCH_2CH$_3$), 2.84-2.69 (4H, m, NCH_2), 1.73 (4H, tt, *J* = 9.9, 3.4 Hz, pyrrolidine-CH_2), 1.45 (9H, s, *t*-Bu), 1.42 (3H, s, 2-CH_3) 1.27 (3H, t, *J* = 7.2 Hz, OCH$_2$CH_3).

Determination of the absolute configuration of 14i

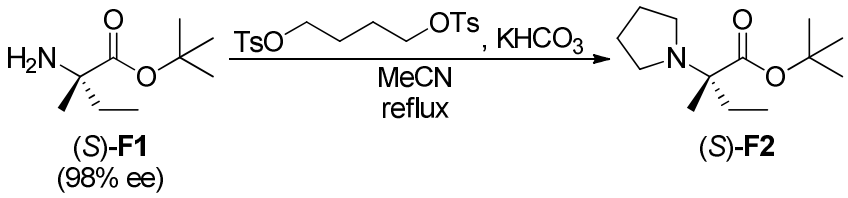
Conversion to *tert*-butyl 2-methyl-2-(pirrolidin-1-yl)butanoate (F2) from 14i



(Step 1) A solution of **14i** (296 mg, 0.779 mmol) in THF (7.8 mL) was added to a suspention of magnesium powder (193 mg, 7.94 mmol) in dry methanol (7.8 mL) at 50 °C. The mixture was stirred for 2 h at the same temperature and quenched with saturated aqueous ammonium chlolride at 0 °C. Extractive work-up and purification by chromatography on silica gel (hexane/ethyl acetate = 2/1 as eluent) gave *tert*-butyl 2-methyl-2-(pyrrolidin-1-yl)but-3-enoate **F3** (73 mg, 42% yield) as a colorless oil.

(Step 2) A mixture of **F3** (63 mg, 0.28 mmol) and palladium on carbon (loading: 10 wt.%, 5 mg) in ethyl acetate (2.8 mL) was stirred for 1 h under a hydrogen atmosphere. The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated. The residue was purified by chromatography on silica gel (dichloromethane/methanol = 10/1 as eluent) to give **F2** (52 mg, 82% yield) as a colorless oil. $[\alpha]^{24}_{589}$ +8.0 (*c* 1.00 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.90-2.82 (2H, m, NCH_2), 2.76-2.68 (2H, m, NCH_2), 1.84 (1H, dq, *J* = 13.6, 7.6 Hz, CH_2CH$_3$), 1.74 (4H, tt, *J* = 3.6, 3.0 Hz, pyrrolidine-CH_2), 1.63 (1H, dq, *J* = 13.6, 7.6 Hz, CH_2CH$_3$), 1.46 (9H, s, *t*-Bu), 1.24 (3H, s, 2-CH_3), 0.88 (3H, t, *J* = 7.6 Hz, CH$_2$CH_3).

Preparation of the authentic sample (*S*)-F2

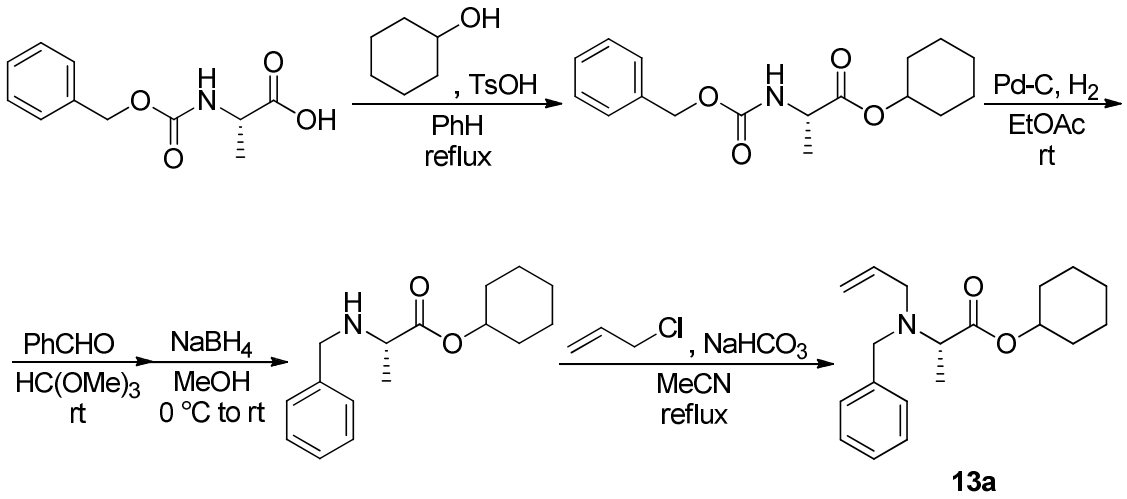


A mixture of (*S*)-**F1** (68 mg, 0.39 mmol), 1,4-butanediol di-*p*-toluenesulfonate (163 mg, 0.41 mmol), and potassium hydrogen carbonate (0.12 g, 0.12 mmol) in acetonitrile (2 mL) was refluxed for 6 h. The resulting mixture was cooled to room

temperature and concentrated. The residue was purified twice by chromatography on silica gel (1st: dichloromethane/methanol = 20/1 to 10/1 as eluent, 2nd: hexane/ethyl acetate = 3/1 to 1.5/1 as eluent) to obtaine (*S*)-**F2** (25.6 mg, 29% yield) as a colorless oil; $[\alpha]^{23}_{589}$ +8.7 (*c* 1.00 in $CHCl_3$).

Preparation of substrates

(*S*)-Cyclohexyl 2-[*N*-benzyl-*N*-(prop-2-en-1-yl)amino]propanoate (13a)



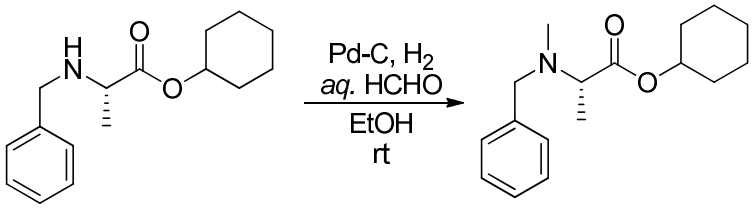
(Step 1) A solution of (*S*)-Cbz-alanine (1.60 g, 7.0 mmol), cyclohexanol (0.82 mL, 7.8 mmol) and *p*-toluenesulfonic acid, monohydrate (0.15 g, 0.78 mmol) in benzene (14 mL) was refluxed for 15 h with azeotropic removal of water by a Dean-Stark trap. The resulting mixture was cooled to room temperature and quenched with saturated aqueous sodium hydrogen carbonate. The mixture was extracted with ethyl acetate and the combined extracts were washed with brine. The solution was dried over sodium sulfate and concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 3:1 as eluent) to obtain (*S*)-Cbz-alanine cyclohexyl ester (1.80 g, 83% yield) as a colorless oil.

(Step 2) A mixture of (*S*)-Cbz-alanine cyclohexyl ester (0.33 g, 1.1 mmol) and palladium on activated carbon (loading: 10 wt.%, 25 mg) in ethyl acetate (2.2 mL) was stirred for 2 h at room temperature under a hydrogen atmosphere. The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated. The residual oil was dissolved in trimethyl orthoformate (2.2 mL). The solution was added benzaldehyde (0.11 mL, 1.1 mmol) and stirred for 48 h at room temperature. The resulting mixture was concentrated and the residue was dissolved in methanol (4.2 mL). The solution was treated with sodium borohydride (55 mg, 1.5 mmol) at 0 °C and stirred for 12 h at room temperature. The resulting mixture was diluted with water and extracted with ethyl acetate. The combined extracts were washed with bride, dried over

sodium sulfate and concentrated. Purification of the residue by chromatography on silica gel afforded (*S*)-*N*-benzylalanine cyclohexyl ester (0.22 g, 79% yield) as a colorless oil.

(Step 3) A mixture of (*S*)-*N*-benzylalanine cyclohexyl ester (0.29 g, 1.1 mmol), allyl chloride (99 μL, 1.2 mmol), and sodium hydrogen carbonate (0.29 g, 3.4 mmol) in acetonitrile (5 mL) was refluxed for 13 h. The resulting mixture was cooled to room temperature and filtered. The filtrate was concentrated and the residue was purified by chromatography on silica gel (hexane/ethyl acetate = 20:1 as eluent) to obtain **13a** (0.13 g, 38% yield) as a colorless oil. $[\alpha]^{22}_{589}$ –87.8 (*c* 1.00 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (2H, d, *J* = 7.4 Hz, Ph), 7.29 (1H, td, *J* = 7.4, 1.6 Hz, Ph), 7.21 (1H, tt, *J* = 7.4, 2.0 Hz, Ph), 5.80 (1H, dddd, *J* = 16.9, 10.2, 7.2, 5.4 Hz, CH_2CH=CH_2), 5.21 (1H, ddd, *J* = 16.9, 3.2, 2.0 Hz, CH_2CH=CH_2), 5.09 (1H, ddd, *J* = 10.2, 3.2, 1.6 Hz, CH_2CH=CH_2), 4.83 (1H, tt, *J* = 8.8, 3.8 Hz, OCH), 3.86 (1H, d, *J* = 14.4 Hz, CH_2Ph), 3.63 (1H, d, *J* = 14.4 Hz, CH_2Ph), 3.53 (1H, q, *J* = 7.2 Hz, NCHCO), 3.28 (1H, dddd, *J* = 14.5, 5.4, 2.0, 1.6 Hz, CH_2CH=CH_2), 3.14 (1H, dd, *J* = 14.5, 7.2 Hz, CH_2CH=CH_2), 1.92-1.67 (4H, m, *c*-Hex), 1.58-1.24 (6H, m, *c*-Hex), 1.28 (3H, d, *J* = 7.2 Hz, 2-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 140.2, 136.8, 128.5, 128.1, 126.7, 116.9, 72.4, 56.9, 54.3, 53.5, 31.9, 31.7, 25.4, 23.7, 23.6, 15.3; IR (film) 3065, 3028, 2937, 2859, 1728, 1642, 1603, 1494, 1452, 1418, 1371, 1332, 1246, 1196, 1161, 1063, 1039, 1016, 994, 920, 865, 811, 776, 737, 698 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{19}H_{28}NO_2$: 302.2115. found: 302.2105.

(*S*)-Cyclohexyl 2-(*N*-benzyl-*N*-methylamino)propanoate (13b)

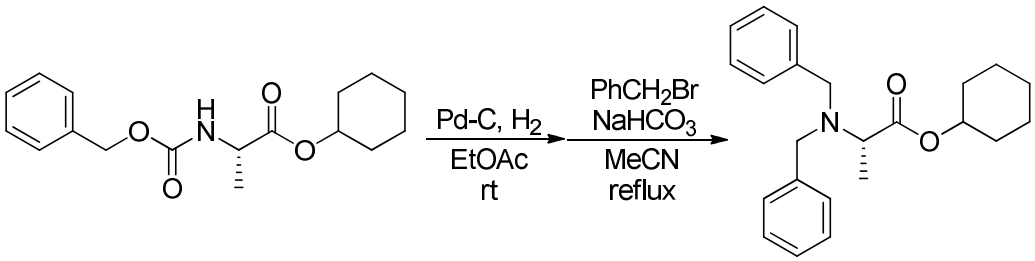


13b

A solution of (*S*)-*N*-benzylalanine cyclohexyl ester (0.22 g, 0.85 mmol), palladium on activated carbon (loading: 10 wt.%, 24 mg), and formaldehyde solution (37 wt.% in water, 0.65 mL, 8.7 mmol) in ethanol (1.7 mL) was stirred for 12 h under a hydrogen atmosphere. The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 8:1 as eluent) to obtain **13b** (0.11 g, 49% yield) as a colorless oil. $[\alpha]^{23}_{589}$ –54.3 (*c* 1.00 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.27 (4H, m, Ph), 7.23 (1H, tt, *J* = 7.0, 1.6 Hz, Ph), 4.85 (1H, tt, *J* = 9.0, 3.8 Hz, OCH), 3.76 (1H, d, *J* = 13.6 Hz, CH_2Ph), 3.63 (1H, d, *J* = 13.6 Hz, CH_2Ph), 3.43 (1H, q, *J* = 7.2 Hz, NCHCO), 2.29 (3H, s, NCH_3), 1.94-1.81 (2H, m, *c*-Hex), 1.80-1.69 (2H, m, *c*-Hex), 1.60-1.23 (6H, m, *c*-Hex), 1.33 (3H, d, *J* = 7.2 Hz, CHCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6,

139.4, 128.7, 128.1, 126.8, 72.4, 60.8, 58.2, 37.8, 31.9, 31.7, 25.3, 23.6, 15.2; IR (film) 3028, 2938, 2859, 2799, 1726, 1494, 1452, 1366, 1326, 1217, 1179, 1123, 1096, 1074, 1039, 1015, 959, 943, 922, 808, 772, 735, 698 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{17}H_{26}NO_2$: 276.1958. found: 276.1956.

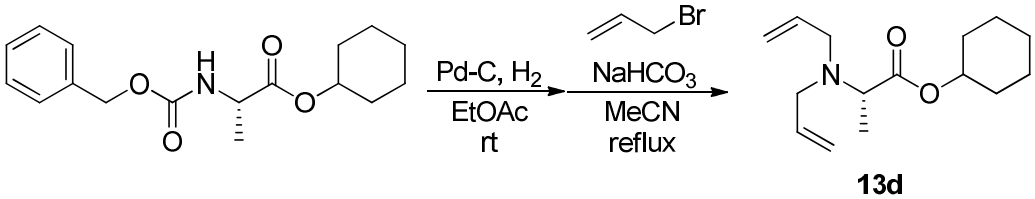
(*S*)-Cyclohexyl 2-(*N*,*N*-dibenzylamino)propanoate (13c)



13c

A mixture of (*S*)-Cbz-alanine cyclohexyl ester (1.20 g, 4.0 mmol) and palladium on activated carbon (loading: 10 wt.%, 83 mg) in ethyl acetate (8 mL) was stirred for 1.5 h at room temperature under a hydrogen atmosphere. The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated. A mixture of the residual oil, benzyl bromide (1.1 mL, 8.8 mmol), and sodium hydrogen carbonate (1.1 g, 13 mmol) in acetonitrile (20 mL) was refluxed for 24 h. The resulting mixture was filtered and the filtrate was concentrated. Purification of the residue by chromatography on silica gel (hexane/ethyl acetate = 10:1 as eluent) gave **13c** (0.61 g, 44% yield) as a colorless oil. $[\alpha]^{24}_{589}$ –98.5 (*c* 1.00 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (4H, d, *J* = 7.6 Hz, Ph), 7.26 (4H, dd, *J* = 7.6, 7.2 Hz, Ph), 7.17 (2H, t, *J* = 7.2 Hz, Ph), 4.87 (1H, tt, *J* = 8.8, 3.6 Hz, OCH), 3.84 (2H, d, *J* = 14.0 Hz, C*H*$_2$Ph), 3.65 (2H, d, *J* = 14.0 Hz, C*H*$_2$Ph), 3.47 (1H, q, *J* = 7.2 Hz, NCHCO), 1.95-1.78 (2H, m, *c*-Hex), 1.78-1.61 (2H, m, *c*-Hex), 1.57-1.22 (6H, m, *c*-Hex), 1.29 (3H, d, *J* = 7.2 Hz, 2-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 139.8, 128.4, 128.0, 126.7, 72.2, 56.0, 54.3, 31.8, 31.5, 25.2, 23.5, 23.4, 14.8; IR (film) 3062, 3028, 2937, 2858, 1725, 1494, 1452, 1373, 1327, 1247, 1195, 1147, 1076, 1015, 954, 909, 828, 810, 734, 698 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{23}H_{30}NO_2$: 352.2271. found: 352.2266.

(*S*)-Cyclohexyl 2-(*N*,*N*-diallylamino)propanoate (13d)

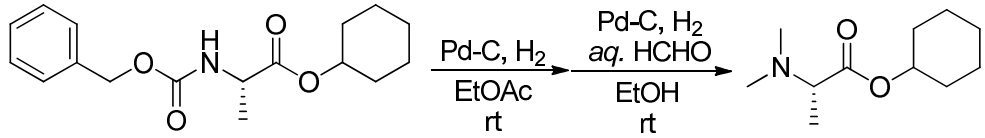


13d

A mixture of (*S*)-Cbz-alanine cyclohexyl ester (1.20 g, 4.0 mmol) and palladium on activated carbon (loading: 10 wt.%, 83 mg) in ethyl acetate (8 mL) was stirred for 1.5 h at room temperature under a hydrogen atmosphere. The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated. A mixture of the residual oil,

benzyl bromide (1.1 mL, 8.8 mmol), and sodium hydrogen carbonate (1.1 g, 13 mmol) in acetonitrile (20 mL) was refluxed for 24 h. The resulting mixture was filtered and the filtrate was concentrated. Purification of the residue by chromatography on silica gel (hexane/ethyl acetate = 10:1 as eluent) gave **13d** (0.61 g, 44% yield) as a colorless oil. $[\alpha]^{24}_{589}$ –98.5 (*c* 1.00 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (2H, dddd, *J* = 17.2, 10.1, 7.2, 5.6 Hz, CH_2CH=CH_2), 5.17 (2H, ddd, *J* = 17.2, 3.2, 1.6 Hz, CH_2CH=CH_2), 5.07 (2H, ddd, *J* = 10.1, 3.2, 1.6 Hz, CH_2CH=CH_2), 4.78 (1H, tt, *J* = 8.8, 3.6 Hz, OCH), 3.54 (1H, q, *J* = 7.2 Hz, NCHCO), 3.28 (2H, dddd, *J* = 14.4, 5.6, 1.6, 1.6 Hz, CH_2CH=CH_2), 3.11 (2H, dd, *J* = 14.4, 7.2 Hz, CH_2CH=CH_2), 1.87-1.76 (2H, m, *c*-Hex), 1.74-1.65 (2H, m, *c*-Hex), 1.56-1.20 (6H, m, *c*-Hex), 1.24 (3H, d, *J* = 7.2 Hz, 2-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 136.6, 116.9, 72.4, 57.4, 53.5, 31.8, 31.6, 25.4, 23.6, 15.3; IR (film) 3078, 2979, 2938, 2860, 1727, 1642, 1451, 1418, 1361, 1339, 1247, 1197, 1164, 1040, 1016, 994, 919, 864, 812, 775 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{15}H_{26}NO_2$: 252.1958. found: 252.1948.

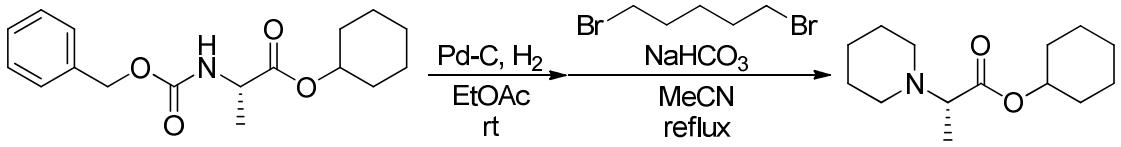
(*S*)-Cyclohexyl 2-(*N*,*N*-dimethylamino)propanoate (13e)



13e

A mixture of (*S*)-Cbz-alanine cyclohexyl ester (1.1 g, 3.5 mmol) and palladium on activated carbon (loading: 10 wt.%, 92 mg) in ethyl acetate (7 mL) was stirred for 2 h at room temperature under a hydrogen atmosphere. The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated. A mixture of the residual oil, palladium on activated carbon (loading: 10 wt.%, 0.14 g), and formaldehyde solution (37 wt.% in water, 5.8 mL, 77 mmol) in ethanol (14 mL) was stirred for 21 h under a hydrogen atmosphere. The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated. The residue was purified by chromatography on silica gel (ethyl acetate only as eluent) to obtain **13e** (0.32 g, 46% yield) as a colorless oil. $[\alpha]^{24}_{589}$ –20.8 (*c* 1.00 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.82 (1H, tt, *J* = 9.0, 3.6 Hz, OCH), 3.19 (1H, q, *J* = 7.2 Hz, NCHCO), 2.35 (6H, s, $N(CH_3)_2$), 1.91-1.81 (2H, m, *c*-Hex), 1.78-1.68 (2H, m, *c*-Hex), 1.59-1.20 (6H, m, *c*-Hex), 1.28 (3H, d, *J* = 7.2 Hz, $CHCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 72.6, 63.0, 41.7, 31.7, 31.6, 25.3, 23.7, 15.4; IR (film) 2938, 2861, 2785, 1727, 1452, 1373, 1330, 1216, 1175, 1107, 1042, 1016, 971, 942, 924, 864, 798, 757 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{11}H_{22}NO_2$: 200.1645. found: 200.1645.

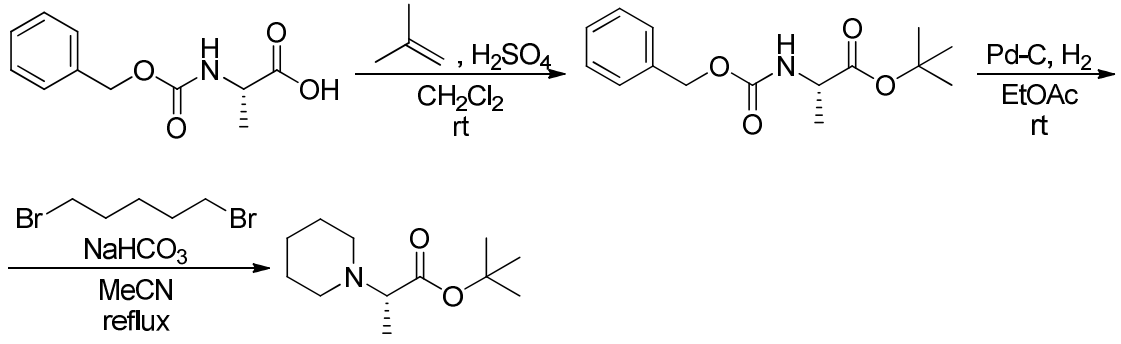
(*S*)-Cyclohexyl 2-(piperidin-1-yl)propanoate (13f)



13f

A mixture of (*S*)-Cbz-alanine cyclohexyl ester (1.0 g, 3.3 mmol) and palladium on activated carbon (loading: 10 wt.%, 78 mg) in ethyl acetate (6 mL) was stirred for 2 h at room temperature under a hydrogen atmosphere. The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated. A mixture of the residual oil, 1,5-dibromopentane (0.49 mL, 3.6 mmol), and sodium hydrogen carbonate (0.95 g, 11 mmol) in acetonitrile (16 mL) was refluxed for 6 h. The resulting mixture was cooled to room temperature and filtered. The filtrate was concentrated and the residue was purified by chromatography on silica gel (hexane/ethyl acetate = 4:1 as eluent) to obtain **13f** (0.54 g, 68% yield) as a colorless oil. $[\alpha]^{23}_{589}$ –25.5 (*c* 1.00 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.81 (1H, tt, *J* = 9.0, 4.0 Hz, OCH), 3.23 (1H, q, *J* = 7.2 Hz, NCHCO), 2.60 (2H, ddd, *J* = 11.1, 7.0, 4.0 Hz, NCH_2), 2.52 (2H, ddd, *J* = 11.1, 7.0, 4.0 Hz, NCH_2), 1.90-1.80 (2H, m, *c*-Hex), 1.77-1.68 (2H, m, *c*-Hex), 1.65-1.22 (12H, m, piperidine-CH_2 and *c*-Hex), 1.28 (3H, d, *J* = 7.2 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 72.4, 63.3, 50.5, 31.8, 31.6, 26.3, 25.3, 24.6, 23.7, 15.1; IR (film) 2935, 2857, 2810, 1728, 1451, 1379, 1338, 1309, 1231, 1178, 1130, 1096, 1037, 1019, 957, 935, 923, 862, 793, 749 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{14}H_{26}NO_2$: 240.1958. found: 240.1954.

(*S*)-*tert*-Butyl 2-(piperidin-1-yl)propanoate (13g)



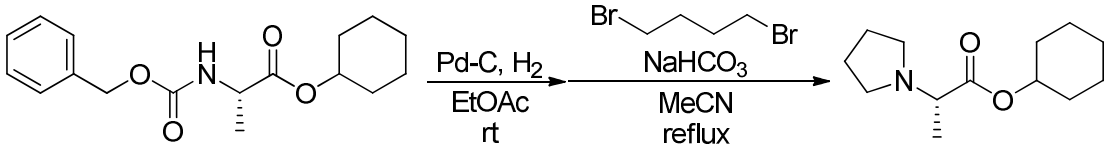
13g

(Step 1) A round-bottomed flask with septum-inlet was equipped with a septa and a dry-ice condenser. The flask was charged with (*S*)-Cbz-alanine (1.10 g, 5.0 mmol), *conc.* sulfuric acid (98%, 0.05 mL), and dichloromethane (10mL). Excess amount of isobutene gas was introduced to a flask with condensation by dry-ice. The resulting mixture was stirred for 48 h at room temperature and quenched with saturated aqueous sodium hydrogen carbonate. The mixture was extracted with dichloromethane and the

combined extracts were washed with brine. The solution was dried over sodium sulfate and concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 4:1 as eluent) to obtain (*S*)-Cbz-alanine *tert*-butyl ester (1.20 g, 84% yield) as a colorless oil.

(Step 2) A mixture of (*S*)-Cbz-alanine *tert*-butyl ester (0.70 g, 2.5 mmol) and palladium on activated carbon (loading: 10 wt.%, 64 mg) in ethyl acetate (5 mL) was stirred for 3 h at room temperature under a hydrogen atmosphere. The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated. A mixture of the residual oil, 1,5-dibromopentane (0.38 mL, 2.8 mmol), and sodium hydrogen carbonate (0.69 g, 8.2 mmol) in acetonitrile (13 mL) was refluxed for 13 h. The resulting mixture was cooled to room temperature and filtered. The filtrate was concentrated and the residue was purified by chromatography on silica gel (hexane/ethyl acetate = 4:1 as eluent) to give **13g** (0.40 g, 74% yield) as a colorless oil. $[\alpha]^{23}_{589}$ –31.5 (*c* 1.00 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.15 (1H, q, *J* = 7.2 Hz, NCHCO), 2.61 (2H, ddd, *J* = 11.1, 6.9, 4.0 Hz, NCH_2), 2.53 (2H, ddd, *J* = 11.1, 6.9, 4.0 Hz, NCH_2), 1.65-1.39 (6H, m, piperidine-CH_2), 1.47 (9H, s, *t*-Bu), 1.25 (3H, d, *J* = 7.2 Hz, 2-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 80.5, 63.7, 50.4, 28.2, 26.4, 24.6, 15.0; IR (film) 2977, 2935, 2854, 2809, 2756, 1726, 1452, 1367, 1342, 1308, 1255, 1205, 1152, 1132, 1053, 1028, 953, 882, 850, 793, 761 cm^{-1}; HRMS–ESI (*m/z*): $[M+H]^+$ calcd for $C_{12}H_{24}NO_2$: 214.1802. found: 214.1798.

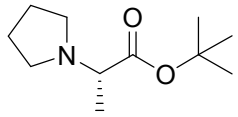
(*S*)-Cyclohexyl 2-(pyrrolidin-1-yl)propanoate (13h)



A mixture of (*S*)-Cbz-alanine cyclohexyl ester (2.00 g, 6.5 mmol) and palladium on activated carbon (loading: 10 wt.%, 78 mg) in ethyl acetate (13 mL) was stirred for 4 h at room temperature under a hydrogen atmosphere. The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated. A mixture of the residual oil, 1,4-dibromobutane (0.86 mL, 7.2 mmol), and sodium hydrogen carbonate (1.60 g, 19 mmol) in acetonitrile (13 mL) was refluxed for 5 h. The resulting mixture was cooled to room temperature and filtered. The filtrate was concentralted and the residue was purified by chromatography on silica gel (hexane/ethyl acetate = 1:1 as eluent) to give **13h** (0.53 g, 36% yield) as a colorless oil. $[\alpha]^{24}_{589}$ –19.5 (*c* 1.00 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.82 (1H, tt, *J* = 9.2, 3.6 Hz, OCH), 3.14 (1H, q, *J* = 7.0 Hz, NCHCO), 2.71-2.58 (4H, m, NCH_2), 1.91-1.68 (8H, m, pyrrolidine-CH_2 and *c*-Hex), 1.60-1.19 (6H, m, *c*-Hex), 1.36 (3H, d, *J* = 7.0 Hz, 2-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 72.7, 62.2, 50.9, 31.6, 31.5, 25.3, 23.8, 23.5; IR (film) 2937, 2859,

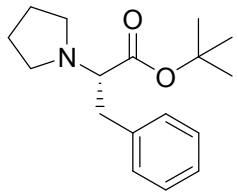
2807, 1728, 1452, 1367, 1320, 1261, 1165, 1080, 1039, 1016, 984, 943, 925, 908, 871, 842, 799, 757 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{13}H_{24}NO_2$: 226.1802. found: 226.1797.

(*S*)-*tert*-Butyl 2-(pyrrolidin-1-yl)propanoate (13i)



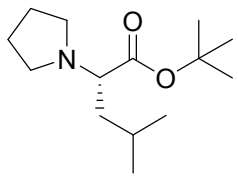
Prepared in 65% yield by the same procedure with **13h** using (*S*)-Cbz-alanine *tert*-butyl ester as a starting material. Colorless oil; $[\alpha]^{24}_{589}$ –22.8 (*c* 1.00 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.05 (1H, q, *J* = 6.8 Hz, NCHCO), 2.72-2.59 (4H, m, NCH_2), 1.82-1.76 (4H, m, pyrrolidine-CH_2), 1.47 (9H, s, *t*-Bu), 1.32 (3H, d, *J* = 6.8 Hz, 2-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 80.5, 62.5, 50.7, 28.1, 23.5, 17.3; IR (film) 2974, 2937, 2877, 2808, 1726, 1457, 1368, 1290, 1254, 1213, 1147, 1081, 1060, 1035, 982, 883, 850, 793, 754 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{11}H_{22}NO_2$: 200.1645. found: 200.1643.

(*S*)-*tert*-Butyl 3-phenyl-2-(pyrrolidin-1-yl)propanoate (13j)



Prepared in 73% yield by the same procedure with **13h** using (*S*)-Cbz-phenylalanine as a starting material. Colorless oil; $[\alpha]^{25}_{589}$ +45.0 (*c* 1.00 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.12 (5H, m, Ph), 3.31 (1H, dd, *J* = 9.8, 5.8 Hz, NCHCO), 3.01 (1H, dd, *J* = 13.2, 5.8 Hz, C*H*$_2$Ph), 2.97 (1H, dd, *J* = 13.2, 9.8 Hz, C*H*$_2$Ph), 2.82-2.72 (2H, m, NCH_2), 2.70-2.62 (2H, m, NCH_2), 1.77 (4H, tt, *J* = 9.9, 3.4 Hz, pyrrolidine-CH_2), 1.25 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 138.0, 129.3, 128.1, 126.3, 80.7, 68.7, 50.4, 38.0, 27.9, 23.5; IR (film) 3029, 2971, 2875, 2812, 1723, 1495, 1455, 1391, 1367, 1294, 1253, 1218, 1147, 1078, 1053, 1031, 982, 905, 847, 742, 699 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{17}H_{26}NO_2$: 276.1958. found: 276.1949.

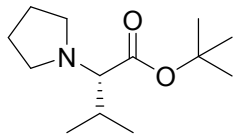
(*S*)-*tert*-Butyl 4-methyl-2-(pyrrolidin-1-yl)pentanoate (13k)



Prepared in 59% yield by the same procedure with **13h** using (*S*)-Cbz-leucine as a starting material. Colorless oil; $[\alpha]^{24}_{589}$ +7.8 (*c* 1.00 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.11 (1H, dd, *J* = 9.6, 5.6 Hz, NCHCO), 2.75-2.64 (2H, m, NCH_2), 2.62-2.52 (2H, m, NCH_2), 1.76-1.37 (3H, m, $CH_2CH(CH_3)_2$ and $CH_2CH(CH_3)_2$), 1.71 (4H, tt, *J*

= 10.0, 3.6 Hz, pyrrolidine-CH_2), 1.43 (9H, s, *t*-Bu), 0.89 (3H, d, *J* = 7.6 Hz, $CH_2CH(CH_3)_2$), 0.87 (3H, d, *J* = 6.8 Hz, $CH_2CH(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 80.5, 64.8, 49.9, 40.7, 28.2, 25.3, 23.5, 23.4, 22.1; IR (film) 2960, 2871, 2816, 1726, 1458, 1390, 1367, 1293, 1254, 1204, 1144, 1050, 937, 849, 793, 755 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{14}H_{28}NO_2$: 242.2115. found: 242.2109.

(*S*)-*tert*-Butyl 3-methyl-2-(pyrrolidin-1-yl)butanoate (13l)



Prepared in 45% yield by the same procedure with **13h** using (*S*)-Cbz-valine as a starting material. Colorless oil; $[\alpha]^{23}_{589}$ +7.9 (*c* 1.00 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.77 (1H, d, *J* = 8.8 Hz, NCHCO), 2.72-2.64 (2H, m, NCH_2), 2.61-2.52 (2H, m, NCH_2), 1.95 (1H, d septet, *J* = 8.8, 6.8 Hz, $CHCH(CH_3)_2$), 1.69 (4H, tt, *J* = 9.8, 3.3 Hz, pyrrolidine-CH_2), 1.43 (9H, s, *t*-Bu), 0.94 (3H, d, *J* = 6.8 Hz, $CHCH(CH_3)_2$), 0.89 (3H, d, *J* = 6.8 Hz, $CHCH(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 80.4, 72.2, 49.1, 29.0, 28.3, 23.5, 19.8, 18.8; IR (film) 2966, 2874, 2808, 1723, 1461, 1389, 1367, 1250, 1204, 1142, 1111, 1035, 980, 910, 863, 790 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{13}H_{26}NO_2$: 228.1958. found: 228.1954.

References

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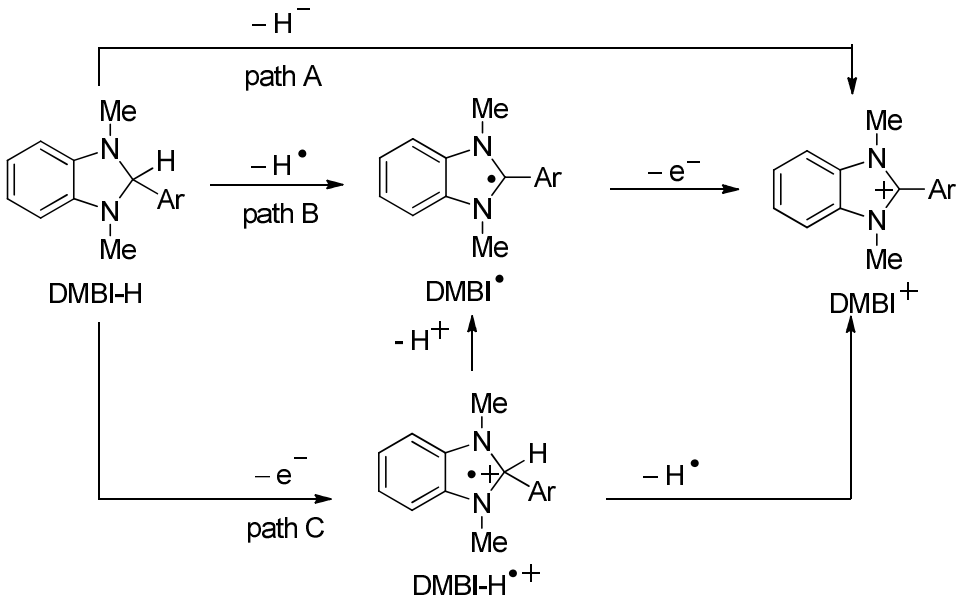
4) (a) Kawabata, T.; Kawakami, S.; Majumdar, S. *J. Am. Chem. Soc.* **2003**, *125*, 13012-13013. (b) Kawabata, T.; Moriyama, K.; Kawakami, S.; Tsubaki, K. *J. Am. Chem. Soc.* **2008**, *130*, 4153-4157.
5) (a) Soai, K.; Shibata, T.; Morioka, H.; Choji, K. *Nature* **1995**, *378*, 767-768. (b) Shibata, T.; Morioka, H.; Hayase, T.; Choji, K.; Soai, K. *J. Am. Chem. Soc.* **1996**, *118*, 471-472.

Chapter 4.
Carbon–carbon bond formation via benzoyl umpolung attained by photoinduced electron-transfer with benzimidazolines

4-1 Background

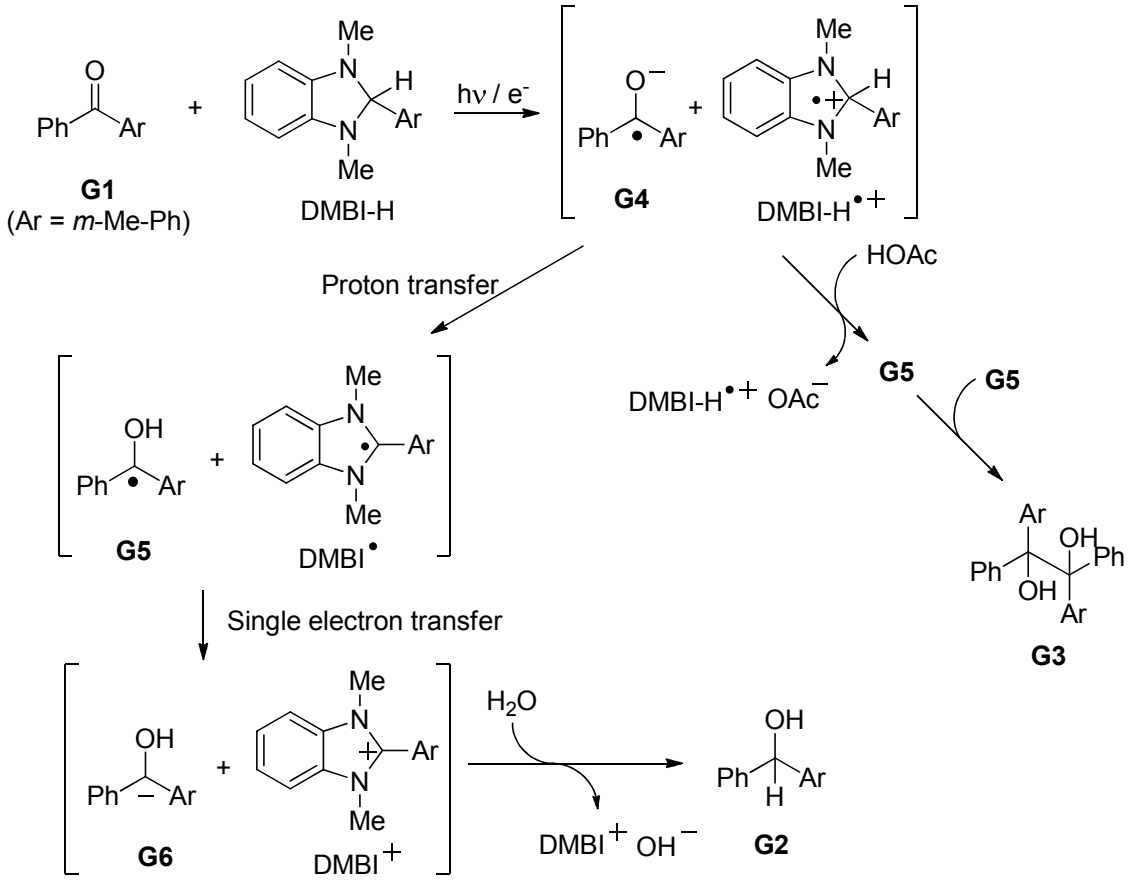
Described in section 1 "Introduction", 2-aryl-1,3-dimethylbenzimidazolines (DMBI-H) act as useful reductive reagents, and there are three initially oxidative paths for the reaction of benzimidazolines (Scheme 4-1). Reported by Chikashita et al., DMBI-H is the efficient reagent for directly reductive dehalogenation (path A).[1] Tanner et al. has discovered that DMBI radical (DMBI$^{\bullet}$) occurred by abstracting hydrogen atom of DMBI-H is used as the single electron-transfer reagent (path B).[2] On the other hand, the single electron transferred from DMBI-H to the excited substrate by photoinduced electron-transfer, and subsequently reductive reaction proceeded via donating the hydrogen atom or proton (path C).[3] Each reaction paths as efficient reductive reagent attract chemists and biochemists, while it is necessary to explore other potential reaction using DMBI-H.

Scheme 4-1



Herein, we are interested in the photoinduced reduction of the benzophenone derivative with DMBI-H previously reported by our group.[3g] The reactivity of ketyl radical derived from *m*-methylbenzophenone **G1** changes in dependence on the acidity of proton donors (Scheme 4-2). The addition of water as the proton donor affords benzhydrol derivative **G2**, while the reaction with acetic acid produces benzopinacol **G3**. Photoinduced electron-transfer produces a radical ion pair [**G4** and DMBI-H$^{\bullet+}$]. The subsequent proton transfer gives a radical pair [**G5** and DMBI$^{\bullet}$], which successively undergoes single electron-transfer to afford an ion pair [**G6** and DMBI^{+}]. Protonation to **G6** produces **G2** in the presence of water. On the other hand, using acetic acid instead of water, the proton donor intercepts **G4** with protonation to give **G5**. Because the potential reducing agent DMBI$^{\bullet}$ is not generated in this case, **G5** survives to undergo dimerization with another **G5** to **G3**.

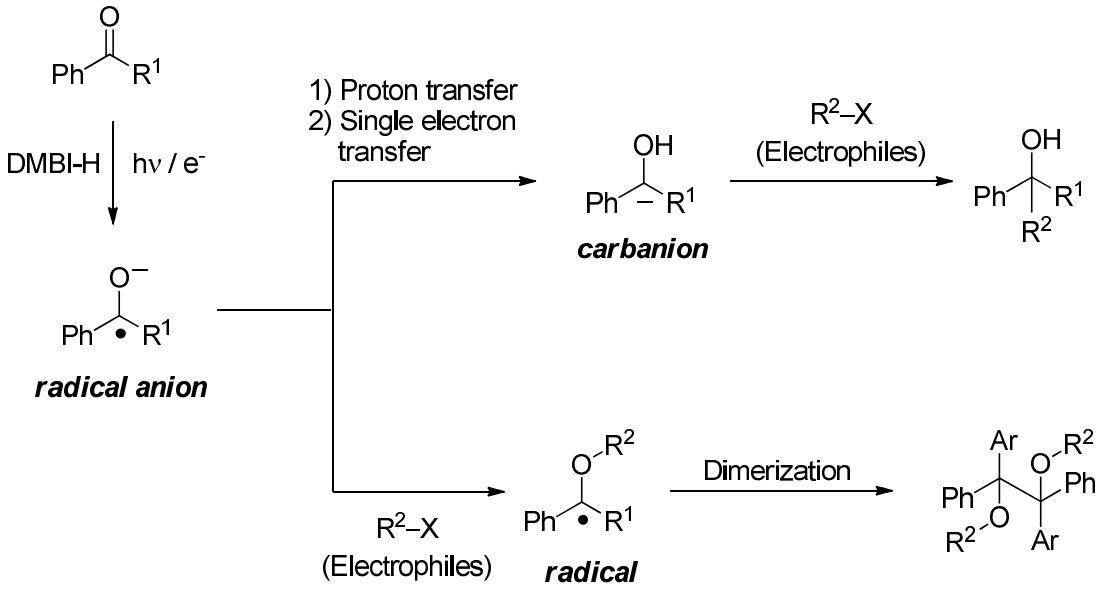
Scheme 4-2



Encouraged by this method, we attempted the carbon–carbon bond formation of benzoyl compounds when the appropriate carbon electrophiles are used instead of water (Scheme 4-3).

First, photoinduced electron-transfer between the excited benzoyl compounds and DMBI-H produces the radical anions. The anion part of radical anions abstracts the proton derived from DMBI-H$^{\bullet+}$ or the carbon electrophiles. If the proton transfer from DMBI-H$^{\bullet+}$ to radical anion proceeds quickly than the attack of radical anion to the electrophiles, the carbanion will be generated via subsequently single electron-transfer. Finally, the carbanion reacts with electrophiles to induce carbon–carbon bond formation.

Scheme 4-3

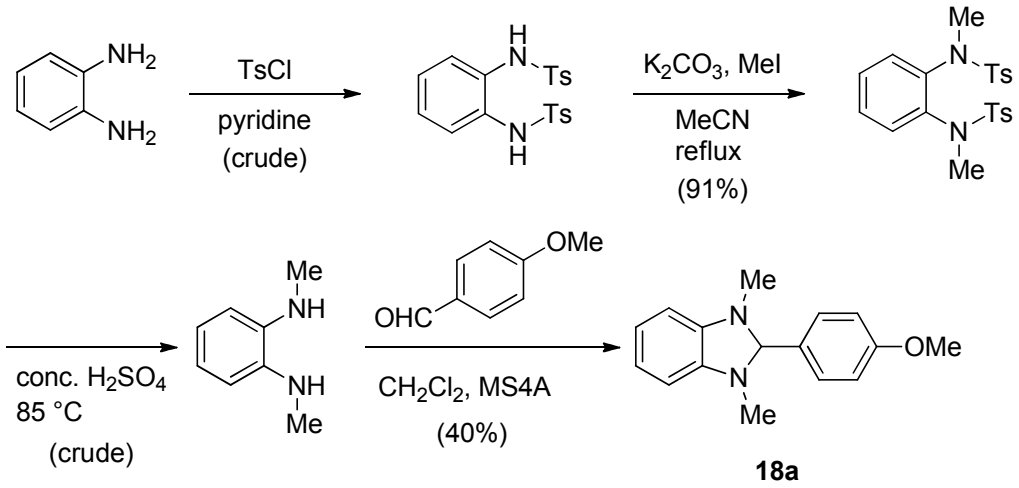


4-2 Carbon–carbon bond formation by photoinduced electron-transfer

First, we prepared the reactant.

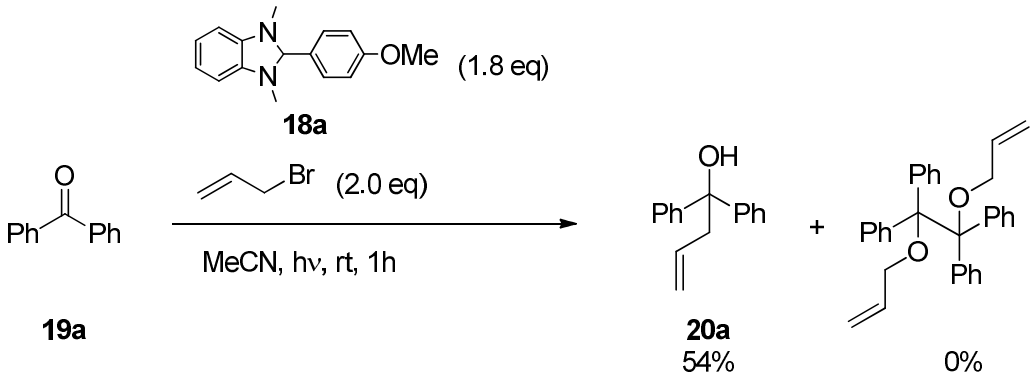
We synthesized 2-(*p*-anisyl)-1,3-dimethylbenzimidazoline **18a** (Scheme 4-4). Protection of commercial *o*-phenylenediamine by tosyl chloride gave *N*,*N*'-di-*p*-tosyl-*o*-phenylenediamine, of which methylation with iodomethane afforded *N*,*N*'-dimethyl-*N*,*N*'-di-*p*-tosyl-*o*-phenylenediamine. Deprotection of tosyl group and subsequently condensation by *p*-anisaldehyde produced **18a**.

Scheme 4-4



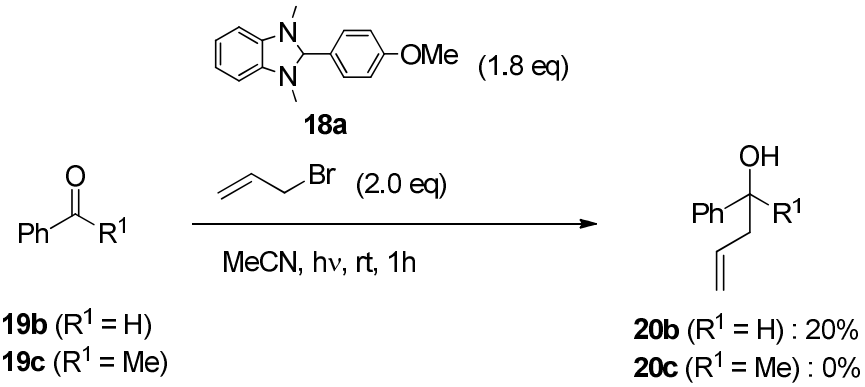
On the basis of "4-1 Background", the results of the experiments would be shown. We conducted the photoreaction (λ > 280 nm, 500 W Hg–Xe lamp) using **18a** and benzophenone **19a**, capturing the resultant species in situ with allyl bromide in acetonitrile at room temperature for 1 h (Scheme 4-5). Then, α-allyl adduct **20a** was obtained in 54% yield, while the product derived from dimerization was not obtained. As a result, carbon–carbon bond formation proceeded via umpolung reactivity.

Scheme 4-5



Next, we explored benzaldehyde **19b** and acetophenone **19c**, which are mostly recognized in organic chemistry (Scheme 4-6). While the reaction of **19b** gave **20b**, albeit in low yield, acetophenone **19c** was inactive. We thought that the carbanion, which is expected as intermediate in the reaction, would not be stabilized in these cases.

Scheme 4-5

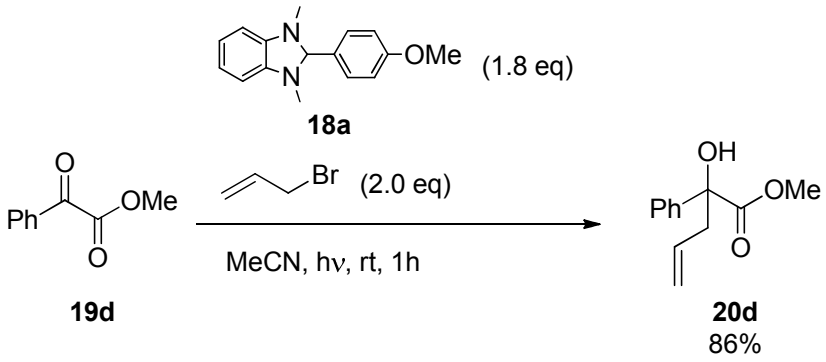


19b (R^1 = H)
19c (R^1 = Me)

20b (R^1 = H) : 20%
20c (R^1 = Me) : 0%

Herein, we conducted the reaction of methyl benzoylformate **19d**, which have electron withdraw group to stabilize the intermediate of carbanion, to give α-allyl adduct **20d** in good yield (Scheme 4-6). Thus, we decided to examine the photoreaction of benzoylformates in detail.

Scheme 4-6



19d

20d
86%

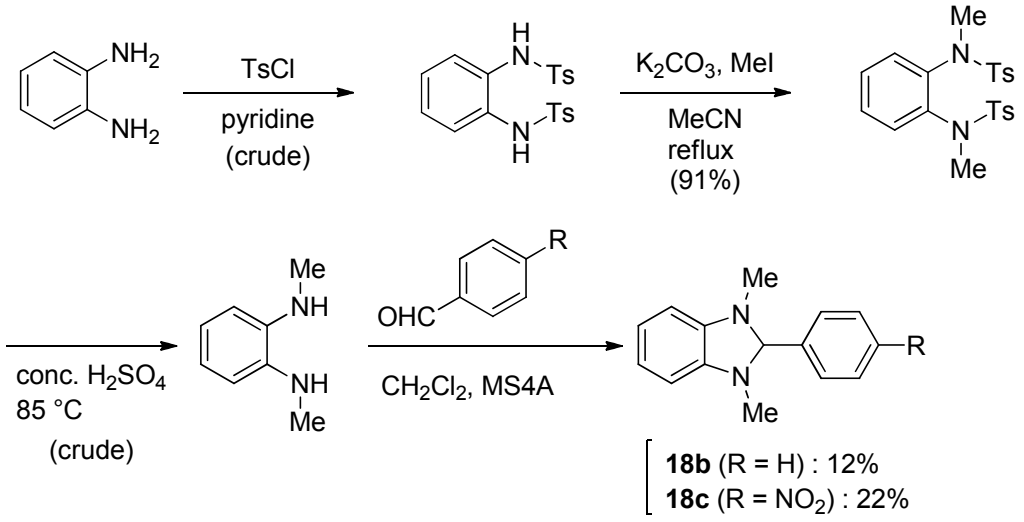
4-3 The investigation of optimal conditions

First, we prepared the reactants.

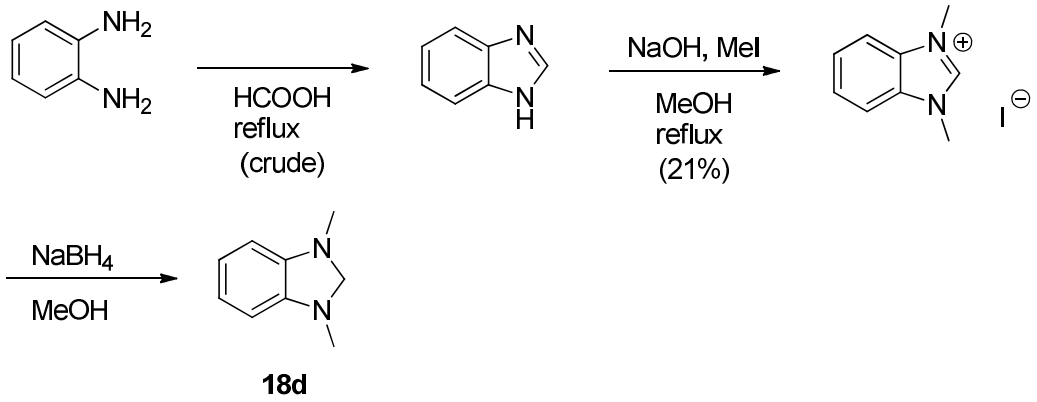
We synthesized 1,3-dimethyl-2-phenylbenzimidazoline **18b** (Scheme 4-7). Protection of commercial *o*-phenylenediamine by tosyl chloride gave *N*,*N*'-di-*p*-tosyl-*o*-phenylenediamine, of which methylation with iodomethane afforded *N*,*N*'-dimethyl-*N*,*N*'-di-*p*-tosyl-*o*-phenylenediamine. Deprotection of tosyl group and subsequently condensation by benzaldehyde produced **18b**. 1,3-dimethyl-2-(*p*-nitrophenyl)benzimidazoline **18c** was synthesized by the same

procedure with **18b** using *p*-nitrobenzaldehyde instead of benzaldehyde. 1,3-Dimethylbenzimidazoline **18d** was synthesized (Scheme 4-8). Condensation of commercial *o*-phenylenediamine by formic acid gave benzimidazole, of which methylation with iodomethane afforded *N*,*N*-dimethylbenzimidazolium. Reduction by sodium borohydride produced **18d**.

Scheme 4-7

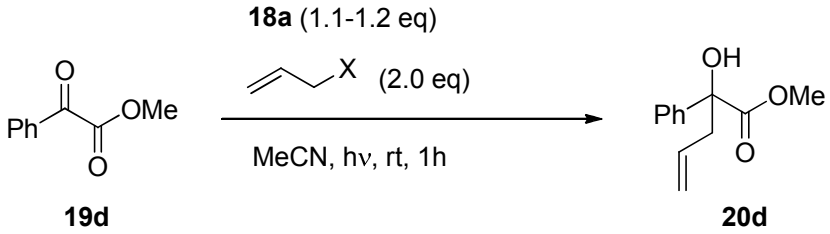


Scheme 4-8



We conducted a photoreaction between **18a** and **19d** in the presence of allyl halides to form the desired products (Table 4-1). When the quantity of **19d** was less than 1.8 equiv shown in Scheme 4-6, **20d** was still obtained in good yield (entry 1). Without light, the reaction was not able to proceed (entry 2). Additionally, the use of allyl chloride greatly decreased the yield of **20d** (entry 3) and the reaction of **19d** with allyl iodide produced **20d** in low yield (entry 4).

Table 4-1



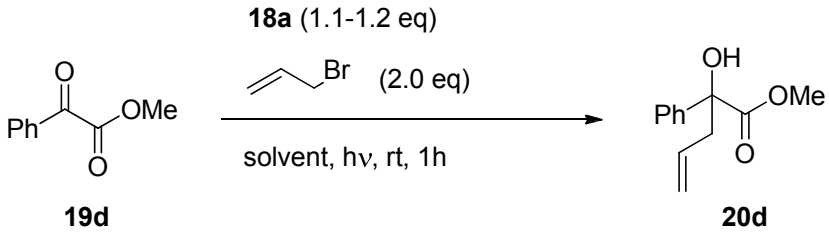
19d **20d**

Entry	X	Yield[a] (%)
1	Br	76
2[b]	Br	0
3	Cl	14
4	I	31

[a] Isolated yield. [b] Without light, 14 h

Next, different solvents were explored to discover those suitable for the photo-allylation reaction (Table 4-2). The α-allyl adduct **20d** was obtained in dichloromethane, THF, toluene, ethyl acetate, and DMF instead of acetonitrile in moderate yields (entries 1-5). While no reaction proceeded in dimethyl sulfoxide (DMSO), the origin of this unexpected effect caused by DMSO is unclear (entry 6). Isopropanol was also ineffective, possibly due to interfering proton transfer in the radical ion pairs by this protic solvent (entry 7).

Table 4-2



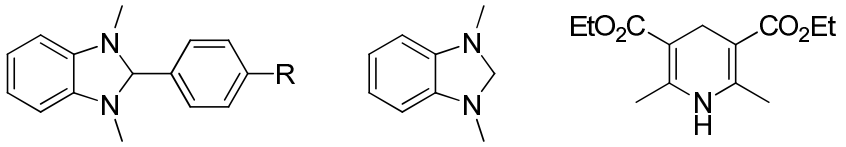
19d **20d**

Entry	Solvent	Yield[a] (%)
1	CH_2Cl_2	63
2	THF	42
3	toluene	48
4	EtOAc	52
5	DMF	40
6	DMSO	0
7	*i*-PrOH	trace

[a] Isolated yield.

We also examined the steric and electronic effects of the 2-substituent of DMBI-H by using a series of DMBI-H derivatives **18a-d** and the applicability of Hantzsch ester (HE), the most recognized organic hydride donor in organic synthesis (Figure 4-1),[4] in the photo-allylation reaction of **19d** and allyl bromide (Table 4-3). While 2-phenyl substituted **18b** was moderately effective, giving **20d** in 59% yield (entry 1), 2-*p*-nitrophenyl substituted **18c** did not display any of the desired reactivity (entry 2). Using less sterically hindered **18d**,[5] the yield of **20d** was unexpectedly decreased to 38% yield (entry 3). It is considered that the generated intermediate, DMBI$^{\bullet}$ or DMBI-H$^{\bullet+}$ derived from **18d**, cannot be stabilized in the absence of 2-aryl substituent. In addition, **18d** was discovered to be rather unstable in air. Notably, Hantzsch ester did not produce **20d** at all (entry 4).

Figure 4-1

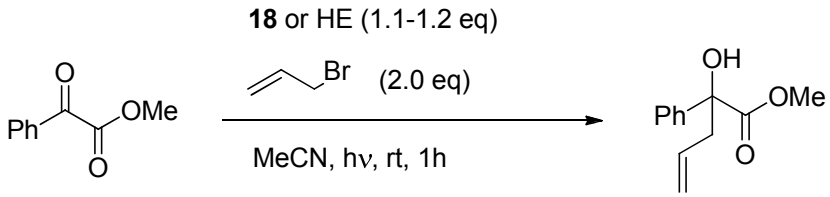


R = OMe, **18a**
R = H, **18b**
R = NO_2, **18c**

18d

Hantzsch ester (HE)

Table 4-3



19d **20d**

Entry	**18** or HE	Yield[a] (%)
1	**18b**	59
2	**18c**	0
3	**18d**	38
4	HE	0

[a] Isolated yield.

4-4 A proposed mechanism

The ultraviolet absorption spectra of benzimidazoline **18a** (blue line) and methyl benzoylformate **19d** (red line) in 5.0×10^{-2} M (Figure 4-2) or 5.0×10^{-5} M (Figure 4-3) of acetonitrile were recorded. Figure 4-3 shows that there are two absorbance bands at λ_{max} = 268 nm and 312 nm for **18a** and two absorbance bands at λ_{max} = 255 nm and 338 nm for **19d**. The value of the absorption coefficient of **18a** was determined to be ε_{max} = 11,400 (268 nm) and 14,100 (312 nm), while the value of the absorption coefficient of **19d** was ε_{max} = 12,000 (255 nm) and 265 (338 nm). We guess that both of n-π* and π-π* excitation will be possible, because n-π* and π-π* absorption bands are observed in **19d**. According to Figure 4-2 and 4-3, we understood that both of compounds **18a** and **19d** would absorb light, when a borosilicate glass flask was used as the reactor vessel. Further, Figure 4-3 shows that the amount of photoabsorption of **18a** was higher than that of **19d**.

Figure 4-2

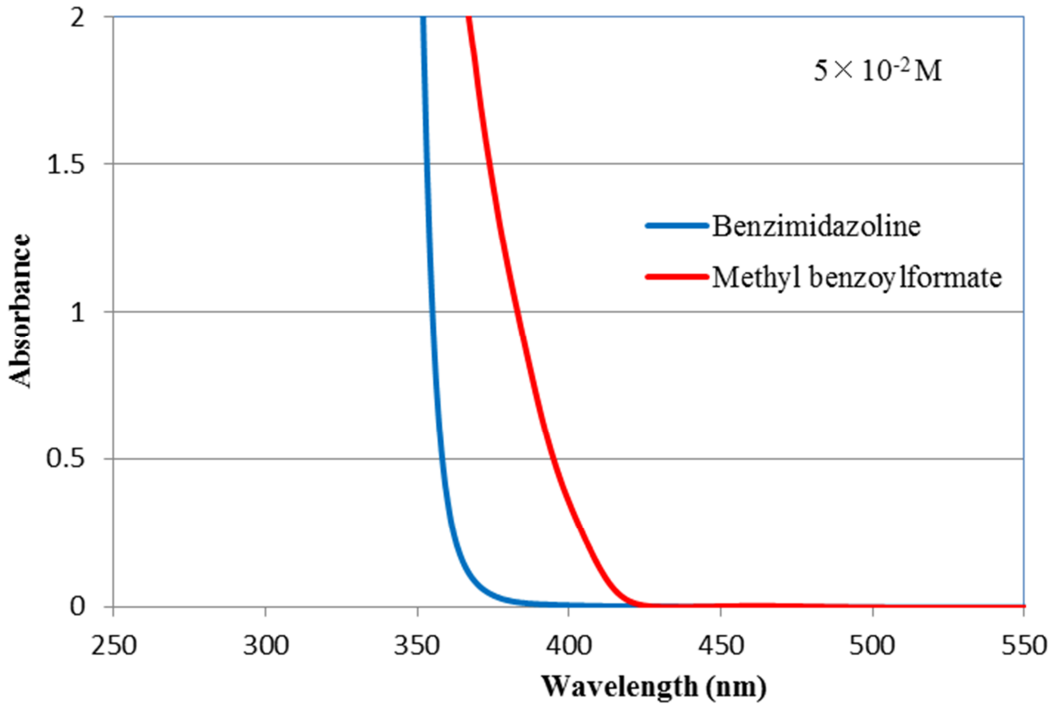
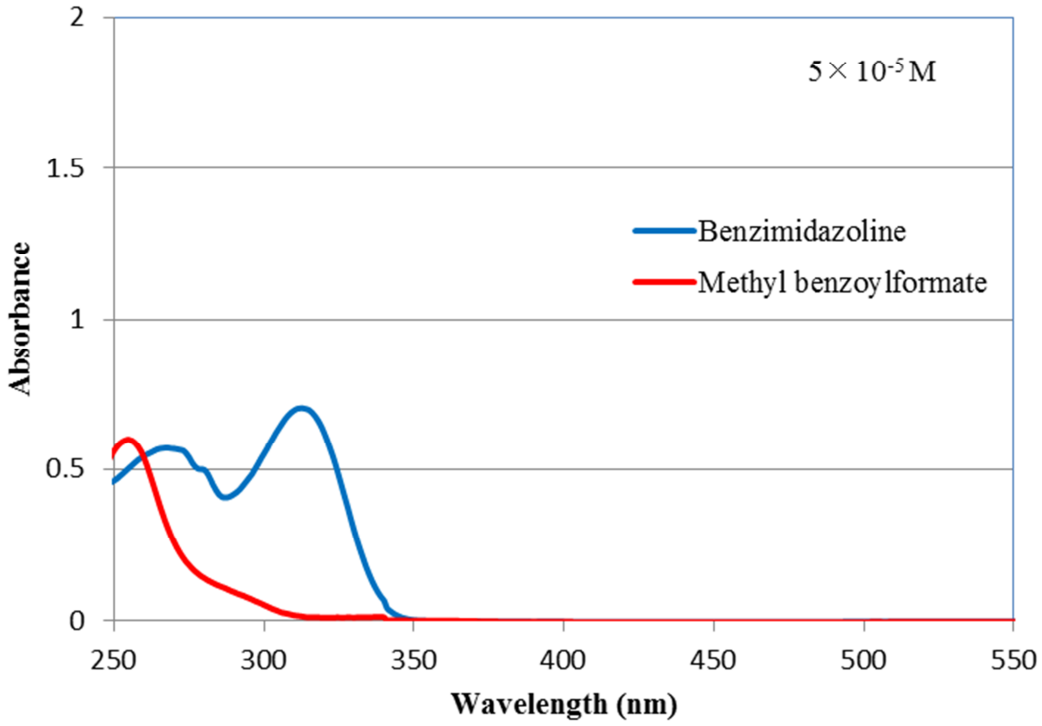


Figure 4-3

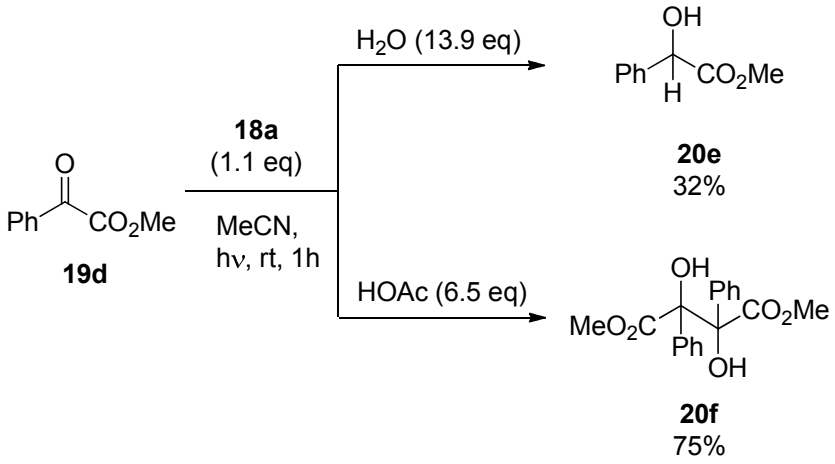


First, it was postulated that **19d** absorbs light. The Gibbs free energy change associated with a full electron-transfer from DMBI-H to benzoylformates can be calculated using the equation $\Delta G_{ET} = 23.06(E_D^{ox} - E_A^{red}) - E_T - C$, in which E_D^{ox} and E_A^{red} are the oxidation and reduction potentials of the donor (**18a**, 0.28 V vs SCE)[3h] and acceptor (**19d**, −1.23 V vs SCE),[6] E_T is the triplet energy of the acceptor (benzoylformates, 66 kcal/mol)[6] and C is Coulombic interaction term (in MeCN, 0.06 eV)[3h, 7] As a result, a negative value (ΔG_{ET} = −32.6 kcal/mol) suggest the electron-transfer from **18a** to the excited triplet state of **19d** is feasible.

Next, it was supposed that **18a** absorbs light. The Gibbs free energy change associated with a full electron-transfer from DMBI-H to benzoylformates can be calculated using the equation $\Delta G_{ET} = 23.06(E_D^{ox} - E_A^{red}) - E_S - C$, in which E_S is the singlet energy of the donor (DMBI-H, 82 kcal/mol) when 350 nm in which the absorbance of **18a** was hardly observed was assumed the singlet state. As a result, a negative value (ΔG_{ET} = −48.6 kcal/mol) suggest the electron-transfer from the excited singlet state of **18a** to **19d** is feasible.

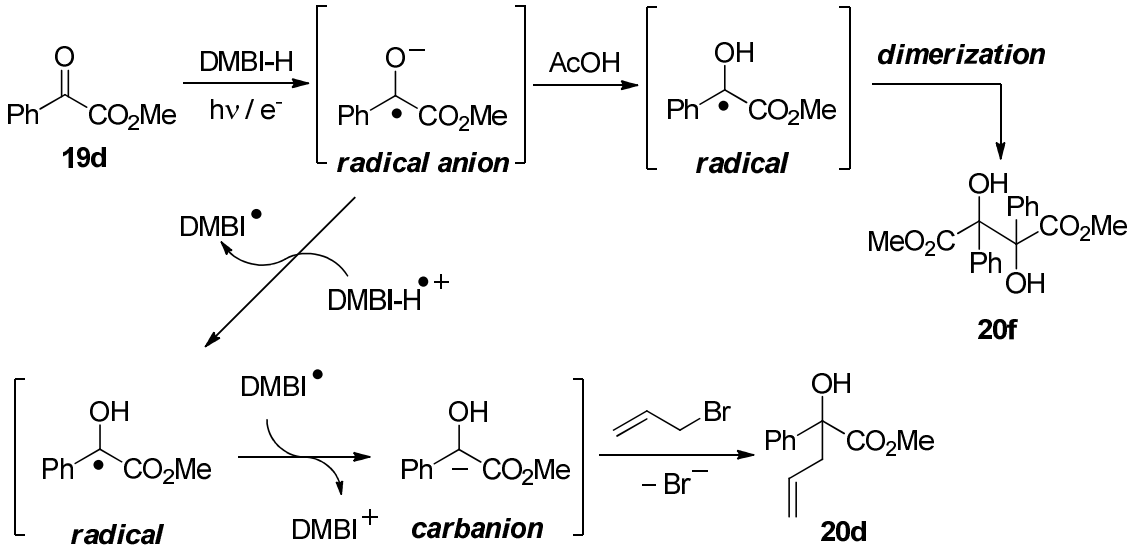
Further, in order to explore the nature of the intermediate for the photoreaction of **18a** and **19d**, allyl bromide was replaced by proton donors (Scheme 4-9). While the reaction of **19d** with water gave alcohol **19e**, an addition of acetic acid produced 1,2-diol **19f**. These results were similar to those of the reactions reported in the literature (Scheme 4-2).

Scheme 4-9



We propose a plausible mechanism for the reaction of **19d** and DMBI-H with allyl bromide on the basis of the observations described above (Scheme 4-10). The reaction pathway begins with a photoinduced electron-transfer in which initially formed radical anion abstracts a proton from DMBI-H$^{\bullet+}$ to give the radical. The subsequent electron-transfer between the radical derived from **19d** and DMBI$^{\bullet}$ generates the carbanion, in which the carbonyl carbon becomes nucleophilic (umpolung reactivity). DMBI$^{\bullet}$ is stronger single electron donor than the radicals derived from other organic hydride donors.[8] Finally, the carbanion reacts with allyl bromide to produce **20d**, while the carbanion is protonated by water to give **20e** in the absence of allyl bromide. If acetic acid exists, the radical anion is protonated by acetic acid instead of DMBI-H$^{\bullet+}$ to give the radical, which dimerizes to produce **20f**.

Scheme 4-10

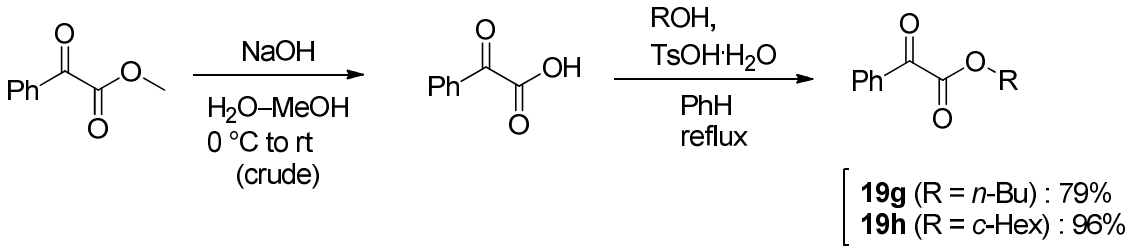


4-5 The application to the other benzoyl compounds

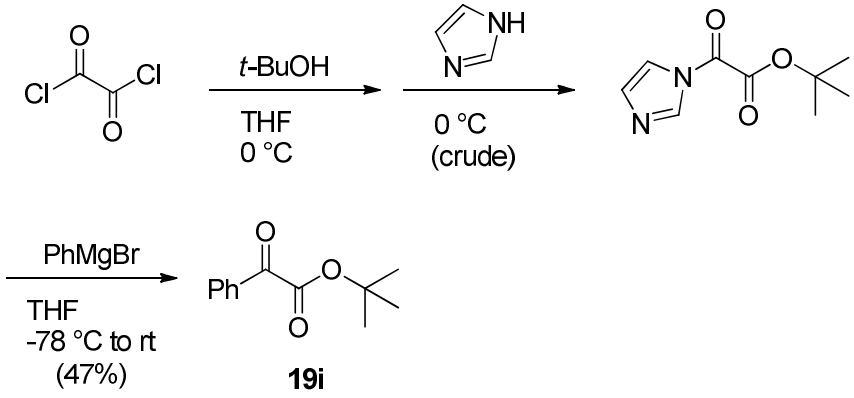
First, we prepared the substrates.

n-Butyl benzoylformate **19g** was synthesized (Scheme 4-11). Hydrolysis of commercial methyl benzoylformate by sodium hydroxide gave benzoylformic acid, of which esterification with *n*-butanol afforded **19g**. Cyclohexyl benzoylformate **19h** was synthesized by the same procedure with **19g** using cyclohexanol instead of *n*-butanol. *tert*-Butyl benzoylformate **19i** was synthesized (Scheme 4-12). Esterification with *tert*-butanol and subsequently phenylation by phenylmagnesium bromide gave **19i**. *N*,*N*-Diethylbenzoylformamide **19j** was synthesized from benzoylformic acid and diethylamine (Scheme 4-13). 1-Phenyl-1,2-dioxohexane **19l** was synthesized (Scheme 4-14). Phenylation of 1-hexyne by iodobenzene and copper(I) iodide gave 1-phenylhex-1-yne. Oxidation of 1-phenylhex-1-yne by potassium permanganate produced **19l**.

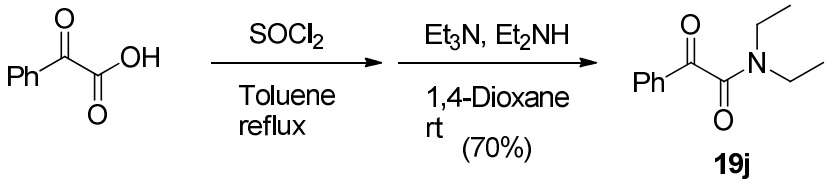
Scheme 4-11



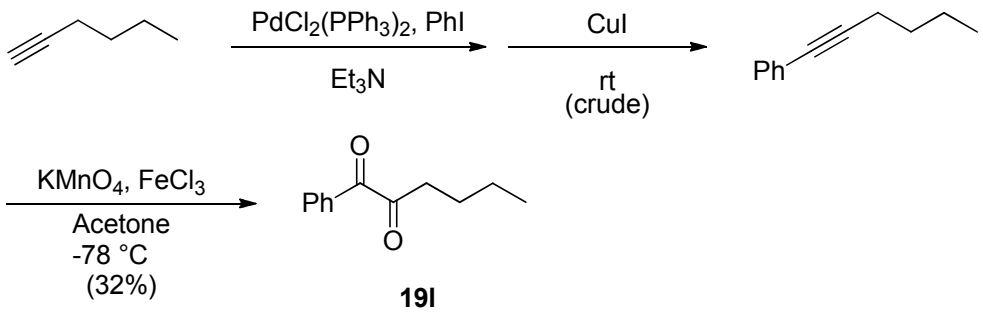
Scheme 4-12



Scheme 4-13

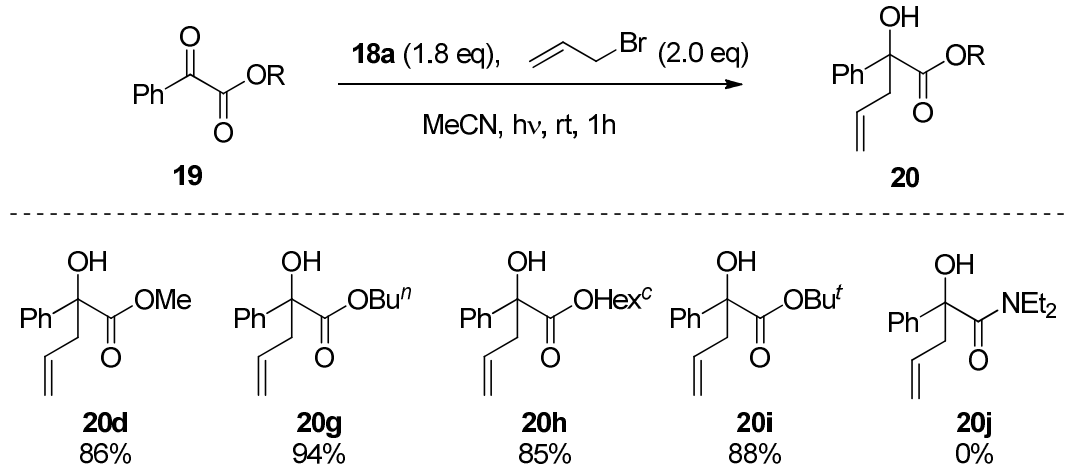


Scheme 4-14



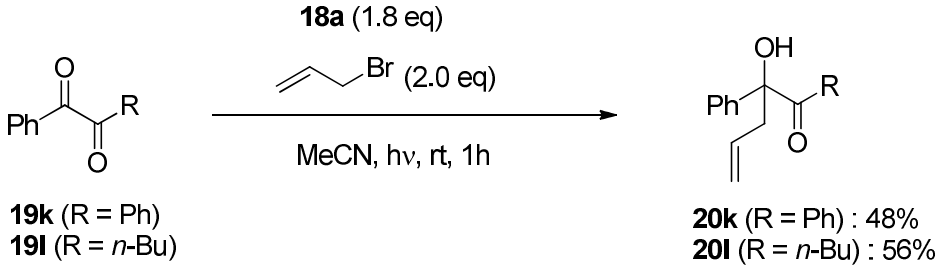
We applied the optimized conditions (**18a** : **19** : allyl bromide = 1.8 : 1 : 2.0) to a variety of benzoyl compounds (Scheme 4-15). When the reaction with *n*-butyl ester **19g**, cyclohexyl ester **19h**, and *tert*-butyl ester **19i** were performed under the same conditions, the respective α-allyl adducts **20g**, **20h**, and **20i** were obtained in good to excellent yields. *N*,*N*-Diethylbenzoylformamide **19j** was completely unreactive

Scheme 4-15



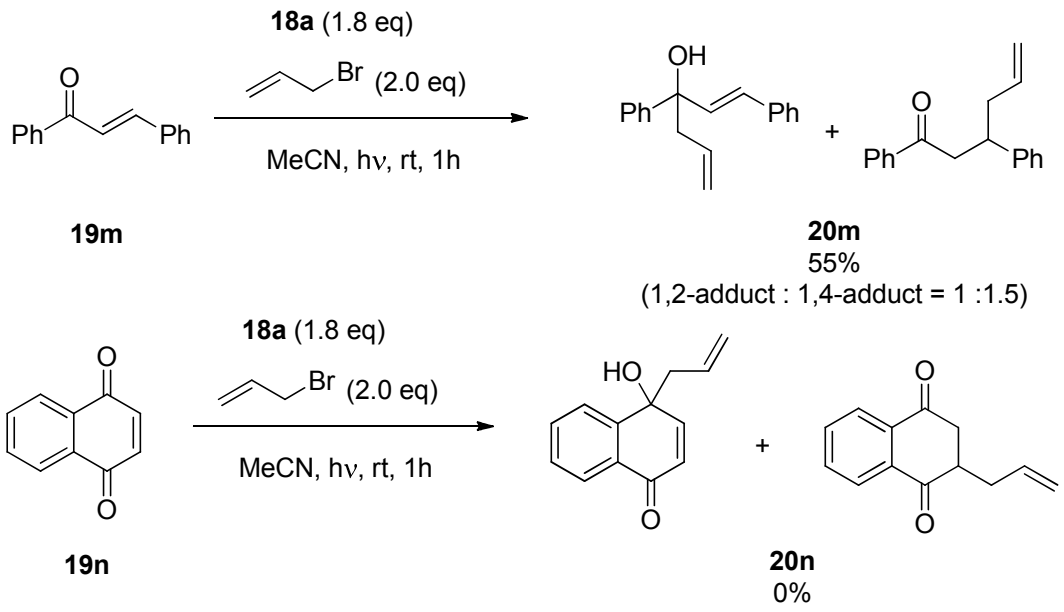
Next, the reactions of α-diketones, such as benzil **19k** and 1-phenyl-1,2-dioxohexane **19l**, resulted in the formation of **20k** and **20l** in moderate yields (Scheme 4-16). The reaction of **19l** proceeded regioselectively, with the *n*-butyl carbonyl remaining intact in **20l**. Either properly electron withdrawing or conjugated substituents adjacent to benzoyl are necessary to promote the reactions.

Scheme 4-16



We conducted the reaction of conjugated enone, such as chalcone **19m** and naphthoquinone **19n** (Scheme 4-17). When the reaction of chalcone **19m** was carried out with allyl bromide, the allylated product **20m** was obtained as the mixture of 1,2- and 1,4-adduct (1 : 1.5) in moderate yield. On the other hand, naphthoquinone **19n** did not afford the corresponding products, while some quantity of **19n** was consumed.

Scheme 4-17

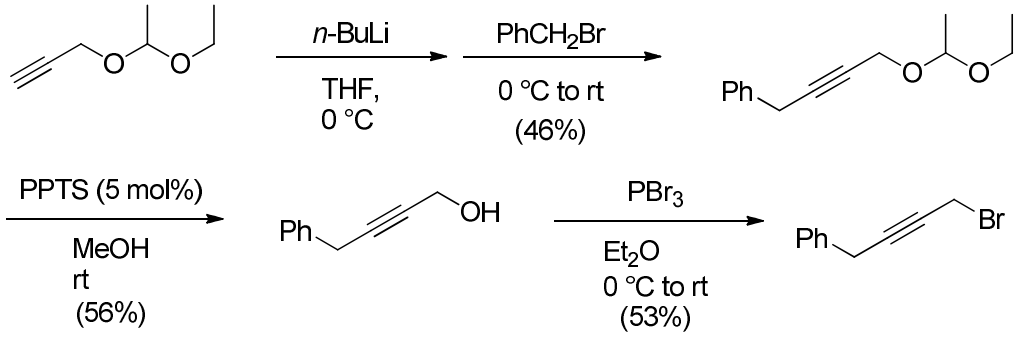


4-6 The photo-addition reaction of benzoylformate with the various electrophiles

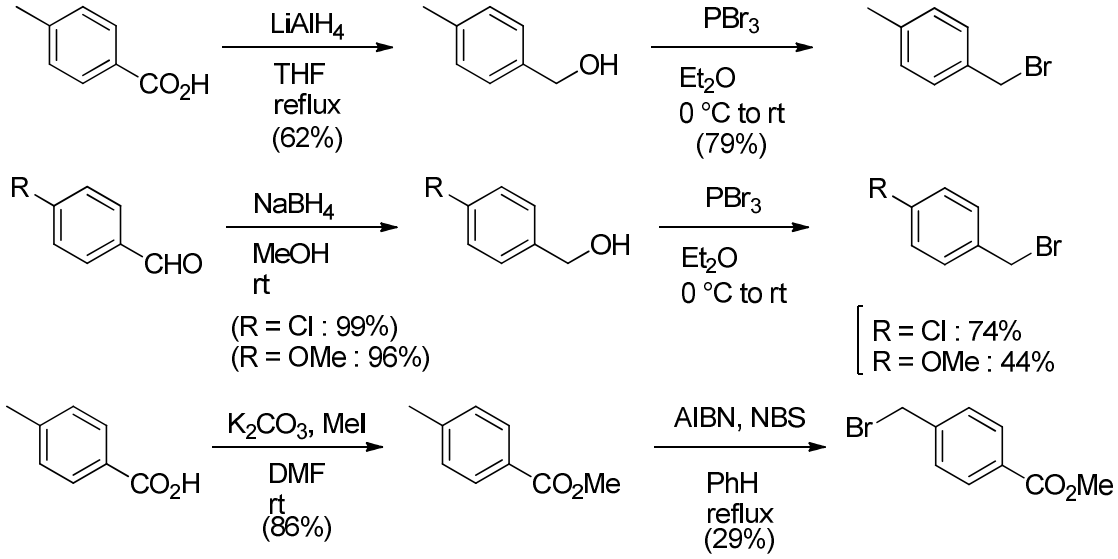
First, we prepared the substrate and reactants.

1-Bromo-4-phenyl-2-butyne was synthesized (Scheme 4-18). Benzylation of the protected propargyl alcohol by benzyl bromide and subsequently deprotection gave 4-phenyl-2-butyn-1-ol, of which bromination by phosphorus tribromide afforded 1-bromo-4-phenyl-2-butyne. *p*-Methylbenzyl bromide, *p*-chlorobenzyl bromide, *p*-methoxybenzyl bromide, and (*p*-methoxycarbonyl)benzyl bromide were synthesized (Scheme 4-19) *p*-Methylbenzyl bromide was synthesized from reduction by lithium aluminum hydride and subsequently bromination by phosphorus tribromide. *p*-Chlorobenzyl bromide and *p*-methoxybenzyl bromide were synthesized from reduction of corresponding aldehyde and subsequently bromination. (*p*-Methoxycarbonyl)benzyl bromide was synthesized from esterification of *p*-toluic acid and subsequently bromination by *N*-bromosuccinimide (NBS).

Scheme 4-18

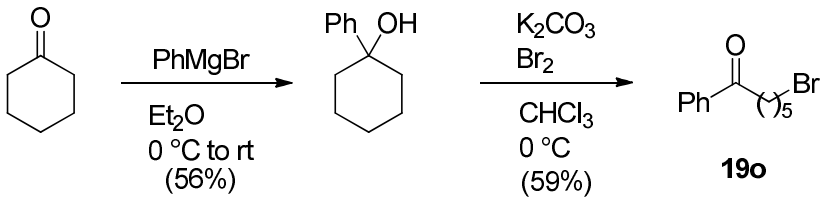


Scheme 4-19



6-Bromohexanophenone **19o** was synthesized from phenylation by phenylmagnesium bromide and subsequently ring-opening by bromine (Scheme 4-20).

Scheme 4-20

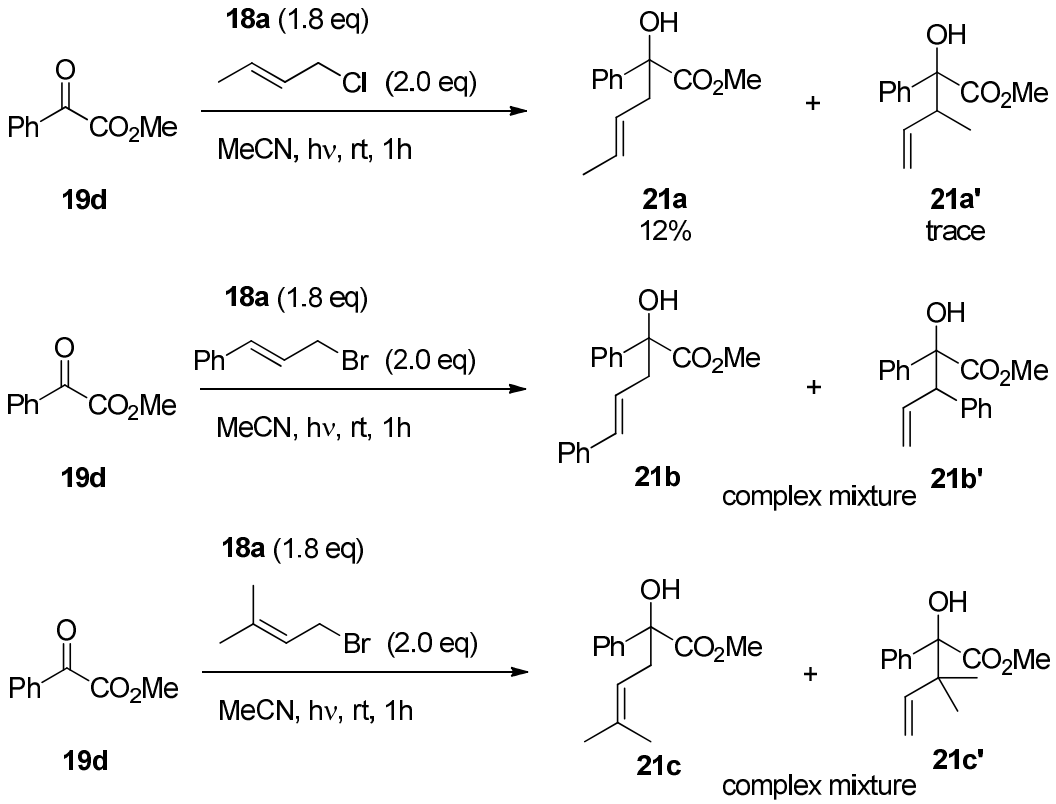


19o

We examined the reaction of **19d** with the various electrophiles to further explore the nucleophilic reactivity of the proposed anionic intermediate in Scheme 4-10.

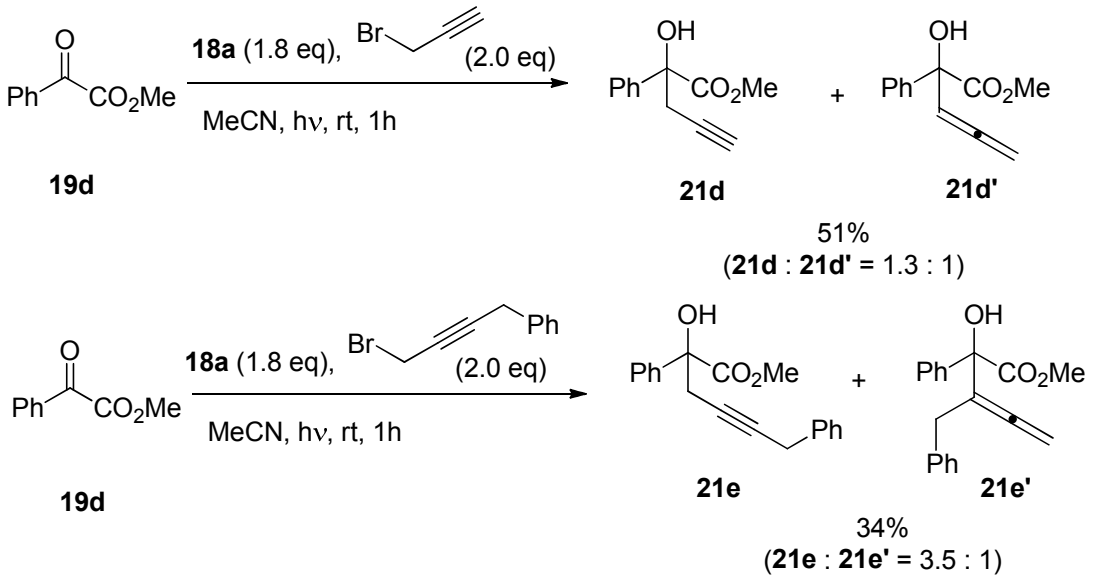
We investigated the reaction of **19d** with allyl halide derivatives under the same conditions (Scheme 4-21). The reaction with crotyl chloride gave α-adduct **21a** in 12% yield and γ-adduct was obtained slightly. When cinnamyl bromide and prenyl bromide were used, the desired adduct could not be isolated by some of unexpected side reactions.

Scheme 4-21



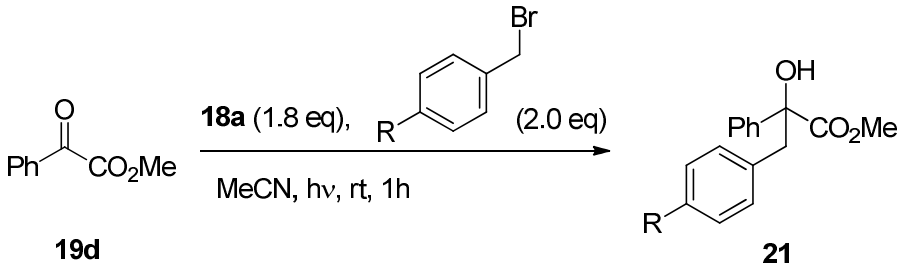
When the reaction of **19d** with propargyl bromide was carried out under the same conditions, **21d** as a mixture of α- and γ-adduct (1.3 : 1) was obtained in moderate yield (Scheme 4-22). On the other hand, the reaction of **19d** with 1-bromo-4-phenyl-2-butyne (simply adding a terminal substituent to propargyl bromide) gave **21e** as a mixture of α- and γ-adduct (3.5 : 1). Notably, α-adducts were preferentially formed in above reactions, particularly, when the S_N2' pathway was hindered by the terminal substituents.

Scheme 4-22



Next, we chose the several benzyl bromide derivatives as electrophiles (Table 4-4). Reaction of **19d** with benzyl bromide gave the benzyl adduct **21f** in 71% yield (entry 1). Addition of *p*-methylbenzyl bromide produced **21g** in 71% yield (entry 2). The reaction of *p*-chlorobenzyl bromide resulted in the formation of **21h** in moderate yield (entry 3), while (*p*-methoxycarbonyl)benzyl bromide did not produce the expected adduct at all (entry 4). When *p*-methoxybenzyl bromide was used as an electrophile, the desired alcohol was not also obtained (entry 5).

Table 4-4

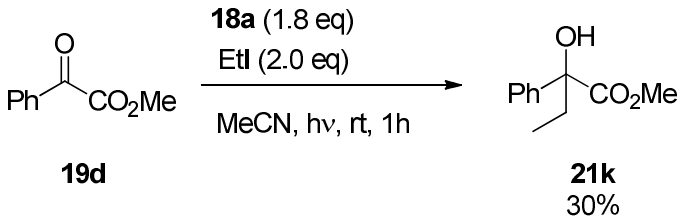


Entry	R	**21**	Yield[a] (%)
1	H	**21f**	71
2	Me	**21g**	71
3	Cl	**21h**	52
4	CO_2Me	**21i**	0
5	OMe	**21j**	0

[a] Isolated yield.

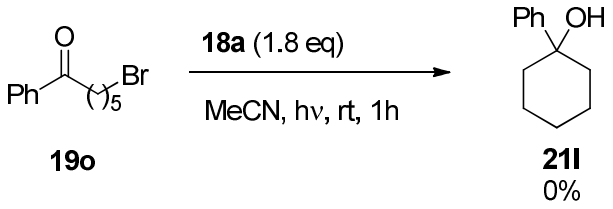
Further, we conducted the reaction of **19d** with alkyl halide (Scheme 4-23). While bromoethane was unreactive in this system, the use of iodoethane gave **21k** in low yield.

Scheme 4-23



We explored the intramolecular photo-addition reaction of 6-bromohexanophenone **19o**, while the desired cyclization product **21l** was not obtained (Scheme 4-24).

Scheme 4-24



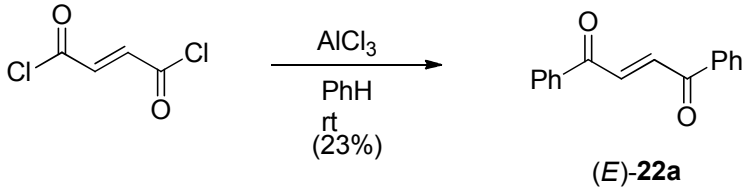
4-7 The photo-allylation reaction by the photosensitizer

The photosensitization by $Ru(bpy)_3Cl_2$ is a well-known system for reductive reaction, and our group also have used a set of $Ru(bpy)_3Cl_2$ and DMBI-H.[3h] We applied this system to the photo-allyation reaction to explore how effective the reaction would proceed.

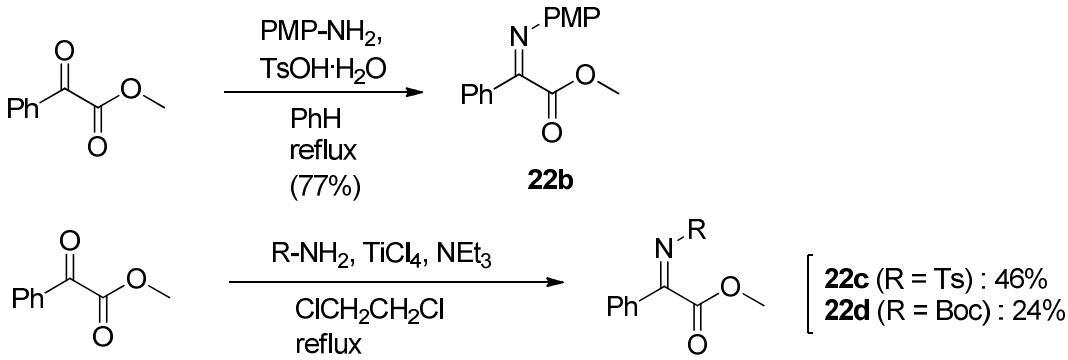
First, we prepared the substrates.

(*E*)-1,4-Diphenyl-2-butene-1,4-dione **22a** was synthesized by Friedel–Crafts reaction of 1,4-dichloro-2-butene-1,4-dione (Scheme 4-25). *N*-Substituent iminoesters **22b-d** were synthesized from methyl benzoylformate and the corresponding amines (Scheme 4-26).

Scheme 4-25

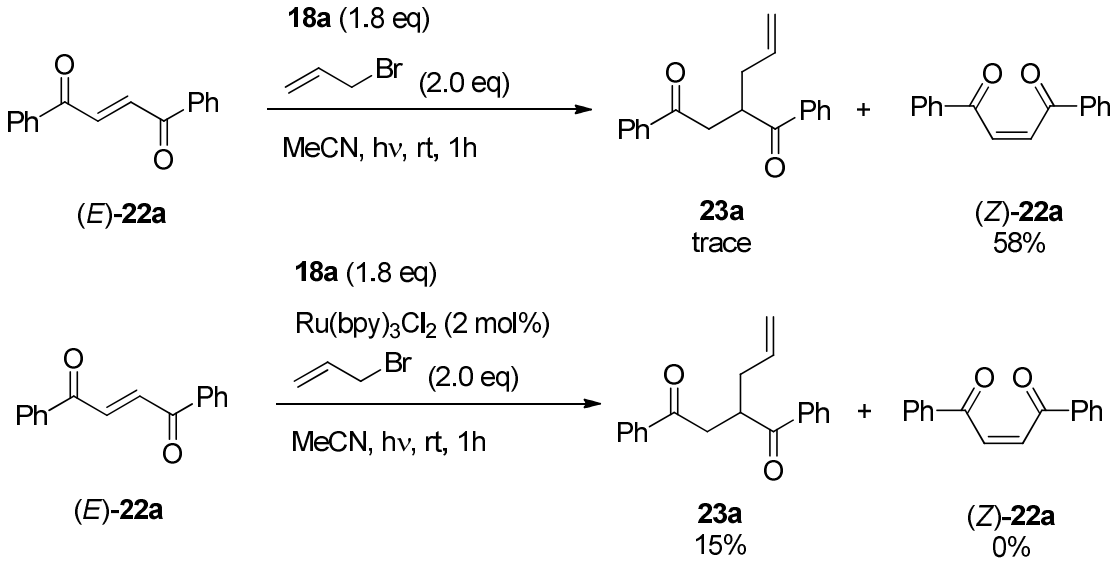


Scheme 4-26



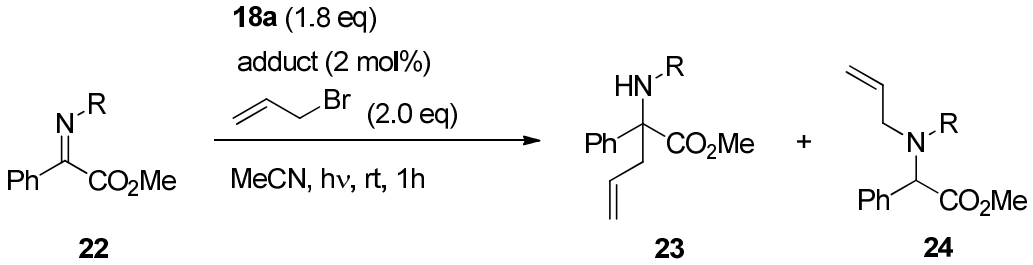
When we conducted the reaction of (*E*)-**22a** under the same conditions (Scheme 4-27). The reaction of (*E*)-**22a** gave (*Z*)-**22a** by cis-trans isomerization, while allyl adduct was not obtained. On the other hand, we attempted the reaction of (*E*)-**22a** with $Ru(bpy)_3Cl_2$ as photosensitizer to afford the expected allyl adduct **23a**, albeit in low yield.

Scheme 4-27



Next, we applied the photosensitization reaction to α-iminoesters **22b-d** (Table 4-5). *p*-Methoxyphenyl substituent **22b** did not react at all regardless of the presence or absence of the photosensitizer (entries 1,2). The expected product **23c** was not obtained in the reaction of tosyl substituent **22c**, while *N*-allylated **24c** was afforded in low yield (entry 3). The addition of $Ru(bpy)_3Cl_2$ improved the yield of **24c** slightly (entry 4). While the reaction of *tert*-butoxycarbonyl substituent **22d** did not give **23d** and **24d** in absence of $Ru(bpy)_3Cl_2$ (entry 5), the α-allylated product **23d** was obtained in using the photosensitizer (entry 6).

Table 4-5



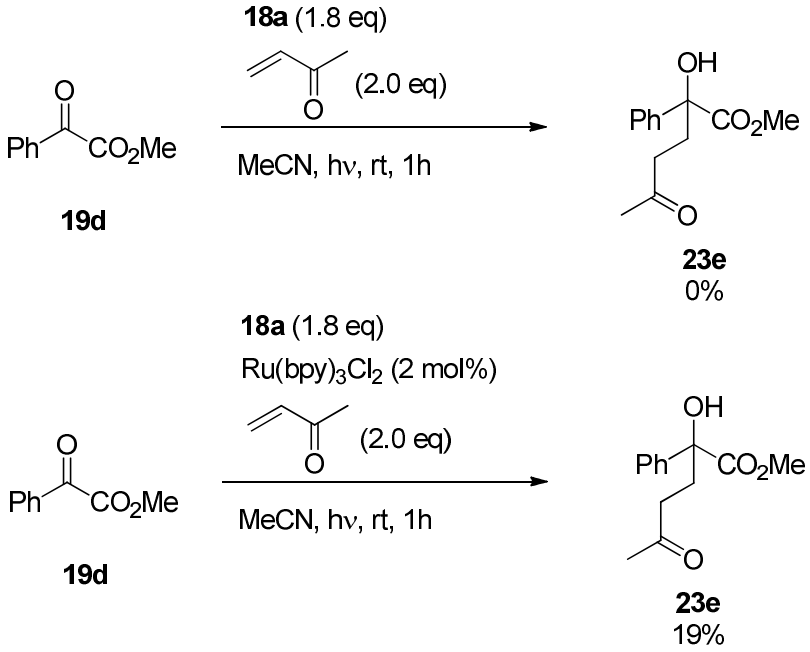
22 **23** **24**

Entry	**22**	R	Adduct	Yield of **23**[a] (%)	Yield of **24**[a] (%)
1	**22b**	PMP	–	0	0
2[b]	**22b**	PMP	$Ru(bpy)_3Cl_2$	0	0
3	**22c**	Ts	–	0	21
4[b]	**22c**	Ts	$Ru(bpy)_3Cl_2$	0	32
5	**22d**	Boc	–	0	0
6[b]	**22d**	Boc	$Ru(bpy)_3Cl_2$	33	0

[a] Isolated yield. [b] $\lambda > 390$ nm.

We explored the reaction of **19d** with Micheal acceptor, such as methyl vinyl ketone (Scheme 4-28). Micheal acceptor did not afford an α-adduct **23e**, while some quantity of methyl vinyl ketone was consumed. On the other hand, the reaction with the photosensitizer produced **23e** in low yield.

Scheme 4-28



4-8 Summary

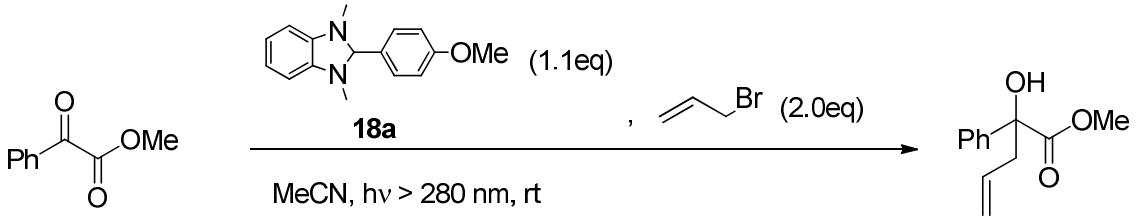
We have demonstrated a novel carbon–carbon bond formation reaction of benzoylformate derivatives initiated by photoinduced electron-transfer with DMBI-H. This is the first successful application of DMBI-H to photoinduced carbon–carbon bond formation. Although not fully elucidated, the reaction mechanism proposed involves the coupling of halide-bearing alkylating agents and hydroxyl methyl anions; the reactivity of these anions must be properly tuned by adjacent substituents. This process enacts the carbon–carbon bond formation between an electrophile and a polarity invert carbonyl carbon of a substrate (umpolung reactivity). This mild method allows to avoid using reactive or strongly basic reagents.

Experimental Section

General

Infrared spectra were recorded on a Perkin Elmer Spectrum GX FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were measured on a Varian 400 MHz (^{1}H: 400 MHz, ^{13}C: 100 MHz) spectrometer. Splitting patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. High-resolution mass spectra were measured on a Thermo Fisher Scientific LC/FT-MS spectrometer. Reactions were conducted in appropriate round-bottomed flask with a magnetic stirring bar under an argon atmosphere. *N*,*N*-Dimethylformamide (DMF) was dried over molecular sieves 4Å. CH_2Cl_2 was distilled with CaH_2. Photoreactions were conducted in a borosilicate glass flask at room temperature with a 500W Hg–Xe lamp as a light source. For thin layer chromatography (TLC) analysis throughout this work, Merck TLC plates (silica gel 60 F_{254}) were used. The products were purified by preparative column chromatography on silica gel (silica gel 60N, spherical neutral, KANTO Chemical Co., Inc., Japan). Benzimidazoline derivatives **18a-d** were prepared. Substrates **19g-i**, **19k**, **19l** were prepared. 1-Bromo-4-phenyl-2-butyne, *p*-methylbenzyl bromide and *p*-chlorobenzyl bromide were prepared. Other reagents and solvents were purchased and without further purification.

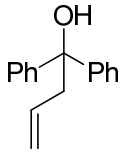
Photoreaction of methyl benzoylformate 19d and 2-(*p*-anisyl)-1,3-dimethylbenzimidazoline 18a with allyl bromide



19d **20d**

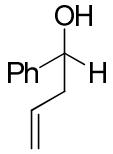
To a solution of methyl benzoylformate **1d** (31.4 mg, 0.191 mmol) and 2-(*p*-anisyl)-1,3-dimethylbenzimidazoline **2a** (52.4 mg, 0.206 mmol) in MeCN (3.8 mL) was added allyl bromide (33 μL, 0.38 mmol) at room temperature under an argon atmosphere. After the solution was irradiated (λ > 280 nm) for 1 h, the photolysate was concentrated. Purification of the residue by chromatography on silica gel (hexane/ethyl acetate = 20 : 1 to 10 : 1 as eluent) gave produced **20d** (29.9 mg, 76% yield) as a colorless oil.

1,1-Diphenyl-3-buten-1-ol (20a)



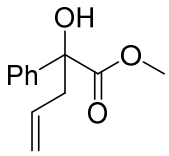
Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.41 (4H, m, Ph), 7.34-7.26 (4H, m, Ph), 7.24-7.18 (2H, m, Ph), 5.66 (1H, ddt, *J* = 17.0, 10.2, 7.2 Hz, CH_2CH=CH_2), 5.23 (1H, ddt, *J* = 17.0, 2.2, 1.2 Hz, CH_2CH=CH_2), 5.17 (1H, ddt, *J* = 10.2, 2.2, 1.2 Hz, CH_2CH=CH_2), 3.07 (2H, ddd, *J* = 7.2, 1.2, 1.2 Hz, CH_2CH=CH_2), 2.56 (1H, br, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.4, 133.4, 128.1, 126.8, 125.9, 120.5, 76.8, 46.7. Spectral data were consistent with those previously reported in the literature.[9]

1-Phenyl-3-buten-1-ol (20b)



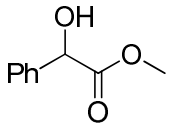
Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.23 (5H, m, Ph), 5.88-5.75 (1H, m, CH_2CH=CH_2), 5.21-5.10 (2H, m, CH_2CH=CH_2), 4.74 (1H, dd, *J* = 6.6, 5.8 Hz, CHPh), 2.59-2.44 (2H, m, CH_2CH=CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8, 134.4, 128.4, 127.5, 125.8, 118.5, 73.3, 43.8. Spectral data were consistent with those previously reported in the literature.[10]

Methyl 2-hydroxy-2-phenyl-4-pentenate (20d)



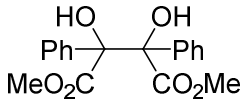
Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63-7.56 (2H, m, Ph), 7.40-7.32 (2H, m, Ph), 7.32-7.26 (1H, m, Ph), 5.79 (1H, dddd, *J* = 17.3, 10.1, 7.6, 6.4 Hz, CH_2CH=CH_2), 5.17 (1H, dddd, *J* = 17.3, 1.8, 1.2, 1.2 Hz, CH_2CH=CH_2), 5.14 (1H, dddd, *J* = 10.1, 1.8, 1.2, 0.8 Hz, CH_2CH=CH_2), 3.77 (3H, s, CH_3), 3.74 (1H, br, OH), 2.98 (1H, dddd, *J* = 14.1, 7.6, 1.2, 0.8 Hz, CH_2CH=CH_2), 2.77 (1H, dddd, *J* = 14.1, 6.4, 1.2, 1.2 Hz, CH_2CH=CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 141.1, 132.3, 128.3, 127.8, 125.2, 119.4, 78.1, 53.2, 44.1. Spectral data were consistent with those previously reported in the literature.[11]

Methyl 2-hydroxy-2-phenylacetate (20e)



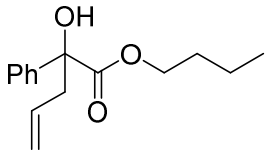
White solids; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.30 (5H, m, Ph), 5.18 (1H, s, PhC*H*), 3.75 (3H, s, CH_3), 3.51 (1H, br, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 138.2, 128.6, 128.5, 126.5, 72.8, 53.0. Spectral data were consistent with those previously reported in the literature.[12]

Dimethyl 2,3-dihydroxy-2,3-diphenylbutanedioate (20f)



White solids; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.20 (2H, m, Ph), 7.18-7.11 (4H, m, Ph), 7.10-7.03 (4H, m, Ph), 5.12 (2H, s, OH), 3.85 (6H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 134.4, 128.2, 127.0, 82.0, 53.5. dl-isomer: White solids; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.27 (6H, m, Ph), 7.27-7.19 (4H, m, Ph), 4.29 (2H, s, OH), 3.80 (6H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 135.6, 128.4, 127.9, 127.0, 83.1, 53.2. Spectral data were consistent with those previously reported in the literature.[13]

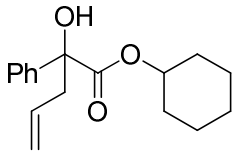
***n*-Butyl 2-hydroxy-2-phenyl-4-pentenate (20g)**



Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (2H, d, *J* = 7.2 Hz, Ph), 7.36 (2H, dd, *J* = 7.6, 7.2 Hz, Ph), 7.29 (1H, dd, *J* = 7.6, 7.6 Hz, Ph), 5.80 (1H, dddd, *J* = 17.3, 10.1, 7.4, 6.6 Hz, CH_2CH=CH_2), 5.17 (1H, d, *J* = 17.3 Hz, CH_2CH=CH_2), 5.14 (1H, d, *J* = 10.1 Hz, CH_2CH=CH_2), 4.19 (1H, ddd, *J* = 10.6, 7.0, 6.4 Hz, O$CH_2CH_2CH_2CH_3$), 4.13 (1H, ddd, *J* = 10.6, 6.8, 6.4 Hz, O$CH_2CH_2CH_2CH_3$), 3.80 (1H, br, OH), 2.97 (1H, dd, *J* = 14.2, 7.4 Hz, CH_2CH=CH_2), 2.77 (1H, dd, *J* = 14.2, 6.6 Hz, CH_2CH=CH_2), 1.62 (2H, ddt, *J* = 7.0, 7.0, 6.8 Hz, $OCH_2CH_2CH_2CH_3$), 1.33 (2H, tq, *J* = 7.6, 7.0 Hz, $OCH_2CH_2CH_2CH_3$), 0.90 (3H, t, *J* = 7.6 Hz, $OCH_2CH_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 141.4, 132.4, 128.2, 127.7, 125.5, 119.2, 77.9, 66.3, 44.1, 30.4, 19.0, 13.6; IR (film) 3507, 3076, 3026, 2960, 2934, 2874, 1729, 1692, 1641, 1599, 1581, 1494, 1462, 1448, 1434, 1413, 1381, 1359, 1336, 1263, 1223, 1191, 1145, 1095, 1070, 1033, 1000, 920, 842, 778, 731, 698, 677, 646 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{15}H_{20}NaO_3$: 271.1305.

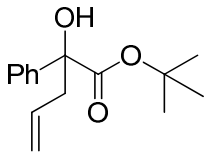
Found: 271.1302.

Cyclohexyl 2-hydroxy-2-phenyl-4-pentenate (20h)



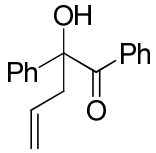
Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66-7.59 (2H, m, Ph), 7.39-7.32 (2H, m, Ph), 7.32-7.25 (1H, m, Ph), 5.81 (1H, dddd, *J* = 17.2, 10.1, 7.5, 6.4 Hz, CH_2CH=CH_2), 5.18 (1H, dddd, *J* = 17.2, 2.0, 1.6, 1.2 Hz, CH_2CH=CH_2), 5.13 (1H, dddd, *J* = 10.1, 2.0, 1.2, 1.2 Hz, CH_2CH=CH_2), 4.84 (1H, tt, *J* = 8.8, 3.6 Hz, OCH), 3.84 (1H, s, OH), 2.97 (1H, dddd, *J* = 14.0, 7.5, 1.6, 1.2 Hz, CH_2CH=CH_2), 2.75 (1H, dddd, *J* = 14.0, 6.4, 1.2, 1.2 Hz, CH_2CH=CH_2), 1.92-1.67 (4H, m, OCHCH_2), 1.67-1.23 (6H, m, OCHCH_2CH_2 and OCH$CH_2CH_2CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 141.6, 132.4, 128.1, 127.7, 125.5, 119.1, 77.7, 75.1, 44.1, 31.3, 31.1, 25.2, 23.4, 23.3; IR (film) 3504, 3075, 3025, 2939, 2860, 2661, 1724, 1641, 1600, 1493, 1448, 1432, 1412, 1372, 1359, 1349, 1334, 1317, 1263, 1230, 1190, 1146, 1121, 1095, 1070, 1036, 1009, 915, 892, 865, 843, 827, 776, 732, 698, 679, 646 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{17}H_{22}NaO_3$: 297.1461. Found: 297.1459.

***tert*-Butyl 2-hydroxy-2-phenyl-4-pentenate (20i)**



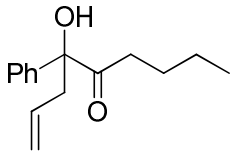
Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64-7.58 (2H, m, Ph), 7.37-7.31 (2H, m, Ph), 7.31-7.24 (1H, m, Ph), 5.83 (1H, dddd, *J* = 17.3, 10.2, 7.8, 6.2 Hz, CH_2CH=CH_2), 5.17 (1H, dddd, *J* = 17.3, 1.8, 1.2, 1.2 Hz, CH_2CH=CH_2), 5.13 (1H, dddd, *J* = 10.2, 1.8, 1.4, 1.2 Hz, CH_2CH=CH_2), 3.88 (1H, br, OH), 2.92 (1H, dddd, *J* = 13.8, 7.8, 1.2, 1.2 Hz, CH_2CH=CH_2), 2.71 (1H, dddd, *J* = 13.8, 6.2, 1.4, 1.2 Hz, CH_2CH=CH_2), 1.44 (9H, s, *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 141.9, 132.6, 128.0, 127.5, 125.4, 118.8, 83.2, 77.7, 44.2, 27.8; IR (film) 3499, 3075, 3002, 2979, 2932, 1719, 1641, 1599, 1492, 1477, 1449, 1433, 1411, 1394, 1370, 1272, 1253, 1240, 1155, 1144, 1096, 1070, 1033, 999, 918, 844, 781, 750, 732, 698, 644 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{15}H_{20}NaO_3$: 271.1305. Found: 271.1302.

1,2-Diphenyl-2-hydroxy-4-pentenone (20j)



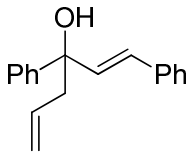
Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (2H, d, *J* = 8.0 Hz, Ph), 7.50 (2H, d, *J* = 7.6 Hz, Ph), 7.43 (1H, t, *J* = 7.4 Hz, Ph), 7.38 (2H, dd, *J* = 8.0, 7.4 Hz, Ph), 7.30 (1H, t, *J* = 7.6 Hz, Ph), 7.28 (2H, dd, *J* = 7.6, 7.6 Hz, Ph), 5.73 (1H, dddd, *J* = 17.4, 10.2, 7.5, 7.0 Hz, CH_2CH=CH_2), 5.11 (1H, d, *J* = 10.2 Hz, CH_2CH=CH_2), 5.01 (1H, d, *J* = 17.4 Hz, CH_2CH=CH_2), 4.20 (1H, s, OH), 3.13 (1H, dd, *J* = 13.7, 7.5 Hz, CH_2CH=CH_2), 2.97 (1H, dd, *J* = 13.7, 7.0 Hz, CH_2CH=CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.7, 141.7, 134.4, 132.7, 132.2, 130.1, 128.8, 128.1, 128.0, 125.6, 120.3, 81.3, 43.9. Spectral data were consistent with those previously reported in the literature.[14]

4-Hydroxy-5-oxo-4-phenyl-1-nonene (20k)



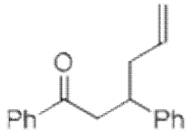
Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.43 (2H, m, Ph), 7.41-7.33 (2H, m, Ph), 7.33-7.27 (1H, m, Ph), 5.75 (1H, dddd, *J* = 17.2, 10.2, 7.5, 6.3 Hz, CH_2CH=CH_2), 5.21 (1H, dd, *J* = 17.2, 1.6 Hz, CH_2CH=CH_2), 5.16 (1H, d, *J* = 10.2 Hz, CH_2CH=CH_2), 4.33 (1H, br, OH), 2.99 (1H, dd, *J* = 14.1, 7.5 Hz, CH_2CH=CH_2), 2.92 (1H, dd, *J* = 14.1, 6.3 Hz, CH_2CH=CH_2), 2.43 (1H, dt, *J* = 18.0, 7.2 Hz, $COCH_2CH_2CH_2CH_3$), 2.38 (1H, dt, *J* = 18.0, 6.8 Hz, $COCH_2CH_2CH_2CH_3$), 1.44 (1H, dddt, *J* = 13.4, 7.4, 7.2, 6.8 Hz, $COCH_2CH_2CH_2CH_3$), 1.38 (1H, dddt, *J* = 13.4, 7.4, 7.2, 6.8 Hz, $COCH_2CH_2CH_2CH_3$), 1.12 (2H, tq, *J* = 7.4, 7.4 Hz, $COCH_2CH_2CH_2CH_3$), 0.76 (3H, t, *J* = 7.4 Hz, $COCH_2CH_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.1, 140.6, 132.2, 128.6, 127.9, 126.0, 119.6, 81.9, 41.5, 35.6, 25.7, 22.0, 13.7; IR (film) 3454, 3245, 3075, 3025, 2957, 2932, 2872, 1705, 1668, 1640, 1600, 1579, 1558, 1540, 1511, 1494, 1464, 1447, 1404, 1360, 1302, 1281, 1258, 1248, 1178, 1158, 1125, 1059, 1033, 999, 920, 886, 846, 759, 726, 700, 641 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{15}H_{20}NaO_2$: 255.1356. Found: 255.1352.

(*E*)-1,3-Diphenyl-3-hydroxyhexa-1,5-diene (20m)



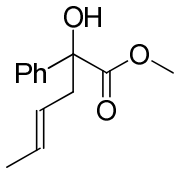
Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60-7.44 (2H, m, Ph), 7.44-7.12 (8H, m, Ph), 6.65 (1H, d, *J* = 16.0 Hz, PhC*H*=CH), 6.53 (1H, d, *J* = 16.0 Hz, PhCH=C*H*), 5.72 (1H, dddd, *J* = 17.2, 10.0, 7.2, 7.2 Hz, CH_2CH=CH_2), 5.21 (1H, dddd, *J* = 17.2, 2.0, 1.2, 1.2 Hz, CH_2CH=CH_2), 5.18 (1H, dddd, *J* = 10.0, 2.0, 1.2, 0.8 Hz, CH_2CH=CH_2), 2.83 (1H, dddd, *J* = 13.8, 7.2, 1.2, 0.8 Hz, CH_2CH=CH_2), 2.78 (1H, dddd, *J* = 13.8, 7.2, 1.2, 1.2 Hz, CH_2CH=CH_2), 2.31 (1H, br, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2, 136.7, 135.1, 133.1, 128.5, 128.3, 127.5, 127.0, 126.5, 125.4, 120.2, 75.6, 47.1. Spectral data were consistent with those previously reported in the literature.[15]

1,3-Diphenyl-5-hexen-1-one (20m')



Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (2H, d, *J* = 6.8 Hz, Ph), 7.53 (1H, t, *J* = 7.6 Hz, Ph), 7.42 (2H, t, *J* = 7.6 Hz, Ph), 7.28 (2H, dd, *J* = 7.6, 7.0 Hz, Ph), 7.24 (2H, dd, *J* = 7.6, 6.8 Hz, Ph), 7.17 (1H, t, *J* = 7.0 Hz, Ph), 5.69 (1H, ddt, *J* = 18.0, 10.4, 7.2 Hz, CH_2CH=CH_2), 5.00 (1H, d, *J* = 18.0 Hz, CH_2CH=CH_2), 4.96 (1H, d, *J* = 10.4 Hz, CH_2CH=CH_2), 3.48 (1H, tt, *J* = 7.2, 6.8 Hz, C*H*Ph), 3.32 (1H, dd, *J* = 17.1, 7.2 Hz, PhCOCH_2), 3.27 (1H, dd, *J* = 17.1, 7.2 Hz, PhCOCH_2), 2.48 (1H, ddd, *J* = 14.3, 7.2, 6.8 Hz, CH_2CH=CH_2), 2.44 (1H, ddd, *J* = 14.3, 7.2, 6.8 Hz, CH_2CH=CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.9, 144.3, 137.2, 136.2, 132.9, 128.5, 128.4, 128.0, 127.5, 126.3, 116.8, 44.5, 40.69, 40.68. Spectral data were consistent with those previously reported in the literature.[16]

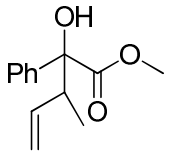
(*E*)-Methyl 2-hydroxy-2-phenyl-4-hexenate (21a)



Colorless oil; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.59 (2H, d, *J* = 7.0 Hz, Ph), 7.39-7.32 (2H, m, Ph), 7.29 (1H, t, *J* = 7.0 Hz, Ph), 5.61 (1H, dq, *J* = 14.8, 6.3 Hz, CH_2CH=C*H*CH_3), 5.40 (1H, ddt, *J* = 14.8, 7.0, 1.4 Hz, CH_2CH=CHCH_3), 3.76 (3H, s,

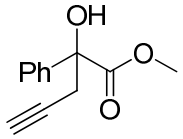
OCH_3), 3.64 (1H, br, OH), 2.93 (1H, dd, J = 14.0, 7.0 Hz, CH_2CH=CHCH$_3$), 2.67 (1H, dd, J = 14.0, 7.0 Hz, CH_2CH=CHCH$_3$), 1.66 (3H, dd, J = 6.3, 1.4 Hz, CH_2CH=CHCH_3); ^{13}C NMR (175 MHz, $CDCl_3$) δ 175.1, 141.3, 130.5, 128.2, 127.8, 125.5, 124.5, 78.2, 53.1, 43.1, 18.1; IR (film) 3519, 3504, 3059, 3029, 2963, 2914, 2852, 2651, 2532, 2015, 1989, 1963, 1940, 1886, 1865, 1839, 1824, 1790, 1732, 1692, 1648, 1633, 1617, 1599, 1576, 1555, 1540, 1519, 1506, 1493, 1470, 1434, 1395, 1372, 1356, 1336, 1315, 1257, 1214, 1176, 1135, 1097, 1070, 1032, 1000, 969, 915, 780, 757, 732, 698, 654 cm^{-1}; HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{13}H_{16}NaO_3$: 243.0992. Found: 243.0991.

Methyl 2-hydroxy-3-methyl-2-phenyl-4-pentenate (21a')



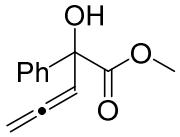
Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66-7.56 (2H, m, Ph), 7.39-7.22 (3H, m, Ph), 5.59 (1H, ddd, J = 17.3, 10.8, 7.4 Hz, CHCH=CH_2), 4.91 (1H, d, J = 17.3 Hz, CHCH=CH_2), 4.90 (1H, d, J = 10.8 Hz, CHCH=CH_2), 3.81 (3H, s, OCH_3), 3.20 (1H, dq, J = 7.4, 6.8 Hz, CHCH=CH_2), 1.11 (3H, d, J = 6.8 Hz, CHCH_3).

Methyl 2-hydroxy-2-phenyl-4-pentynate (21d)



Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62-7.55 (2H, m, Ph), 7.42-7.29 (3H, m, Ph), 3.94 (1H, s, OH), 3.83 (3H, s, CH_3), 3.19 (1H, dd, J = 16.7, 2.4 Hz, CH_2C≡CH), 2.86 (1H, dd, J = 16.7, 2.6 Hz, CH_2C≡CH), 2.06 (1H, dd, J = 2.6, 2.4 Hz, CH_2C≡CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 139.8, 128.4, 128.3, 125.4, 79.0, 77.5, 71.2, 53.6, 30.9. Spectral data were consistent with those previously reported in the literature.[17]

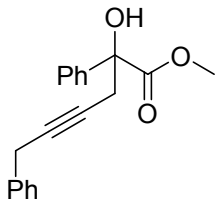
Methyl 2-hydroxy-2-phenyl-3,4-pentadienate (21d')



Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63-7.55 (2H, m, Ph), 7.42-7.29 (3H, m, Ph), 5.77 (1H, t, J = 6.8 Hz, CH=C=CH_2), 5.01 (2H, d, J = 6.8 Hz, CH=C=CH_2), 3.87 (1H, s, OH), 3.79 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.9, 174.0, 140.4, 128.3, 128.2, 126.2, 95.3, 79.7, 76.8, 53.4; IR (film) 3519, 3501, 3291, 3062,

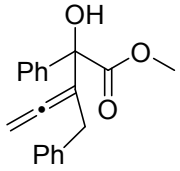
3028, 2997, 2953, 2919, 2847, 1957, 1888, 1865, 1842, 1826, 1790, 1732, 1718, 1697, 1682, 1669, 1651, 1633, 1599, 1557, 1540, 1519, 1507, 1490, 1470, 1449, 1435, 1395, 1372, 1362, 1338, 1250, 1184, 1152, 1090, 1066, 1031, 1000, 961, 930, 856, 782, 734, 698, 636 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{12}H_{12}NaO_3$: 227.0679. Found: 227.0677.

Methyl 2,6-diphenyl-2-hydroxy-4-hexynate (21e)



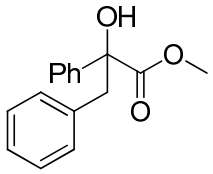
Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (2H, d, *J* = 8.0 Hz, Ph), 7.42-7.17 (8H, m, Ph), 3.92 (1H, s, OH), 3.77 (3H, s, CH_3), 3.58 (2H, dd, *J* = 2.0, 2.0 Hz, C*H*$_2$Ph), 3.23 (1H, dt, *J* = 16.4, 2.0 Hz, C*H*$_2$C≡CCH$_2$Ph), 2.90 (1H, dt, *J* = 16.4, 2.0 Hz, C*H*$_2$C≡CH$_2$Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 140.0, 136.8, 128.37, 128.35, 128.2, 127.8, 126.4, 125.5, 81.0, 77.8, 77.0, 53.4, 31.4, 25.0; IR (film) 3501, 3085, 3061, 3029, 2953, 2918, 2843, 2234, 1956, 1741, 1732, 1697, 1649, 1600, 1558, 1540, 1494, 1452, 1434, 1392, 1338, 1310, 1263, 1223, 1181, 1120, 1074, 1052, 1030, 1002, 973, 943, 886, 817, 730, 698, 652 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{19}H_{18}NaO_3$: 317.1148. Found: 317.1149.

Methyl 3-benzyl-2-hydroxy-2-phenyl-3,4-pentadienate (21e')



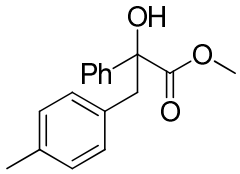
Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69-7.61 (2H, m, Ph), 7.42-7.10 (8H, m, Ph), 4.71 (2H, t, *J* = 3.2 Hz, C=C=C*H*$_2$), 3.97 (1H, s, OH), 3.67 (3H, s, CH_3), 3.33 (1H, dt, *J* = 15.6, 3.2 Hz, C*H*$_2$Ph), 3.18 (1H, dt, *J* = 15.6, 3.2 Hz, C*H*$_2$Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.8, 174.1, 139.1, 138.8, 129.3, 128.01, 127.96, 127.9, 127.3, 126.1, 107.5, 81.1, 79.4, 53.1, 34.1; IR (film) 3519, 3502, 3478, 3059, 3029, 2950, 2919, 2842, 2733, 2661, 2542, 2015, 1987, 1956, 1888, 1868, 1842, 1824, 1790, 1767, 1744, 1733, 1715, 1697, 1682, 1669, 1650, 1633, 1650, 1620, 1599, 1557, 1540, 1519, 1507, 1488, 1470, 1455, 1436, 1395, 1369, 1361, 1338, 1315, 1261, 1170, 1093, 1064, 1028, 983, 938, 897, 853, 793, 767, 742, 718, 700, 674, 634 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{19}H_{18}NaO_3$: 317.1148. Found: 317.1146.

Methyl 2,3-diphenyl-2-hydroxypropanate (21f)



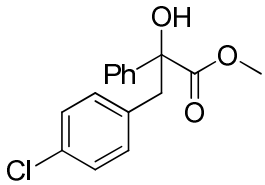
Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73-7.64 (2H, m, Ph), 7.43-7.17 (8H, m, Ph), 3.73 (3H, s, CH_3), 3.603 (1H, s, OH), 3.598 (1H, d, *J* = 13.8 Hz, C*H*$_2$Ph), 3.21 (1H, d, *J* = 13.8 Hz, C*H*$_2$Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 141.4, 135.6, 130.4, 128.3, 128.1, 127.9, 126.9, 125.7, 78.8, 53.0, 45.8. Spectral data were consistent with those previously reported in the literature.[18]

Methyl 2-hydroxy-3-(*p*-methylphenyl)-2-phenylpropanate (21g)



Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72-7.64 (2H, m, Ph), 7.41-7.34 (2H, m, Ph), 7.34-7.27 (1H, m, Ph), 7.10 (2H, d, *J* = 8.2 Hz, Ar), 7.07 (2H, d, *J* = 8.2 Hz, Ar), 3.72 (3H, s, OCH_3), 3.58 (1H, s, OH), 3.57 (1H, d, *J* = 13.6 Hz, C*H*$_2$Ph), 3.16 (1H, d, *J* = 13.6 Hz, C*H*$_2$Ph), 2.30 (3H, s, PhC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 141.4, 136.5, 132.4, 130.2, 128.8, 128.2, 127.8, 125.7, 78.8, 53.0, 45.5, 21.1; IR (KBr) 3515, 3089, 3046, 3023, 3002, 2961, 2930, 2856, 1721, 1512, 1494, 1446, 1379, 1254, 1205, 1185, 1116, 1098, 1073, 1035, 1000, 966, 948, 916, 887, 832, 795, 782, 752, 731, 714, 695, 650 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{17}H_{18}NaO_3$: 293.1148. Found: 293.1143.

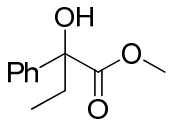
Methyl 3-(*p*-chlorophenyl)-2-hydroxy-2-phenylpropanate (21h)



Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.60 (2H, m, Ph), 7.40-7.28 (3H, m, Ph), 7.22 (2H, ddd, *J* = 8.4, 2.2, 2.2 Hz, Ar), 7.14 (2H, ddd, *J* = 8.4, 2.2, 2.2 Hz, Ar), 3.73 (3H, s, CH_3), 3.65 (1H, s, OH), 3.52 (1H, d, *J* = 13.6 Hz, C*H*$_2$Ph), 3.18 (1H, d, *J* = 13.6 Hz, C*H*$_2$Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 141.1, 134.1, 132.8, 131.8, 128.3, 128.1, 128.0, 125.5, 78.7, 53.2, 45.0; IR (KBr) 3509, 3085, 3064, 3033, 3007, 2958, 2930, 1727, 1597, 1492, 1446, 1407, 1373, 1305, 1285, 1253, 1211, 1183, 1115, 1093, 1073, 1041, 1016, 968, 948, 891, 841, 801, 779, 727, 691, 642 cm^{-1};

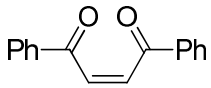
HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{16}H_{15}ClNaO_3$: 313.0602. Found: 313.0602.

Methyl 2-hydroxy-2-phenylbutanate (21k)



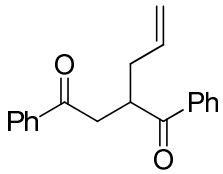
Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63-7.56 (2H, m, Ph), 7.38-7.32 (2H, m, Ph), 7.32-7.25 (1H, m, Ph), 3.98 (1H, s, OH), 3.78 (3H, s, OCH_3), 2.23 (1H, dq, *J* = 14.6, 7.2 Hz, CH_2CH_3), 2.03 (1H, dq, *J* = 14.6, 7.2 Hz, CH_2CH_3), 0.92 (3H, t, *J* = 7.2 Hz, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 141.6, 128.2, 127.7, 125.5, 78.7, 53.2, 32.6, 8.0. Spectral data were consistent with those previously reported in the literature.[19]

(*Z*)-1,4-Diphenyl-2-butene-1,4-dione (22a)



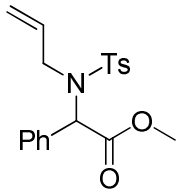
Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (4H, d, *J* = 7.6 Hz, Ph), 7.56 (2H, dd, *J* = 7.6, 7.6 Hz, Ph), 7.44 (4H, dd, *J* = 7.6, 7.6 Hz, Ph), 7.15 (2H, s, CH=CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.4, 136.0, 135.6, 133.5, 128.7, 128.6. Spectral data were consistent with those previously reported in the literature.[20]

1-Phenyl-3-(phenylcarbonyl)-5-hexen-1-one (23a)



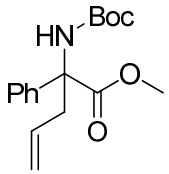
Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (2H, d, *J* = 7.2 Hz, Ph), 7.97 (2H, d, *J* = 7.2 Hz, Ph), 7.58 (1H, dd, *J* = 7.6, 7.6 Hz, Ph), 7.56 (1H, dd, *J* = 7.6, 7.6 Hz, Ph), 7.50 (2H, dd, *J* = 7.6, 7.2 Hz, Ph), 7.45 (2H, dd, *J* = 7.6, 7.2 Hz, Ph), 5.76 (1H, ddt, *J* = 17.2, 10.0, 7.0 Hz, $CH_2CH=CH_2$), 5.09 (1H, dd, *J* = 17.2, 1.2 Hz, $CH_2CH=CH_2$), 5.05 (1H, dd, *J* = 10.0, 1.2 Hz, $CH_2CH=CH_2$), 4.27-4.17 (1H, m, $CHCOPh$), 3.70 (1H, dd, *J* = 18.0, 9.2 Hz, CH_2COPh), 3.20 (1H, dd, *J* = 18.0, 4.0 Hz, CH_2COPh), 2.54 (1H, ddd, *J* = 14.2, 6.8, 6.4 Hz, $CH_2CH=CH_2$), 2.29 (1H, ddd, *J* = 14.2, 8.0, 6.4 Hz, $CH_2CH=CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.5, 198.5, 136.6, 136.5, 134.7, 133.2, 133.0, 128.7, 128.5 (2H), 128.1, 117.7, 41.0, 40.0, 36.4.

Methyl 2-(*N*-2'-propenyl-*N*-tosylamino)-2-phenylacetate (24c)



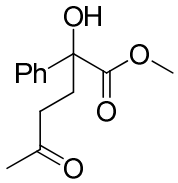
Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77-7.10 (2H, m, Ph), 7.37-7.27 (5H, m, Ph), 7.24-7.15 (2H, m, Ph), 5.80 (1H, s, C*H*Ph), 5.46-5.30 (1H, m, CH_2CH=CH_2), 4.76 (1H, d, *J* = 10.8 Hz, CH_2CH=CH_2), 4.75 (1H, d, *J* = 17.2 Hz, CH_2CH=CH_2), 3.92 (1H, dd, *J* = 16.4, 6.0 Hz, CH_2CH=CH_2), 3.83 (1H, dd, *J* = 16.4, 6.0 Hz, CH_2CH=CH_2), 3.62 (3H, s, OCH_3), 2.44 (3H, s, PhCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 143.4, 136.9, 134.7, 133.8, 129.5, 129.1, 128.8, 128.7, 127.4, 116.5, 62.6, 52.1, 48.2, 21.5. Spectral data were consistent with those previously reported in the literature.[21]

Methyl 2-(*tert*-butoxycarbonylamino)-2-phenyl-4-pentenate (23d)



Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (2H, d, *J* = 7.6 Hz, Ph), 7.34 (2H, dd, *J* = 7.6, 7.2 Hz, Ph), 7.27 (1H, t, *J* = 7.2 Hz, Ph), 6.02 (1H, br, NH), 5.68 (1H, dddd, *J* = 17.0, 9.8, 7.6, 7.2 Hz, CH_2CH=CH_2), 5.16 (1H, d, *J* = 17.0 Hz, CH_2CH=CH_2), 5.14 (1H, d, *J* = 9.8 Hz, CH_2CH=CH_2), 3.67 (3H, s, OCH_3), 3.55-3.37 (1H, m, CH_2CH=CH_2), 3.19 (1H, dd, *J* = 13.6, 7.6 Hz, CH_2CH=CH_2), 1.38 (9H, s, *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 132.5, 128.4 (2H), 127.7, 125.9 (2H), 119.3, 64.9, 53.1, 38.1, 28.3, 28.2. Spectral data were consistent with those previously reported in the literature.[22]

Methyl 2-phenyl-2-hydroxy-5-hexanonate (23e)

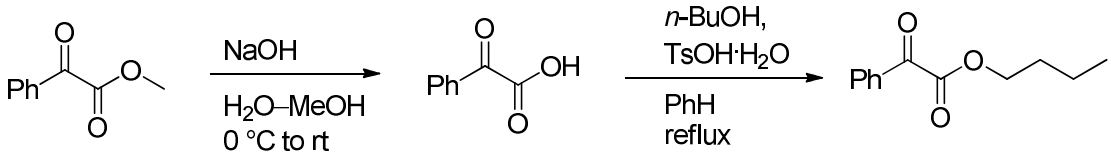


Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (2H, d, *J* = 7.6 Hz, Ph), 7.36 (2H, dd, *J* = 7.6, 7.0 Hz, Ph), 7.30 (1H, t, *J* = 7.0 Hz, Ph), 3.87 (1H, br, OH), 3.79 (3H, s, OCH_3), 2.51-2.44 (2H, m, COCH_2), 2.44-2.37 (2H, m, $COCH_2CH_2$), 2.11 (3H, s, COCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.4, 175.4, 140.8, 128.4, 127.9, 125.5, 77.5, 53.4, 38.1, 33.2, 30.0.

Preparation of substrates and reactants

1. Carbonyl compounds

***n*-Butyl benzoylformate (19g)**

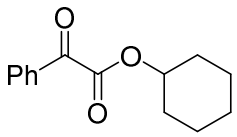


19g

(Step 1) To a solution of NaOH (0.58 g, 14.5 mmol) in H_2O (10 mL) and MeOH (30 mL) was added methyl benzoylformate (1.5 mL, 11 mmol) at 0 °C and the mixture was stirred at the room temperature for 4 h. The resulting mixture was neutralized with 1M aqueous hydrogen chloride and added brine and ethyl acetate. The mixture was extracted with ethyl acetate and washed with brine, before dried over sodium sulfate. The extract was concentrated to obtain crude benzoylformic acid (9.1 mmol, 83% yield) as white solids. This crude product was used for the following reaction without purification

(Step 2) To a solution of benzoylformic acid (0.71 g, 4.7 mmol) and *n*-butanol (0.48 mL, 5.2 mmol) in benzene (9.5 mL) was added *p*-toluenesulfonic acid monohydrate (99 mg, 0.52 mmol) at room temperature and the mixture was refluxed for 18 h with azeotropic removal of water by a Dean-Stark trap. The resulting mixture was cooled to room temperature and quenched with saturated aqueous sodium hydrogen carbonate. The mixture was extracted with ethyl acetate and the extract was washed with brine, before dried over sodium sulfate. The resulting mixture was concentrated and the residue was purified by chromatography on silica gel (hexane/ethyl acetate = 10 : 1 as eluent) to obtain *n*-butyl benzoylformate (**19g**) (0.77 g, 79% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (2H, d, J = 7.6 Hz, Ph), 7.66 (1H, t, J = 7.6 Hz, Ph), 7.52 (2H, t, J = 7.6 Hz, Ph), 4.40 (2H, t, J = 6.6 Hz, $OCH_2CH_2CH_2CH_3$), 1.77 (2H, tt, J = 7.6, 6.6 Hz, $OCH_2CH_2CH_2CH_3$), 1.45 (2H, tq, J = 7.6, 7.4 Hz, $OCH_2CH_2CH_2CH_3$), 0.97 (3H, t, J = 7.4 Hz, $OCH_2CH_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.5, 164.0, 134.9, 132.4, 130.0, 128.9, 66.1, 30.4, 19.0, 13.6. Spectral data were consistent with those previously reported in the literature.[23]

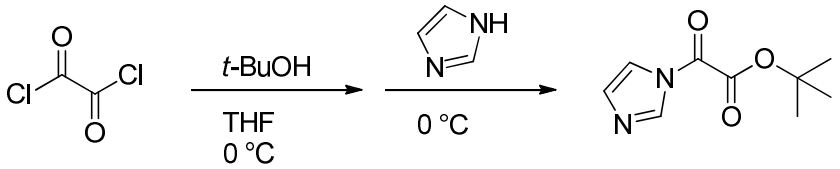
Cyclohexyl benzoylformate (19h)

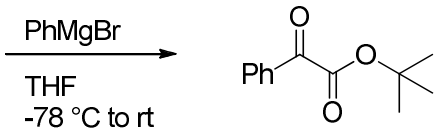


Prepared in 96% yield from benzoylformic acid by the same procedure with **19g** using

cyclohexanol instead of *n*-butanol. Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (2H, d, *J* = 7.6 Hz, Ph), 7.66 (1H, t, *J* = 7.6 Hz, Ph), 7.52 (2H, dd, *J* = 7.6, 7.6 Hz, Ph), 5.10 (1H, tt, *J* = 9.2, 4.4 Hz, OCH), 2.08-1.95 (2H, m, OCHCH_2), 1.87-1.73 (2H, m, OCHCH_2), 1.68-1.22 (6H, m, OCHCH$_2$CH_2 and OCHCH$_2$CH$_2$CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.8, 163.6, 134.8, 132.5, 129.9, 128.8, 75.4, 31.4, 25.1, 23.6. Spectral data were consistent with those previously reported in the literature.[24]

***tert*-Butyl benzoylformate (19i)[25]**





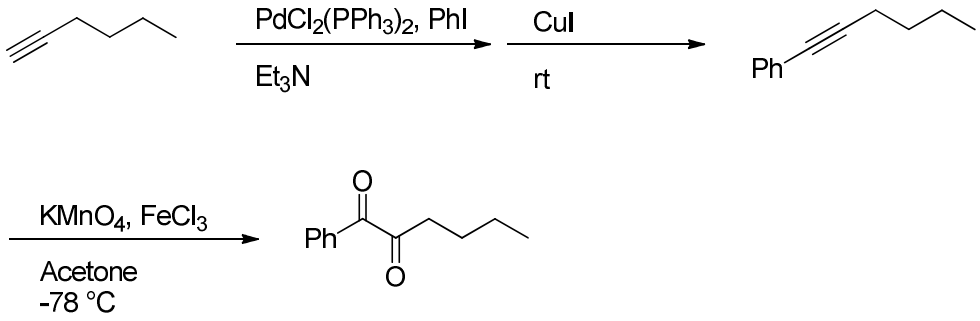
19i

(Step 1) To a solution of oxalyl chloride (0.85 mL, 10 mmol) in THF (15 mL) was added *tert*-butanol (0.96 mL, 10 mmol) at 0 °C and the resulting mixture was stirred at the same temperature for 1 h under an argon atmosphere. And then, a solution of imidazole (2.0 g, 29 mmol) in THF (10 mL) was added dropwise over 30 min. The mixture was stirred 25 min at 0 °C, filtered through a pad of Celite and washed with THF. After evaporated, *tert*-butyl 2-(1*H*-imidazol-1-yl)-2-oxoacetate as a yellow oil. This crude product was used for the following reaction without purification because it was found to be unstable for moisture.

(Step 2) Phenylmagnesium bromide was prepared from magnesium metal (0.25 g, 10 mmol), 1,2-dibromoethane (43 μL, 0.50 mmol) and phenyl bromide (1.1 mL, 10 mmol) in Et_2O (10 mL). To a solution of *tert*-butyl 2-(1*H*-imidazol-1-yl)-2-oxoacetate in THF (30 mL) was added dropwise a solution of phenylmagnesium bromide in Et_2O at -78 °C. The resulting mixture was stirred at the same temperature for 1 h. After stirred at room temperature for 3 h, the mixture was quenched with saturated ammonium chloride and extracted with ethyl acetate. The extract was washed with brine and dried over sodium sulfate. The resulting mixture was concentrated and the residue was purified by chromatography on silica gel (hexane/dichloroethane = 2 : 1 to dichloroethane as eluent) to obtaine **19i** (0.97 g, 47% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (2H, d, *J* = 7.6 Hz, Ph), 7.64 (1H, t, *J* = 7.6 Hz, Ph), 7.51 (2H, dd, *J* = 7.6 Hz, Ph), 1.63 (9H, s, *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.8, 163.7, 134.6, 132.5,

129.9, 128.8, 84.8, 28.1. Spectral data were consistent with those previously reported in the literature.[25]

1-Phenyl-1,2-dioxohexane (19k)[26,27]

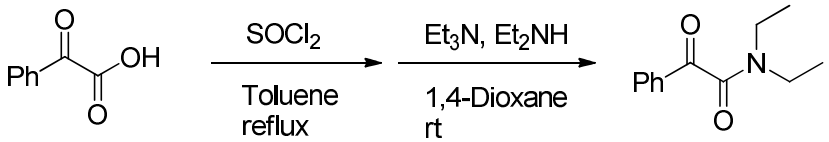


19k

(Step 1) A mixture of 1-hexyne (0.34 mL, 3.0 mmol), $PdCl_2(PPh_3)_2$ (47.9 mg, 68.2 μmol), iodobenzene (0.40 mL, 3.6 mmol) in Et_3N (30 mL) was stirred at room temperature for 5 min under an argon atmosphere. And then, CuI (6.5 mg, 34 μmol) was added and stirred at the same temperature for 23 h. After the reaction mixture was filtered, the filtrate was washed with water. The mixture was extracted with diethyl ether and washed with brine, before dried over sodium sulfate. The extract was concentrated and the residue was purified by chromatography on silica gel (hexane as eluent) to obtain 1-phenylhex-1-yne (quant.) as a colorless oil.

(Step 2) To a solution of 1-phenylhex-1-yne (389 mg, 2.46 mmol) in acetone (25 mL) was added $KMnO_4$ (1.9 g, 12 mmol) and $FeCl_3$ (1.1 g, 6.8 mmol) at -78 °C and stirred at the same temperature for 16 h. The flask was removed from the cooling bath, and the mixture was filtered to separate precipitated MnO_2. The precipitate was washed with dichloromethane. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 20 : 1 as eluent) to obtain **19k** (150 mg, 32% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (2H, ddd, J = 7.2, 1.6, 1.6 Hz, Ph), 7.64 (1H, tt, J = 7.6, 1.6 Hz, Ph), 7.50 (2H, dddd, J = 7.6, 7.2, 1.6, 1.6 Hz, Ph), 2.88 (2H, t, J = 7.4 Hz, $COCH_2$), 1.69 (2H, tt, J = 7.4, 7.2 Hz, $COCH_2CH_2$), 1.41 (2H, tq, J = 7.4, 7.2 Hz, $COCH_2CH_2$), 0.95 (3H, t, J = 7.4 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.5, 192.6, 134.5, 132.0, 130.1, 128.8, 38.5, 24.9, 22.3, 13.8. Spectral data were consistent with those previously reported in the literature.[28]

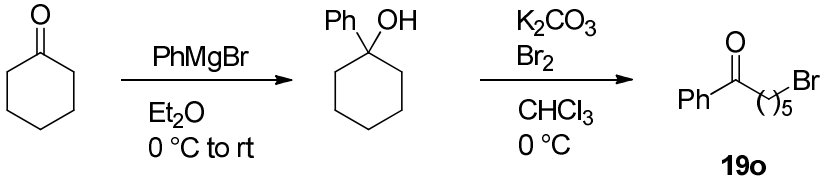
***N*,*N*-Diethylbenzoylformamide (19l)**



19l

To a solution of benzoylformic acid (1.7 g, 11 mmol) in toluene (20 mL) was added thionyl chloride (8.2 mL, 0.11 mol) at 0 °C and the mixture was refluxed for 1 h, and then the resulting mixture was cooled to room temperature, and concentrated. The residue was added to a solution of triethylamine (1.9 mL, 14 mmol) and diethylamine (1.2 mL, 12 mmol) in 1,4-dioxane (10 mL) at room temperature, and the mixture was stirred at the same temperature for 21 h. The resulting mixture was filtered through a pad of Celite. The filtrate was concentrated and the residue was purified by chromatography on silica gel (hexane/ethyl acetate = 4 : 1 to 3 : 1 as eluent) to obtain **19l** (1.58 g, 70% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (2H, ddd, *J* = 7.4, 1.6, 1.6 Hz, Ph), 7.64 (1H, tt, *J* = 7.6, 1.6 Hz, Ph), 7.51 (2H, dddd, *J* = 7.6, 7.4, 1.6, 1.6 Hz, Ph), 3.57 (2H, q, *J* = 7.2 Hz, NCH_2), 3.25 (2H, q, *J* = 7.2 Hz, NCH_2), 1.29 (3H, t, *J* = 7.2 Hz, CH_3), 1.16 (3H, t, *J* = 7.2 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.6, 166.7, 134.5, 133.2, 129.6, 128.9, 42.1, 38.7, 14.1, 12.8. Spectral data were consistent with those previously reported in the literature.[29]

6-Bromo-1-phenyl-1-hexanone (19o)



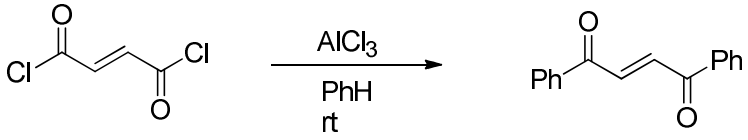
19o

(Step 1) Phenylmagnesium bromide was prepared from magnesium metal (0.14 g, 5.8 mmol), 1,2-dibromoethane (24 μL, 0.28 mmol) and phenyl bromide (0.59 mL, 5.6 mmol) in Et_2O (5 mL). To a solution of cyclohexanone in Et_2O (15 mL) was added dropwise a solution of phenylmagnesium bromide in Et_2O at 0 °C. After stirred at the same temperature for 13 h, the mixture was quenched with saturated ammonium chloride and extracted with ethyl acetate. The extract was washed with brine and dried over sodium sulfate. The resulting mixture was concentrated and the residue was purified by chromatography on silica gel (hexane/ethyl acetate = 10 : 1 as eluent) to obtaine 1-phenylcyclohexanol (2.8 mmol, 56% yield) as white solids.

(Step 2) A mixture of 1-phenylcyclohexanol (0.49 g, 2.8 mmol), K_2CO_3 (2.33 g, 16.9 mmol), bromine (0.71 mL, 14 mmol) in $CHCl_3$ (10 mL) was stirred at 0 °C for 6 h. After the reaction mixture was washed with saturated aqueous sodium sulfite and water, the mixture was dried over sodium sulfate. The extract was concentrated and the residue was purified by chromatography on silica gel (hexane/ethyl acetate = 20 : 1 to 10 : 1 as eluent) to obtain **19o** (423 mg, 59% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99-7.92 (2H, m, Ph), 7.60-7.53 (1H, m, Ph), 7.50-7.43 (2H, m, Ph), 3.43 (2H, t, *J* = 6.8 Hz, $COCH_2$), 3.00 (2H, t, *J* = 7.4 Hz, $BrCH_2$), 1.98-1.87 (2H, m,

$COCH_2CH_2$), 1.83-1.72 (2H, m, $BrCH_2CH_2$), 1.60-1.49 (2H, m, CO $CH_2CH_2CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.0, 136.9, 133.0, 128.6, 128.0, 38.3, 33.6, 32.6, 27.9, 23.3. Spectral data were consistent with those previously reported in the literature.[30]

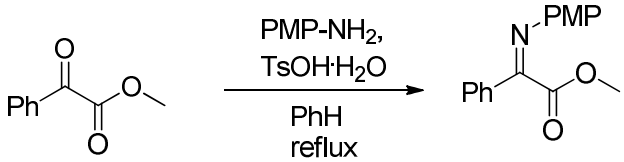
1,4-Diphenyl-2-butene-1,4-dione (22a)[31]



(*E*)-**22a**

1,4-Dichloro-2-butene-1,4-dione (0.37 mL, 3.4 mmol) was added to a suspention of aluminum chloride (461 mg, 3.45 mmol) in benzene (4 mL) at 0 °C. The mixture was stirred for 23 h at room temperature and quenched with ice water at 0 °C. The mixture was extracted with dichloromethane and the combined extracts were washed with water. The solution was dried over sodium sulfate and concentrated. The obtained solids were recrystallized from EtOH. And then, this was filtrated to give (*E*)-**22a** (189 mg, 23% yield) as orange crystal. ^1H NMR (400 MHz, $CDCl_3$) δ 8.10-8.04 (4H, m, Ph), 8.02 (2H, s, CH=CH), 7.64 (1H, tt, J = 7.6, 1.2 Hz, Ph), 7.54 (2H, d, J = 7.6 Hz, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.8, 136.9, 135.1, 133.9, 128.9 (2H). Spectral data were consistent with those previously reported in the literature.[20]

Methyl 2-(*p*-methoxyphenylimino)-2-phenylacetate (22b)[32]

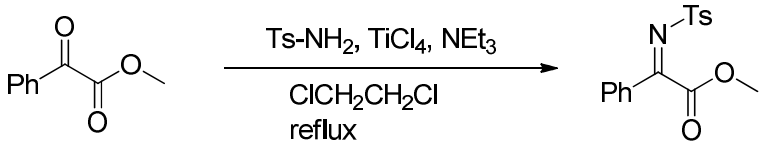


22b

A solution of methyl benzoylformate (0.67 mL, 4.7 mmol), *p*-anisylamine (610 mg, 5.0 mmol) and *p*-toluenesulfonic acid, monohydrate (71 mg, 0.37 mmol) in benzene (15 mL) was refluxed for 13 h with azeotropic removal of water by a Dean-Stark trap. The resulting mixture was cooled to room temperature and quenched with saturated aqueous sodium hydrogen carbonate. The mixture was extracted with ethyl acetate and the combined extracts were washed with brine. The solution was dried over sodium sulfate and concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 5:1 as eluent) to obtain **22b** (0.98 g, 77% yield) as yellow crystal. ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (2H, ddd, J = 6.4, 2.0, 1.6 Hz, Ph), 7.53-7.43 (3H, m, Ph), 6.97 (2H, ddd, J = 9.2, 3.0, 2.4 Hz, Ph), 6.88 (2H, ddd, J = 9.2, 3.0, 2.4 Hz, Ph), 3.81 (3H, s, CO_2CH_3 or $PhOCH_3$), 3.70 (3H, s, CO_2CH_3 or

PhOCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 159.1, 157.3, 143.1, 134.0, 131.6, 128.7, 127.8, 121.1, 114.1, 55.4, 52.0. Spectral data were consistent with those previously reported in the literature.[33]

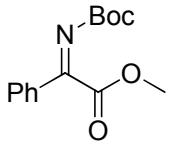
Methyl 2-(tosylimino)-2-phenylacetate (22c)



22c

A mixture of methyl benzoylformate (0.49 mL, 3.4 mmol), tosylamine (709 mg, 4.1 mmol), titanium(Ⅳ) chloride (0.22 mL, 2.0 mmol), and triethylamine (0.95 mL, 6.8 mmol) in 1,2-dichloroethane (14 mL) was refluxed for 13 h. The resulting mixture was cooled to room temperature and quenched with saturated aqueous sodium hydrogen carbonate. The mixture was extracted with dichloromethane and the combined extracts were washed with brine. The solution was dried over sodium sulfate and concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 10:1 to 3:1 as eluent) to obtain **22c** (0.50 g, 46% yield) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (2H, d, *J* = 8.0 Hz, Ph), 7.83 (2H, d, *J* = 8.0 Hz, Ph), 7.60 (2H, t, *J* = 7.4 Hz, Ph), 7.44 (2H, dd, *J* = 8.4, 7.4 Hz, Ph), 7.35 (2H, d, *J* = 8.4 Hz, Ph), 4.10 (3H, s, OCH_3), 2.43 (3H, s, PhCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 165.2, 144.9, 135.4, 134.9, 131.1, 129.9, 129.7, 129.0, 128.1, 53.5, 21.6. Spectral data were consistent with those previously reported in the literature.[34]

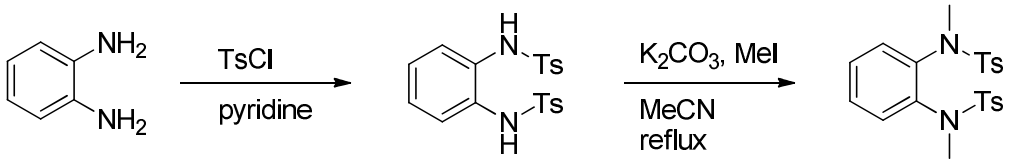
Methyl 2-(*tert*-butoxycarbonylimino)-2-phenylacetate (22d)



Prepared in 24% yield by the same procedure with **22c** using *tert*-butoxycarbonylamine instead of tosylamine. Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94-7.77 (2H, m, Ph), 7.55 (1H, t, *J* = 7.4 Hz, Ph), 7.44 (2H, dd, *J* = 8.0, 7.4 Hz, Ph), 3.94 (3H, s, OCH_3), 1.56 (9H, s, *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.5, 163.2, 161.9, 133.0, 132.2, 129.1, 128.6, 83.1, 52.8, 27.9. Spectral data were consistent with those previously reported in the literature.[35]

2. Benzimidazoline derivatives

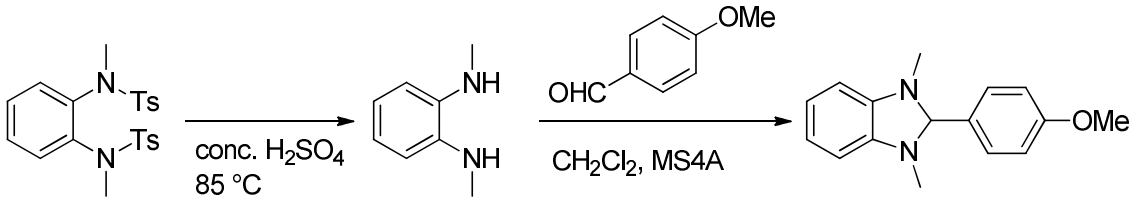
_N_,_N_'-dimethyl-_N_,_N_'-di(_p_-toluenesulfonyl)-_o_-phenylenediamine[3g,8]



(Step 1) To *o*-phenylenediamine (3.77 g, 34.9 mmol) in pyridine (40 mL) was added *p*-toluenesulfonyl chloride (13.5 g, 70.8 mmol) in pyridine (30 mL) and the resulting mixture was stirred at room temperature for 22 h. Slow addition of 2M aqueous hydrogen chloride gave the solids precipitated and filtrated. These solids were dissolved in EtOH and refluxed for 4 h. After filtrated, *N*,*N*'-di(*p*-toluenesulfonyl)-*o*-phenylenediamine was obtained (29.3 mmol, 84% yield) as white solids.

(Step 2) To a solution of *N*,*N*'-di(*p*-toluenesulfonyl)-*o*-phenylenediamine (12.2 g, 29.3 mmol) in MeCN (80 mL) was added K_2CO_3 (16.5 g, 119 mmol), and the solution was stirred at room temperature for 1 h. To the mixture was slowly added iodomethane (5.5 mL, 88 mmol) at 0 °C, and then it was refluxed for 13 h. The solution was filtrated through a pad of Celite. The filtrate was concentrated, and water was added to the residue. The mixture was extracted with CH_2Cl_2 and washed with brine, before dried over sodium solfate. The extract was evaporated, and the obtained solids were recrystallized from EtOH. And then, this was filtrated to give *N*,*N*'-dimethyl-*N*,*N*'-di(*p*-toluenesulfonyl)-*o*-phenylenediamine (26.6 mmol, 91% yield) as white crystal.

2-(_p_-Anisyl)-1,3-dimethylbenzimidazoline (18a)[3g,8]



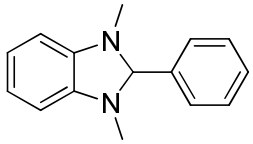
18a

(Step 1) A mixture of *N*,*N*'-dimethyl-*N*,*N*'-di(*p*-toluenesulfonyl)-*o*-phenylenediamine (4.50 g, 10.1 mmol) and concentrated sulfuric acid (4 mL) was heated at 85 °C for 4 h, and then poured into ice. To this was slowly added 4M aqueous sodium hydroxide and the resulting mixture was basified. The mixture was extracted with CH_2Cl_2, and the extract was washed with brine before dried over sodium sulfate. Evaporation of the extract gave crude *N*,*N*'-dimethyl-*o*-phenylenediamine as brown oil. This crude product

was used for the following reaction without purification, because it was found to be unstable under air.

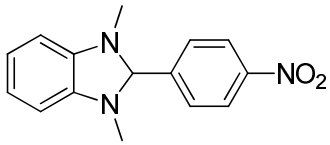
(Step 2) To a solution of *N*,*N*'-dimethyl-*o*-phenylenediamine in dry CH_2Cl_2 (10 mL) with molecular sieves 4A was slowly added 4-anisaldehyde (1.2 mL, 9.9 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C under an argon atmosphere. The resulting mixture was stirred at room temperature for 12 h, and filtered through a pad of Celite. The filtrate was concentrated, and the residue was purified by chromatography on silica gel (hexane/ethyl acetate = 20 : 1 as eluent) to obtain crude as a yellow oil. Yellow oil obtained after evaporation were recrystallized from ethanol under an argon atmosphere, and filtrated to obtain **18a** (4.1 mmol, 40% yield) as colorless crystal. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (2H, ddd, *J* = 8.8, 2.4, 2.4 Hz, Ph), 6.94 (2H, ddd, *J* = 8.8, 2.4, 2.4 Hz, Ph), 6.72 (2H, ddd, *J* = 8.4, 3.2, 3.2 Hz, Ph), 6.43 (2H, ddd, *J* = 8.4, 3.2, 3.2 Hz, Ph), 4.82 (1H, s, CH), 3.84 (3H, s, OCH_3), 2.55 (6H, s, NCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 142.1, 130.9, 130.0, 119.2, 113.8, 105.7, 93.6, 55.3, 33.1. Spectral data were consistent with those previously reported in the literature.[3g,8]

1,3-Dimethyl-2-phenylbenzimidazoline (18b)



Prepared in 12% yield from *N*,*N*'-dimethyl-*N*,*N*'-di(*p*-toluenesulfonyl)-*o*-phenylene-diamine by the same procedure with **18a** using benzaldehyde instead of *p*-anisaldehyde. White crystal; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61-7.54 (2H, m, Ph), 7.45-7.39 (2H, m, Ph), 6.73 (2H, ddd, *J* = 8.6, 4.0, 4.0 Hz, Ph), 6.45 (2H, ddd, *J* = 8.6, 4.0, 4.0 Hz, Ph), 4.88 (1H, s, CH), 2.57 (6H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0, 139.0, 129.3, 128.8, 128.4, 119.3, 105.7, 94.0, 33.1. Spectral data were consistent with those previously reported in the literature.[3g,8]

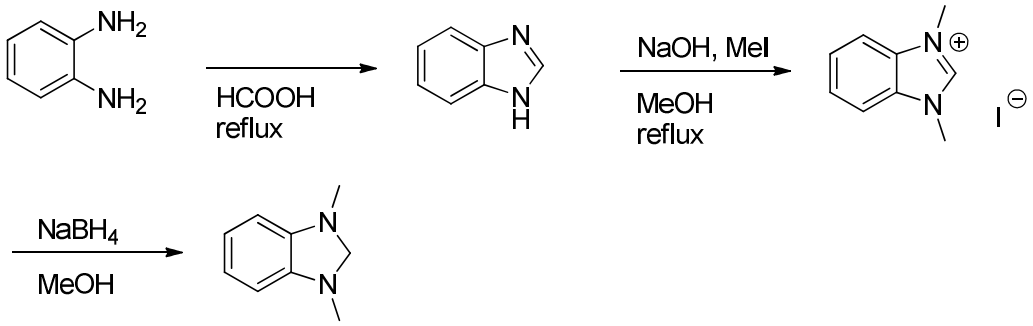
1,3-Dimethyl-2-(*p*-nitrophenyl)benzimidazoline (18c)



Prepared in 22% yield from *N*,*N*'-dimethyl-*N*,*N*'-di(*p*-toluenesulfonyl)-*o*-phenylene-diamine by the same procedure with **18a** using *p*-nitrobenzaldehyde instead of anisaldehyde. Red crystal; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (2H, d, *J* = 8.8 Hz, Ph), 7.78 (2H, d, *J* = 8.8 Hz, Ph), 6.76 (2H, ddd, *J* = 8.6, 4.4, 3.2 Hz, Ph), 6.48 (2H, ddd, *J* = 8.6, 4.4, 3.2 Hz, Ph), 5.01 (1H, s, CH), 2.58 (6H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7, 146.5, 141.6, 129.7, 123.7, 119.7, 106.1, 92.9, 33.4. Spectral data

were consistent with those previously reported in the literature.[3g,8]

1,3-dimethylbenzimidazoline (18d)[3g,8]



18d

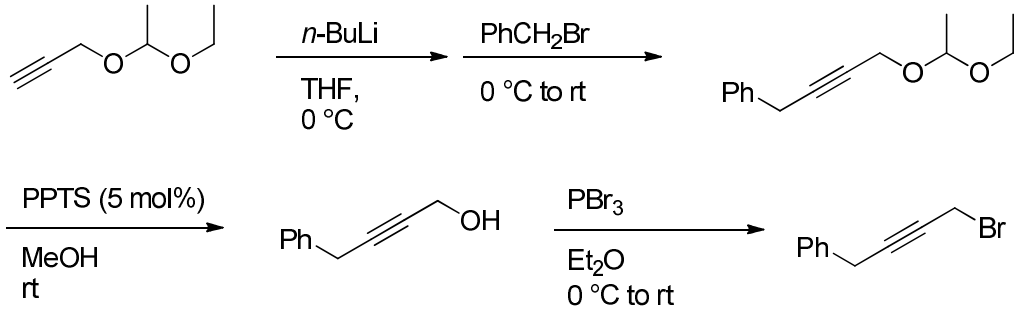
(Step 1) A mixture of *o*-phenylenediamine (4.13 g, 38.2 mmol) and formic acid (2.0 mL) was reflux for 2 h. To this was slowly added 15% aqueous sodium hydroxide and the resulting mixture was basified. The crude benzimidazole was filtrated and washed with ice-cold water. This crude product was used for the following reaction without purification.

(Step 2) To a solution of benzimidazole and sodium hydroxide (185.6 mg, 4.640 mmol) in MeOH (13 mL) was added iodomethane (6.1 mL, 98 mmol) at room temperature and the mixture was refluxed for 24 h. After the mixture was concentrated, the residue were recrystallized from ethanol. The mixture was filtrated to obtain 1,3-dimethylbenzimidazolium (8.03 mmol, 21% yield) as white crystal.

(Step 3) To a solution of 1,3-dimethylbenzimidazolium (563.5 mg, 2.056 mmol) in MeOH (4 mL) was slowly added sodium borohydride (80.7 mg, 2.13 mmol) at 0 °C under an argon atmosphere. The resulting mixture was stirred at room temperature for 40 min. The mixture was purified by chromatography on silica gel (hexane/ethyl acetate = 10 : 1 as eluent) to obtain **18d** as a green oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.67 (2H, ddd, *J* = 8.8, 3.2, 3.2 Hz, Ph), 6.42 (2H, ddd, *J* = 8.8, 3.2, 3.2 Hz, Ph), 4.32 (2H, s, CH_2), 2.73 (6H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1, 119.1, 106.1, 80.2, 34.4. Spectral data were consistent with those previously reported in the literature.[3g,8]

3. Electrophiles

1-Bromo-4-phenyl-2-butyne



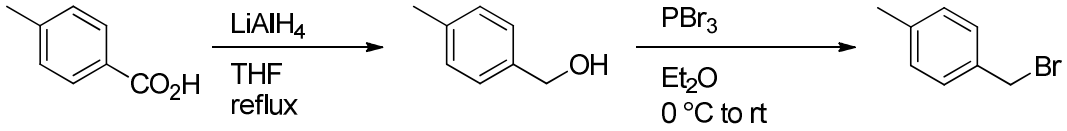
(Step 1) A solution of 1-(1'-ethoxyethoxy)-2-propyne [36] (0.71 g, 5.5 mmol) in THF (15 mL) was treated with a 1.6 M hexane solution of *n*-butyllithium (3.5 mL, 5.6 mmol) at 0 °C under an argon atmosphere. The mixture was stirred for 20 min at the same temperature and benzylbromide (0.66 mL, 5.5 mmol) was added to the resulting mixture at 0 °C. After stirring at the same temperature for 19 h, the resulting mixture was quenched with saturated aqueous ammonium chloride. The mixture was extracted with ethyl acetate and washed with brine, before dried over sodium sulfate. The extract was concentrated and the residue was purified by chromatography on silica gel (hexane/ethyl acetate = 20 : 1 as eluent) to obtain 1-(1'-ethoxyethoxy)-4-phenyl-2-butyne (0.55 g, 46% yield) as a colorless oil.

(Step 2) To a solution of 1-(1'-ethoxyethoxy)-4-phenyl-2-butyne (0.55 g, 2.5 mmol) in methanol (5 mL) was added pyridinium *p*-toluenesulfonate (42 mg, 0.17 mmol) and the mixture was stirred at room temperature for 19 h. The resulting mixture was evaporated to remove methanol and the residue was diluted with saturated aqueous sodium hydrogen carbonate. The mixture was extracted with ethyl acetate and dried over sodium sulfate. The extract was concentrated and the residue was purified by chromatography on silica gel (hexane/ethyl acetate = 4 : 1 as eluent) to obtain 4-phenyl-2-butyn-1-ol (0.21 g, 56% yield) as a colorless oil.

(Step 3) 1-Bromo-4-phenyl-2-butyne were prepared from 4-phenyl-2-butyn-1-ol according to a described procedure.[37] To a solution of 4-phenyl-2-butyn-1-ol (0.21 g, 1.4 mmol) in dry Et_2O (3 mL) was slowly added phosphorus tribromide (0.26 mL, 2.8 mmol) at 0 °C, and the mixture was stirred at room temperature for 24 h. The resulting mixture was cooled at 0 °C, and quenched with water. The mixture was extracted with ethyl acetate and washed with water, before dried over sodium sulfate. The residue was purified by chromatography on silica gel (hexane to hexane/ethyl acetate = 20 : 1 as eluent) to obtain 1-bromo-4-phenyl-2-butyne (154 mg, 53% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.20 (5H, m, Ph), 3.98 (2H, t, *J* =

2.2 Hz, $BrCH_2$), 3.67 (2H, t, J = 2.2 Hz, $PhCH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.0, 128.6, 127.9, 126.8, 85.4, 77.3, 25.3, 15.3.

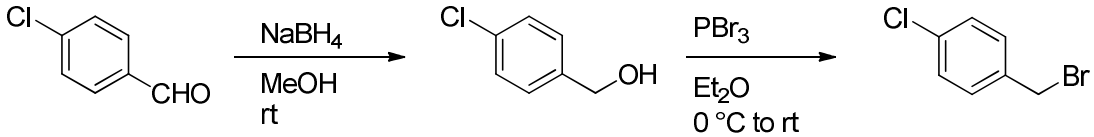
***p*-Methybenzyl bromide**



(Step 1) A solution of *p*-toluic acid (685 mg, 5.03 mmol) in THF (10 mL) was added to a suspension of lithium aluminium hydride (287 mg, 7.56 mmol) in THF (15 mL) at 0 °C and the mixture was refluxed for 26 h. The resulting mixture was cooled at 0 °C, and quenched with water (0.3 mL), 15% aqueous sodium hydroxide solution (0.3 mL) and water (0.9 mL) at 0 °C. The mixture was filtered through a pad of Celite. The filtrate was concentrated and the residue was purified by chromatography on silica gel (hexane/ethyl acetate = 2 : 1 as eluent) to obtain *p*-methylbenzyl alcohol (381 mg, 62% yield) as white solids.

(Step 2) To a solution of *p*-methylbenzyl alcohol (381 mg, 3.12 mmol) in dry Et_2O (6 mL) was slowly added phosphorus tribromide (0.60 mL, 6.4 mmol) at 0 °C, and the mixture was stirred at room temperature for 24 h. The resulting mixture was cooled at 0 °C, and quenched with water. The mixture was extracted with ethyl acetate and washed with water, before dried over sodium sulfate. The residue was purified by chromatography on silica gel (hexane as eluent) to obtain *p*-methybenzyl bromide (453 mg, 79% yield) as white solids. ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (2H, d, J = 8.0 Hz, Ph), 7.14 (2H, d, J = 8.0 Hz, Ph), 4.47 (2H, s, CH_2), 2.33 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 134.8, 129.5, 128.9, 33.7, 21.2. Spectral data were consistent with those previously reported in the literature.[38]

***p*-Chlorobenzyl bromide**

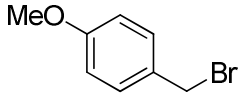


(Step 1) To a solution of *p*-chlorobenzaldehyde (722 mg, 5.1 mmol) in MeOH (10 mL) was slowly added sodium borohydride (195 mg, 5.15 mmol) at 0 °C, and then the mixture was stirred at room temperature for 24 h. The resulting mixture was diluted with water and extracted with ethyl acetate. The combined extracts were dried over sodium sulfate and concentrated. Purification of the residue by chromatography on silica gel (hexane/ethyl acetate = 2 : 1 as eluent) afforded *p*-chlorobenzyl alcohol (0.70 g, 96% yield) as a colorless oil.

(Step 2) To a solution of *p*-chlorobenzyl alcohol (0.70 g, 4.9 mmol) in dry Et_2O (10

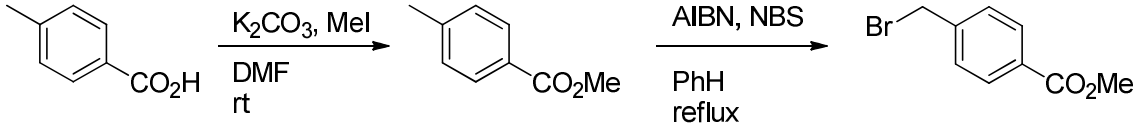
mL) was slowly added phosphorus tribromide (0.88 mL, 9.4 mmol) at 0 °C, and the mixture was stirred at room temperature for 22 h. The resulting mixture was cooled at 0 °C, and quenched with water. The mixture was extracted with ethyl acetate and washed with water, before dried over sodium sulfate. The residue was purified by chromatography on silica gel (hexane as eluent) to obtain *p*-chlorobenzyl bromide (741 mg, 74% yield) as white solids. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.20 (4H, m, Ph), 4.46 (2H, s, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.2, 134.2, 130.3, 128.9, 32.4. Spectral data were consistent with those previously reported in the literature.[39]

***p*-Methoxybenzyl bromide**



Prepared in 45% yield from *p*-anisaldehyde by the same procedure with *p*-chlorobenzyl bromide. Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (2H, d, J = 8.6 Hz, Ph), 6.86 (2H, d, J = 8.6 Hz, Ph), 4.51 (2H, s, CH_2), 3.81 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 130.4, 129.9, 114.2, 55.3, 34.0. Spectral data were consistent with those previously reported in the literature.[40]

***p*-Methoxycarbonylbenzyl bromide**



(Step 1) To a solution of *p*-toluic acid (687 mg, 5.05 mmol) and K_2CO_3 (1.1 g, 8.0 mmol) in DMF (10 mL) was added iodomethane (0.38 mL, 6.1 mmol) at room temperature and stirred at the same temperature for 31 h. The resulting mixture was quenched with saturated aqueous ammonium chloride. The mixture was extracted with ethyl acetate and washed with water and brine, before dried over sodium sulfate. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 10 : 1 as eluent) to obtain methyl *p*-methylbenzoate (653 mg, 86% yield) as a colorless oil.

(Step 2) To a solution of methyl *p*-methylbenzoate (653 g, 4.35 mmol) and 2,2'-azodiisoburyronitrile (35.9 mg, 0.219 mmol) in benzene (9 mL) was added *N*-bromosuccinimide (853 mg, 4.79 mmol), and then the mixture was refluxed for 6 h. The resulting mixture was cooled to room temperature, and quenched with saturated aqueous ammonium chloride. The mixture was extracted with toluene and washed with water and brine, before dried over sodium sulfate. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 10 : 1 as eluent) to obtain *p*-methoxycarbonylbenzyl bromide (289 mg, 28% yield) as white solids. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (2H, d, J = 8.4 Hz, Ph), 7.46 (2H, d, J = 8.4 Hz, Ph), 4.50 (2H,

s, CH_2), 3.92 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 142.6, 130.0, 129.0, 52.2, 32.2. Spectral data were consistent with those previously reported in the literature.[40]

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Chapter 5.
Conclusion

Carbon–carbon bond formations via carbanions are one of the most important intermediate for the synthesis of natural products and biologically active compounds. Oftentimes, it is necessary to generate carbanions in mild condition, because synthetic chemists yet pose particularly onerous mechanistic challenges owing to complex aggregation phenomena. Accordingly, there has been a substantial effort to develop various novel methods.

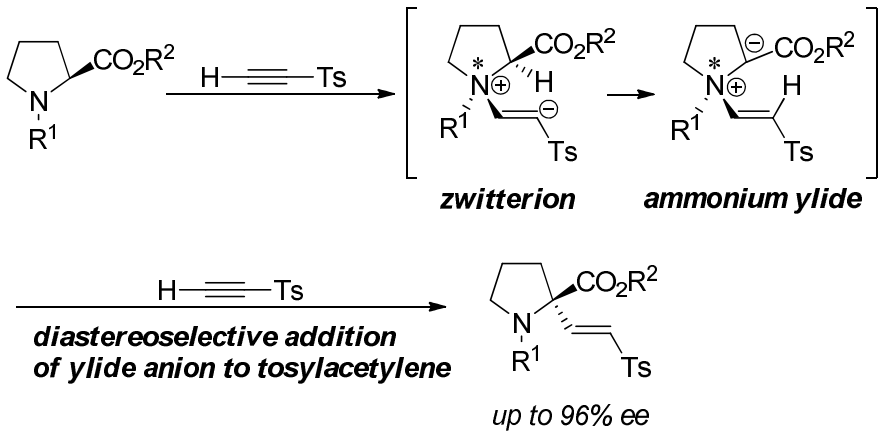
Our group reported that Stevens rearrangement reaction and Sommelet–Hauser rearrangement reaction of quaternary ammonium salts are excellent as the methods of constructing chiral quaternary carbon. However, it was difficult that the steric hindered quaternary ammonium salts were synthesized. Herein, we are interested in the generated *N*-2-tosylvinyl ammonium zwitterion method using ethynyl tolyl sulfone, which is a highly electrophilic reactivity and reacts with steric hindered amines to give quaternary ammoniums in mild condition. Making use of this method, we attempted asymmetric Stevens rearrangement reaction and asymmetric Sommelet–Hauser rearrangement reaction via quaternary ammonium ylides.

On the other hand, our group also reported that the reductive reaction of ketone proceeded via photoinduced electron-transfer. The reaction is proposed to generate carbanion derived from ketone, and this carbanion reacts with water as a proton donor to afford the corresponding alcohol. On the basis of the report, we applied carbon–carbon bond formation by photoinduced electron-transfer.

In section 1 “Introduction”, we demonstrated that asymmetric synthesis by rearrangement of carbanion and photoinduced electron-transfer with benzimidazolines. First, we explained the utility of Stevens rearrangement reaction and Sommelet–Hauser rearrangement reaction, and the problem on synthesis of the substrates. In order to solve this problem, we planned the asymmetric synthesis of the non-natural amino acid derivatives by the generated *N*-2-tosylethenyl ammonium zwitterion method by ethynyl tolyl sulfone. Next, we descripted the features of benzimidazolines in the reductive reaction, particularly for the photoinduced electron-transfer with benzimidazolines. We interested in umpolung reactivity, in which the carbonyl carbon becomes nucleophilic, to plan the carbon–carbon bond formation of benzoyl compounds with the electrophiles.

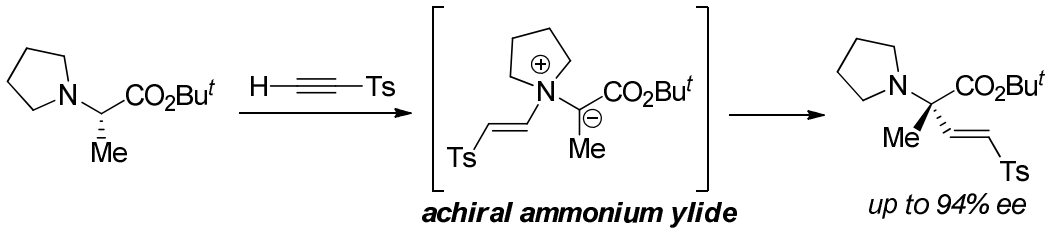
In section 2 “Asymmetric α-2-tosylethenylation of proline derivatives via chiral transfer from nitrogen atom to carbon atom”, we examined the asymmetric synthesis via ammonium ylides obtained by quaternarization of proline derivatives and ethynyl tolyl sulfone. As a result, α-tosylethenylation of proline derivatives proceeded enantioselectively via chiral transfer from nitrogen atom to carbon atom (Scheme 5-1).

Scheme 5-1

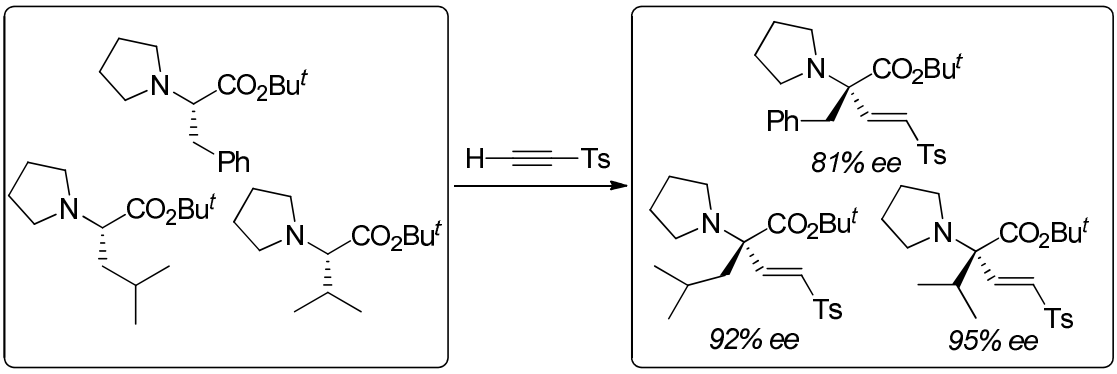


In section 3 “Asymmetric α-2-tosylethenylation of *N*,*N*-dialkyl-L-amino acid esters via the formation of non-racemic ammonium enolates”, we explored asymmetric α-tosylethenylation of the acyclic amino acid derivatives by chiral transfer from nitrogen atom to carbon atom. However, the expected α-tosylethenylated product was not obtained enantioselectively. On the contrary, the reaction of acyclic amino acid derivatives, which have five-membered ring on nitrogen atom, gave the α-tosylethenylated products in an enantio-enriched form, even though the expected reaction intermediates are the achiral ammonium ylides (Scheme 5-2). Further, this asymmetric α-tosylethenylation was applied to the various amino acid derivatives (Scheme 5-3).

Scheme 5-2

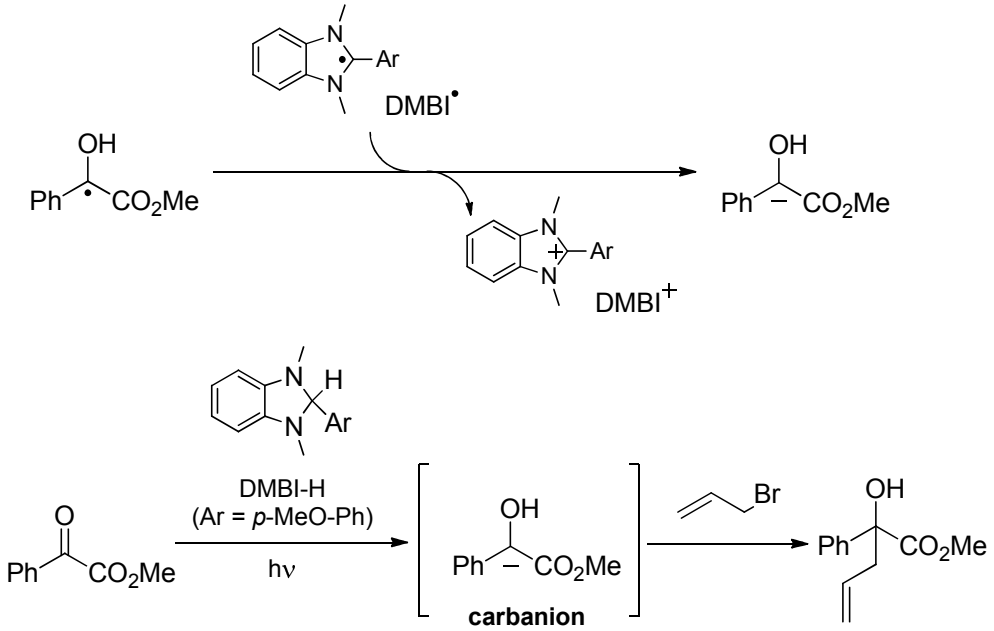


Scheme 5-3



In section 4 “carbon–carbon bond formation via benzoyl umpolung attained by photoinduced electron-transfer with benzimidazolines”, we conducted the reaction of benzoylformates with various electrophiles. Because DMBI radical is stronger single electron donor than the radicals derived from other organic hydride donors, the ketyl radicals derived benzoylformates became the carbanion, which reacted with the electrophiles (Scheme 5-4).

Scheme 5-4



In section 5 “Conclusion”, the results of this study were summarized.

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