

Doctoral Dissertation (Censored)

博士論文（要約）

**Development of Carbon–Carbon Bond Forming Reactions  
via Catalytic Activation of Less Reactive Pronucleophiles**

（低活性求核種の触媒的活性化を鍵とする

炭素－炭素結合形成反応の開発）

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Department of Chemistry, Graduate School of Science,

The University of Tokyo

東京大学大学院理学系研究科化学専攻

Tsubasa Hirata

平田 翼

# Development of Carbon–Carbon Bond Forming Reactions via Catalytic Activation of Less Reactive Pronucleophiles

Name: Tsubasa Hirata

Laboratory: Synthetic Organic Chemistry Laboratory

## Abstract

### Introduction

In synthetic organic chemistry, carbon–carbon (C–C) bond formation is one of the most important reactions to construct fundamental molecular frameworks. Although various methodologies for C–C bond formation have been developed, conventional reactions often require stoichiometric amounts of reagents. On the other hand, catalytic variants are in one of hot research topics from the view point of environmental issues, which tiny amounts of activators promote. Nowadays, atom economy is also recognized to be an important indicator to evaluate how efficient reactions are.<sup>1</sup> Atom-economical reactions are not only environmentally friendly but also enable advanced technologies including one-pot reactions and continuous-flow reactions in which by-products can disturb later steps. From the view point of atom economy, addition reactions are more efficient than substitution reactions because they have a potential to proceed without any loss of leaving groups. Therefore, catalytic C–C bond forming addition reactions have been strongly desired. In my doctoral thesis studies, I have focused on catalytic activation of less reactive pronucleophiles to achieve highly efficient catalytic C–C bond forming reactions.

### 1. Strong Brønsted Base-Catalyzed Asymmetric Addition Reactions of Alkylarenes with Imines

Alkylarenes such as toluene are commonly used as a solvent in organic synthesis because they are abundant, inexpensive, and easy to handle. Furthermore, they can be ideal feedstocks for the introduction of aromatic moieties into organic frameworks. The examples include electrophilic substitution reactions on their aromatic rings in the presence of Lewis acids represented by Friedel-Crafts reactions. On the other hand, C–C bond formation through activation of benzylic carbon(sp<sup>3</sup>)–hydrogen (C(sp<sup>3</sup>)–H) bonds generally requires stoichiometric amounts of radical reagents at elevated temperature because such C–H bonds are quite inert. Therefore, its catalytic variants are challenging work, and their expansion to asymmetric catalysis is especially recognized to be difficult.

Recently, our group has developed strong Brønsted base-catalyzed direct addition reactions of alkylarenes with imines based on “Product-Base Mechanism.”<sup>2,3</sup> The key to success of the reactions is design of reaction intermediates to be strongly basic and promote the catalytic cycle. In the presence of only catalytic amounts of bases, the reactions proceeded smoothly even at –78 °C, and excellent diastereoselectivities were observed when ethylbenzene was employed as a pronucleophile. Thus, modification of alkaline metal cations with chiral ligands was assumed to enable their asymmetric variants. After intensive optimization, it was found that chiral multi-dentate amine ligands and potassium hexamethyldisilazide (KHMDs) as an additive were effective. Under the

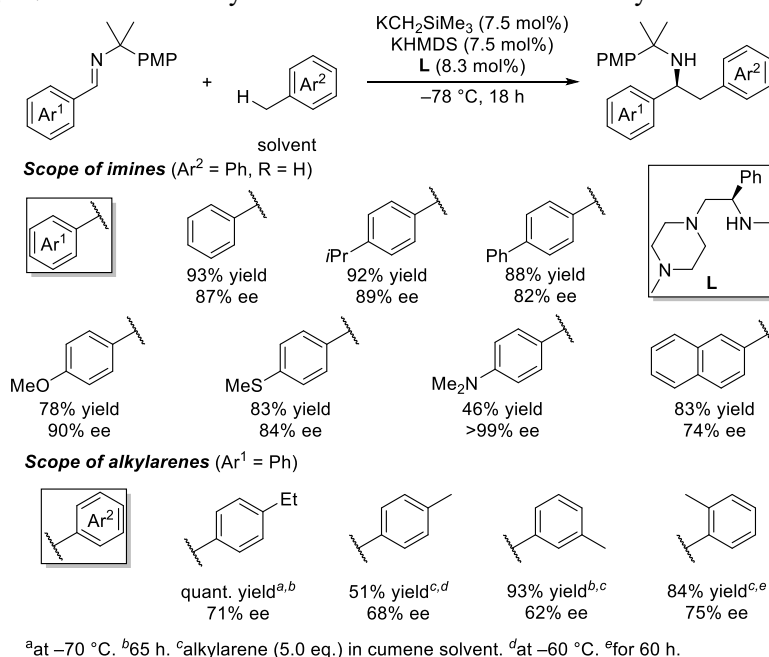


Figure 1. Base-catalyzed reactions asymmetric of alkylarenes

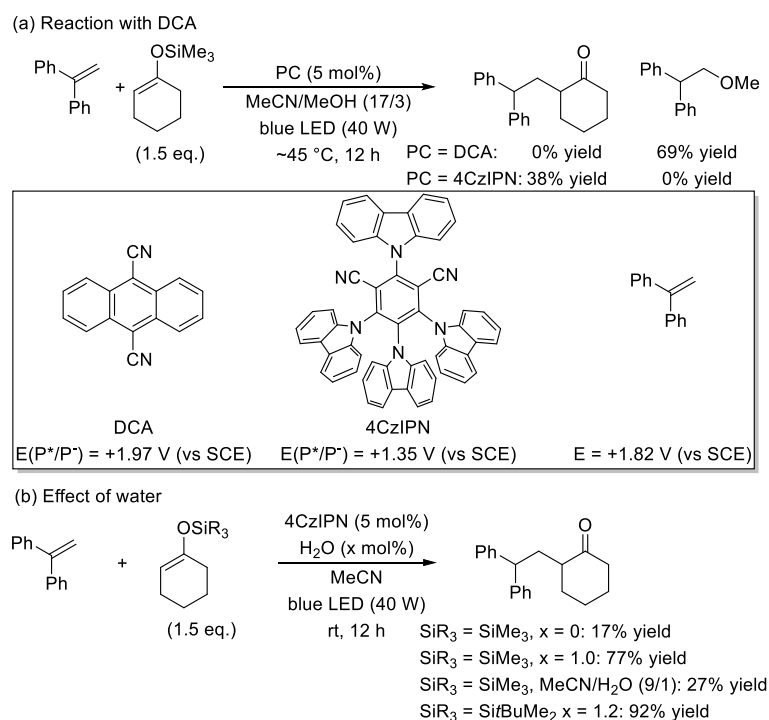
optimized reaction conditions, substrate scope of the reactions was examined with respect to imines (Figure 1). Many kinds of imines bearing various substituents on their aromatic rings were tested, and the reactions proceeded with high enantioselectivities. Then, the scope of alkylarenes was examined. 4-Ethyltoluene afforded the desired product in quantitative yield with good enantioselectivity. When xylenes were employed as pronucleophiles with cumene solvent, the reactions proceeded in moderate to excellent yields with moderate enantioselectivities. The reactions are scalable, and the imine prepared *in situ* is available. Furthermore, the obtained adducts can be transformed into various useful compounds including pharmaceuticals. To gain insight into the effect of KHMDS, non-linear effect experiments and NMR measurements were demonstrated. The results implied that an oligomeric chiral complex was formed in the ratio of 1:1:1 for K<sup>+</sup>Bn:ligand:KHMDS. Judging from these experiments, it is assumed that KHMDS is incorporated in a chiral complex to change a chiral environment. Chiral modification of potassium ion with simple diamine ligands and its application to asymmetric reactions were achieved although clathrate ligands were generally employed due to large ionic radius and low Lewis acidity of potassium ion. It should be noted that this is an atom-economical C–C bond forming reaction, which takes place at an unactivated benzylic position of alkylarenes without using any transition metal catalyst.

## 2. $\alpha$ -Alkylation of Ketones with Alkenes

### 2-1. $\alpha$ -Alkylation of Ketones with Alkenes Enabled by Photo-Induced Activation of Silyl Enol Ethers

$\alpha$ -Alkylation reactions of ketones are one of the most important methodologies to construct molecular frameworks. Conventional methods include reactions between enolate equivalents and alkyl halides such as Stork enamine synthesis. On the other hand, addition reactions of enolates deriving from aldehydes and ketones with alkenes are generally quite slow because of their less electrophilicity. To address this issue, it was hypothesized that  $\alpha$ -carbonyl radicals, which are expected to immediately react with alkenes, has a potential to realize such reactions.  $\alpha$ -Carbonyl radicals can be generated by single-electron oxidation and following desilylation of the corresponding silyl enol ethers. Based on this strategy, solvolysis and  $\alpha$ -functionalization have been developed. Especially,  $\alpha$ -functionalization is restricted to coupling reactions with hetero atom radicals and cyclization reactions.<sup>4</sup> In my doctoral thesis studies, catalytic  $\alpha$ -alkylation reactions of ketones with alkenes via visible light-induced activation of silyl enol ethers have been developed.

The study was started with 1,1-diphenyl ethylene and silyl enol ethers deriving from cyclohexanone as model substrates. In an initial trial, 9,10-dicyanoanthracene (DCA) was employed under blue light irradiation (Figure 2, a). However, an addition reaction of methanol to the alkene proceeded in moderate yield without formation of the desired product. The side reaction might be caused by oxidation of the alkene. To address this issue, photocatalyst was changed to 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyano benzene (4CzIPN), which has lower oxidation ability, and the desired product was obtained in low yield. To suppress solvolysis of the silyl enol ether, the reaction was carried out in acetonitrile; however, the yield was, in contrast, decreased (Figure 2, b). This result implies



**Figure 2.** Optimization of reaction conditions

that a protic Lewis base for trapping a silyl cation might be essential for a higher yield. Addition of 1 equivalent of water to the reaction system was found to be effective to dramatically improve the yield, although the yield became lower in the presence of a solvent amount of water. Finally, the yield was improved up to 92% by changing silyl group from trimethylsilyl group (TMS) to *tert*-butyldimethylsilyl group (TBS), which is more stable. Under the optimized conditions, substrate scope was examined, and various alkenes and silyl enol ethers were found to be available. It should be noted that benzenethiol could play a role of a hydrogen atom transfer (HAT) catalyst to improve the yields. To gain insight into reaction mechanism, several experiments were conducted with the model substrates. The control experiments proved that both photocatalyst and blue light irradiation were essential. Deuterium labeling experiments implied that the proton source was not acetonitrile but water. To the best of my knowledge, this is the first example of photo-induced intermolecular  $\alpha$ -alkylation of silyl enol ethers with alkenes.

## 2-2. Catalytic Addition Reactions of Ketones with Alkenes Based on Base-Photocatalyst Hybrid Systems

In the previous section,  $\alpha$ -alkylation reactions of silyl enol ethers with alkenes have been developed. However, silyl groups are removed in these reactions and they become source of wastes. Therefore, catalytic formation of enolates is demanded. In my doctoral thesis studies, I have achieved catalytic formation of the enolates and its application to fully catalytic addition of ketones to alkenes.

## Conclusion

In my doctoral thesis studies, highly efficient catalytic C–C bond forming reactions toward ideal atom economy have been developed by focusing on catalytic activation of less reactive pronucleophiles. In the first topic, unactivated alkylarenes, which are less acidic compounds, are activated by chiral strong Brønsted base catalysts, and asymmetric addition reactions with imines have been achieved. In the second topic, silyl enol ethers were oxidized by the photocatalyst to afford the corresponding  $\alpha$ -carbonyl radicals, and addition reactions of ketones with alkenes have been developed. Finally, catalytic direct addition reaction of ketone with alkene has been realized

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## *Abbreviation*

Ac	Acetyl group
acac	Acetylacetonate
AIBN	Azobis(isobutyronitrile)
Ar	Aryl group
Bn	Benzyl group
Bz	Benzoyl group
cat.	Catalyst
coe	Cyclooctene
Cp	Cyclopentadienyl anion
CsHMDS	Cesium hexamethyldisilazide
Cy	Cyclohexyl group
DART	Direct analysis in real time
DCM	Dichloromethane
$\Delta$	Heating
DMF	<i>N,N</i> -Dimethylformamide
DMSO	Dimethyl sulfoxide
dppp	Bis(diphenylphosphino)propane
dtbbpy	4,4'-Di- <i>tert</i> -butyl-2,2'-bipyridyl
DTBP	<i>tert</i> -Butyl peroxide
ee	Enantiomeric excess
El	Electrophile
eq.	Equivalent
Et	Ethyl group
EWG	Electron withdrawing group
FG	Functional group
Het	Heteroaryl group
HRMS	High-resolution mass spectrometry
H-TMP	2,2,6,6-Tetramethylpiperidine
h $\nu$	Photo-irradiation
<i>i</i>	Iso
<i>i</i> Pr	<i>iso</i> -Propyl group
KHMDS	Potassium hexamethyldisilazide
KO $t$ Bu	Potassium <i>tert</i> -butoxide
KTMP	Potassium 2,2,6,6-tetramethylpiperidide
LA	Lewis acid
LG	Leaving group
LiO $t$ Bu	Lithium <i>tert</i> -butoxide
LiTMP	Lithium 2,2,6,6-tetramethylpiperidide
M	Metal atom

Me	Methyl group
Mes	Mesityl group
Mp	Melting point
MS 4A	Molecular sieve 4A
<i>n</i>	Normal
NaHMDS	Sodium hexamethyldisilazide
NaOtBu	Sodium <i>tert</i> -butoxide
<i>n</i> Bu	<i>n</i> -Butyl group
<i>n</i> BuLi	<i>n</i> -Butyl lithium
NMR	Nuclear magnetic resonance
Nu	Nucleophile
<i>p</i>	Para
PC	Photocatalyst
Ph	Phenyl group
PMC	<i>p</i> -Methoxycumyl group
PMP	<i>p</i> -Methoxyphenyl group
ppy	2-phenyl pyridine ligand
PTLC	Preparative thin-layer chromatography
rt	Room temperature
<i>t</i>	Tertiary
TBME	<i>tert</i> -Butyl methyl ether
TBS	<i>tert</i> -Butyldimethylsilyl group
<i>t</i> Bu	<i>tert</i> -Butyl group
TEMPO	2,2,6,6-Tetramethylpiperidine- <i>N</i> -oxide
<i>tert</i>	Tertiary
Tf	Trifluoromethane sulfonyl group
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMS	Trimethylsilyl group
Tol	<i>para</i> -Tolyl group
TRIP	2,4,6-Triisopropylphenyl group
Ts	Tosyl group [ <i>para</i> -Toluenesulfonyl group]

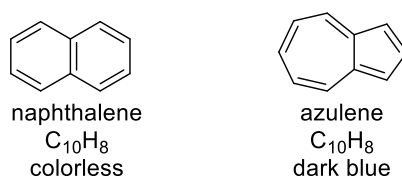


## 1. Introduction

### 1-1. Synthetic Organic Chemistry

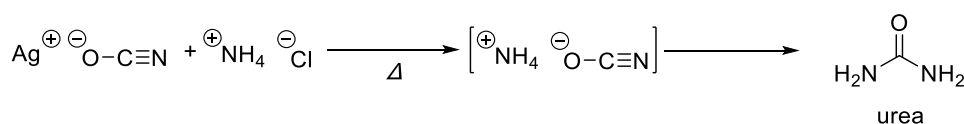
#### Organic Synthesis

In 1803, Dalton hypothesized atomism, which predominantly comprises the followings: (i) Every substance in the world consists of small particles termed atom. (ii) An atom of one element is different from that of another element. (ii) Atoms of the same element have the same size, mass, and properties. (iii) atoms themselves are not divided into smaller particles in chemical reactions. (iv) Compounds are composed of atoms in a certain ratio. (v) Atoms never disappear or newly appear in chemical reactions. His theory has been widely accepted for a long time. Furthermore, Avogadro hypothesized that molecules are the smallest units which exhibit nature of substance in 1811. This theory means nature of substances does not depend on only composing atoms but also how they are connected. For example, both naphthalene and azulene have different appearances although they are composed of 10 carbons and 8 hydrogens (Figure 1-1).<sup>1</sup> Therefore, it is important to control structure of molecules for creation of new functional materials.



**Figure 1-1.** Structure of Naphthalene and Azulene

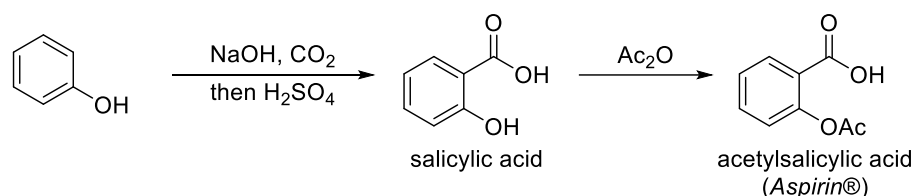
Classically, organic compounds were defined as matters derived from biological systems. They were distinguished from minerals, and artificial synthesis of them was recognized to be impossible. On the other hand, Wöhler succeeded to synthesize urea from inorganic compounds in 1828 (Figure 1-2).<sup>2</sup> He tried to synthesize ammonium cyanate, which is an inorganic compound; however, it was unexpectedly discovered that the reaction afforded urea. Since his success, synthetic organic chemistry, which possess an aspect of manufacturing, has been rapidly developed.



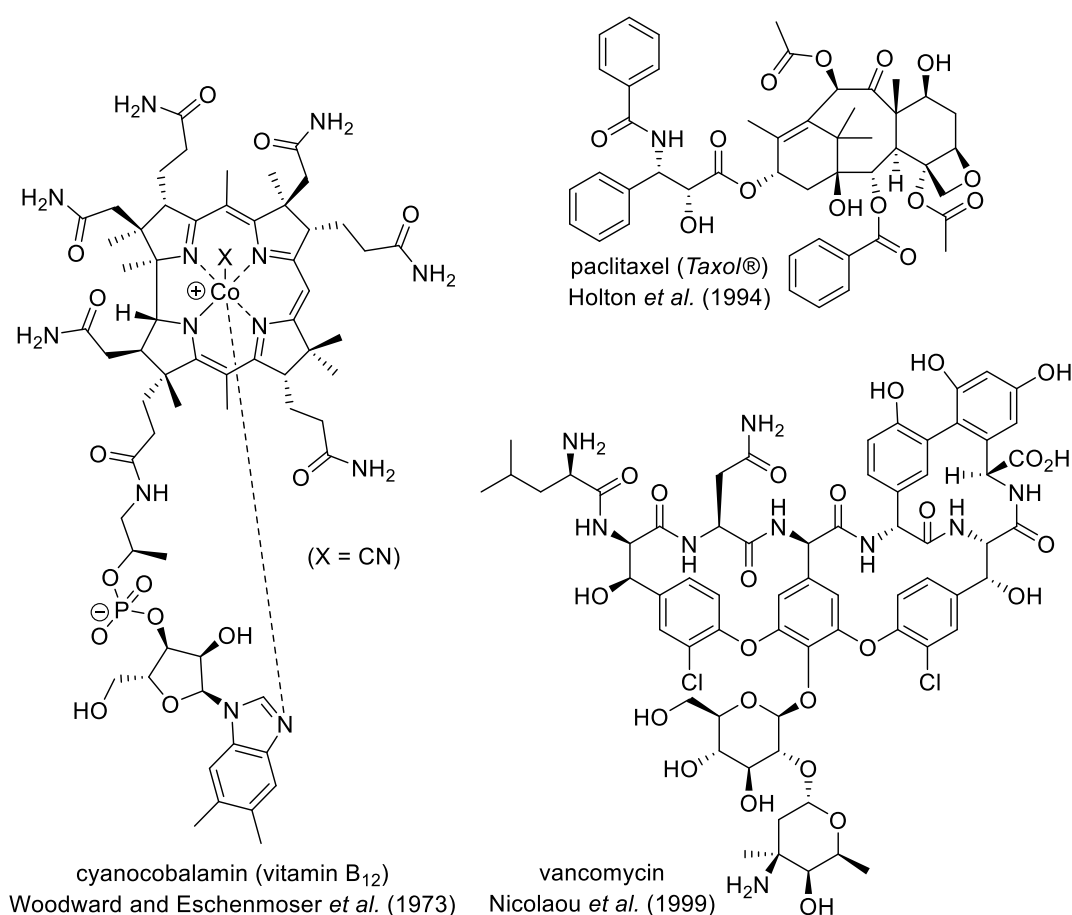
**Figure 1-2.** Wöhler's Urea Synthesis

In synthetic organic chemistry, valuable molecules are constructed step by step through various organic reactions such as connection of two or more inexpensive abundant molecules, molecular transformation, and so on. In 1860, Kolbe reported that alkali metal phenoxide reacted with carbon dioxide to afford salicylic acid (Figure 1-3).<sup>3</sup> Schmitt modified the reaction conditions, and it was found that elevated temperature and

high pressure improve the yield. It is known that treatment of salicylic acid with acetic anhydride afford acetylsalicylic acid, which is an antipyretic analgesic (*Aspirin*<sup>®</sup>). This is one of early examples which prove organic synthesis contributes to production of pharmaceuticals.



**Figure 1-3.** Synthesis of Aspirin via Kolbe-Schmitt Reaction

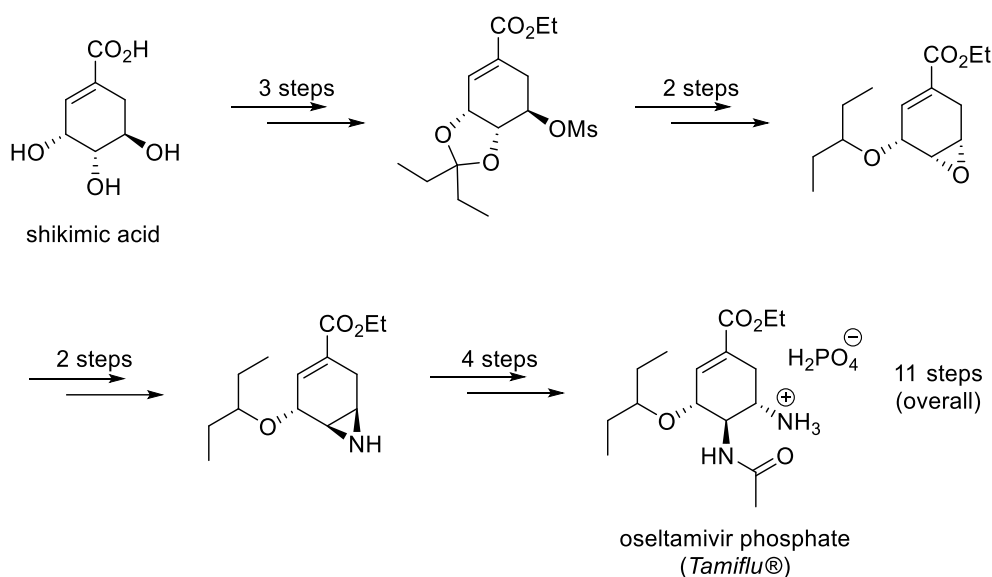


**Figure 1-4.** Examples of Synthesized Complex Natural Products

In the 1900s, synthesis of complex natural products which possess intricate frameworks, various functional groups, and a lot of chiral centers was intensively investigated (Figure 1-4). For example, Woodward and Eschenmoser *et al.* achieved total synthesis of vitamin B<sub>12</sub> in 1973.<sup>4</sup> Vitamin B<sub>12</sub> has not only complex framework but also cobalt atom, and its synthesis is recognized to be challenging. Up to now, only their

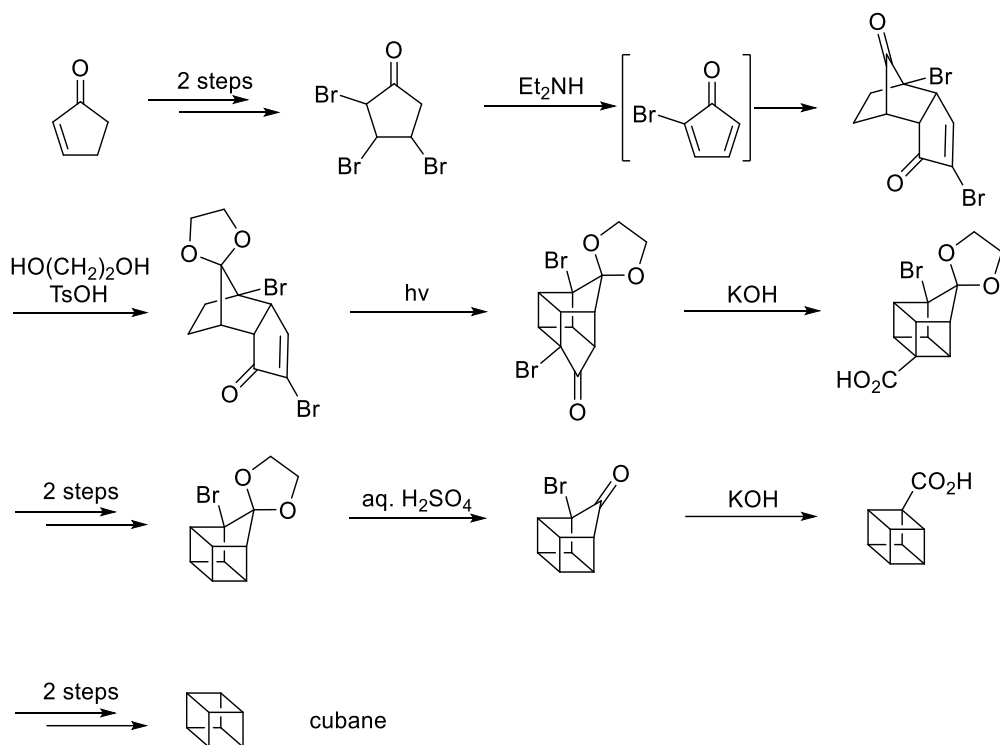
method realize the total synthesis vitamin B<sub>12</sub>. Woodward won the Nobel Prize in 1965 because he reported total synthesis of various natural products such as quinine<sup>5</sup> and strychnine.<sup>6</sup> In 1994, Holton *et al.* realized total synthesis of paclitaxel.<sup>7</sup> Paclitaxel have gathered attention as an anticancer drug (*Taxol*®), and other approaches to access it are still investigated.<sup>8</sup> It is also a challenging target material because of its complex structure, strained ring system, and many chiral centers. In 1999, Nicolaou *et al.* reported total synthesis of vancomycin, which is an antibiotic.<sup>9</sup> Vancomycin has unique structure which compose of several macro cyclic rings. In the 1990s, technologies to synthesize complex natural products have been rapidly developed as described above. These synthetic technologies were applied to creation and supply of fine chemicals.

*Tamiflu*®, which was marketed in 1999, has saved us from the influenza pandemic.<sup>10</sup> It is synthesized from shikimic acid.<sup>11,12</sup> Given that oseltamivir, which is the active ingredient of *Tamiflu*®, has complex structure, this is a remarkable achievement. Although molecular structure of shikimic acid is similar to that of oseltamivir, the synthesis proceeds through 11 steps reactions to construct complex the complex frameworks (Figure 1-5). This fact shows that it is quite difficult and challenging to control molecular structures to access target compounds.



**Figure 1-5.** Synthetic Route of Tamiflu

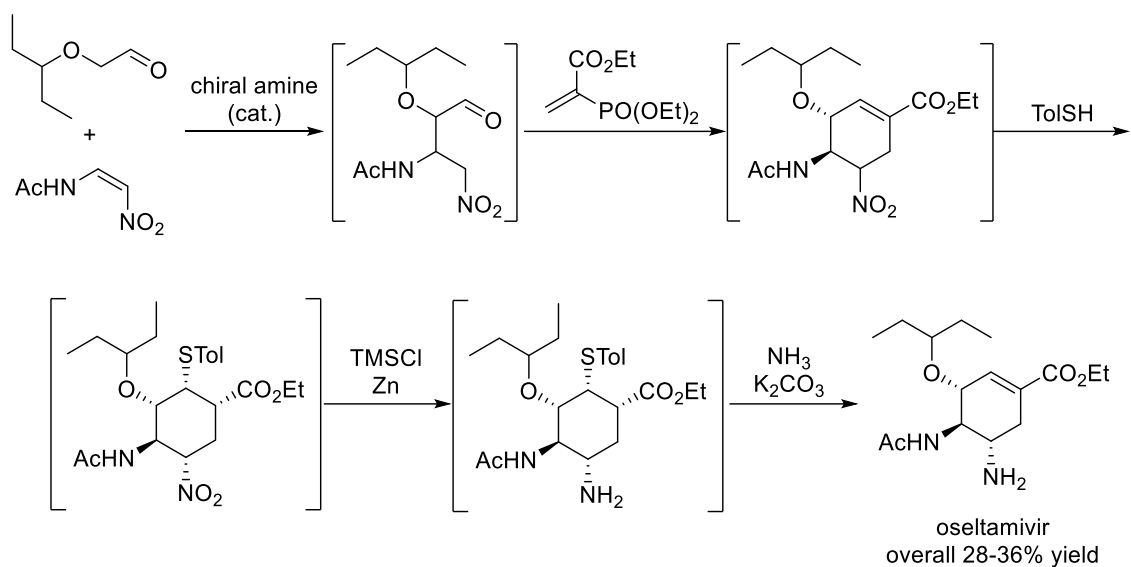
Synthetic organic chemistry has contributed to not only supply of fine chemicals but also creation of unique molecules. In 1964, Eaton *et al.* reported the first example of synthesis of cubane, which is a cubic hydrocarbon (Figure 1-6).<sup>13</sup> Cubane was recognized to be obtained because it has 12 strained C–C bonds. However, synthetic organic chemistry enabled the synthesis by assembling molecules step by step. In the modern world, it is obvious that synthetic organic chemistry is an essential research field for supply of fine chemicals and creation of unique substances.



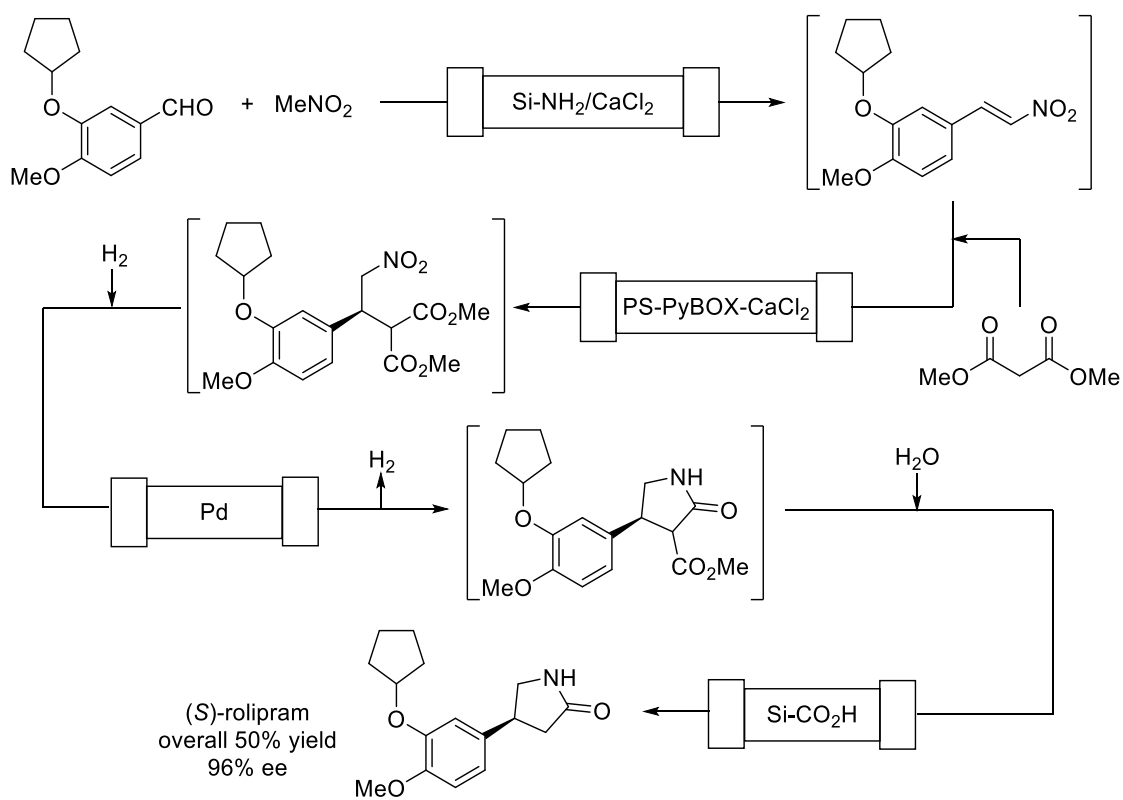
**Figure 1-6.** Synthesis of Cubane

### ***Advanced Synthetic Technology***

Recently, more practical synthetic methodologies such as one-pot synthesis and continuous-flow synthesis have been developed. One-pot enables multiple reactions in only one reaction container and economize purification and time.<sup>14</sup> In 2013, Hayashi's group reported one-pot synthesis of oseltamivir (Figure 1-7).<sup>15</sup> In this work, a sequence of 5 reactions were carried out in one-pot without purification of intermediates, and the target compound was obtained in 28-36% yield. In continuous-flow systems, catalysts are packed in columns, and starting materials and reagents are flowed in the columns. Then, the desired reactions proceed in the columns, and the desired product is obtained from the outlet of the system.<sup>16</sup> In 2015, our group has reported continuous-flow synthesis of rolipram (Figure 1-8).<sup>17</sup> In this work, rolipram was obtained in 50% yield in excellent enantioselectivity (96% ee). The enantiopurity of the obtained product could be enhanced up to >99% ee by recrystallization. In these new technologies, side-products and by-products can inhibit late-stage reactions because each reaction is conducted without purification of intermediates. Therefore, reduction of side-products and by-products is highly demanded for development of these technologies.



**Figure 1-7. One-Pot Synthesis of Oseltamivir**



**Figure 1-8. Continuous-Flow Synthesis of Rolipram**

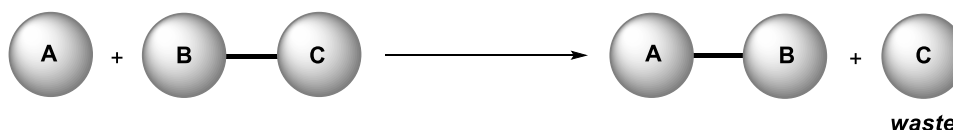
## 1-2. Atom Economy

Synthetic organic chemistry has made our society convenient regarding supply of fine chemicals including pharmaceuticals, agrochemicals, dyes, flavors, fragrances, and so on. However, multistep reactions are generally necessary to synthesize such fine chemicals because they sometimes have a complex structure. Furthermore, excess amounts of reagents are often consumed in each step, and large amounts of wastes are emitted simultaneously. Thus, it is a fact that we concern running out of valuable resource and environmental pollution by industrial wastes. To overcome these issues, development of efficient synthetic methods has been demanded. On the one hand, selectivities (chem-, regio-, diastereo-, and enantio-selectivities) are regarded as an important factor to reduce side-products which are going to become wastes. On the other hand, it is insisted to take atom economy into account (Figure 1-9).<sup>18</sup> Atom economy is defined as a ratio of molecular weight of a product and that of whole employed reactants (Figure 1-9 (a)). In other words, it indicates how many atoms deriving from all the employed reactants are included in the desired product structure. In organic synthesis, substitution reactions represented by S<sub>N</sub>2 and S<sub>N</sub>1 reactions are well-known methodology for molecular transformation and have been intensively developed since long ago. However, loss of leaving groups is problematic and causes low atom economy (Figure 1-9 (b)). On the other hand, addition reactions and rearrangement reactions have a potential to realize high atom economy because the reactions proceed without losing any leaving group (Figure 1-9 (c)). As described above, atom economy varies depending on kinds of reactions. Therefore, we have to carefully design reactions.

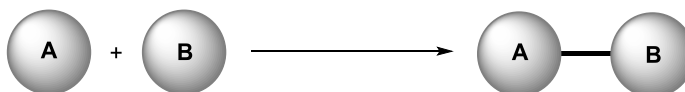
(a) definition of atom economy

$$\text{atom economy} = \frac{\text{molecular weight of a desired product}}{\text{molecular weight of all employed reactants}}$$

(b) reaction with low atom economy



(c) reaction with high atom economy



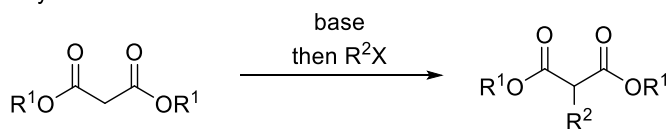
**Figure 1-9.** Concept of Atom Economy

### 1-3. Carbon–Carbon Bond Forming Reactions

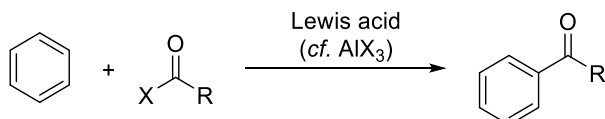
#### Substitution Reactions

In synthetic organic chemistry, fine chemicals are synthesized through construction of molecular frameworks and transformation of functional groups. Among them, construction of molecular frameworks is especially highlight process. Generally, the frameworks are constructed by connecting several building blocks which are molecular fragments, and carbon–carbon (C–C) bond forming reactions are demonstrated to connect the fragments. Thus, C–C bond forming reactions are one of the most important tools in organic synthesis. Alkylation reactions with alkyl halides are classical and fundamental methods, and most of the reactions proceed under  $S_N2$  or  $S_N1$  reaction mechanism which is well-established.<sup>19</sup> Examples of such reactions include alkylation of malonic esters (Figure 1-10 (a)). Regarding C–C bond forming reactions for aromatic compounds, Friedel-Crafts alkylation and acylation are also well-known methodologies (Figure 1-10 (b)).<sup>20</sup>

(a) alkylation of malonic esters

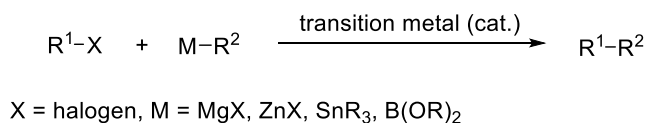


(b) Friedel-Crafts acylation



**Figure 1-10.** Examples of Classical C–C Bond Formation via Substitution

In addition to classical substitution reactions, transition metal catalyzed coupling reactions have been developed since 1960s (Figure 1-11). Tsuji reported the first example of palladium catalyzed allylation reactions of nucleophiles in 1965, and then they were established as Tsuji-Trost reaction.<sup>21</sup> Since this discovery, many kinds of transition metal-catalyzed coupling reactions have been developed such as Kumada,<sup>22</sup> Negishi,<sup>23</sup> Stille,<sup>24</sup> and Suzuki cross coupling reactions.<sup>25</sup> Transition metal catalyzed coupling reactions are so useful for organic synthesis, and their developments are still continued.<sup>26</sup> However, it is difficult to realize atom-economical reactions because they need leaving groups like substitution reactions.

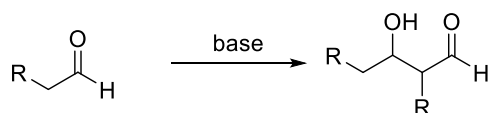


**Figure 1-11.** General Scheme of Transition Metal Catalyzed Cross Coupling Reactions

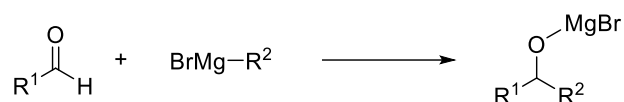
### Addition Reactions

Addition reactions are amenable to high atom economy rather than substitution reactions. Examples of classical addition reactions for C–C bond formation include nucleophilic addition reactions of carbanions to multiple bonds such as aldol and Grignard reaction (Figure 1-12 (a), (b)).<sup>19</sup> Although highly electrophilic compounds such as carbonyl compounds are easy to be employed in such polar reactions, polar addition reactions to less electrophilic substrates are challenging. To address this issue, radical addition reactions such as Giese reaction have been developed (Figure 1-12 (c)).<sup>27</sup>

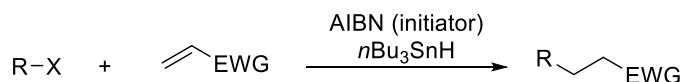
(a) aldol reaction



(b) Grignard reaction



(c) Giese reaction



**Figure 1-12.** Examples of Classical C–C Bond Formation via Addition

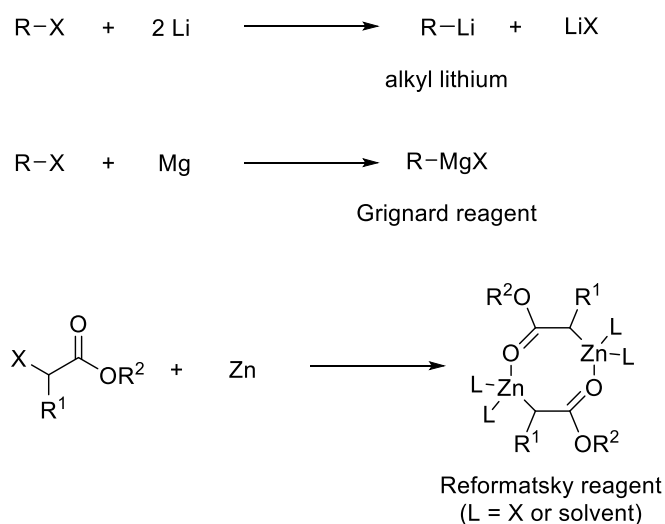
As described above, a lot of C–C bond forming reactions via addition processes have been developed. However, most of the classical addition reactions often require stoichiometric amounts of base, acid, or hydrogen atom transfer (HAT) reagents to activate starting materials, and it unfortunately causes low atom economy. To overcome this problem, catalytic activation of starting materials and its application to efficient addition reactions are highly demanded.



### 1-4. C–C Bond Forming Reactions Utilizing Carbanions

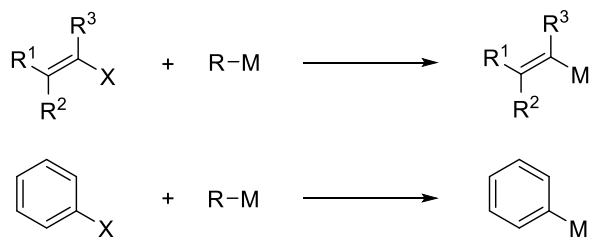
Addition reactions for C–C bond formation are excellent tools to construct molecular frameworks efficiently. Particularly, addition reactions of carbanions such as Grignard reagents have been established and often utilized to conventional organic synthesis.

Nowadays, various carbanions are available and essential for organic synthesis. Preparation protocols to generate carbanions are mainly classified into 4 categories. The most common one is treatments of alkyl halides with metal reagents (Figure 1-13). Alkyl halides react with lithium or magnesium metal to afford alkyl lithium<sup>28</sup> or Grignard reagents.<sup>29,30</sup> Furthermore, zinc metal reacts with  $\alpha$ -halo esters to afford zinc enolates in their dimer form which are less reactive (Reformatsky reagents), and they do not react with any esters but with ketones or aldehydes.<sup>31</sup>



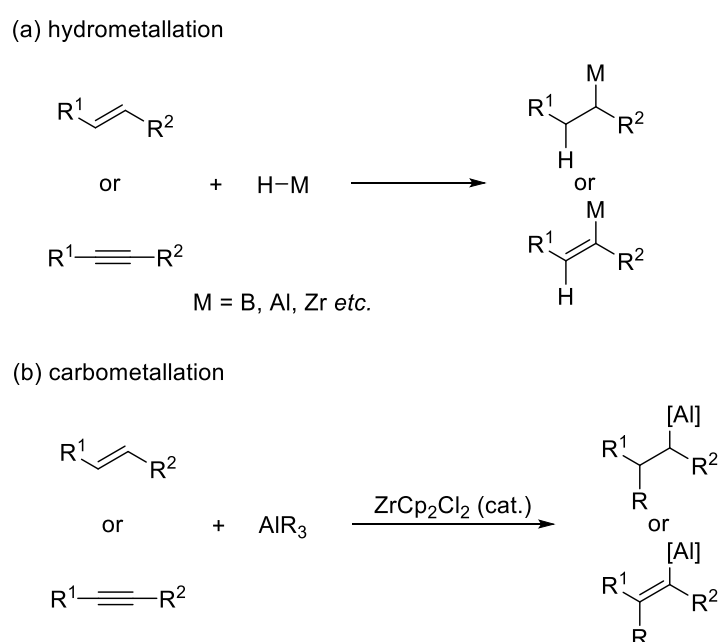
**Figure 1-13.** Generation of Organometallic Reagents by a Treatment with Metals

Organometallic reagents react with alkenyl halides or aryl halides via halogen-metal exchange, and this is useful protocols to prepare  $\text{sp}^2$  carbanions (Figure 1-14).<sup>30d,32</sup> Both treatments with metals and halogen-metal exchange are useful and common. However, they require pre-functionalization such as halogenation, and this issue spontaneously causes low atom economy.



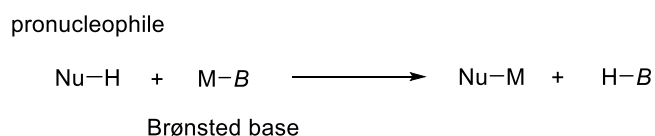
**Figure 1-14.** Halogen-Metal Exchange

Hydrometallation and carbometallation enable to generate carbanions without pre-functionalization. Metal hydrides react with alkenes or alkynes to afford alkyl carbanions or alkenyl carbanions (Figure 1-15 (a)).<sup>33</sup> Furthermore, carbometallation proceeds in the presence of an alkyl aluminum reagent and a zinc catalyst (Figure 1-15 (b)).<sup>34</sup> The carbanions generated by hydrometallation or carbometallation can be employed as a nucleophile, and they react with appropriate electrophiles. Although these protocols were carried out without pre-functionalization, stoichiometric amounts of metal hydrides or alkyl metals are required.



**Figure 1-15.** Hydrometallation and Carbometallation

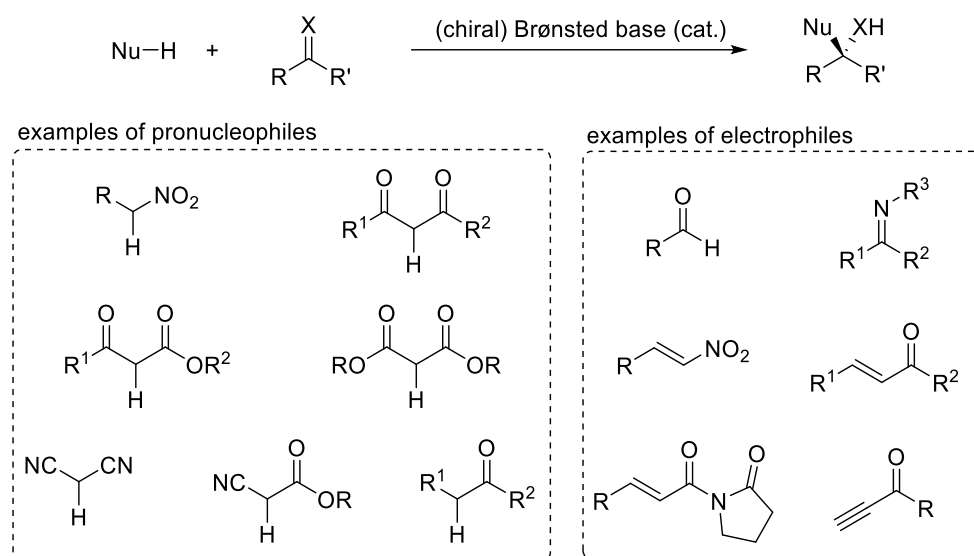
The other protocol is deprotonation of pronucleophiles, and it is widely applied to various organic reactions such as enolates chemistry.<sup>35</sup> When a base is strong enough to deprotonate a pronucleophile, the most acidic proton reacts with the base to afford the corresponding carbanion (Figure 1-16). This method enables direct generation of carbanions without pre-functionalization, and a lot of catalytic variants have been reported.



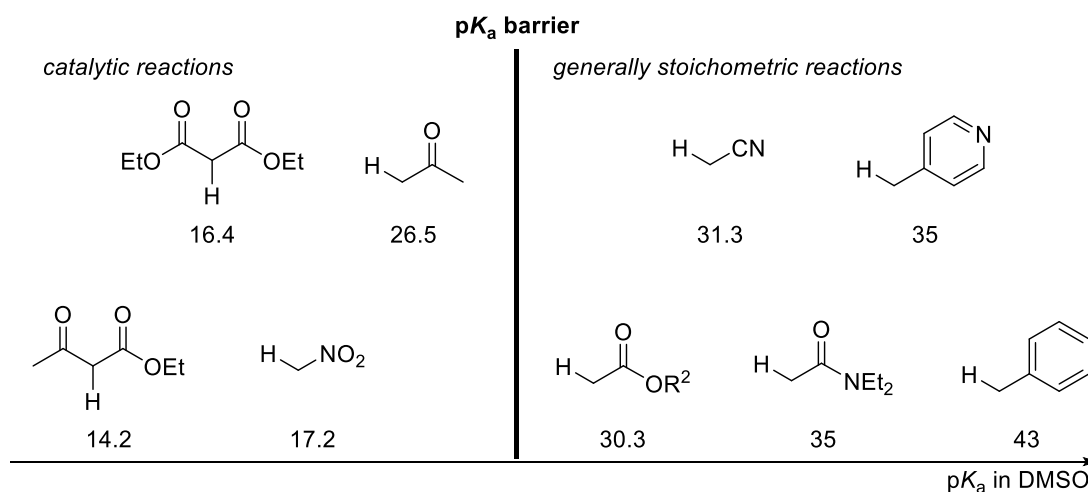
**Figure 1-16.** Deprotonation of Pronucleophiles

### 1-5. Brønsted Base-Catalyzed C–C Bond Forming Reactions

Among C–C bond forming reactions, Brønsted base-catalyzed addition reactions are atom-economical because they proceed under proton transfer conditions.<sup>19,36</sup> In addition to high atom economy, they are applicable to asymmetric reactions (Figure 1-17).<sup>37</sup> However, applicable pronucleophiles are generally limited to relatively acidic pronucleophiles ( $pK_a < \sim 30$  in DMSO) such as nitroalkanes, malonates, malononitriles, and ketones, and stoichiometric amounts of bases are generally required regarding less acidic pronucleophiles (Figure 1-18).



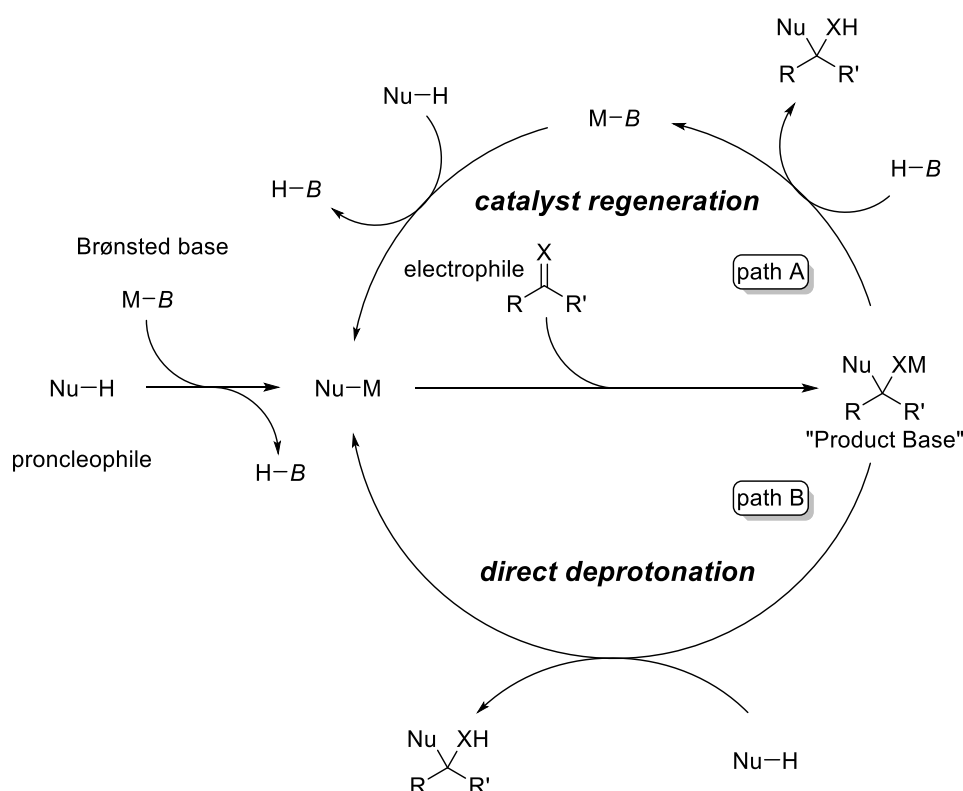
**Figure 1-17.** Brønsted Base-Catalyzed Addition reactions



**Figure 1-18.**  $pK_a$  Barrier in Brønsted Base-Catalyzed Reactions

Reaction mechanism of base-catalyzed reactions are shown below (Figure 1-19).<sup>38</sup> First, nucleophiles which are generated through deprotonation by base catalysts react with

appropriate electrophiles to afford the key reaction intermediates which are termed “Product Base”. Then, two reaction pathways are conceivable. One of them is catalyst regeneration pathway in which the key reaction intermediates deprotonate the conjugate acids to regenerate the base catalysts (path A). The other one is direct deprotonation pathway which looks like anion propagation (path B).

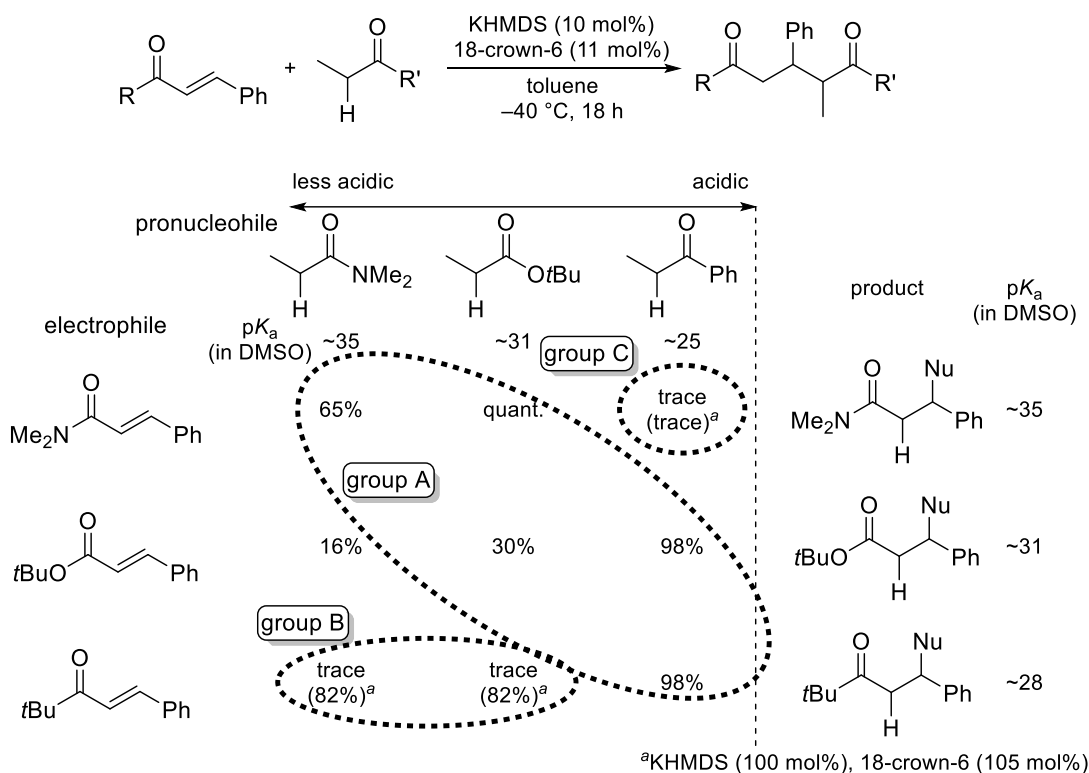


**Figure 1-19.** Reaction Mechanism of Brønsted Base-Catalyzed Addition Reactions

### **Limitation of Base-Catalyzed Reactions**

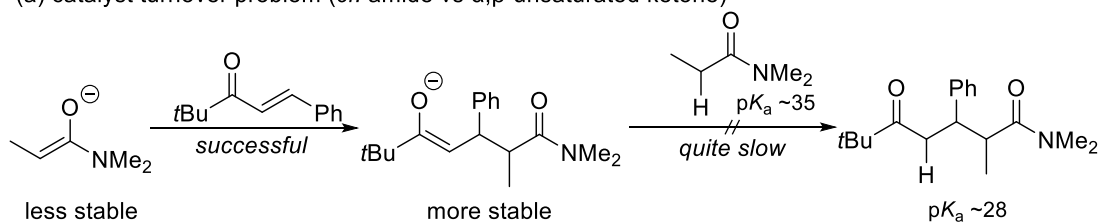
Available substrates are still limited although a variety of base-catalyzed reactions has been developed. In 2016, our group summarized what caused the limitation, and it was found that the limitation was classified into two categories (Figure 1-20).<sup>39d</sup> The base-catalyzed reactions proceeded smoothly when  $pK_a$  values of pronucleophiles were close to those of the desired products (group A). However, the catalytic reactions were unsuccessful when the pronucleophiles were much less acidic than the desired products (group B). This limitation is termed “Catalyst Turnover Problem” because stoichiometric amounts of bases enable the desired addition reactions. For example, combination of amides and  $\alpha,\beta$ -unsaturated ketones causes the problem (Figure 1-21 (a)). Amides are difficult to be deprotonated and require strong bases for their deprotonation. On the other hand, amide enolates are highly nucleophilic, and addition steps of amide enolates to  $\alpha,\beta$ -unsaturated ketones proceed to afford the corresponding anionic reaction intermediates.

However, the anionic reaction intermediates cannot deprotonate the next amides because they are ketone enolates which are much less basic than amide enolates. Thus, the catalytic reactions are unsuccessful although the stoichiometric reactions are possible.

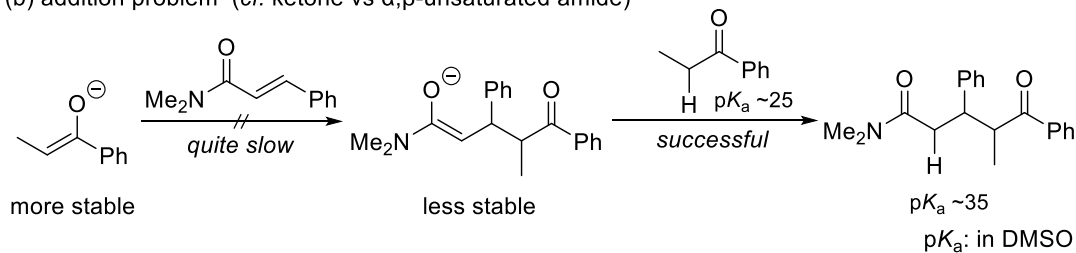


**Figure 1-20.** Base-Catalyzed 1,4-Addition Reactions of Various Substrates

(a) catalyst turnover problem (*cf.* amide vs  $\alpha,\beta$ -unsaturated ketone)



(b) addition problem (cf. ketone vs  $\alpha,\beta$ -unsaturated amide)



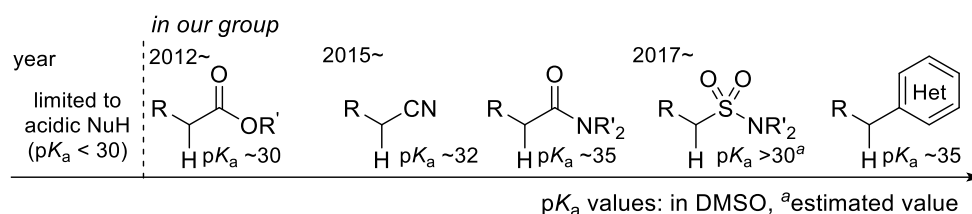
### Figure 1-21. Unsuccessful Examples and Origins of the Limitation

When the pronucleophiles were much acidic than the desired products, the catalytic reactions did not proceed at all (group C). In this case, the desired addition reactions were unsuccessful even if stoichiometric amounts of bases were employed. This limitation is termed “Addition Problem” because it is caused by low nucleophilicities of carbanions. For example, combination of ketones and  $\alpha,\beta$ -unsaturated amides causes it (Figure 1-21 (b)). Carbanion regeneration is easier because ketones are acidic substrates. However, addition of ketone enolates to  $\alpha,\beta$ -unsaturated amides is quite slow because carbanions of acidic compounds are relatively stable and their nucleophilicities are low. Thus, the desired addition reactions do not proceed even in the presence of stoichiometric amounts of bases.

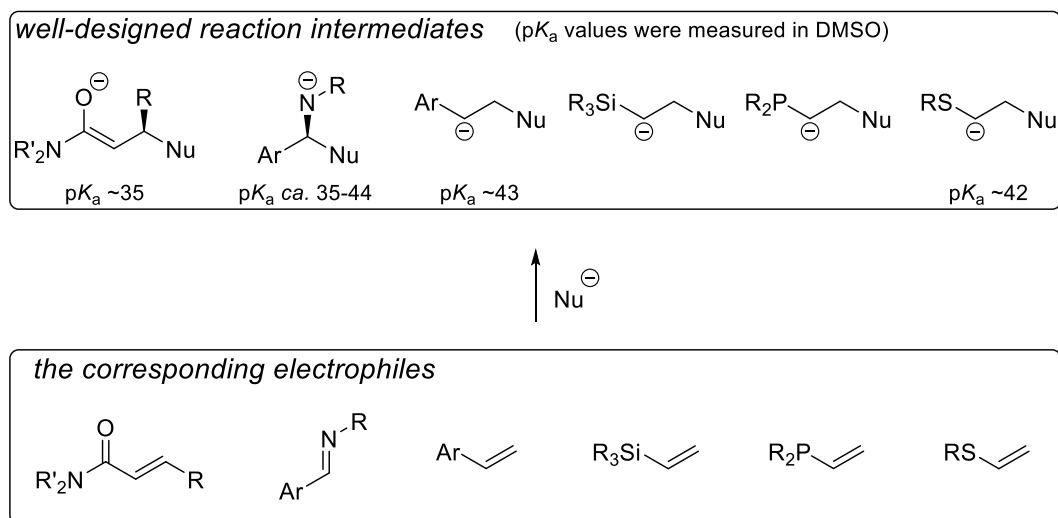
### ***Strong Brønsted Base-Catalyzed Reactions (Approach to “Catalyst Turnover Problem”)***

Brønsted base-catalyzed addition reactions which proceed under proton transfer conditions are atom-economical and applicable to asymmetric variants because they are successful even at low temperature. However, pronucleophiles have been restricted to relatively acidic compounds ( $pK_a < \sim 30$  in DMSO) because less acidic pronucleophiles make carbanion regeneration difficult, which is termed catalyst turnover problem. Therefore, strong Brønsted base-catalyzed reactions using less acidic pronucleophiles are still challenging.

On the other hand, our group has developed many kinds of Brønsted base-catalyzed reactions using less acidic pronucleophiles such as esters, alkynitriles, amides, alkanesulfonamides, and alkylazaarenes (Figure 1-22).<sup>38,39</sup> The key to success of these reactions is designing anionic reaction intermediates to be strongly basic (Figure 1-23). For example, an amide enolate which is strongly basic is formed as a reaction intermediate after nucleophilic addition step when  $\alpha,\beta$ -unsaturated amide is employed as an electrophile. Similarly, imines and alkenes have a potential to enable strong Brønsted base-catalyzed addition reactions.

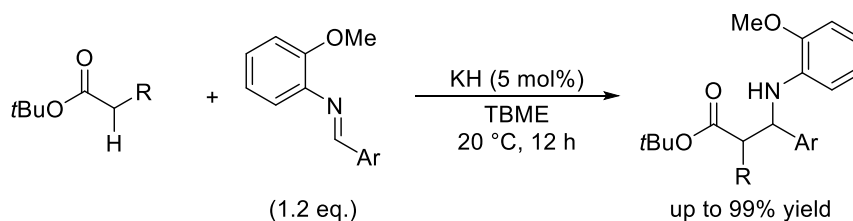


**Figure 1-22.** History of Strong Brønsted Base-Catalyzed Addition Reactions



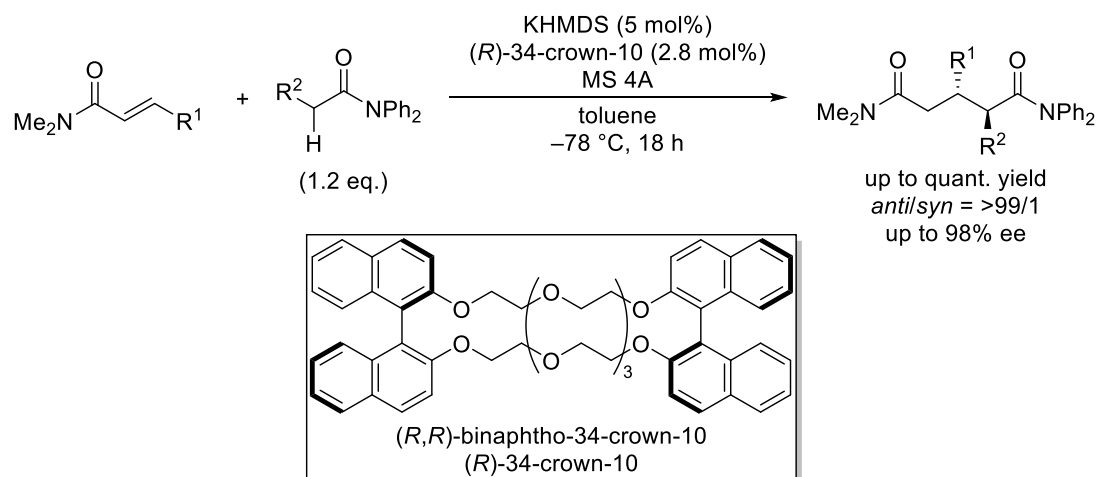
**Figure 1-23.** Design of the Reaction Intermediates

Based on this strategy, our group reported direct Mannich-type reactions of unactivated esters in 2012 (Figure 1-24).<sup>39a</sup> In the presence of only 5 mol% of potassium hydride (KH), the reactions proceed smoothly. *N*-Aryl-imines were employed as electrophiles to afford potassium alkyl aryl amides which are basic enough to deprotonate esters.

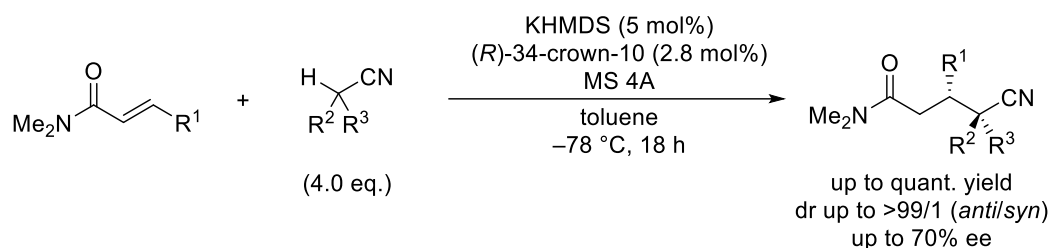


**Figure 1-24.** Base-Catalyzed Mannich-Type Reactions of Unactivated Esters

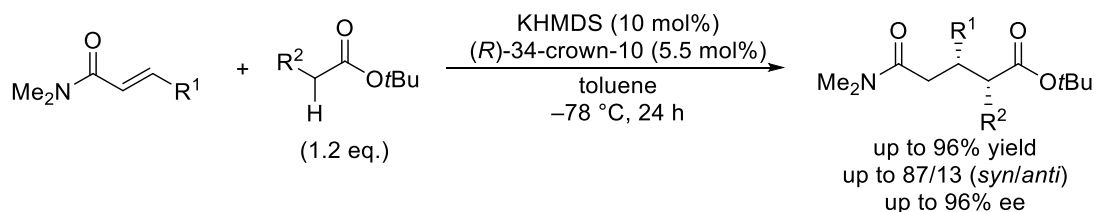
In 2015, our group achieved strong Brønsted base-catalyzed asymmetric 1,4-addition reactions of unactivated amides with  $\alpha,\beta$ -unsaturated amides (Figure 1-25).<sup>39b</sup> Chiral macrocyclic ether ((*R,R*)-binaphtho-34-crown-10) was employed for modification of potassium ion. This is the first report of strong Brønsted base-catalyzed asymmetric addition reactions. The chiral modification of potassium base with the chiral macrocyclic ether was found to be effective to in base-catalyzed asymmetric 1,4-addition reactions of other pronucleophiles such as alkylnitriles (Figure 1-26),<sup>39c</sup> esters (Figure 1-27),<sup>39d</sup> and alkanesulfonamides (Figure 1-28).<sup>39e</sup>



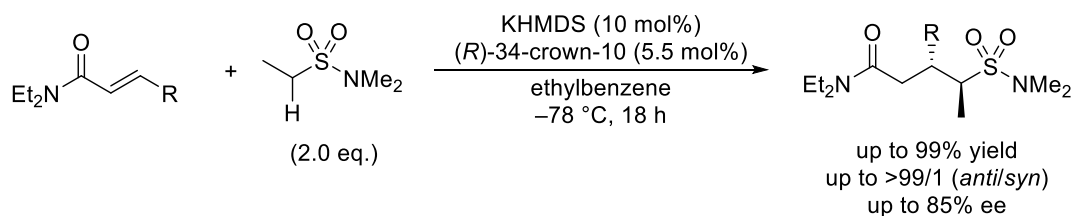
**Figure 1-25.** Base-Catalyzed Asymmetric 1,4-Addition Reactions of Amides



**Figure 1-26.** Base-Catalyzed Asymmetric 1,4-Addition Reactions of Alkynitriles



**Figure 1-27.** Base-Catalyzed Asymmetric 1,4-Addition Reactions of Esters

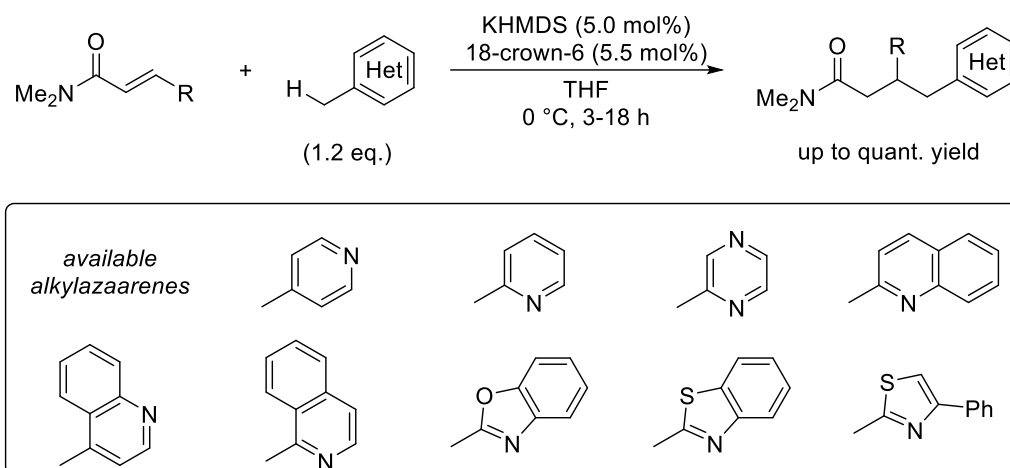


**Figure 1-28.** Catalytic Asymmetric 1,4-Addition Reactions of Alkanesulfonamides

Since 2017, our group has reported several kinds of base-catalyzed addition reactions using alkylazaarenes which are more challenging substrates.<sup>39f</sup> First, catalytic addition



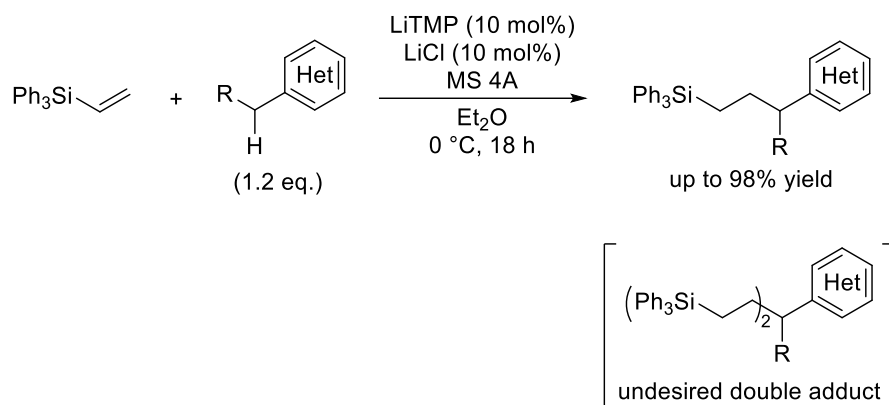
reactions with  $\alpha,\beta$ -unsaturated amides was achieved (Figure 1-29). The applicable pronucleophiles are not only alkylpyridines but also methylpyrazine, methylquinolines, methylisoquinoline, methylbenzoxazole, methylbenzothiazole, methylthiazole, and methylbenzimidazole. Furthermore, several examples of asymmetric variants are included. In the presence of (*R,R*)-binaphtho-34-crown-10, the catalytic asymmetric addition reactions of 1-methylisoquinoline proceeded with high enantioselectivities (76-83% ee).



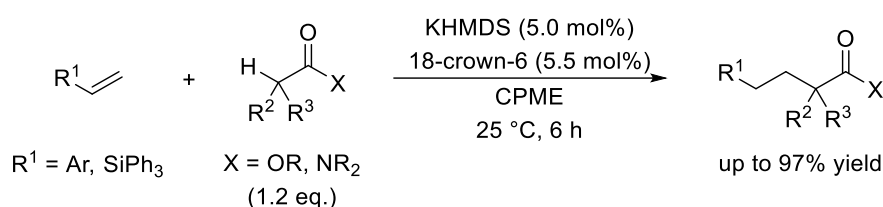
**Figure 1-29.** Base-Catalyzed 1,4-Addition Reactions of Alkylazaarenes

In 2018, strong Brønsted base-catalyzed addition reactions of alkylazaarenes with vinylsilanes were reported (Figure 1-30).<sup>39g</sup> When KHMDS and 18-crown-10 were employed, an undesired double adduct was obtained in a significant amount. On the other hand, LiTMP catalyzed the reactions effectively in the absence of 18-crown-10, and the desired adduct was obtained selectively without formation of the undesired double adduct.

In the same year, it was found that amides and esters reacted with alkenes to afford the corresponding alkylated carbonyl compounds in base catalysis (Figure 1-31).<sup>39h</sup> In addition to vinylsilanes, styrene analogues are available as electrophiles in this report.

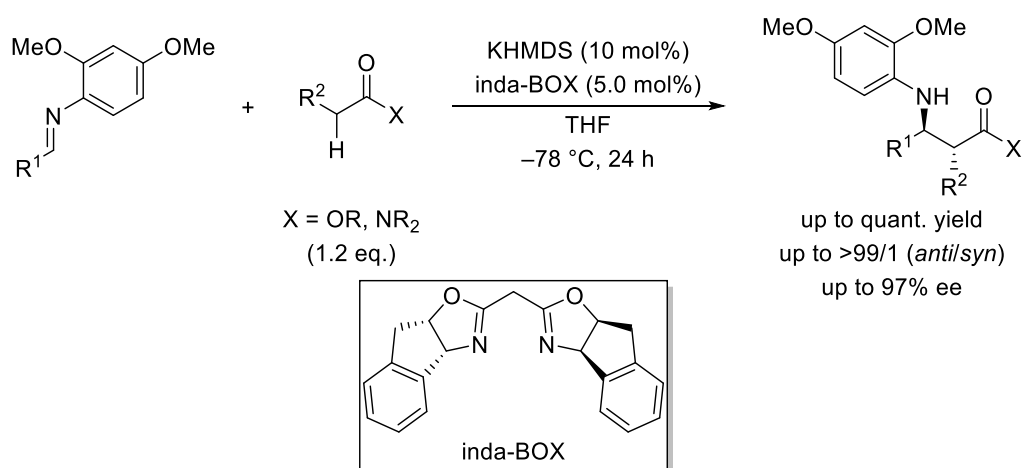


**Figure 1-30.** Base-Catalyzed Addition Reactions of Alkylazaarenes with Vinylsilanes



**Figure 1-31.** Base-Catalyzed Addition Reactions of Amides and Esters with Alkenes

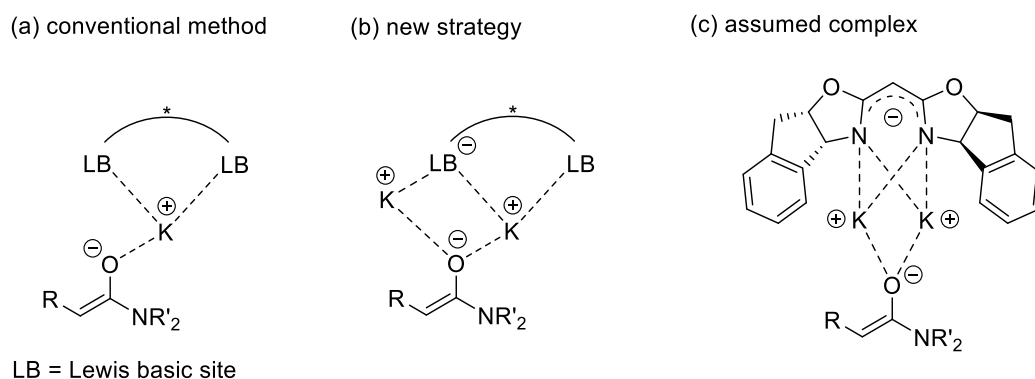
In 2021, our group reported catalytic asymmetric Mannich-type reactions with simple amides (Figure 1-32).<sup>39i</sup> The reactions proceeded smoothly with excellent enantioselectivities in the presence of a chiral potassium salt and a base catalyst.



**Figure 1-32.** Base-Catalyzed Asymmetric Mannich-Type Reactions of Amides

Strong Brønsted base-catalyzed asymmetric addition reactions, which our group has developed, were limited to 1,4-addition reactions using (*R,R*)-binaphtho-34-crown-10 before discovery of this system (Figure 1-33 (a)). Generally, chiral modification of potassium ion is recognized to be difficult presumably because of its low Lewis acidity

and large ionic radius. In order to overcome this problem, it was hypothesized that a chiral potassium salt might be effective to construct an aggregate chiral environment (Figure 1-33 (b)). Regarding catalytic asymmetric Mannich-type reactions with simple amides, inda-BOX was employed as a chiral source, of which active methylene can be deprotonated by KHMDS. Half of KHMDS is used for deprotonation of inda-BOX, and the rest react with amide to afford the corresponding enolate. It was assumed that the formed chiral potassium salt aggregated the potassium enolate by computational studies (Figure 1-33 (c)).



**Figure 1-33.** Chiral Modification Methods for Potassium Ion

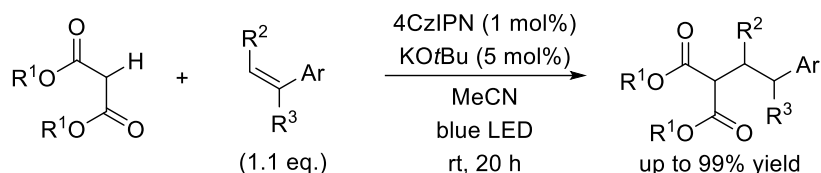
A variety of strong Brønsted base-catalyzed C–C bond forming reactions have been developed ( $pK_a$  30–35 in DMSO). In this context, application of more challenging substrate to such reaction systems is highly demanded. Therefore, I have developed strong Brønsted base-catalyzed C–C bond forming reactions utilizing less reactive pronucleophiles ( $pK_a > 40$  in DMSO) in one of my doctoral thesis studies. Especially, I focused on enantioselective C–C bond forming reactions enabled by base catalysis.

### ***Brønsted Base-Photoredox Catalyst Hybrid System (“Approach to Addition Problem”)***

Alkylation is one of the most fundamental and important reactions to construct molecular frameworks. Conventionally, alkyl halides have been often employed for alkylation reactions. However, substitution reactions are not efficient from the viewpoint of atom economy. On the other hand, alkenes are one of ideal alkylating reagents because they enable alkylation reactions under addition reaction conditions as mentioned in section 1-3.

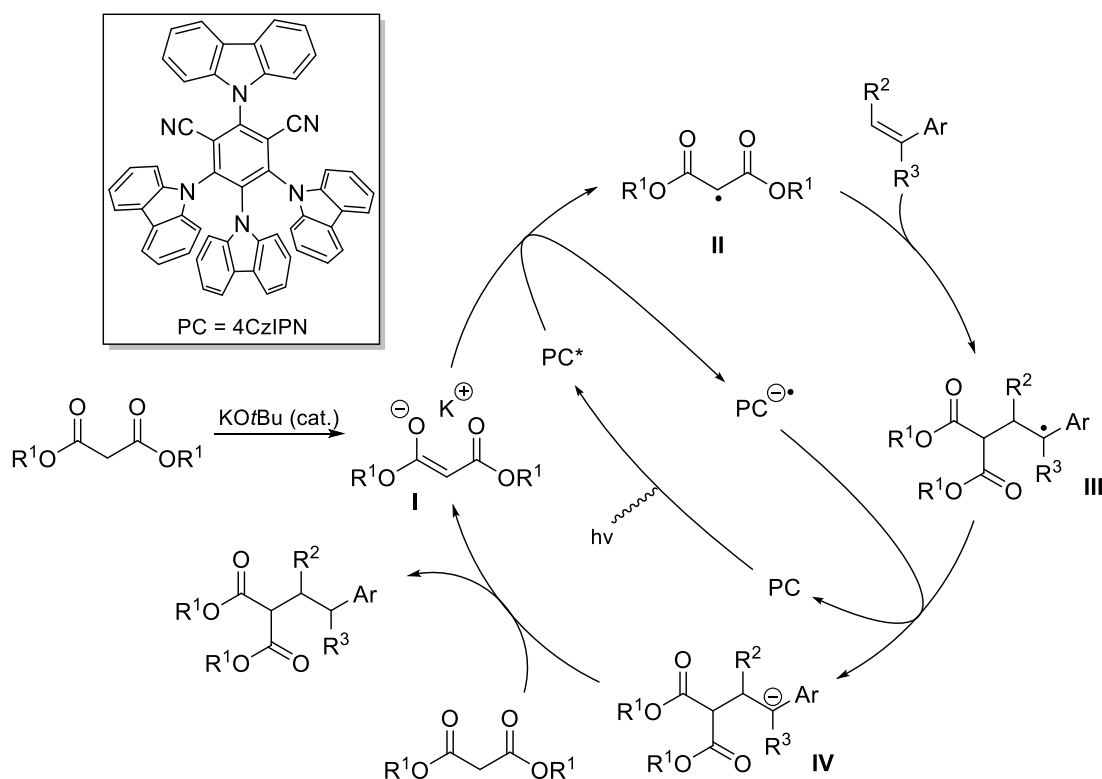
Although alkenes are one of good alkylation reagents, they are difficult to be employed as an electrophile because of their low electrophilicities, which means “Addition Problem”. To access this problem, radical addition reactions can be breakthrough because alkenes are recognized to be good radical acceptors.<sup>27, 40, 41</sup>

Therefore, addition reactions with alkenes might be easier if radical species were generated. Based on this idea, our group has developed addition reactions of malonates with alkenes although nucleophilic variants are quite slow (Figure 1-34).<sup>42</sup>



**Figure 1-34.** Catalytic Addition Reactions of Malonates with Alkenes

The key to success of this reaction is transformation of their enolates into the corresponding  $\alpha$ -carbonyl radicals (Figure 1-35). First, the corresponding enolate **I** is generated by the base catalyst. Then, the enolate **I** is oxidized by the excited photoredox catalyst via single-electron transfer, and the corresponding  $\alpha$ -carbonyl radical **II** is formed. The formed radical **II** reacts with the employed alkene to afford the radical intermediate **III**, and the photoredox catalyst reduces it. The formed anionic intermediate **IV** is protonated by the next malonate to afford the desired product, and the enolate **I** is regenerated simultaneously.



**Figure 1-35.** Reaction Mechanism of Base-Photo Catalyst Hybrid System

Although this hybrid system is promising to overcome addition problem in Brønsted base catalysis, only one example has been reported. Therefore, there is still much room to expand applicable substrates. In my doctoral thesis studies, I have developed catalytic addition reaction using more challenging substrate based on this strategy.

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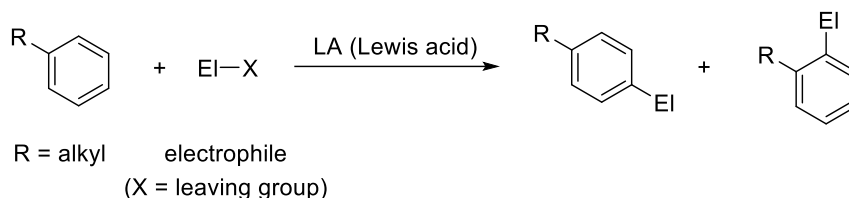
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## 2. Strong Brønsted Base-Catalyzed Asymmetric Addition Reactions of Alkylarenes with Imines

### 2-1. Background

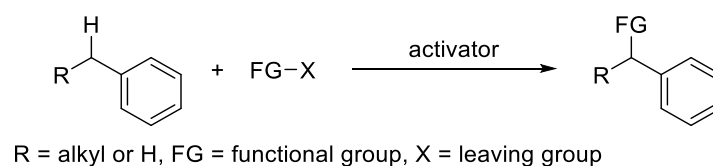
#### Alkylarenes

Unactivated alkylarenes such as toluene and xylenes have been employed as common solvents in organic synthesis because they are stable, abundant, inexpensive, readily available, and easy to handle. On the other hand, they have also been utilized as ideal feedstocks for introduction of aromatic moieties into molecular frameworks. For example, electrophilic substitution reactions on their aromatic rings in the presence of Lewis acids, represented by Friedel–Crafts reactions, are a well-established methodology (Figure 2-1).<sup>1</sup>



**Figure 2-1.** Electrophilic Aromatic Substitution of Alkylarenes

Alkylarenes have reactive C(sp<sup>3</sup>)–H bonds which locate at their benzylic positions while a variety of C(sp<sup>2</sup>)–H bond functionalization has been developed (Figure 2-2). However, benzylic C–H bond activation for C–C bond formation is still challenging although benzylic heterofunctionalization including oxidation to afford aldehydes, ketones, and carboxylic acid has established.



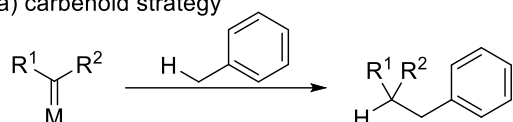
**Figure 2-2.** Benzylic C–H Bond Functionalization

#### Catalytic Benzylic C–H Activation for C–C Bond Forming Reactions

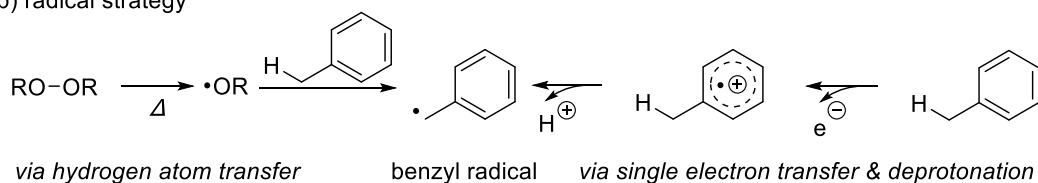
Catalytic benzylic C–H activation for C–C bond formation is mainly classified into carbenoid,<sup>2</sup> radical, palladium-catalyzed, and deprotonative activation strategies (Figure 2-3).<sup>3</sup> Carbenoid strategy is efficient approach to realize direct benzylic C–H functionalization and applicable to asymmetric functionalization although available substrates are limited (Figure 2-3 (a)).<sup>2</sup> In 2002, Davis' group reported C–C bond forming reactions at benzylic position of alkylarenes using metal carbenoid species (Figure 2-4).<sup>2a</sup> In the presence of Rh<sub>2</sub>(S-DOSP)<sub>4</sub>, insertion reactions of carbenoids deriving from methyl

aryldiazoacetates into ethylbenzene proceeded in moderate to high yields with good deastereoselectivities and enantioselectivities. However, toluene and isopropylbenzene were unsuccessful substrates. Although this strategy enabled stereoselective reactions, applicable substrates were limited.

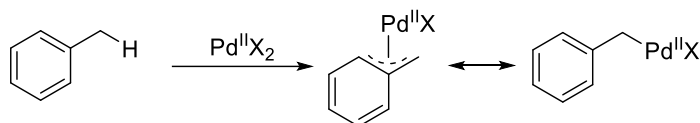
(a) carbenoid strategy



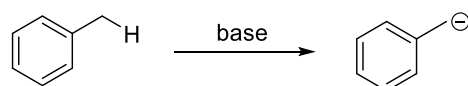
(b) radical strategy



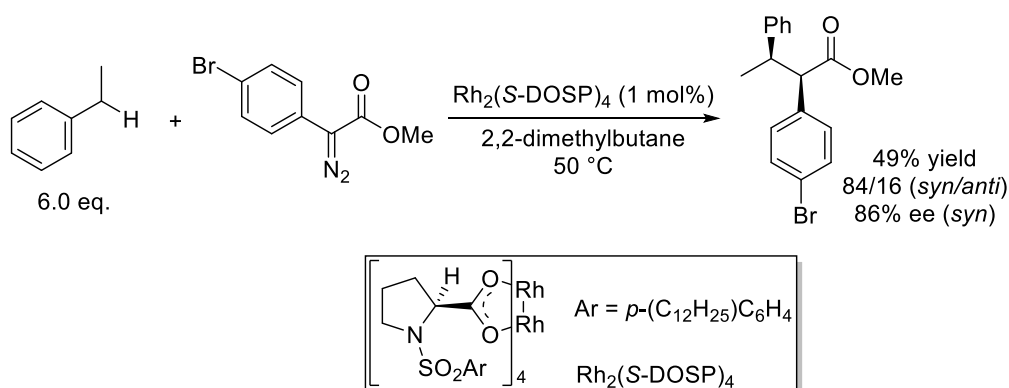
(c) palladium-catalyzed strategy



(d) deprotonative strategy



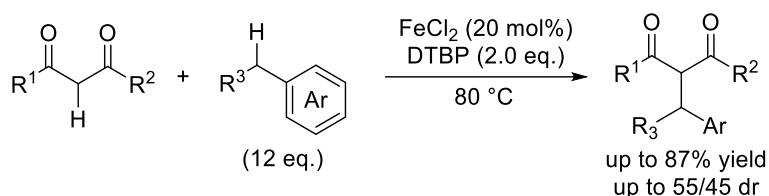
**Figure 2-3.** Classification of Catalytic Benzylic C–H Activation



**Figure 2-4.** Rhodium-Catalyzed Asymmetric Insertion Reactions into Alkylarenes

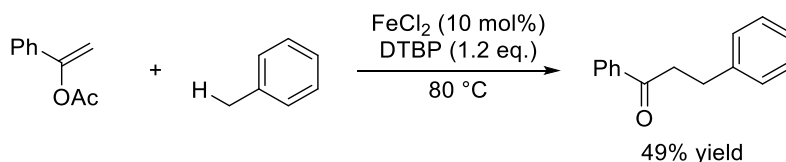
Benzylic C–H bonds are relatively reactive in radical formation because of

delocalization of benzyl radicals (BDEs:  $375.5 \pm 5.0$  kJ/mol for H-CH<sub>2</sub>Ph (toluene),  $472.2 \pm 2.2$  kJ/mol for H-C<sub>6</sub>H<sub>5</sub> (benzene),  $400.4 \pm 2.9$  kJ/mol for H-CMe<sub>3</sub> (isobutane)).<sup>4</sup> Benzylic C-H bonds of toluene are weaker than the C-H bond of isobutane although tertiary radicals are generally more stable than primary radicals. Therefore, it is efficient to utilize benzyl radicals in benzylic C-H functionalization, and various C-C bond forming reactions through abstraction of benzylic hydrogen have been developed (Figure 2-3 (b)). However, preparation of benzyl radicals often requires a stoichiometric amount of oxidant which plays a role of radical reagent such as *tert*-butyl peroxide (DTBP, *t*BuOO*t*Bu) at elevated temperature while metallic species are employed as a catalyst. In 2007, Li *et al.* reported iron-catalyzed coupling of alkylarenes with 1,3-dicarbonyls as pioneering work on benzylic C-H functionalization toward C-C bond formation based on radical strategy (Figure 2-5).<sup>5a</sup> Benzyl radicals react with metal enolates through addition to their C=C double bonds. Similarly, various related catalyst systems have developed including 2-acylimidazoles, which are not 1,3-dicarbonyls but ketones.<sup>5</sup>



**Figure 2-5.** Iron-Catalyzed Coupling of Alkylarenes with 1,3-Dicarbonyls

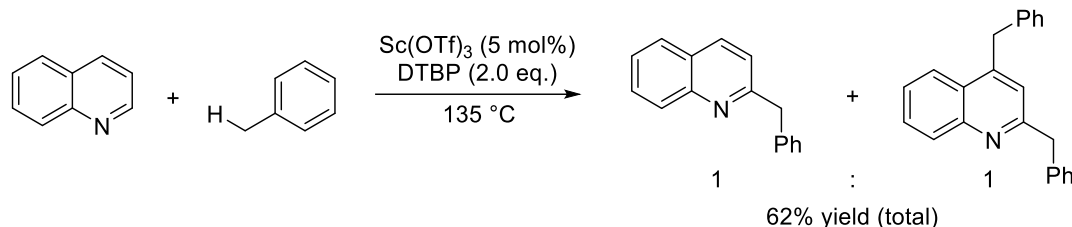
A variety of benzylic C-H functionalization via addition of benzyl radicals to C=C double bonds has been developed because they are good radical acceptors.<sup>6</sup> For example, Gan and Shi reported iron-catalyzed direct functionalization of benzylic C-H bonds with vinyl acetates in 2009 (Figure 2-6).<sup>6b</sup> Benzylic hydrogens are abstracted by *tert*-butoxy radical deriving from DTBP to afford benzyl radicals, and benzyl radicals react with vinyl acetates, which are activated by the iron catalyst.



**Figure 2-6.** Iron-Catalyzed Direct Functionalization of Benzylic C-H Bonds

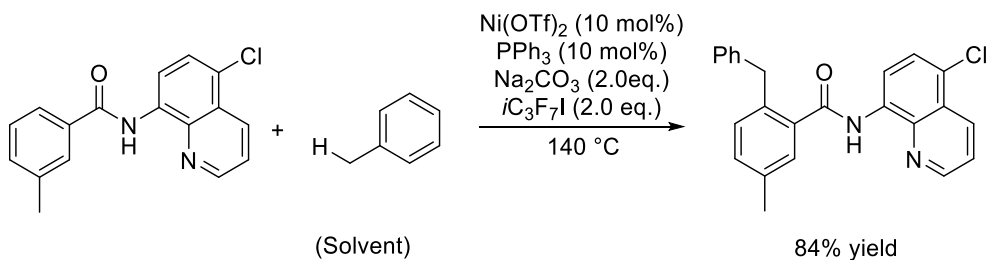
In addition to reactions through addition of benzyl radicals to C=C double bonds, their addition to C=N double bonds also developed.<sup>7</sup> For example, Li *et al.* reported scandium-catalyzed direct alkylation of quinones and pyridines in 2009 (Figure 2-7).<sup>7a</sup> This reaction is applicable to aliphatic substrates. However, an example of benzylic C-H

bond functionalization included only the reaction using toluene, and the selectivity was problematic.

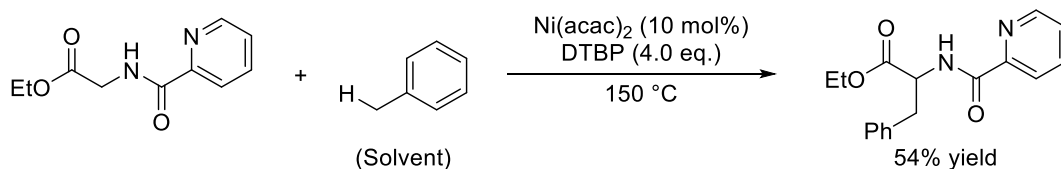


**Figure 2-7.** Scandium-Catalyzed Direct Alkylation of Quinones and Pyridines

While many reactions through addition of benzyl radicals to double bonds have been developed, C–H/C–H coupling reactions based on directing group-assisted C–H activation also have gotten attention.<sup>8</sup> The first example of such reactions was developed by Chatani's group in 2014.<sup>8a</sup> They reported nickel-catalyzed benzylic C(sp<sup>3</sup>)–H/C(sp<sup>2</sup>)–H coupling reactions between alkylarenes and benzamides (Figure 2-8). C(sp<sup>2</sup>)–H bonds of benzamides are activated by the nickel catalyst based on directing group strategy, and the formed nickel complex traps benzyl radicals. Then, following reductive elimination afford the desired products. Similarly, You *et al.* reported nickel-catalyzed benzylic C(sp<sup>3</sup>)–H/C(sp<sup>3</sup>)–H coupling to access β-aromatic α-amino acids in 2015 (Figure 2-9).<sup>8d</sup> They utilized 2-pyridinecarbonyl group as a directing group to activate α-positions of the esters.



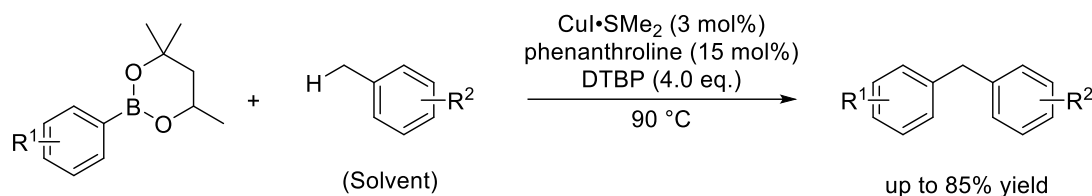
**Figure 2-8.** Nickel-Catalyzed Benzylic C(sp<sup>3</sup>)–H/C(sp<sup>2</sup>)–H Coupling



**Figure 2-9.** Nickel-Catalyzed Benzylic C(sp<sup>3</sup>)–H/C(sp<sup>3</sup>)–H Coupling

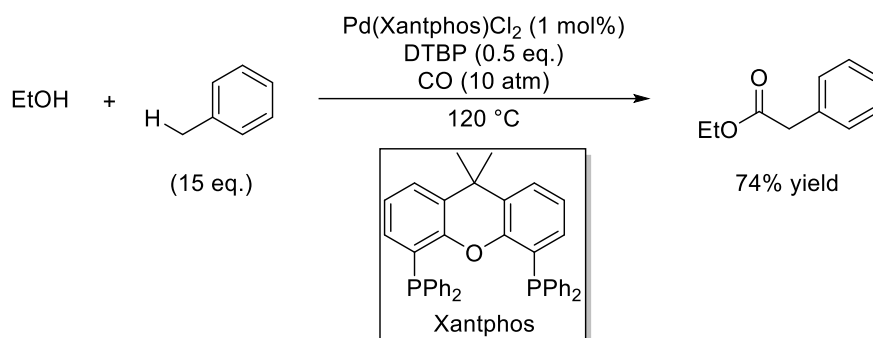
Recently, combination of benzyl radical formation and transition metal catalysis without any directing group has been developed.<sup>9</sup> For example, Stahl's group reported Copper-catalyzed benzylic arylation in 2017 (Figure 2-10).<sup>9c</sup> First, Cu (I) is oxidized by

DTBP to afford Cu (II) species and *tert*-butoxy radical, which abstracts benzylic hydrogen from alkylarenes to generate benzyl radicals. Following transmetalation with aryl boronic acids gives aryl copper (II) complex, which traps the benzyl radicals. Subsequently, reductive elimination affords the desired products.



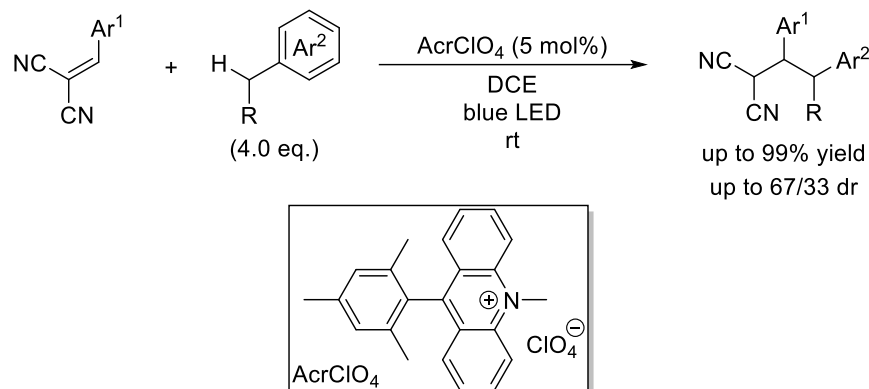
**Figure 2-10.** Copper-Catalyzed Benzylic Arylation

Furthermore, carbon monoxide also reacts with benzyl radicals to afford carbonyl compounds in the presence of a transition metal catalyst.<sup>10</sup> In 2012, Huang's group reported palladium-catalyzed carbonylation of benzylic C–H bonds (Figure 2-11). Various alkylarenes are available, and the reactions proceed in moderate to good yields to afford the desired esters.



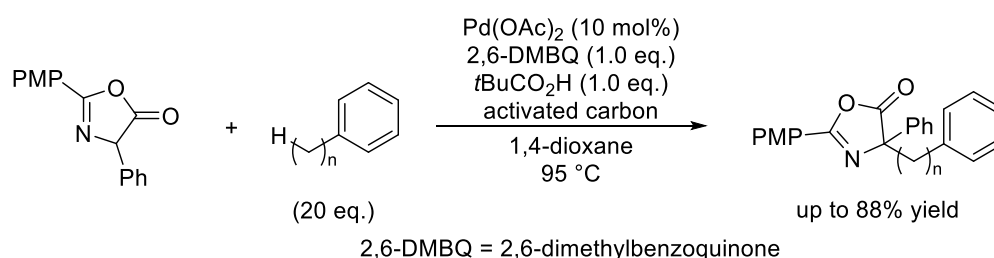
**Figure 2-11.** Palladium-Catalyzed Carbonylation of Benzylic C–H Bonds

Abstraction of benzylic radical is well-established approach to activate directly benzylic C–H bonds as described above. However, radical chain reactions are minor methods among them, and they often offer a stoichiometric amount of an oxidant, which means low atom economy. On the other hand, photoredox catalysis has enabled truly catalytic benzylic C–H functionalization.<sup>11</sup> For example, Wu *et al.* reported photocatalytic Giese-type radical addition reactions in 2017 (Figure 2-12).<sup>11i</sup> The reactions proceed smoothly in the presence of only a photocatalyst and blue light irradiation, which realize fully catalytic transformation. Firstly, alkylarenes are transformed into the corresponding radicals via single electron oxidation followed by deprotonation, and radical addition proceeds. The formed radical adducts are reduced, and following protonation affords the desired adducts.



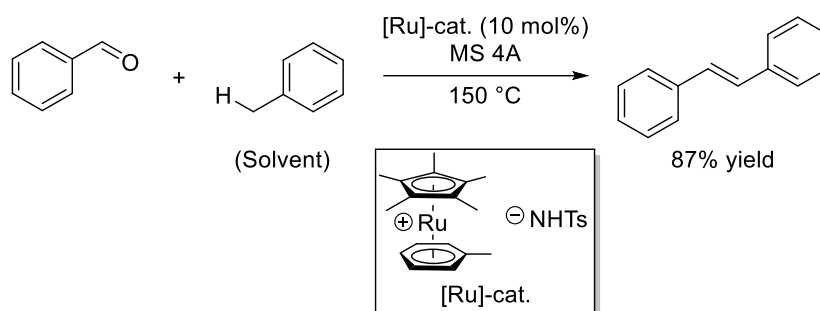
**Figure 2-12.** Photocatalytic Giese-Type Radical Addition Reactions

Palladium has a potential to activate benzylic C(sp<sup>3</sup>)-H bonds with chemoselectivities against aromatic C(sp<sup>2</sup>)-H bonds (Figure 2-3 (c)).<sup>12</sup> In 2015, Kozlowski's group developed palladium-catalyzed benzylic C-H activation for coupling with azlactone (Figure 2-13).<sup>12a</sup> However, this reaction system exhibits chemoselectivity for the terminal methyl group due to migration of palladium via its  $\beta$ -hydride elimination and re-addition. Therefore, benzylic functionalization is limited to the reactions using toluene or its analogues such as xylenes and methyl naphthalenes.



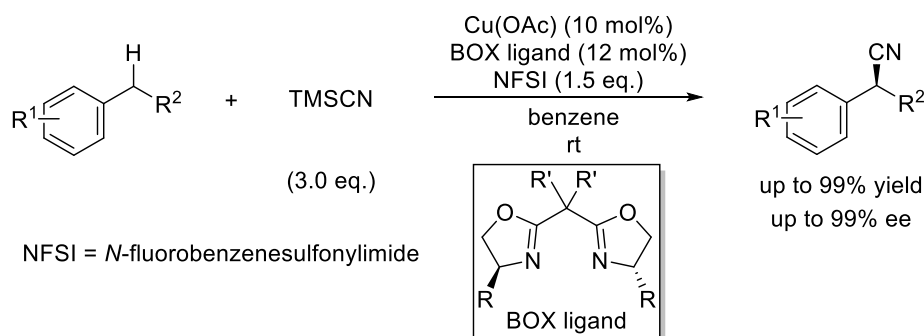
**Figure 2-13.** Palladium-Catalyzed Benzylic C-H Activation

Deprotonation of benzylic hydrogen is also another approach for benzylic C-H functionalization (Figure 2-3 (d)). However, a stoichiometric amount of a strong base or its precursor is generally required for deprotonation of unactivated alkylarenes ( $\text{p}K_{\text{a}} \sim 43$  in DMSO) although palladium-,<sup>13a</sup> nickel-,<sup>13b</sup> cesium-,<sup>13c</sup> or tetramethylammonium fluoride-catalyzed<sup>13d</sup> benzylic C-H functionalization have been developed. Several examples of catalytic use of strong bases also have been reported.<sup>14</sup> However, elevated temperature is necessary. For example, Takemoto and Matsuzaka *et al.* reported ruthenium-catalyzed condensation of alkylarenes with aldehydes based on deprotonation strategy in 2016 (Figure 2-14).<sup>14d</sup> The key to success of these reactions is  $\pi$ -activation of alkylarenes by the catalyst to enhance acidities of their benzylic hydrogens.



**Figure 2-14.** Ruthenium-Catalyzed Condensation of Alkylarenes with Aldehydes

Various methods for catalytic benzylic C–H functionalization toward C–C bond formation have been reported as described above. In this context, several catalytic enantioselective variants have been developed. In 2016, Zhang *et al.* reported enantioselective catalytic cyanation of benzylic C–H bonds (Figure 2-15).<sup>9b</sup> This is the first example of catalytic asymmetric C–C bond forming reactions via benzylic C–H activation. The reactions proceeded in excellent yields with excellent enantioselectivities. However, a stoichiometric amount of the oxidant (NFSI) was needed.

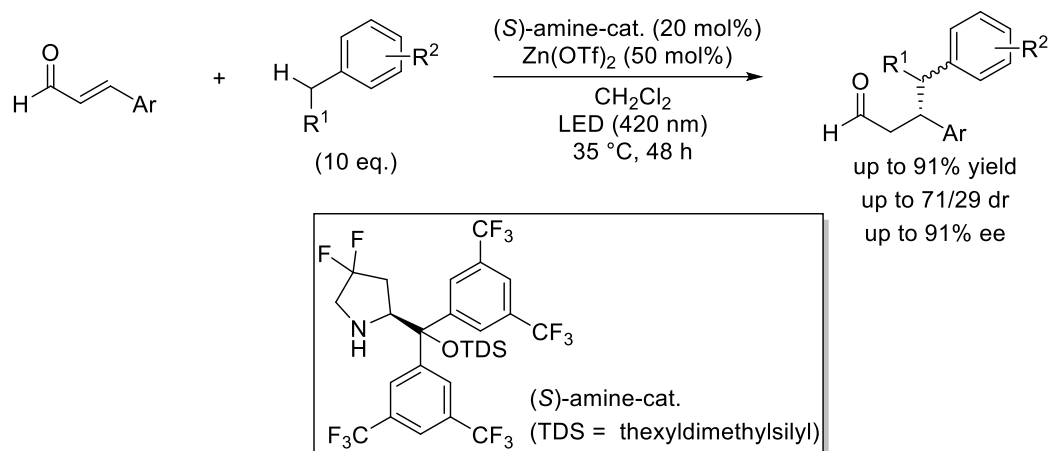


**Figure 2-15.** Enantioselective Catalytic Cyanation of Benzylic C–H Bonds

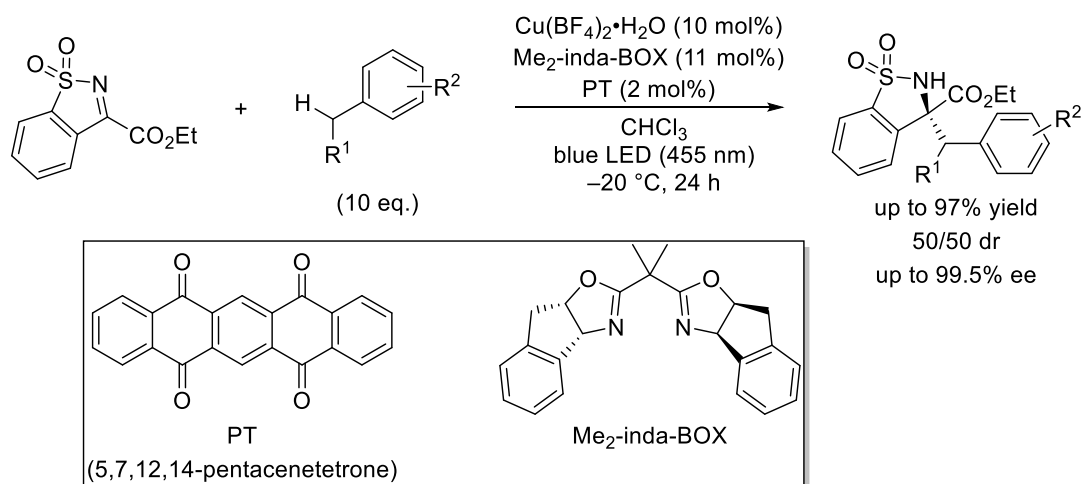
In 2018, Melchiorre's group reported photocatalytic asymmetric 1,4-addition reactions of alkylarenes with  $\alpha,\beta$ -unsaturated aldehydes (Figure 2-16).<sup>11k</sup> The authors assumed benzyl radicals were generated through oxidation of alkylarenes by photo-excited iminium ion intermediates deriving from  $\alpha,\beta$ -unsaturated aldehydes and a chiral secondary amine catalyst. A wide range of alkylarenes were applicable, and the reactions proceeded in excellent yields with high enantioselectivities.

In 2019, Gong's group reported photocatalytic asymmetric addition reactions of alkylarenes with imines (Figure 2-17),<sup>11l</sup> and Jiang's group reported photocatalytic asymmetric addition reactions of alkylarenes with  $\alpha$ -ketoamides (Figure 2-18).<sup>11m</sup> These reactions are atom-economical and proceed in high yields with excellent enantioselectivities. However, specific structures such as benzo[*d*]isothiazole 1,1-dioxides and *N*-tosylated isatins of substrates are needed to achieve the desired reactions.

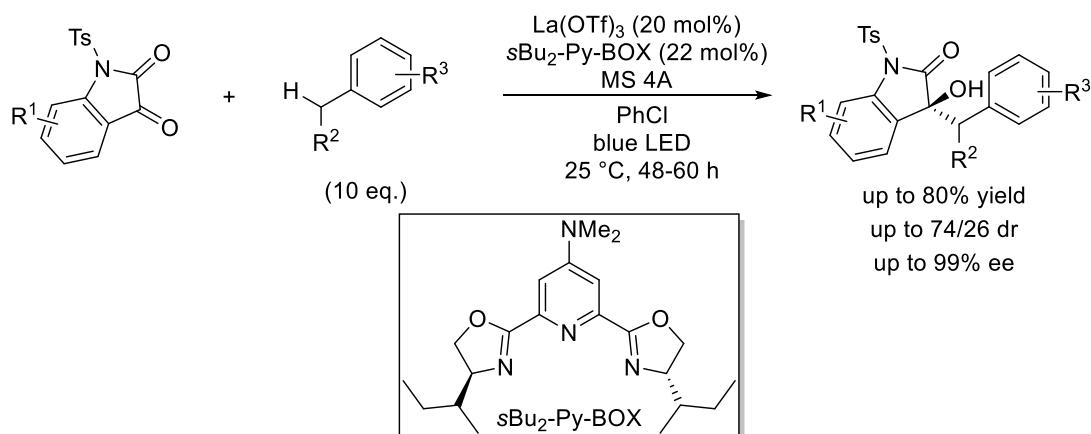




**Figure 2-16.** Photocatalytic Asymmetric 1,4-Addition Reactions of Alkylarenes



**Figure 2-17.** Photocatalytic Asymmetric Addition Reactions of Alkylarenes with Imines

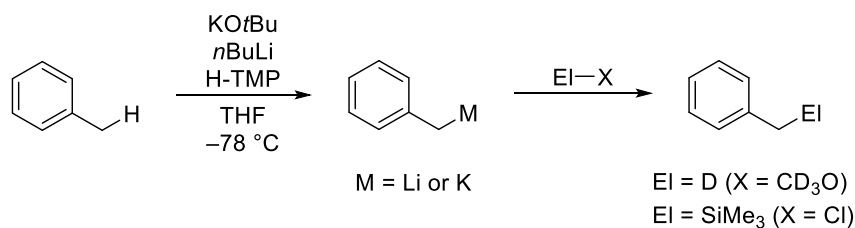


**Figure 2-18.** Asymmetric Addition Reactions of Alkylarenes with α-Ketoamides

Although several catalytic asymmetric C–C bond forming reactions through activation of benzylic C–H bonds have been developed, there is much room to improve and expand applicable substrates. Therefore, they are still challenging. To get a new method enabling them, I focused on strong Brønsted base-catalyzed reactions, which our group has developed (described in section 1-5), because chiral modification of nucleophiles is relatively established.<sup>15</sup> Herein, I describe development of strong Brønsted base-catalyzed asymmetric addition reactions of unactivated alkylarenes in my doctoral thesis studies.

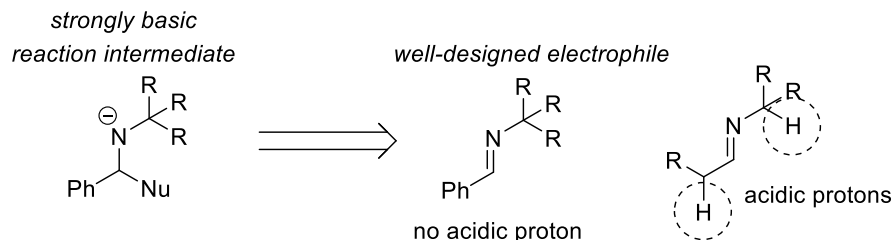
## 2-2. Reaction Design

Benzylic hydrogens of unactivated alkylarenes are inert to common Brønsted bases ( $pK_a \sim 43$  in DMSO), and strong bases are required to deprotonate them. O'Shea *et al.* reported a mixed bases system comprising potassium *tert*-butoxide (KO*t*Bu), *n*-butyl lithium (*n*BuLi), and 2,2,6,6-tetramethylpiperidine (H-TMP) was effective to deprotonate benzylic hydrogens selectively (Figure 2-19).<sup>16</sup>



**Figure 2-19.** Deprotonation of Benzylic Hydrogens

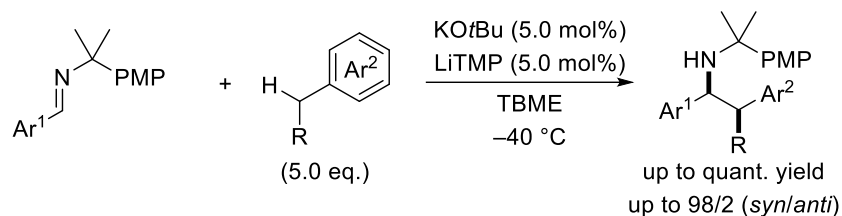
According to this report, it was hypothesized that strong base-catalyzed addition reactions of alkylarenes might be realized if the anionic reaction intermediate is metal secondary alkyl amide (Figure 2-20). They would be generated via addition to *N*-alkyl imines, and acidic protons of the electrophiles were avoided for selective deprotonation.



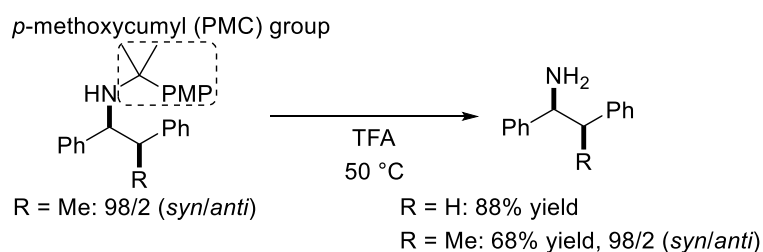
**Figure 2-20.** Reaction Design Toward Base-Catalyzed Reactions of Alkylarenes

Based on this idea, I developed strong Brønsted base-catalyzed addition reactions of unactivated alkylarenes with imines (Figure 2-21), and addition to alkenes also was achieved similarly.<sup>17</sup> Especially, I focused on catalytic stereoselective addition reactions of alkylarenes with imines in my master's thesis studies. In the presence of KO*t*Bu and lithium and 2,2,6,6-tetramethylpiperidine (LiTMP), and the reactions proceeded smoothly in excellent yields with excellent diastereoselectivities. The reaction did not proceed at all when only LiTMP was employed as a base catalyst, which means potassium ion is essential for effective benzylic deprotonation. Removal of *p*-methoxycumyl (PMC) group is possible by acidic treatment with trifluoroacetic acid, and the obtained amine can be transformed into the corresponding free amines (Figure 2-22). This reaction system might be applicable to enantioselective variants because the reactions proceeded even at  $-78\text{ }^\circ\text{C}$ . In this context, I had started preliminary investigation on strong Brønsted base-

catalyzed asymmetric addition reactions of unactivated alkylarenes with imines in my master's thesis studies, and further improvement and mechanistic investigations were achieved in my doctoral thesis studies.



**Figure 2-21.** Strong Base-Catalyzed Addition Reactions of Unactivated Alkylarenes



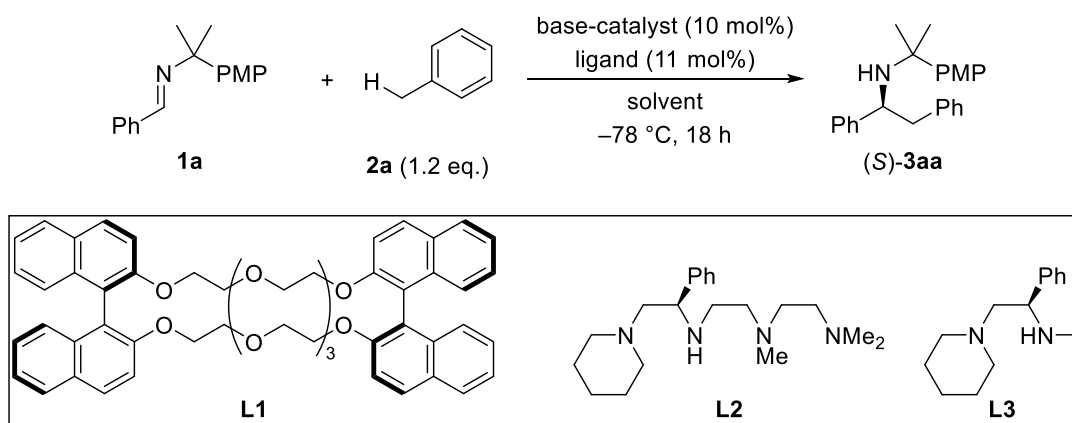
**Figure 2-22.** Removal of *p*-Methoxycumyl Group

## 2-3. Optimization

### Initial Investigation

Initial investigation of chiral ligand was conducted under the previously optimized reaction conditions (Table 2-1).<sup>17a</sup> The chiral macrocyclic ether **L1**, which our group has utilized to chiral modification of potassium ion, was not effective and decomposed during the reaction presumably due to strongly basic reaction conditions (entry 1). In order to overcome this issue, I focused on chiral amine ligands which tolerate basic reaction conditions. They are often used for chiral modification of a lithium ion.<sup>18</sup> When tetradentate ligand **L2** was employed, the desired adduct was obtained in moderate yield with low enantioselectivity (entry 2). The reaction did not proceed at all in toluene, which is convenient to suppress the background reaction affording the racemic product without any chiral ligands (entry 3). **L2** and **L3** were tested in the presence of an alkyl potassium base (KCH<sub>2</sub>SiMe<sub>3</sub>), and **L3** slightly improved the enantioselectivity (entries 4, 5). The alkyl potassium base of which the conjugate acid is non-coordinative tetramethylsilane was employed to simplify the catalyst system by removing lithium ion.

**Table 2-1.** Initial Investigation



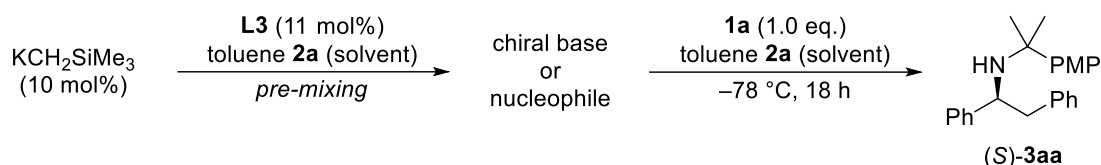
entry	base-catalyst	ligand	solvent	yield (%)	ee (%)
1	KOtBu-LiTMP <sup>a</sup>	<b>L1</b> <sup>b</sup>	TBME	43	0
2	KOtBu-LiTMP <sup>a</sup>	<b>L2</b>	TBME	46	12 <sup>c</sup>
3	KOtBu-LiTMP <sup>a</sup>	none	toluene	trace <sup>d</sup>	—
4	KCH <sub>2</sub> SiMe <sub>3</sub>	<b>L2</b>	toluene <sup>e</sup>	85	11 <sup>c</sup>
5	KCH <sub>2</sub> SiMe <sub>3</sub>	<b>L3</b>	toluene <sup>e</sup>	25	21

Reaction conditions (unless otherwise noted): **1a** (0.50 mmol), **2a** (0.60 mmol), base catalyst (0.050 mmol), ligand (0.055 mmol), solvent (1.0 mL), -78 °C, 18 h. The shown yields were determined based on the isolated product. <sup>a</sup>KOtBu (0.050 mmol) and LiTMP (0.050 mmol) were employed as base catalysts. <sup>b</sup>**L1** decomposed during the reaction. <sup>c</sup>(*R*)-**3aa** was obtained as a major enantiomer. <sup>d</sup>A trace amount of the desired product **3aa** was detected by NMR analysis of the crude sample. <sup>e</sup>Toluene **2a** (1.0 mL) was employed as a solvent.

Pre-mixing of catalysts which is termed catalyst preparation sometimes affect results

of the asymmetric reactions dramatically. Here, temperature (entries 1-4) and time (entries 5,6) of catalyst preparation were optimized (Table 2-2). It was found that the preparation at  $-40\text{ }^{\circ}\text{C}$  for 30 min gave the best result, and the enantiomeric excess was improved up to 56% (entry 5). After catalyst preparation was optimized, further investigation was carried out with the optimal catalyst preparation.

**Table 2-2.** Optimization of Catalyst Preparation



entry	conditions of pre-mixing	yield (%)	ee (%)
— <sup>a</sup>	$-78\text{ }^{\circ}\text{C}$ , 30 min	25	21
2	$-60\text{ }^{\circ}\text{C}$ , 60 min	80	41
3	$-40\text{ }^{\circ}\text{C}$ , 60 min	88	50
4	$-20\text{ }^{\circ}\text{C}$ , 60 min	11	7
5	$-40\text{ }^{\circ}\text{C}$ , 30 min	86	56
6	$-40\text{ }^{\circ}\text{C}$ , 15 min	46	18

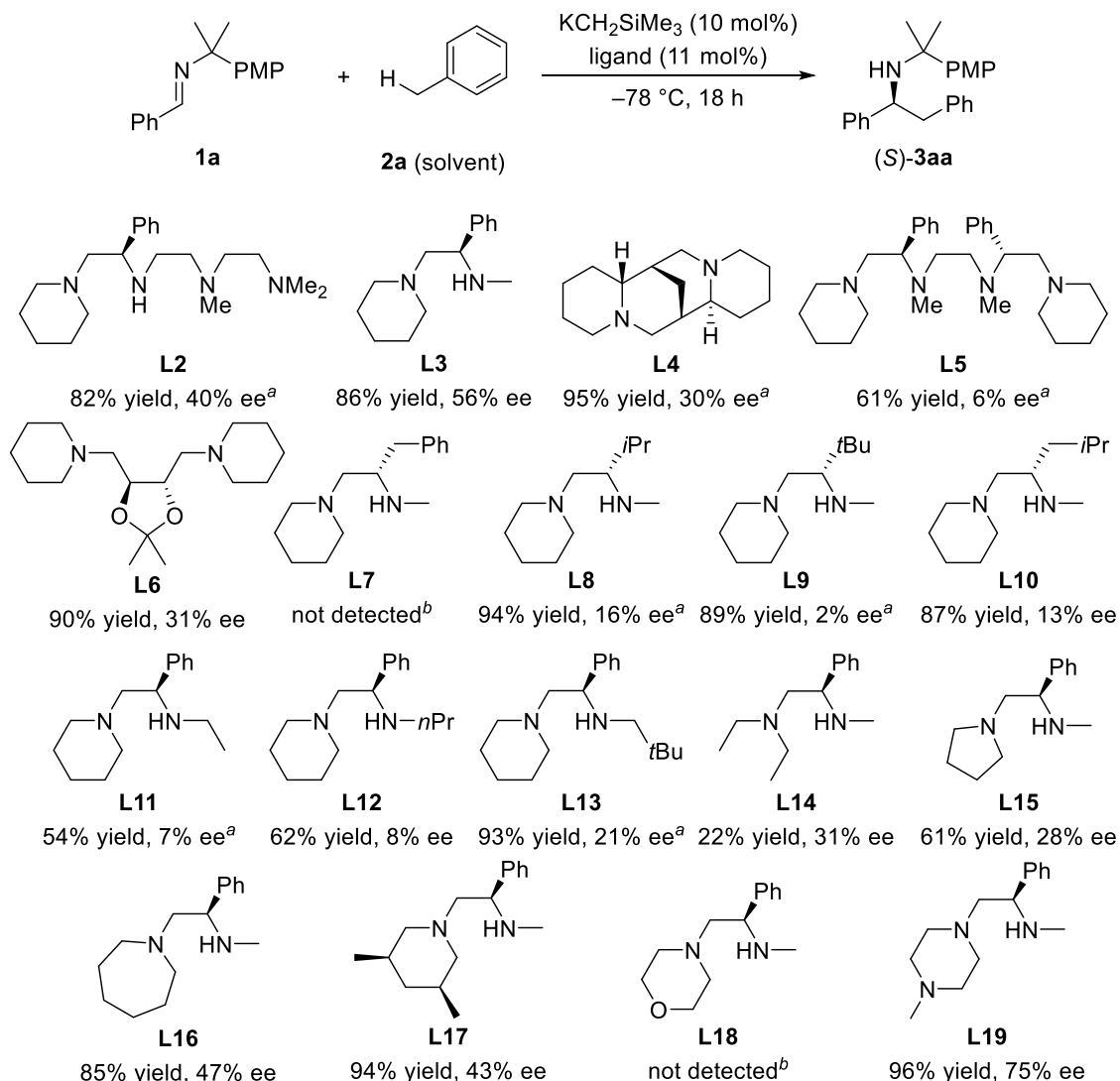
Reaction conditions: **1a** (0.50 mmol), **2a** (1.0 mL),  $\text{KCH}_2\text{SiMe}_3$  (0.050 mmol), **L3** (0.055 mmol),  $-78\text{ }^{\circ}\text{C}$ , 18 h. The shown yields were determined based on the isolated product. <sup>a</sup>The same result as entry 5 in Table 2-1.

### Ligand Screening

The structure of the chiral amine ligands was then investigated. Tetraamine ligand **L2** was tested again with the optimal catalyst preparation, and the enantioselectivity was improved compared with entry 4 in Table 2-1 but less than **L1**. Although several varieties of  $C_2$ -symmetric chiral amine ligands were examined, the enantioselectivity was not improved (**L4-L6**). Then, we investigated effect of chiral diamine ligands related to **L3** because it showed the most promising enantioselectivity. Firstly, diamines deriving from other chiral amino acids were examined (**L7-L10**); however, the selectivity was not improved. Next, the alkyl substituents on the secondary amine moiety were tested, and it was found that longer alkyl groups were not effective (**L11-L13**). Subsequently, the tertiary amine moiety was modified. However, noncyclic (**L14**), other ring sizes (**L15**, **L16**), or bulkier substituent (**L17**) was investigated; however, further improvement of the enantioselectivity was not observed. Although oxygen atom was introduced at the 4-position of the piperidine ring, the reaction did not proceed at all (**L18**). On the other hand, chiral amine ligand **L19**, bearing a 4-methylpiperazine component, afforded the desired adduct in excellent yield with good enantioselectivity (75% ee). Successful chiral modification of a potassium cation using a chiral multidentate amine ligand is rare. Early examples of chiral modification of potassium ion and its application for asymmetric

catalysis are mainly limited to clathrate compounds such as chiral macrocyclic ethers because of large ionic radius and low Lewis acidity of potassium ion.<sup>19</sup> Therefore, this is a pioneering method to utilize chiral amine ligands for modification of potassium ion.

**Table 2-3. Optimization of Chiral Amine Ligands**



Reaction conditions: **1a** (0.50 mmol), **2a** (1.0 mL),  $\text{KCH}_2\text{SiMe}_3$  (0.050 mmol), chiral ligand **L** (0.055 mmol),  $-78^\circ\text{C}$ , 18 h. The shown yields were determined based on the isolated product. <sup>a</sup>(R)-**3aa** was obtained as a major enantiomer. <sup>b</sup>The desired product was not detected by NMR analysis of the crude sample.

Simultaneously, effect of base catalysts also was investigated in the presence of **L3** (Table 2-4). When 11 mol% of **L3** was used for the mixed base system of  $\text{KO}t\text{Bu}$  (10 mol%) and  $\text{LiTMP}$  (10 mol%), the reaction did not proceed at all (entry 1). However, 22 mol% of **L3** afforded the desired adduct **3aa** in excellent yield with significantly low enantioselectivity (entry 2). These results imply that the ligand **L3** coordinate to lithium ion more strongly rather than potassium ion to afford the ligand-free benzyl potassium, which does not react with the imine. It is noted that the mixed base system exhibits the

different enantioselectivity from  $\text{KCH}_2\text{SiMe}_3$  (entry 5 in Table 2-2 vs. entry 2 in Table 2-4). Based on these results, I hypothesized that addition of another basic salt as an additive had a potential to change the asymmetric environment and the enantioselectivity.

**Table 2-4.** Investigation of Base Catalysts

<b>1a</b>	<b>2a (solvent)</b>			<b>(S)-3aa</b>
entry	base catalyst	x (mol%)	yield (%)	ee (%)
— <sup>a</sup>	$\text{KCH}_2\text{SiMe}_3$	11	86	56
1	$\text{KO}^t\text{Bu-LiTMP}^b$	11	trace <sup>c</sup>	—
2	$\text{KO}^t\text{Bu-LiTMP}^b$	22	92	36

Reaction conditions (unless otherwise noted): **1a** (0.50 mmol), **2a** (1.0 mL), base catalyst (0.050 mmol), **L3** (0.055 mmol),  $-78\text{ }^\circ\text{C}$ , 18 h. The shown yields were determined based on the isolated product. <sup>a</sup>The same result as entry 5 in Table 2-2. <sup>b</sup> $\text{KO}^t\text{Bu}$  (0.050 mmol) and  $\text{LiTMP}$  (0.050 mmol) were employed as base catalysts. <sup>c</sup>The trace amount of the desired product **3aa** was detected by NMR analysis of the crude sample.

### Effect of Additives

For further improvement of the enantioselectivity, various additives were examined in the presence of **L19** (Table 2-5). Firstly,  $\text{LiO}^t\text{Bu}$  and  $\text{KO}^t\text{Bu}$  were tested; however, the reactions did not proceed at all in both cases (entries 1, 2). Secondly,  $\text{LiTMP}$  and  $\text{KTMP}$  were found to be not effective to improve the enantioselectivity although the reactions proceeded in excellent yields (entries 3, 4). Thirdly, various metal hexamethyldisilazides ( $\text{LiHMDS}$ ,  $\text{NaHMDS}$ ,  $\text{KHMDS}$ ,  $\text{CsHMDS}$ ) were evaluated, and the reactions did not proceed in the presence of lithium hexamethyldisilazide ( $\text{LiHMDS}$ ) and sodium hexamethyldisilazide ( $\text{NaHMDS}$ ) (entries 5, 6). On the other hand,  $\text{KHMDS}$  afforded the desired product **3aa** in excellent yield in good enantioselectivity (entry 7). In the presence of cesium hexamethyldisilazide ( $\text{CsHMDS}$ ), the reaction proceeded in low yield but the enantioselectivity decreased, which indicates the background reaction was presumably major (entry 8). Next, investigation of the structure of the alkyl substituents on the potassium disilylamide revealed that bulkier substituents decreased the reactivity significantly (entries 9, 10). Furthermore, potassium monosilylamide was tested; however, the additive was not effective (entry 11). It was attractive and interesting that  $\text{KHMDS}$  is a significantly effective additive to improve the enantioselectivity because the additive accelerated the background reaction (entry 12). This result implies that  $\text{KHMDS}$  might affect an aggregation structure of the active benzyl potassium species. Although the actual role of  $\text{KHMDS}$  in the system remains unclear, it is assumed that  $\text{KHMDS}$  changes the asymmetric environment around the benzyl potassium species.<sup>13b,13c, 20</sup> Subsequently, the ratio of the base catalyst, the additive, and the ligand was investigated.



When 5 or 20 mol% of KHMDS was employed with 10 mol% of  $\text{KCH}_2\text{SiMe}_3$  and 11 mol% of **L19**, the enantioselectivity decreased slightly (entries 13, 14). When 22 mol% of **L19** was employed with 10 mol% of  $\text{KCH}_2\text{SiMe}_3$  and KHMDS for the chiral modification of all the potassium ions, no improvement was observed (entry 15). Finally, the catalyst loading was decreased and it was found that the desired adduct was obtained in excellent yield with high enantioselectivity in the presence of 7.5 mol% of  $\text{KCH}_2\text{SiMe}_3$  and KHMDS, and 8.3 mol% of **L19** (entry 16)

**Table 2-5.** Investigation of Additives

Reaction scheme: **1a** + **2a** (solvent)  $\xrightarrow[\text{-78 } ^\circ\text{C, 18 h}]{\text{KCH}_2\text{SiMe}_3 \text{ (x mol\%)}, \text{additive (y mol\%)}, \text{L19 (z mol\%)}}$  **(S)-3aa**

entry	additive	x	y	z	yield (%)	ee (%)
— <sup>a</sup>	none	10	—	11	86	56
1	LiOtBu	10	10	11	trace <sup>b</sup>	—
2	KOtBu	10	10	11	trace <sup>b</sup>	—
3	LiTMP	10	10	11	95	63
4	KTMP	10	10	11	91	70
5	LiHMDS	10	10	11	nd <sup>c</sup>	—
6	NaHMDS	10	10	11	trace <sup>b</sup>	—
7	KHMDS	10	10	11	96	87
8	CsHMDS	10	10	11	33	9
9	KN(TMS)(TBS)	10	10	11	79	86
10	KN(TBS) <sub>2</sub>	10	10	11	25	67
11	KNMe(TBS)	10	10	11	61	59
12	KHMDS	10	10	0	36	—
13	KHMDS	10	5.0	11	92	86
14	KHMDS	10	20	11	92	85
15	KHMDS	10	10	22	94	84
16 <sup>d</sup>	KHMDS	7.5	7.5	8.3	93	87

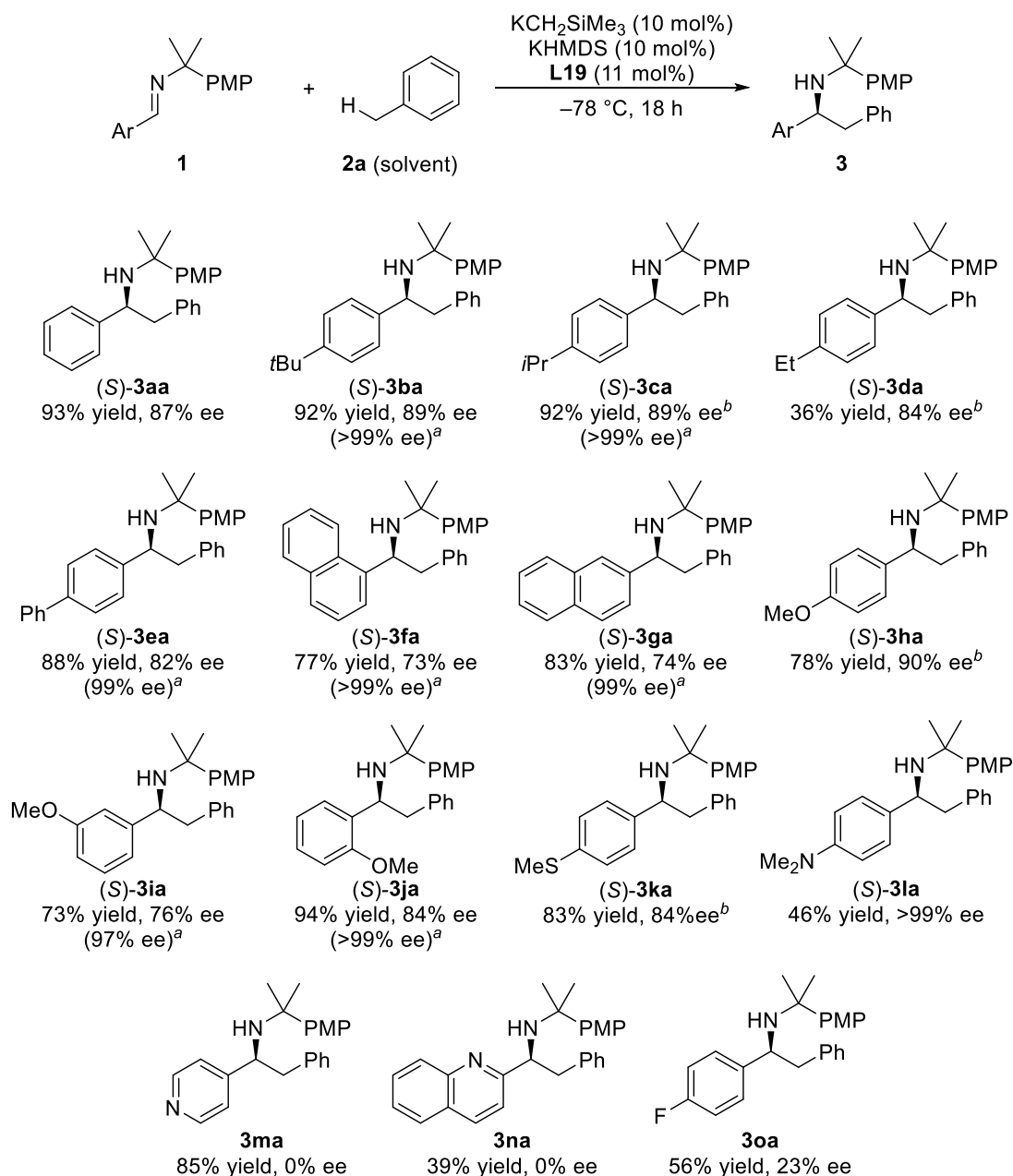
Reaction conditions (unless otherwise noted): **1a** (0.50 mmol), **2a** (1.0 mL),  $\text{KCH}_2\text{SiMe}_3$  (0.050 mmol), additive (0.050 mmol), **L19** (0.055 mmol),  $-78\text{ }^\circ\text{C}$ , 18 h. The shown yields were determined based on the isolated product. <sup>a</sup>The same result as entry 5 in Table 2-2. <sup>b</sup>The trace amount of the desired product **3aa** was detected by NMR analysis of the crude sample. <sup>c</sup>The desired product was not detected by NMR analysis of the crude sample. <sup>d</sup>The reaction was carried out in double scale: **1a** (1.0 mmol), **2a** (2.0 mL),  $\text{KCH}_2\text{SiMe}_3$  (0.075 mmol), KHMDS (0.075 mmol), and **L19** (0.083 mmol) were employed.

## 2-4. Substrate Scope

### Generality of Imines

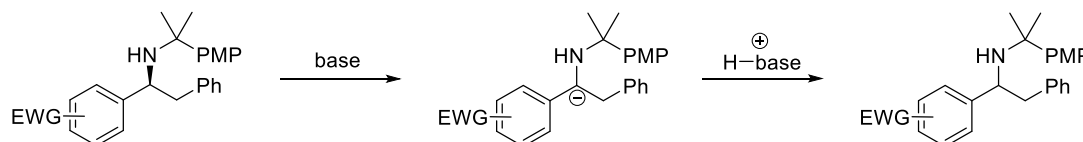
The scope of the reaction with respect to imines was examined under the optimized reaction conditions (Table 2-6).

**Table 2-6.** Scope of Imines



Reaction conditions: **1** (1.0 mmol), **2a** (2.0 mL), KCH<sub>2</sub>SiMe<sub>3</sub> (0.075 mmol), KHMDS (0.075 mmol), and **L19** (0.083 mmol), -78 °C, 18 h. The shown yields were determined based on the isolated product. <sup>a</sup>After recrystallization. <sup>b</sup>The enantiomeric excess was determined after transformation into the corresponding free amine.

As described in the optimization part, imine **1aa** afforded the desired product **3aa** in excellent yield with high enantioselectivity. When imines bearing tertiary or secondary alkyl substituents at the *para*-positions of their benzene rings were employed, the desired adducts **3ba** and **3ca** were obtained in excellent yields with high enantioselectivities. Although an imine substituted with an ethyl group exhibited high enantioselectivity, the yield was moderate because this substrate has another reactive benzylic hydrogen atom, of which acidity is enhanced by the imino group on the aromatic ring (**3da**). Additionally, an imine bearing a biphenyl moiety afforded the desired adduct **3ea** in good yields with good enantioselectivities. Imines having 1- or 2-naphthyl group were applicable, and the reactions proceeded in good yields with good enantioselectivities (**3ea**, **3fa**). When imines bearing a methoxy group on their benzene ring afforded the desired adducts **3ga-3ia** in good yields with good to high enantioselectivities. It was also possible to employ imines substituted with a methylthio or dimethylamino group (**3ka**, **3la**). Various imines are applicable to the reaction system, and the enantio-enriched products were obtained. Furthermore, it is noted that the enantiopurities could be enhanced by recrystallization in several cases. On the other hand, imines having an electro deficient aromatic ring were not promising. Although the desired products **3ma-3oa** were obtained in moderate to high yields, the enantioselectivities were quite low. These were presumably caused by racemization of the desired products (Figure 2-23). Regarding **3ma** and **3na**, pyridine might coordinate to benzyl potassium to deaggregate the chiral complex.



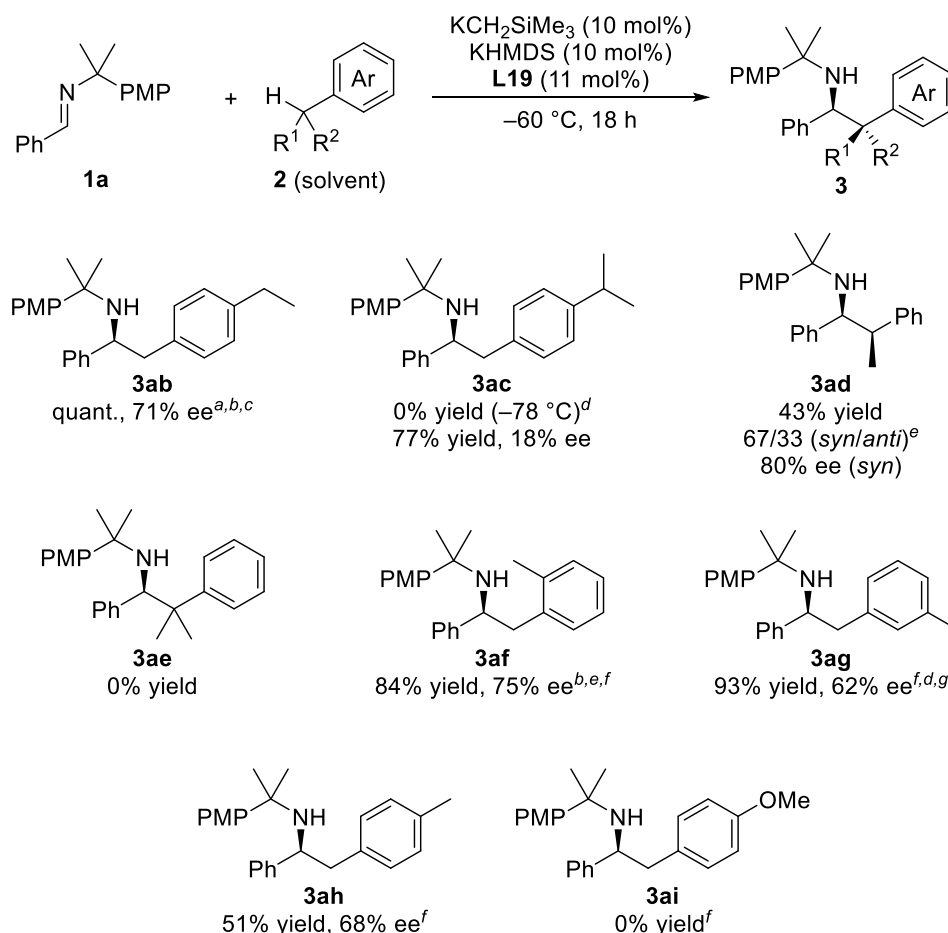
**Figure 2-23.** Hypothesis for Loss of Enantiomeric Excess

### Generality of Alkylarenes

Next, other alkylarenes were employed to examine the scope of the reaction with respect to alkylarenes (Table 2-7). The reaction using 4-ethyltoluene proceeded in quantitative yield with excellent regioselectivity and moderate enantioselectivity (**3ab**). However, *p*-cymene did not react with the imine at  $-78\text{ }^{\circ}\text{C}$  (**3ac**). The reaction was carried out at  $-60\text{ }^{\circ}\text{C}$  to enhance its reactivity, and the desired product was obtained in good yield but the enantioselectivity was quite low. Ethylbenzene afforded the desired product **3ad** with good enantioselectivity, although the yield and the diastereoselectivity were moderate. Unfortunately, cumene, which has a potential to form tertiary benzylic carbanion, did not react with the imine even at  $-60\text{ }^{\circ}\text{C}$  because of its low reactivity (low acidity or nucleophilicity) (**3ae**). On the other hand, I hypothesized that cumene could be employed as a solvent in those reactions, because its freezing point is less than  $-78\text{ }^{\circ}\text{C}$  ( $-96\text{ }^{\circ}\text{C}$ ). This might solve a problem that various alkylarenes froze at low temperature. Based on this idea, it was tried to use xylenes in cumene solvent. In the cases of *ortho*-

and *para*-xylenes, the reactions proceeded in moderate to good yields with moderate enantioselectivities (**3af**, **3ah**). Furthermore, *meta*-xylene afforded the desired adduct **3ag** in excellent yield with moderate enantioselectivity. In this context, 4-methoxytoluene was tested but the reaction did not proceed even at  $-60\text{ }^{\circ}\text{C}$  (**3ah**).

**Table 2-7.** Scope of Alkylarenes



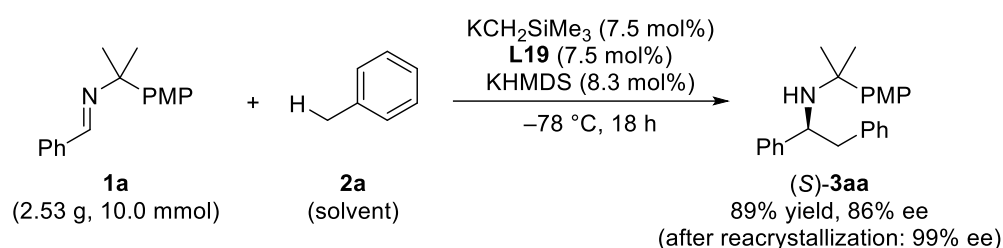
Reaction conditions (unless otherwise noted): **1a** (0.50 mmol), **2a** (1.0 mL),  $\text{KCH}_2\text{SiMe}_3$  (0.050 mmol), KHMDS (0.050 mmol), **L19** (0.055 mmol),  $-60\text{ }^{\circ}\text{C}$ , 18 h. The shown yields were determined based on the isolated product. <sup>a</sup>The enantiomeric excess was determined after transformation into the corresponding free amine. <sup>b</sup>The reaction was conducted at  $-70\text{ }^{\circ}\text{C}$ . <sup>c</sup>The reaction was carried out for 65 h. <sup>d</sup>The reaction was conducted at  $-78\text{ }^{\circ}\text{C}$ . <sup>e</sup>The relative configuration of the product shown in the table is defined as *syn*. <sup>f</sup>Reaction conditions: **1a** (0.50 mmol), **2** (2.5 mmol),  $\text{KCH}_2\text{SiMe}_3$  (0.10 mmol), KHMDS (0.10 mmol), **L19** (0.11 mmol), cumene (1.0 mL). <sup>g</sup>The reaction was carried out for 60 h.

## 2-5. Synthetic Utility

### Synthetic Application

To demonstrate the synthetic utility of the reactions, advanced methods and transformation of the obtained product were investigated. When 2.53 gram of the imine **1a** was employed, the desired adduct was obtained without any significant decrease in either yield or enantioselectivity (Figure 2-24 (a)). For easier preparation of imines, the enantioselective reaction using the imine **1a** prepared *in situ* was conducted. (Figure 2-24 (b)). The desired reaction proceeded in good yield with slightly lower but promising enantioselectivity.

(a) gram-scale reaction



(b) *in situ* preparation of the imine

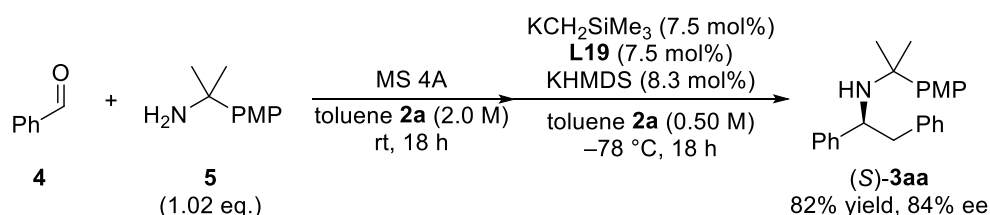


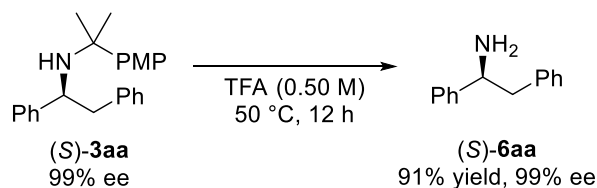
Figure 2-24. Synthetic Application

### Transformation of the Obtained Product

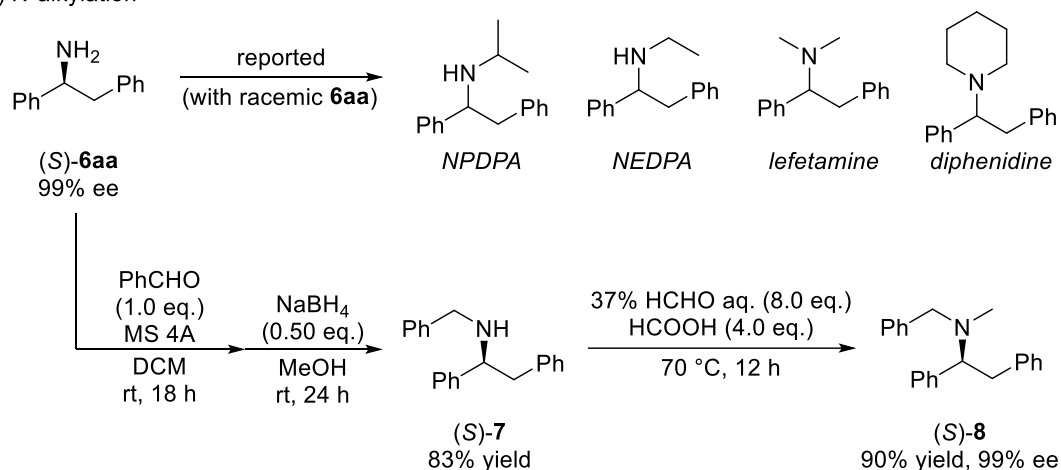
1,2-Diarylethan-1-amine frameworks are sometimes included in natural products and pharmaceuticals. Therefore, transformation of the obtained products into such useful compounds are valuable. Removal of PMC group from (S)-**3aa** was achieved through acidic treatment to afford the corresponding free amine (S)-**6aa** without loss of optical purity (Figure 2-25 (a)). It is reported that the obtained free amine **6aa** can be further transformed into various pharmaceuticals, such as lefetamine and diphenidine, via *N*-alkylation.<sup>13b</sup> Thus, it was tested if the enantiopurity was retained during common *N*-alkylation reactions, and subsequent benzylation and methylation reactions proceeded smoothly without loss of optical purity (Figure 2-25 (b)). Furthermore, the free amine (S)-**6aa** was derivatized into optically active 4-phenyl-1,2,3,4-tetrahydroisoquinoline (S)-**9** thorough Pictet-Spengler reaction (Figure 2-25 (c)). Although the corresponding transformation via *N*-formylation strategy had already been reported, I achieved the direct transformation in similar yield without decrease of the enantiopurity.<sup>21</sup> Therefore, the

base-catalyzed asymmetric reactions and the transformation can be a simple synthetic route to access 1,2,3,4-tetrahydroisoquinoline frameworks bearing a chiral center at the 3-position, which is an important moiety contained in natural products such as bharatamine. To the best of my knowledge, early examples of asymmetric synthesis of **9** include only hydrogenation of isoquinolines, in which high pressure (40 atm) of hydrogen gas is required.<sup>22</sup>

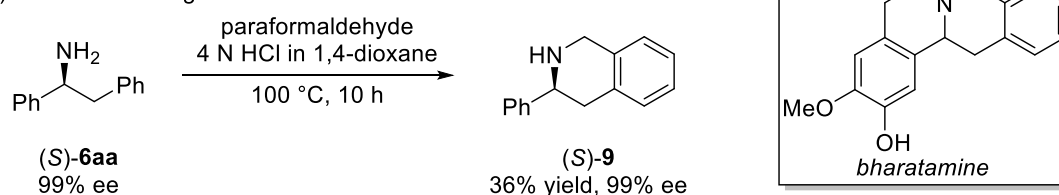
(a) removal of PMC group



(b) *N*-alkylation



(c) 6-membered ring formation



**Figure 2-25.** Transformation of the Obtained Product

## 2-6. Mechanistic Studies

### Investigation of Backward Reaction

To gain insight into the reaction mechanism, several investigations were conducted. It was examined if the backward reaction proceeded (Figure 2-26). When the product (*S*)-**3aa** with 99% ee was treated by the chiral base catalyst system, the product was recovered in high yield with the same enantiomeric excess. If the backward reaction proceeded, the enantiomeric excess would converge to 87% ee. Therefore, this result indicates that the backward reaction in the process under the reaction conditions could be ignored, which mean that the addition step is irreversible.

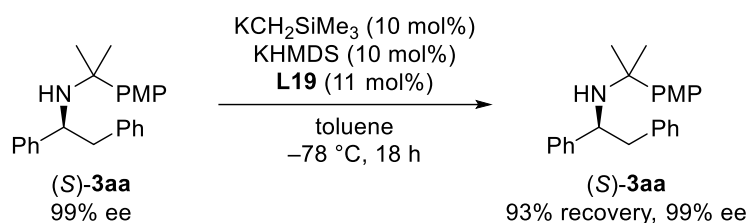
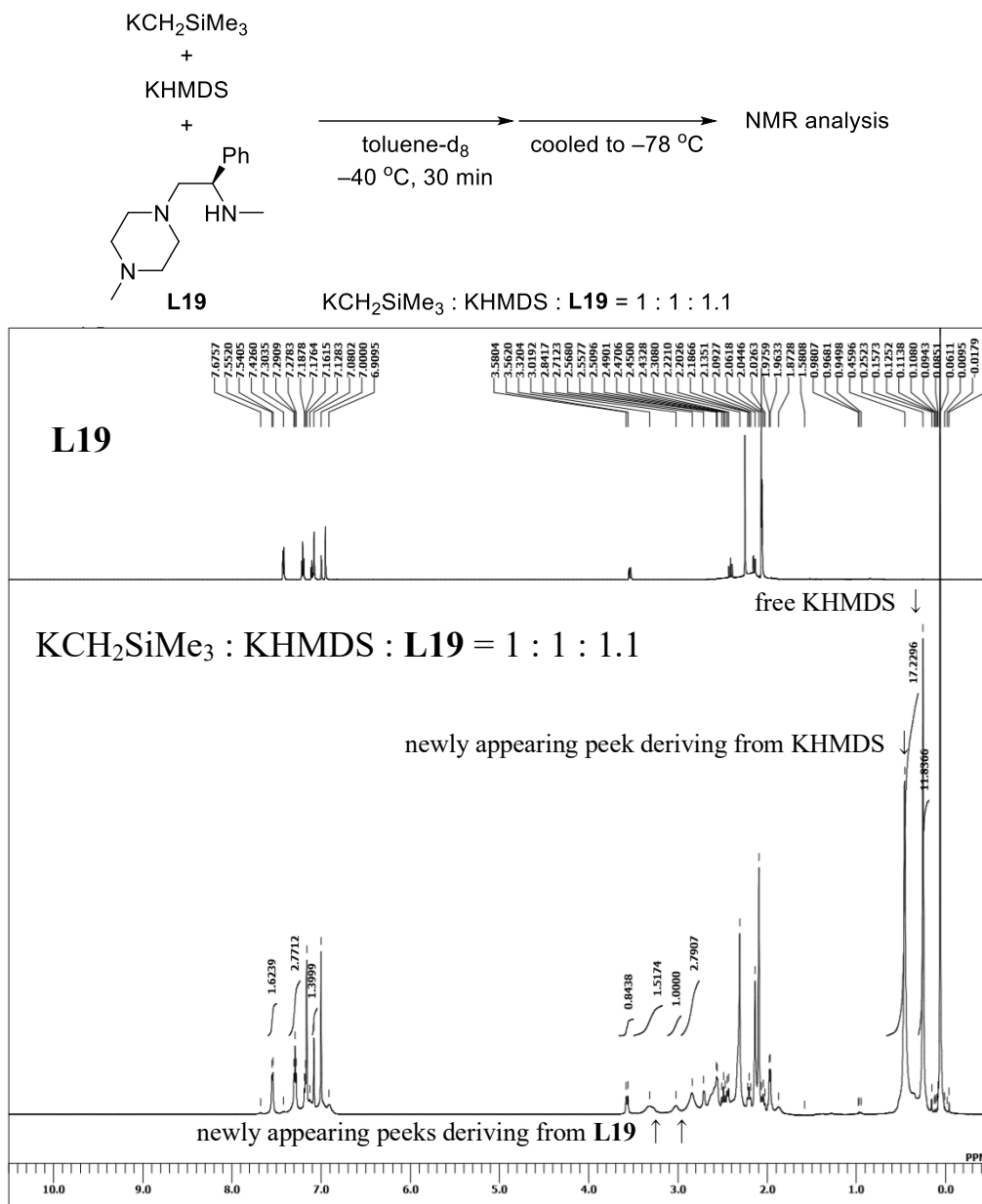


Figure 2-26. Investigation of the Backward Reaction

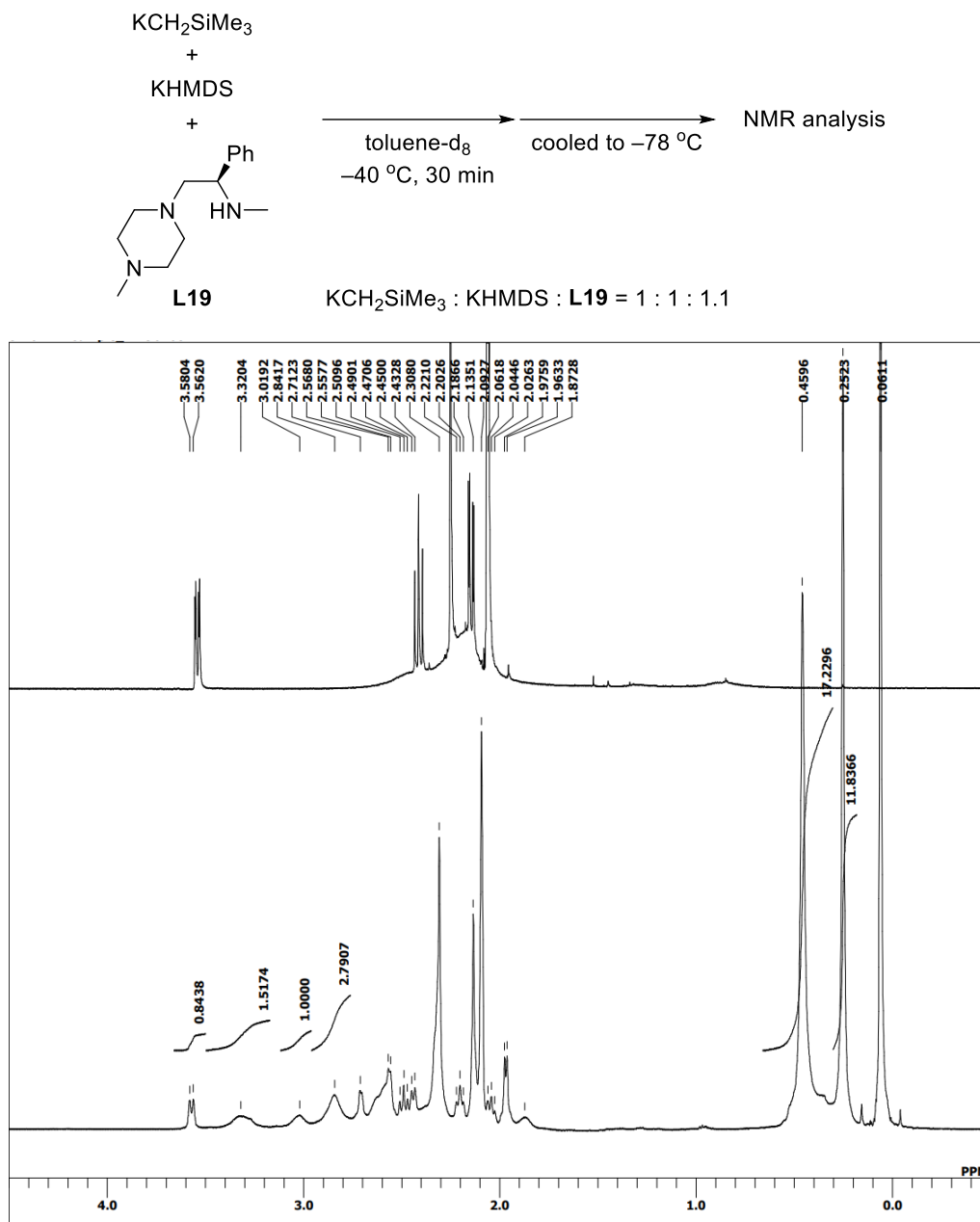
### NMR Experiments

NMR analysis of the catalyst system were conducted to assume the structure of the chiral base catalyst complex. Firstly, KCH<sub>2</sub>SiMe<sub>3</sub>, KHMDS, and **L19** were mixed in 1:1:1.1 ratio in toluene-*d*<sub>8</sub>, and NMR analysis was conducted at -78 °C (Figure 2-27, Figure 2-28). A new set of peaks deriving from **L19**, free KHMDS, and other new KHMDS species were observed on the spectrum. The ratio of the new KHMDS species (Me<sub>3</sub>Si protons, 18 H), which might be included in the catalyst complex, and a newly appearing species derived from **L19** looks almost 1:1. This result might support that the catalyst complex is composed of benzyl potassium, **L6** and KHMDS in 1:1:1 ratio. The complex prepared from **L3** was also analyzed because the spectrum of the mixture including **L19** was a little messy (Figure 2-29, Figure 2-30). KCH<sub>2</sub>SiMe<sub>3</sub>, KHMDS, and **L1** were mixed in 1:1:1.1 ratio in toluene-*d*<sub>8</sub>, and NMR analysis was conducted at -78 °C. The ratio of the new KHMDS species (Me<sub>3</sub>Si protons, 2 peaks) and a newly appeared peak derived from **L3** was almost 1:1. Furthermore, almost the same spectrum was observed when KCH<sub>2</sub>SiMe<sub>3</sub>, KHMDS, and **L3** were mixed in 2:1:2.2 ratio in toluene-*d*<sub>8</sub> (Figure 2-31, Figure 2-32). These results might support that the active complex is composed of benzyl potassium, **L3** and KHMDS in 1:1:1. However, the newly appearing species was minor, and the free ligand and KHMDS were left as major species.

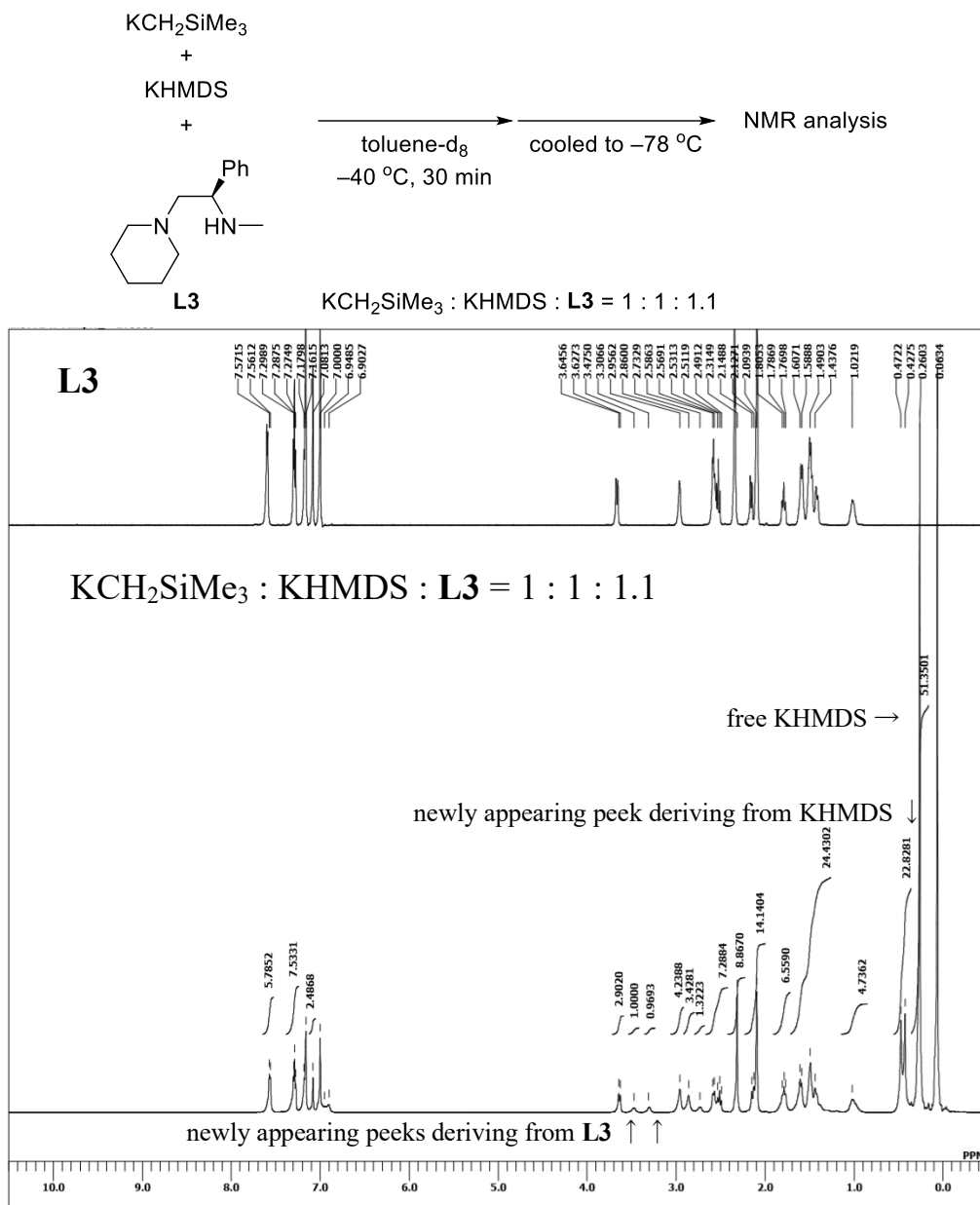


**Figure 2-27.** NMR Analysis of Catalyst Mixture Deriving from **L19**

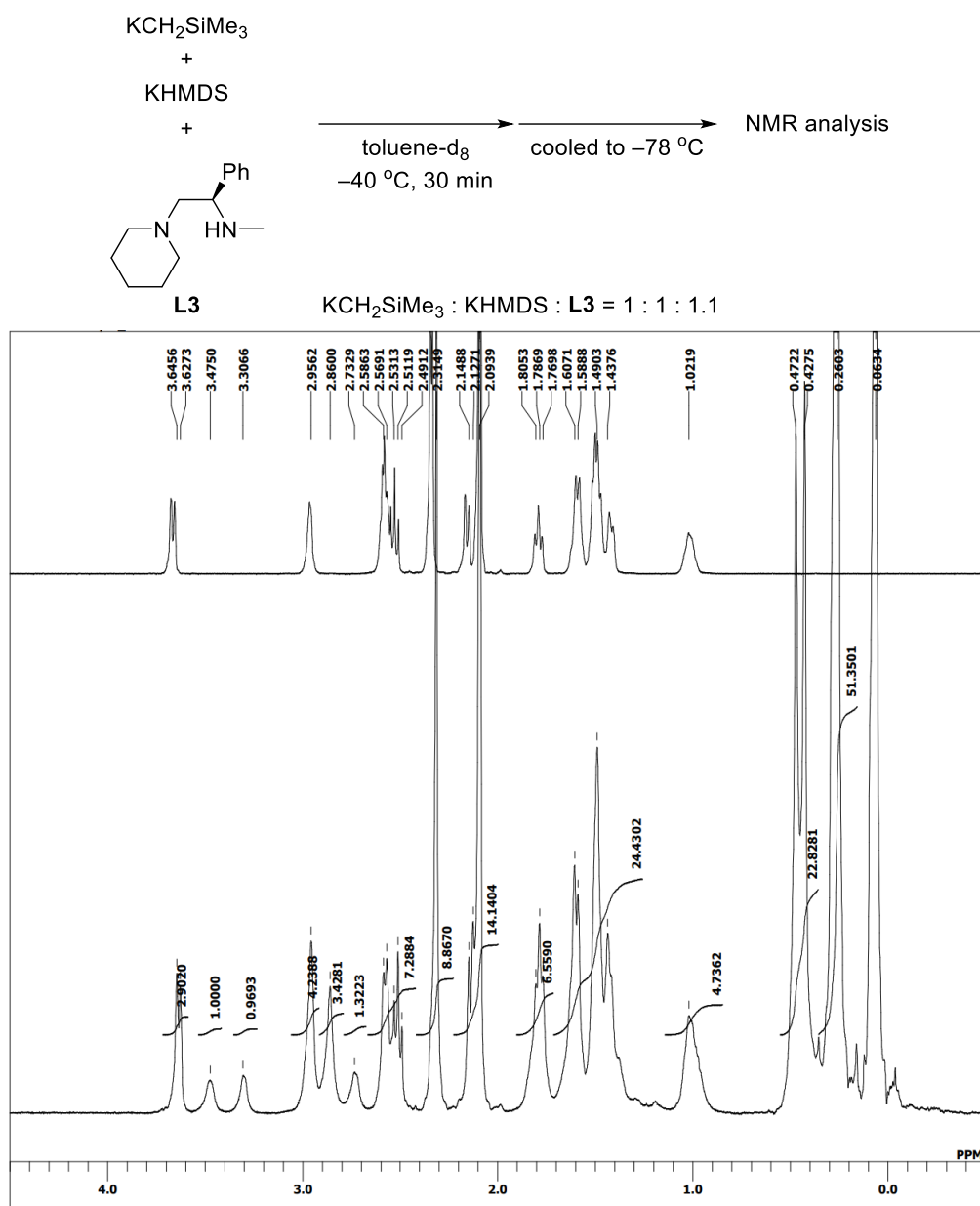




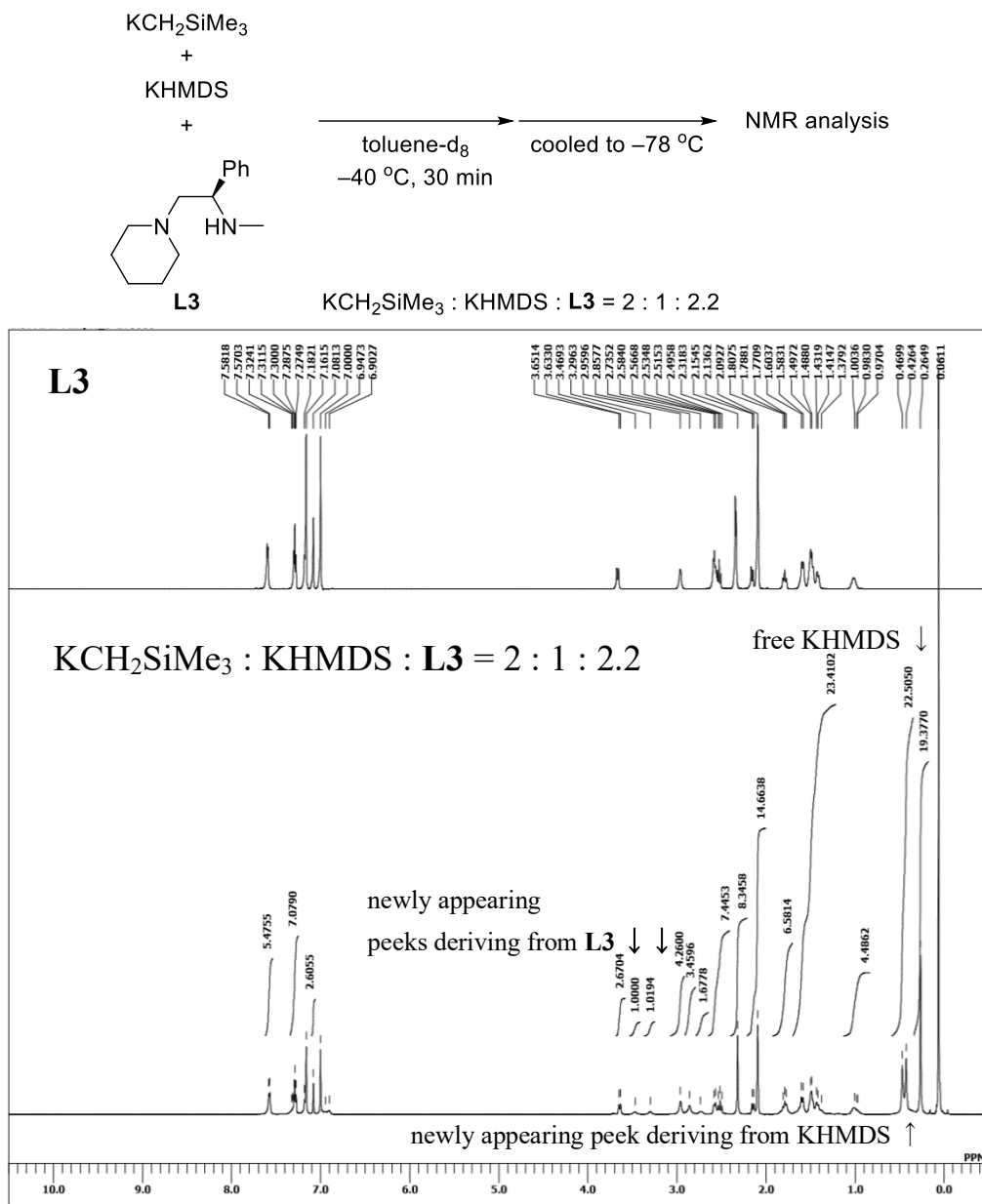
**Figure 2-28.** NMR Analysis of Catalyst Mixture Deriving from **L19** (expanded)



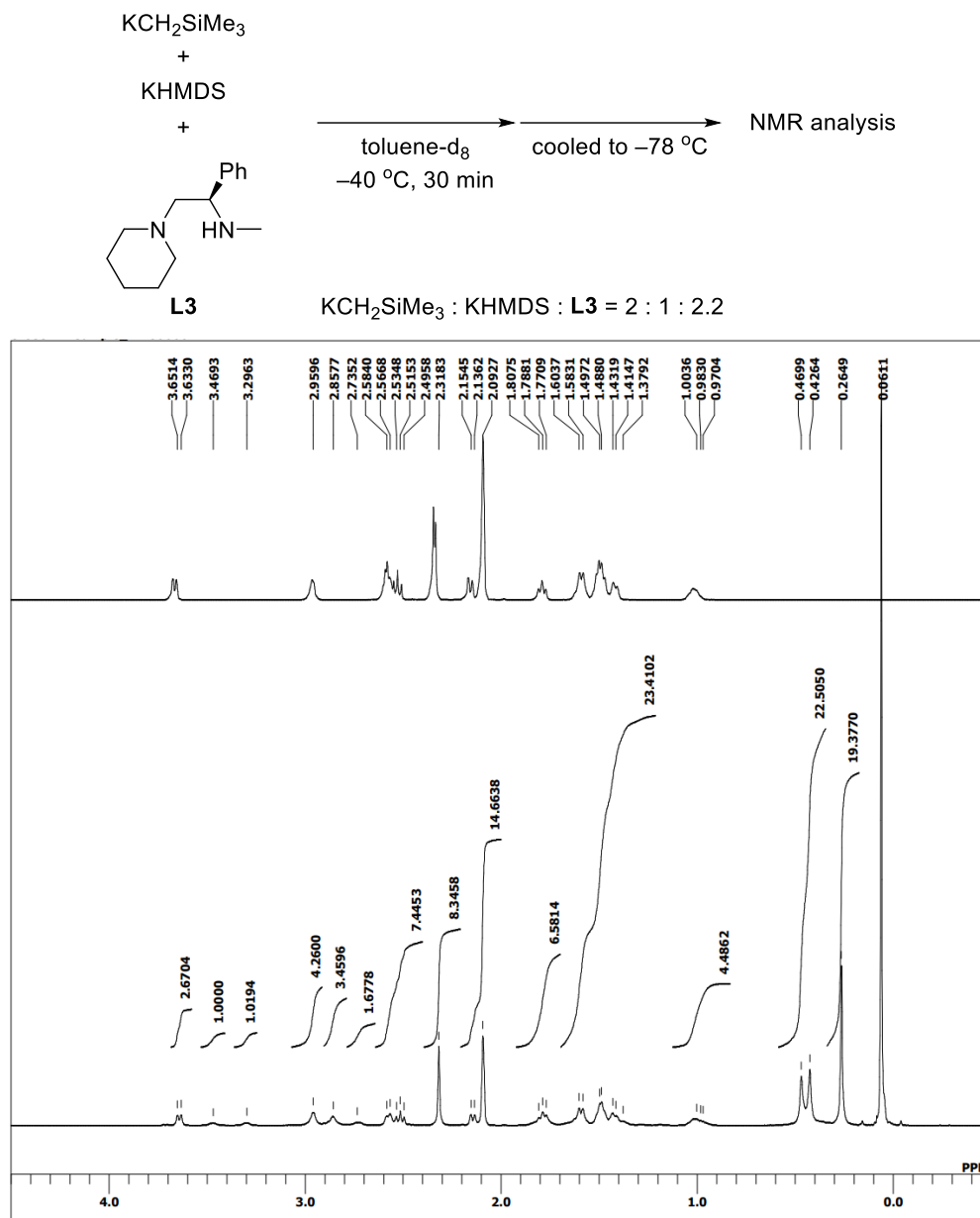
**Figure 2-29.** NMR Analysis of Catalyst Mixture Deriving from **L3**



**Figure 2-30.** NMR Analysis of Catalyst Mixture Deriving from **L3** (expanded)



**Figure 2-31.** NMR Analysis of Catalyst Mixture (1:1:2.2) Deriving from **L3**

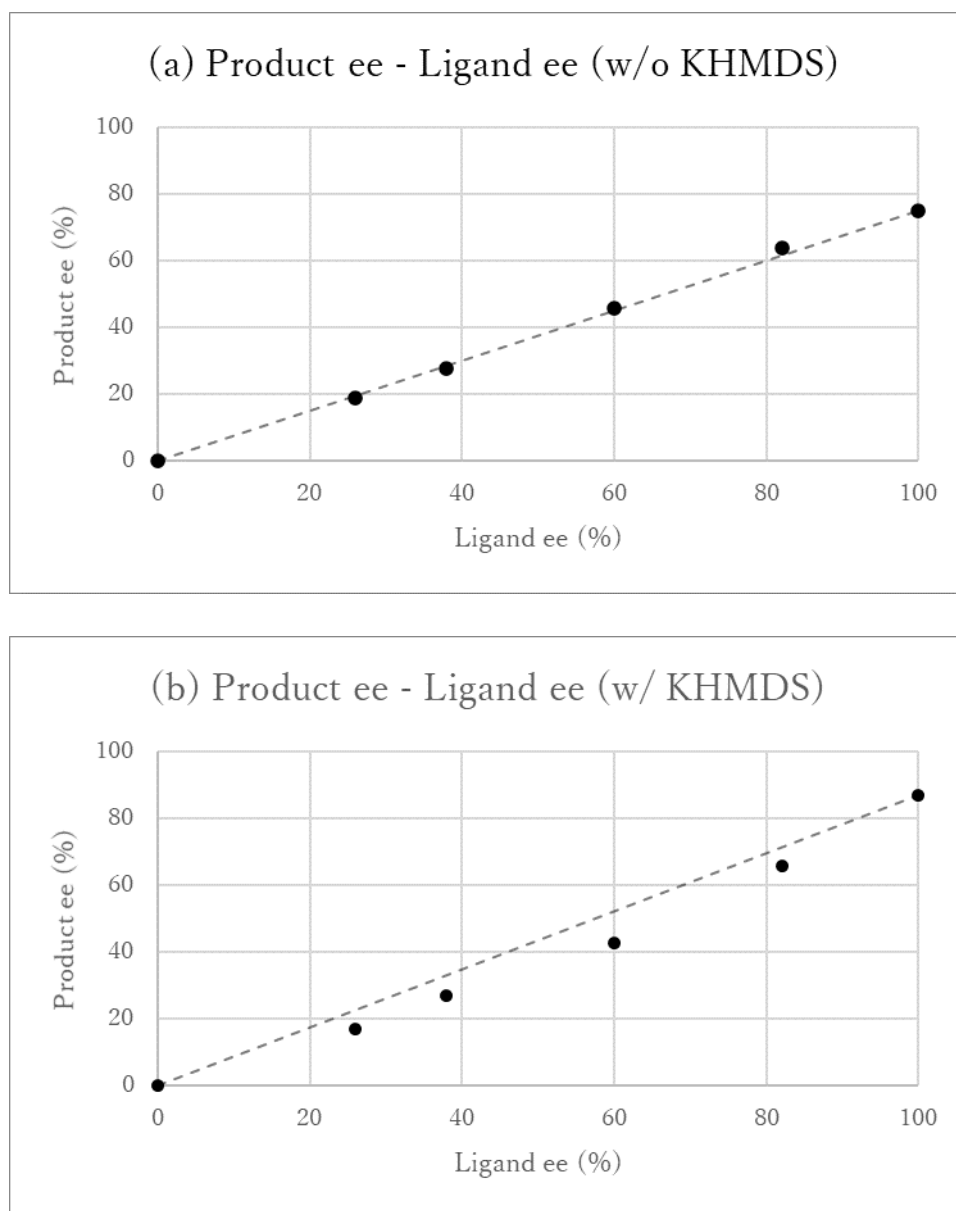
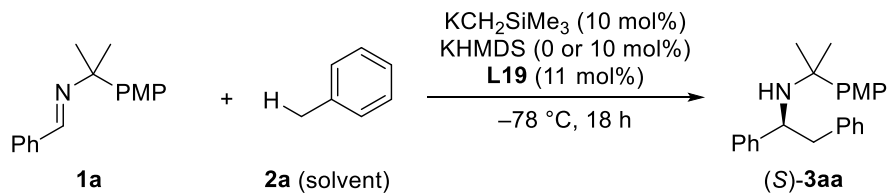


**Figure 2-32.** NMR Analysis of Catalyst Mixture (1:1:2.2) Deriving from **L3** (expanded)

### *Non-Linear Effect Experiments*

Non-linear effect experiments become a clue to confirm if oligomeric species participate catalysis.<sup>23</sup> Thus, relationship between optical purity of **L19** and that of the obtained product **3aa** in the presence or absence of KHMDs was examined. In the absence of KHMDs, almost linear relationship was observed (Figure 2-33 (a)). On the other hand, negative non-linear effect was observed but the level was not significant in the presence of KHMDs (Figure 2-33 (b)). Those results support that more reactive hetero-oligomer species of the active catalyst formed in the presence of KHMDs.

However, they did not deny formation of homooligomer species of the active catalyst in the reaction system.

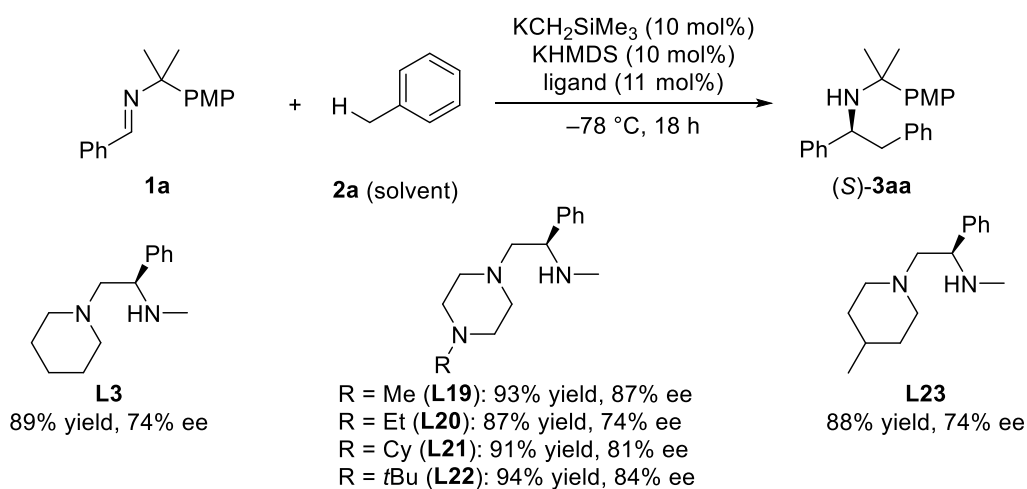


**Figure 2-33.** Non-Linear Effect Experiments

### *Effect of the Ligand Structure (the Piperazine Part)*

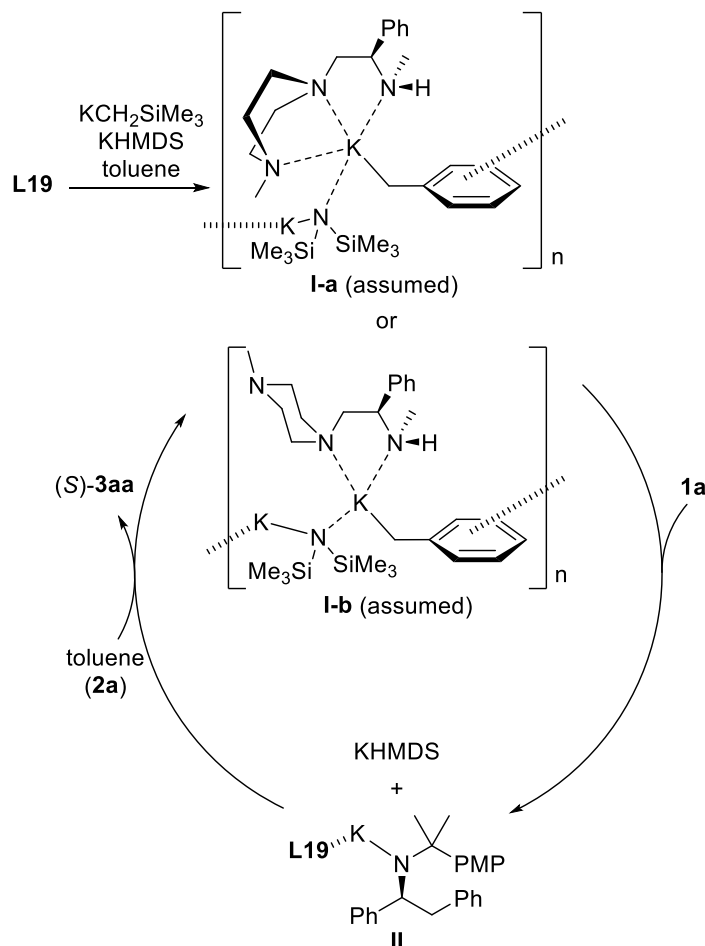
The structure of the piperazine part of **L19** was investigated to survey a role of the nitrogen atom which **L3** does not have (Table 2-8). When the methyl group on the piperazine part was changed into bulkier alkyl groups, the enantioselectivity was not improved but was higher than that of **L3** (**L20-L22**). The ligand **L23**, which has 4-methyl group on the piperidine part of **L1**, exhibited as high enantioselectivity as **L1**. Those results imply that the nitrogen atom of the piperazine ring played an important role to construct the asymmetric environment.

**Table 2-8. Effect of the Ligand Structure**



## 2-7. Proposed Mechanism

A plausible reaction mechanism for the addition reaction is shown in Figure 2-34.



**Figure 2-34.** Proposed Mechanism

Given that a slight nonlinear effect was observed, chiral oligomeric species **I-a** or **b**, which consist of benzyl potassium,  $\text{KHMDS}$ , and chiral amine ligand **L19** in 1:1:1 ratio, might be formed.<sup>13b,13c,20,24</sup> The postulated ratio of the components was based on NMR experiments. Considering the large ionic radius and low Lewis acidity of potassium ion, it is generally harder to form boat-type coordination species **I-a**, and **I-b** is thus more plausible from a thermodynamic standpoint. However, the ligand bearing a 4-methylpiperidine moiety gave a similar result to **L3** rather than **L19**, which means that the additional nitrogen atom of **L19** might be effective in improving the enantioselectivity. Therefore, we cannot discard the possibility of formation of **I-a**. The oligomeric species **I** is deaggregated and attacks the imine to afford strongly basic reaction intermediate **II**, which is termed “Product Base”. The absolute configuration of the product is determined in this step. Subsequently, “Product Base” **II** deprotonates toluene to afford the desired adduct (*S*)-**3aa**. Simultaneously, chiral nucleophilic species **I** is regenerated, and the



catalytic cycle is completed. At the current stage, an asymmetric environment of the active chiral catalyst complex with its detailed structure is not clear.

## 2-8. Conclusion

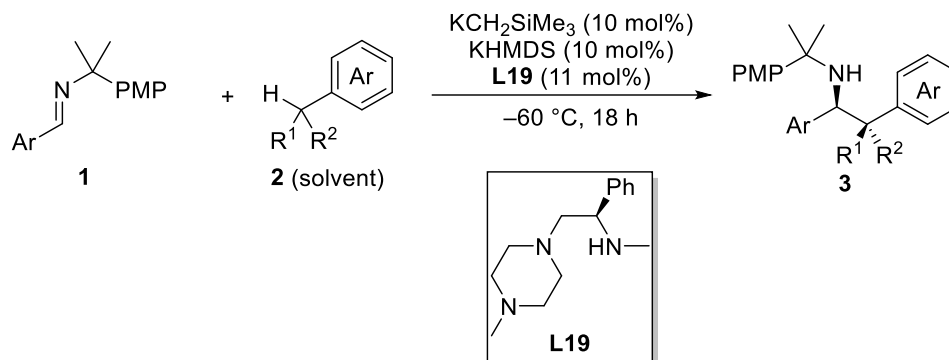


Figure 2-35. General Scheme

In summary, I achieved strong Brønsted base-catalyzed asymmetric addition reactions of unactivated alkylarenes with imines (Figure 2-35). The desired reactions proceeded smoothly in high yields with high enantioselectivities. It should be noted that these reactions are atom-economical C–C bond formation without using any transition-metal catalyst. A chiral base prepared from an alkyl potassium and a chiral amine ligand formed a promising asymmetric environment. I achieved chiral modification of the potassium ion using simple diamine ligands and applied it to asymmetric reactions although clathrate ligands were generally employed for chiral modification of the potassium ion. These results expand possibilities of chiral alkali metal catalysis. Interestingly, the enantioselectivity was significantly improved by using  $\text{KHMDs}$  as an additive. These reactions are synthetically valuable because both gram-scale reaction and asymmetric reaction via *in situ*-prepared imine were achieved. The obtained adducts can be transformed into various useful compounds.

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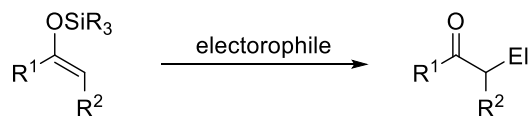
### 3. $\alpha$ -Alkylation of Ketones and Esters with Alkenes Enabled by Photo-Induced Activation of Silyl Enol Ethers

#### 3-1. Background

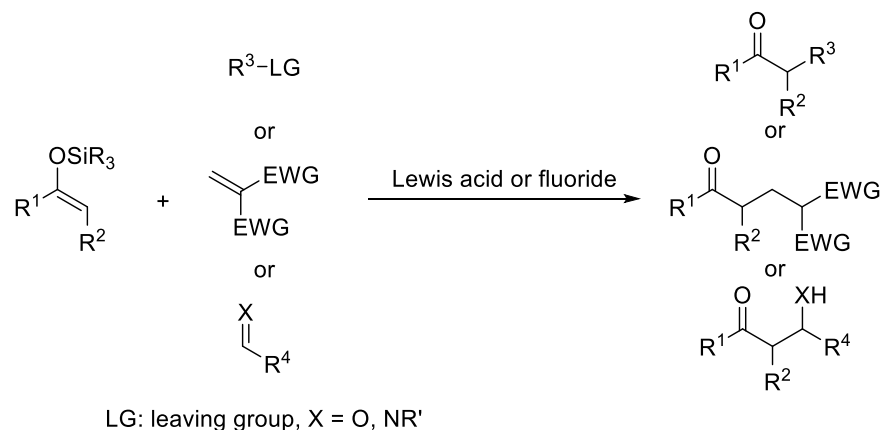
##### Silyl Enol Ether

Silyl enol ethers are prepared from carbonyl compounds with silyl halides or silyl triflates by well-established protocols and recognized to be one of versatile reagents especially for  $\alpha$ -functionalization of carbonyl compounds.<sup>1,2</sup> They are often employed as a useful equivalent of enolate anions because they are stable, isolable, and storable. Early examples of  $\alpha$ -functionalization of carbonyl compounds utilizing them include nucleophilic addition reactions with appropriate electrophiles such as Mukaiyama aldol and Michael reactions (Figure 3-1 (a)).<sup>2</sup> Furthermore, silyl enol ethers react with oxidants such as Rubottom<sup>3</sup> and Saegusa-Ito oxidation.<sup>4</sup> Although they have been utilized to a variety of  $\alpha$ -functionalization reactions, their C–C bond forming reactions are still limited to substitution and addition reactions with electron-deficient electrophiles (Figure 3-1 (b)). Therefore,  $\alpha$ -functionalization of silyl enol ethers with simple alkyl groups which contain no hetero atom is challenging.

(a)  $\alpha$ -functionalization of carbonyl compounds using silyl enol ethers



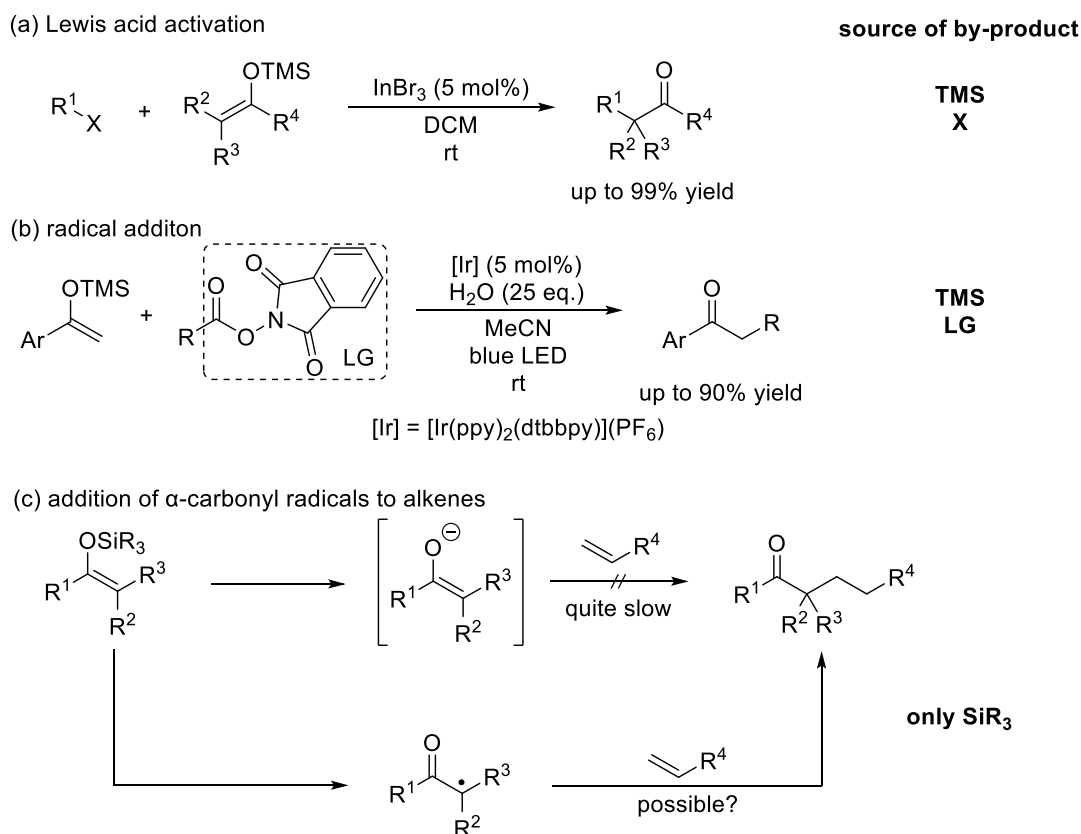
(b) nucleophilic C–C bond formation using silyl enol ethers



**Figure 3-1.**  $\alpha$ -Functionalization of Silyl Enol Ethers

In 2009, Baba *et al.* reported indium-catalyzed coupling reactions of silyl enol ethers with alkyl chlorides and alkyl ethers (Figure 3-2 (a)).<sup>5</sup> Indium(III) bromide worked as a Lewis acid catalyst, and the reactions proceeded under substitution conditions which is not atom-economical. Applicable nucleophiles include silyl enol ethers deriving from aldehydes, ketones, and esters. However, the scope of electrophiles is restricted to

introduction of benzylic, allylic, and tertiary alkyl groups. Introduction of a secondary or primary aliphatic substituent is unsuccessful. While silyl enol ethers have often been employed as a useful equivalent of enolate anions, they can be radical acceptors.<sup>6</sup> For example, Song *et al.* reported photocatalytic alkylation of silyl enol ethers in 2018 (Figure 3-2 (b)).<sup>6a</sup> *N*-(Acyloxy)phthalimides were employed as radical precursors, which afford the corresponding alkyl radicals through single electron reduction and decarboxylation. However, nucleophilic substitution and radical addition to silyl enol ethers cause low atom economy because both the silyl group and the leaving groups are source of by-products. On the other hand, addition of silyl enol ethers to alkenes enable to reduce wastes, and only the silyl group can be the waste (Figure 3-2 (c)). However, polar approach is recognized to be quite slow. Therefore, I focused on another approach that silyl enol ethers themselves are transformed into  $\alpha$ -carbonyl radicals which easily reacts with C=C double bonds.

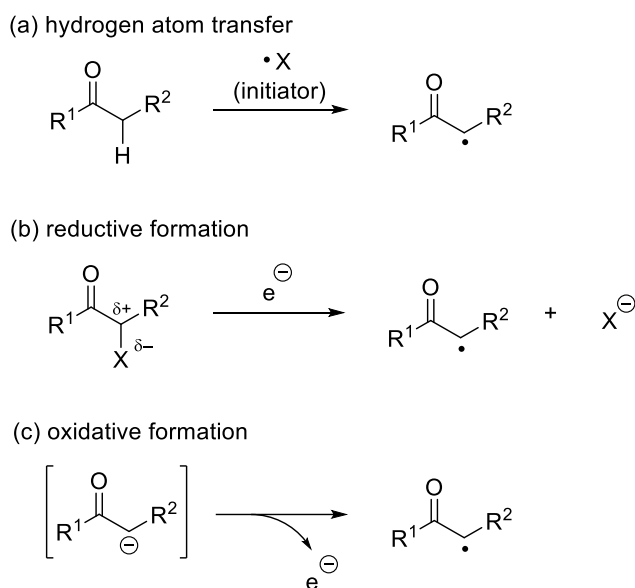


**Figure 3-2.** Catalytic Coupling of Silyl Enol Ethers with Alkyl Chlorides and Ethers

### ***$\alpha$ -Keto Radicals***

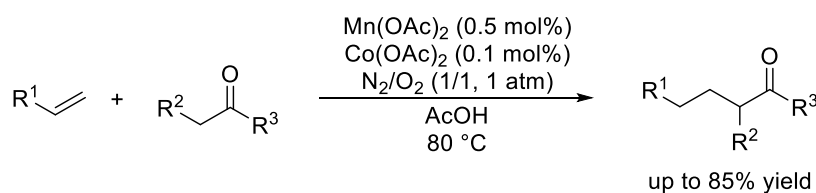
Conventionally, many kinds of  $\alpha$ -functionalization of ketones through formation of  $\alpha$ -keto radicals have been developed. Methodologies to generate  $\alpha$ -keto radicals are mainly classified into hydrogen atom transfer (HAT) reactions,<sup>7</sup> reductive formation,<sup>8,9</sup>

and oxidative formation (Figure 3-3).<sup>10,11,12</sup>



**Figure 3-3.** Generation of  $\alpha$ -Keto Radicals

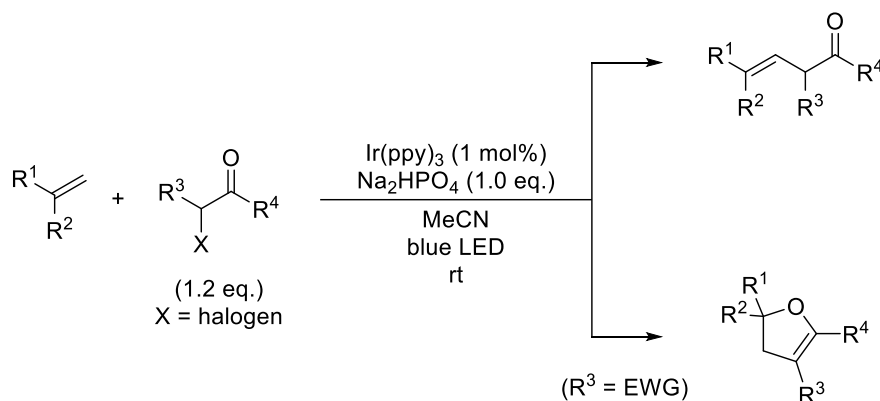
It is known that several kinds of metal salts catalyze oxidation of ketones to afford the corresponding  $\alpha$ -keto radicals.<sup>7</sup> For example, Ishii's group reported catalytic radical addition reactions of ketones with alkenes.<sup>7c</sup> This reaction system is efficient and enable ideal atom economy; however, harsh conditions (elevated temperature and a corrosive solvent) are required.



**Figure 3-4.** Catalytic Radical Addition of Ketones to Alkenes

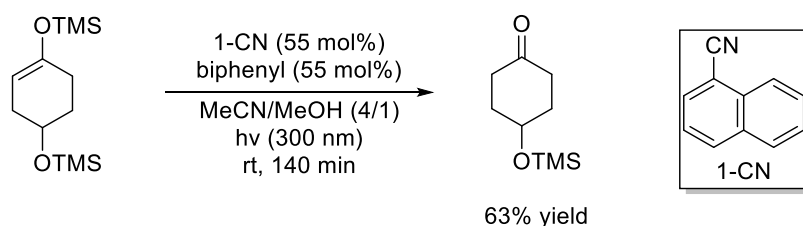
Furthermore, reduction of  $\alpha$ -haloketones is applicable to formation of  $\alpha$ -keto radicals.<sup>8</sup> It is well-known that single electron reduction leads removal of halide ions to afford  $\alpha$ -keto radicals. Based on this strategy, Quintavalla *et al.* reported photocatalytic synthesis of dihydrofurans and  $\beta,\gamma$ -unsaturated ketones (Figure 3-5).<sup>8f</sup> Initially, the photocatalyst reduces the  $\alpha$ -haloketone, and the formed  $\alpha$ -keto radical reacts with the alkene to afford a radical intermediate. Then,  $\beta,\gamma$ -unsaturated ketone is formed by oxidation of the formed radical intermediate and following deprotonation. On the other hand, dihydrofuran is obtained through cyclization when the  $\alpha$ -proton is acidic.





**Figure 3-5.** Photocatalytic Synthesis of Dihydrofurans and  $\beta,\gamma$ -Unsaturated Ketones

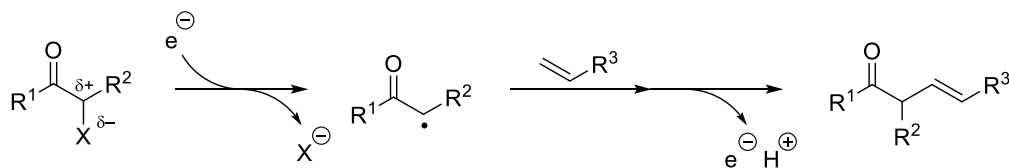
Furthermore, silyl enol ethers can be precursors of  $\alpha$ -keto radicals. The corresponding radical cations are formed after single electron oxidation, and desilylation leads formation of  $\alpha$ -keto radicals.<sup>10,11,12</sup> In 1988, Gassmann *et al.* reported photocatalytic solvolysis of silyl enol ethers.<sup>10</sup> The photo catalyst oxidizes a silyl enol ether to generate the corresponding radical cation, and the  $\alpha$ -keto radical is generated via desilylation. Then, the  $\alpha$ -keto radical is reduced and protonated to afford the ketone product.



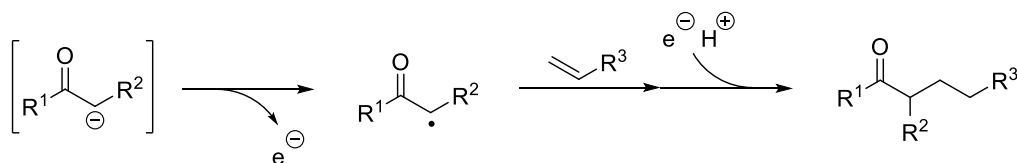
**Figure 3-6.** Photocatalytic Solvolysis of Silyl Enol Ethers

As described above, HAT reactions, reductive formation, and oxidative formation are applicable to formation of  $\alpha$ -keto radicals; however, HAT reactions generally require harsh conditions. Among redox reactions, redox neutral reactions are efficient from the viewpoint of atom economy. On the other hand, reductive formation of  $\alpha$ -keto radicals lead alkenylation reactions because the radical intermediates formed after radical addition are oxidized under redox neutral conditions (Figure 3-7 (a)).<sup>8f</sup> In contrast, introduction of saturated alkyl groups is possible if the radical intermediates are reduced to afford the corresponding carbanions (Figure 3-7 (b)). Theoretically, enolates and their equivalents afford  $\alpha$ -keto radicals via oxidation, and it is known that silyl enol ethers can be precursors of  $\alpha$ -carbonyl radicals. Therefore, silyl enol ethers have a potential to realize efficient  $\alpha$ -alkylation with alkenes

(a) reductive formation of  $\alpha$ -keto radicals

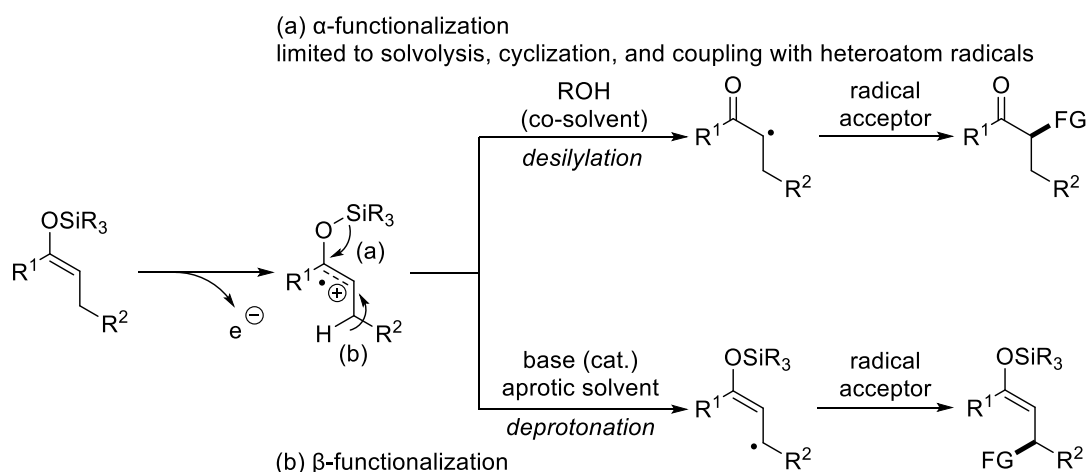


(b) oxidative formation of  $\alpha$ -keto radicals



**Figure 3-7.** Comparison between Reductive and Oxidative Formation

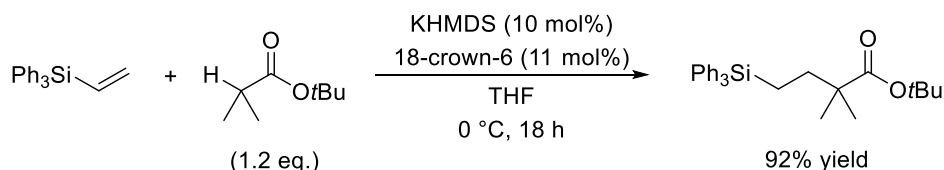
$\alpha$ -Functionalization of silyl enol ethers via formation of  $\alpha$ -keto radicals has been developed (Figure 3-8 (a)). The examples include solvolysis,<sup>10</sup> cyclization,<sup>11</sup> and coupling with heteroatom radicals.<sup>12</sup> Among them, C–C bond formation has been limited to intramolecular reactions presumably because of rapid solvolysis. For example, Mattay's group reported photocatalytic cyclization of unsaturated silyl enol ethers; however, the yields are not so high and long reaction time is necessary. On the contrary, Ooi *et al.* reported  $\beta$ -functionalization of silyl enol ethers by photoredox-Brønsted base hybrid catalysis (Figure 3-8 (b)).<sup>13</sup> The reactions were conducted in an aprotic solvent to suppress solvolysis, and following deprotonation of  $\beta$ -hydrogen enabled formation of allylic radicals. To the best of my knowledge, intermolecular  $\alpha$ -alkylation of silyl enol ethers with alkenes has not been reported yet, and it is still challenging.



**Figure 3-8.** Functionalization of Silyl Enol Ethers via Radical Cation Formation

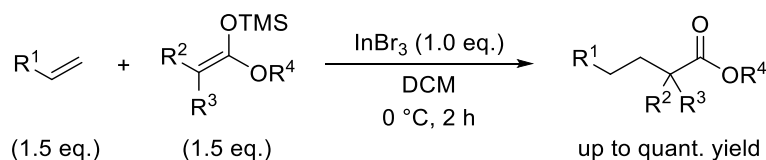
### ***$\alpha$ -Alkylation Reactions of Esters with Alkenes***

Development of intermolecular  $\alpha$ -alkylation of silyl enol ethers with alkenes might contribute to new methodology for  $\alpha$ -alkylation of esters. Enolates derived from esters possess stronger nucleophilicities than those derived from ketones, and polar addition of esters to alkenes are possible. In 2018, our group reported base-catalyzed addition reactions of esters with alkenes as described in section 1-5 (Figure 3-9).<sup>14</sup> However, applicable esters are limited to isobutylates because Claisen condensation competes with the desired reactions.



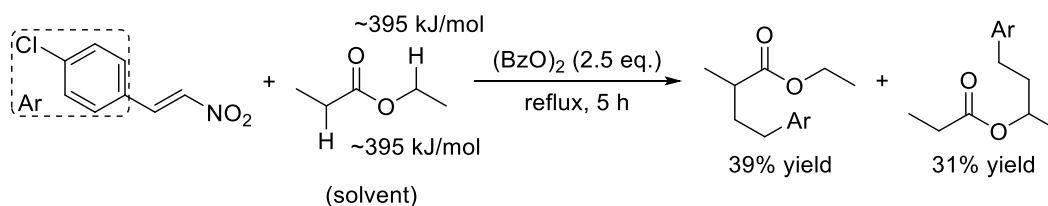
**Figure 3-9.** Base-Catalyzed Addition Reactions of Ester with Alkene

In 2010, Baba's group reported alkylation of ketene silyl acetals, which are silyl enol ethers derived from esters, with alkenes (Figure 3-10).<sup>15</sup> In this reaction system, alkylation of propionates is possible; however, stoichiometric amount of iridium (III) bromide is required as a Lewis acid reagent.



**Figure 3-10.** Alkylation of Ketene Silyl Acetals with Alkenes

Regarding esters, polar approach is difficult due to competition with Claisen condensation as described above. Furthermore, radical approach is also challenging because  $\alpha$ -hydrogens of their alkoxy group is as reactive as  $\alpha$ -hydrogens of their carbonyl group (Figure 3-11).<sup>16</sup> This low chemoselectivity is caused by similar bond dissociation energies (BDEs).<sup>17</sup>



**Figure 3-11.** Chemoselectivity in HAT of Esters

Therefore, selective formation of  $\alpha$ -carbonyl radicals derived from esters and its application to alkylation are still challenging. Thus, I have developed catalytic alkylation of silyl enol ethers derived from ketones and esters with alkenes in my doctoral thesis studies

### 3-2. Optimization of $\alpha$ -Alkylation of Ketones

In the presence of 1,1-diphenylethylene **1a** and trimethylsilyl (TMS) enol ether TMS-**2a**, initial investigation was conducted to find appropriate photocatalysts for the desired reaction (Table 3-1). Initially, 9,10-dicyanoanthracene (DCA) was chosen for a photocatalyst based on Mattay's reaction system. However, side-adduct **4** deriving from the employed alkene **1a** and methanol was obtained without formation of the desired adduct **3aa** (entry 1). Similarly, 1,4-dicyanonaphthalene (DCN) also afforded the side-adduct **4** under UV irradiation (entry 2). Judging from reduction their potentials, the side-reaction was caused by oxidation of the alkene **1a**.<sup>18,19</sup> To suppress the undesired oxidation, the photocatalyst was change to 4CzIPN, which has lower reduction potential, and the desired adduct **3aa** was obtained without formation of the side-adduct **4**.

**Table 3-1.** Initial Investigation

**1a**  
 $E(1a^{+}/1a) = +1.82$  V

**TMS-2a**  
 (1.5 eq.)

photocatalyst (5 mol%)  
 MeCN/MeOH (17/3)  
 blue LED (40 W)  
 ~45 °C, 12 h

**3aa**

**4**

DCA

$E(P^{+}/P^{\bullet-}) = +1.99$  V (vs SCE)

$E(P/P^{\bullet-}) = -0.91$  V (vs SCE)

DCN

$E(P^{+}/P^{\bullet-}) = +2.3$  V (vs SCE)

$E(P/P^{\bullet-}) = -1.27$  V (vs SCE)

4CzIPN

$E(P^{+}/P^{\bullet-}) = +1.35$  V (vs SCE)

$E(P/P^{\bullet-}) = -1.21$  V (vs SCE)

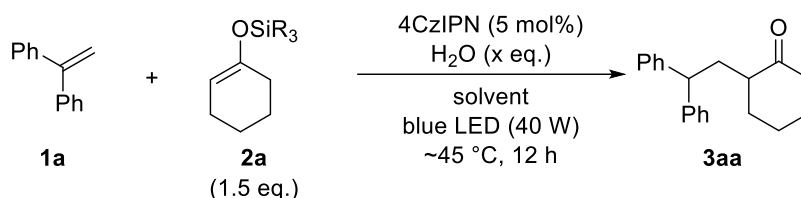
entry	photocatalyst	<b>3aa</b>	<b>4</b>
1	DCA	0%	69%
2 <sup>a</sup>	DCN	0%	12%
3	4CzIPN	38%	0%

Reaction conditions (unless otherwise noted): **1a** (0.50 mmol), TMS-**2a** (0.75 mmol), photocatalyst (0.025 mmol), MeCN (4.25 mL), MeOH (0.75 mL), under blue light irradiation, 18 h. The yields were determined by <sup>1</sup>H NMR analysis (internal standard: CH<sub>2</sub>Br<sub>2</sub>). <sup>a</sup>UV-light was used instead of blue LED.

In the presence of 4CzIPN, effect of protic additives was then investigated (Table 3-2). To suppress solvolysis of the silyl enol ether, the reaction was conducted in

acetonitrile (without methanol); however, the yield decreased (entry 1). This result indicates that a protic additive is essential for trapping a silyl cation. On the one hand, it was found that addition of 1 equivalent of water to the reaction system was effective to improve the yield dramatically (entry 2). On the contrary, the yield became lower when water was employed as a co-solvent (entry 3). It was assumed that gradual formation of the  $\alpha$ -keto radical is important to suppress solvolysis. Considering the stability of the TMS enol ether TMS-**2a**, the silyl group was changed to a *tert*-butyldimethylsilyl (TBS) group, which is a bulkier and more stable silyl group. Then, the desired product was obtained in higher yield (entry 4). Further optimization revealed that a slight excess of water (1.2 eq.) was more effective (entries 5, 6).

**Table 3-2.** Effect of Water

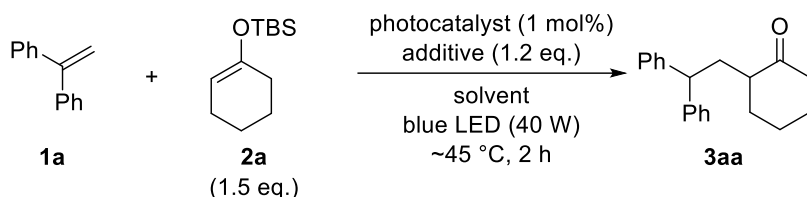


entry	SiR <sub>3</sub>	x	solvent	yield (%)
— <sup>a</sup>	SiMe <sub>3</sub>	—	MeCN/MeOH (17/3)	38
1	SiMe <sub>3</sub>	—	MeCN	17
2	SiMe <sub>3</sub>	1.0	MeCN	77
3	SiMe <sub>3</sub>	—	MeCN/H <sub>2</sub> O (9/1)	27
4	Si <i>t</i> BuMe <sub>2</sub>	1.0	MeCN	86
5	Si <i>t</i> BuMe <sub>2</sub>	1.2	MeCN	92
6	Si <i>t</i> BuMe <sub>2</sub>	2.0	MeCN	85

Reaction conditions (unless otherwise noted): **1a** (0.50 mmol), **2a** (0.75 mmol), photocatalyst (0.025 mmol), H<sub>2</sub>O, solvent (totally 5.0 mL), under blue light irradiation, 12 h. The yields were determined by <sup>1</sup>H NMR analysis (internal standard: CH<sub>2</sub>Br<sub>2</sub>). <sup>a</sup>The same result as entry 3 in Table 3-1.

In this context, it was found that the desired product was obtained in 77% yield within 2 hours in the presence of only 1 mol% of 4CzIPN (Table 3-3, entry 1). To realize more efficient reaction system, photocatalysts, additives, and solvents were examined with 1 mol% of a photocatalyst. Although several photocatalysts such as 4DPAIPN or 4CzTPN were initially tested; however, the desired product was not obtained at all (entries 2, 3). Then, methanol or isopropyl alcohol was examined as a protic additive instead of water, and the desired product was obtained in lower yields (entries 4, 5). Although various solvents were tested, the yields were not improved (entries 6-9). Next, the reaction time was prolonged up to 6 hours, and the yield was improved up to 86% (entry 10). Eventually, the reaction proceeded in excellent yield within 2 hours in the presence of 2 mol% of the photocatalyst 4CzIPN (entry 11).

**Table 3-3. Further Optimization**



<p><b>4CzIPN</b>  <math>E(P^*/P^{*-}) = +1.35</math> V (vs SCE)  <math>E(P/P^{*-}) = -1.21</math> V (vs SCE)</p>	<p><b>4DPAIPN</b>  <math>E(P^*/P^{*-}) = +1.10</math> V (vs SCE)  <math>E(P/P^{*-}) = -1.52</math> V (vs SCE)</p>	<p><b>4CzTPN</b>  <math>E(P^*/P^{*-}) = +1.41</math> V (vs SCE)  <math>E(P/P^{*-}) = -1.01</math> V (vs SCE)</p>
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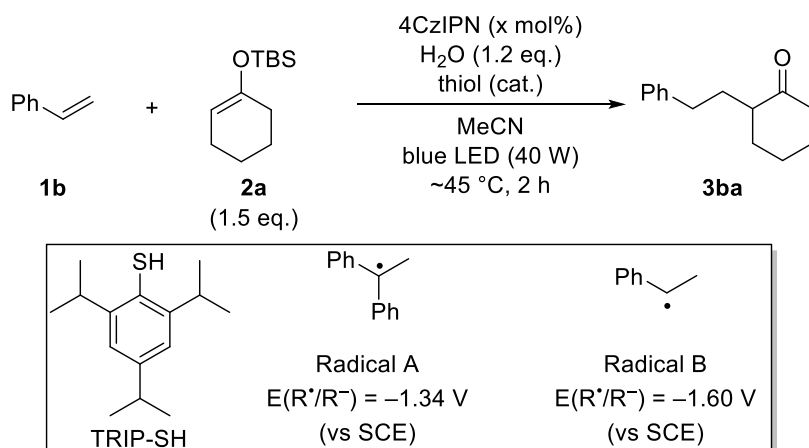
entry	photocatalyst	additive	solvent	yield (%)
1	4CzIPN	H <sub>2</sub> O	MeCN	77
2	4DPAIPN	H <sub>2</sub> O	MeCN	0
3	4CzTPN	H <sub>2</sub> O	MeCN	0
4	4CzIPN	MeOH	MeCN	73
5	4CzIPN	<i>i</i> PrOH	MeCN	67
6	4CzIPN	H <sub>2</sub> O	MeOH	0
7	4CzIPN	H <sub>2</sub> O	THF	0
8	4CzIPN	H <sub>2</sub> O	acetone	25
9	4CzIPN	H <sub>2</sub> O	DMF	13
10 <sup>a</sup>	4CzIPN	H <sub>2</sub> O	MeCN	86
11 <sup>b</sup>	4CzIPN	H <sub>2</sub> O	MeCN	92 (90) <sup>c</sup>

Reaction conditions (unless otherwise noted): **1a** (0.50 mmol), **2a** (0.75 mmol), photocatalyst (0.025 mmol), additive (0.60 mmol), solvent (5.0 mL), under blue light irradiation, 12 h. The yields were determined by <sup>1</sup>H NMR analysis (internal standard: CH<sub>2</sub>Br<sub>2</sub>). <sup>a</sup>The reaction was carried out for 6 h. <sup>b</sup>2 mol% of 4CzIPN was used. <sup>c</sup>The yields shown in parentheses are based on the isolated product.

For expansion of the substrate scope to styrene derivatives, the reaction with styrene was optimized (Table 3-4). The reaction was carried out under the optimized conditions; however, the desired product **3ba** was not obtained at all (entry 1). Judging from the reduction potentials, reduction of radical B is more difficult than that of radical A.<sup>20</sup> To overcome this issue, benzenethiol (PhSH) was added as a hydrogen atom transfer (HAT) catalyst, and the desired product **4ba** was obtained in moderate yield (entry 2).<sup>21</sup> By using 5 mol% of the photocatalyst, the reaction proceeded in good yield (entry 3). Next, several

thiols were examined; however, the yield was not improved eventually (entries 4, 5). Finally, the desired product was obtained in high yield in the presence of 50 mol% of PhSH. This result implies that 50 mol% of PhSH can improve the yields if necessary.

**Table 3-4.** Investigation of HAT Catalysts



entry	x (mol%)	thiol (mol%)	yield (%)
1	2	none	0
2	2	PhSH (20)	46
3	5	PhSH (20)	73 (63) <sup>a</sup>
4	5	TRIP-SH (20)	33
5	5	HSCO <sub>2</sub> Me (20)	8
6	5	PhSH (50)	86 (75) <sup>a</sup>

Reaction conditions (unless otherwise noted): **1b** (0.50 mmol), **2a** (0.75 mmol), photocatalyst (0.025 mmol), H<sub>2</sub>O (0.60 mmol), thiol (0.10-0.25 mmol), MeCN (5.0 mL), under blue light irradiation, 2 h. The yields were determined by <sup>1</sup>H NMR analysis (internal standard: CH<sub>2</sub>Br<sub>2</sub>). <sup>a</sup>The yields shown in parentheses are based on the isolated product.

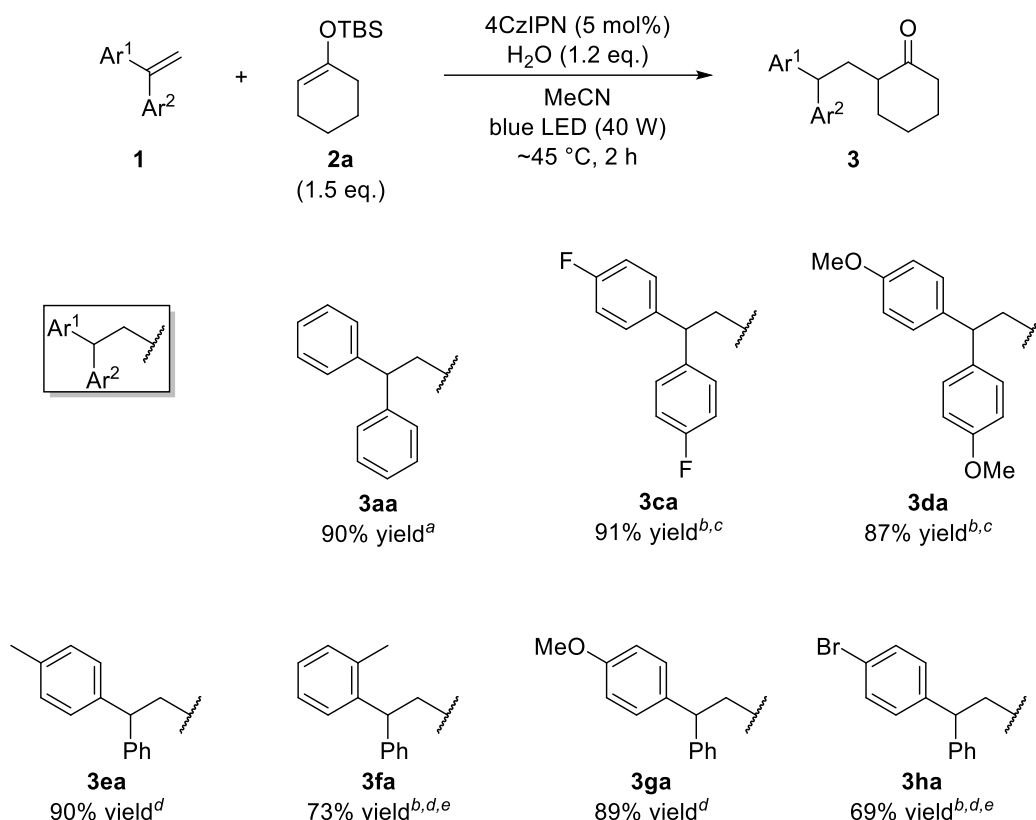


### 3-3. Substrate Scope of $\alpha$ -Alkylation of Ketones

#### Scope of Alkenes

The scope of the reaction with respect to alkenes was examined under the optimized reaction conditions (Table 3-5).

**Table 3-5.** Scope of 1,1-Diarylethylenes



Reaction conditions (unless otherwise noted): **1** (0.50 mmol), **2a** (0.75 mmol), 4CzIPN (0.025 mmol), H<sub>2</sub>O (0.60 mmol), MeCN (5.0 mL), under blue light irradiation, 2 h. The shown yields are based on the isolated product. <sup>a</sup>0.010mmol (2 mol%) of 4CzIPN was employed. <sup>b</sup>0.10 mmol (20 mol%) of PhSH was added. <sup>c</sup>The reaction was carried out for 12 h. <sup>d</sup>The diastereoselectivity was approximately 1:1 dr. <sup>e</sup>The reaction was carried out for 24 h.

As described in the optimization part, the reaction using **1aa** proceeded in excellent yield (**3aa**). 1,1-Diarylethylenes having dimethoxy or difluoro groups at the 4- and 4'-positions of their aromatic rings reacted smoothly to afford the desired products in high yields (**3ca**, **3da**). Regarding these substrates, PhSH was effective to improve the yields. Subsequently, the reaction with 1,1-diarylethylene bearing a methyl group at the 4-position of its aromatic ring was examined, and the desired product was obtained in excellent yield (**3ea**). However, the desired adduct was obtained in low yield when a methyl group was substituted at the 2-position. The low yield was presumably caused by a twisted aryl group due to steric hinderance of the methyl group. To overcome this problem, PhSH was employed and improved the yield up to 73% (**3fa**). An alkene

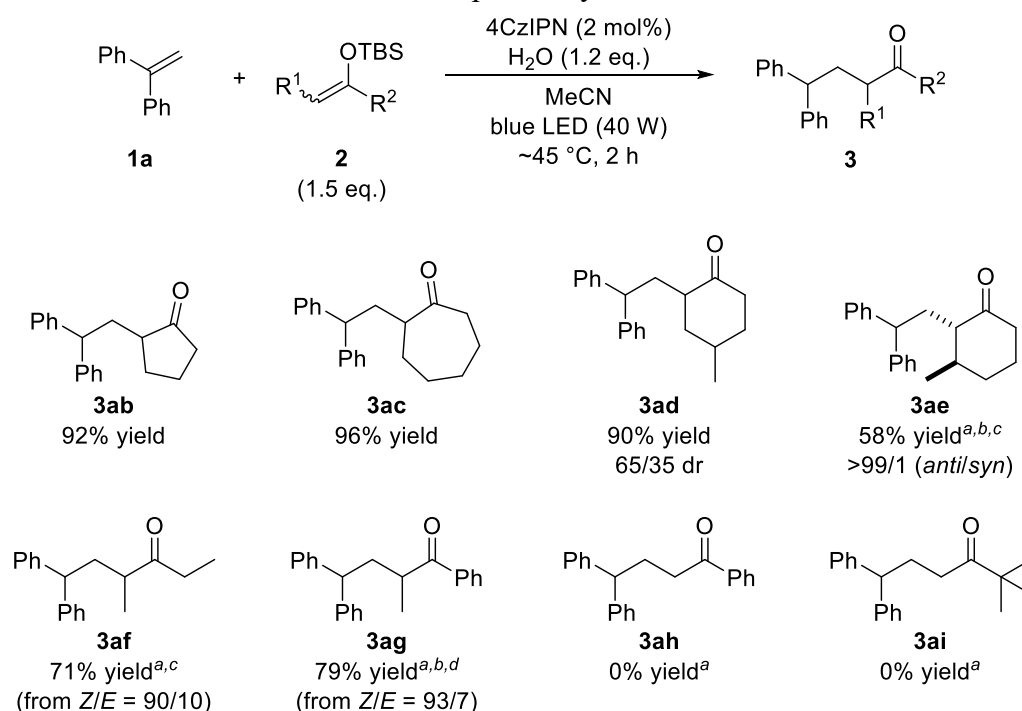


to high yields (**3ia-3ka**). Styrenes substituted with an electron-donating group such as a methoxy group were also available (**3la-3na**). When 4-chlorostyrene was employed, the reaction proceeded in good yield (**3oa**). The reactions with styrenes having an electron-withdrawing group, such as carbonyl and cyano groups, proceeded in moderate yields (**3pa, 3qa**). When 2-vinylnaphthalene was employed, the reaction proceeded in moderate yield (**3ra**). An internal alkene such as indene also reacted with the silyl enol ether in high yield (**3sa**). It was also found that simple alkenes that do not have phenyl groups such as methylenecyclopentane and methylenecyclohexane afforded the desired adducts in moderate to good yields (**3ta, 3ua**). For further generality,  $\alpha,\beta$ -unsaturated ketone and ester were tested; however the reactions did not proceed at all in spite of easier reduction of the radical intermediates presumably because  $\alpha$ -keto radicals were electrophilic radicals (**3va, 3wa**).

### Scope of Silyl Enol Ethers

Next, the scope of silyl enol ethers was also investigated (Table 3-7).

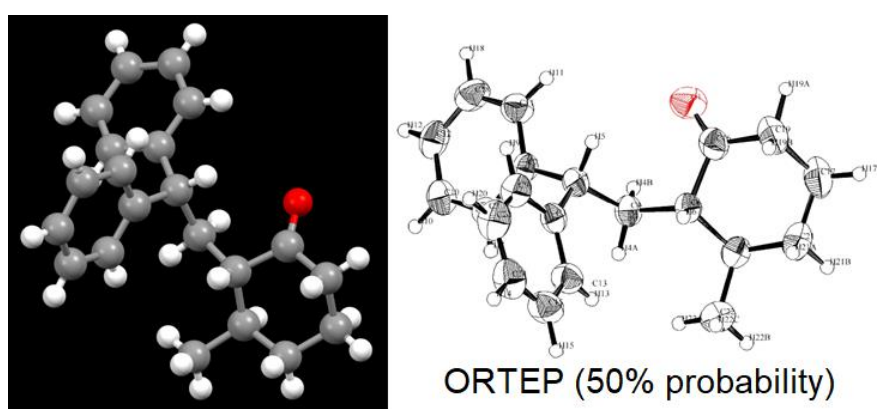
**Table 3-7.** Scope of Silyl Enol Ethers



Reaction conditions (unless otherwise noted): **1a** (0.50 mmol), **2** (0.75 mmol), 4CzIPN (0.010 mmol),  $H_2O$  (0.60 mmol), MeCN (5.0 mL), under blue light irradiation, 2 h. The shown yields are based on the isolated product. <sup>a</sup>0.025 mmol (5 mol%) of 4CzIPN was employed. <sup>b</sup>0.10 mmol (20 mol%) of PhSH was added. <sup>c</sup>The reaction was carried out for 12 h. <sup>d</sup>The reaction was carried out for 48 h.

The silyl enol ethers derived from cyclic ketones such as cyclopentanone and cycloheptanone, reacted smoothly to afford the desired products in excellent yields (**3ab**, **3ac**). The silyl enol ethers derived from methyl-substituted cyclohexanones were also

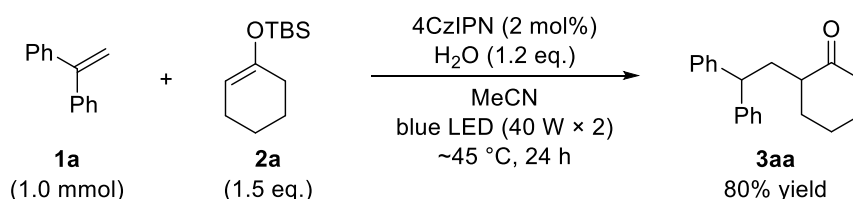
applicable, and the desired adducts were obtained in moderate to high yields (**3ad**, **3ae**). It is an advantage of using silyl enol ethers that bulkier sites can be alkylated.<sup>22</sup> When the silyl enol ether derived from 3-methylcyclohexanone was employed, the product **3ae** was obtained with excellent diastereoselectivity. X-ray single crystal structure analysis of **3ae** indicated that the major diastereomer was *anti* (Figure 3-12). The silyl enol ethers derived from acyclic ketones were also examined. Silyl enol ethers derived from 3-pentanone and propiophenone reacted smoothly to afford the desired products in good yields (**3af**, **3ag**). The reactions of the silyl enol ethers derived from acetophenone and *tert*-butyl methyl ketone were unsuccessful under the optimized conditions (**3ah**, **3ai**). These reactions were unsuccessful presumably due to instability of primary  $\alpha$ -keto radical.



**Figure 3-12.** X-Ray Structure of **3ae**

### Double-Scale Reaction

The scalability was also tested, and a double-scale reaction proceeded to afford the desired product in high yield (Figure 3-13).

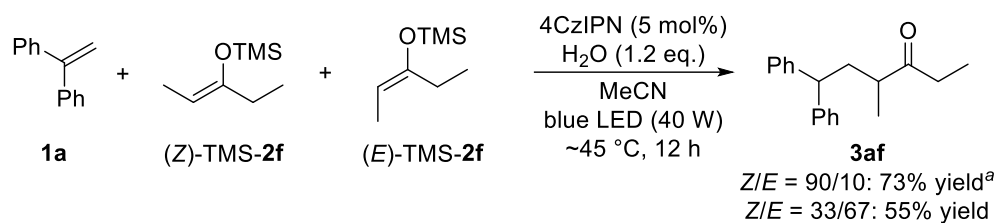


**Figure 3-13.** Double-Scale Reaction

### Comparison of the Reactivities between (*Z*)- and (*E*)-Isomers

Silyl enol ethers sometimes have (*Z*)- or (*E*)-forms. I was interested in the difference of their reactivities between those forms, and the reactivities were compared by using a mixture of the isomers (Figure 3-14). When the (*Z*)-isomer was the main component, the reaction proceeded in good yield. On the other hand, the (*E*)-isomer afforded the desired product in moderate yield. Those results implied that (*Z*)-isomer was more reactive than

the other. But, the yield of (*E*)-isomer was not so low, and it seemed to be employable as a starting material.

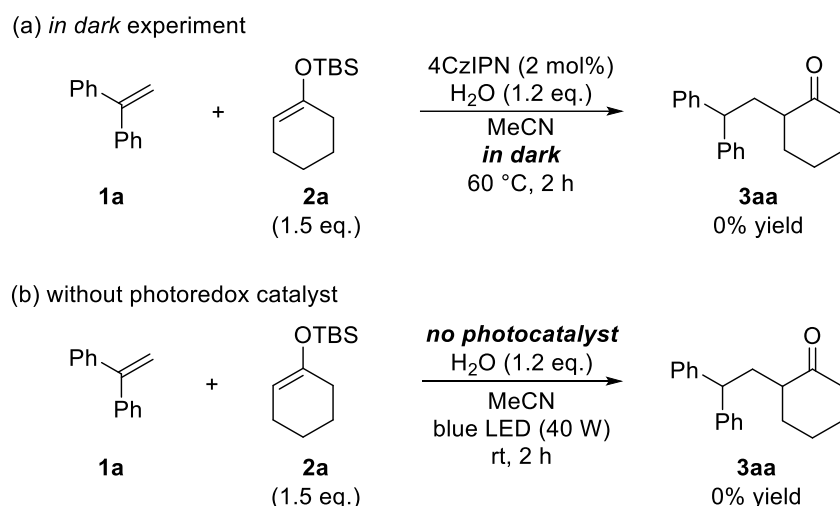


The yields were determined by <sup>1</sup>H NMR analysis (internal standard: CH<sub>2</sub>Br<sub>2</sub>). <sup>a</sup>The isolated yield was 71%.

**Figure 3-14.** Comparison of the Reactivities between (*Z*)- and (*E*)-Isomers

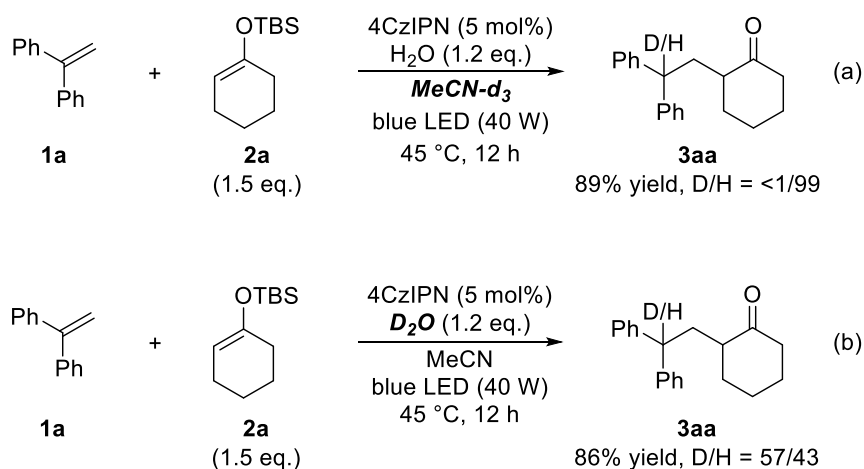
### 3-4. Mechanistic Studies of $\alpha$ -Alkylation of Ketones

To gain insight into the reaction mechanism, several investigations were conducted. The desired product was not obtained under dark conditions (Figure 3-15 (a)). Similarly, the reaction did not proceed at all in the absence of the photoredox catalyst (Figure 3-15 (b)). These results imply that the photoredox catalyst activated by visible-light irradiation plays a key role in the reaction.



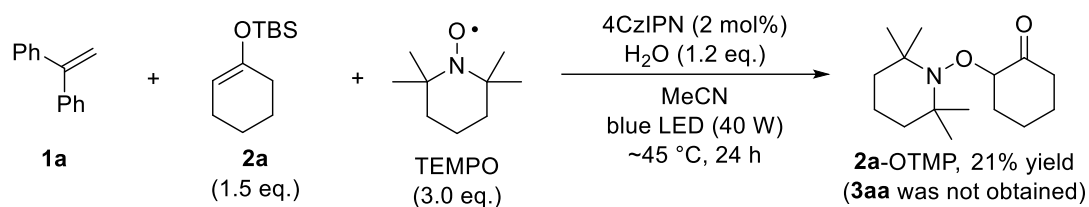
**Figure 3-15.** Importance of Photocatalyst and Photo-Irradiation

Deuterium labeling experiments were also conducted to identify the proton source (Figure 3-16). When deuterated acetonitrile ( $\text{MeCN-}d_3$ ) was employed as a solvent, almost no deuterium was incorporated into the obtained product (a). On the contrary, the desired product containing deuterium at its benzylic position was obtained when  $\text{D}_2\text{O}$  was used (b). These results imply that the proton source is not acetonitrile but water.



**Figure 3-16.** D-Labeling Experiments

A radical trapping experiment was conducted (Figure 3-17). The reaction was carried out in the presence of TEMPO, and the desired product **3aa** was not obtained at all. Instead, **2a**-OTMP was obtained, which indicates that the reactions proceeded in radical addition mechanism.



The yield was determined by <sup>1</sup>H NMR analysis (internal standard: 1,3,5-trimethoxybenzene).

**Figure 3-17.** Radical Trapping Experiment

### 3-5. Optimization of $\alpha$ -Alkylation of Esters

#### Optimization for Lactone

In addition to alkylation of ketones, the reaction using a ketene silyl acetal which is a silyl enol ether derived from esters was investigated (Table 3-8).

**Table 3-8.** Initial Investigation

Entry	Additive	x (eq.)	Yield (%)
1	H <sub>2</sub> O	1.2	75
2	none	—	35
3	<i>t</i> BuOH	1.2	43
4	<i>i</i> PrOH	1.2	22
5	EtOH	1.2	32
6	MeOH	1.2	33
7	PhSH	1.2	68
8	<i>t</i> BuSH	1.2	92
9	<i>i</i> PrSH	1.2	73
10	EtSH	1.2	quant.
11	H <sub>2</sub> O	0.6	quant.
12 <sup>a</sup>	H <sub>2</sub> O	0.6	quant. (93) <sup>b</sup>

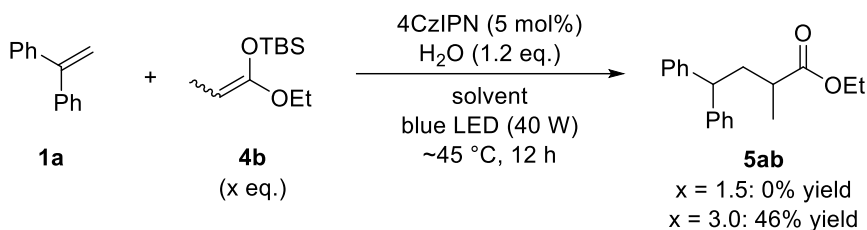
Reaction conditions (unless otherwise noted): **1a** (0.50 mmol), **4a** (0.75 mmol), 4CzIPN (0.025 mmol), MeCN (5.0 mL), additive, under blue light irradiation, 12 h. The yields were determined by <sup>1</sup>H NMR analysis (internal standard: CH<sub>2</sub>Br<sub>2</sub>). <sup>a</sup>0.015 mmol (3 mol%) of 4CzIPN was employed. <sup>b</sup>The yield shown in parentheses is based on the isolated product

Initially, the reaction was conducted under the optimized reaction conditions for ketones, and the desired product was obtained in good yield (entry 1). Given that ketene silyl acetals are moisture sensitive, the reaction was carried out in the absence of water; however, the yield decreased (entry 2). For further improvement, various alcohols and thiols were examined (entries 3-10), and *t*BuSH and EtSH were significantly effective to improve the yield. On the other hand, the reaction proceeded in quantitative yield in the presence of 0.6 equivalents of water (entry 11). Finally, it was found that the desired product was obtained in quantitative yield in the presence of only 3 mol% of the photocatalyst (entry 12).



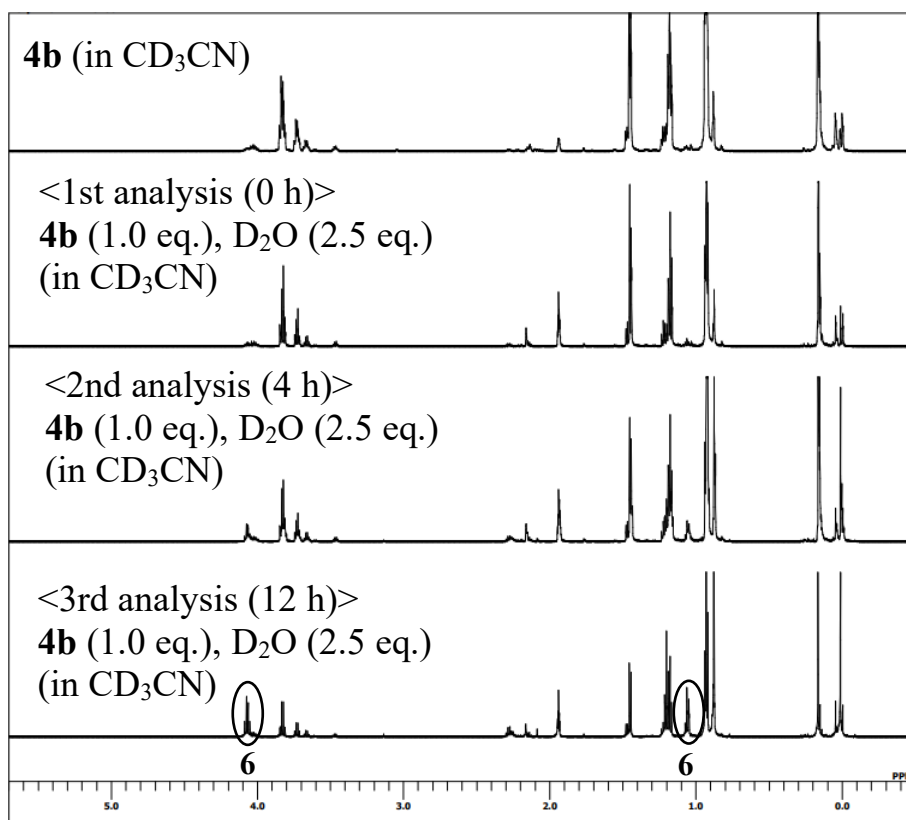
### Optimization for Linear Ester

For wide substrate scope, ketene silyl acetal **4b** derived from ethyl propionate was then examined; however, the reaction did not proceed in the presence of 1.5 equivalents of the ketene silyl acetal (Figure 3-18). On the other hand, the desired product was obtained in moderate yield when 3.0 equivalents of **4b** were employed. These results implied that the ketene silyl acetal might be decomposed during the reaction.



The yields were determined by  $^1\text{H}$  NMR analysis (internal standard:  $\text{CH}_2\text{Br}_2$ ).

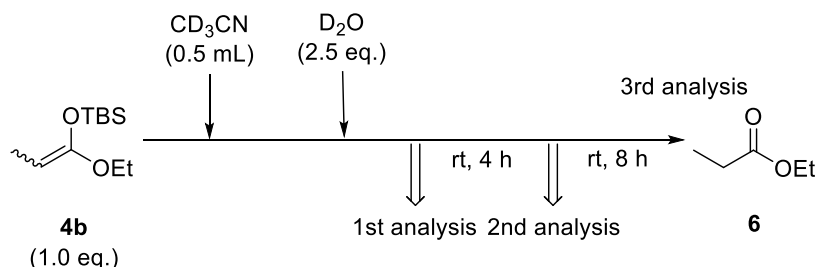
**Figure 3-18.** Initial Trial of Alkylation of Ethyl Propionate



**Figure 3-19.** NMR Analysis to Check the Stability of **4a**

To check the stability of **4b**, NMR experiments were carried out (Figure 3-19). The NMR sample was prepared according to the procedure shown in Figure 3-20. When the mixture was immediately measured after its preparation, **4b** was slightly decomposed (1st

analysis). Furthermore, it was found that **4b** was completely transformed to ethyl propionate **6** (2nd and 3rd analysis). Based on these results, I concluded that the instability of the ketene silyl acetal caused the low yield.



**Figure 3-20.** Procedure of Stability Test

In order to suppress the decomposition, further screening of additives was conducted (Table 3-9). When 0.6 equivalent of water was added, the yield was slightly improved (entry 1). Then, various alkyl thiols were tested instead of water (entries 2-5), and the yield was dramatically improved up to 79% yield by using 1.2 equivalent of *tert*-butyl mercaptan. On the other hand, a stoichiometric amount of the thiol is necessary presumably to trap the silyl cation *in situ* formed (entry 6).

**Table 3-9.** Effect of Additives

entry	additive	x (eq.)	yield (%)
— <sup>a</sup>	H <sub>2</sub> O	1.2	46
1	H <sub>2</sub> O	0.6	56
2	MeOCOCH <sub>2</sub> SH	1.2	43
3	EtSH	1.2	74
4	<i>i</i> PrSH	1.2	77
5	<i>t</i> BuSH	1.2	79 (79) <sup>b</sup>
6	<i>t</i> BuSH	0.6	62

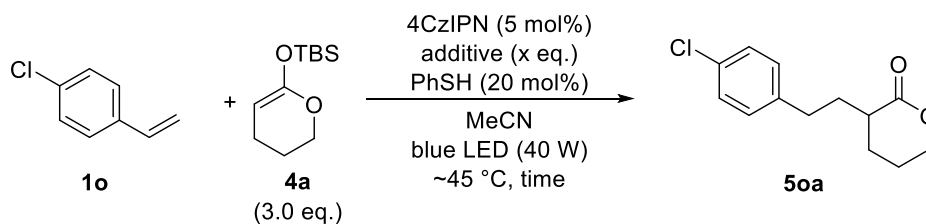
Reaction conditions: **1a** (0.50 mmol), **4b** (0.75 mmol), 4CzIPN (0.025 mmol), MeCN (5.0 mL), additive, under blue light irradiation, 12 h. The yields were determined by <sup>1</sup>H NMR analysis (internal standard: CH<sub>2</sub>Br<sub>2</sub>). <sup>a</sup>The same result as Figure 3-18. <sup>b</sup>The yield shown in parentheses is based on the isolated product

### Optimization for Styrene Analogue

To expand the scope of alkenes, the reaction with 4-chlorostyrene was then investigated. Based on the results of  $\alpha$ -alkylation of ketones with styrene analogues

(section 3-2), benzenethiol was effective to apply them to the reaction system. Therefore, various additives were initially tested in the presence of 20 mol% of benzenethiol (Table 3-10). When water was employed as an additive, the desired product was obtained in moderate yield (entry 1). Various alkyl thiols were tested (entries 2-5), and it was found that ethyl mercaptan was effective to improve the yield. Because the yield was still moderate, further optimization (especially for photocatalysts and protic additives) was demonstrated in the presence of ethyl mercaptan.

**Table 3-10.** Screening of Additives for Styrene Analogues

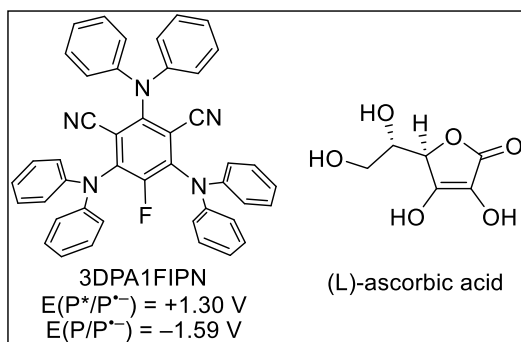
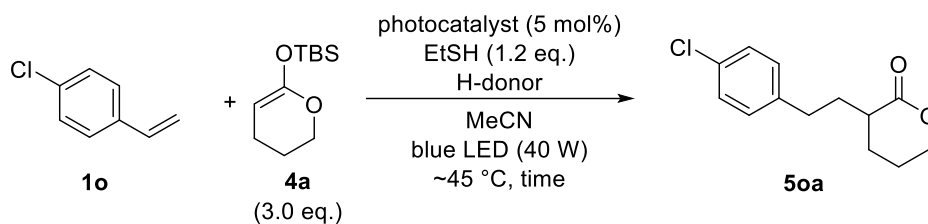


entry	additive	x (eq.)	yield (%)
1	H <sub>2</sub> O	0.6	42
2	EtSH	1.2	48
3	<i>i</i> PrSH	1.2	36
4	<i>t</i> BuSH	1.2	27
5	MeOCOCH <sub>2</sub> SH	1.2	27

Reaction conditions: **1o** (0.50 mmol), **4a** (1.50 mmol), 4CzIPN (0.025 mmol), MeCN (5.0 mL), additive, PhSH (0.10 mmol) under blue light irradiation, 12 h. The yields were determined by <sup>1</sup>H NMR analysis (internal standard: CH<sub>2</sub>Br<sub>2</sub>).

Subsequently, various photocatalysts were examined in the presence of ethyl mercaptan (Table 3-11). When 4CzTPN, which has higher oxidation potential than 4CzIPN, was employed, the yield was slightly improved (entry 1). Then, 4DPAIPN, which plays a role of a stronger reductant, were examined, and the desired product was obtained in 19% yield (entry 2). Presumably, relatively high oxidation potential is required to realize the reaction. Therefore, 3DPA1FIPN was next tested, and the yield was improved up to 58% yield (entry 3). Subsequently, effects of HAT catalysts were evaluated. In the absence of HAT catalysts, the reaction proceeded in lower yield, which means HAT catalysts are effective to improve the yield (entry 4). Thus, ascorbic acid (BDE = 78.0 kcal/mol) was examined as another HAT catalyst.<sup>23,24</sup> When 20 mol% of (L)-ascorbic acid was employed, the yield was improved up to 64% (entry 5). Next, 3 equivalents of ethyl mercaptan were used to promote formation of α-carbonyl radical, and the yield was slightly improved (entry 6). Then, it was found that 10 mol% of (L)-ascorbic acid was effective enough to improve the yield (entry 7). For further improvement, the reaction time was prolonged up to 24 h, and the reaction proceeded in good yield (entry 8).

**Table 3-11. Further Optimization for Styrene Analogues**



entry	photocatalyst	H-donor (mol%)	time (h)	yield (%)
— <sup>a</sup>	4CzIPN	PhSH (20)	12	48
1	4CzTPN	PhSH (20)	12	54
2	4DPAIPN	PhSH (20)	12	19
3	3DPA1FIPN	PhSH (20)	12	58
4	3DPA1FIPN	none	12	31
5	3DPA1FIPN	(L)-ascorbic acid (20)	12	64
6 <sup>b</sup>	3DPA1FIPN	(L)-ascorbic acid (20)	12	69
7 <sup>b</sup>	3DPA1FIPN	(L)-ascorbic acid (10)	12	70
8 <sup>b</sup>	3DPA1FIPN	(L)-ascorbic acid (10)	24	77 (72) <sup>c</sup>

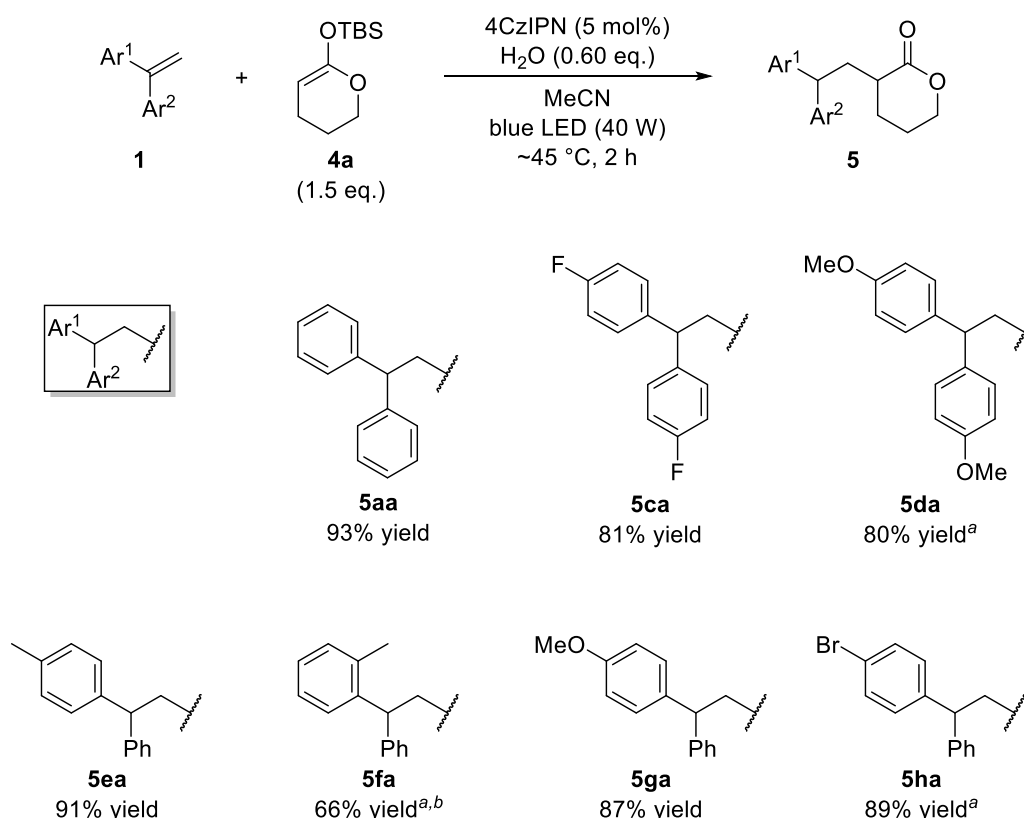
Reaction conditions: **1o** (0.50 mmol), **4a** (1.50 mmol), photocatalyst (0.025 mmol), MeCN (5.0 mL), EtSH (0.60 mmol), PhSH (0.10 mmol) under blue light irradiation, 12 h. The yields were determined by <sup>1</sup>H NMR analysis (internal standard: CH<sub>2</sub>Br<sub>2</sub>). <sup>a</sup>The same result as entry 2 in Table 3-10. <sup>b</sup>1.5 mmol (3.0 eq.) of EtSH was employed. <sup>c</sup>The yield shown in parentheses is based on the isolated product.

### 3-6. Substrate Scope of $\alpha$ -Alkylation of Esters

#### Scope of 1,1-Diarylethylenes

The scope of the reaction with respect to alkenes was examined under the optimized reaction conditions (Table 3-12).

**Table 3-12.** Scope of 1,1-Diarylethylenes



Reaction conditions (unless otherwise noted): **1** (0.50 mmol), **4a** (0.75 mmol), 4CzIPN (0.025 mmol), MeCN (5.0 mL), water (0.30 mmol), under blue light irradiation, 12 h. The shown yields are based on the isolated product. <sup>a</sup>0.60 mmol (1.2 eq.) of EtSH was employed instead of water. <sup>b</sup>0.10 mmol (20 mol%) of PhSH was added.

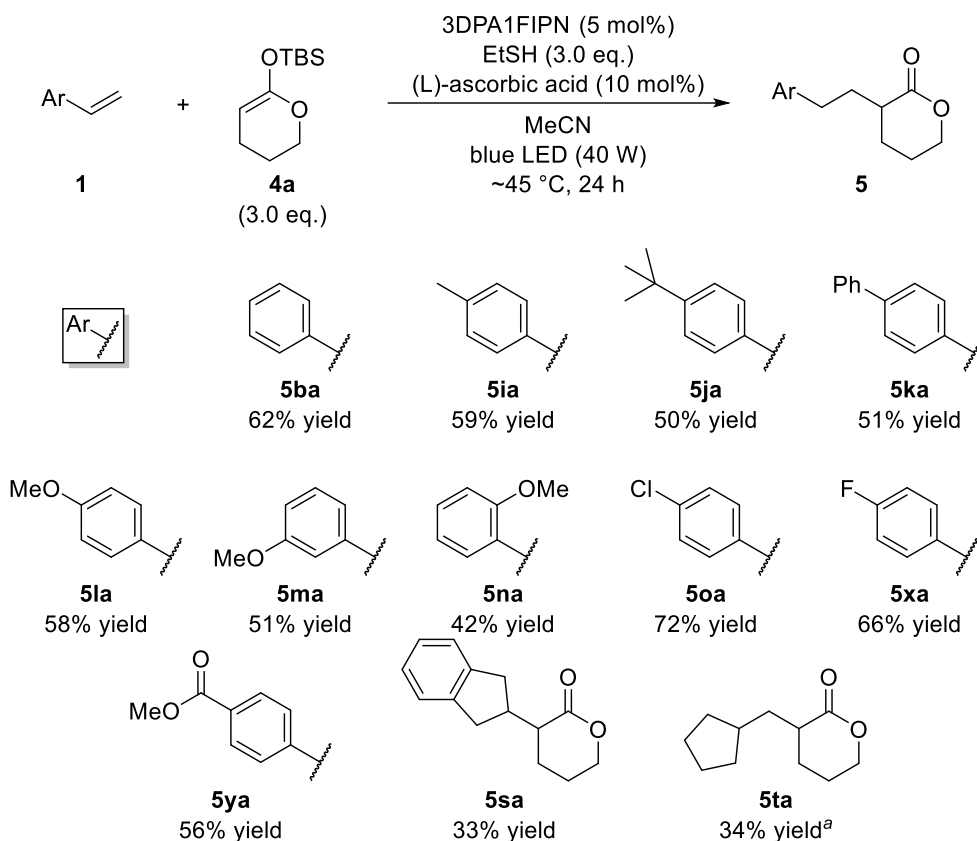
As described in the optimization part, the reaction using **1aa** proceeded in excellent yield (**5aa**). 1,1-Diarylethylenes having dimethoxy or difluoro groups at the 4- and 4'-positions of their aromatic rings reacted smoothly to afford the desired products in high yields (**5ca**, **5da**). Then, 1,1-diarylethylene bearing a methyl group at the 4-position of its aromatic ring were examined, and the desired product was obtained in excellent yields (**5ea**). 1,1-Diarylethylene substituted with a methyl group at the 2-position of its aromatic ring afforded the desired product in moderate yield (**5fa**). An alkene substrate bearing an electron-donating group, such as a 4-methoxy group, was applicable, and the reaction proceeded in high yield (**5ga**). The reaction using an alkene substituted with a bromo group was available, and the desired product was obtained in good yield (**5ha**). The mono-substituted 1,1-diarylethylenes afforded each pair of the diastereomers; however, the

diastereoselectivities were approximately 1:1 (**3ea-3ha**).

### Scope of Styrene Analogues and Simple Alkenes

Subsequently, the scope of the reaction with respect to styrene analogues and simple alkenes was examined under the optimized reaction conditions (Table 3-13).

**Table 3-13.** Scope of Styrene Analogues and Simple Alkenes



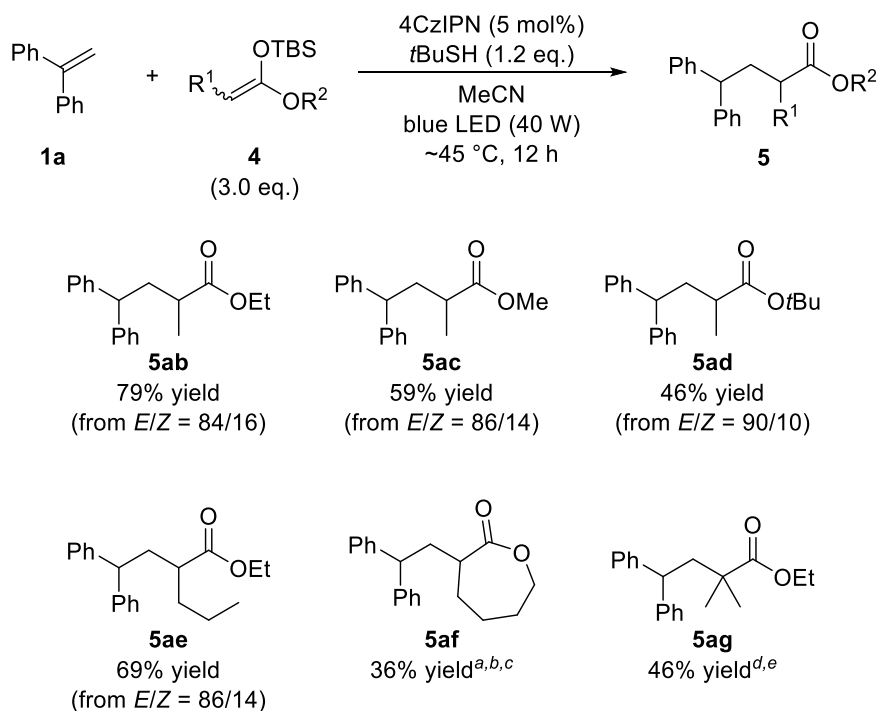
Reaction conditions: **1** (0.50 mmol), **4a** (1.50 mmol), photocatalyst (0.025 mmol), MeCN (5.0 mL), EtSH (1.50 mmol), (L)-ascorbic acid (0.050 mmol) under blue light irradiation, 24 h. The shown yields are based on the isolated product. <sup>a</sup>Alkene **1t** (2.5 mmol, 5.0 eq.), ketene silyl acetal **4a** (0.50 mmol, 1.0 eq.), and EtSH (0.50 mmol, 1.0 eq.) were employed.

When styrene was employed, the reaction proceeded in moderate yield (**5ba**). Styrene analogues bearing alkyl or phenyl group were also available, and the desired products were obtained in moderate yields (**5ia-5ka**). When styrene analogues substituted with an electron-donating group such as methoxy group were employed, the reactions proceeded in moderate yields (**5la-5na**). When 4-chlorostyrene and 4-fluorostyrene were employed, the desired products were obtained in moderate to good yields (**5oa**, **5xa**). An electron deficient styrene analogue was also applicable, and the desired product was obtained in moderate yield (**5ya**). Furthermore, an internal alkene, indene, afforded the desired product; however, the yield was low (**5sa**). Methylenecyclopentane, which does not have any aromatic ring, was available although the yield was not so high (**5ta**).

### Scope of Ketene Silyl Acetals

Next, the scope of the reactions with respect to silyl enol ethers was also investigated (Table 3-14).

**Table 3-14.** Scope of Ketene Silyl Acetals

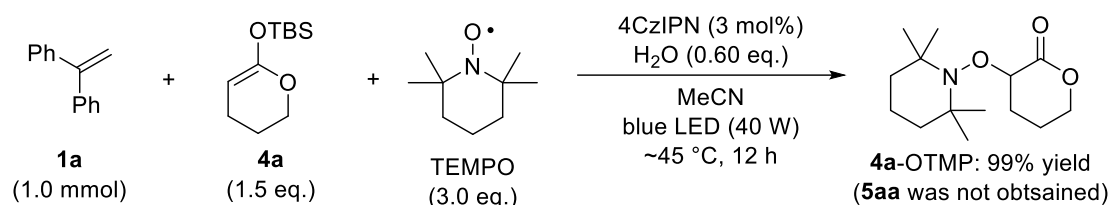


Reaction conditions (unless otherwise noted): **1a** (0.50 mmol), **4** (1.5 mmol), 4CzIPN (0.025 mmol), *t*BuSH (0.60 mmol), MeCN (5.0 mL), under blue light irradiation, 12 h. The shown yields are based on the isolated product. <sup>a</sup>0.015 mmol (3 mol%) of 4CzIPN was employed. <sup>b</sup>0.3 mmol (0.6 eq.) of water was used instead of *t*BuSH. <sup>c</sup>0.75 mmol (1.5 eq.) of ketene silyl acetal **4** was employed. <sup>d</sup>0.6 mmol (1.2 eq.) of water was used instead of *t*BuSH. <sup>e</sup>The reaction was performed for 36 h.

As described in the optimization part, ketene silyl acetal deriving from ethyl propionate reacted with **1a** in good yield (**5ab**). Similarly, alkylation of methyl and *tert*-butyl propionate was successful, and the desired products were obtained in moderate yields (**5ac**, **5ad**). A ketene silyl acetal prepared from ethyl valerate was also applicable to afford the desired product in good yield (**5ae**). When ketene silyl acetal deriving from  $\epsilon$ -caprolactone was employed, the desired product was obtained in low yield (**5af**). Furthermore, it was found that ketene silyl acetal derived from ethyl isobutyrate afforded the desired product in moderate yield (**5ag**).

### 3-7. Mechanistic Studies of $\alpha$ -Alkylation of Esters

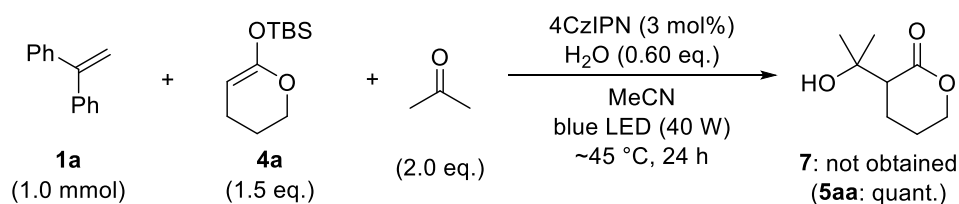
To gain insight into the reaction mechanism, mechanistic studies were conducted. When the reaction carried out in the presence of TEMPO, the adduct **4a**-OTMP was obtained in 99% yield, which implies that the reaction proceeded through formation of the  $\alpha$ -carbonyl radical (Figure 3-21).



The yield was determined by <sup>1</sup>H NMR analysis (internal standard: CH<sub>2</sub>Br<sub>2</sub>).

**Figure 3-21.** Radical Trapping Experiment

When the reaction was carried out in the presence of 2.0 equivalents of acetone, the desired product was obtained in quantitative yield without formation of the aldol-type adduct **7** (Figure 3-22). This result also indicates that the reaction proceeds in radical pathway because ketones are more reactive electrophiles than alkenes in polar mechanism.



The yield was determined by <sup>1</sup>H NMR analysis (internal standard: CH<sub>2</sub>Br<sub>2</sub>).

**Figure 3-22.** Chemoselectivity of the Reaction



### 3-8. Proposed Mechanism

The proposed mechanism is shown in Figure 3-23. First, a silyl enol ether is oxidized by an excited photoredox catalyst (4CzIPN\*) under single-electron transfer (SET) conditions to afford the corresponding cation radical **I**. Then, an employed protic additive including both water and thiols promote desilylation. Given that the reactions proceeded smoothly in the presence of 0.6 equivalent of water, a promotor of desilylation was not only water and thiol but also TBSOH. After removal of the silyl cation by water,  $\alpha$ -carbonyl radical **II** is formed, which easily reacts with an alkene to afford radical intermediate **III**. When the reduced catalyst (4CzIPN<sup>•-</sup>) has sufficient reduction potential to give a single electron to intermediate **III**, the reaction proceeds through path A. After reduction of **III**, the formed intermediate **IV** is immediately protonated to afford the desired product. When 4CzIPN<sup>•-</sup> does not have a potential to reduce radical intermediate **III**, a thiol cocatalyst is required as a HAT catalyst (path B). Radical intermediate **III** [BDE = 357.3  $\pm$  6.3 kJ/mol for H-CH(Me)Ph] abstracts the hydrogen atom from benzenethiol (PhS-H: BDE = 349.4  $\pm$  4.5 kJ/mol) to afford desired product and the thiyl radical. <sup>17</sup> The formed thiyl radical is reduced by 4CzIPN<sup>•-</sup> and immediately protonated to regenerate benzenethiol. Thereby, the reactions proceed in the presence of catalytic amounts of 4CzIPN and benzenethiol.

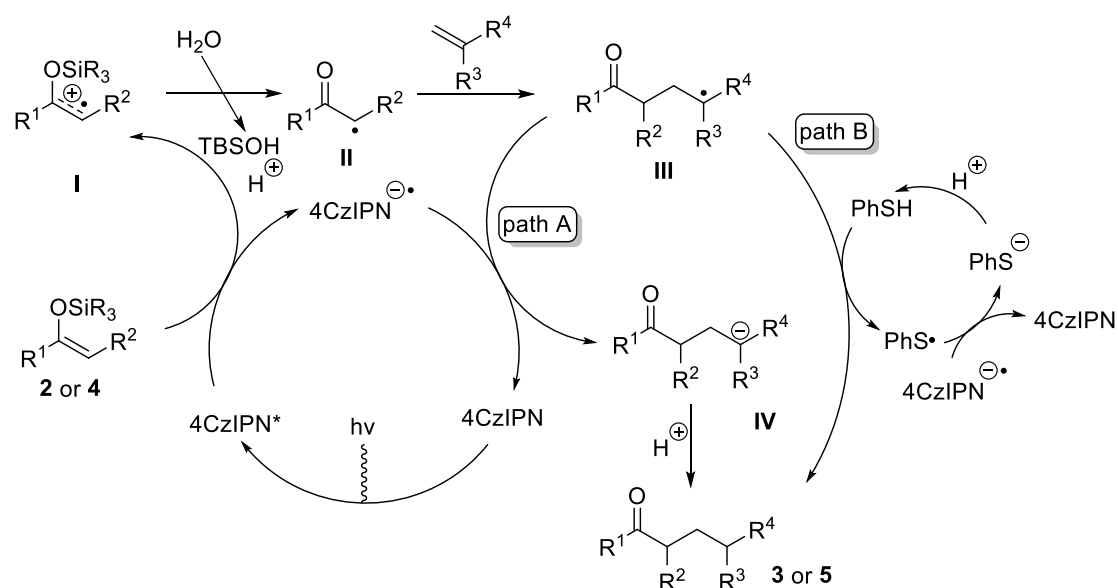
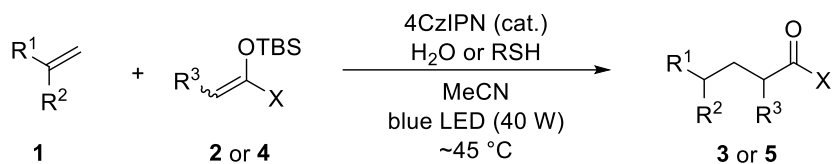


Figure 3-23. Proposed Mechanism

### 3-9. Conclusion



**Figure 3-24.** General Scheme

In summary, I have developed  $\alpha$ -alkylation reactions of ketones and esters with alkenes through photo-induced activation of their silyl enol ethers. Under blue-light irradiation conditions, the alkylation reactions proceeded smoothly in the presence of a photocatalyst and a small amount of water or a thiol to afford the desired products in good to excellent yields. By using benzenethiol as a HAT catalyst, the substrate scope was expanded not only to styrene derivatives but also to simple alkenes bearing no aromatic ring. To the best of my knowledge, this is the first example of photo-induced intermolecular  $\alpha$ -alkylation reactions of silyl enol ethers with alkenes.

### 3-10. References

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#### ***4. Brønsted Base-Photoredox Catalyst Hybrid Systems for $\alpha$ -Alkylation Reactions of Ketones with Alkenes***

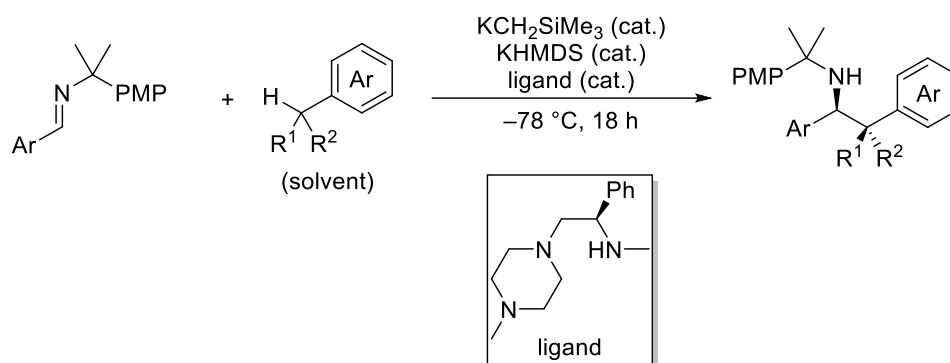
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## 5. Summary

In my doctoral thesis studies, I have developed catalytic C–C bond forming reactions of less reactive pronucleophiles (less acidic and less nucleophilic). In particular, benzylic C–H functionalization of unactivated alkylarenes and catalytic  $\alpha$ -alkylation of carbonyl compounds with alkenes have been achieved. They are remarkable for their excellent atom economy because they proceed under proton transfer conditions.

### Chapter 2

In chapter 2, I have investigated strong Brønsted base-catalyzed asymmetric addition reactions of alkylarenes with imines (Figure 5-1).



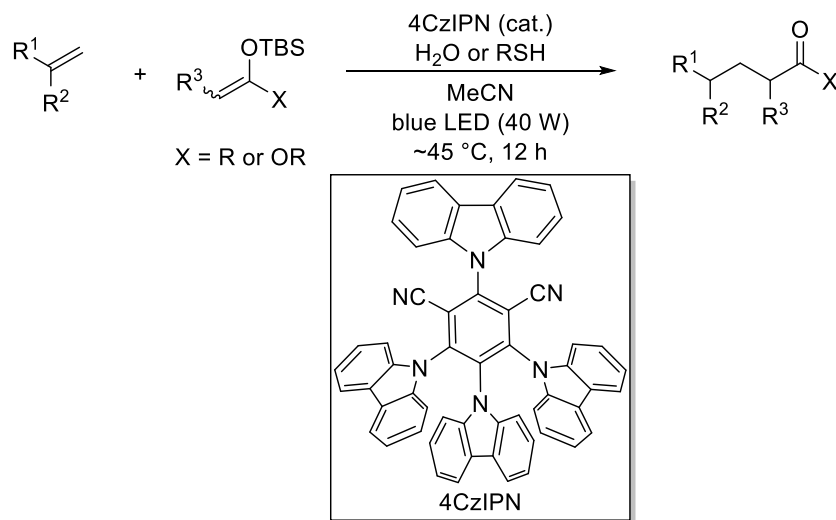
**Figure 5-1.** Catalytic Asymmetric Addition Reactions of Unactivated Alkylarenes

In the presence of only catalytic amount of alkyl potassium, KHMDS, and a chiral amine ligand, unactivated alkylarenes reacted with imines to afford the desired adduct in good to excellent yields with high enantioselectivities. Up to now, that application of less acidic pronucleophiles ( $\text{p}K_{\text{a}} > 30$  in DMSO) to base-catalyzed reactions has been recognized to be challenging. Therefore, it is remarkable that unactivated alkylarenes ( $\text{p}K_{\text{a}} \sim 43$  in DMSO) are applicable in base-catalyzed reactions. The key to success of these reactions is to design anionic reaction intermediates to be strongly basic, which is termed “Product Base”. Based on this strategy, I overcame “Catalyst Turnover Problem”. So far benzyl radicals have been often employed for benzylic C–H functionalization, and its application to asymmetric catalysis is recognized to be difficult. On the other hand, these reactions proceed via formation of benzyl anions, and I succeeded to apply them to asymmetric variants. It should be noted that I achieved chiral modification of the potassium ion using simple diamine ligands and applied it to asymmetric reactions. Conventionally, clathrate ligands were generally employed for chiral modification of potassium ion because of its low Lewis acidity and large ionic radius. These results expand a possibility of chiral alkali metal catalysis. Interestingly, the enantioselectivity was significantly improved by using KHMDS as an additive. Furthermore, the mechanistic investigation indicated that oligomeric chiral aggregation was formed in 1:1:1 ration for benzyl potassium, KHMDS, and the chiral amine ligand.

These reactions are synthetically valuable because both gram-scale reaction and asymmetric reaction via *in situ*-prepared imine were achieved. The obtained adducts can be transformed into various useful compounds.

### Chapter 3

In chapter 3, I have developed  $\alpha$ -alkylation of ketones and esters with alkenes through photo-induced activation of their silyl enol ethers (Figure 5-2).



**Figure 5-2.** Photocatalytic  $\alpha$ -Alkylation of Silyl Enol Ethers with Alkenes

Conventionally, addition of enolates derived from ketones to alkenes have been recognized to be quite slow. On the other hand, I focused on transformation of enolates such as silyl enol ethers into  $\alpha$ -carbonyl radicals which can smoothly react with alkenes. Based on this idea, I tried to develop addition reactions of silyl enol ethers with alkenes in the presence of a photoredox catalyst. Under blue-light irradiation conditions, the alkylation reactions proceeded smoothly in the presence of a photocatalyst and a small amount of water or a thiol to afford the desired products in good to excellent yields. I figured out that approximate 1 equivalent of water or a thiol to trap silyl cation *in situ* formed was effective to promote the reactions. By using benzenethiol as a HAT catalyst, the substrate scope was expanded not only to styrene derivatives but also to simple alkenes bearing no aromatic ring. Furthermore, applicable carbonyl compounds include not only ketones but also esters. The mechanistic investigation indicated the reactions proceeded via formation of  $\alpha$ -carbonyl radicals. Because the reactions proceed under radical conditions, silyl enol ethers react with alkenes rather than ketones which can afford aldol products. This is interesting chemoselectivity compared with polar addition reactions. To the best of my knowledge, this is the first example of photo-induced intermolecular  $\alpha$ -alkylation reactions of silyl enol ethers with alkenes.



## ***Chapter 4***

In the previous section,  $\alpha$ -alkylation reactions of silyl enol ethers with alkenes have been developed. However, silyl groups are removed in these reactions and they become source of wastes. Therefore, catalytic formation of enolates is demanded. In my doctoral thesis studies, I have achieved catalytic formation of the enolates and its application to fully catalytic addition of ketones to alkenes.

In my doctoral thesis studies, I have developed advanced Brønsted base-catalyzed reactions. Initially, I have overcome “Catalyst Turnover Problem” by designing “Product Base” to be strongly basic and achieved catalytic asymmetric addition reactions of alkylarenes which are less reactive (less acidic) pronucleophiles with imines. Next, I have overcome “Addition Problem” by using single electron transfer properly and realized catalytic  $\alpha$ -alkylation of ketones which are less reactive (less nucleophilic) pronucleophiles with alkenes. I believe that a range of possibilities of approach to atom-economical reactions has been widely expanded.

## *Experimental section*

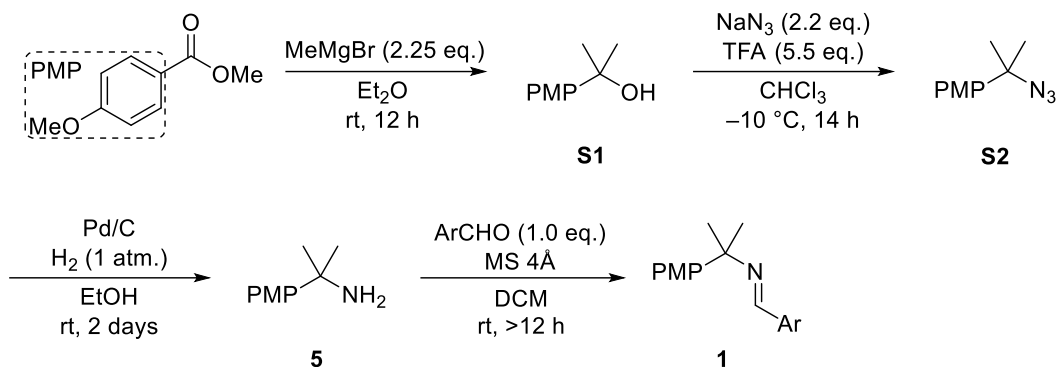
### *Experimental Procedure (Chapter 2)*

#### *General*

Melting points were measured with Büchi Melting Point D-545.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on JEOL JNM-ECA500 and JNM-ECX600 spectrometers in  $\text{CDCl}_3$  unless otherwise noted. Tetramethylsilane (TMS) served as internal standard ( $\delta = 0$ ) for  $^1\text{H}$  NMR, and  $\text{CDCl}_3$  served as internal standard ( $\delta = 77.0$ ) for  $^{13}\text{C}$  NMR. Benzotrifluoride (BTF) served as internal standard ( $\delta = -63.72$ ) for  $^{19}\text{F}$  NMR. IR spectra were measured on JASCO FT/IR-610 spectrometer. WILMAD screw-cap NMR tube (Aldrich Co., Ltd.) was used for NMR experiments. HPLC analysis was performed on Shimadzu SPD-M20A. DART mass spectra were recorded on JEOL JMS-T100TD mass spectrometer. Preparative thin-layer chromatography (PTLC) was carried out using Wakogel B-5F. Potassium *tert*-butoxide ( $\text{KO}t\text{Bu}$ ) was purchased from Kanto Chemical Co., Inc. Lithium 2,2,6,6-tetramethylpiperizide (LiTMP), potassium bis(trimethylsilyl)amide (KHMDs), sodium bis(trimethylsilyl)amide (NaHMDs), and lithium bis(trimethylsilyl)amide (LiHMDs) were purchased from Aldrich Co., Ltd. Trimethylsilylmethylpotassium ( $\text{KCH}_2\text{SiMe}_3$ ) was prepared according to literature.<sup>1</sup> Potassium 2,2,6,6-tetramethylpiperidide (KTMP) was prepared by deprotonation of 2,2,6,6-tetramethylpiperidine with  $\text{KCH}_2\text{SiMe}_3$ . Potassium bis(trialkylsilyl)amides were also prepared by deprotonation of the corresponding bis(trialkylsilyl)amine. Ethylbenzene was purchased from Tokyo Chemical Industry Co., Ltd. and was distilled and stored in an ampule. Toluene was purchased from Kanto Chemical Co., Inc. and purified further by Glass Contour NIKKO HANSEN & Co., LTD. TBME was distilled in the presence of benzophenone and sodium. **L1**,<sup>2</sup> **L2**,<sup>3</sup> and **L3**<sup>4</sup> were prepared according to the literatures.

### Preparation of Imines

The imines were synthesized according to our previous literature.<sup>5</sup>



### Synthesis of alcohol S1

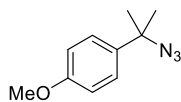
A solution of MeMgBr in Et<sub>2</sub>O (3.0 M, 75.0 mL, 225 mmol) was charged in a flame-dried 300 mL 3-way flask, and then a solution of methyl *p*-anisate in Et<sub>2</sub>O (1.0 M, 100 mL, 100.0 mmol) was slowly added via a dropping funnel over 30 min at 0 °C. After completing the addition, the mixture was warmed to room temperature and stirred for 12 h. The reaction was quenched by slow addition of sat. aq. NH<sub>4</sub>Cl and the whole became a clear solution. The solution was extracted with Et<sub>2</sub>O (50 mL × 3), and the combined organic layer was dried over anhydrous MgSO<sub>4</sub>. After filtration and evaporation, the desired colorless liquid was obtained. The oil (**S1**) was used without purification in the next synthesis.

**2-(4-Methoxyphenyl)propan-2-ol (S1);** The structure was confirmed by comparison with data of <sup>1</sup>H and <sup>13</sup>C NMR shown in a literature.<sup>6</sup> Colorless oil; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz) δ: 7.42 (2H, d, *J* = 8.94 Hz), 6.88 (2H, d, *J* = 8.94 Hz), 3.81 (3H, s), 1.57 (6H, s); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 Hz) δ: 158.35, 141.35, 125.60, 113.49, 72.20, 55.28, 31.80.

### Synthesis of azide S2

The oil (**S1**) obtained in the previous synthesis and NaN<sub>3</sub> (14.30 g, 220.0 mmol) were placed in a 2-necked 500 mL round bottom flask, and CHCl<sub>3</sub> (100 mL) was added at -10 °C. A solution of TFA (42.1 mL, 550 mmol) in CHCl<sub>3</sub> (100 mL) was then slowly added to the solution over period of 1 h, and the whole mixture was stirred at -10 °C for 14 h. H<sub>2</sub>O (100 mL) was added to the mixture to quench the reaction, and the mixture was extracted with DCM (50 mL × 3). The combined organic layer was washed with brine (100 mL × 2) and dried over anhydrous MgSO<sub>4</sub>. After filtration and evaporation, the desired pale-yellow oil was obtained. The oil (**S2**) was used in next step without purification.

**1-(2-Azidopropan-2-yl)-4-methoxybenzene (S2);** The structure was confirmed by



comparison with data of  $^1\text{H}$  and  $^{13}\text{C}$  NMR shown in a literature.<sup>7</sup>

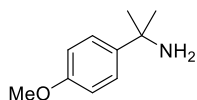
Colorless oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$ : 7.28 (2H, d,  $J = 9.07$  Hz), 6.81 (2H, d,  $J = 8.50$  Hz), 3.72 (3H, s), 1.53 (6H, s);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ,

125 Hz)  $\delta$ : 158.74, 136.65, 126.37, 113.72, 63.46, 55.22, 28.17.

### Synthesis of amine 5

The oil (S2) obtained in the previous synthesis was put in a 1 L round bottom flask, and 10% Pd/C and EtOH were added. The solution was vigorously stirred at room temperature under 1 atm of  $\text{H}_2$ . After 2 days, the mixture was filtered off through a Celite pad, and the filtrate was evaporated under vacuum to afford a colorless oil. The oil was distilled under reduced pressure to afford the desired amine **5** in a pure form (11.90 g, 72.02 mmol, 72% yield in 3 steps).

**2-(4-Methoxyphenyl)propan-2-amine (5);** Colorless liquid;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 600



MHz)  $\delta$ : 7.41 (2H, d,  $J = 8.94$  Hz), 6.84 (2H, d,  $J = 8.94$  Hz), 3.78 (3H, s), 1.46 (6H, s);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 150 MHz)  $\delta$ : 157.87, 142.51, 125.77,

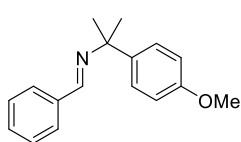
113.39, 55.22, 51.91, 32.93; IR (neat,  $\text{cm}^{-1}$ ) 3360, 3290, 3037, 2962,

2837, 2548, 2046, 1892, 1609, 1512, 1462, 1411, 1363, 1300, 1247, 1181, 1115, 1035; HRMS (DART) calcd for  $\text{C}_{10}\text{H}_{16}\text{N}_1\text{O}_1$   $[\text{M} + \text{H}]^+$  166.1232, found 166.1234.

### Typical experimental procedure for synthesis of *p*-methoxycumylimine

*p*-Methoxycumylamine **5** (10.0 mmol) was added to a solution of aldehyde (1.0 eq.) and MS 4 A (5 g) in DCM (10 mL). The whole mixture was stirred for 12 h or more at room temperature, and then filtered through a Celite pad. The filtrate was concentrated under reduced pressure, and the crude product obtained was purified by recrystallization (for **1e**, **1g**, and **1n**) or distillation (for the others) to afford the corresponding imine **1**.

**(E)-N-(2-(4-Methoxyphenyl)propan-2-yl)-1-phenylmethanimine (1a);** White solid;



Mp 34-36 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 600 MHz)  $\delta$ : 8.16 (1H, s), 7.77-7.76 (2H, m), 7.40 (3H, t,  $J = 3.09$  Hz), 7.35 (2H, d,  $J = 8.94$  Hz), 6.87

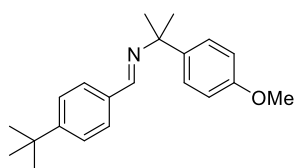
(2H, d,  $J = 8.94$  Hz), 3.80 (3H, s), 1.63 (6H, s);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 150 MHz) 157.98, 157.07, 140.17, 136.97, 130.33, 128.48, 128.06,

127.33, 113.42, 62.24, 55.23, 29.90; IR (KBr disk,  $\text{cm}^{-1}$ ) 3060, 2957, 2913, 2833, 1642, 1605, 1578, 1507, 1450, 1413, 1381, 1358, 1296, 1243, 1174, 1105, 1035; HRMS

(DART) calcd for  $\text{C}_{17}\text{H}_{20}\text{N}_1\text{O}_1$   $[\text{M} + \text{H}]^+$  254.15449, found 254.15419.

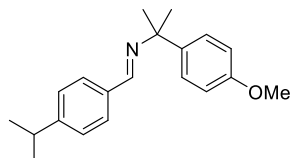
**(E)-1-(4-(tert-Butyl)phenyl)-N-(2-(4-methoxyphenyl)propan-2-yl)methanimine**

**(1b);** White solid; Mp 73-74 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$ : 8.14 (1H, s), 7.70 (2H, d,  $J = 7.94$  Hz), 7.42 (2H, d,  $J = 8.50$  Hz), 7.33 (2H, d,  $J = 9.07$  Hz), 6.86 (2H, d,  $J = 9.07$  Hz), 3.80 (3H, s), 1.62 (6H, s), 1.32 (9H, s);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz) 157.92, 156.91,



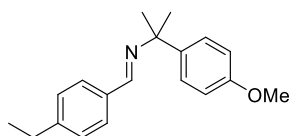
153.71, 140.39, 134.31, 127.82, 127.32, 125.44, 113.37, 62.12, 55.21, 34.82, 31.21, 29.95; IR (KBr disk,  $\text{cm}^{-1}$ ) 3453, 2965, 2903, 2868, 2836, 1646, 1608, 1576, 1509, 1461, 1407, 1366, 1303, 1246, 1175, 1110, 1033; HRMS (DART) calcd for  $\text{C}_{21}\text{H}_{28}\text{N}_1\text{O}_1$   $[\text{M} + \text{H}]^+$  310.21709, found 310.21628.

**(E)-1-(4-Isopropylphenyl)-N-(2-(4-methoxyphenyl)propan-2-yl)methanimine (1c);**



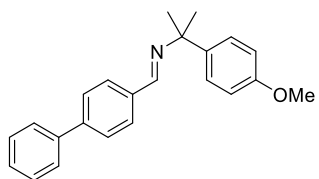
Colorless oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 600 MHz)  $\delta$ : 8.06 (1H, s), 7.62 (2H, d,  $J = 7.56$  Hz), 7.26 (2H, d,  $J = 8.94$  Hz), 7.19 (2H, d,  $J = 8.25$  Hz), 6.79 (2H, d,  $J = 8.94$  Hz), 3.73 (3H, s), 2.89-2.82 (1H, m), 1.55 (6H, s), 1.18 (6H, d,  $J = 6.87$  Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 150 MHz) 157.94, 157.02, 151.52, 140.38, 134.75, 128.13, 127.33, 126.60, 113.38, 62.11, 55.22, 34.10, 29.5, 23.85; IR (neat,  $\text{cm}^{-1}$ ) 2964, 2873, 2836, 1643, 1609, 1577, 1510, 1462, 1363, 1301, 1248, 1177, 1105, 1037; HRMS (DART) calcd for  $\text{C}_{20}\text{H}_{26}\text{N}_1\text{O}_1$   $[\text{M} + \text{H}]^+$  296.20144, found 296.20282.

**(E)-1-(4-Ethylphenyl)-N-(2-(4-methoxyphenyl)propan-2-yl)methanimine (1d);**



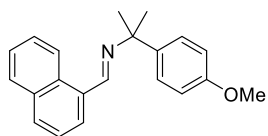
Colorless oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$ : 8.13 (1H, s), 7.68 (2H, d,  $J = 8.50$  Hz), 7.34 (2H, d,  $J = 9.07$  Hz), 7.23 (2H, d,  $J = 8.50$  Hz), 6.86 (2H, d,  $J = 9.07$  Hz), 3.80 (3H, s), 2.67 (2H, q,  $J = 7.56$  Hz), 1.62 (6H, s), 1.24 (3H, t,  $J = 7.65$  Hz);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ):  $\delta = 157.9, 157.0, 146.9, 140.3, 134.6, 128.1, 128.0, 127.3, 113.4, 62.1, 55.2, 29.9, 28.8, 15.5$ ; IR (neat,  $\text{cm}^{-1}$ ): 798, 827, 977, 1034, 1180, 1244, 1298, 1509, 1609, 1644, 2966; HRMS (DART) calcd for  $\text{C}_{19}\text{H}_{24}\text{NO}$   $[\text{M} + \text{H}]^+$  282.18579, found: 282.18523.

**(E)-1-([1,1'-Biphenyl]-4-yl)-N-(2-(4-methoxyphenyl)propan-2-yl)methanimine (1e);**



Colorless solid; Mp: 88-89  $^{\circ}\text{C}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 600 MHz)  $\delta$ : 8.19 (1H, s), 7.84 (2H, d,  $J = 8.25$  Hz), 7.63-7.61 (4H, m), 7.43 (2H, t,  $J = 7.56$  Hz), 7.36-7.33 (3H, m), 6.88 (2H, d,  $J = 8.94$  Hz), 3.79 (3H, s), 1.65 (6H, s);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ):  $\delta$ : 158.0, 156.7, 143.1, 140.6, 140.2, 135.9, 128.8, 128.5, 127.6, 127.4, 127.2, 127.1, 113.5, 62.3, 55.2, 29.9; IR (neat,  $\text{cm}^{-1}$ ): 418, 558, 769, 811, 832, 1035, 1246, 1508, 1559; HRMS (DART) calcd for  $\text{C}_{23}\text{H}_{24}\text{NO}$   $[\text{M} + \text{H}]^+$  330.18524, found: 330.18627.

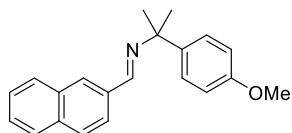
**(E)-N-(2-(4-Methoxyphenyl)propan-2-yl)-1-(naphthalen-1-yl)methanimine (1f);**



Colorless oil;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.80-8.78 (2H, m), 7.90-7.88 (3H, m), 7.55-7.51 (3H, m), 7.42 (2H, d,  $J = 9.07$  Hz), 6.91 (2H, d,  $J = 8.50$  Hz), 3.82 (3H, s), 1.74 (6H, s);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 158.1, 157.1, 140.0, 133.8, 132.4, 131.4, 130.6,

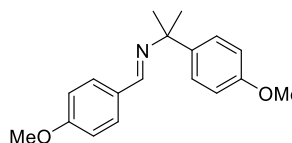
128.6, 128.1, 127.5, 126.9, 125.9, 125.3, 124.2, 113.5, 63.1, 55.3, 30.1; IR (neat,  $\text{cm}^{-1}$ ) 2970, 1637, 1611, 1508, 1242, 1177, 1034, 828, 800, 774, 565; HRMS (DART) calcd for  $\text{C}_{21}\text{H}_{22}\text{NO}$   $[\text{M} + \text{H}]^+$  304.17014, found 304.16882.

**(E)-N-(2-(4-Methoxyphenyl)propan-2-yl)-1-(naphthalen-2-yl)methanimine (1g);**



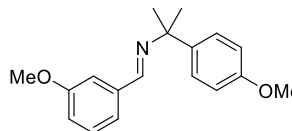
White solid; Mp 87-88 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$ : 8.29 (1H, s), 8.06 (1H, dd,  $J = 8.50, 1.13$  Hz), 8.01 (1H, s), 7.86-7.82 (3H, m), 7.49-7.47 (2H, m), 7.37 (2H, d,  $J = 9.07$  Hz), 6.88 (2H, d,  $J = 8.50$  Hz), 3.80 (3H, s), 1.66 (6H, s);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz) 158.02, 157.24, 140.16, 134.64, 134.61, 133.14, 129.76, 128.52, 128.30, 127.82, 127.39, 126.89, 126.30, 123.97, 113.46, 62.41, 55.25, 29.99; IR (KBr disk,  $\text{cm}^{-1}$ ) 3454, 3053, 2962, 2871, 2837, 1635, 1606, 1578, 1506, 1464, 1359, 1299, 1242, 1174, 1117, 1093, 1036; HRMS (DART) calcd for  $\text{C}_{21}\text{H}_{22}\text{N}_1\text{O}_1$   $[\text{M} + \text{H}]^+$  304.17014, found 340.16957.

**(E)-1-(4-Methoxyphenyl)-N-(2-(4-methoxyphenyl)propan-2-yl)methanimine (1h);**



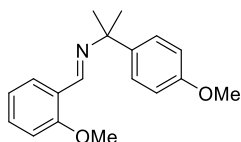
White solid; Mp 69-70 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 600 MHz)  $\delta$ : 8.09 (1H, s), 7.70 (2H, d,  $J = 8.25$  Hz), 7.34 (2H, d,  $J = 8.94$  Hz), 6.91 (2H, d,  $J = 8.94$  Hz), 6.87 (2H, d,  $J = 8.94$  Hz), 3.83 (3H, s), 3.80 (3H, s), 1.62 (6H, s);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 150 MHz)  $\delta$ : 161.39, 157.92, 156.38, 140.48, 130.00, 129.55, 127.33, 113.85, 113.37, 61.94, 55.33, 55.22, 30.00; IR (KBr disk,  $\text{cm}^{-1}$ ) 3046, 2969, 2933, 2862, 2841, 1645, , 1509, 1458, 1381, 1363, 1307, 1245, 1158, 1100, 1027; HRMS (DART) calcd for  $\text{C}_{18}\text{H}_{22}\text{N}_1\text{O}_1$   $[\text{M} + \text{H}]^+$  284.16505, found 284.16381.

**(E)-1-(3-Methoxyphenyl)-N-(2-(4-methoxyphenyl)propan-2-yl)methanimine (1i);**



Colorless oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 600 MHz) 8.12 (1H, s), 7.38-7.26 (5H, m), 6.96-6.94 (1H, m), 6.87 (2H, d,  $J = 8.25$  Hz), 3.85 (3H, s), 3.81 (3H, s), 1.63 (6H, s);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 150 MHz) 159.87, 157.99, 156.93, 140.16, 138.48, 129.45, 127.33, 121.25, 116.90, 113.42, 111.80, 62.26, 55.37, 55.23, 29.91; IR (neat,  $\text{cm}^{-1}$ ) 2970, 2836, 1642, 1586, 1511, 1462, 1364, 1249, 1177, 1107, 1039; HRMS (DART) calcd for  $\text{C}_{18}\text{H}_{22}\text{N}_1\text{O}_1$   $[\text{M} + \text{H}]^+$  284.16505, found 284.16442.

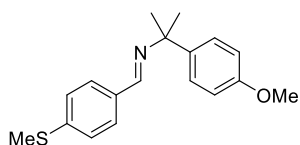
**(E)-1-(2-Methoxyphenyl)-N-(2-(4-methoxyphenyl)propan-2-yl)methanimine (1j);**



Colorless oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$ : 8.60 (1H, s), 7.98 (1H, dd,  $J = 7.37, 1.70$  Hz), 7.30-7.26 (3H, m), 6.91 (1H, t,  $J = 7.65$  Hz), 6.82-6.77 (3H, m), 3.75 (3H, s), 3.72 (3H, s), 1.55 (6H, s);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$ : 158.72, 157.84, 152.90, 140.88, 131.45, 127.18, 127.15, 125.49, 120.73, 113.34, 110.85, 62.33, 55.44, 55.21, 29.95; IR (neat,  $\text{cm}^{-1}$ ) 2969, 2837, 2052, 1919, 1885, 1634, 1604, 1510, 1487, 1463, 1364, 1292, 1247, 1178, 1108, 1033; HRMS (DART) calcd for  $\text{C}_{18}\text{H}_{22}\text{N}_1\text{O}_1$   $[\text{M} + \text{H}]^+$  284.16505, found

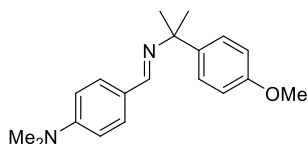
284.16493.

**(E)-N-(2-(4-Methoxyphenyl)propan-2-yl)-1-(4-(methylthio)phenyl)methanimine**



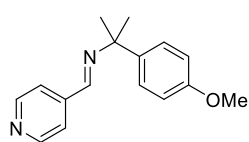
**(1k)**; Colorless solid; Mp: 55-57 °C;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.09 (1H, s), 7.67 (2H, d,  $J = 8.50$  Hz), 7.33 (2H, d,  $J = 9.07$  Hz), 7.25 (2H, m), 6.87 (2H, d,  $J = 8.50$  Hz), 3.81 (3H, s), 2.50 (3H, s), 1.62 (6, s);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 157.9, 156.4, 141.5, 140.2, 133.7, 128.4, 127.3, 125.8, 113.4, 62.2, 55.2, 29.9, 15.3; IR (neat,  $\text{cm}^{-1}$ ) 1634, 1511, 1300, 1240, 1177, 1085, 1034, 825, 557, 494; HRMS (DART) calcd for  $\text{C}_{18}\text{H}_{22}\text{NOS}$   $[\text{M} + \text{H}]^+$  300.14221, found 300.14115.

**(E)-4-(((2-(4-Methoxyphenyl)propan-2-yl)imino)methyl)-N,N-dimethylaniline (1l);**



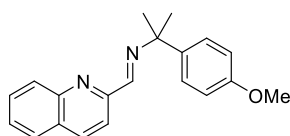
Pale-yellow solid; Mp 63-64 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 600 MHz)  $\delta$ : 8.03 (1H, s), 7.62 (2H, d,  $J = 8.94$  Hz), 7.33 (2H, d,  $J = 8.94$  Hz), 6.84 (2H, d,  $J = 8.25$  Hz), 6.68 (2H, d,  $J = 8.94$  Hz), 3.78 (3H, s), 2.98 (6H, s), 1.59 (6H, s);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 150 MHz)  $\delta$ : 157.81, 157.07, 151.94, 141.04, 129.36, 127.37, 125.37, 113.31, 111.66, 61.66, 55.22, 40.29, 30.16; IR (KBr disk,  $\text{cm}^{-1}$ ) 3453, 2963, 2897, 2815, 1635, 1605, 1555, 1523, 1445, 1360, 1302, 1235, 1165, 1118, 1066, 1036; HRMS (DART) calcd for  $\text{C}_{19}\text{H}_{25}\text{N}_2\text{O}_1$   $[\text{M} + \text{H}]^+$  297.19669 found 297.19736.

**(E)-N-(2-(4-Methoxyphenyl)propan-2-yl)-1-(pyridin-4-yl)methanimine (1m);**



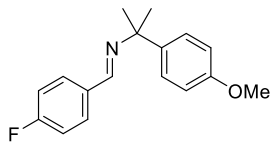
Colorless oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 600 MHz)  $\delta$ : 8.59 (2H, d,  $J = 6.19$  Hz), 8.02 (1H, s), 7.54 (2H, d,  $J = 6.19$  Hz), 7.25 (2H, d,  $J = 8.94$  Hz), 6.81 (2H, d,  $J = 8.25$  Hz), 3.74 (3H, s), 1.57 (6H, s);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 150 MHz) 158.23, 155.15, 150.32, 143.64, 139.13, 127.28, 121.97, 113.56, 63.00, 55.24, 29.64; IR (neat,  $\text{cm}^{-1}$ ) 3032, 2973, 2836, 1643, 1603, 1557, 1512, 1462, 1410, 1363, 1301, 1249, 1180, 1109, 1034; HRMS (DART) calcd for  $\text{C}_{16}\text{H}_{19}\text{N}_2\text{O}_1$   $[\text{M} + \text{H}]^+$  255.14974, found 255.15080.

**(E)-N-(2-(4-Methoxyphenyl)propan-2-yl)-1-(quinolin-2-yl)methanimine (1n);**



Yellow solid; Mp 67-68 °C;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.48 (1H, s), 8.30 (1H, d,  $J = 8.50$  Hz), 8.19 (1H, d,  $J = 8.50$  Hz), 8.11 (1H, d,  $J = 8.50$  Hz), 7.85 (1H, d,  $J = 7.94$  Hz), 7.73 (1H, t,  $J = 7.65$  Hz), 7.57 (1H, t,  $J = 7.37$  Hz), 7.39 (2H, d,  $J = 8.50$  Hz), 6.89 (2H, d,  $J = 7.49$  Hz), 3.81 (3H, s), 1.70 (6H, s);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 158.45, 158.11, 155.66, 147.71, 139.62, 136.46, 129.72, 129.40, 128.77, 127.72, 127.25, 127.20, 118.42, 113.55, 62.94, 55.25, 29.68; IR (KBr disk,  $\text{cm}^{-1}$ ) 3033, 2973, 2907, 2836, 1637, 1601, 1508, 1460, 1354, 1295, 1247, 1179, 1109, 1027; HRMS (DART) calcd for  $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_1$   $[\text{M} + \text{H}]^+$  305.16539, found 305.16578.

**(E)-1-(4-Fluorophenyl)-N-(2-(4-methoxyphenyl)propan-2-yl)methanimine (1o);**

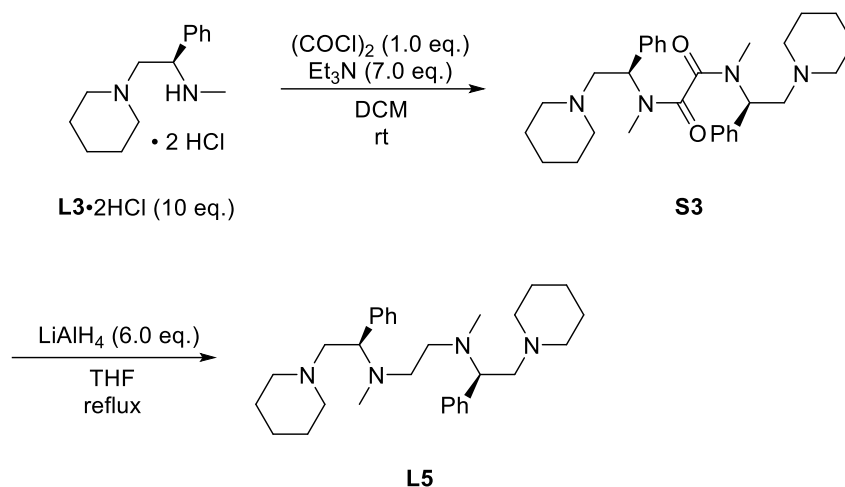


Colorless oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$ : 7.89 (1H, s), 7.54 (2H, dd,  $J = 8.50, 5.67$  Hz), 7.12 (2H, d,  $J = 8.50$  Hz), 6.86 (2H, t,  $J = 8.79$  Hz), 6.66 (2H, d,  $J = 8.50$  Hz), 3.59 (3H, s), 1.41 (6H, s);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 150 MHz) 164.13 ( $J_{\text{C-F}} = 250.34$  Hz), 158.03, 155.62, 140.00, 133.25 ( $J_{\text{C-F}} = 3.58$  Hz), 129.90 ( $J_{\text{C-F}} = 8.34$  Hz), 127.31, 115.51 ( $J_{\text{C-F}} = 21.46$  Hz), 113.45, 62.23, 55.24, 29.88;  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ , 465 MHz)  $\delta$ : -110.25; IR (neat,  $\text{cm}^{-1}$ ) 3039, 2973, 2934, 2837, 2056, 1893, 1644, 1603, 1463, 1413, 1363, 1298, 1179, 1153, 1096, 1036; HRMS (DART) calcd for  $\text{C}_{17}\text{H}_{19}\text{F}_1\text{N}_1\text{O}_1$   $[\text{M} + \text{H}]^+$  272.14507, found 272.14424.



## Preparation of Chiral Ligands

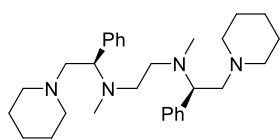
### Preparation of chiral ligand **L5**



Ammonium chloride salt **L3**·2HCl was prepared by acidic treatment of **L3** with 4N HCl (in ethyl acetate) and was recrystallized in EtOH. Then, Ammonium chloride salt **L3**·2HCl was converted to ligand **L5** by the following procedure. Triethylamine (4.88 mL, 35.0 mmol) was added to dispersion of **L3**·2HCl (2.91 g, 10.0 mmol) in dichloromethane (DCM, 50 mL). After the mixture was cooled to 0 °C, oxalyl chloride (0.43 mL, 5.0 mmol) was added. Subsequently, the reaction mixture was stirred overnight at room temperature. After the reaction was quenched by adding saturated aq. NaHCO<sub>3</sub>, the mixture was extracted with DCM (30 mL × 3). The combined organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After filtration and concentration under reduced pressure, the obtained crude product was purified by column chromatography (hexane-ethyl acetate) and recrystallization (in hexane-ethyl acetate) to afford the desired amide **S3** (0.930 mg, 38% yield). The obtained product was used without further purification in the next step.

Solution of the obtained amide **S3** (0.900 mg, 1.83 mmol) in THF (20 mL) was added to dispersion of LiAlH<sub>4</sub> (417.5 mg, 10.98 mmol) in THF (15 mL) at 0 °C. Subsequently, the reaction mixture was refluxed overnight and quenched with 3% aq. NaOH (5 mL). After filtration through a Celite pad and concentration under reduced pressure, the crude product was distilled to afford the desired tetraamine **L5** (296.5 mg, 35% yield).

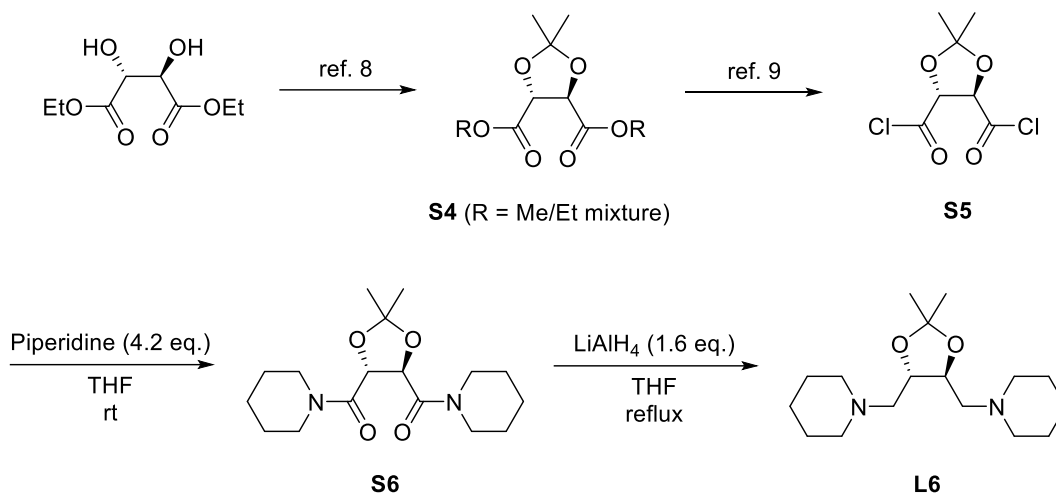
### *N*<sup>1</sup>,*N*<sup>2</sup>-Dimethyl-*N*<sup>1</sup>,*N*<sup>2</sup>-bis((*R*)-1-phenyl-2-(piperidin-1-yl)ethyl)ethane-1,2-diamine



(**L5**); Colorless oil; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ: 7.21-7.20 (4H, m), 7.15-7.13 (6H, m), 3.62 (2H, dd, *J* = 7.33, 3.67 Hz), 2.75 (2H, dd, *J* = 6.42, 3.21 Hz), 2.52 (2H, dd, *J* = 6.42, 3.21 Hz), 2.46-2.38 (4H, m), 2.28 (8H, s), 2.08 (6H, s), 1.43-1.39 (8H, m), 1.29 (4H, d, *J* = 4.81 Hz).; <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ: 140.1, 128.6, 127.7, 126.6, 65.8, 61.7, 55.1, 52.5, 39.0, 25.9, 24.3; IR (neat, cm<sup>-1</sup>) 2932, 2783, 1451, 1305, 1154, 1111, 1040,

994, 867, 781, 740, 698, 591, 530; HRMS (DART) calcd for  $C_{30}H_{47}N_4$   $[M + H]^+$  463.38007, found 463.37806;  $[\alpha]_D^{20} = -13.69$  ( $c = 0.93$ ,  $CHCl_3$ ).

### Preparation of chiral ligand L6



Carbonyl chloride **S5** was synthesized from diethyl tartrate according to the literatures.<sup>8,9</sup> Ester mixture **S4** was used instead of pure methyl ester, which was employed in the literature. Then, carbonyl chloride **S6** was converted to ligand **L6** by the following procedure.

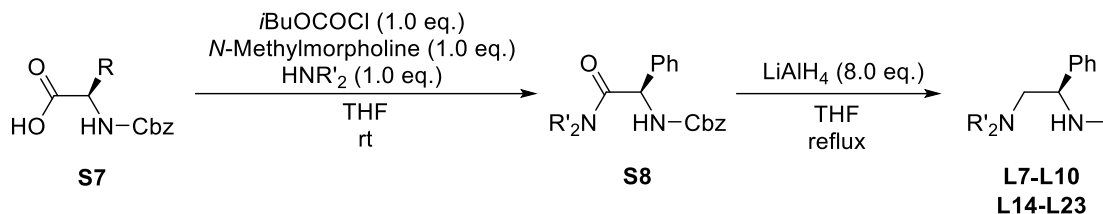
Carbonyl chloride **S5** (2.10 g, 9.25 mmol) dissolved in THF (10 mL) was added to a solution of piperidine (4.57 mL, 46.3 mmol) in THF (8.50 mL) at 0 °C. Then, the reaction mixture was stirred overnight at room temperature, and quenched with water. The mixture was extracted with DCM (20 mL  $\times$  3). Then, the combined organic layer was washed with saturated  $NaHCO_3$  and was dried over  $Na_2SO_4$ . After filtration and concentration under reduced pressure, the crude product obtained was recrystallized (in hexane) to afford the desired amide **S6** (2.22 g, 6.86 mmol, 74% yield). In the next step, hydride reduction similar to ligand **L5** was performed to afford ligand **L6** (70% yield).

### 1,1'-(((4*S*,5*S*)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene))dipiperidine

**(L6)**; Colorless solid; Mp 37-39 °C;  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$ : 3.83 (2H, dd,  $J = 12.47, 10.20$  Hz), 2.51-2.45 (12H, m), 1.60-1.56 (4H, m), 1.43-1.39 (10H, m);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ )  $\delta$ : 109.0, 77.9, 62.1, 55.3, 27.2, 25.8, 24.2; IR (neat,  $cm^{-1}$ ) 2932, 2853, 1442, 1368, 1301, 1214, 1157, 1124, 1077, 1058, 995, 863, 845, 805, 780, 513; HRMS (DART) calcd for  $C_{17}H_{33}N_2O_2$   $[M + H]^+$  297.25358, found 297.25420;  $[\alpha]_D^{20} = -23.73$  ( $c = 1.22$ ,  $CHCl_3$ ).

### Preparation of chiral ligands L7-L10 and L14-L23

The title ligands were synthesized from Cbz-protected amino acids according to the reported procedure for synthesis of **L3**.



Isobutyl chloroformate (6.57 mL, 50.0 mmol) was added to a solution of *N*-Cbz-protected amino acid **S7** (50.0 mmol) and 4-methylmorpholine (5.50 mL, 50.0 mmol) in 125 mL of THF at  $-15\text{ }^{\circ}\text{C}$  with stirring, and the corresponding secondary amine (50.0 mmol) was subsequently added to the reaction mixture. The reaction mixture was stirred for 1 h at the same temperature, and then stirring was continued at room temperature overnight. The reaction mixture was concentrated and dissolved in 200 mL of ethyl acetate. The obtained mixture was washed with 1 N HCl (100 mL  $\times$  2), water (100 mL), saturated  $\text{NaHCO}_3$  aqueous solution (100 mL  $\times$  2), and water (100 mL). The ethyl acetate layer was dried over anhydrous  $\text{Na}_2\text{SO}_4$ . After filtration, the corrected organic layer was concentrated under vacuum condition to afford crude **S8**, and the obtained product **S8** was used in the next step without further purification.

The crude product obtained above was dissolved in THF (100 mL) and was added dropwise to a dispersion of  $\text{LiAlH}_4$  (15.2 g, 400 mmol) in THF (150 mL) at  $0\text{ }^{\circ}\text{C}$  under argon atmosphere. Subsequently, the dispersion was refluxed overnight. The dispersion was cooled to  $0\text{ }^{\circ}\text{C}$  and quenched with 15 mL of water followed sequentially by 15 mL of 15% NaOH aq. and 10 mL of water. After filtration to remove white solid, the filtrate was concentrated to afford an oily residue. The oily residue was dissolved in 200 mL of  $\text{Et}_2\text{O}$ , and 50 mL of 4N HCl in EtOAc was added to this solution to afford an ammonium salt derived from the desired amine. The salt was collected by filtration and dried under reduced pressure. Subsequently, the obtained salt was recrystallized in EtOH to enhance the enantiopurity. The purified salt was dissolved in 100 mL water and was basified with 15% aq. NaOH. The mixture was extracted with DCM (50 mL  $\times$  3), and the combined organic layer was dried over anhydrous  $\text{Na}_2\text{CO}_3$ . After filtration and concentration, the obtained crude product was distilled under vacuum condition to afford the desired amine. Structures of **L7-L9**, **L14-L16**, **L18**, and **L23** were confirmed by comparison with data shown in the literature.<sup>4</sup>

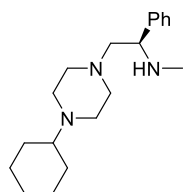
**(S)-N,4-Dimethyl-1-(piperidin-1-yl)pentan-2-amine (L10);** Colorless oil;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 2.56-2.35 (6H, m), 2.28-2.15 (4H, m), 2.00 (1H, s), 1.69-1.61 (1H, m), 1.59-1.50 (4H, m), 1.42-1.33 (3H, m), 1.10-1.03 (1H, m), 0.93-0.87 (6H, m);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 63.8, 54.9, 54.2, 42.1, 34.1, 26.1, 24.9, 24.5, 23.5, 22.6; IR (neat,  $\text{cm}^{-1}$ ) 2933, 2785, 1468, 1442, 1365, 1302, 1155, 1121, 1105, 1040, 992, 780, 418; HRMS (DART) calcd for  $\text{C}_{12}\text{H}_{27}\text{N}_2$   $[\text{M} + \text{H}]^+$  199.21742, found 199.21766;  $[\alpha]_{\text{D}}^{20} = +96.98$  (c 1.33,  $\text{CHCl}_3$ ).

**(R)-2-(meso-3,5-Dimethylpiperidin-1-yl)-N-methyl-1-phenylethan-1-amine (L17);** Colorless oil;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.35-7.32 (4H, m), 7.25-7.23 (1H, m), 3.63 (1H, dd,  $J = 11.34, 3.40$  Hz), 2.97 (1H, dt,  $J = 10.77, 1.70$  Hz), 2.71 (1H, dt,  $J = 10.58, 1.56$  Hz), 2.47 (1H, dd,  $J = 12.47, 10.77$  Hz), 2.34-2.30 (4H, m), 2.24 (1H, dd,  $J = 12.75, 3.12$  Hz), 1.76-1.58 (4H, m), 1.37 (1H, t,  $J = 11.05$  Hz), 0.88 (3H, d,  $J = 6.24$  Hz), 0.82 (3H, d,  $J = 6.24$  Hz), 0.51 (1H, q,  $J = 12.28$  Hz);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 142.8, 128.3, 127.3, 127.0, 66.2, 63.7, 62.5, 60.2, 42.3, 34.7, 31.3, 31.2, 19.7, 19.5; IR (neat,  $\text{cm}^{-1}$ ) 2949, 2785, 1454, 1354, 1312, 1191, 1137, 1080, 1023, 881, 755, 700, 635, 576, 501; HRMS (DART) calcd for  $\text{C}_{16}\text{H}_{27}\text{N}_2$   $[\text{M} + \text{H}]^+$  247.21742, found 247.21673;  $[\alpha]_{\text{D}}^{20} = -83.14$  (c 1.33,  $\text{CHCl}_3$ ).

**(R)-N-Methyl-2-(4-methylpiperazin-1-yl)-1-phenylethan-1-amine (L19);** Colorless solid; Mp 31–33 °C;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.35-7.32 (4H, m), 7.26-7.24 (1H, m), 3.62 (1H, dd,  $J = 11.00, 3.44$  Hz), 2.66-2.29 (17H, m);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 142.3, 128.3, 127.4, 127.2, 65.7, 62.2, 55.3, 53.3 (broaden), 46.1, 34.7; IR (neat,  $\text{cm}^{-1}$ ) 2930, 2789, 1454, 1357, 1282, 1164, 1132, 1117, 1033, 1011, 910, 837, 763, 703, 608, 566; HRMS (DART) calcd for  $\text{C}_{14}\text{H}_{24}\text{N}_3$   $[\text{M} + \text{H}]^+$  234.29702, found 234.19794;  $[\alpha]_{\text{D}}^{20} = -93.04$  (c 1.86,  $\text{CHCl}_3$ ).

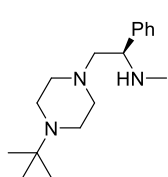
**(R)-2-(4-Ethylpiperazin-1-yl)-N-methyl-1-phenylethan-1-amine (L20);** Colorless solid; Mp 51–55 °C;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.34-7.32 (4H, m), 7.26-7.23 (1H, m), 3.62 (1H, dd,  $J = 11.00, 3.44$  Hz), 2.67-2.26 (16H, m), 1.09 (3H, t,  $J = 7.22$  Hz);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 142.4, 128.3, 127.4, 127.1, 65.8, 62.1, 53.3 (broaden), 52.9, 52.3, 34.7, 12.0; IR (neat,  $\text{cm}^{-1}$ ) 2942, 2809, 1448, 1350, 1290, 1162, 1121, 1011, 837, 757, 701, 640, 606, 563, 514; HRMS (DART) calcd for  $\text{C}_{15}\text{H}_{26}\text{N}_3$   $[\text{M} + \text{H}]^+$  248.21267, found 248.21301;  $[\alpha]_{\text{D}}^{20} = -73.42$  (c 2.19,  $\text{CHCl}_3$ ).

**(*R*)-2-(4-Cyclohexyl-1-yl)-*N*-methyl-1-phenylethan-1-amine (L21);** Colorless solid;



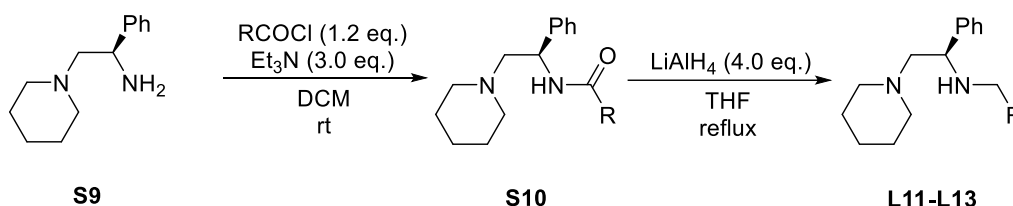
Mp 56–60 °C;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.34–7.32 (4H, m), 7.26–7.21 (2H, m), 3.61 (1H, dd,  $J$  = 11.00, 2.75 Hz), 2.62–2.17 (14H, m), 1.90–1.62 (6H, m), 1.24–1.20 (4H, m), 1.14–1.03 (1H, m);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 142.5, 128.3, 127.4, 127.1, 65.9, 63.5, 62.2, 49.1, 34.7, 29.1, 29.0, 26.3, 25.9; IR (neat,  $\text{cm}^{-1}$ ) 2926, 2853, 2809, 1452, 1345, 1292, 1157, 1122, 1052, 1008, 979, 754, 701; HRMS (DART) calcd for  $\text{C}_{19}\text{H}_{32}\text{N}_3$   $[\text{M} + \text{H}]^+$  302.25962, found 302.25934;  $[\alpha]_{\text{D}}^{20}$  = –54.82 (c 1.05,  $\text{CHCl}_3$ ).

**(*R*)-2-(4-(*tert*-Butyl)piperazin-1-yl)-*N*-methyl-1-phenylethan-1-amine (L22);**



Colorless solid; Mp 58–64 °C;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.34–7.32 (4H, m), 7.26–7.24 (1H, m), 3.61 (1H, dd,  $J$  = 11.00, 3.44 Hz), 2.65–2.26 (14H, m), 1.09 (9H, s);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 142.5, 128.3, 127.4, 127.1, 65.8, 62.2, 53.9 (broaden), 45.8, 34.7, 25.8; IR (neat,  $\text{cm}^{-1}$ ) 2966, 2938, 2803, 1438, 1357, 1297, 1207, 1128, 1010, 967, 907, 838, 753, 728, 700, 601, 494; HRMS (DART) calcd for  $\text{C}_{17}\text{H}_{30}\text{N}_3$   $[\text{M} + \text{H}]^+$  276.24397, found 276.24364;  $[\alpha]_{\text{D}}^{20}$  = –66.02 (c 1.20,  $\text{CHCl}_3$ ).

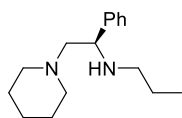
### Preparation of chiral ligands L11-L13



Diamine **S9** was synthesized according to the literature<sup>4</sup> and converted to the desired ligands **L11-L13**. To a mixture of diamine **S9** (5.0 mmol), triethylamine (25 mmol), and DCM (25 mL), the corresponding alkanoyl chloride (6.0 mmol) was added. Then, the reaction mixture was stirred overnight at room temperature and was quenched with saturated  $\text{NaHCO}_3$ . Subsequently, the mixture was extracted with DCM (20 mL  $\times$  3), and the combined organic layer was dried over  $\text{Na}_2\text{SO}_4$ . After filtration and concentration under reduced pressure, the crude product **S10** was obtained and used without further purification in the next step.

The crude product **S10** dissolved in THF (5.0 mL) was added to dispersion of  $\text{LiAlH}_4$  (20 mmol) in THF (5.0 mL) at 0 °C. Then, the reaction mixture was refluxed overnight and was quenched with saturated  $\text{Na}_2\text{SO}_4$ . After filtration through a Celite pad, the crude product obtained was distilled to afford the desired amine. Structure of **L11**<sup>4</sup> and **L13**<sup>10</sup> was confirmed by comparison with data shown in the literature.

**(R)-N-Propyl-1-phenyl-2-(piperidin-1-yl)ethan-1-amine (L12);** Colorless oil;  $^1\text{H}$



NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.37 (2H, d,  $J = 7.37$  Hz), 7.31 (2H, t,  $J = 7.37$  Hz), 7.24 (1H, q,  $J = 6.99$  Hz), 3.75 (1H, dd,  $J = 11.34, 3.40$  Hz), 2.55-2.24 (9H, m), 1.65-1.43 (8H, m), 0.89 (3H, t,  $J = 7.37$  Hz).;  $^{13}\text{C}$

NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 143.4, 128.2, 127.3, 126.8, 66.6, 60.0, 54.6, 49.8, 26.2, 24.5, 23.1, 11.8; IR (neat,  $\text{cm}^{-1}$ ) 2933, 2799, 1452, 1357, 1301, 1154, 1110, 994, 865, 753, 700, 627, 583, 528; HRMS (DART) calcd for  $\text{C}_{16}\text{H}_{27}\text{N}_2$   $[\text{M} + \text{H}]^+$  247.21742, found 247.21691;  $[\alpha]_{\text{D}}^{20} = -94.91$  (c 1.13,  $\text{CHCl}_3$ ).

### Optimization

#### General procedure of initial investigation (Table 2-1)

A mixed base (KO<sup>t</sup>Bu 5.6 mg,  $5.0 \times 10^{-2}$  mmol; LiTMP 7.4 mg,  $5.0 \times 10^{-2}$  mmol) or KCH<sub>2</sub>SiMe<sub>3</sub> (6.3 mg,  $5.0 \times 10^{-2}$  mmol) was placed in a flame-dried 10 mL flask inside a glove box fulfilled with argon. The flask was cooled to  $-78\text{ }^{\circ}\text{C}$ , then the corresponding ligand ( $5.5 \times 10^{-2}$  mmol) dissolved in the employed solvent (0.40 mL) was added. When TBME was employed as a solvent, toluene (63.8  $\mu\text{L}$ , 0.60 mmol) was also introduced into the flask. After the mixture was stirred at the same temperature for 30 min, *p*-methoxycumylimine **1a** (126.7 mg, 0.50 mmol) dissolved in the solvent (0.60 mL) was successively introduced into the flask via a well-dried cannula, and the whole mixture was stirred for 18 h at the same temperature. The reaction was quenched by adding a few drops of MeOH, and the obtained mixture was extracted with DCM (10 mL  $\times$  3). The combined organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After filtration and concentration under reduced pressure, the obtained crude product was purified by PTLC (hexane-ethyl acetate) to afford the desired amine **3aa**. The enantioselectivity was determined by HPLC.

#### General procedure for optimization of catalyst preparation conditions (Table 2-2)

A mixed base (KO<sup>t</sup>Bu 5.6 mg,  $5.0 \times 10^{-2}$  mmol; LiTMP 7.4 mg,  $5.0 \times 10^{-2}$  mmol) or KCH<sub>2</sub>SiMe<sub>3</sub> (6.3 mg,  $5.0 \times 10^{-2}$  mmol) was placed in a flame-dried 10 mL flask inside a glove box fulfilled with argon. The flask was cooled to the temperature shown in Table S2, then the corresponding amine **L3** (12.0 mg,  $5.0 \times 10^{-2}$  mmol) in the solvent (0.40 mL) was added. When TBME was employed as a solvent, toluene (63.8  $\mu\text{L}$ , 0.60 mmol) was also introduced into the flask. After the mixture was stirred under the conditions shown in Table S2, the flask was cooled to  $-78\text{ }^{\circ}\text{C}$ , and then *p*-methoxycumylimine **1a** (126.7 mg, 0.50 mmol) dissolved in the solvent (0.60 mL) was successively introduced into the flask via a well-dried cannula, and the whole mixture was stirred for 18 h. The reaction was quenched by adding a few drops of MeOH, and the obtained mixture was extracted with DCM (10 mL  $\times$  3). The combined organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After filtration and concentration under reduced pressure, the obtained crude product was purified by PTLC (hexane-ethyl acetate) to afford the desired amine **3aa**. The enantioselectivity was determined by HPLC.

#### General procedure for ligand screening (Table 2-3, Table 2-4)

A mixed base (KO<sup>t</sup>Bu 5.6 mg,  $5.0 \times 10^{-2}$  mmol; LiTMP 7.4 mg,  $5.0 \times 10^{-2}$  mmol) or KCH<sub>2</sub>SiMe<sub>3</sub> (6.3 mg,  $5.0 \times 10^{-2}$  mmol) was placed in a flame-dried 10 mL flask inside a glove box fulfilled with argon. After the flask was cooled to  $-40\text{ }^{\circ}\text{C}$ , the corresponding amine ligand **L** ( $5.5 \times 10^{-2}$  mmol) in toluene (0.40 mL) was added, and the mixture was stirred at the same temperature for 30 minutes. Subsequently, the flask was cooled to  $-78\text{ }^{\circ}\text{C}$ , and imine **1a** (126.7 mg, 0.500 mmol) dissolved in toluene (0.60 mL) was successively introduced into the flask via a well-dried cannula. After the whole mixture

was stirred for 18 h at the same temperature, the reaction was quenched by adding a few drops of MeOH, and the obtained mixture was extracted with DCM (10 mL  $\times$  3), then combined organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After filtration and concentration under reduced pressure, the obtained crude product was purified by PTLC (hexane-ethyl acetate) to afford the desired amine **3aa**. The enantioselectivities were determined by HPLC.

#### General procedure for investigation of additives (Table 2-5)

KCH<sub>2</sub>SiMe<sub>3</sub> (6.3 mg,  $5.0 \times 10^{-2}$  mmol) and the employed additive ( $5.0 \times 10^{-2}$  mmol) were placed in a flame-dried 10 mL flask inside a glove box fulfilled with argon. After the flask was cooled to the corresponding temperature, the corresponding amine ligand **L19** (12.8 mg,  $5.5 \times 10^{-2}$  mmol) in toluene (0.40 mL) was added, and the mixture was stirred at  $-40$  °C for 30 minutes. Subsequently, the flask was cooled to  $-78$  °C, and imine **1a** (126.7 mg, 0.500 mmol) dissolved in toluene (0.60 mL) was successively introduced into the flask via a well-dried cannula. After the whole mixture was stirred for 18 h at the same temperature, the reaction was quenched by adding a few drops of MeOH, and the obtained mixture was extracted with DCM (10 mL  $\times$  3), then combined organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After filtration and concentration under reduced pressure, the obtained crude product was purified by PTLC (hexane-ethyl acetate) to afford the desired amine **3aa**. The enantioselectivities were determined by HPLC.

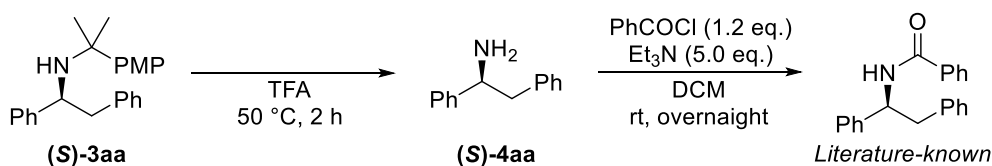


### Substrate Scope

#### Experimental procedure for substrate scope (Table 2-6, Table 2-7)

KCH<sub>2</sub>SiMe<sub>3</sub> (9.6 mg,  $7.5 \times 10^{-2}$  mmol) and KHMDS (15.0 mg,  $7.5 \times 10^{-2}$  mmol) were placed in a flame-dried 10 mL flask inside a glove box fulfilled with argon. The flask was cooled to  $-40$  °C, then diamine ligand **L19** (19.4 mg,  $8.3 \times 10^{-2}$  mmol) in toluene (0.60 mL) was added, and the chiral base mixture was stirred for 30 min at the same temperature. After the flask was cooled at  $-78$  °C, *p*-methoxycumylimine **1a** (253.4 mg, 1.000 mmol) dissolved in toluene (1.40 mL) was successively introduced via a well-dried cannula, and the whole mixture was stirred for 18 h at the same temperature. After the reaction was quenched by adding water, the mixture was extracted with DCM (10 mL  $\times$  3). The combined organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After filtration and concentration under reduced pressure, the crude product obtained was purified by PTLC (hexane-ethyl acetate) to afford the desired adduct **3aa**. Regarding **3aa**, **3ea**, **3fa**, and **3ga**, the enantiopurities could be enhanced by recrystallization.

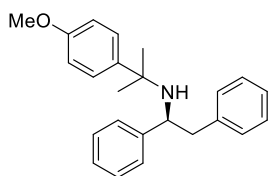
In order to determine the absolute configuration of **3aa**, it was derivatized to the corresponding amide via removal of PMC group and typical amidation as shown below.<sup>11</sup> The absolute configuration of the other adducts were determined as analogies.



#### Experimental procedure of the catalytic asymmetric addition reaction in cumene solvent (Table 2-7, for **3ad**, **3ae**, **3af**)

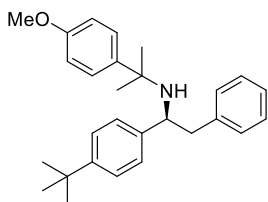
KCH<sub>2</sub>SiMe<sub>3</sub> (12.3 mg, 0.100 mmol) and KHMDS (20.0 mg, 0.100 mmol) were placed in a flame-dried 10 mL flask inside a glove box fulfilled with argon. The flask was cooled to  $-40$  °C, and cumene (0.20 mL) was added. Then alkylarene (2.50 mmol) was introduced into the flask, and diamine ligand **L19** (25.7 mg, 0.110 mmol) in cumene (0.20 mL) was added, and the chiral base mixture was stirred for 30 min at the same temperature. After the flask was cooled at  $-60$  °C, *p*-methoxycumylimine **1a** (126.7 mg, 0.5000 mmol) dissolved in cumene (0.60 mL) was successively introduced via a well-dried cannula, and the whole mixture was stirred for 18 h at the same temperature. After the reaction was quenched by adding water, the mixture was extracted with DCM (10 mL  $\times$  3). The combined organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After filtration and concentration under reduced pressure, the crude product obtained was purified by PTLC (hexane-ethyl acetate) to afford the desired adduct **3**.

**(S)-N-(1,2-Diphenylethyl)-2-(4-methoxyphenyl)propan-2-amine (3aa)**; The structure was confirmed by comparison with data of <sup>1</sup>H and <sup>13</sup>C NMR shown in literature which



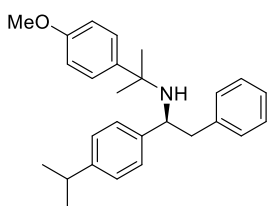
our group reported.<sup>5</sup> <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ: 7.25-7.15 (8H, m), 6.98 (2H, dd, *J* = 7.37, 1.70 Hz), 6.94 (2H, td, *J* = 5.95, 3.78 Hz), 6.69 (2H, td, *J* = 6.09, 3.59 Hz), 3.79 (3H, s), 3.55 (1H, dd, *J* = 9.15, 5.15 Hz), 2.78 (1H, dd, *J* = 13.60, 5.10 Hz), 2.67 (1H, dd, *J* = 13.60, 9.07 Hz), 1.75 (1H, s), 1.21 (3H, s), 1.07 (3H, s); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ: 157.7, 147.3, 140.1, 138.9, 129.5, 128.3, 128.0, 127.1, 126.9, 126.4, 126.3, 113.1, 59.8, 56.0, 55.2, 46.9, 32.4, 27.9; HPLC analysis using Shinwa Chemical Industries Ltd. ULTRON ES-PhCD column (20 mM KH<sub>2</sub>PO<sub>4</sub>:MeCN = 75:25, 1.0 mL/min, 210 nm, t<sub>R</sub> = 42.4 min (*R*), 47.6 min (*S*)); [α]<sub>D</sub><sup>20</sup> = −47.12 (99% ee, c 0.63, CHCl<sub>3</sub>).

**(*S*)-*N*-(1-(4-(*tert*-Butyl)phenyl)-2-phenylethyl)-2-(4-methoxyphenyl)propan-2-amine (3ba)**



The structure was confirmed by comparison with data of <sup>1</sup>H and <sup>13</sup>C NMR shown in literature which our group reported.<sup>5</sup> <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ: 7.24-7.22 (5H, m), 7.16 (2H, d, *J* = 7.94 Hz), 7.01 (2H, dd, *J* = 7.65, 1.42 Hz), 6.91 (2H, d, *J* = 8.50 Hz), 6.67 (2H, d, *J* = 8.50 Hz), 3.79 (3H, s), 3.53 (1H, dd, *J* = 4.72, 2.36 Hz), 2.79 (1H, dd, *J* = 13.60, 5.10 Hz), 2.65 (1H, dd, *J* = 13.60, 9.07 Hz), 1.74 (1H, s), 1.31 (9H, s), 1.20 (3H, s), 1.06 (3H, s); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ: 157.6, 149.2, 144.1, 140.1, 139.2, 129.5, 128.2, 127.0, 126.7, 126.2, 124.8, 113.0, 59.4, 55.9, 55.1, 46.8, 34.4, 32.2, 31.5, 28.1; HPLC analysis using Shinwa Chemical Industries Ltd. ULTRON ES-OVM column (20 mM KH<sub>2</sub>PO<sub>4</sub>:MeCN = 85:15, 1.0 mL/min, 210 nm, t<sub>R</sub> = 5.8 min (*R*), 7.7 min (*S*)); [α]<sub>D</sub><sup>20</sup> = −45.86 (89% ee, c 1.47, CHCl<sub>3</sub>).

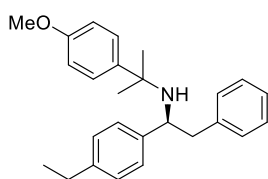
**(*S*)-*N*-(1-(4-Isopropylphenyl)-2-phenylethyl)-2-(4-methoxyphenyl)propan-2-amine (3ca)**



The structure was confirmed by comparison with data of <sup>1</sup>H and <sup>13</sup>C NMR shown in literature which our group reported.<sup>5</sup> <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ: 7.23-7.21 (3H, m), 7.16 (2H, d, *J* = 8.50 Hz), 7.09 (2H, d, *J* = 7.94 Hz), 7.00 (2H, d, *J* = 6.24 Hz), 6.91 (2H, d, *J* = 9.07 Hz), 6.67 (2H, d, *J* = 8.50 Hz), 3.79 (3H, s), 3.53 (1H, dd, *J* = 4.72, 2.36 Hz), 2.91-2.83 (1H, m), 2.78 (1H, dd, *J* = 13.32, 4.82 Hz), 2.65 (1H, dd, *J* = 13.32, 9.35 Hz), 1.58 (1H, s), 1.23-1.21 (9H, m), 1.06 (3H, s); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ: 157.6, 146.9, 144.5, 140.1, 139.2, 129.5, 128.3, 127.0, 126.9, 126.2, 126.0, 113.0, 59.5, 56.0, 55.2, 46.8, 33.7, 32.3, 28.0, 24.08, 24.06; The ee value was evaluated after derivatization to **6ca**.

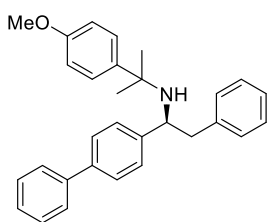
**(*S*)-*N*-(1-(4-Ethylphenyl)-2-phenylethyl)-2-(4-methoxyphenyl)propan-2-amine (3da)**

Colorless solid; Mp: 65-67 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ: 7.24-7.20 (3H, m), 7.16 (2H, d, *J* = 7.94 Hz), 7.07 (2H, td, *J* = 7.94 Hz), 6.99 (2H, d, *J* = 6.24 Hz), 6.92 (2H,



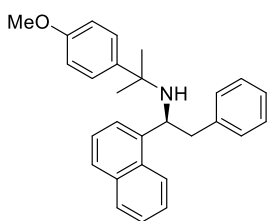
d,  $J = 8.50$  Hz), 6.68 (2H, d,  $J = 9.07$  Hz), 3.79 (3H, s), 3.53 (1H, dd,  $J = 4.72, 2.36$  Hz), 2.78 (1H, dd,  $J = 13.32, 4.82$  Hz), 2.65-2.62 (3H, m), 1.73 (1H, s), 1.23-1.22 (6H, m), 1.07 (3H, s);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 157.6, 144.5, 142.3, 140.2, 130.1, 129.5, 128.3, 127.5, 127.5, 127.00, 126.95, 126.2, 113.0, 59.5, 56.0, 55.2, 46.9, 32.4, 28.4, 28.0, 15.5; IR (neat,  $\text{cm}^{-1}$ ) 2970, 1608, 1579, 1508, 1457, 1300, 1251, 1180, 1031, 825, 737, 697, 548; HRMS (DART) calcd for  $\text{C}_{26}\text{H}_{32}\text{NO}$  [ $\text{M} + \text{H}$ ] $^+$  374.24839, found 374.24985; The ee value was evaluated after derivatization to **6da**.

**(S)-N-(1-([1,1'-Biphenyl]-4-yl)-2-phenylethyl)-2-(4-methoxyphenyl)propan-2-amine**



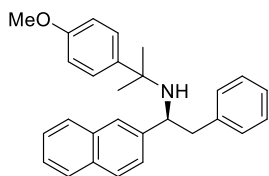
**(3ea)**; Colorless solid, Mp: 78-81  $^{\circ}\text{C}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.60 (2H, d,  $J = 8.50$  Hz), 7.49 (2H, d,  $J = 7.94$  Hz), 7.43 (2H, t,  $J = 7.65$  Hz), 7.32-7.22 (6H, m), 7.02 (2H, d,  $J = 7.94$  Hz), 6.95 (2H, d,  $J = 8.50$  Hz), 6.69 (2H, d,  $J = 8.50$  Hz), 3.79 (3H, s), 3.61 (1H, dd,  $J = 4.72, 2.36$  Hz), 2.83 (1H, dd,  $J = 13.32, 5.38$  Hz), 2.70 (1H, dd,  $J = 13.60, 9.07$  Hz), 1.80 (1H, s), 1.24 (3H, s), 1.11 (3H, s);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 157.7, 146.5, 141.1, 140.0, 139.2, 138.9, 129.5, 128.7, 128.3, 128.0, 127.8, 127.6, 127.5, 126.9, 126.7, 126.3, 113.1, 59.5, 56.1, 55.2, 46.8, 32.3, 28.1; IR (neat,  $\text{cm}^{-1}$ ) 3022, 1602, 1508, 1482, 1105, 1248, 1180, 1028, 825, 763, 725, 691, 614, 586, 554, 526, 491; HRMS (DART) calcd for  $\text{C}_{30}\text{H}_{32}\text{NO}$  [ $\text{M} + \text{H}$ ] $^+$  422.24839, found 422.24712; HPLC analysis using Shinwa Chemical Industries Ltd. ULTRON ES-OVM column (20 mM  $\text{KH}_2\text{PO}_4$ :MeCN = 85:15, 1.0 mL/min, 210 nm,  $t_R = 16.0$  min (*S*), 70.0 min (*R*));  $[\alpha]_D^{20} = -71.73$  (99% ee, c 0.46,  $\text{CHCl}_3$ ).

**(S)-2-(4-Methoxyphenyl)-N-(1-(naphthalen-1-yl)-2-phenylethyl)propan-2-amine**



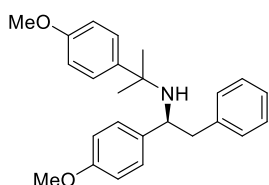
**(3fa)**; Colorless solid, Mp: 104-108  $^{\circ}\text{C}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.95-7.89 (2H, m, broaden), 7.72 (1H, d,  $J = 7.94$  Hz), 7.46-7.43 (3H, m, broaden), 7.27-7.21 (4H, overlapped with  $\text{CHCl}_3$ ), 7.05 (2H, d,  $J = 5.67$  Hz), 6.91 (2H, d,  $J = 9.07$  Hz), 6.65 (2H, d,  $J = 8.50$  Hz), 4.47 (1H, s, broaden), 3.79 (3H, s), 2.97 (1H, d,  $J = 11.34$ ), 2.65 (1H, s, broaden), 1.90 (1H, s), 1.22 (3H, s), 0.99 (3H, s);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 157.6, 143.3, 140.1, 139.1, 133.9, 130.5, 129.4, 128.9, 128.4, 126.9, 126.7, 126.3, 125.54, 125.48, 125.0, 124.9, 122.0, 113.1, 56.1, 55.2, 53.4, 45.8, 32.1, 27.4; IR (neat,  $\text{cm}^{-1}$ ) 1608, 1508, 1462, 1374, 1302, 1251, 1180, 1034, 831, 803, 785, 743, 697, 622, 517, 500, 431; HRMS (DART) calcd for  $\text{C}_{28}\text{H}_{30}\text{NO}$  [ $\text{M} + \text{H}$ ] $^+$  396.23274, found 396.23452; HPLC analysis using Shinwa Chemical Industries Ltd. ULTRON ES-OVM column (20 mM  $\text{KH}_2\text{PO}_4$ :MeCN = 80:20, 1.0 mL/min, 210 nm,  $t_R = 4.6$  min (*R*), 5.7 min (*S*));  $[\alpha]_D^{20} = -37.61$  (>99% ee, c 0.60,  $\text{CHCl}_3$ ).

**(S)-2-(4-Methoxyphenyl)-N-(1-(naphthalen-2-yl)-2-phenylethyl)propan-2-amine**



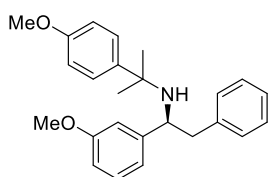
**(3ga)**; The structure was confirmed by comparison with data of  $^1\text{H}$  and  $^{13}\text{C}$  NMR shown in literature which our group reported.<sup>5</sup>  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.80-7.75 (3H, m), 7.59 (1H, s), 7.52 (1H, d,  $J = 8.50$  Hz), 7.43-7.42 (2H, m), 7.29-7.20 (3H, m), 7.02 (2H, d,  $J = 7.37$  Hz), 6.93 (2H, d,  $J = 9.07$  Hz), 6.68 (2H, d,  $J = 8.50$  Hz), 3.77 (3H, s), 3.73 (1H, dd,  $J = 8.79, 5.38$  Hz), 2.86 (1H, dd,  $J = 13.60, 5.10$  Hz), 2.75 (1H, dd,  $J = 13.60, 9.07$  Hz), 1.87 (1H, s), 1.23 (3H, s), 1.07 (3H, s);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 157.7, 144.9, 140.0, 138.9, 133.4, 132.6, 129.5, 128.3, 127.67, 127.65, 127.58, 126.9, 126.3, 125.8, 125.6, 125.5, 125.2, 113.1, 59.9, 56.1, 55.2, 46.7, 32.3, 28.0; HPLC analysis using Shinwa Chemical Industries Ltd. ULTRON ES-OVM column (20 mM  $\text{KH}_2\text{PO}_4$ :MeCN = 85:15, 1.0 mL/min, 210 nm,  $t_R = 51.4$  min (S), 47.1 min (R));  $[\alpha]_D^{20} = -81.11$  (99% ee, c 0.51,  $\text{CHCl}_3$ ).

**(S)-2-(4-Methoxyphenyl)-N-(1-(4-methoxyphenyl)-2-phenylethyl)propan-2-amine**



**(3ha)**; The structure was confirmed by comparison with data of  $^1\text{H}$  and  $^{13}\text{C}$  NMR shown in literature which our group reported.<sup>5</sup>  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.24-7.16 (3H, m), 7.14 (2H, d,  $J = 8.25$  Hz), 6.97 (2H, d,  $J = 6.19$  Hz), 6.93 (2H, d,  $J = 8.94$  Hz), 6.78 (2H, d,  $J = 8.25$  Hz), 6.70 (2H, d,  $J = 8.94$  Hz), 3.79 (6H, m), 3.50 (1H, dd,  $J = 8.25, 5.50$  Hz), 2.76 (1H, dd,  $J = 6.19, 3.09$  Hz), 2.66 (1H, dd,  $J = 13.75, 8.94$  Hz), 1.56 (1H, s), 1.21 (3H, s), 1.07 (3H, s);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 158.2, 157.7, 140.1, 139.3, 139.1, 129.5, 128.2, 128.1, 126.9, 126.2, 113.4, 113.1, 59.1, 56.0, 55.21, 55.19, 46.9, 32.4, 28.0; The ee value was evaluated after derivatization to **6ha**.

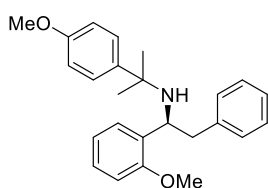
**(S)-2-(4-Methoxyphenyl)-N-(1-(3-methoxyphenyl)-2-phenylethyl)propan-2-amine**



**(3ia)**; The structure was confirmed by comparison with data of  $^1\text{H}$  and  $^{13}\text{C}$  NMR shown in literature which our group reported.<sup>5</sup>  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.24-7.22 (3H, m), 6.99 (2H, dd,  $J = 7.37, 1.70$  Hz), 6.93 (2H, d,  $J = 9.07$  Hz), 6.84-6.82 (2H, m), 6.72-6.69 (3H, m), 3.79 (6H, m), 3.53 (1H, dd,  $J = 4.72, 2.36$  Hz), 2.79 (1H, dd,  $J = 13.60, 5.10$  Hz), 2.66 (1H, dd,  $J = 11.34, 5.67$  Hz), 1.62 (1H, s), 1.21 (3H, s), 1.09 (3H, s);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 159.4, 157.7, 149.2, 140.0, 138.9, 129.5, 128.9, 128.3, 126.9, 126.3, 119.6, 113.1, 112.6, 111.9, 59.8, 56.0, 55.2, 46.8, 32.3, 27.9; HPLC analysis using Shinwa Chemical Industries Ltd. ULTRON ES-OVM column (20 mM  $\text{KH}_2\text{PO}_4$ :MeCN = 80:20, 1.0 mL/min, 210 nm,  $t_R = 2.6$  min (R), 2.9 min (S));  $[\alpha]_D^{20} = -34.12$  (73% ee, c 1.33,  $\text{CHCl}_3$ ).

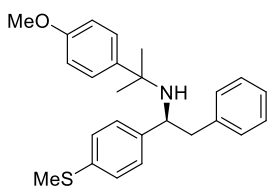
**(S)-2-(4-Methoxyphenyl)-N-(1-(2-methoxyphenyl)-2-phenylethyl)propan-2-amine**

**(3ja)**; The structure was confirmed by comparison with data of  $^1\text{H}$  and  $^{13}\text{C}$  NMR shown



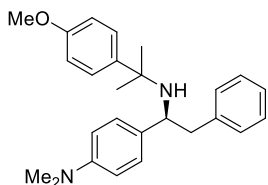
in literature which our group reported.<sup>5</sup> <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.38 (1H, s), 7.20-7.12 (4H, m), 7.09 (2H, d,  $J$  = 9.07 Hz), 6.98 (2H, d,  $J$  = 6.80 Hz), 6.86 (1H, t,  $J$  = 7.37 Hz), 6.77 (1H, d,  $J$  = 7.94 Hz), 6.68 (2H, d,  $J$  = 9.07 Hz), 4.06 (1H, s), 3.77 (3H, s), 2.86 (1H, dd,  $J$  = 13.32, 5.38 Hz), 2.61 (1H, dd,  $J$  = 10.20, 5.10 Hz), 1.75 (1H, s), 1.18 (3H, s), 1.09 (3H, s); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>)  $\delta$ : 157.6, 156.3, 140.8, 139.8, 135.5, 129.5, 128.5 (broaden), 128.0, 126.98, 126.95, 125.9, 120.3, 112.9, 110.3, 55.9, 55.24, 55.18, 45.0, 31.7, 27.9; HPLC analysis using Shinwa Chemical Industries Ltd. ULTRON ES-OVM column (20 mM KH<sub>2</sub>PO<sub>4</sub>:MeCN = 80:20, 1.0 mL/min, 210 nm, tR = 2.9 min (*S*), 4.7 min (*R*)); [ $\alpha$ ]<sub>D</sub><sup>20</sup> = -24.8 (84% ee, c 1.71, CHCl<sub>3</sub>).

**(*S*)-2-(4-Methoxyphenyl)-*N*-(1-(4-(methylthio)phenyl)-2-phenylethyl)propan-2-amine (3ka);**



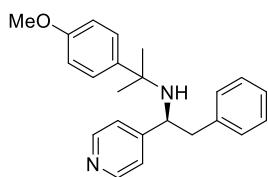
Slightly yellow solid, Mp = 86-88 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.24-7.19 (3H, m), 7.17-7.14 (4H, m), 6.97 (2H, dd,  $J$  = 7.37, 1.70 Hz), 6.92 (2H, d,  $J$  = 8.50 Hz), 6.69 (2H, d,  $J$  = 9.07 Hz), 3.79 (3H, s), 3.52 (1H, dd,  $J$  = 8.79, 5.38 Hz), 2.75 (1H, dd,  $J$  = 13.60, 5.10 Hz), 2.65 (1H, dd,  $J$  = 13.60, 9.07 Hz), 2.47 (3H, s), 1.75 (1H, s), 1.21 (3H, s), 1.07 (3H, s); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>)  $\delta$ : 157.7, 144.5, 140.0, 138.8, 135.8, 129.4, 128.3, 127.7, 126.9, 126.5, 126.3, 113.1, 59.3, 56.0, 55.2, 46.8, 32.3, 28.1, 16.1; IR (neat, cm<sup>-1</sup>) 2976, 1605, 1508, 1494, 1434, 1297, 1248, 1180, 1094, 1028, 825, 700, 646, 543; HRMS (DART) calcd for C<sub>25</sub>H<sub>30</sub>NOS [M + H]<sup>+</sup> 392.20481, found 392.20409; The ee value was evaluated after derivatization to **6ka**.

**(*S*)-4-(1-((2-(4-Methoxyphenyl)propan-2-yl)amino)-2-phenylethyl)-*N,N*-dimethylaniline (3la);**



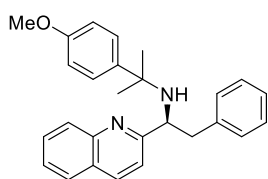
The structure was confirmed by comparison with data of <sup>1</sup>H and <sup>13</sup>C NMR shown in literature which our group reported.<sup>5</sup> <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.23-7.20 (3H, m), 7.10 (2H, d,  $J$  = 8.94 Hz), 6.99 (2H, d,  $J$  = 6.19 Hz), 6.93 (2H, d,  $J$  = 8.94 Hz), 6.70 (2H, d,  $J$  = 8.94 Hz), 6.65 (2H, d,  $J$  = 8.94 Hz), 3.80 (3H, s), 3.46 (1H, d,  $J$  = 4.81 Hz), 2.92 (6H, s), 2.78 (1H, dd,  $J$  = 13.75, 5.50 Hz), 2.67 (1H, dd,  $J$  = 13.06, 8.94 Hz), 1.73 (1H, s), 1.22 (3H, s), 1.09 (3H, s); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>)  $\delta$ : 157.6, 149.4, 140.2, 139.4, 129.5, 128.2, 127.8, 127.0, 126.1, 113.0, 112.4, 59.1, 56.0, 55.2, 46.9, 40.8, 32.5, 27.9; HPLC analysis using Shinwa Chemical Industries Ltd. ULTRON ES-OVM column (20 mM KH<sub>2</sub>PO<sub>4</sub>:MeCN = 85:15, 1.0 mL/min, 210 nm, tR = 3.1 min (*R*), 4.9 min (*S*)); [ $\alpha$ ]<sub>D</sub><sup>20</sup> = -36.33 (99% ee, c 0.51, CHCl<sub>3</sub>).

**2-(4-Methoxyphenyl)-*N*-(2-phenyl-1-(pyridin-4-yl)ethyl)propan-2-amine (3ma);** Colorless oil; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)  $\delta$ : 8.45 (2H, d,  $J$  = 6.19 Hz), 7.25-7.23 (3H, m), 7.18 (2H, d,  $J$  = 5.50 Hz), 6.96-6.92 (4H, m), 6.68 (2H, d,  $J$  = 8.94 Hz), 3.79 (3H, s), 3.55 (1H, dd,  $J$  = 8.94, 5.52 Hz), 2.73 (1H, dd,  $J$  = 13.75, 5.50 Hz), 2.63 (1H, dd,  $J$  =



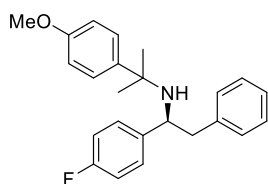
13.06, 8.94 Hz), 1.69 (1H, s), 1.21 (3H, s), 1.07 (3H, s);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 157.80, 156.57, 149.46, 139.42, 137.77, 129.39, 128.45, 126.84, 126.65, 122.46, 113.15, 58.92, 56.10, 55.19, 46.11, 31.88, 28.11; IR (neat,  $\text{cm}^{-1}$ ) 3742, 3651, 2967, 1601, 1513, 1457, 1360, 1247, 1179, 1033; HRMS (DART) calcd for  $\text{C}_{23}\text{H}_{27}\text{N}_1\text{O}_1$   $[\text{M} + \text{H}]^+$  347.21234, found 347.21253.

**2-(4-Methoxyphenyl)-N-(2-phenyl-1-(quinolin-2-yl)ethyl)propan-2-amine (3na);**



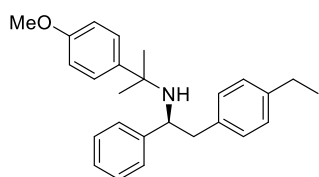
Yellow oil;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.07 (1H, d,  $J = 8.50$  Hz), 7.96 (1H, d,  $J = 8.50$  Hz), 7.77 (1H, d,  $J = 7.94$  Hz), 7.69 (1H, t,  $J = 8.22$  Hz), 7.49 (1H, t,  $J = 7.65$  Hz), 7.35 (1H, d,  $J = 8.50$  Hz), 7.22-7.21 (3H, m), 7.06-7.02 (4H, m), 6.62 (2H, d,  $J = 7.37$  Hz), 3.95 (1H, dd,  $J = 9.07, 4.53$  Hz), 3.73 (3H, s), 2.99 (1H, dd,  $J = 13.60, 5.67$  Hz), 2.82 (1H, dd,  $J = 13.60, 9.07$  Hz), 2.37 (1H, s), 1.24 (3H, s), 1.09 (3H, s);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 166.75, 157.61, 147.61, 140.12, 138.58, 135.56, 129.64, 129.03, 128.98, 128.27, 127.48, 127.21, 127.00, 126.30, 125.69, 120.62, 113.00, 61.38, 55.99, 55.14, 45.15, 31.59, 28.30; IR (KBr disk,  $\text{cm}^{-1}$ ) 3325, 3061, 3031, 2967, 2837, 2250, 2200, 1605, 1507, 1459, 1379, 1363, 1302, 1248, 1179, 1111, 1094, 1035, ; HRMS (DART) calcd for  $\text{C}_{27}\text{H}_{28}\text{N}_2\text{O}$   $[\text{M} + \text{H}]^+$  397.22799, found 397.22814.

**N-(1-(4-Fluorophenyl)-2-phenylethyl)-2-(4-methoxyphenyl)propan-2-amine (3oa);**



Colorless oil;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.26-7.17 (6H, m), 6.96-6.90 (6H, m), 6.69 (2H, d,  $J = 8.94$  Hz), 3.79 (3H, s), 3.54 (1H, dd,  $J = 8.94, 5.52$  Hz), 2.73 (1H, dd,  $J = 13.08, 5.52$  Hz), 2.65 (1H, dd,  $J = 13.40, 8.59$  Hz), 1.69 (1H, s), 1.21 (3H, s), 1.06 (3H, s);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 161.55 ( $J_{\text{C-F}} = 245.36$  Hz), 157.76, 142.87 ( $J_{\text{C-F}} = 2.40$  Hz), 139.90, 138.63, 129.41, 128.50 ( $J_{\text{C-F}} = 8.39$  Hz), 128.30, 126.90, 126.35, 114.66 ( $J_{\text{C-F}} = 21.54$  Hz), 113.14, 59.10, 56.02, 55.18, 46.91, 32.16, 28.09;  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ , 465 MHz)  $\delta$ : -116.87; IR (neat,  $\text{cm}^{-1}$ ) 3441, 3061, 3029, 2968, 2838, 1606, 1508, 1459, 1299, 1248, 1223, 1180, 1035; HRMS (DART) calcd for  $\text{C}_{24}\text{H}_{27}\text{F}_1\text{N}_1\text{O}_1$   $[\text{M} + \text{H}]^+$  364.20767, found 364.20758.

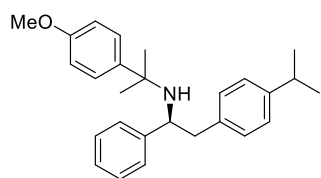
**(S)-N-(2-(4-Ethylphenyl)-1-phenylethyl)-2-(4-methoxyphenyl)propan-2-amine (3ab);**



The structure was confirmed by comparison with data of  $^1\text{H}$  and  $^{13}\text{C}$  NMR shown in literature which our group reported.<sup>5</sup>  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.26-7.23 (4H, m), 7.18-7.16 (1H, m), 7.07 (2H, d,  $J = 7.56$  Hz), 6.92-6.90 (4H, m), 6.67 (2H, d,  $J = 8.25$  Hz), 3.79 (3H, s), 3.54 (1H, dd,  $J = 4.58, 2.29$  Hz), 2.75 (1H, dd,  $J = 13.40, 5.15$  Hz), 2.64-2.62 (3H, m), 1.71 (1H, s), 1.24 (3H, t,  $J = 7.56$  Hz), 1.20 (3H, s), 1.06 (3H, s);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 157.6, 147.5, 142.2, 140.1, 136.0, 129.4, 128.0, 127.8, 127.1, 126.9, 126.3, 113.0, 59.8, 56.0,

55.2, 46.4, 32.5, 28.5, 27.9, 15.8; The ee value was evaluated after derivatization to **6ab**.

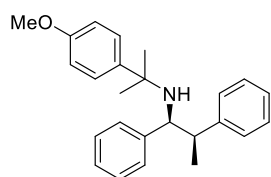
**(S)-N-(2-(4-Isopropylphenyl)-1-phenylethyl)-2-(4-methoxyphenyl)propan-2-amine**



**(3ac)**; The structure was confirmed by comparison with data of  $^1\text{H}$  and  $^{13}\text{C}$  NMR shown in literature which our group reported.<sup>5</sup>  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.27-7.23 (4H, m), 7.17 (1H, t,  $J = 7.22$  Hz), 7.11 (2H, d,  $J = 8.25$  Hz), 6.94 (2H, d,  $J = 8.25$  Hz), 6.86 (2H, d,  $J = 8.25$  Hz), 6.66 (2H, d,  $J = 8.25$

Hz), 3.78 (3H, s), 3.52 (1H, dd,  $J = 4.81, 2.41$  Hz), 2.90 (1H, dd,  $J = 27.49, 13.75$  Hz), 2.77-2.74 (1H, m), 2.62 (1H, dd,  $J = 13.40, 9.28$  Hz), 1.81 (1H, s), 1.26 (6H, dd,  $J = 3.44, 1.72$  Hz), 1.19 (3H, s), 1.05 (3H, s);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 150 MHz)  $\delta$ : 157.6, 147.4, 140.1, 135.72, 135.67, 129.3, 128.9, 128.0, 127.1, 126.9, 126.3, 59.7, 56.0, 55.1, 46.4, 32.4, 27.9, 21.0; HPLC analysis using Shinwa Chemical Industries Ltd. ULTRON ES-PhCD column (20 mM  $\text{KH}_2\text{PO}_4$ :MeCN = 70:30, 1.0 mL/min, 210 nm,  $t_R = 53.8$  min (*R*), 94.3 min (*S*));  $[\alpha]_D^{20} = +2.39$  (18% ee, c 1.39,  $\text{CHCl}_3$ ).

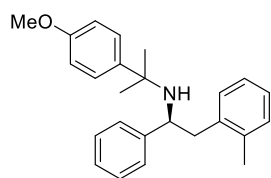
**(1*SR*,2*RS*)-N-(2-(4-Methoxyphenyl)propan-2-yl)-1,2-diphenylpropan-1-amine**



**(3ad)**; The structure was confirmed by comparison with data of  $^1\text{H}$  and  $^{13}\text{C}$  NMR shown in literature which our group reported.<sup>5</sup>  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.26-7.11 (8H, m), 7.05 (2H, d,  $J = 6.87$  Hz), 6.72 (2H, d,  $J = 8.94$  Hz), 6.63 (2H, d,  $J = 8.25$  Hz), 3.74 (3H, s), 3.21 (1H, d,  $J = 8.94$  Hz), 2.64 (1H, dt,  $J = 16.50, 6.87$

Hz), 1.64 (1H, s), 1.00 (3H, s), 0.85 (3H, s), 0.73 (3H, d,  $J = 6.87$  Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 150 MHz)  $\delta$ : 157.6, 145.8, 144.7, 139.7, 128.4, 128.3, 128.1, 127.8, 127.1, 126.6, 126.5, 112.9, 64.5, 55.7, 55.2, 47.8, 32.4, 27.6, 19.3; HPLC analysis using Shinwa Chemical Industries Ltd. ULTRON ES-PhCD column (20 mM  $\text{KH}_2\text{PO}_4$ :MeCN = 60:40, 2.0 mL/min, 210 nm,  $t_R = 12.4$  min (*1R,2S*), 31.3 min (*1R,3S*)).

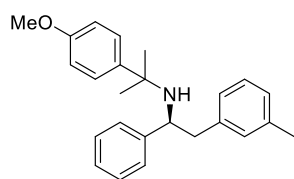
**(S)-2-(4-Methoxyphenyl)-N-(1-phenyl-2-(*o*-tolyl)ethyl)propan-2-amine (3af)**; The



structure was confirmed by comparison with data of  $^1\text{H}$  and  $^{13}\text{C}$  NMR shown in literature which our group reported.<sup>5</sup>  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.18-7.14 (4H, m), 7.09 (1H, t,  $J = 6.87$  Hz), 7.05 (1H, t,  $J = 7.22$  Hz), 6.99 (2H, t,  $J = 6.53$  Hz), 6.85 (1H, d,  $J = 6.87$  Hz), 6.78 (2H, d,  $J = 8.94$  Hz), 6.59 (2H, t,  $J = 5.84$  Hz),

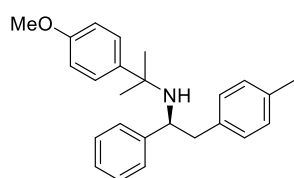
3.70 (3H, s), 3.44 (1H, dd,  $J = 4.81, 2.41$  Hz), 2.70 (1H, dd,  $J = 13.40, 5.15$  Hz), 2.59 (1H, dd,  $J = 13.75, 9.62$  Hz), 1.95 (3H, s), 1.75 (1H, s), 1.13 (3H, s), 0.96 (3H, s);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 150 MHz)  $\delta$ : 157.63, 147.7, 140.0, 137.0, 136.8, 130.5, 130.4, 128.0, 126.9, 126.8, 126.5, 126.3, 125.6, 113.1; HPLC analysis using Shinwa Chemical Industries Ltd. ULTRON ES-OVM column (20 mM  $\text{KH}_2\text{PO}_4$ :MeCN = 85:15, 1.0 mL/min, 210 nm,  $t_R = 4.4$  min (*S*), 6.3 min (*R*));  $[\alpha]_D^{20} = -57.45$  (75% ee, c 1.22,  $\text{CHCl}_3$ ).

**(S)-2-(4-Methoxyphenyl)-N-(1-phenyl-2-(*m*-tolyl)ethyl)propan-2-amine (3ag);** The



structure was confirmed by comparison with data of  $^1\text{H}$  and  $^{13}\text{C}$  NMR shown in literature which our group reported.<sup>5</sup>  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.21-7.13 (4H, m), 7.11-7.04 (2H, m), 6.95 (1H, d,  $J = 7.37$  Hz), 6.80 (2H, d,  $J = 8.50$  Hz), 6.74 (1H, d,  $J = 7.37$  Hz), 6.71 (1H, s), 6.59 (2H, d,  $J = 9.07$  Hz), 3.70 (3H, s), 3.45 (1H, dd,  $J = 4.72, 2.36$  Hz), 2.67 (1H, dd,  $J = 13.60, 4.53$  Hz), 2.52 (1H, dd,  $J = 13.32, 9.35$  Hz), 2.21 (3H, s), 1.71 (1H, s), 1.12 (3H, s), 0.97 (3H, s);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$ : 157.6, 147.5, 140.0, 138.7, 137.8, 130.2, 128.1, 128.0, 127.1, 127.0, 126.9, 126.5, 126.3, 113.0, 59.7, 56.0, 55.1, 46.8, 32.5, 27.8, 21.3; The ee value was evaluated after derivatization to **6ag**.

**(S)-2-(4-Methoxyphenyl)-N-(1-phenyl-2-(*p*-tolyl)ethyl)propan-2-amine (3ah);** The



structure was confirmed by comparison with data of  $^1\text{H}$  and  $^{13}\text{C}$  NMR shown in literature which our group reported.<sup>5</sup>  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.25-7.21 (4H, m), 7.17-7.15 (1H, m), 7.02 (2H, d,  $J = 7.56$  Hz), 6.92 (2H, d,  $J = 8.25$  Hz), 6.86 (2H, d,  $J = 7.56$  Hz), 6.67 (2H, d,  $J = 8.94$  Hz), 3.78 (3H, s), 3.52 (1H, dd,  $J = 4.81, 2.41$  Hz), 2.74 (1H, dd,  $J = 13.40, 5.15$  Hz), 2.61 (1H, dd,  $J = 13.75, 8.94$  Hz), 2.32 (3H, s), 1.75 (1H, s), 1.19 (3H, s), 1.05 (3H, s);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 150 MHz)  $\delta$ : 157.6, 147.4, 140.1, 135.72, 135.67, 129.3, 128.9, 128.0, 127.1, 126.9, 126.3, 113.0, 59.7, 56.0, 55.1, 46.4, 32.4, 27.9, 21.0; HPLC analysis using Shinwa Chemical Industries Ltd. ULTRON ES-PhCD column (20 mM  $\text{KH}_2\text{PO}_4$ :MeCN = 75:25, 1.0 mL/min, 210 nm, tR = 48.1 min (*R*), 68.7 min (*S*));  $[\alpha]_{\text{D}}^{20} = -10.57$  (68% ee, c 1.01,  $\text{CHCl}_3$ ).



### ***Synthetic Utility***

#### **Gram-scale reaction (Figure 2-24 a)**

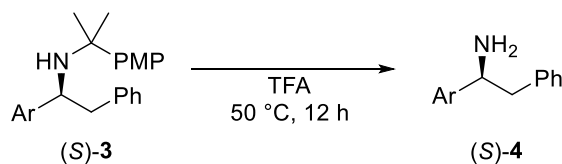
KCH<sub>2</sub>SiMe<sub>3</sub> (94.7 mg, 0.750 mmol) and KHMDS (149.6 mg, 0.750 mmol) were placed in a flame-dried 10 mL flask inside a glove box fulfilled with argon. The flask was cooled to –40 °C, and toluene (3.0 mL) was added. Additionally, diamine ligand **L19** (193.7 mg, 0.830 mmol) dissolved in toluene (3.0 mL) was added. Subsequently, the mixture was stirred for 30 min at the same temperature. After the flask was cooled at –78 °C, toluene was added to the reaction mixture. Then, *p*-methoxycumylimine **1a** (2.53 g, 10.0 mmol) dissolved in toluene (14.0 mL) was successively introduced via a well-dried cannula, and the whole mixture was stirred for 18 h at the same temperature. After the reaction was quenched by adding MeOH, the mixture was extracted with DCM (10 mL × 3). The combined organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After filtration and concentration under reduced pressure, the crude product obtained was purified by PTLC (hexane-ethyl acetate) to afford the desired amine **3aa** (3.09 g, 85% yield). The enantioselectivity was determined by HPLC (86% ee).

#### ***In situ* preparation of imine (Figure 2-24 b)**

*p*-Methoxycumylamine **5** (337.1 mg, 2.04 mmol), aldehyde (212.2 mg, 2.00 mmol), and pellet-type MS 4 A (1.00 g) were placed in a flame-dried 10 mL flask inside a glove box fulfilled with argon. Toluene (1.0 mL) was introduced to the flask, and the reaction mixture was gently stirred for 18 h at room temperature with preventing the pellets of MS 4 A from being broken. The obtained solution was directly used in the next step.

KCH<sub>2</sub>TMS (18.9 mg, 0.150 mmol) and KHMDS (29.9 mg, 0.150 mmol) were placed in another flame-dried 10 mL flask inside a glove box fulfilled with argon. The flask was cooled to –40 °C, then diamine ligand **L19** (38.7 mg, 0.166 mmol) dissolved in toluene (1.0 mL) was added, and the chiral base mixture was stirred for 30 min at the same temperature. After the flask was cooled at –78 °C, toluene (0.80 mL) was added, and the imine solution prepared above was successively introduced via a well-dried cannula. The flask for imine preparation was rinsed with toluene (1.0 mL), and the solution was also added in the reaction mixture. The whole mixture was stirred for 18 h at the same temperature. After the reaction was quenched by adding MeOH, the mixture was extracted with DCM (10 mL × 3). The combined organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After filtration and concentration under reduced pressure, the crude product obtained was purified by PTLC (hexane-ethyl acetate) to afford the desired amine **3aa** (559.7 mg, 81% yield). The enantioselectivity was determined by HPLC (84% ee).

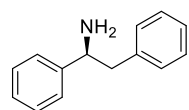
### Removal of *p*-methoxy group (Figure 2-25 a)



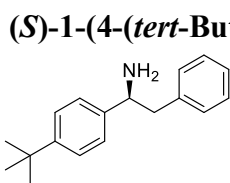
*p*-Methoxycumylamine **3** was placed in a 10 mL flask, and TFA (2.0 mL per mmol of **3**) was subsequently added to the flask. The mixture was heated to 50 °C and stirred for 12 h at the same temperature. Subsequently, water (1.0 mL per mmol of **3**) was added to the flask, and the mixture was stirred for 15 min at the same temperature. After cooling to room temperature, the reaction was basified with 15% NaOH aq. and extracted with DCM (20 mL  $\times$  3). The combined organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After filtration and evaporation, the obtained crude was diluted with Et<sub>2</sub>O, and was extracted with 1N HCl aq. (20 mL  $\times$  2). The combined aqueous layer was washed with Et<sub>2</sub>O (10 mL  $\times$  2) and then was basified with 15% aq. NaOH. The basified aqueous layer was extracted with DCM (20 mL  $\times$  3). The combined organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced vacuum after filtration to afford the desired almost pure primary amine **4**. If the purity was not enough, the product was further purified by PTLC (Et<sub>2</sub>O-Hexane-Et<sub>2</sub>NH).

As for **4ba**, **4ca**, **4ia**, and **4ja**, the enantiopurities could be enhanced by recrystallization (in CPME-Acetone-EtOH) of the corresponding ammonium chloride salt formed with 1N HCl in Et<sub>2</sub>O.

### (*S*)-*N*-(1,2-Diphenylethyl)-2-(4-methoxyphenyl)propan-2-amine (**6aa**); (*S*)-**3aa**



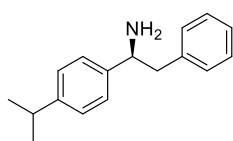
(345.5 mg, 1.00 mmol, 99% ee) was used, and **6aa** (179.2 mg, 91% yield, 99% ee) was obtained. The structure was confirmed by comparison with data of <sup>1</sup>H and <sup>13</sup>C NMR shown in the literature which our group reported.<sup>5</sup> <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.36-7.17 (10H, m), 4.19 (1H, dd, *J* = 4.58, 2.29 Hz), 3.01 (1H, dd, *J* = 13.06, 4.81 Hz), 2.82 (1H, dd, *J* = 13.75, 8.94 Hz), 1.50 (2H, s); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>)  $\delta$ : 145.6, 139.1, 129.3, 128.4, 127.0, 126.4, 124.3, 57.5, 46.5; HPLC analysis using Daicel Chiralcel OD-H column (Hexane:*i*PrOH:Et<sub>2</sub>NH = 90:10:0.1, 1.0 mL/min, 254 nm, t<sub>R</sub> = 7.6 min (*R*), 11.4 min (*S*)); [ $\alpha$ ]<sub>D</sub><sup>20</sup> = -0.27 (99% ee, c 1.36, CHCl<sub>3</sub>).



(*S*)-**1**-(4-(*tert*-Butyl)phenyl)-2-phenylethan-1-amine (**6ba**); **3ba** (324.3 mg, 0.808 mmol, 89% ee) was used, and **6ba** (132.8 mg, 65% yield, 89% ee) was obtained. The structure was confirmed by comparison with data of <sup>1</sup>H and <sup>13</sup>C NMR shown in the literature.<sup>12</sup> The enantiopurity was enhanced by recrystallization of the corresponding ammonium chloride salt (>99% ee, 31% recovery). <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.30-7.28 (2H,

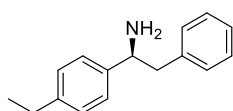
m), 7.25-7.21 (4H, m), 7.16-7.13 (3H, m), 4.10 (1H, dd,  $J = 4.58, 2.29$  Hz), 2.96 (1H, dd,  $J = 13.40, 4.47$  Hz), 2.73 (1H, dd,  $J = 13.75, 9.62$  Hz), 1.63 (2H, s), 1.25 (9H, s);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 150.0, 142.5, 139.3, 129.3, 128.4, 126.3, 126.1, 125.3, 57.1, 46.3, 34.5, 31.4; HPLC analysis using Daicel Chiralcel OD-H column (Hexane: $i$ PrOH: $\text{Et}_2\text{NH} = 90:10:0.1$ , 1.0 mL/min, 254 nm,  $t_R = 5.9$  min ( $R$ ), 6.7 min ( $S$ )), using Daicel Chiralcel OD-RH column (for **6ba**·HCl, 20 mM NaB(OH) $_4$ / MeCN = 60/40, 0.5 mL/min, 210 nm,  $t_R = 79.3$  min ( $R$ ), 82.7 min ( $S$ ));  $[\alpha]_D^{20} = +105.62$  (as **6ba**·HCl, >99% ee, c 0.14, EtOH).

**(S)-1-(4-Isopropylphenyl)-2-phenylethan-1-amine (6ca); 3ca** (277.2 mg, 0.715 mmol)



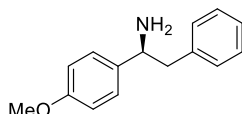
was used, and **6ca** (135.5 mg, 79% yield, 89% ee) was obtained. The structure was confirmed by comparison with data of  $^1\text{H}$  and  $^{13}\text{C}$  NMR shown in the literature.<sup>12</sup> The enantiopurity was enhanced by recrystallization of the corresponding ammonium chloride salt (>99% ee, 15% recovery).  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.30-7.28 (4H, m), 7.23-7.19 (5H, m), 4.17 (1H, dd,  $J = 4.58, 2.29$  Hz), 3.02 (1H, dd,  $J = 13.40, 4.47$  Hz), 2.94-2.87 (1H, m), 2.80 (1H, dd,  $J = 13.40, 9.28$  Hz), 1.61 (s, 3H), 1.25 (6H, d,  $J = 6.87$  Hz);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 147.7, 142.8, 139.2, 129.3, 128.4, 126.4, 126.3, 57.2, 46.3, 33.7, 24.0; HPLC analysis using Daicel Chiralcel OD-H column (Hexane: $i$ PrOH: $\text{Et}_2\text{NH} = 90:10:0.1$ , 1.0 mL/min, 254 nm,  $t_R = 5.8$  min ( $R$ ), 6.5 min ( $S$ )), using Daicel Chiralcel OD-RH column (for **6ca**·HCl, 20 mM NaB(OH) $_4$ / MeCN = 60/40, 0.5 mL/min, 210 nm,  $t_R = 57.9$  min ( $R$ ), 60.9 min ( $S$ ));  $[\alpha]_D^{20} = +103.25$  (as **6ca**·HCl, >99% ee, c 0.10, EtOH).

**(S)-1-(4-Ethylphenyl)-2-phenylethan-1-amine (6da); 3da** (134.5 mg, 0.360 mmol)



was used, and **6da** (72.8 mg, 90% yield, 81% ee) was obtained. Colorless oil;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.32-7.15 (9H, m), 4.20 (1H, dd,  $J = 8.25, 5.50$  Hz), 3.04 (1H, dd,  $J = 13.75, 5.50$  Hz), 2.91 (1H, dd,  $J = 13.40, 7.90$  Hz), 2.62 (2H, q,  $J = 7.56$  Hz), 1.22 (3H, t,  $J = 7.56$  Hz);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 143.2, 142.4, 139.1, 129.3, 128.4, 127.9, 126.4, 126.36, 57.2, 46.2, 28.5, 15.5; IR (neat,  $\text{cm}^{-1}$ ) 2965, 1602, 1511, 1494, 1454, 1077, 1031, 1020, 828, 700, 543; HRMS (DART) calcd for  $\text{C}_{16}\text{H}_{20}\text{N}$   $[\text{M} + \text{H}]^+$  226.15957, found 226.15966; HPLC analysis using Daicel Chiralcel OD-H column (Hexane: $i$ PrOH: $\text{Et}_2\text{NH} = 90:10:0.1$ , 1.0 mL/min, 254 nm,  $t_R = 6.4$  min ( $R$ ), 7.5 min ( $S$ ));  $[\alpha]_D^{20} = +16.38$  (84% ee, c 0.24,  $\text{CHCl}_3$ ).

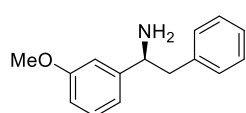
**(S)-1-(4-Methoxyphenyl)-2-phenylethan-1-amine (6ha); 3ha** (256.7 mg, 0.684 mmol)



was used, and **6ca** (134.2 mg, 86% yield, 90% ee) was obtained. The structure was confirmed by comparison with data of  $^1\text{H}$  and  $^{13}\text{C}$  NMR shown in the literature.<sup>12</sup>  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.29-7.26 (4H, m), 7.21 (1H, t,  $J = 7.56$  Hz), 7.16 (2H, d,  $J = 7.56$  Hz), 6.86 (2H, d,  $J = 8.25$  Hz), 4.15 (1H, dd,  $J = 4.58, 2.29$  Hz), 3.80 (3H, s), 2.98 (1H, dd,  $J = 13.06, 4.81$  Hz),

2.81 (1H, dd,  $J = 13.40, 8.59$  Hz), 1.63 (2H, s);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 158.6, 139.1, 137.6, 129.3, 128.4, 127.5, 126.3, 113.7, 56.9, 55.3, 46.5; HPLC analysis using Daicel Chiralcel OD-H column (Hexane: $i$ PrOH: $\text{Et}_2\text{NH} = 90:10:0.1$ , 1.0 mL/min, 254 nm,  $t_R = 9.2$  min ( $R$ ), 11.7 min ( $S$ ));  $[\alpha]_D^{20} = +29.02$  (90% ee, c 0.10,  $\text{CHCl}_3$ ).

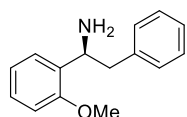
**(*S*)-1-(3-Methoxyphenyl)-2-phenylethan-1-amine (6ia); 3ia** (256.7 mg, 0.684 mmol,



76% ee) was used, and **6ia** (76.8 mg, quant., 76% ee) was obtained. The enantiopurity was enhanced by recrystallization of the corresponding ammonium chloride salt (97% ee, 11% recovery).

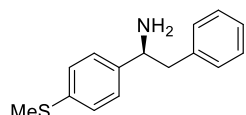
Colorless oil;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.30-7.17 (6H, m), 6.94-6.93 (2H, m), 6.80 (1H, dd,  $J = 8.25, 2.06$  Hz), 4.18 (1H, dd,  $J = 4.58, 2.29$  Hz), 3.79 (3H, s), 3.02 (1H, dd,  $J = 13.40, 5.15$  Hz), 2.84 (1H, dd,  $J = 13.40, 8.59$  Hz), 1.86 (2H, s);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 159.7, 146.9, 138.9, 129.4, 129.3, 128.4, 126.4, 118.8, 112.7, 111.9, 57.5, 55.2, 46.2; IR (neat,  $\text{cm}^{-1}$ ) 3002, 1599, 1585, 1485, 1454, 1434, 1254, 1074, 1043, 871, 780, 697, 511, 468; HRMS (DART) calcd for  $\text{C}_{15}\text{H}_{18}\text{NO}$   $[\text{M} + \text{H}]^+$  228.13884, found 228.13782; HPLC analysis using Daicel Chiralcel OD-H column (Hexane: $i$ PrOH: $\text{Et}_2\text{NH} = 90:10:0.1$ , 1.0 mL/min, 254 nm,  $t_R = 10.2$  min ( $R$ ), 13.0 min ( $S$ ));  $[\alpha]_D^{20} = +110.66$  (as **6ia**·HCl, 97% ee, c 0.10, EtOH).

**(*S*)-1-(2-Methoxyphenyl)-2-phenylethan-1-amine (6ja); 3ja** (335.3 mg, 0.893 mmol, 84% ee) was used, and **6ja** (163.2 mg, 80% yield, 84% ee) was obtained.



The structure was confirmed by comparison with data of  $^1\text{H}$  and  $^{13}\text{C}$  NMR shown in the literature.<sup>12</sup> The enantiopurity was enhanced by recrystallization of the corresponding ammonium chloride salt (>99% ee, 37% recovery).  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.26 (1H, dd,  $J = 7.56, 1.37$  Hz), 7.22-7.12 (6H, m), 6.86 (1H, t,  $J = 7.90$  Hz), 6.81 (1H, d,  $J = 8.25$  Hz), 4.40 (1H, dd,  $J = 4.35, 2.18$  Hz), 3.77 (3H, s), 3.05 (1H, dd,  $J = 13.75, 4.81$  Hz), 2.71 (1H, dd,  $J = 13.06, 8.94$  Hz), 1.68 (2H, s);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 156.7, 139.8, 133.5, 129.4, 128.3, 127.8, 126.7, 126.1, 120.6, 110.4, 55.3, 52.2, 44.2; HPLC analysis using Daicel Chiralcel OD-H column (Hexane: $i$ PrOH: $\text{Et}_2\text{NH} = 90:10:0.1$ , 1.0 mL/min, 254 nm,  $t_R = 7.7$  min ( $R$ ), 8.1 min ( $S$ ));  $[\alpha]_D^{20} = +90.76$  (as **6ja**·HCl, >99% ee, c 0.11, EtOH).

**(*S*)-1-(4-(Methylthio)phenyl)-2-phenylethan-1-amine (6ka); 3ka** (308.9 mg, 0.789 mmol) was used, and **6ka** (117.9 mg, 61% yield, 80% ee) was obtained.



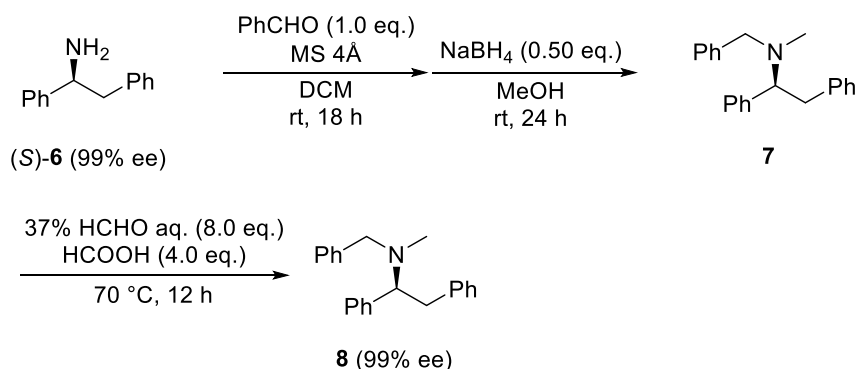
The structure was confirmed by comparison with data of  $^1\text{H}$  and  $^{13}\text{C}$  NMR shown in the literature.<sup>12</sup>  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.27-7.25 (5H, m), 7.21-7.19 (3H, m), 7.14 (2H, d,  $J = 6.80$  Hz), 4.14 (1H, dd,  $J = 4.53, 2.27$  Hz), 2.96 (1H, dd,  $J = 13.32, 4.82$  Hz), 2.78 (1H, dd,  $J = 13.32, 8.79$  Hz), 2.46 (3H, s), 1.52 (2H, s);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 142.7, 138.9, 136.8, 129.3, 128.4, 127.0, 126.8, 126.4, 57.1, 46.4, 16.1; HPLC analysis using Daicel Chiralcel OD-H column (Hexane: $i$ PrOH: $\text{Et}_2\text{NH} = 90:10:0.1$ , 1.0 mL/min, 254 nm,

tR = 10.7 min (*R*), 11.8 min (*S*));  $[\alpha]_{\text{D}}^{20} = +106.44$  (as **6ka**·HCl, 84% ee, c 0.12, EtOH).

**(*S*)-2-(4-Ethylphenyl)-1-phenylethan-1-amine (6ab)**; **3ab** (167.8 mg, 0.449 mmol) was used, and **6ab** (63.4 mg, 65% yield, 62% ee) was obtained. Colorless oil;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.38-7.07 (9H, m), 4.19 (1H, dd,  $J = 4.53, 2.27$  Hz), 3.01 (1H, dd,  $J = 13.60, 5.10$  Hz), 2.86 (1H, dd,  $J = 13.32, 8.79$  Hz), 2.64-2.42 (4H, m), 1.24-1.19 (3H, m);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 145.6, 142.2, 136.2, 129.2, 128.4, 127.9, 127.0, 126.4, 57.5, 46.0, 28.4, 15.6; IR (neat,  $\text{cm}^{-1}$ ) 3025, 2963, 2929, 1602, 1514, 1492, 1452, 813, 760, 698, 554, 537; HRMS (DART) calcd for  $\text{C}_{15}\text{H}_{18}\text{NO}$   $[\text{M} + \text{H}]^+$  226.15957, found 226.15912; HPLC analysis using Daicel Chiralcel OD-H column (Hexane:*i*PrOH: $\text{Et}_2\text{NH} = 90:10:0.1$ , 1.0 mL/min, 254 nm, tR = 6.6 min (*R*), 11.1 min (*S*));  $[\alpha]_{\text{D}}^{20} = +9.92$  (62% ee, c 0.94,  $\text{CHCl}_3$ ).

**(*S*)-1-Phenyl-2-(*m*-tolyl)ethan-1-amine (6ag)**; **3ag** (167.6 mg, 0.459 mmol) was used, and **6ag** (65.7 mg, 64% yield, 71% ee) was obtained. The structure was confirmed by comparison with data of  $^1\text{H}$  and  $^{13}\text{C}$  NMR shown in the literature.<sup>12</sup>  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.38-7.31 (4H, m), 7.27-7.24 (2H, m), 7.17 (1H, t,  $J = 7.37$  Hz), 7.04-6.95 (3H, m), 4.20 (1H, dd,  $J = 4.53, 2.27$  Hz), 3.00 (1H, dd,  $J = 13.04, 5.10$  Hz), 2.84 (1H, dd,  $J = 6.52, 3.26$  Hz), 2.33-2.31 (5H, m);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 145.6, 139.0, 138.0, 130.1, 128.4, 128.3, 127.1, 127.0, 126.4, 126.3, 57.5, 46.4, 21.4; HPLC analysis using Daicel Chiralcel OD-H column (Hexane:*i*PrOH: $\text{Et}_2\text{NH} = 90:10:0.1$ , 1.0 mL/min, 254 nm, tR = 6.7 min (*R*), 12.2 min (*S*));  $[\alpha]_{\text{D}}^{20} = +16.50$  (71% ee, c 0.61,  $\text{CHCl}_3$ ).

#### *N*-alkylation (Figure 2-25 b)



*p*-Methoxycumylamine (**S**)-**3aa** (197.3 mg, 1.00 mmol), benzaldehyde (106.1 mg, 1.00 mmol), MS 4 Å (1 g) were placed in a 10 mL flask, and DCM was added to the flask. The mixture was stirred for 18 h at room temperature. After MS 4 Å was removed by filtration through a Celite pad, the filtrate was concentrated and dried to afford the corresponding imine. The obtained imine was placed in 30 mL flask and was dissolved in 5.0 mL of MeOH. Subsequently,  $\text{NaBH}_4$  was added to the flask, and the reaction

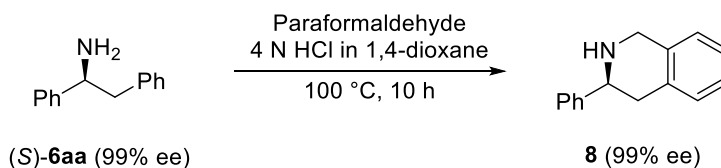
mixture was stirred for 24h at room temperature. The mixture was concentrated under vacuum condition, and the obtained solid was dissolved in DCM and water. The two layers solution was extracted with DCM (20 mL  $\times$  3). The combined organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After filtration and concentration under reduced pressure, the crude product obtained was purified by PTLC (hexane-ethyl acetate) to afford the desired amine **6** (239.9 mg, 83% yield).

Furthermore, amine **7** was derivatized to tertiary amine **6**. Amine **5** (71.9 mg, 0.25 mmol) was placed in a 8 mL tube, and 37% HCHO aq. (162  $\mu$ L, 2.0 mmol) and formic acid (38  $\mu$ L, 4.0 mmol) added to the flask. The mixture was stirred for 12 h at 70 °C. The reaction was quenched with 15% NaOH aq., and the mixture was extracted with DCM (10 mL  $\times$  3). The combined organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After filtration and concentration under reduced pressure, the crude product obtained was purified by PTLC (hexane-ethyl acetate) to afford the desired amine **6** (67.6 mg, 90% yield).

**(S)-N-Benzyl-1,2-diphenylethan-1-amine (6)**; The structure was confirmed by comparison with data of <sup>1</sup>H and <sup>13</sup>C NMR shown in the literature.<sup>11</sup> <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.35-7.33 (4H, m), 7.28-7.23 (5H, m), 7.21-7.19 (2H, m), 7.10 (4H, d,  $J$  = 7.37 Hz), 3.88 (1H, dd,  $J$  = 8.50, 5.67 Hz), 3.65 (1H, d,  $J$  = 13.60 Hz), 3.46 (1H, d,  $J$  = 13.60 Hz), 2.92 (2H, m), 1.60 (s, 1H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>)  $\delta$ : 143.7, 140.4, 138.8, 129.2, 128.35, 128.33, 128.2, 127.9, 127.4, 127.1, 126.7, 126.3, 63.6, 51.3, 45.3;  $[\alpha]_D^{20}$  = -31.82 (c 0.55, CHCl<sub>3</sub>).

**(S)-N-Benzyl-N-methyl-1,2-diphenylethan-1-amine (7)**; The structure was confirmed by comparison with data of <sup>1</sup>H and <sup>13</sup>C NMR shown in the literature.<sup>12</sup> <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.27-7.21 (12H, m), 7.13 (1H, dd,  $J$  = 8.59, 5.84 Hz), 7.06 (2H, d,  $J$  = 6.87 Hz), 3.82 (1H, dd,  $J$  = 7.56, 3.78 Hz), 3.63 (1H, d,  $J$  = 13.75 Hz), 3.37 (1H, dd,  $J$  = 6.87, 3.44 Hz), 3.30 (1H, d,  $J$  = 13.06 Hz), 3.02 (1H, dd,  $J$  = 13.75, 8.25 Hz), 2.19 (3H, s); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>)  $\delta$ : 139.9, 139.8, 139.4, 129.4, 128.8, 128.7, 128.1, 127.9, 127.8, 127.0, 126.7, 125.7, 69.5, 58.8, 38.9, 38.0; HPLC analysis using Shinwa Chemical Industries Ltd. ULTRON ES-PhCD column (20 mM KH<sub>2</sub>PO<sub>4</sub>:MeCN = 75:25, 1.0 mL/min, 210 nm, t<sub>R</sub> = 74.3 min (*R*), 96.9 min (*S*));  $[\alpha]_D^{20}$  = +22.50 (c 0.51, CHCl<sub>3</sub>).

### Transformation to 1,2,3,4-tetrahydroisoquinoline (Figure 2-25 c)



*p*-Methoxycumylamine (*S*)-**6aa** (98.6 mg, 0.500 mmol) and paraformaldehyde (18.0 mg, 0.600 mmol as HCHO) were placed in a 10 mL flask, and 4 N HCl in dioxane was subsequently added. The reaction mixture was stirred for 10 h at 100 °C. After cooling, the mixture was basified with 15% aq. NaOH aq., and was extracted with DCM (20 mL × 3). The combined organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After filtration and concentration under reduced pressure, the crude product obtained was purified by PTLC (hexane-ethyl acetate) to afford the desired tetrahydroisoquinoline **8** (36.1 mg, 36% yield).

**(*S*)-3-Phenyl-1,2,3,4-tetrahydroisoquinoline (8)**; The structure was confirmed by comparison with data of <sup>1</sup>H and <sup>13</sup>C NMR shown in the literature.<sup>13</sup> <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ: 7.44 (2H, d, *J* = 7.56 Hz), 7.37 (2H, m), 7.29 (1H, t, *J* = 7.56 Hz), 7.16-7.15 (m, 2H), 7.10-7.08 (m, 2H), 4.27 (1H, d, *J* = 15.81 Hz), 4.17 (1H, d, *J* = 15.81 Hz), 4.02 (dd, 1H, *J* = 8.25, 6.87 Hz), 2.99 (2H, d, *J* = 7.56 Hz), 2.04 (s, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ: 144.3, 135.0, 134.9, 129.1, 128.6, 127.4, 126.5, 126.2, 126.1, 125.9, 58.6, 49.2, 37.7; HPLC analysis using Daicel Chiralcel OJ-3 column (Hexane:*i*PrOH = 98:2, 1.0 mL/min, 254 nm, tR = 34.5 min (*S*), 44.7 min (*R*)); [α]<sub>D</sub><sup>20</sup> = -123.02 (98% ee, c 0.35, CHCl<sub>3</sub>).

## ***Mechanistic Studies***

### **Investigation of backward reaction**

#### **Experimental procedure (Figure 2-26)**

KCH<sub>2</sub>SiMe<sub>3</sub> (6.3 mg,  $5.0 \times 10^{-2}$  mmol) and KHMDS (10.0 mg,  $5.0 \times 10^{-2}$  mmol) were placed in a flame-dried 10 mL flask inside a glove box fulfilled with argon. After the flask was cooled to the corresponding temperature, ligand **L19** ( $5.5 \times 10^{-2}$  mmol) in toluene (0.40 mL) was added, and the mixture was stirred at  $-40$  °C for 30 minutes. Subsequently, the flask was cooled to  $-78$  °C, and the corresponding imine **3aa** (126.7 mg, 0.50 mmol, 99% ee) dissolved in toluene (0.60 mL) was successively introduced into the flask via a well-dried cannula. After the whole mixture was stirred for 18 h at the same temperature, the reaction was quenched by adding a few drops of MeOH, and the obtained mixture was extracted with DCM (10 mL  $\times$  3), then combined organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After filtration and concentration under reduced pressure, the obtained crude product was purified by PTLC (hexane-ethyl acetate) to afford the desired amine **3aa** (93% yield). The enantiopurity was determined by HPLC as 99% ee.

### **NMR experiments**

#### **Preparation of samples (Figure 2-27-Figure 2-32)**

KCH<sub>2</sub>TMS (6.3 mg,  $5.0 \times 10^{-2}$  mmol) KHMDS (10.0 mg,  $5.0 \times 10^{-2}$  mmol) were placed in a flame-dried 10 mL flask inside a glove box fulfilled with argon. The flask was cooled to  $-40$  °C, then diamine ligand **L2** or **L19** ( $5.5 \times 10^{-2}$  mmol) in toluene-d<sub>8</sub> (0.40 mL) was added, and the mixture was stirred for 30 min at the same temperature. After the flask was cooled to  $-78$  °C, the mixture was diluted with toluene-d<sub>8</sub> (0.60 mL) and was successively transferred into a screw-cap NMR tube via a well-dried cannular. Subsequently, NMR measurement was conducted with keeping  $-78$  °C.

### **General procedure for nonlinear effect**

#### **Experimental procedure (Figure 2-33)**

KCH<sub>2</sub>TMS (6.3 mg,  $5.0 \times 10^{-2}$  mmol) and KHMDS (10.0 mg,  $5.0 \times 10^{-2}$  mmol) were placed in a flame-dried 10 mL flask inside a glove box fulfilled with argon. The flask was cooled to  $-40$  °C, then diamine ligand **L6** (19.4 mg,  $8.3 \times 10^{-2}$  mmol) in toluene (0.20 mL) was added, and the chiral base mixture was stirred for 30 min at the same temperature. After the flask was cooled at  $-78$  °C, *p*-methoxycumylimine **1a** (2.53 g, 10.0 mmol) dissolved in toluene (0.80 mL) was successively introduced via a well-dried cannula, and the whole mixture was stirred for 18 h at the same temperature. After the reaction was quenched by adding water, the mixture was extracted with DCM (10 mL  $\times$  3). The combined organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After filtration and concentration under reduced pressure, the crude product obtained was purified by PTLC (hexane-ethyl acetate) to afford the desired adduct **3**.

### **Effect of the piperazine part**



**General procedure for ligand structure activity (Table 2-8)**

KCH<sub>2</sub>SiMe<sub>3</sub> (6.3 mg,  $5.0 \times 10^{-2}$  mmol) and KHMDS (10.0 mg,  $5.0 \times 10^{-2}$  mmol) were placed in a flame-dried 10 mL flask inside a glove box fulfilled with argon. After the flask was cooled to the corresponding temperature, the corresponding amine ligand **L** ( $5.5 \times 10^{-2}$  mmol) in toluene (0.40 mL) was added, and the mixture was stirred at  $-40\text{ }^{\circ}\text{C}$  for 30 minutes. Subsequently, the flask was cooled to  $-78\text{ }^{\circ}\text{C}$ , and the corresponding imine **1a** (126.7 mg, 0.50 mmol) dissolved in toluene (0.60 mL) was successively introduced into the flask via a well-dried cannula. After the whole mixture was stirred for 18 h at the same temperature, the reaction was quenched by adding a few drops of MeOH, and the obtained mixture was extracted with DCM (10 mL  $\times$  3), then combined organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After filtration and concentration under reduced pressure, the obtained crude product was purified by PTLC (hexane-ethyl acetate) to afford the desired amine **3aa**. The enantioselectivities were determined by HPLC.

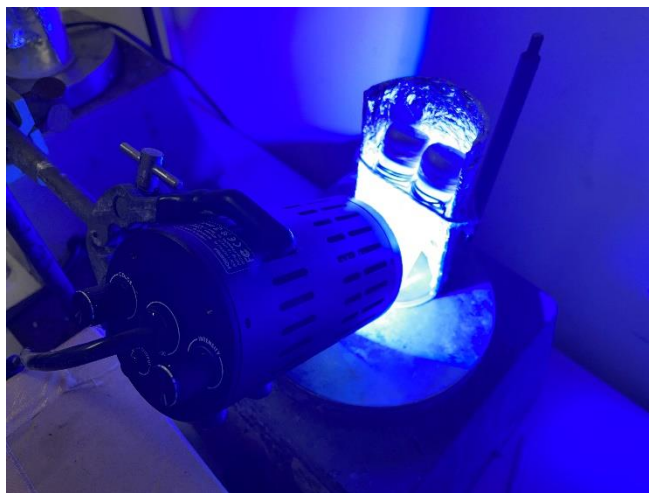
## ***Experimental Procedure (Chapter 3)***

### ***General Information***

Melting points were measured with AS ONE Melting Temperature Measurement Device (ATM-02).  $^1\text{H}$ ,  $^{13}\text{C}$ , and  $^{19}\text{F}$  NMR spectra were recorded on JEOL JNM-ECA500 and JNM-ECX600 spectrometers in  $\text{CDCl}_3$  unless otherwise noted. Tetramethylsilane (TMS) served as internal standard ( $\delta = 0$ ) for  $^1\text{H}$  NMR, and  $\text{CDCl}_3$  served as internal standard ( $\delta = 77.0$ ) for  $^{13}\text{C}$  NMR. Benzotrifluoride (BTF) served as internal standard ( $\delta = -63.72$ ) for  $^{19}\text{F}$  NMR. IR spectra were measured on JASCO FT/IR-610 spectrometer. DART mass spectra (TOF) were recorded on JEOL JMS-T100TD mass spectrometer. X-ray crystal structures were analyzed on a Rigaku R-Axis RAPID diffractometer using multi-layer mirror monochromated Mo-K $\alpha$  radiation. Preparative thin-layer chromatography (PTLC) was carried out using Wakogel B-5F. Kessil LED Aquarium Light A160WE Tuna Blue was used as a blue light source. 200W Hg lamp was employed as UV-light source, and the reactions under UV irradiation were carried out in quartz tube. Alkenes (**1a**,<sup>13</sup> **1b**,<sup>13</sup> **1c**,<sup>13</sup> **1d**,<sup>13</sup> **1e**,<sup>13</sup> **1f**,<sup>14</sup> **1g**,<sup>13</sup> **1k**,<sup>15</sup> **1l**,<sup>13</sup> **1m**,<sup>13</sup> **1n**,<sup>16</sup> **1p**,<sup>13</sup> **1q**,<sup>13</sup> **1r**,<sup>16</sup> **1v**,<sup>17</sup> **1x**,<sup>18</sup> **1y**<sup>13</sup>), silyl enol ethers (**2a**,<sup>19</sup> **2b**,<sup>19</sup> **2c**,<sup>19</sup> **2d**,<sup>20</sup> **2f**,<sup>21,22,23</sup> **2g**,<sup>21</sup> **2h**,<sup>24</sup> **2i**,<sup>25</sup> **4b**,<sup>26</sup> **4d**,<sup>27</sup> **4c**,<sup>28</sup> **4g**<sup>29</sup>), photocatalysts (DCA,<sup>30</sup> DCN,<sup>31</sup> 4CzIPN,<sup>32</sup> 4DPAIPN,<sup>32</sup> 4CzTPN<sup>32</sup>) were synthesized according to the cited literatures. The other starting materials were commercially available and used after distillation.

### ***Photoreactor System Utilized in the Described Research***

The reaction tubes were irradiated by Kessil LED Aquarium Light A160WE Tuna Blue (highest blue and intensity setting, The distance between the tubes and the LED: ~2 cm). A simple cooling fan was equipped for cooling (Supplementary figure 1, Supplementary figure 2). It was measured that the equilibrium temperature of the reaction mixture was ~45 °C with a standard alcohol thermometer.



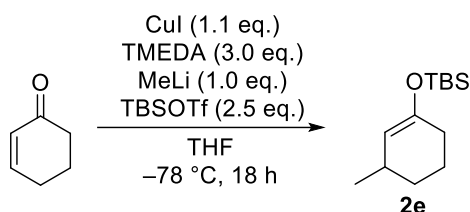
**Supplementary figure 1. Photo-Reactor**



**Supplementary figure 2. the Outside Appearance of the Photo-Reactor**

## Synthesis of Silyl Enol Ethers

### Synthesis of *tert*-butyldimethyl((3-methylcyclohex-1-en-1-yl)oxy)silane (**2e**)

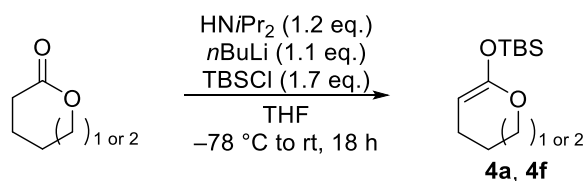


The title compound (**2e**) was synthesized according to the literature.<sup>33</sup> Copper (I) iodide (6.29 g, 33.0 mmol) and TMEDA (13.5 mL, 90.0 mmol) were added to a clean dry, three-necked 300 mL flask equipped with a magnetic stirrer and an addition funnel. The apparatus was then flushed with argon and 50 mL of dry THF was added. After the contents were stirred at room temperature for 30 minutes, the flask was cooled to  $-78\text{ }^\circ\text{C}$  and methyl lithium (3.1 M in diethoxymethane, 9.7 mL, 30.0 mmol) was added followed by stirring at  $-78\text{ }^\circ\text{C}$  for 20 min. Then, cyclohex-2-enone (2.88 g, 30.0 mmol) in 20 mL of dry THF was added dropwise for 30 minutes followed by *tert*-butyldimethylsilyl trifluoromethanesulfonate (17.2 mL, 75.0 mmol) in 20 mL of dry THF was added, and the reaction mixture was stirred at  $-78\text{ }^\circ\text{C}$  for 18 hours. The reaction was quenched by saturated  $\text{NaHCO}_3$  aqueous solution and the obtained mixture was extracted with hexane (100 mL  $\times$  3). The combined organic layer was washed with brine ( $\times$  3) and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . After filtration and concentration under reduced pressure, the obtained crude product was purified by short column chromatography (hexane/ $\text{Et}_3\text{N}$  = 95/5) on silica gel. Then, the residue was distilled to afford the silyl enol ether **2e** (3.08 g, 45% yield).

***tert*-Butyldimethyl((3-methylcyclohex-1-en-1-yl)oxy)silane (**2e**)**; Colorless liquid;<sup>1</sup>H

NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 4.74 (s, 1H), 2.24-2.22 (m, 1H), 2.03-1.91 (m, 2H), 1.76-1.74 (m, 1H), 1.70-1.67 (m, 1H), 1.57-1.53 (m, 1H), 1.08-1.01 (m, 1H), 0.94 (d, 3H,  $J$  = 6.80 Hz), 0.92 (s, 9H), 0.12 (s, 6H); <sup>13</sup>C NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 150.2, 111.1, 31.2, 29.8, 29.5, 25.7, 22.5, 21.8, 18.0, -4.4, -4.5; IR (neat,  $\text{cm}^{-1}$ ) 2954, 2929, 2859, 1194, 1181; HRMS (DART) calcd for  $\text{C}_{13}\text{H}_{27}\text{OSi}$   $[\text{M} + \text{H}]^+$  227.1831, found 227.1829.

### Synthesis of Ketene Silyl Acetals (**4a**, **4f**)

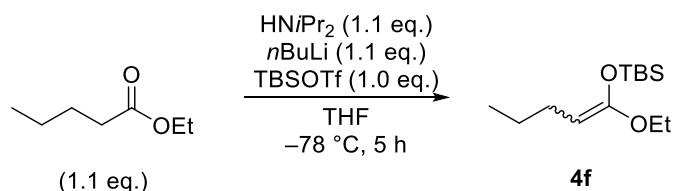


Diisopropylamine (10.7 mL, 48.0 mmol) and THF (50 mL) were placed in a well-dried three-necked 300 mL flask equipped with a dropping funnel. After the flask was cooled to  $-78\text{ }^{\circ}\text{C}$ , *n*-butyl lithium (1.6 M in hexane, 28.0 mL, 44.0 mmol) was added, then the mixture was stirred at  $-78\text{ }^{\circ}\text{C}$  for 30 min. Subsequently, the corresponding lactone (40.0 mmol) dissolved in THF (30 mL) was added dropwise for 30 minutes, and the reaction mixture was stirred at the same temperature for an additional 1 h. *tert*-Butyldimethylsilyl chloride (10.3 g, 68.0 mmol) dissolved in THF (20 mL) was added dropwise for 30 minutes, and the reaction mixture was stirred at the same temperature for 1 h. The solution allowed to stir at room temperature for 18 h. The reaction was quenched by saturated aq.  $\text{NaHCO}_3$ , and the obtained mixture was extracted with hexane (100 mL  $\times$  3). The combined organic layer was dried over anhydrous  $\text{Na}_2\text{SO}_4$ . After filtration and concentration under reduced pressure, the residue was distilled to afford the ketene silyl acetal **4a** and **4f** (**4a**: 6.43 g, 75% yield. **4f**: 6.40 g, 70% yield).

***tert*-Butyl((3,4-dihydro-2H-pyran-6-yl)oxy)dimethylsilane (4a)**; Colorless oil;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 4.04 (t, 2H,  $J = 5.15\text{ Hz}$ ), 3.83 (t, 1H,  $J = 3.78\text{ Hz}$ ), 2.04-2.03 (m, 2H), 1.76-1.74 (m, 2H), 0.93 (s, 9H), 0.16 (s, 6H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 154.7, 74.2, 67.2, 25.6, 22.4, 20.0, 18.0,  $-4.6$ ; IR (neat,  $\text{cm}^{-1}$ ) 2930, 2886, 2856, 1248, 1063, 910, 784; HRMS(DART) calcd for  $\text{C}_{11}\text{H}_{23}\text{O}_2\text{Si}$   $[\text{M} + \text{H}]^+$  215.1467, found; 215.1471.

***tert*-Butyldimethyl((4,5,6,7-tetrahydrooxepin-2-yl)oxy)silane (4f)**; Colorless oil;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 4.10 (t, 1H,  $J = 5.84\text{ Hz}$ ), 3.97 (t, 2H,  $J = 5.50\text{ Hz}$ ), 1.99 (q, 2H,  $J = 5.73\text{ Hz}$ ), 1.82-1.78 (m, 2H), 1.63-1.61 (m, 2H), 0.92 (s, 9H), 0.15 (s, 6H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 160.2, 83.1, 71.4, 31.2, 26.2, 25.7, 23.3, 18.0,  $-4.5$ ; IR (neat,  $\text{cm}^{-1}$ ) 2929, 2858, 1235, 1200, 1172, 877, 783; HRMS(DART) calcd for  $\text{C}_{12}\text{H}_{25}\text{O}_2\text{Si}$   $[\text{M} + \text{H}]^+$  229.1624, found; 229.1621.

### Synthesis of Ketene Silyl Acetals (**4e**)



Diisopropylamine (5.6 mL, 40.0 mmol) and dry THF (80 mL) were added to a three-necked 300 mL flask equipped with an addition funnel. After the flask was cooled to  $-78\text{ }^{\circ}\text{C}$ , *n*-butyl lithium (1.6 M in hexane, 25.5 mL, 40.0 mmol) was added, and the mixture was stirred at  $-78\text{ }^{\circ}\text{C}$  for 30 min. Then, ethyl valerate (5.2 g, 40.0 mmol) dissolved in dry THF (20 mL) was added dropwise for 30 minutes, and the reaction

mixture was stirred at  $-78\text{ }^{\circ}\text{C}$  for an additional 1 hour. Subsequently, *tert*-butyldimethylsilyl trifluoromethanesulfonate (8.3 mL, 36.0 mmol) was added dropwise for 30 minutes, and the reaction mixture was stirred at  $-78\text{ }^{\circ}\text{C}$  for 5 hours. After concentration under reduced pressure, the residue was diluted with hexane. After filtration and concentration under reduced pressure, the residue was distilled to afford the ketene silyl acetal **4e** (5.21 g, 53% yield).

***tert*-Butyl((1-ethoxypent-1-en-1-yl)oxy)dimethylsilane (4f)**; Colorless oil;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ , As a mixture of (*E*, *Z*)-isomers)  $\delta$ : 3.83 (q, (*E*) 2H,  $J = 7.10\text{ Hz}$ ), 3.71 (t, (*E*) 1H,  $J = 7.56\text{ Hz}$ ), 3.67 (q, (*Z*) 2H,  $J = 6.87\text{ Hz}$ ), 3.41 (t, (*Z*) 1H,  $J = 7.22\text{ Hz}$ ), 1.94-1.91 (m, 2H), 1.33-1.28 (m, 2H), 1.24-1.22 (m, 3H), 0.92 (s, 9H), 0.87 (t, 3H,  $J = 7.22\text{ Hz}$ ), 0.16 (s, 6H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 152.8, 86.5, 63.0, 26.7, 25.6, 23.8, 18.1, 14.9, 13.7, -5.0; IR (neat,  $\text{cm}^{-1}$ ) 2932, 2860, 1678, 1252, 1194, 1070, 838, 781; HRMS (DART) calcd for  $\text{C}_{13}\text{H}_{29}\text{O}_2\text{Si}$   $[\text{M} + \text{H}]^+$  245.1937, found; 245.1949.

### Substrate Scope

#### General procedure for the photo-induced reactions for alkylation of ketones

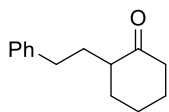


4CzIPN (7.9 mg, 10.0  $\mu$ mol), alkene (0.500 mmol), and silyl enol ether (0.750 mmol) were placed in an 8 mL pyrex tube (Diameter: 14 mm), and the tube was sealed with a septum. The tube was evacuated to remove air and refilled with argon via a needle. Acetonitrile (5.0 mL) and pure water (10.8  $\mu$ L) were then added. When benzenethiol was used, it (10.2  $\mu$ L, 0.100 mmol) was added through the septum. A vent needle was attached, and the reaction mixture was degassed by sparging with argon under sonication for 15 min. The reaction mixture was stirred at room temperature under blue LED irradiation for 12 h. Subsequently, 1 N aq. HCl (1.0 mL) was added, and the mixture was stirred for additional 30 min. The mixture was basified with saturated NaHCO<sub>3</sub> and extracted with dichloromethane (10 mL  $\times$  3). The combined organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After filtration and concentration under reduced pressure, the crude mixture was purified by PTLC to afford the desired product **3**.

In the double scale reaction (Figure 3-13), a 15 mL pyrex tube (Diameter: 14 mm) was used as a reaction container. Following the general procedure, the reaction was carried out using 4CzIPN (15.8 mg, 20.0  $\mu$ mol), **1a** (180.3 mg, 1.000 mmol), silyl enol ether (318.6 mg, 1.500 mmol), Acetonitrile (10.0 mL), and pure water (21.6  $\mu$ L, 1.20 mmol) were employed. The reaction container was placed between two light sources for more effective irradiation, and the mixture were stirred for 24 h under blue light irradiation. The desired product **3aa** was obtained in 80% yield (221.4 mg).

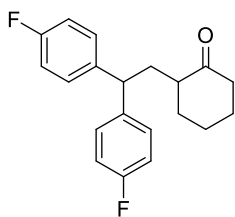
**2-(2,2-Diphenylethyl)cyclohexan-1-one (3aa)**; 90% yield (131.6 mg, Table 1, entry 9); The product was purified by PTLC (hexane/acetone = 9/1); Colorless solid; Mp: 85-87  $^{\circ}$ C; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.28-7.21 (m, 8H), 7.18-7.15 (m, 2H), 4.06 (t, 1H,  $J$  = 7.90 Hz), 2.67-2.62 (m, 1H), 2.36 (m, 1H), 2.22-2.11 (m, 3H), 2.01 (m, 1H), 1.84-1.79 (m, 2H), 1.64 (m, 1H), 1.54 (m, 1H), 1.43-1.37 (m, 1H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>)  $\delta$ : 213.1, 144.7, 144.6, 128.5, 127.9, 127.8, 126.2, 126.2, 48.3, 48.1, 42.2, 35.3, 34.3, 28.0, 25.0; IR (neat, cm<sup>-1</sup>) 1695, 1492, 1450, 1137, 747, 704, 694, 593, 531; HRMS (DART) calcd for C<sub>20</sub>H<sub>23</sub>O [M + H]<sup>+</sup> 279.1749, found 279.1735.

**2-(2-Phenylethyl)cyclohexan-1-one (3ba)**; 75% yield (133.3 mg); The product was



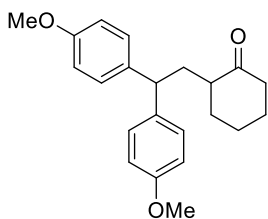
purified by PTLC (hexane/acetone = 9/1); The structure was confirmed by comparison with data of  $^1\text{H}$  and  $^{13}\text{C}$  NMR shown in a literature.<sup>34</sup>  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.28-7.27 (m, 2H), 7.19-7.18 (m, 3H), 2.63 (t, 2H,  $J$  = 6.53 Hz), 2.41-2.39 (m, 1H), 2.30-2.29 (m, 2H), 2.16-2.11 (m, 2H), 2.04-2.03 (m, 1H), 1.87-1.85 (m, 1H), 1.72-1.59 (m, 2H), 1.53-1.40 (m, 2H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 213.2, 142.2, 128.4, 128.3, 125.8, 49.9, 42.1, 34.1, 33.2, 31.2, 28.1, 24.9; MS (DART)  $m/z$  = 203.

**2-(2,2-Bis(4-fluorophenyl)ethyl)cyclohexan-1-one (3ca);** 91% yield (143.0 mg); The



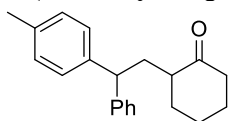
obtained crude mixture was purified by PTLC (hexane/ethyl acetate = 9/1). pale yellow oil;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.18-7.12 (m, 4H), 6.96 (td, 4H,  $J$  = 8.50, 3.40 Hz), 4.05 (t, 1H,  $J$  = 8.22 Hz), 2.60-2.54 (m, 1H), 2.38-2.36 (m, 1H), 2.20 (td, 1H,  $J$  = 12.90, 5.86 Hz), 2.10-2.04 (m, 3H), 1.84-1.81 (m, 1H), 1.77-1.72 (m, 1H), 1.66-1.53 (m, 2H), 1.44-1.39 (m, 1H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 212.8, 161.3 (d,  $J_{\text{C-F}}$  = 244.45 Hz), 161.3 (d,  $J_{\text{C-F}}$  = 244.45 Hz), 140.2 (d,  $J_{\text{C-F}}$  = 3.71 Hz), 140.1 (d,  $J_{\text{C-F}}$  = 3.70 Hz), 129.1 (d,  $J_{\text{C-F}}$  = 7.41 Hz), 129.0 (d,  $J_{\text{C-F}}$  = 7.41 Hz), 115.3 (d,  $J_{\text{C-F}}$  = 22.23 Hz), 115.2 (d,  $J_{\text{C-F}}$  = 20.37 Hz), 48.1, 46.5, 42.1, 35.7, 34.4, 27.9, 25.0;  $^{19}\text{F}$  NMR (565 MHz,  $\text{CDCl}_3$ )  $\delta$ : -117.82, -117.91; IR (neat,  $\text{cm}^{-1}$ ) 1702, 1510, 1222, 811, 721, 698; HRMS (DART) calcd for  $\text{C}_{20}\text{H}_{21}\text{F}_2\text{O}$   $[\text{M} + \text{H}]^+$  315.1555, found ; 315.1561.

**2-(2,2-Bis(4-methoxyphenyl)ethyl)cyclohexan-1-one (3da);** 87% yield (150.2 mg);



The obtained crude mixture was roughly purified by PTLC (hexane/ethyl acetate = 4/1), and further PTLC (hexane/acetone = 7/1) was conducted to afford the pure product. Colorless oil;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.12 (t, 4H,  $J$  = 8.50 Hz), 6.80 (dd, 4H,  $J$  = 8.50, 1.70 Hz), 3.96 (t, 1H,  $J$  = 7.94 Hz), 3.76 (d, 6H,  $J$  = 2.27 Hz), 2.60-2.54 (m, 1H), 2.36 (dt, 1H,  $J$  = 13.23, 3.12 Hz), 2.23-2.11 (m, 3H), 2.01-1.99 (m, 1H), 1.83-1.79 (m, 1H), 1.77-1.71 (m, 1H), 1.66-1.53 (m, 2H), 1.39 (ddd, 1H,  $J$  = 24.09, 11.90, 3.40 Hz);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 213.1, 157.8, 137.2, 137.1, 128.7, 128.6, 128.6, 128.5, 113.8, 113.7, 55.2, 55.1, 48.3, 46.4, 46.3, 42.1, 35.6, 34.2, 27.9, 25.0; IR (neat,  $\text{cm}^{-1}$ ) 1705, 1508, 1242, 1175, 1033, 820; HRMS (DART) calcd for  $\text{C}_{22}\text{H}_{27}\text{O}_3$   $[\text{M} + \text{H}]^+$  339.1960, found; 339.1947.

**2-(2-Phenyl-2-(p-tolyl)ethyl)cyclohexan-1-one (3ea);** 90% yield (133.3 mg); The

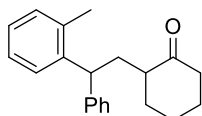


obtained crude mixture was roughly purified by PTLC (hexane/acetone = 9/1), and further PTLC (hexane/ethyl acetate = 9/1) was conducted to afford the pure product.; Colorless solid; Mp: 61-63  $^{\circ}\text{C}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ , As a mixture of diastereomers)  $\delta$ : 7.23 (td, 4H,  $J$  = 14.61, 6.64 Hz), 7.16-7.10 (m, 3H), 7.07 (d, 2H,  $J$  = 8.25 Hz), 4.02 (td, 1H,  $J$  = 7.90, 3.89 Hz), 2.64-2.60 (m, 1H), 2.35 (d, 1H,  $J$  = 13.06 Hz), 2.29 (d, 3H,  $J$  = 2.75 Hz), 2.18-



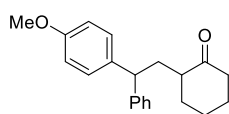
2.15 (m, 3H), 2.00-1.99 (m, 1H), 1.80-1.79 (m, 2H), 1.64-1.61 (m, 1H), 1.55-1.53 (m, 1H), 1.40-1.38 (m, 1H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ , As a mixture of diastereomers)  $\delta$ : 212.9, 144.9, 144.9, 141.6, 141.5, 135.5, 135.5, 129.1, 128.3, 127.7, 127.7, 127.6, 127.5, 126.0 (two peaks), 48.2, 48.2, 47.6 (two peaks), 42.1, 35.3, 35.3, 34.3, 34.2, 27.9, 27.9, 24.9, 20.9; IR (neat,  $\text{cm}^{-1}$ ) 1702, 1492, 1447, 811, 721, 698; HRMS (DART) calcd for  $\text{C}_{21}\text{H}_{25}\text{O}$   $[\text{M} + \text{H}]^+$  293.1905, found; 293.1895.

**2-(2-Phenyl-2-(*o*-tolyl)ethyl)cyclohexan-1-one (3fa);** 73% yield (107.7 mg); The



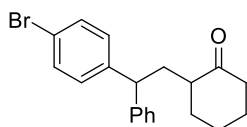
product was purified by PTLC (hexane/acetone = 9/1); Colorless solid; Mp: 61-63 °C;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ , As a mixture of diastereomers)  $\delta$ : 7.32-7.07 (m, 9H), 4.32-4.26 (m, 1H), 2.61-2.55 (m, 1H), 2.38-2.35 (m, 1H), 2.26-2.12 (m, 6H), 2.01-1.99 (m, 1H), 1.82-1.77 (m, 2H), 1.68-1.53 (m, 2H), 1.44-1.40 (m, 1H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ , As a mixture of diastereomers)  $\delta$ : 213.1, 213.0, 144.4, 144.2, 142.3, 142.2, 136.5, 136.4, 130.5, 128.3, 128.2, 128.0, 126.5 (two peaks), 126.0, 125.9, 48.2, 48.2, 43.7, 43.6, 42.2, 35.8, 35.8, 34.6, 34.5, 28.0, 25.1, 25.0, 19.9, 19.8; IR (neat,  $\text{cm}^{-1}$ ) 1699, 1447, 750, 727, 700; HRMS (DART) calcd for  $\text{C}_{21}\text{H}_{25}\text{O}$   $[\text{M} + \text{H}]^+$  293.1905, found; 293.1913.

**2-(2-(4-Methoxyphenyl)-2-phenylethyl)cyclohexan-1-one (3ga);** 89% yield (138.7



mg); The obtained crude mixture was purified by PTLC (hexane/ethyl acetate = 9/1). Colorless oil;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ , As a mixture of diastereomers)  $\delta$ : 7.26-7.21 (m, 4H), 7.17-7.12 (m, 3H), 6.81 (dd, 2H,  $J$  = 8.50, 1.70 Hz), 4.01 (td, 1H,  $J$  = 7.94, 5.10 Hz), 3.77 (d, 3H,  $J$  = 2.83 Hz), 2.64-2.58 (m, 1H), 2.37-2.35 (m, 1H), 2.19-2.15 (m, 3H), 2.02-1.99 (m, 1H), 1.81-1.76 (m, 2H), 1.62-1.58 (m, 2H), 1.42-1.37 (m, 1H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ , As a mixture of diastereomers)  $\delta$ : 213.0, 157.9, 145.1, 145.0, 136.7, 136.7, 128.8, 128.6, 128.4, 127.7, 127.6, 126.0, 126.0, 113.8, 55.1 (two peaks), 48.3, 48.2, 47.2, 47.2, 42.1, 35.5, 35.4, 34.3, 34.2, 27.9, 27.9, 24.9; IR (neat,  $\text{cm}^{-1}$ ) 1705, 1609, 1510, 1448, 1247, 1177, 1034, 700; HRMS (DART) calcd for  $\text{C}_{21}\text{H}_{25}\text{O}_2$   $[\text{M} + \text{H}]^+$  309.1855, found; 309.1848.

**2-(2-(4-Bromophenyl)-2-phenylethyl)cyclohexan-1-one (3ha);** 69% yield (123.6 mg);



The obtained crude mixture was purified by PTLC (hexane/ethyl acetate = 9/1). Colorless oil;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ , As a mixture of diastereomers)  $\delta$ : 7.40-7.37 (m, 2H), 7.29-7.26 (m, 2H), 7.21-7.16 (m, 3H), 7.10 (dd, 2H,  $J$  = 10.20, 8.50 Hz), 4.04 (t, 1H,  $J$  = 7.94 Hz), 2.64-2.55 (m, 1H), 2.38-2.35 (m, 1H), 2.23-2.09 (m, 3H), 2.04-2.01 (m, 1H), 1.83-1.74 (m, 2H), 1.62-1.57 (m, 2H), 1.44-1.36 (m, 1H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ , As a mixture of diastereomers)  $\delta$ : 212.8, 143.9, 143.9, 143.8, 143.7, 131.5, 131.4, 129.6, 129.5, 128.6, 128.5, 127.8, 127.6, 126.4, 126.3, 119.9 (two peaks), 48.2, 48.1, 47.6, 47.5, 42.2, 42.1, 35.2 (two peaks), 34.4, 34.3, 27.9, 27.9, 25.0, 24.9; IR (neat,  $\text{cm}^{-1}$ ) 1695, 1491, 1451, 1073, 1010, 745, 704, 695; HRMS (DART) calcd for  $\text{C}_{20}\text{H}_{22}\text{BrO}$   $[\text{M} + \text{H}]^+$

357.0854, found; 357.0862.

**2-(2-(4-Tolyl)ethyl)cyclohexan-1-one (3ia);** 76% yield (87.9 mg); The product was purified by PTLC (hexane/acetone = 9/1); The structure was confirmed by comparison with data of  $^1\text{H}$  and  $^{13}\text{C}$  NMR shown in a literature.<sup>35</sup>  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.07-7.07 (m, 4H), 2.59 (t, 2H,  $J = 7.90$  Hz), 2.40-2.38 (m, 1H), 2.30-2.27 (m, 5H), 2.13-2.10 (m, 2H), 2.03-2.01 (m, 1H), 1.86-1.84 (m, 1H), 1.71-1.61 (m, 2H), 1.47-1.43 (m, 2H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 213.2, 139.1, 135.2, 129.0, 128.3, 49.8, 42.1, 34.0, 32.7, 31.3, 28.1, 24.9, 21.0; MS (DART)  $m/z = 217$ .

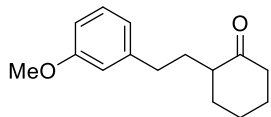
**2-(2-(4-*tert*-Butylphenyl)ethyl)cyclohexan-1-one (3ja);** 81% yield (110.2 mg); The product was purified by PTLC (hexane/acetone = 9/1); Colorless oil;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.30 (d, 2H,  $J = 8.25$  Hz), 7.12 (d, 2H,  $J = 8.25$  Hz), 2.59 (t, 2H,  $J = 6.53$  Hz), 2.40-2.39 (m, 1H), 2.32-2.27 (m, 2H), 2.16-2.10 (m, 2H), 2.04-2.03 (m, 1H), 1.86-1.86 (m, 1H), 1.73-1.62 (m, 2H), 1.52-1.41 (m, 2H), 1.31 (s, 9H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 213.3, 148.5, 139.1, 128.0, 125.2, 49.9, 42.1, 34.3, 34.0, 32.6, 31.4, 31.2, 28.0, 24.9; IR (neat,  $\text{cm}^{-1}$ ) 1709, 1515, 1448, 1364, 1128, 834, 560; HRMS (DART) calcd for  $\text{C}_{18}\text{H}_{27}\text{O}$  [ $\text{M} + \text{H}$ ] $^+$  259.2062, found 259.2063.

**2-(2-([1,1'-Biphenyl]-4-yl)ethyl)cyclohexan-1-one (3ka);** 62% yield (87.2 mg); The product was purified by PTLC (hexane/acetone = 9/1); Colorless solid; Mp: 71-73  $^\circ\text{C}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.58 (d, 2H,  $J = 6.87$  Hz), 7.51 (d, 2H,  $J = 8.25$  Hz), 7.42 (t, 2H,  $J = 7.56$  Hz), 7.32 (t, 1H,  $J = 7.22$  Hz), 7.26-7.25 (m, 2H), 2.71-2.63 (m, 2H), 2.42-2.39 (m, 1H), 2.33-2.29 (m, 2H), 2.19-2.16 (m, 2H), 2.06-2.05 (m, 1H), 1.88-1.87 (m, 1H), 1.74-1.63 (m, 2H), 1.55-1.53 (m, 1H), 1.47-1.43 (m, 1H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 213.2, 141.1, 138.8, 128.8, 128.7, 127.1, 127.0 (two peaks), 49.8 (two peaks), 42.2, 34.0 (two peaks), 32.9, 31.2, 28.1, 25.0; IR (neat,  $\text{cm}^{-1}$ ) 1698, 1488, 1447, 1128, 821, 758, 721, 690, 598, 573, 546, 516, 488; HRMS (DART) calcd for  $\text{C}_{20}\text{H}_{23}\text{O}$  [ $\text{M} + \text{H}$ ] $^+$  279.1749, found 279.1757.

**2-(2-(4-Methoxyphenyl)ethyl)cyclohexan-1-one (3la);** 90% yield (104.4 mg); The product was purified by PTLC (hexane/acetone = 9/1); Colorless oil;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.09 (d, 2H,  $J = 8.25$  Hz), 6.82 (d, 2H,  $J = 8.25$  Hz), 3.78 (s, 3H), 2.58-2.55 (m, 2H), 2.40-2.38 (m, 1H), 2.31-2.25 (m, 2H), 2.14-2.07 (m, 2H), 2.05-2.02 (m, 1H), 1.86-1.84 (m, 1H), 1.70-1.61 (m, 2H), 1.49-1.39 (m, 2H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 213.2, 157.7, 134.2, 129.2, 113.7, 55.2, 49.7, 42.1, 34.0, 32.2, 31.4, 28.0, 24.9; IR (neat,  $\text{cm}^{-1}$ ); 1705, 1511, 1448, 1242, 1177, 1034, 815, 518; HRMS (DART) calcd for  $\text{C}_{15}\text{H}_{21}\text{O}_2$

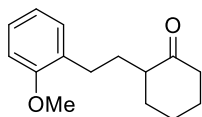
$[M + H]^+$  233.1542, found 233.1540.

**2-(2-(3-Methoxyphenyl)ethyl)cyclohexan-1-one (3ma);** 64% yield (79.1 mg); The



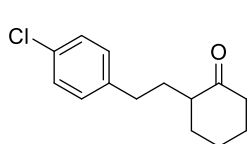
product was purified by PTLC (hexane/acetone = 9/1); Colorless oil;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.17 (t, 1H,  $J = 7.90$  Hz), 7.13 (d, 1H,  $J = 7.56$  Hz), 6.88 (t, 1H,  $J = 7.56$  Hz), 6.83 (d, 1H,  $J = 8.25$  Hz), 3.81 (s, 3H), 2.67-2.57 (m, 2H), 2.41-2.39 (m, 1H), 2.30-2.28 (m, 2H), 2.20-2.15 (m, 1H), 2.12-2.06 (m, 1H), 2.03-2.02 (m, 1H), 1.86-1.84 (m, 1H), 1.74-1.61 (m, 2H), 1.50-1.40 (m, 2H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 213.5, 157.4, 130.6, 129.8, 127.0, 120.4, 110.2, 55.2, 50.2, 42.0, 34.0, 29.6, 28.2, 27.5, 24.8; IR (neat,  $\text{cm}^{-1}$ ) 1708, 1584, 1488, 1451, 1260, 1152, 1048, 783, 697; HRMS (DART) calcd for  $\text{C}_{15}\text{H}_{21}\text{O}_2$   $[M + H]^+$  233.1542, found 233.1546.

**2-(2-(2-Methoxyphenyl)ethyl)cyclohexan-1-one (3na);** 68% yield (90.4 mg); The



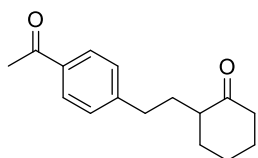
product was purified by PTLC (hexane/acetone = 9/1); Colorless oil;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.19 (t, 1H,  $J = 7.90$  Hz), 6.77 (d, 1H,  $J = 7.56$  Hz), 6.73 (d, 2H,  $J = 6.19$  Hz), 3.79 (s, 3H), 2.65-2.57 (m, 2H), 2.40-2.39 (m, 1H), 2.31-2.26 (m, 2H), 2.15-2.12 (m, 2H), 2.04-2.02 (m, 1H), 1.86-1.85 (m, 1H), 1.72-1.61 (m, 2H), 1.52-1.39 (m, 2H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 213.1, 159.6, 143.8, 129.2, 120.8, 114.1, 111.1, 55.1, 49.8, 42.1, 34.0, 33.2, 31.0, 28.0, 24.9; IR (neat,  $\text{cm}^{-1}$ ) 1708, 1599, 1494, 1242, 1120, 1030, 754; HRMS (DART) calcd for  $\text{C}_{15}\text{H}_{21}\text{O}_2$   $[M + H]^+$  233.1542, found 233.1535.

**2-(2-(4-Chlorophenyl)ethyl)cyclohexan-1-one (3oa);** 78% yield (97.8 mg); The product



was purified by PTLC (hexane/acetone = 9/1); Colorless oil;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.23 (d, 2H,  $J = 8.25$  Hz), 7.11 (d, 2H,  $J = 8.25$  Hz), 2.61-2.58 (m, 2H), 2.41-2.38 (m, 1H), 2.29-2.25 (m, 2H), 2.15-2.03 (m, 3H), 1.86-1.86 (m, 1H), 1.69-1.63 (m, 2H), 1.49-1.38 (m, 2H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 212.9, 140.6, 131.4, 129.7, 128.4, 49.7, 42.1, 34.1, 32.6, 31.1, 28.0, 25.0; IR (neat,  $\text{cm}^{-1}$ ) 1708, 1492, 1448, 1130, 1090, 1015, 835, 805; HRMS (DART) calcd for  $\text{C}_{14}\text{H}_{18}\text{ClO}$   $[M + H]^+$  237.1046, found 237.1044.

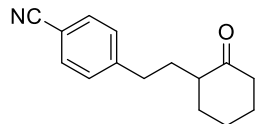
**2-(2-(4-Acetylphenyl)ethyl)cyclohexan-1-one (3pa);** 56% yield (72.9 mg); The product



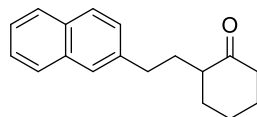
was purified by PTLC (hexane/acetone = 9/1); Colorless solid; Mp: 71-73  $^{\circ}\text{C}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.88 (d, 2H,  $J = 8.25$  Hz), 7.28-7.27 (m, 2H), 2.74-2.64 (m, 2H), 2.58 (s, 3H), 2.42-2.39 (m, 1H), 2.31-2.27 (m, 2H), 2.17-2.12 (m, 2H), 2.07-2.06 (m, 1H), 1.88-1.87 (m, 1H), 1.69-1.64 (m, 2H), 1.53-1.50 (m, 1H), 1.45-1.42 (m, 1H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 212.8, 197.8, 148.1, 135.1, 128.6 (two peaks), 128.5, 126.7, 49.8, 42.2, 34.1, 33.3, 30.9, 28.0, 26.5, 25.0; IR (neat,  $\text{cm}^{-1}$ ) 1698, 1672, 1604, 1411, 1355, 1267, 1128, 950, 851, 843, 824, 717, 690, 603, 588, 573; HRMS (DART) calcd for

C<sub>16</sub>H<sub>21</sub>O<sub>2</sub> [M + H]<sup>+</sup> 245.1542, found 245.1535.

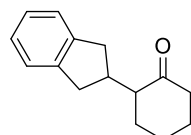
**2-(2-(4-Cyanophenyl)ethyl)cyclohexan-1-one (3qa);** 65% yield (71.5 mg); The product was purified by PTLC (hexane/acetone = 9/1); Colorless oil; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ: 7.56 (d, 2H, *J* = 7.56 Hz), 7.29-7.28 (m, 2H), 2.74-2.63 (m, 2H), 2.41-2.40 (m, 1H), 2.31-2.28 (m, 2H), 2.14-2.07 (m, 3H), 1.88-1.87 (m, 1H), 1.69-1.64 (m, 2H), 1.50-1.43 (m, 2H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ: 212.6, 148.0, 132.2, 129.1, 119.1, 109.7, 49.8, 42.2, 34.2, 33.5, 30.9, 28.0, 25.0; IR (neat, cm<sup>-1</sup>) 1704, 1608, 1504, 1448, 1128, 844, 818, 554; HRMS (DART) calcd for C<sub>15</sub>H<sub>18</sub>NO [M + H]<sup>+</sup> 228.1388, found 228.1398.



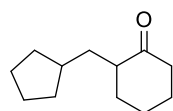
**2-(2-(2-Naphthyl)ethyl)cyclohexan-1-one (3ra);** 42% yield (53.5 mg); The product was purified by PTLC (hexane/acetone = 9/1); Colorless solid; Mp: 61-63 °C; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ: 7.80-7.75 (m, 3H), 7.61 (s, 1H), 7.46-7.40 (m, 2H), 7.34 (d, 1H, *J* = 7.56 Hz), 2.84-2.76 (m, 2H), 2.41-2.40 (m, 1H), 2.34-2.16 (m, 4H), 2.05-2.03 (m, 1H), 1.87-1.85 (m, 1H), 1.74-1.56 (m, 3H), 1.46-1.44 (m, 1H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ: 213.2, 139.7, 133.6, 132.0, 127.9, 127.6, 127.4, 127.3, 126.3, 125.9, 125.1, 49.8, 42.2, 34.1, 33.3, 31.0, 28.1, 25.0; IR (neat, cm<sup>-1</sup>) 1704, 1505, 1445, 1202, 1125, 910, 861, 815, 748, 476; HRMS (DART) calcd for C<sub>18</sub>H<sub>21</sub>O [M + H]<sup>+</sup> 253.1592, found 253.1585.



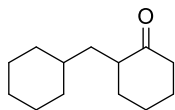
**2-(2,3-Dihydro-1H-inden-2-yl)cyclohexan-1-one (3sa);** 82% yield (89.8 mg); The product was purified by PTLC (hexane/acetone = 9/1); The structure was confirmed by comparison with data of <sup>1</sup>H and <sup>13</sup>C NMR shown in a literature.<sup>36</sup> <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ: 7.18-7.17 (m, 2H), 7.12-7.11 (m, 2H), 3.23 (dd, 1H, *J* = 8.02, 4.01 Hz), 3.03 (dd, 1H, *J* = 7.79, 3.89 Hz), 2.76 (td, 1H, *J* = 17.18, 8.94 Hz), 2.64 (dd, 1H, *J* = 15.46, 9.28 Hz), 2.54 (dd, 1H, *J* = 15.81, 8.94 Hz), 2.46-2.40 (m, 2H), 2.35-2.33 (m, 1H), 2.16-2.14 (m, 1H), 2.05-2.03 (m, 1H), 1.90-1.89 (m, 1H), 1.77-1.65 (m, 2H), 1.55-1.50 (m, 1H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ: 213.2, 143.6, 142.7, 126.2, 126.0, 124.3, 124.2, 56.3, 42.3, 39.4, 38.2, 36.7, 32.2, 28.3, 24.7; MS (DART) *m/z* = 215.



**2-Cyclopentylmethylcyclohexan-1-one (3ta);** 78% yield (71.3 mg); The product was purified by PTLC (hexane/acetone = 9/1); Colorless liquid; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ: 2.37-2.31 (m, 3H), 2.13-2.11 (m, 1H), 2.02-2.00 (m, 1H), 1.85-1.36 (m, 12H), 1.21-1.20 (m, 1H), 1.06-1.03 (m, 2H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ: 213.8, 49.8, 41.9, 37.4, 35.6, 34.1 (two peaks), 33.0, 32.4, 28.1, 25.0, 24.7; IR (neat, cm<sup>-1</sup>) 1708, 1448, 1127, 734, 521; HRMS (DART) calcd for C<sub>12</sub>H<sub>21</sub>O [M + H]<sup>+</sup> 181.1592, found 181.1591.

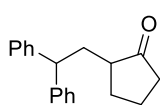


**2-Cyclohexylmethylcyclohexan-1-one (3ua)**; 56% yield (54.4 mg); The product was



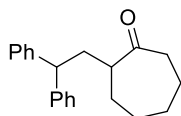
purified by PTLC (hexane/acetone = 9/1); The structure was confirmed by comparison with data of  $^1\text{H}$  and  $^{13}\text{C}$  NMR shown in a literature.<sup>37</sup>  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 2.40-2.27 (m, 3H), 2.08-2.01 (m, 2H), 1.85-1.84 (m, 1H), 1.73-1.58 (m, 8H), 1.39-1.33 (m, 1H), 1.25-1.10 (m, 4H), 1.06-1.01 (m, 1H), 0.87-0.83 (m, 2H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 213.9, 47.8, 42.0, 36.9, 34.8, 34.2, 33.8, 33.0, 28.1, 26.6, 26.3 (two peaks), 24.8; MS (DART)  $m/z$  = 195.

**2-(2,2-Diphenylethyl)cyclopentan-1-one (3ab)**; 92% yield (126.2 mg); The obtained



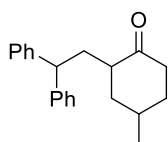
crude mixture was purified by PTLC (hexane/ethyl acetate = 9/1). Colorless solid; Mp: 111-114 °C;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.28-7.26 (m, 8H), 7.17-7.16 (m, 2H), 4.07 (q, 1H,  $J$  = 5.27 Hz), 2.68-2.63 (m, 1H), 2.27 (q, 1H,  $J$  = 8.94 Hz), 2.19-2.18 (m, 1H), 2.13-2.07 (m, 1H), 1.98-1.97 (m, 1H), 1.89-1.86 (m, 2H), 1.68-1.65 (m, 1H), 1.53-1.50 (m, 1H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 221.0, 144.8, 143.5, 128.5, 128.4, 127.8, 127.6, 126.3, 126.1, 48.9, 47.2, 37.9, 35.8, 29.9, 20.5; IR (neat,  $\text{cm}^{-1}$ ) 1725, 1492, 1451, 1157, 705, 697; HRMS (DART) calcd for  $\text{C}_{19}\text{H}_{21}\text{O}$  [ $\text{M} + \text{H}$ ] $^+$  265.1592, found; 265.1584.

**2-(2,2-Diphenylethyl)cycloheptan-1-one (3ac)**; 96% yield (139.5 mg); The obtained



crude mixture was purified by PTLC (hexane/ethyl acetate = 9/1). Colorless solid; Mp: 54-57 °C;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.27-7.23 (m, 8H), 7.17-7.16 (m, 2H), 3.97 (t, 1H,  $J$  = 7.90 Hz), 2.53-2.49 (m, 1H), 2.45-2.41 (m, 2H), 2.34-2.32 (m, 1H), 1.99-1.95 (m, 1H), 1.84-1.78 (m, 4H), 1.47-1.45 (m, 1H), 1.38 (q, 1H,  $J$  = 11.23 Hz), 1.30 (q, 2H,  $J$  = 11.23 Hz);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 215.7, 144.4, 144.4, 128.4, 128.3, 127.9, 127.7, 126.1, 126.1, 49.4, 48.2, 42.8, 37.7, 31.4, 29.0, 28.3, 24.1; IR (neat,  $\text{cm}^{-1}$ ) 1698, 1494, 1451, 1031, 744, 697; HRMS (DART) calcd for  $\text{C}_{21}\text{H}_{25}\text{O}$  [ $\text{M} + \text{H}$ ] $^+$  293.1905, found; 293.1920.

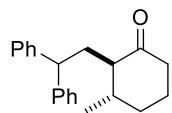
**2-(2,2-Diphenylethyl)-4-methylcyclohexan-1-one (3ad)**; 90% yield (133.7 mg); The



product was purified by PTLC (hexane/acetone = 9/1); Colorless solid; Mp: 67-69 °C;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ , As a mixture of diastereomers)  $\delta$ : 7.26-7.22 (m, major 8H, minor 8H), 7.18-7.16 (m, major 2H, minor 2H), 4.08 (t, minor 1H,  $J$  = 7.90 Hz), 3.96 (t, major 1H,  $J$  = 7.90 Hz), 2.67-2.62 (m, minor 1H), 2.57-2.53 (m, major 1H), 2.39-2.22 (m, major 3H, minor 2H), 2.18-2.17 (m, minor 1H), 2.12-1.91 (m, major 3H, minor 2H), 1.84-1.82 (m, minor 1H), 1.77-1.71 (m, major 2H, minor 1H), 1.56-1.55 (m, major 1H), 1.38-1.31 (m, minor 1H), 1.13 (q, minor 1H,  $J$  = 12.37 Hz), 0.98-0.97 (m, major 3H, minor 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ , As a mixture of diastereomers)  $\delta$ : 214.1, 213.0, 144.7, 144.6, 144.3 (two peaks), 128.4, 127.8, 127.7, 126.2, 126.1, 48.1, 47.9, 47.0, 45.1, 42.6, 41.5, 39.6, 37.8, 36.3, 35.8, 35.1, 33.9, 31.7, 26.6, 21.2, 19.5; IR (neat,  $\text{cm}^{-1}$ ) 1695, 1492, 1451, 1135, 1030, 744, 704, 694, 533; HRMS (DART) calcd for  $\text{C}_{21}\text{H}_{25}\text{O}$  [ $\text{M} + \text{H}$ ] $^+$  293.1905,

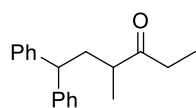
found; 293.1915.

**2-(2,2-Diphenylethyl)-3-methylcyclohexan-1-one (3ae);** 58% yield (87.6 mg); The



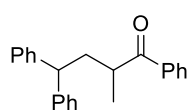
product was purified by PTLC (hexane/acetone = 9/1); The desired product was obtained in high diastereoselectivity (>99/1), and the major related configuration was determined by X-ray single crystal structure analysis. Colorless solid; Mp: 102-104 °C; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ: 7.30-7.25 (m, 6H), 7.20 (d, 3H, *J* = 7.56 Hz), 7.15-7.14 (m, 1H), 4.12 (q, 1H, *J* = 5.27 Hz), 2.47-2.42 (m, 1H), 2.36-2.34 (m, 1H), 2.19 (td, 1H, *J* = 12.72, 5.50 Hz), 2.12-2.08 (m, 1H), 1.98-1.95 (m, 1H), 1.89 (t, 1H, *J* = 9.62 Hz), 1.80 (dd, 1H, *J* = 13.75, 2.75 Hz), 1.35 (dt, 1H, *J* = 28.18, 7.22 Hz) 1.03 (d, 3H, *J* = 6.19 Hz); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ: 213.0, 145.6, 143.9, 128.5, 128.3 (two peaks), 127.6, 126.2, 125.9, 55.2, 49.1, 41.9, 40.0, 33.7, 33.0, 26.2, 20.6; IR (neat, cm<sup>-1</sup>) 1697, 1492, 1448, 1120, 751, 698, 551; HRMS (DART) calcd for C<sub>21</sub>H<sub>25</sub>O [M + H]<sup>+</sup> 293.1905, found; 293.1917.

**4-Methyl-6,6-diphenylhexan-3-one (3af);** 71% yield (98.3 mg); The product was



purified by PTLC (hexane/acetone = 9/1); Colorless oil; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ: 7.29-7.16 (m, 10H), 3.91 (t, 1H, *J* = 7.94 Hz), 2.47-2.38 (m, 3H), 2.24-2.20 (m, 1H), 2.01-1.95 (m, 1H), 1.10 (d, 3H, *J* = 6.80 Hz), 0.97 (t, 3H, *J* = 7.37 Hz); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ: 214.9, 144.2, 128.5, 128.5, 127.8 (two peaks), 126.3, 126.2, 48.8, 43.7, 38.6, 34.5, 17.2, 7.7; IR (neat, cm<sup>-1</sup>) 1709, 1494, 1451, 1375, 1104, 1030, 974, 748, 698; HRMS (DART) calcd for C<sub>19</sub>H<sub>23</sub>O [M + H]<sup>+</sup> 267.1749, found; 267.1761.

**2-Methyl-1,4,4-triphenylbutan-1-one (3ag);** 79% yield (124.7 mg); The product was



purified by PTLC (hexane/acetone = 9/1); Colorless oil; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ: 7.67 (d, 2H, *J* = 7.56 Hz), 7.51 (t, 1H, *J* = 7.56 Hz), 7.37 (t, 2H, *J* = 7.56 Hz), 7.29-7.25 (m, 6H), 7.21-7.16 (m, 4H), 3.99 (t, 1H, *J* = 7.90 Hz), 3.34-3.33 (m, 1H), 2.63-2.58 (m, 1H), 2.14-2.09 (m, 1H), 1.22 (d, 3H, *J* = 6.87 Hz); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ: 204.1, 144.3, 144.2, 136.4, 132.8, 128.5, 128.2, 127.9, 126.3 (two peaks), 48.7, 39.4, 38.3, 17.5; IR (neat, cm<sup>-1</sup>) 1679, 1494, 1448, 1230, 971, 750, 700; HRMS (DART) calcd for C<sub>23</sub>H<sub>23</sub>O [M + H]<sup>+</sup> 315.1749, found; 315.1755.

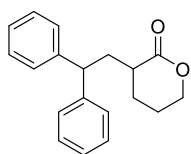
### General procedure for the photo-induced reactions for alkylation of esters



4CzIPN (19.7 mg, 25.0 μmol), alkene (0.500 mmol), ketene silyl acetal (0.750 mmol) and

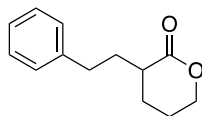
degassed acetonitrile (5 mL) were placed in a tube inside a glove box fulfilled with argon, and the tube was sealed with a septum. Pure water (5.4  $\mu$ L, 0.30 mmol) or ethyl mercaptan (43.2  $\mu$ L, 0.600 mmol) was then added. When benzenethiol was used, it (10.2  $\mu$ L, 0.100 mmol) was added through the septum. The reaction mixture was stirred at room temperature under blue LED irradiation for 12 h. Subsequently, the resulting mixture was treated with silica gel (Sigma-Aldrich: high-purity grade, pore size 60 Å, 200-400 mesh particle size). After concentration under reduced pressure, the crude mixture was purified by PTLC to afford the desired product.

**3-(2,2-Diphenylethyl)tetrahydro-2H-pyran-2-one (5aa);** Colorless solid; Mp: 151-



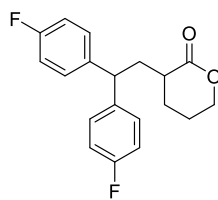
152 °C;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.28-7.25 (m, 8H), 7.20-7.17 (m, 2H), 4.25-4.22 (m, 1H), 4.19-4.17 (m, 2H), 2.83-2.78 (m, 1H), 2.31-2.28 (m, 1H), 2.13-2.10 (m, 1H), 2.05-2.03 (m, 1H), 1.92-1.85 (m, 1H), 1.83-1.76 (m, 1H), 1.60-1.52 (m, 1H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 174.6, 144.2, 143.5, 128.6, 128.5, 127.8, 127.8, 127.7, 126.4, 126.4, 67.8, 48.0, 37.1 (two peaks), 24.8, 21.8; IR (neat,  $\text{cm}^{-1}$ ) 1713, 1492, 1452, 1236, 1165, 1088, 747, 610; HRMS (DART) calcd for  $\text{C}_{19}\text{H}_{21}\text{O}_2$   $[\text{M} + \text{H}]^+$  281.1541, found; 281.1554.

**3-Phenethyltetrahydro-2H-pyran-2-one (5ba);** The structure was confirmed by



comparison with data of  $^1\text{H}$  and  $^{13}\text{C}$  NMR shown in a literature.<sup>38</sup>  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.29 (t, 2H,  $J = 7.56$  Hz), 7.21-7.20 (m, 3H), 4.29 (t, 2H,  $J = 5.84$  Hz), 2.79-2.70 (m, 2H), 2.47-2.44 (m, 1H), 2.29-2.23 (m, 1H), 2.14-2.12 (m, 1H), 1.96-1.84 (m, 2H), 1.80-1.74 (m, 1H), 1.61-1.59 (m, 1H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 174.5, 141.3, 128.4 (two peaks), 126.0, 68.1, 38.6, 32.9, 32.8, 24.7, 21.9; MS (DART)  $m/z = 205$ .

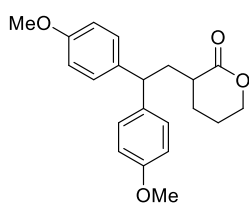
**3-(2,2-Bis(4-fluorophenyl)ethyl)tetrahydro-2H-pyran-2-one (5ca);** Colorless oil;  $^1\text{H}$



NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.21-7.18 (m, 4H), 7.00-6.96 (m, 4H), 4.27-4.23 (m, 1H), 4.21-4.17 (m, 2H), 2.73-2.68 (m, 1H), 2.26-2.23 (m, 1H), 2.11-2.05 (m, 1H), 2.00-1.96 (m, 1H), 1.93-1.86 (m, 1H), 1.83-1.80 (m, 1H), 1.60-1.52 (m, 1H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 174.5, 161.5 (d,  $J_{\text{C-F}} = 244.45$  Hz), 161.4 (d,  $J_{\text{C-F}} = 244.46$  Hz), 139.5 (d,  $J_{\text{C-F}} = 1.86$  Hz), 139.4 (d,  $J_{\text{C-F}} = 3.70$  Hz), 129.1 (d,  $J_{\text{C-F}} = 7.40$  Hz), 129.1 (d,  $J_{\text{C-F}} = 7.41$  Hz), 115.5 (d,  $J_{\text{C-F}} = 22.22$  Hz), 115.4 (d,  $J_{\text{C-F}} = 22.22$  Hz), 67.9, 46.5, 37.5, 37.0, 24.9, 21.8;  $^{19}\text{F}$  NMR (565 MHz,  $\text{CDCl}_3$ )  $\delta$ : -117.4; IR (neat,  $\text{cm}^{-1}$ ) 1729, 1505, 1220, 1155, 1071, 825, 733, 573; HRMS (DART) calcd for  $\text{C}_{19}\text{H}_{19}\text{F}_2\text{O}_2$   $[\text{M} + \text{H}]^+$  317.1353, found; 317.1338.

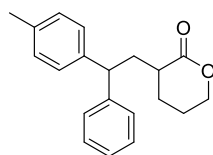
**3-(2,2-Bis(4-methoxyphenyl)ethyl)tetrahydro-2H-pyran-2-one (5da);** Colorless oil;

$^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.19-7.13 (m, 4H), 6.84-6.80 (m, 4H), 4.25-4.23 (m, 1H), 4.20-4.17 (m, 1H), 4.08-4.06 (m, 1H), 3.77 (d, 6H,  $J = 1.37$  Hz), 2.76-2.71 (m, 1H), 2.31-



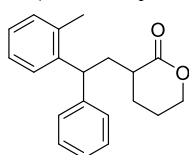
2.25 (m, 1H), 2.11-2.09 (m, 1H), 1.99-1.94 (m, 1H), 1.92-1.85 (m, 1H), 1.81-1.78 (m, 1H), 1.58-1.52 (m, 1H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 174.7, 157.9, 157.9, 136.7, 135.9, 128.5, 128.5, 113.9, 113.8, 67.8, 55.1, 46.2, 37.3, 37.0, 24.6, 21.7; IR (neat,  $\text{cm}^{-1}$ ) 1731, 1508, 1245, 1177, 1150, 1034, 828, 732; HRMS (DART) calcd for  $\text{C}_{21}\text{H}_{25}\text{O}_4$   $[\text{M} + \text{H}]^+$  341.1753, found; 341.1762.

**3-(2-Phenyl-2-(*p*-tolyl)ethyl)tetrahydro-2*H*-pyran-2-one (5ea);** Colorless oil;  $^1\text{H}$



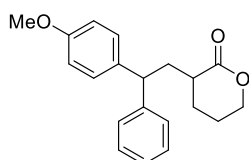
NMR (600 MHz,  $\text{CDCl}_3$ , As a mixture of diastereomers)  $\delta$ : 7.29-7.24 (m, 5H), 7.18-7.15 (m, 2H), 7.09 (t, 2H,  $J = 7.22$  Hz), 4.25-4.21 (m, 1H), 4.20-4.10 (m, 1H), 2.80-2.78 (m, 1H), 2.31-2.28 (m, 1H), 2.15-2.08 (m, 1H), 2.03-2.01 (m, 1H), 1.92-1.85 (m, 1H), 1.83-1.76 (m, 1H), 1.58-1.54 (m, 1H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ , As a mixture of diastereomers)  $\delta$ : 174.6, 144.5, 143.8, 141.2, 140.4, 135.9, 135.8, 129.3, 129.2, 128.5, 128.5, 127.7, 127.6, 127.6, 126.3, 126.2, 67.8, 67.8, 47.5, 47.5, 37.1, 37.0, 24.8, 24.7, 21.8, 20.9, 20.9; IR (neat,  $\text{cm}^{-1}$ ) 1731, 1451, 1248, 1147, 1070, 724, 700; HRMS (DART) calcd for  $\text{C}_{20}\text{H}_{23}\text{O}_2$   $[\text{M} + \text{H}]^+$  295.1698, found; 295.1709.

**3-(2-Phenyl-2-(*o*-tolyl)ethyl)tetrahydro-2*H*-pyran-2-one (5fa);** Colorless solid; Mp:



126-127  $^{\circ}\text{C}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ , As a mixture of diastereomers, the peak of  $\delta = 2.7$  put as one proton.)  $\delta$ : 7.37 (d, 0.5H,  $J = 7.56$  Hz), 7.32 (d, 0.5H,  $J = 7.56$  Hz), 7.28-7.15 (m, 6H), 7.14-7.11 (m, 2H), 4.46 (t, 0.5H,  $J = 8.25$  Hz), 4.41 (t, 0.5H,  $J = 8.25$  Hz), 4.26-4.17 (m, 2H), 2.76-2.69 (m, 1H), 2.40-2.38 (m, 0.5H), 2.38-2.20 (m, 0.5H+3H), 2.20-2.18 (m, 0.5 H), 2.05-1.96 (m, 0.5H+1H), 1.94-1.76 (m, 2H), 1.61-1.55 (m, 1H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ , As a mixture of diastereomers)  $\delta$ : 174.6, 143.7, 143.4, 141.7, 141.1, 136.5, 130.7, 130.7, 128.5, 128.5, 128.2, 128.1, 126.4, 126.3, 126.3, 126.2, 126.2, 126.1, 67.9, 67.8, 43.7, 43.6, 37.6, 37.6, 37.1, 37.0, 25.1, 25.0, 21.9, 21.8, 19.8; IR (neat,  $\text{cm}^{-1}$ ) 1714, 1452, 1237, 1158, 1095, 751, 728, 701; HRMS (DART) calcd for  $\text{C}_{20}\text{H}_{23}\text{O}_2$   $[\text{M} + \text{H}]^+$  295.1698, found; 295.1689.

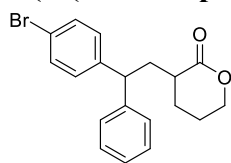
**3-(2-(4-Methoxyphenyl)-2-phenylethyl)tetrahydro-2*H*-pyran-2-one (5ga);** Colorless



oil;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ , As a mixture of diastereomers)  $\delta$ : 7.27-7.25 (m, 4H), 7.19-7.18 (m, 3H), 6.83-6.82 (m, 2H), 4.25-4.22 (m, 1H), 4.20-4.10 (m, 2H), 3.77 (d, 3H,  $J = 1.37$  Hz), 2.80-2.74 (m, 1H), 2.32-2.26 (m, 1H), 2.14-2.08 (m, 1H), 2.02-1.98 (m, 1H), 1.92-1.85 (m, 1H), 1.81-1.79 (m, 1H), 1.59-1.53 (m, 1H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ , As a mixture of diastereomers)  $\delta$ : 174.7, 158.1, 158.0, 144.6, 144.0, 136.3, 135.5, 128.7, 128.7, 128.6, 128.5, 127.6, 127.6, 126.3, 126.2, 114.0, 113.9, 67.9, 67.8, 55.1, 47.1, 47.1, 37.3, 37.2, 37.1, 37.1, 24.8, 24.7, 21.8; IR (neat,  $\text{cm}^{-1}$ ) 1729, 1510, 1452, 1245, 1148, 1033, 727, 700; HRMS (DART) calcd for  $\text{C}_{20}\text{H}_{23}\text{O}_3$   $[\text{M} + \text{H}]^+$  311.1647, found; 311.1640.

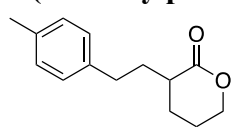


**3-(2-(4-Bromophenyl)-2-phenylethyl)tetrahydro-2H-pyran-2-one (5ha);** Pale yellow



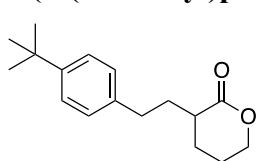
oil;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ , As a mixture of diastereomers)  $\delta$ : 7.41-7.40 (m, 2H), 7.31-7.28 (m, 2H), 7.25-7.24 (m, 1H), 7.22-7.20 (m, 2H), 7.15-7.13 (m, 2H), 4.26-4.22 (m, 1H), 4.19-4.17 (m, 2H), 2.79-2.70 (m, 1H), 2.29-2.24 (m, 1H), 2.11-2.07 (m, 1H), 2.02-1.99 (m, 1H), 1.92-1.85 (m, 1H), 1.84-1.77 (m, 1H), 1.57-1.54 (m, 1H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ , As a mixture of diastereomers)  $\delta$ : 174.5, 174.4, 143.4, 143.3, 142.9, 142.8, 131.6, 131.6, 129.5, 129.5, 128.7, 128.7, 127.7, 127.6, 126.6, 126.6, 120.2, 120.1, 67.9, 67.8, 47.5, 47.4, 37.0, 36.9, 24.9, 24.8, 21.8; IR (neat,  $\text{cm}^{-1}$ ) 1729, 1487, 1250, 1148, 1071, 1010, 731, 700; HRMS (DART) calcd for  $\text{C}_{19}\text{H}_{20}\text{BrO}_2$   $[\text{M} + \text{H}]^+$  359.0647, found; 359.0662.

**3-(4-Methylphenethyl)tetrahydro-2H-pyran-2-one (5ia);** Colorless oil;  $^1\text{H}$  NMR (600



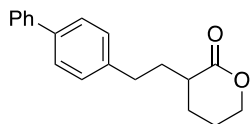
MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.10 (br s, 4H), 4.28 (t, 2H,  $J = 5.84$  Hz), 2.75-2.66 (m, 2H), 2.45-2.44 (m, 1H), 2.32 (s, 3H), 2.29-2.21 (m, 1H), 2.13-2.11 (m, 1H), 1.94-1.83 (m, 2H), 1.76-1.74 (m, 1H), 1.61-1.56 (m, 1H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 174.5, 138.2, 135.4, 129.1, 128.3, 68.1, 38.5, 32.8, 32.4, 24.7, 21.9, 20.9; IR (neat,  $\text{cm}^{-1}$ ) 1729, 1514, 1457, 1388, 1250, 1144, 1071, 808; HRMS(DART) calcd for  $\text{C}_{14}\text{H}_{19}\text{O}_2$   $[\text{M} + \text{H}]^+$  219.1385, found; 219.1395.

**3-(4-(tert-Butyl)phenethyl)tetrahydro-2H-pyran-2-one (5ja);** Colorless oil;  $^1\text{H}$  NMR



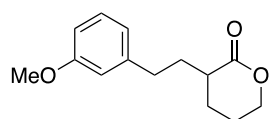
(600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.31 (d, 2H,  $J = 8.25$  Hz), 7.14 (d, 2H,  $J = 8.25$  Hz), 4.29 (t, 2H,  $J = 5.84$  Hz), 2.76-2.66 (m, 2H), 2.48-2.45 (m, 1H), 2.29-2.23 (m, 1H), 2.15-2.13 (m, 1H), 1.96-1.84 (m, 2H), 1.79-1.73 (m, 1H), 1.62-1.56 (m, 1H), 1.31 (s, 9H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 174.5, 148.8, 138.2, 128.0, 125.3, 68.2, 38.6, 34.3, 32.8, 32.3, 31.4, 24.7, 22.0; IR (neat,  $\text{cm}^{-1}$ ) 1731, 1251, 1145, 1071, 834, 564; HRMS (DART) calcd for  $\text{C}_{17}\text{H}_{25}\text{O}_2$   $[\text{M} + \text{H}]^+$  261.1855, found; 261.1843.

**3-(2-([1,1'-Biphenyl]-4-yl)ethyl)tetrahydro-2H-pyran-2-one (5ka);** Colorless solid;

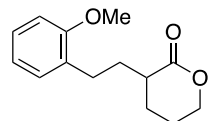


Mp 84-85  $^{\circ}\text{C}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.58 (dd, 2H,  $J = 8.25$ , 1.37 Hz), 7.53 (d, 2H,  $J = 8.25$  Hz), 7.43 (t, 2H,  $J = 7.90$  Hz), 7.33 (t, 1H,  $J = 7.22$  Hz), 7.28 (d, 2H,  $J = 8.25$  Hz), 4.30 (t, 2H,  $J = 5.84$  Hz), 2.84-2.75 (m, 2H), 2.50-2.48 (m, 1H), 2.31-2.29 (m, 1H), 2.16-2.14 (m, 1H), 1.94-1.89 (m, 2H), 1.84-1.78 (m, 1H), 1.65-1.58 (m, 1H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 174.4, 140.9, 140.4, 139.0, 128.8, 128.7, 127.2, 127.0, 126.9, 68.2, 38.6, 32.8, 32.5, 24.7, 22.0; IR (neat,  $\text{cm}^{-1}$ ) 1731, 1487, 1260, 1145, 1073, 750, 695; HRMS (DART) calcd for  $\text{C}_{19}\text{H}_{21}\text{O}_2$   $[\text{M} + \text{H}]^+$  281.1542, found; 281.1549.

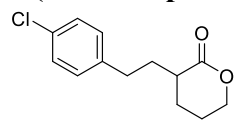
**3-(4-Methoxyphenethyl)tetrahydro-2H-pyran-2-one (5la);** Colorless oil;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.12 (d, 2H,  $J = 8.25$  Hz), 6.83 (d, 2H,  $J = 8.25$  Hz), 4.28 (t, 2H,  $J = 5.84$  Hz), 3.79 (s, 3H), 2.73-2.64 (m, 2H), 2.45-2.43 (m, 1H), 2.24-2.22 (m, 1H), 2.13-2.10 (m, 1H), 1.96-1.83 (m, 2H), 1.76-1.70 (m, 1H), 1.61-1.54 (m, 1H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 174.5, 157.9, 133.3, 129.3, 113.8, 68.2, 55.3, 38.5, 33.0, 32.0, 24.7, 22.0; IR (neat,  $\text{cm}^{-1}$ ): 1729, 1511, 1242, 1145, 1033, 820; HRMS (DART) calcd for  $\text{C}_{14}\text{H}_{19}\text{O}_3$   $[\text{M} + \text{H}]^+$  235.1334, found; 235.1338.



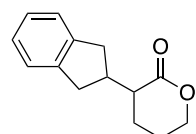
**3-(3-Methoxyphenethyl)tetrahydro-2H-pyran-2-one (5ma);** Colorless oil;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.20 (t, 1H,  $J = 7.56$  Hz), 6.80 (d, 1H,  $J = 7.56$  Hz), 6.75 (d, 2H,  $J = 8.25$  Hz), 4.29 (t, 2H,  $J = 5.84$  Hz), 3.80 (s, 3H), 2.74-2.71 (m, 2H), 2.47-2.44 (m, 1H), 2.26-2.23 (m, 1H), 2.14-2.12 (m, 1H), 1.93-1.87 (m, 2H), 1.78-1.75 (m, 1H), 1.61-1.58 (m, 1H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 174.5, 159.7, 143.0, 129.4, 120.8, 114.1, 111.3, 68.1, 55.1, 38.5, 32.9, 32.7, 24.7, 21.9; IR (neat,  $\text{cm}^{-1}$ ): 1729, 1584, 1488, 1255, 1148, 1070, 1045, 781, 697; HRMS (DART) calcd for  $\text{C}_{14}\text{H}_{19}\text{O}_3$   $[\text{M} + \text{H}]^+$  235.1334, found; 235.1340.



**3-(2-Methoxyphenethyl)tetrahydro-2H-pyran-2-one (5na);** Colorless oil;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.18 (t, 1H,  $J = 7.90$  Hz), 7.16 (d, 1H,  $J = 7.56$  Hz), 6.89 (t, 1H,  $J = 7.22$  Hz), 6.84 (d, 1H,  $J = 8.25$  Hz), 4.29 (t, 2H,  $J = 5.84$  Hz), 3.82 (s, 3H), 2.78-2.68 (m, 2H), 2.50-2.44 (m, 1H), 2.26-2.15 (m, 2H), 1.96-1.84 (m, 2H), 1.75-1.72 (m, 1H), 1.61-1.60 (m, 1H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 174.7, 157.4, 129.8, 129.7, 127.2, 120.4, 110.2, 68.1, 55.2, 38.9, 31.2, 27.3, 24.5, 21.9; IR (neat,  $\text{cm}^{-1}$ ): 1729, 1492, 1240, 1145, 1070, 1028, 753; HRMS (DART) calcd for  $\text{C}_{14}\text{H}_{19}\text{O}_3$   $[\text{M} + \text{H}]^+$  235.1334, found; 235.1344.



**3-(4-Chlorophenethyl)tetrahydro-2H-pyran-2-one (5oa);** Colorless oil;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.25 (d, 2H,  $J = 8.94$  Hz), 7.14 (d, 2H,  $J = 8.25$  Hz), 4.30 (t, 2H,  $J = 5.84$  Hz), 2.72 (t, 2H,  $J = 7.56$  Hz), 2.45-2.42 (m, 1H), 2.23-2.21 (m, 1H), 2.12-2.10 (m, 1H), 1.96-1.85 (m, 2H), 1.75-1.73 (m, 1H), 1.60-1.58 (m, 1H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 174.3, 139.8, 131.7, 129.8, 128.5, 68.2, 38.5, 32.7, 32.3, 24.7, 21.9; IR (neat,  $\text{cm}^{-1}$ ): 1727, 1491, 1251, 1145, 1090, 1014, 730; HRMS (DART) calcd for  $\text{C}_{13}\text{H}_{16}\text{ClO}_2$   $[\text{M} + \text{H}]^+$  239.0839, found; 239.0839.



**3-(2,3-Dihydro-1H-inden-2-yl)tetrahydro-2H-pyran-2-one (5sa);** Pale yellow solid; Mp 101-103  $^{\circ}\text{C}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.19-7.18 (m, 2H), 7.14-7.13 (m, 2H), 4.33-4.31 (m, 2H), 3.34 (q, 1H,  $J = 8.02$  Hz), 3.09 (q, 1H,  $J = 8.02$  Hz), 2.93-2.90 (m, 1H), 2.79-2.70 (m, 2H), 2.64-2.62 (m, 1H), 2.13-2.11 (m, 1H), 1.94-1.90 (m, 2H), 1.64-1.58 (m, 1H);  $^{13}\text{C}$  NMR (150

MHz, CDCl<sub>3</sub>)  $\delta$ : 173.9, 143.1, 142.3, 126.3, 124.2, 67.9, 44.0, 40.4, 38.0, 36.4, 22.5, 21.8; IR (neat, cm<sup>-1</sup>); 1731, 1255, 1145, 1071, 835, 748; HRMS (DART) calcd for C<sub>14</sub>H<sub>17</sub>O<sub>2</sub> [M + H]<sup>+</sup> 217.1229, found; 217.1239.

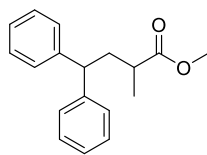
**3-(Cyclopentylmethyl)tetrahydro-2H-pyran-2-one (5ta)**; Colorless oil; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)  $\delta$ : 4.30 (t, 2H, *J* = 5.50 Hz), 2.49-2.47 (m, 1H), 2.17-2.11 (m, 1H), 1.98-1.84 (m, 4H), 1.79-1.76 (m, 2H), 1.66-1.59 (m, 2H), 1.56-1.45 (m, 4H), 1.16-1.07 (m, 2H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>)  $\delta$ : 175.0, 68.2, 38.7, 37.5, 37.1, 33.0, 31.9, 25.0, 25.0, 24.8, 21.9; IR (neat, cm<sup>-1</sup>); 1732, 1452, 1391, 1252, 1144, 1071, 837; HRMS (DART) calcd for C<sub>11</sub>H<sub>19</sub>O<sub>2</sub> [M + H]<sup>+</sup> 183.1385, found; 183.1378.

**3-(4-Fluorophenethyl)tetrahydro-2H-pyran-2-one (5xa)**; Colorless oil; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.17-7.15 (m, 2H), 6.97 (tt, 2H, *J* = 8.94, 2.29 Hz), 4.30 (t, 2H, *J* = 5.84 Hz), 2.75-2.69 (m, 2H), 2.45-2.43 (m, 1H), 2.23-2.21 (m, 1H), 2.13-2.11 (m, 1H), 1.97-1.85 (m, 2H), 1.78-1.71 (m, 1H), 1.60-1.59 (m, 1H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>)  $\delta$ : 174.3, 161.3 (d, *J*<sub>C-F</sub> = 242.77 Hz), 137.0 (d, *J*<sub>C-F</sub> = 3.47 Hz), 129.7 (d, *J*<sub>C-F</sub> = 8.66 Hz), 115.1 (d, *J*<sub>C-F</sub> = 20.81 Hz), 68.2, 38.5, 33.0, 32.1, 24.7, 21.9; <sup>19</sup>F NMR (565 MHz, CDCl<sub>3</sub>)  $\delta$ : -118.4; IR (neat, cm<sup>-1</sup>); 1728, 1508, 1218, 1147, 1070, 824; HRMS (DART) calcd for C<sub>13</sub>H<sub>16</sub>FO<sub>2</sub> [M + H]<sup>+</sup> 223.1134, found; 223.1141.

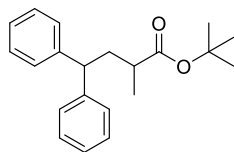
**Methyl 4-(2-(2-oxotetrahydro-2H-pyran-3-yl)ethyl)benzoate (5ya)**; Colorless oil; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.96 (d, 2H, *J* = 8.25 Hz), 7.28 (d, 2H, *J* = 8.25 Hz), 4.30 (t, 2H, *J* = 5.84 Hz), 3.91 (s, 3H), 2.81 (t, 2H, *J* = 7.90 Hz), 2.47-2.42 (m, 1H), 2.28-2.22 (m, 1H), 2.13-2.11 (m, 1H), 1.93-1.89 (m, 2H), 1.80-1.78 (m, 1H), 1.61-1.59 (m, 1H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>)  $\delta$ : 174.2, 167.0, 146.9, 129.8, 128.5, 128.0, 68.2, 52.0, 38.6, 33.0, 32.5, 24.8, 21.9; IR (neat, cm<sup>-1</sup>); 1712, 1435, 1278, 1151, 1107, 1068, 761, 705; HRMS (DART) calcd for C<sub>15</sub>H<sub>19</sub>O<sub>4</sub> [M + H]<sup>+</sup> 263.1283, found; 263.1286.

**Ethyl 2-methyl-4,4-diphenylbutanoate (5ab)**; Colorless oil; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.27-7.23 (m, 8H), 7.19-7.16 (m, 2H), 4.08 (q, 2H, *J* = 7.10 Hz), 3.98 (t, 1H, *J* = 7.90 Hz), 2.51-2.48 (m, 1H), 2.34-2.32 (m, 1H), 2.10-2.05 (m, 1H), 1.24 (t, 3H, *J* = 7.22 Hz), 1.17 (d, 3H, *J* = 7.56 Hz); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>)  $\delta$ : 176.5, 144.3, 144.1, 128.5, 128.5, 127.9, 127.8, 126.3, 126.2, 60.2, 48.9, 39.5, 37.6, 17.4, 14.2; IR (neat, cm<sup>-1</sup>) 1728, 1451, 1162, 1057, 1028, 751, 698; HRMS (DART) calcd for C<sub>19</sub>H<sub>23</sub>O<sub>2</sub> [M + H]<sup>+</sup> 283.1698, found; 283.1684.

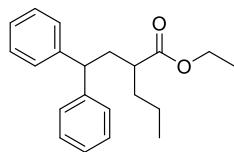
**Methyl 2-methyl-4,4-diphenylbutanoate (5ac);** The structure was confirmed by comparison with data of  $^1\text{H}$  and  $^{13}\text{C}$  NMR shown in a literature.<sup>39</sup>  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.29-7.22 (m, 8H), 7.19-7.16 (m, 2H), 3.97 (t, 1H,  $J = 8.25$  Hz), 3.62 (s, 3H), 2.52-2.50 (m, 1H), 2.37-2.34 (m, 1H), 2.10-2.05 (m, 1H), 1.18 (d, 3H,  $J = 6.87$  Hz);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 176.9, 144.3, 144.0, 128.5, 128.5, 127.8, 126.3, 51.5, 48.8, 39.4, 37.5, 17.4; MS (DART)  $m/z = 269$ .



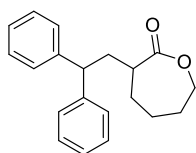
***tert*-Butyl 2-methyl-4,4-diphenylbutanoate (5ad);** Colorless oil;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.29-7.22 (m, 8H), 7.19-7.16 (m, 2H), 4.00 (t, 1H,  $J = 7.90$  Hz), 2.44-2.41 (m, 1H), 4.24-2.17 (m, 1H), 2.04-2.01 (m, 1H), 1.45 (s, 9H), 1.12 (d, 3H,  $J = 6.87$  Hz);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 175.9, 144.4, 144.3, 128.4, 128.0, 127.8, 126.3, 126.2, 48.9, 39.7, 38.4, 28.1, 28.1, 17.5; IR (neat,  $\text{cm}^{-1}$ ) 1725, 1367, 1147, 745, 698; HRMS (DART) calcd for  $\text{C}_{21}\text{H}_{27}\text{O}_2$   $[\text{M} + \text{H}]^+$  311.2011, found; 311.2015.



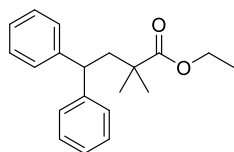
**Ethyl 2-(2,2-diphenylethyl)pentanoate (5ae) ;** Colorless oil;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.30-7.24 (m, 5H), 7.23-7.21 (m, 3H), 7.20-7.15 (m, 2H), 4.08-4.06 (m, 2H), 3.92 (dd, 1H,  $J = 9.62, 6.19$  Hz), 2.41-2.39 (m, 1H), 2.29-2.24 (m, 1H), 2.18-2.13 (m, 1H), 1.64-1.58 (m, 1H), 1.49-1.43 (m, 1H), 1.24-1.22 (m, 5H), 0.84 (t, 3H,  $J = 7.56$  Hz);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 176.1, 144.6, 144.0, 128.5, 128.4, 128.0, 127.7, 126.3, 126.2, 60.0, 49.2, 43.5, 38.1, 35.0, 20.3, 14.3, 13.9; IR (neat,  $\text{cm}^{-1}$ ) 1726, 1451, 1158, 1031, 741, 698; HRMS (DART) calcd for  $\text{C}_{21}\text{H}_{27}\text{O}_2$   $[\text{M} + \text{H}]^+$  311.2011, found; 311.2017.



**3-(2,2-Diphenylethyl)oxepan-2-one (5af);** Colorless solid; Mp 111-112  $^{\circ}\text{C}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.31-7.16 (m, 10H), 4.17-4.16 (m, 1H), 4.11 (t, 1H,  $J = 7.90$  Hz), 3.91 (t, 1H,  $J = 11.68$  Hz), 2.67-2.62 (m, 1H), 2.37-2.34 (m, 1H), 2.08-2.03 (m, 1H), 1.93-1.91 (m, 1H), 1.84-1.82 (m, 2H), 1.71-1.65 (m, 1H), 1.53-1.45 (m, 2H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 177.3, 144.5, 144.0, 128.6, 128.5, 128.0, 127.8, 126.4, 126.3, 68.1, 48.1, 40.4, 38.4, 30.2, 28.5, 28.0; IR (neat,  $\text{cm}^{-1}$ ) 1719, 1492, 1147, 1054, 747, 704, 573; HRMS (DART) calcd for  $\text{C}_{20}\text{H}_{23}\text{O}_2$   $[\text{M} + \text{H}]^+$  295.1698, found; 295.1707.



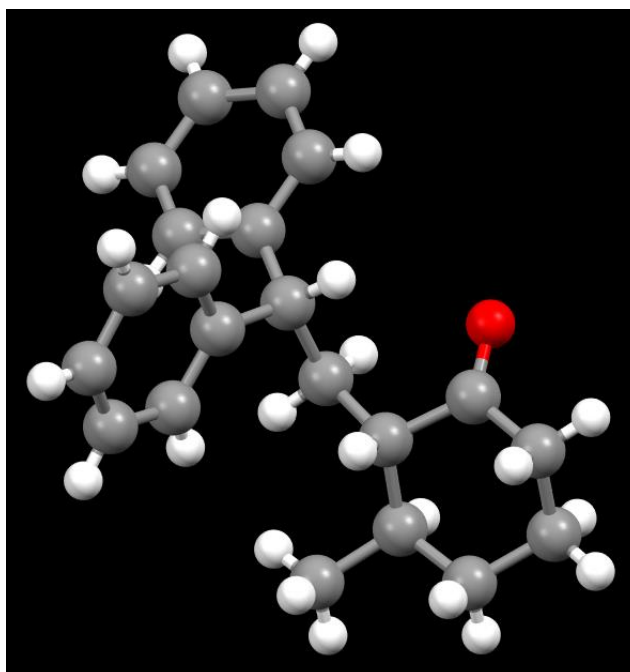
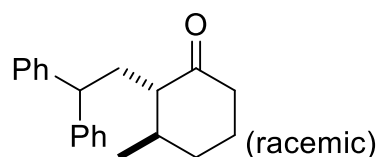
**Ethyl 2,2-dimethyl-4,4-diphenylbutanoate (5ag);** Colorless oil;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.26-7.24 (m, 8H), 7.13-7.12 (m, 2H), 4.01 (t, 1H,  $J = 6.87$  Hz), 3.63 (q, 2H,  $J = 7.10$  Hz), 2.42 (d, 2H,  $J = 6.87$  Hz), 1.16 (s, 6H), 1.08 (t, 3H,  $J = 6.87$  Hz);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 177.2, 145.2, 128.3, 127.9, 126.1, 60.1, 48.2, 46.2, 42.0, 26.0, 13.9; IR (neat,  $\text{cm}^{-1}$ ) 1722, 1451, 1181, 1131, 1030, 745, 698; HRMS(DART) calcd for  $\text{C}_{20}\text{H}_{25}\text{O}_2$   $[\text{M} +$



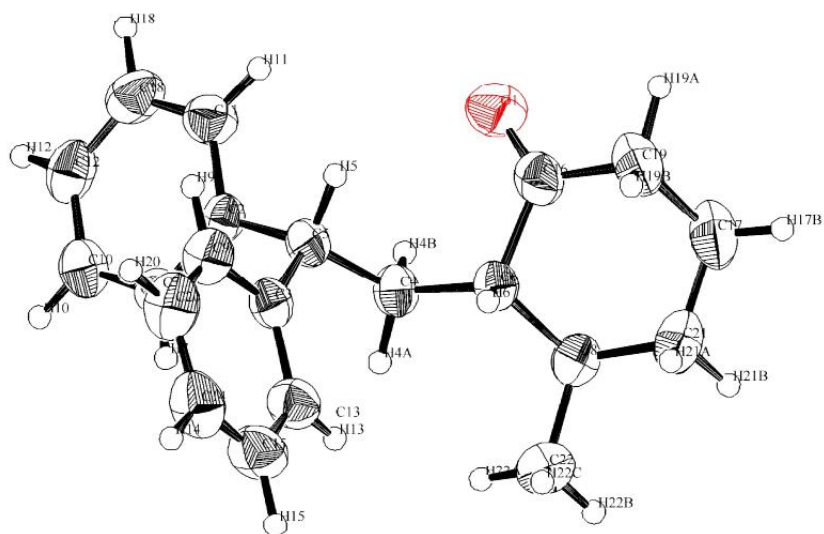
HJ<sup>+</sup> 297.1855, found; 297.1854.

### ***Determination of Related Configuration of 3ae***

**3ae** was dissolved in chloroform (0.4 mL), and the whole was put at room temperature under hexane vapor atmosphere. After 3 days, small colorless crystals appeared and were collected by filtration. Then, X-ray single crystal structure analysis was conducted using the obtained crystal (Supplementary figure 3, Supplementary figure 4). It was found that the configuration of the major diastereomer was anti. The analytical data was available on website of The Cambridge Crystallographic Data Centre (CCDC 2080743).<sup>40</sup>



**Supplementary figure 3. X-ray Structure of 3ae**



**Supplementary figure 4.** X-Ray Structure (ORTEP, probability: 50%) of **3ae**

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