Doctorate Dissertation (Censored)

博士論文 (要約)

Development of Strong Brønsted Base-catalyzed Carbon–Carbon Bond Forming Reactions Using Alkenes

(強塩基触媒によるアルケンを用いた 炭素–炭素結合生成反応の開発)

A Dissertation Submitted for Degree of Doctor of Philosophy

December 2018

平成 30 年 12 月博士（理学）申請

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Abstract

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Introduction

Alkenes are an important class of starting materials for carbon–carbon (C–C) bond forming reactions, and many types of the reactions have been developed such as addition reactions to C–C double bond, Heck-type reactions, olefin metathesis, allylic C–H functionalizations, and so on. As for activated alkenes such as α,β-unsaturated carbonyl compounds, there are many efficient reactions reported; however, as for less activated alkenes, harsh reaction conditions, stoichiometric amounts of reagents, by-product formation and using of transition metals as catalysts are normally inevitable; therefore, there is still room to improve the reactions from the view point of efficiency and environmental benefits.

Brønsted base-catalyzed C–C bond forming reactions are one of the most efficient methods, because only proton transfer occurs during the process, thus the reactions essentially show high level of atom economy. However, there are severe limitation of an acidity of hydrogen of pronucleophiles (pK_a ~25). To conquer this limitation, we have developed a strategy by focusing on the basicity of reaction intermediates (Fig. 1).[a] In our strategy, the reaction intermediates produced by the addition of carbanions to electrophiles are designed to possess strong basicity. These strongly basic reaction intermediates can regenerate the strong base catalysts or generate the next nucleophilic species *via* deprotonation of the conjugate acids or pronucleophiles, respectively; therefore, the desired reaction can proceed with only a catalytic amount of strong base. Based on the strategy, several catalytic C–C bond forming reactions of weakly acidic pronucleophiles such as amides, esters, and so on have been investigated. However, applicable substrates for these reactions are still limited, and drastic expansion of this strategy is highly desired to develop efficient catalytic C–C bond forming reactions using less reactive alkenes as starting materials. In my Ph.D. course study, I have developed strong Brønsted base-catalyzed C–C bond forming reactions using less reactive alkenes as both electrophiles and pronucleophiles by newly developed catalytic systems.

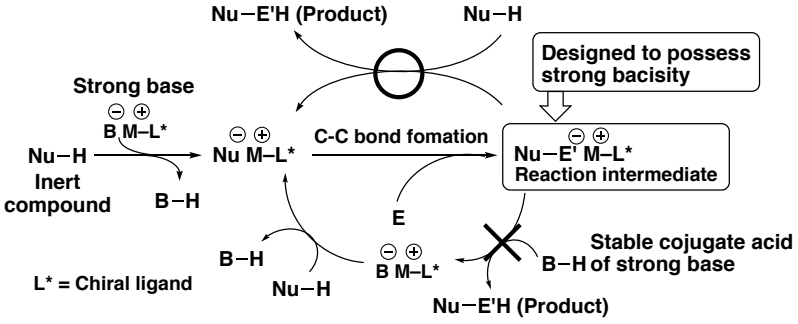


Fig. 1. "Product base" mechanism

1. Catalytic Asymmetric 1,4-Addition Reactions of Amides with α,β-Phosphonates

Although we developed catalytic asymmetric 1,4-addition reactions of several weakly acidic pronucleophiles such as amides, esters, alkyl nitriles, and so on, electrophiles were only limited to α,β-unsaturated amides. On the other hand, phosphonates are often seen in natural products and biologically active compounds, and effective methods for the synthesis of functionalized phosphonates are demanded. After investigations, it was found that α,β-unsaturated phosphonates were attractive and appropriate electrophiles for the catalytic asymmetric 1,4-addition reactions.

(5 年以内に雑誌等に投稿予定のため、該当部分を一部略)

2. Alkyl Potassium-catalyzed Addition Reactions of Alkylarenes with Alkenes

Direct catalytic C–C bond forming reactions of alkylarenes such as toluene and xylene *via* benzylic C–H functionalization is among the most attractive methods for installation of a benzyl moiety into carbon framework,

because alkylarenes are generally inexpensive, safe and easy-to-handle compounds, and there is no need of pre-modification of starting materials to more reactive compounds.[b] However, because of low reactivity of benzylic C–H bond (BDE ~ 90 kcal/mol, pK_a ~43), these reactions have not been much explored so far. One main approach for the reactions is radical-mediated C–H functionalization of an alkylarene. In this approach, benzylic C–H bond is homolytically cleaved to form a benzylic radical intermediate, then this radical species reacts with an acceptor (normally an electron deficient alkene) to give a product. Recently, combination of this radical intermediate and transition-metal catalysis has been investigated, and also the other approaches such as carbene insertion and Pd- and Ru- catalyzed reactions were reported. However, precious and toxic transition metal and/or harsh reaction conditions are generally required; thus, much milder and efficient reactions are demanded. For this demanding, I hypothesized that strong Brønsted base catalyzed C–C bond forming reactions through benzylic anion intermediates might be a good solution (Fig.2). The key factor for the catalytic reactions was considered that the basicity of the reaction intermediates and the strong Brønsted base catalysts. As for the strongly basic reaction intermediates, quite strong basicity enough to deprotonate less acidic benzylic hydrogens of alkylarenes was considered to be required, then it was assumed that styrene derivatives could produce such strongly basic intermediates. As for the strong Brønsted base catalysts, it is known that mixture of a KO^{t}Bu/LiTMP (Lithium tetramethylpiperidide) can deprotonate benzylic hydrogen of toluene smoothly at low temperature.[c] With this hypothesis, the catalytic reaction of toluene with β-phenyl styrene was conducted in the presence of catalytic amounts of KO^{t}Bu/LiTMP to afford the desired product in moderate yield. After intensive investigations, it was found that alkyl potassium as a catalyst minimized the formation of by-products, and I found that, in the presence of a catalytic amount of KCH_2TMS and PMDTA (*N*,*N*,*N*′,*N*′′,*N*′′-pentamethyldiethylenetriamine) as a ligand, the catalytic addition reactions of alkylarenes with β-substituted styrene derivatives proceeded smoothly under mild reaction conditions to afford the target functionalized aromatic compounds in moderate to high yields (Scheme 2). As for nucleophiles, not only toluene, but also several substituted alkylarenes were proper substrates for the reactions. And as for the electrophiles, several unsymmetrical stilbene derivatives showed high yields with high regioselectivities. The lowest catalyst loading was 1 mol% for the reaction of toluene and stilbene, which showed high efficiency of this system.

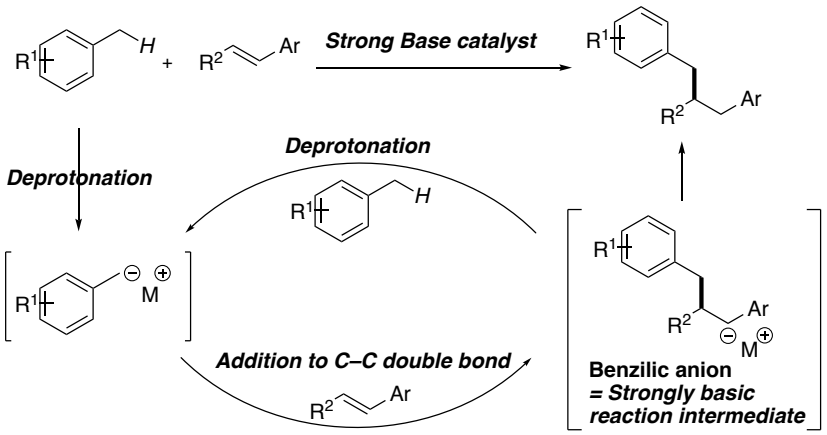
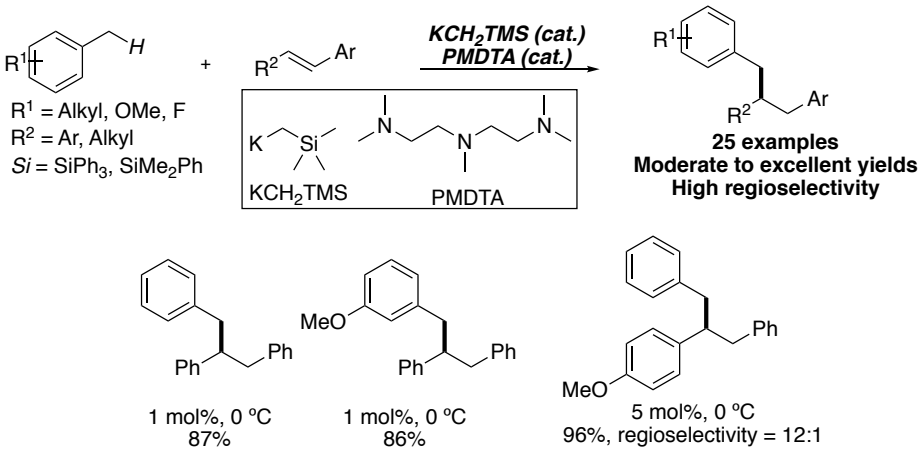


Fig. 2. Catalytic addition reactions of alkylarenes with styrenes



Scheme 1. Alkyl potassium-catalyzed addition reactions of alkylarenes with alkenes

(5 年以内に雑誌等に投稿予定のため、該当部分を一部略)

3. Catalytic Allylation Reactions of Imines Using Simple Alkenes

(5 年以内に雑誌等に投稿予定のため、非公開)

Conclusion

In my Ph.D. course study, I have developed strong Brønsted base-catalyzed C–C bond forming reactions using less reactive alkenes by focusing on the basicity of reaction intermediates. For the first topic, it was found that α,β-unsaturated phosphonates were appropriate electrophiles for catalytic 1,4-addition reactions of amides. For the second topic, it was revealed that alkyl potassium was an effective catalyst for the catalytic addition reactions of alkylarenes with styrene derivatives to afford the desired functionalized aromatic compounds and silanes in moderate to high yields.

(5 年以内に雑誌等に投稿予定のため、該当部分を一部略)

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[a] Yamashita, Y.; Kobayashi, S. *Chem. A Eur. J.* **2018**, *24*, 10. [b] Vanjari, R.; Singh, K. N. *Chem. Soc. Rev.* **2015**, *44*, 8062. [c] Fleming, P.; O'Shea, D. F. *J. Am. Chem. Soc.* **2011**, *133*, 1698. [d] Yus, M.; González-Gómez, J. C.; Foubelo, F. *Chem. Rev.* **2013**, *113*, 5595.

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Chapter 3
Catalytic Allylation Reactions of Imines Using Simple Alkenes

(5 年以内に雑誌等に投稿予定のため、非公開)

Abbreviations

Ac	acetyl
acac	acetylacetonate
Alk	alkyl
Ar	aryl
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bu	butyl
conc.	concentration
CPME	cyclopentyl methyl ether
DCE	dichloroethane
DCM	dichloromethane
DMA	*N,N*-dimethylacetamide
DMSO	dimethyl sulfoxide
DTBP	di-*tert*-butyl peroxide
eq.	equivalent
Et	ethyl
EWG	electron-withdrawing group
HMDS	hexamethyldisilazide
HOMO	highly occupied molecular orbital
i	*iso*
LDA	lithium diisopropylamide
LUMO	lowest unoccupied molecular orbital
m	*meta*
MCH	methylcyclohexane
Me	methyl
n	normal
NFSI	*N*-Fluorobenzenesulfonimide
NMP	*N*-methyl pyrrolidone
o	*ortho*
p	*para*
Ph	phenyl
Pr	propyl
r.t.	room temperature
SM	starting material
solv.	solvent
t	tertiary, *tert*-
TBME	*tert*-butyl methyl ether
TEA	triethylamine
temp.	temperature
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl

Chapter 0

General Introduction

0-1 Carbon–carbon Bond Forming Reactions using Alkenes

Alkenes are among the most common starting materials for carbon-carbon (C–C) bond forming reactions.[1] In general, the origin of reactivity of alkenes intrinsically derives from their C(sp^2)-C(sp^2) π -bonds, and the reactivity of alkenes can be tuned by adjacent functional groups. For examples, electron-withdrawing functional groups attached on their vinyl positions can reduce energy levels of LUMOs, then reactions such as Diels-Alder reactions and conjugate additions of nucleophiles can be facilitated. Also, a coordination of metal species to C–C double bond can enhance reactions such as palladium-catalyzed Mizoroki-Heck type reactions. Furthermore, allylic C–H bond activation can be facilitated by an adjacent C–C double bond (**Figure 0-1-1**).[2]

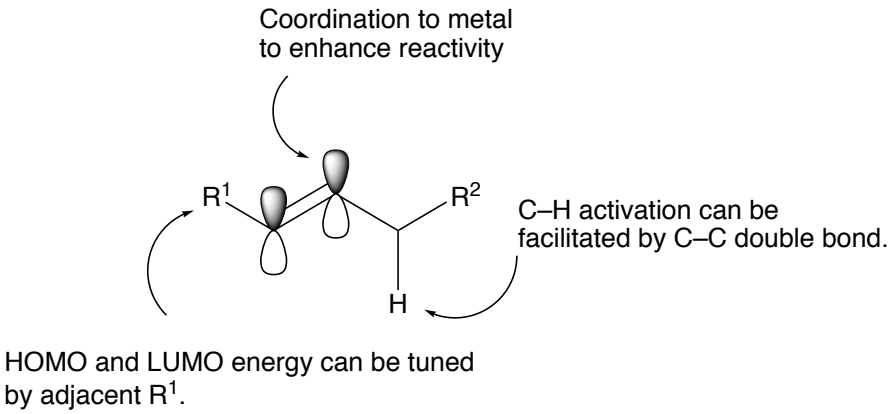


Figure 0-1-1. General consideration of reactivity of alkene

Based on the general reactivity of alkenes as mentioned above, to date, thousands of C–C bond forming reactions using alkenes, especially efficient catalytic reactions of them have been extensively developed and applied for syntheses of complex organic molecules (Typical C–C bond forming reactions using alkenes were shown in **Figure 0-1-2**). Recently, chemists have paid much attention to the reactions using less activated alkenes such as styrene and unactivated alkenes such as hexene, because of their cheapness, high stability and easy availability;[3] however, compared to the reactions using activated alkenes such as α,β-unsaturated carbonyl compounds and nitroalkenes, the reactions using less activated alkenes such as styrene and unactivated alkenes such as hexene have some drawbacks to be resolved from the viewpoint of atom economy and environmental benign:[4] (1) precious and/or toxic transition metals are used as reagents or catalysts; (2) excess amounts of reagents (e.g. bases, oxidants) are required; (3) harsh reaction

conditions are necessary; (4) stereocontrol of the reaction is relatively difficult (**Figure 0-1-3**). Therefore, there is a room for improvement of C–C bond forming reactions using less or unactivated alkenes as starting materials, and it was hypothesized that Brønsted base-catalyzed reactions could be the solution to overcome these drawbacks.

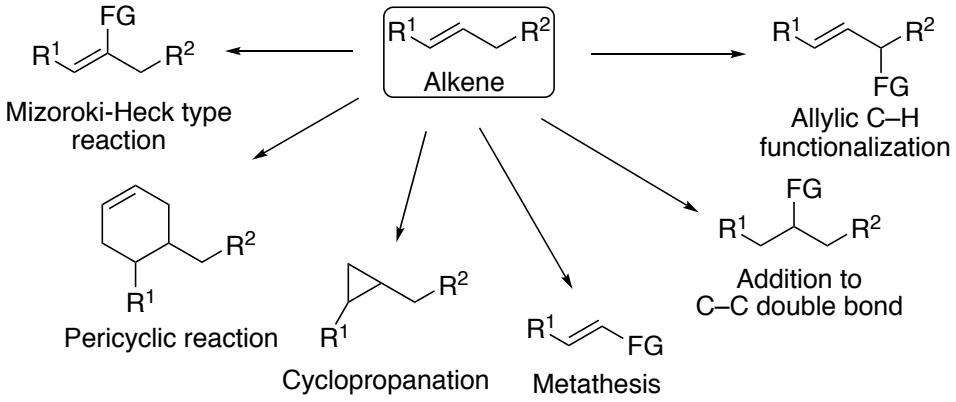


Figure 0-1-2. Typical C–C bond forming reactions using alkenes

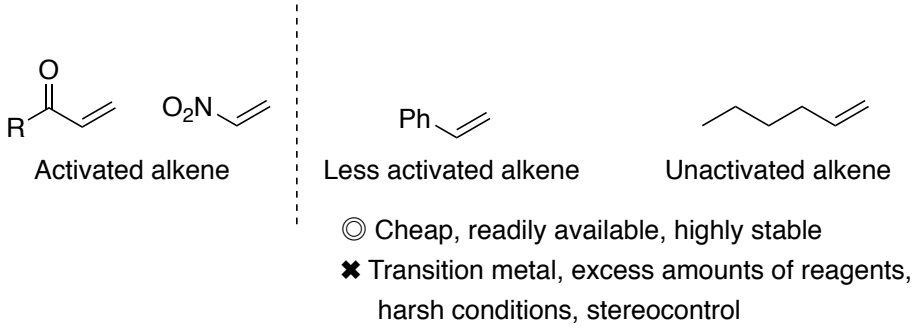


Figure 0-1-3. Features of less or unactivated alkenes

0-2 Brønsted Base-catalyzed Carbon–Carbon Bond Forming Reactions

Nowadays, contributions of organic compounds such as functional materials, medicines, agricultural chemicals and so on, produced by the art of organic chemistry for human society have grown dramatically. Accordingly, mass consumption of energy and environmental damages arose from productions of organic compounds are urgent tasks to realize a sustainable development of our society. To conquer the tasks, recently, much more efficient and environmentally benign methods of organic synthesis have been energetically developed.[5]

Among them, Brønsted base-catalyzed C–C bond forming reactions are one of the most efficient and reliable methodologies for constructions of complex carbon frameworks of organic molecules, because only proton transfers occur during these reactions, thus high atom economy and reduction of the amounts of wastes can be expected.[6] Moreover, the reaction can be carried out under relatively mild conditions, and also inexpensive and less toxic alkaline metal bases can be utilized as catalysts. In this reaction, a catalytic amount of base deprotonates an acidic proton of pronucleophile to produce a carbanion. This carbanion attacks an electrophile to afford the reaction intermediate, then this reaction intermediate works as a base to deprotonate the conjugate acid of base species, which is produced by deprotonation of pronucleophile to afford a desired product and to regenerate a base catalyst. Thus, C–C bond forming reaction occurs using only a catalytic amount of base species (**Figure 0-2-1**).[7]

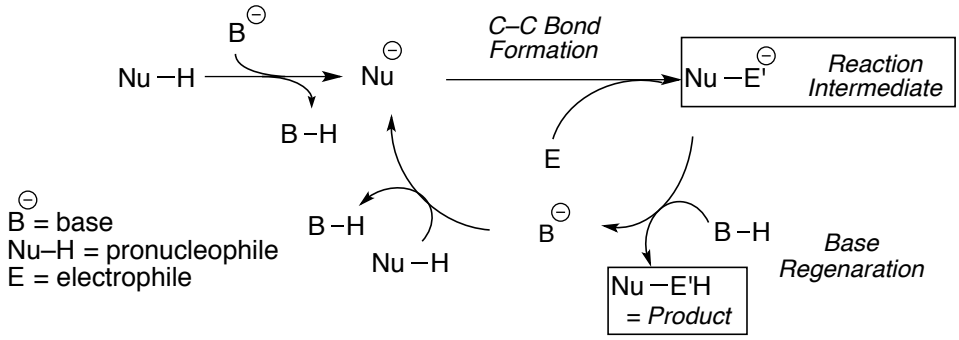


Figure 0-2-1. Brønsted base catalyzed C–C bond forming reaction

Until now, Brønsted base-catalyzed C–C bond forming reactions have been extensively developed in many combinations of pronucleophiles and electrophiles, and also their enantioselective variants have been widely investigated with asymmetric catalysts.[8] However, pronucleophiles of these reactions have been limited to fairly acidic compounds such as β-ketoesters and ketones that have electron withdrawing groups on adjacent carbons to acidic hydrogen atoms to stabilize carbanions, and catalytic activation of weakly acidic pronucleophiles such as esters, and amides for C–C bond forming reactions have been less investigated. Moreover, Brønsted base-catalyzed C–C bond forming

reactions using aromatic, benzylic and allylic compounds bearing much less acidic hydrogens have been scarcely developed (**Figure 0-2-2**).

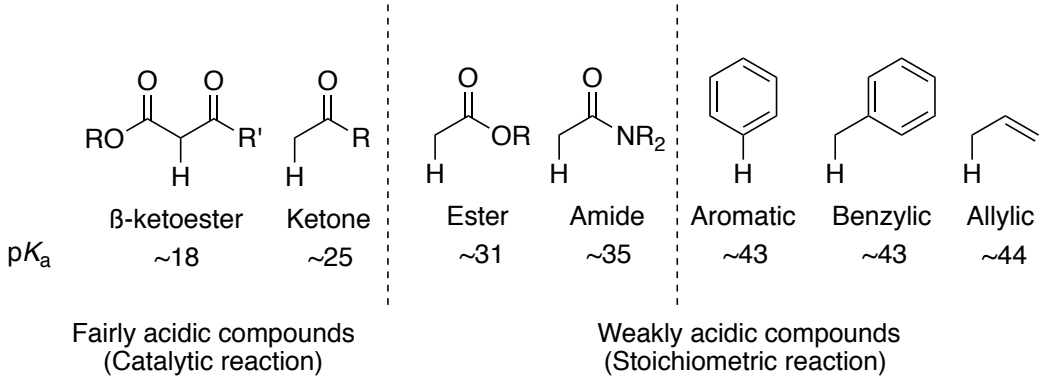


Figure 0-2-2. Acidity of pronucleophiles[9]

For deprotonation of weakly acidic α-hydrogen atoms of these compounds, strong base species such as LDA and BuLi are needed. However, conjugate acids of these strong base species are inherently inert and regeneration of the strong bases by the reaction intermediates is quite slow; therefore, excess amounts of strong base species are generally required for C–C bond forming reactions using weakly acidic compounds as pronucleophiles, and it is not an efficient method from the view point of atom economy (**Figure 0-2-3**).

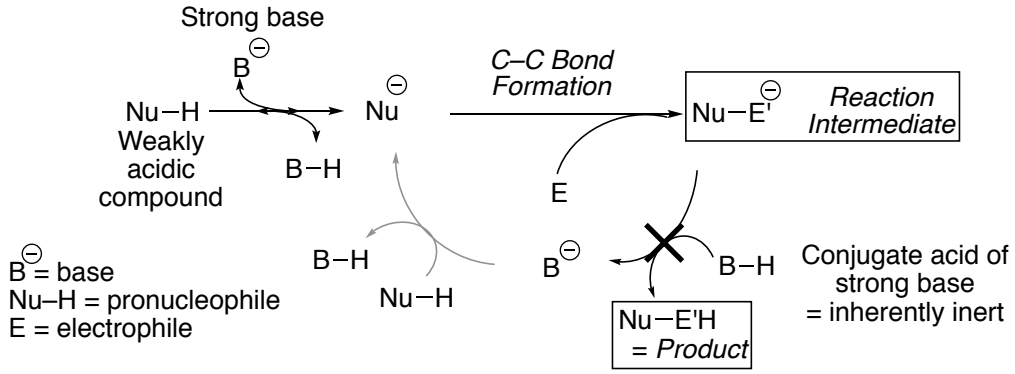


Figure 0-2-3. Difficulty of catalytic activation of weakly acidic compounds

To overcome the difficulty, recently our group has developed catalytic C–C bond forming reactions using weakly acidic compounds by focusing on basicity of reaction intermediates, this is termed as "Product base". As mentioned above, the problem for the catalytic reactions of weakly acidic compounds is regeneration of strong base species because of inherently inert nature of the conjugate acids. Then, we designed electrophiles to possess strong basicity on the reaction intermediates for efficient deprotonation of conjugate acids to regenerate strong base species or direct deprotonation of next weakly acidic hydrogen atoms of pronucleophiles; thus, Brønsted base-catalyzed C–C bond forming reactions of weakly acidic compounds might be achieved (**Figure 0-2-4**).[10]

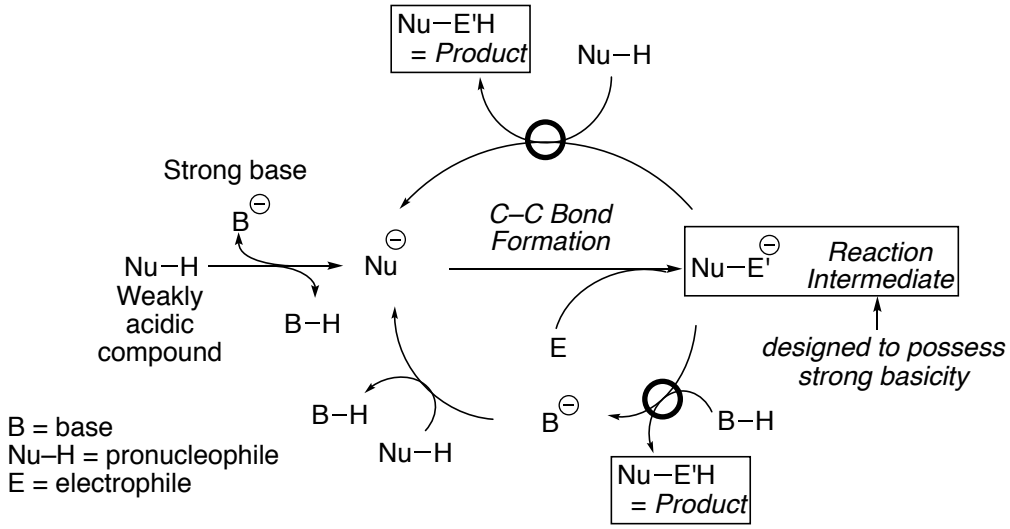
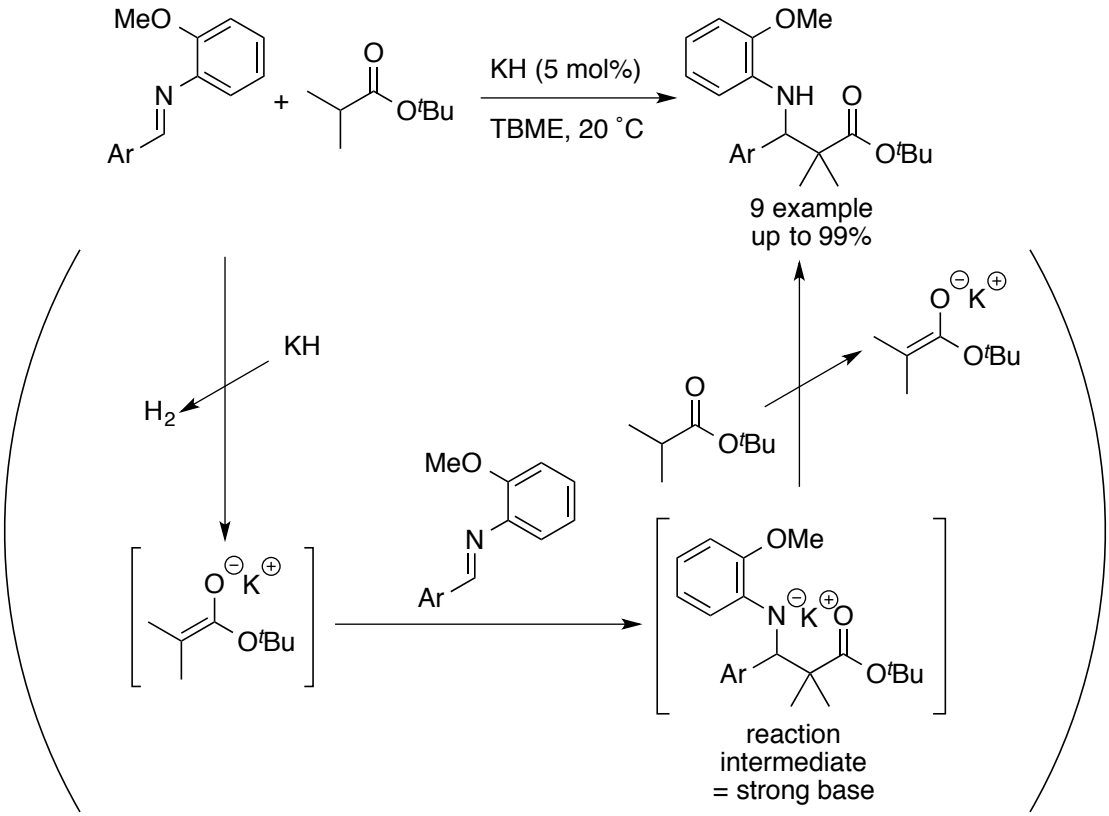


Figure 0-2-4. "Product base" strategy

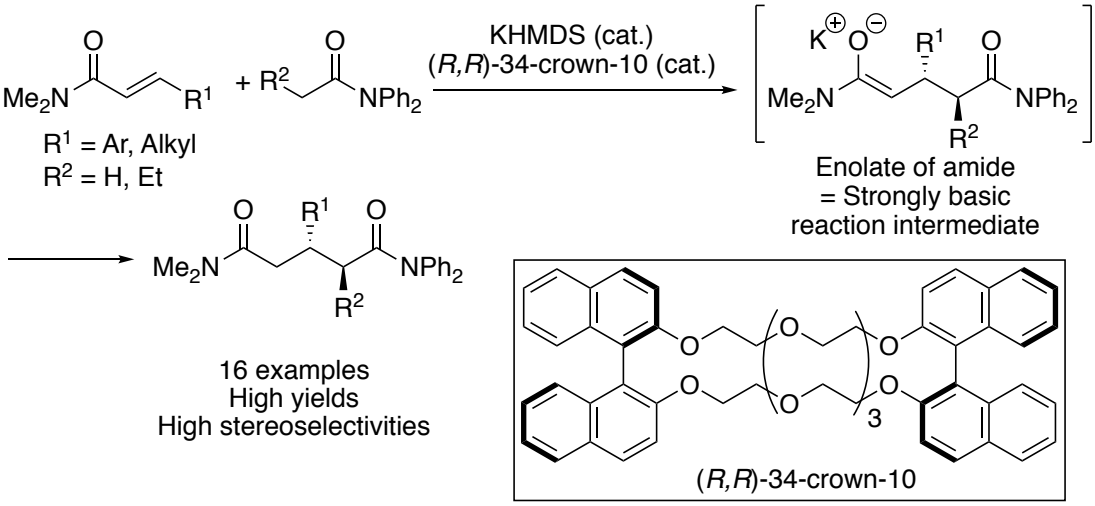
Based on this hypothesis, our group reported catalytic direct-type Mannich reactions of simple esters bearing no activating functionality on their α-positions (**Scheme 0-2-5**).[11] In these reactions, firstly KH deprotonated an α-hydrogen of ester to afford the corresponding potassium enolate intermediate. The intermediate attacked the designed imine that had an electron-donating *p*-methoxy aryl group on the nitrogen atom. The intermediate, which was produced after addition of the enolate to the imine, contained a nitrogen anion, and it worked as a strong base because of strong electron donating nature of the aryl functional group to deprotonate an α-hydrogen of next ester, then the desired β-aminoester was produced, and also the next enolate was reproduced.

Scheme 0-2-5. Catalytic direct-type Mannich reactions of esters



Our group also reported catalytic asymmetric 1,4-addition reactions of amides with α,β-unsaturated amides (**Scheme 0-2-6**).[12] In the reactions, α,β-unsaturated amides were chosen as electrophiles to produce strongly basic enolates of amides as the reaction intermediate, then the reaction intermediates deprotonated α-hydrogens of amides or the conjugate acids of KHMDS to form the products, and catalytic turnover took place. Moreover, chiral macrocyclic crown ether, (*R,R*)-34-crown-10 made an effective chiral environment by coordination to a potassium cation to show excellent level of enantioselectivity (up to 98% ee).

Scheme 0-2-6. Catalytic asymmetric 1,4-additions of amides to α,β-unsaturated amides



With similar reaction conditions, we reported that catalytic asymmetric 1,4-addition reactions using weakly acidic pronucleophiles such as enters,[13] alkylnitriles[14] and so on.[15] However, available substrates for the catalytic reactions had been still limited. As for pronucleophiles, the range of pK_a values of available pronucleophiles were 30~35 (in DMSO). In order to break the limitation of acidity of pronucleophile, new catalytic systems must be required, especially for the reaction using inert compounds such as alkylarenes and allylic compounds (**Figure 0-2-7**). Moreover, applicable electrophiles for the catalytic reactions had been also limited to imines and α,β-unsaturated amides. To attain more broader generality of electrophiles for the reactions, especially to use less activated alkenes such as styrene, development of new catalytic system was in demand (**Figure 0-2-8**).

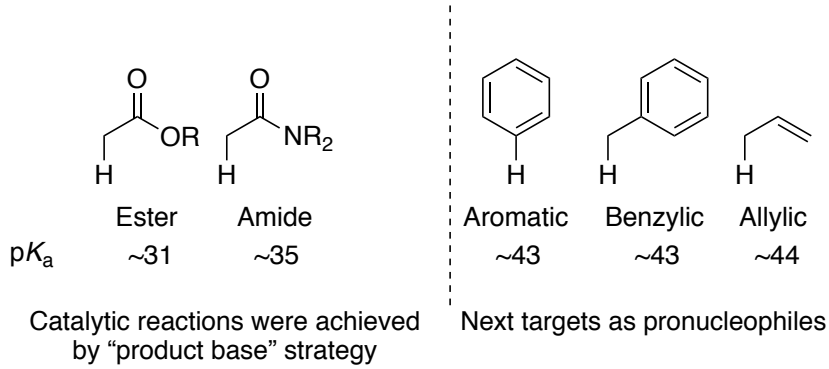


Figure 0-2-7. Target pronucleophiles

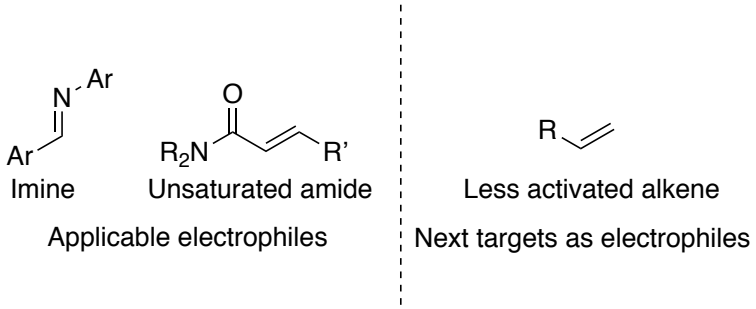


Figure 0-2-8. Target electrophiles

In my Ph.D. study, I have developed new reaction systems for Brønsted base-catalyzed C–C bond forming reactions using less reactive substrates, especially less reactive alkenes by "product base" strategy as mentioned before.

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Chapter 1

Catalytic Asymmetric 1,4-Addition Reactions of Amides with α,β-Unsaturated Phosphonates

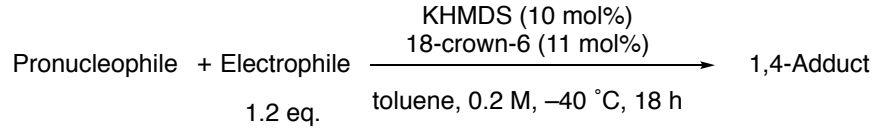
1-1 Combination Screening for The Strong Base-catalyzed 1,4-Addition Reactions

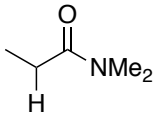
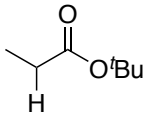
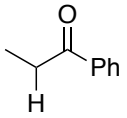
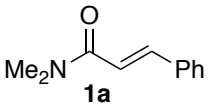
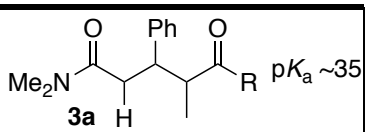
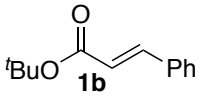
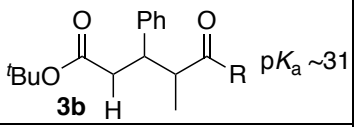
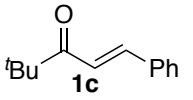
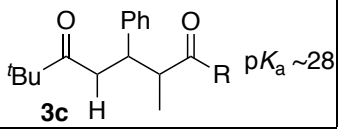
As mentioned in Chapter 0, various kinds of weakly acidic carbon pronucleophiles such as amides[1], alkylnitriles[2], and esters[3] were investigated for the catalytic asymmetric 1,4-addition reactions based on the strategy. However, applicable electrophiles were limited to only α,β-unsaturated amides for these reactions; therefore, development of the other suitable electrophiles for the reactions was demanded.

The key of the catalytic cycle of the reactions is that the reaction intermediates have strong basicity to deprotonate α-hydrogen atoms of next pronucleophiles or less acidic hydrogen atoms of conjugate acids of the strong bases. The basicity of the reaction intermediates depends on the structure of electrophiles, and the electrophilicity of the electrophiles also depends on it; thus, suitable choice of structure of the electrophiles was seemed to be needed for the reaction. In order to explore suitable electrophiles for the reaction, the reactions of several kinds of nucleophiles, which have different acidity of α-hydrogen atoms, with several kinds of electrophiles, which have different electrophilicity, were conducted in the presence of 10 mol% of KHMDS and 11 mol% of 18-crown-6 (**Table 1-1-1**).[4] It should be noted that there was almost no byproduct, and consumptions of the starting materials were coincident with the yields of the products, which meant that the reactivity of these reactions could be argued by the yields of them. The reaction of ester **2b (**pK_a ~31) with α,β-unsaturated amide **1a** proceeded to afford the product in higher yield than the reaction of amide **2a** (pK_a ~35) with α,β-unsaturated amide **1a**. The basicity of the reaction intermediate was almost the same for both reactions, because structures of these products are almost the same, and the reaction rate of deprotonation of α-hydrogen of the ester should be faster than that of the amide because of lower pK_a value of ester than that of amide. From these facts, it was assumed that the deprotonation step was the key step, and might be a rate determining step for these reactions. On the other hand, the reaction of ketone **2c (**pK_a ~25) with α,β-unsaturated amide **1a** did not proceed. Furthermore, the reaction of ketone **2c** with α,β-unsaturated amide **1a** in the presence of stoichiometric amounts of KHMDS and 18-crown-6 provided only a trace amount of the product (**Scheme 1-1-1**, top). These results indicated that the electrophilicity of α,β-unsaturated amide **1a** was too weak to be attacked by the enolate of ketone **2c**. Although the catalytic reaction of ketone **2c** with α,β-unsaturated ketone **1c** showed excellent yield, the catalytic reaction of ester **2b** or amide **2a** with α,β-unsaturated ketone **1c** did not proceed. The reason was assumed that the acidity of the product **3c** (pK_a ~28) was higher

than that of the ester and amide, that is, the basicity of the reaction intermediate was too weak to deprotonate α-hydrogen atoms of next pronucleophiles or less acidic hydrogen atom of the conjugate acids of the strong bases. By contrast, the stoichiometric reactions of esters **2b** or amide **2a** with α,β-unsaturated ketone **1c** proceeded smoothly to afford the desired products (**Scheme 1-1-1**, middle and bottom). These results indicated that nucleophilicity of the enolates of the ester and amide was strong enough to attack to α,β-unsaturated ketone **1c**. From this combination screening, it was proved that proper difference of acidity between the pronucleophiles and the products, whose acidity depended on the structure of the electrophiles, was crucial for the catalytic reaction, and when acidity of the products was appropriately higher (4-6 as pK_a values) than that of pronucleophiles, the catalytic reaction proceeded smoothly.

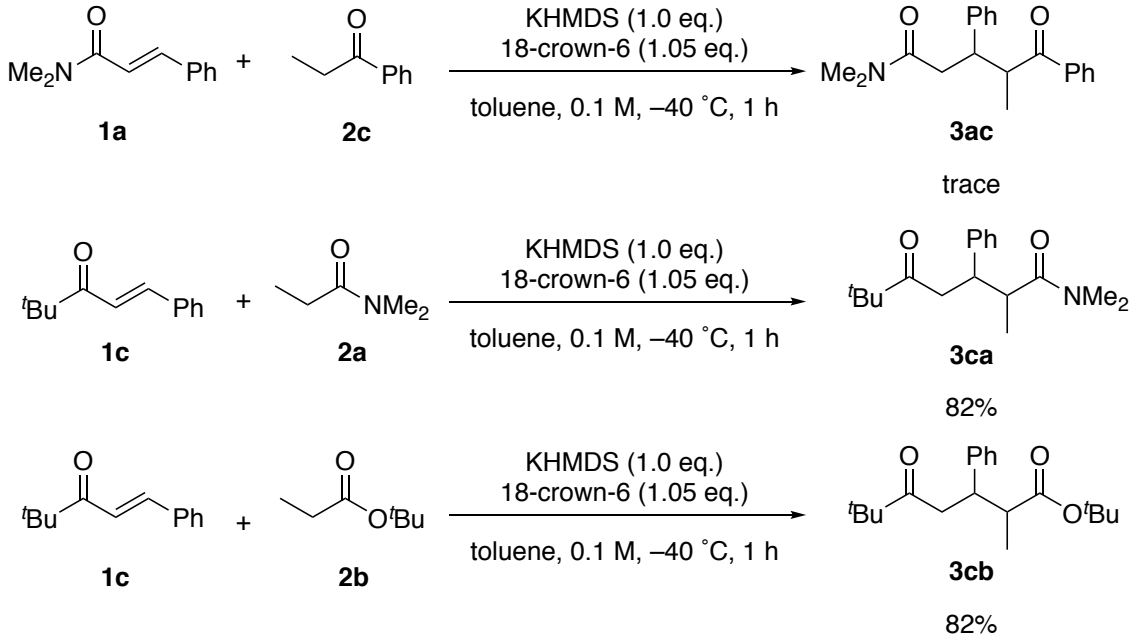
Table 1-1-1. Combination screening[a]



Pronucleophile / Electrophile	 **2a** pK_a ~35	 **2b** pK_a ~31	 **2c** pK_a ~25	1,4-Adduct
 **1a**	65%	quant.	trace	 **3a** pK_a ~35
 **1b**	16%	30%	98%	 **3b** pK_a ~31
 **1c**	trace	trace	98%	 **3c** pK_a ~28

[a] The yield was determined by ^{1}H NMR analysis of the crude mixture.

Scheme 1-1-1. Stoichiometric reactions[a]



[a] The yield was determined by ^{1}H NMR analysis of the crude mixture.

Based on this mechanistic insight of the catalytic reaction, suitable electrophiles of the catalytic 1,4-addition reactions of weakly acidic pronucleophiles was supposed to be alkenyl compounds bearing appropriate electron-withdrawing group such as an amide, with which pK_a value of the product should be around 35-37. From this assumption, it was assumed that alkenyl phosphonates might be applicable for the catalytic reactions. Acidity of an α-hydrogen atom of a phosphonate is estimated to be similar to that of an amide by comparison of acidity of non-substituted amides, α-phenyl amides, and α-phenyl phosphonates (**Figure 1-1-1**).

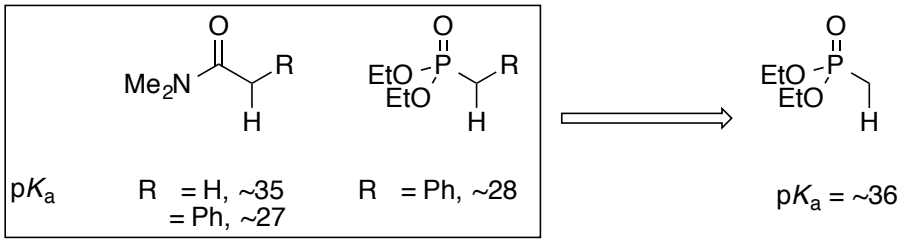


Figure 1-1-1. Estimation of acidity of non-substituted phosphonates[4]

Thus, it was supposed that alkenyl phosphonates might be suitable electrophiles for the catalytic asymmetric direct-type 1,4-addition reactions of weakly acidic pronucleophiles, because the reaction intermediates derived from the addition reactions of nucleophiles to alkenyl phosphonates could show comparable basicity with the reaction intermediates derived from unsaturated amides (**Figure 1-1-2**).

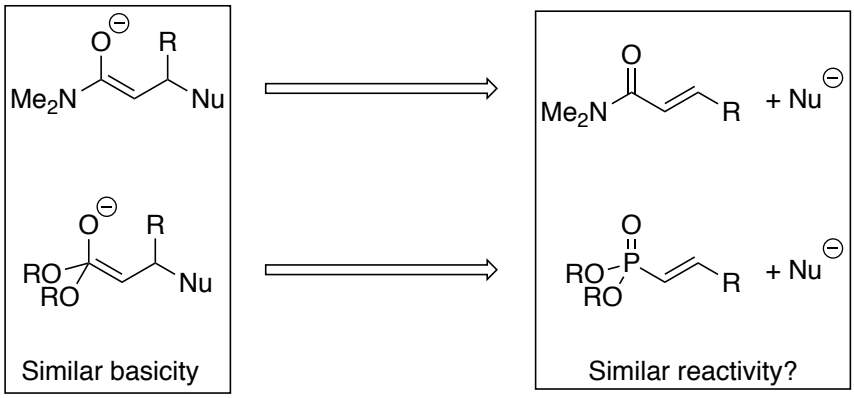


Figure 1-1-2. Assumed reactivity of alkenyl phosphonate

1-2 Background of Phosphonates

Phosphonates are quite abundant in nature,[5] and many kinds of natural and bioactive compounds with these moieties have been investigated.[6] Furthermore, they have been investigated as synthetic intermediates,[7] ligands for the catalytic reaction,[8] ligands for MOF [9] and so on; thus, catalytic stereoselective, especially enantioselective introductions of phosphonate moieties into carbon frameworks are important and useful reactions in organic synthesis, and many types of the reactions have been developed.[10] Among them, catalytic asymmetric 1,4-addition reactions using α,β-unsaturated phosphonates are powerful tools for syntheses of phosphonates bearing stereogenic center at the β-positions.[11] Although there are some reports of base-mediated 1,4-addition reactions of carbon pronucleophiles with vinyl and alkenyl phosphonates,[12] and there are many examples of catalytic asymmetric 1,4-addition reactions of carbon pronucleophiles with activated vinyl phosphonates such as vinylidenbis(phosphonates)[13] and so on,[14] catalytic asymmetric 1,4-addition reactions of carbon pronucleophiles with unactivated vinyl and alkenyl phosphonates are still less investigated due to low reactivity of them toward 1,4-addition reactions (**Figure 1-2-1**).

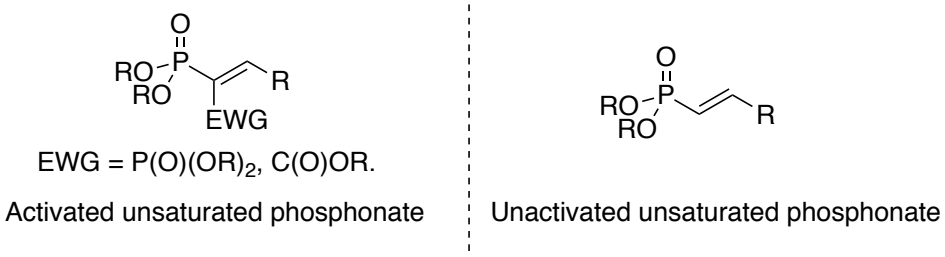
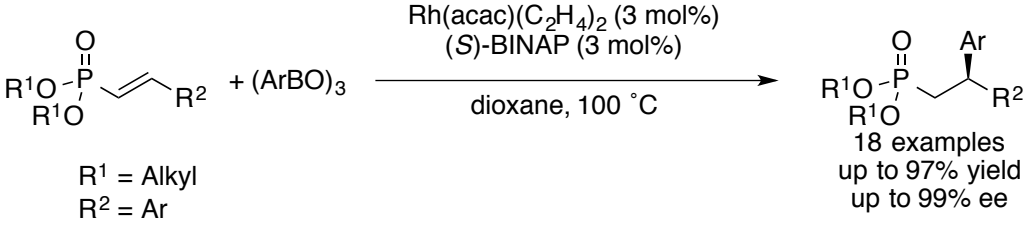


Figure 1-2-1. Activated and unactivated phosphonate

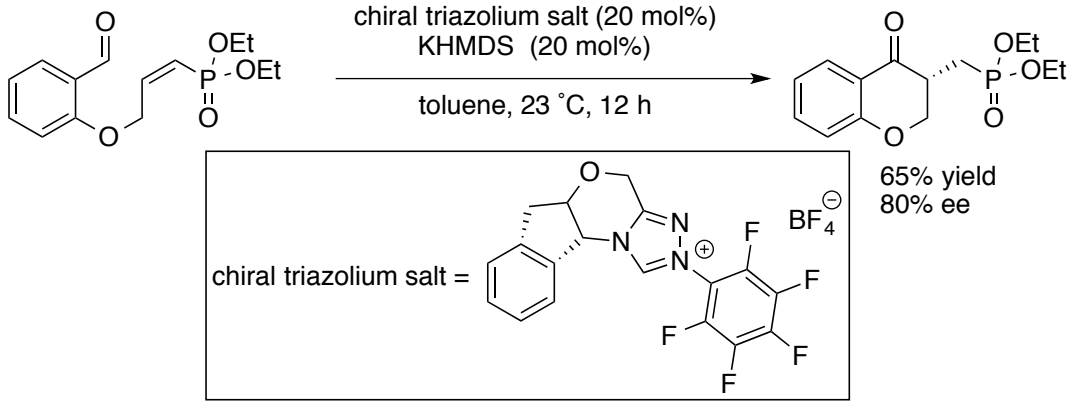
A first example of catalytic asymmetric 1,4-additions using unactivated alkenyl phosphonates was reported by Hayashi *et al.* They reported Rh-catalyzed asymmetric 1,4-addition reactions of arylboroxines with alkenyl phosphonates to afford the optically active β-aryl phosphonates in high yields with excellent enantioselectivities (**Scheme 1-2-1**).[15]

Scheme 1-2-1. Rh-catalyzed asymmetric 1,4-addition reactions of arylboroxines



In 2009, Rovis *et al.* reported catalytic asymmetric intramolecular Stetter-type reactions of alkenyl phosphonates bearing aldehyde moieties (**Scheme 1-2-2**).[16]

Scheme 1-2-2. Catalytic asymmetric intramolecular Stetter reactions of vinylphosphonate



As shown above, catalytic asymmetric 1,4-addtion reactions using unactivated alkenyl phosphonate have not been so much explored, and there is still a room for improvement from the viewpoint of atom economy and reaction efficiency. Therefore, alkenyl phosphonates were chosen and investigated as possible electrophiles for the strong base-catalyzed asymmetric 1,4-addition reactions of weakly acidic compounds based on "Product base" strategy.

1-3 以下の節については、5年以内に雑誌等で刊行予定のため、非公開

1-6 Conclusion

For development of the catalytic asymmetric direct-type 1,4-addition reactions of weakly acidic compounds with other applicable electrophiles than α,β-unsaturated amides, KHMDS-catalyzed 1,4-addtion reactions of several kinds of combinations of pronucleophiles and electrophiles were investigated. It was found that the proper difference of acidity between the pronucleophiles and the products, whose acidity depended on structure of the electrophiles, was crucial for the catalytic reaction, and when the acidity of the products was appropriately higher (4-6 as pK_a values) than that of the pronucleophiles, the catalytic reaction proceeded smoothly.

(5 年以内に雑誌等で刊行予定のため、該当箇所に当たる内容を一部略)

1-7 References

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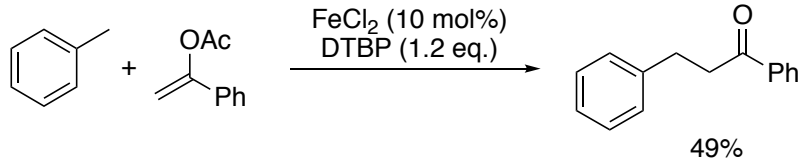
Chapter 2

Alkyl Potassium-catalyzed Addition Reactions of Alkylarenes with Alkenes

2-1 Background

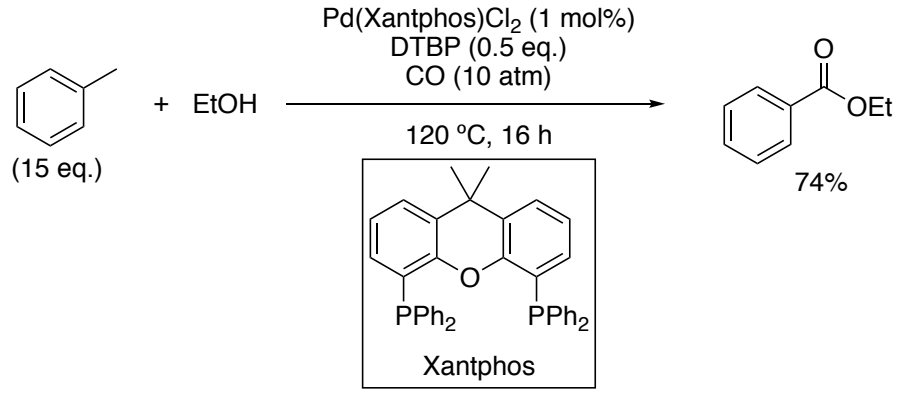
Catalytic direct C–H functionalization of inert C–H bond toward C–C bond formation is among the most efficient methods in organic synthesis from the viewpoint of step and atom economy.[1] Particularly, direct C–H functionalization using petroleum-derived materials such as alkylarenes, alkenes and aromatic compounds[2] is an attractive method because these compounds have advantageous features for feedstocks of organic syntheses: (1) Inexpensive; (2) Stable; (3) Easy-to-handle; (4) Mass-productive. Among them, catalytic benzylic C(sp^3)–H functionalizations using alkylarenes can be considered as ideal benzylation reactions of organic molecules compared to conventional methods using pre-activated benzylation reagents such as benzyl halides. However, compared to recent excellent development of catalytic aromatic and vinyl C(sp^2)–H functionalization of inert aromatic compounds and alkenes, catalytic benzylic C(sp^3)–H functionalization using unactivated alkylarenes such as toluene and xylene have not been so much explored.[3] One of the general approachs for the catalytic reactions of them is a radical-mediated process. It is known that a benzyl radical can be generated from an alkelarene bearing a benzylic hydrogen via a homolytic C–H bond cleavage by a radical species;[4] however, control of reactivity and selectivity of radical reactions of alkelarenes were normally hard.[4] To control them, a transition metal as a catalyst plays a key role for the reaction. For example, in 2009, Gan and Shi *et al*. reported Fe-catalyzed addition reactions of alkylarenes with vinyl acetates (**Scheme 2-1-1**).[5] In this reaction, benzylic radicals generated by C–H abstractions of benzylic hydrogens attached to iron catalysts, followed by addition reactions to alkenes and deacylation to form the product.[6]

Scheme 2-1-1. Fe-catalyzed addition reaction of toluene with vinyl acetate



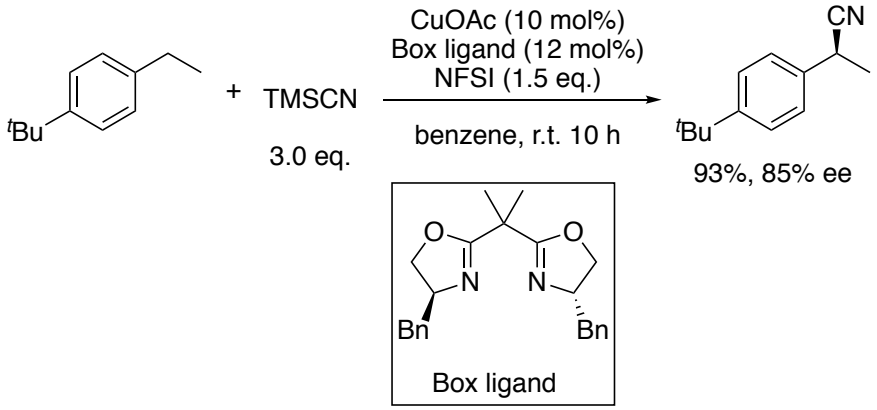
Not only the addition reactions with alkenes, but also the other reactions have been developed. For example, Huang *et al*. reported Pd-catalyzed oxidative carbonylation reactions of alkylarenes using CO. (**Scheme 2-1-2**).[7] In this reaction, palladium species also caught benzylic radicals to form benzyl palladium intermediate, then carbonylation with CO took place to form the product.

Scheme 2-1-2. Pd-catalyzed carbonylation reaction of toluene using CO



Based on a similar mechanism, many kinds of reactions such as acylation reactions,[8] arylation reactions [9] and so on[8] have been achieved. Furthermore, Cu-catalyzed enantioselective cyanation reactions of alkylarenes were developed by Stahl and Liu *et al* (**Scheme 2-1-3**).[10]

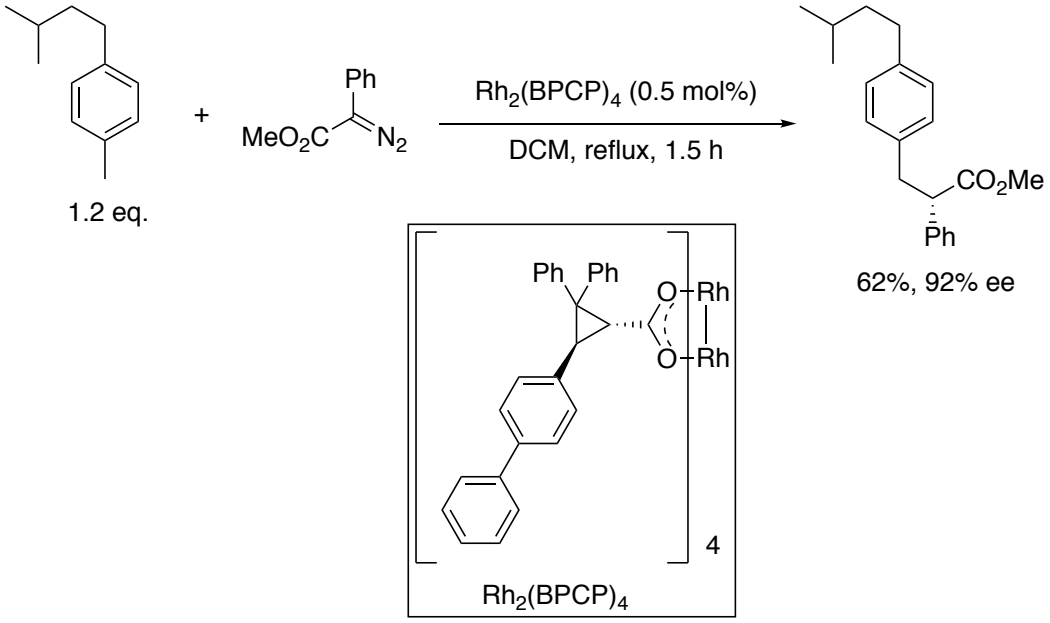
Scheme 2-1-3. Cu-catalyzed enantioselective cyanation reaction of alkylarene



As shown above, the combination of radical reactivity and transition metal catalysis is a powerful tool for benzylic C–H functionalization of alkylarenes. However, stoichiometric amounts of reagents (e.g. oxidants, radical initiators) and/or precious metals as catalysts are generally required for the reactions. Recently, photocatalytic system for the benzylic C–H functionalization have been investigated,[11] while harmful UV irradiation are normally required, and the scope of reactions were still narrow.

One of the other methods for benzylic C–H fuctionalizations is a benzylic C–H activation via a carbine insertion.[12] Although the asymmetric variants of the reaction have been achieved (**Scheme 2-1-4**),[12f] precursors of carbene intermediates, normally diazo compounds are required for the starting materials, and also precious metals such as rhodium and iridium as catalysts are needed.

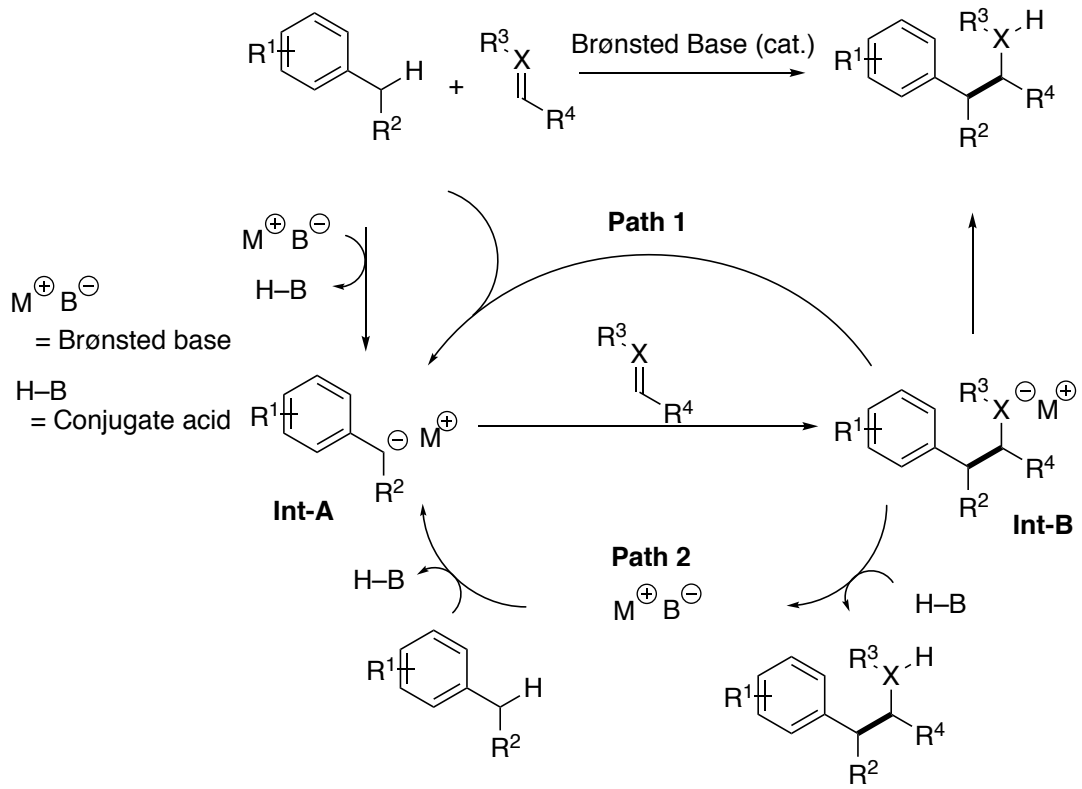
Scheme 2-1-4. Asymmetric carbene insertion of alkylarene



In contrast to these reactions shown above, Brønsted base-catalyzed benzylic C–H functionalizations of alkelarenes would be ideal methods for the reactions because transition metal-free, mild and highly atom-economical reactions could be achieved.[13] However, because of low acidity of a benzylic hydrogen of an alkylarene (pK_a in DMSO ~43),[14] Brønsted base-catalyzed benzylic C–H functionalizations of alkelarenes have not been so much investigated compared to the reactions using much more acidic pronucleophiles such as malonates, ketones and so on. As mentioned in Chapter 0, our group have developed strong Brønsted base-catalyzed C–C bond forming reactions by focusing on the basicity of the reaction intermediates, then it was hypothesized that this strategy could be employed for catalytic benzylic C–H functionalizations of alkelarenes. Proposed catalytic cycle is shown in **Scheme 2-1-5**. Firstly, a strong Brønsted base catalyst deprotonated a benzylic hydrogen of an alkylarene to form a highly nucleophilic benzylic anion **Int-A**. Next, an addition reaction of **Int-A** to C–X double bond took place to produce an anionic intermediate **Int-B**, which was designed to possess strong Brønsted basicity. Then, there were possible two pathways (**Path 1** and **2**). In **Path 1**, a strongly basic reaction intermediate **Int-B** deprotonated a benzylic hydrogen of an alkylarene directly to afford the product, and a benzylic anion **Int-A** was again produced. In **Path 2**, a strongly basic reaction intermediate **Int-B** deprotonated a hydrogen of the conjugate acid of the catalyst to afford the product, and a strong Brønsted base catalyst was regenerated. Therefore, the desired C–C bond formation using alkylarenes could be achieved in the presence of a catalytic amount of a strong Brønsted base catalyst. The key for the catalytic cycle was seemed to be strong basicity of a Brønsted base species and the reaction intermediate enough to deprotonate a benzylic hydrogen of an alkylarene

efficiently.

Scheme 2-1-5. Proposed catalytic cycle



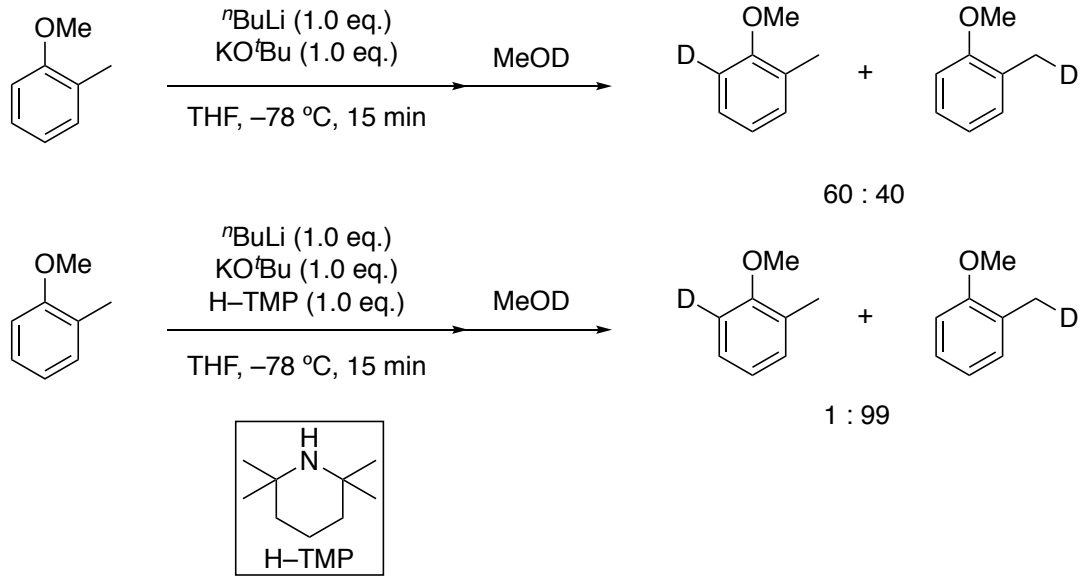
As for a strong Brønsted base catalyst to deprotonate a benzylic hydrogen of an alkylarene, it is known that mixtures of an alkyllitium and a potassium alkoxide, called Lochmann-Schlosser base, can deprotonate it to form a benzylic anionic species effectively.[15] A first example of the deprotonation was reported in 1987 by Lochmann *et al*. In this reaction, mixtures of 2-ethylhexyllithium and potassium *tert*-pentoxide deprotonated a benzylic hydrogen of toluene to form a benzyl potassium as a precipitate (**Scheme 2-1-6**).[15b]

Scheme 2-1-6. First example of deprotonation of toluene by Lochmann-Schlosser base

Although Lochmann-Schlosser bases effectively deprotonate benzylic hydrogens of alkylarenes, undesired addition of alkyl anions and undesired aromatic C(sp^2)–H deprotonations are sometimes problematic. Recently, O'Shea *et al*. reported that mixtures of ^{n}BuLi, KO^{t}Bu and tatramethylpiperadine (H–TMP) showed high affinity toward

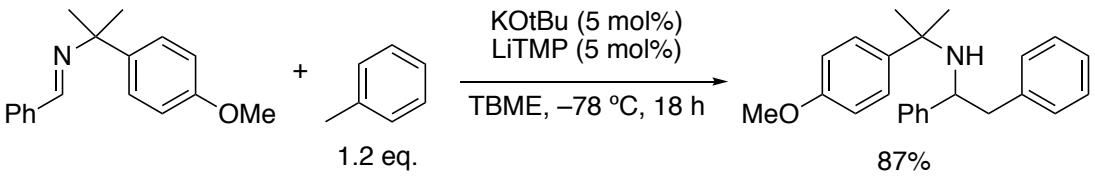
benzylic C(sp^3)–H deprotonation compared to aromatic C(sp^2)–H deprotonations.[16] For example, a deprotonation of 2-methoxyanisol by mixtures of ^{n}BuLi and KO^{t}Bu showed low selectivity between a benzylic deprotonation and a directed *ortho* metalation. On the other hand, ^{n}BuLi/KO^{t}Bu/H–TMP mixtures selectively deprotonated benzylic hydrogens of 2-methylanisole over directed *ortho* metalation (**Scheme 2-1-7**).[16a] In this paper, they suggested that this ^{n}BuLi/KO^{t}Bu/H–TMP mixtures generated mixed K/Li amides in *situ* to deprotonate kinetically more facile aromatic hydrogens *via* directed *ortho* metalation, then anion migrations took place to form benzylic anions.[17]

Scheme 2-1-7. Deprotonation of 2-methylanisole by ^{n}BuLi/KO^{t}Bu/H–TMP mixture



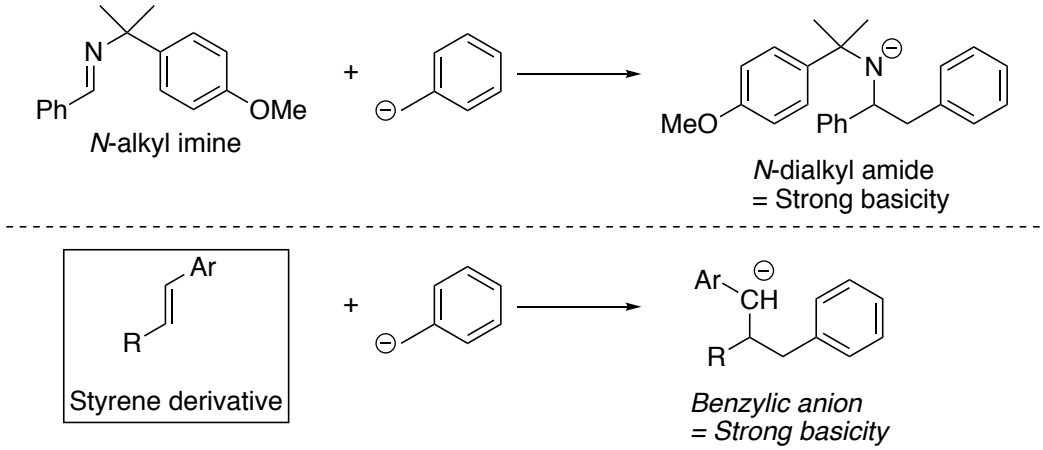
Based on these knowledges, recently, our group has developed KO^{t}Bu/LiTMP-catalyzed addition reactions of alkylarenes with *N*-alkylimines.[18] In this reaction, 5 mol% of KO^{t}Bu and LiTMP worked as strong Brønsted base catalysts to deprotonate benzylic hydrogens of toluene to promote catalytic addition reactions of toluene with *N*-alkyl imines (**Scheme 2-1-8**). Therefore, I decided to adopt this KO^{t}Bu/LiTMP mixtures as the first choice of the catalysts for the reactions.

Scheme 2-1-8. KO^{t}Bu/LiTMP-catalyzed addition reactions of alkylarenes with *N*-alkylimines



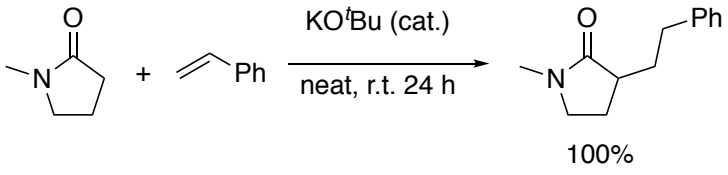
Another key factor of the catalytic cycle was the basicity of the reaction intermediate. As shown in **Scheme 2-1-8**, *N*-alkyl imines showed high reactivity for the catalytic reactions, because the reaction intermediates were *N*-dialkyl amides, which could have high basicity enough to deprotonate benzylic hydrogens. As for the other possible electrophiles for the catalytic reactions, I hypothesized that styrene derivatives could be used as appropriate electrophiles. After an addition of a benzyl anion to a styrene derivative, the reaction intermediate would be a secondary benzylic anion, and this could have enough basicity to deprotonate a benzylic hydrogen of toluene, thus the catalytic cycle could be proceeded (**Scheme 2-1-9**).

Scheme 2-1-9. Hypothesized reaction intermediate



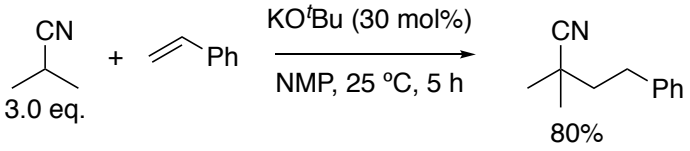
It is well known that stoichiometric addition reactions of highly nucleophilic species such as alkyllithium to styrene derivatives occur to afford corresponding carbometalated species (i.e. carbolithiation).[19] However, Brønsted base-catalyzed, especially alkaline metal base-catalyzed addition reactions of pronucleophiles to styrene derivatives have not been explored so much,[20] although the method could be considered as one of the most ideal alkylation reactions from the viewpoint of atom economy. One of the earliest examples of them was reported by Pines *et al.* in 1971.[21] In the presence of catalytic amounts of KO^{t}Bu, addition reaction of *N*-methyl-2-pyrrolidinone to styrene proceeded to afford the alkylated product in high yield, although the loading of catalysts was not mentioned (**Scheme 2-1-10**).

Scheme 2-1-10. KO^{t}Bu-catalyzed addition reaction of lactam with styrene



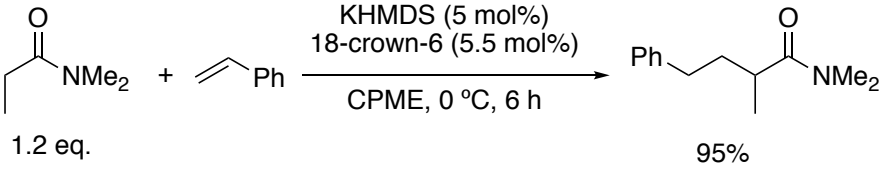
In 2000, Knochel *et al*. developed more general reaction system and expanded the scope of pronucleophiles to nitriles, ketones and so on.[22] In the reactions, highly coordinative solvents such as DMSO and NMP were crucial to enhance the reactivity of anionic species to achieve high yields of the products (**Scheme 2-1-11**).

Scheme 2-1-11. KO^{t}Bu-catalyzed addition reaction of nitrile with styrene



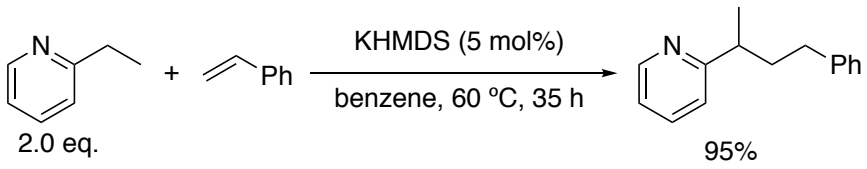
Recently, our group reported KHMDS-catalyzed addition reactions of esters and amides with styrene derivatives.[23] In the reactions, combination of KHMDS and 18-crown-6 realized lower catalyst loading for the reactions (**Scheme 2-1-12**).

Scheme 2-1-12. KHMDS-catalyzed addition reaction of amide with styrene



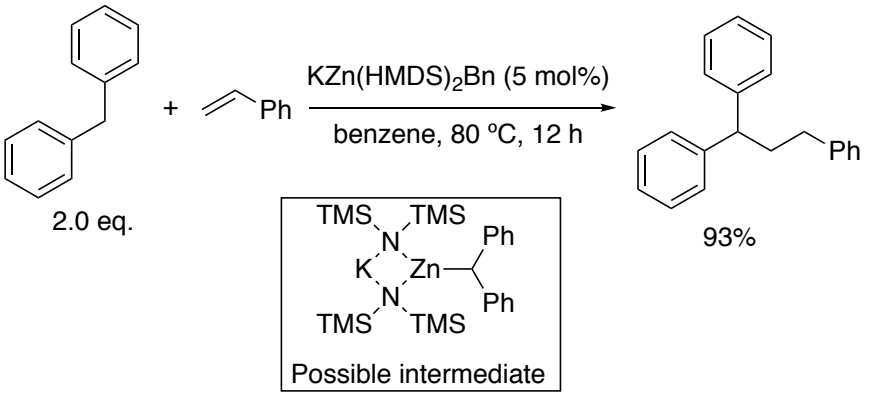
Guan et al. also reported KHMDS-catalyzed addition reactions of alkylpyridines with styrene derivatives in 2018 (**Scheme 2-1-13**).[24]

Scheme 2-1-13. KHMDS-catalyzed addition reactions of alkylpyridine with styrene



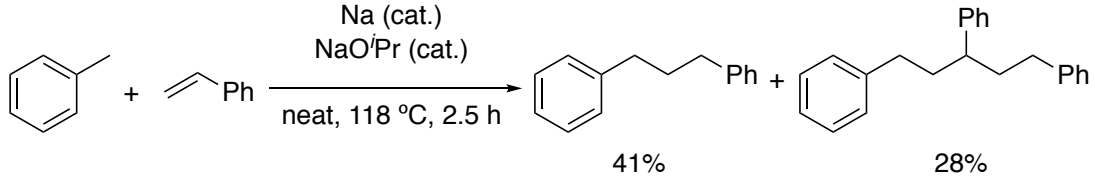
The same group also reported potassium-zincate-catalyzed addition reactions of diarylmethanes to styrene derivatives.[25] In this reaction, amide-bridged potassium/zinc complex effectively worked as catalytic species to suppress the undesired oligomerization of styrenes (**Scheme 2-1-14**).[26]

Scheme 2-1-14. potassium-zincate-catalyzed addition reactions of diarylmethanes to styrene derivatives



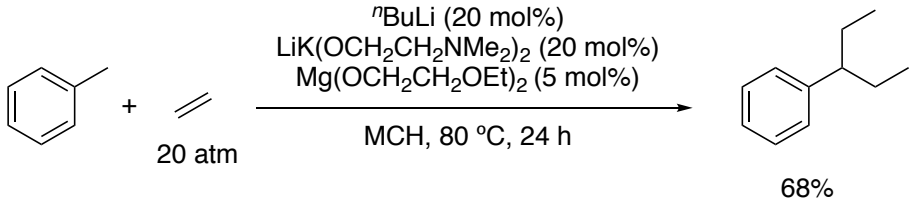
On the other hand, a few examples of Brønsted base-catalyzed addition reactions of alkylarenes bearing no activating functionality such as toluene and xylene to alkenes were reported, although synthetically attractive complex hydrocarbon skeletons could be efficiently synthesized.[27] In 1958, Pines *et al*. reported that, in the presence of catalytic amounts of metal sodium and NaO^{i}Pr, the addition reaction of toluene with styrene took place to form the product in moderate yield, although relatively harsh condition was required, and undesired byproduct formation occurred (**Scheme 2-1-15**).[28]

Scheme 2-1-15. Na/NaOiPr-catalyzed addition reaction of toluene to styrene



Screttas *et al*. reported that mixtures of ^{n}BuLi, LiK(OCH$_2$CH$_2$NMe$_2$)$_2$ and Mg(OCH$_2$CH$_2$OEt)$_2$ can catalyzed double alkylations of alkylarens using ethylene gases to form highly hindered aromatic compounds (**Scheme 2-1-16**).[29] They claimed that the magnesium alkoxide enhanced solubility of the catalytic species in the system to afford the desired hindered alkylarenes in good yield, while the scope with respect to alkenes were only ethylene, and harsh reaction condition was needed.

Scheme 2-1-16. Mixed base-catalyzed double alkylation of toluene

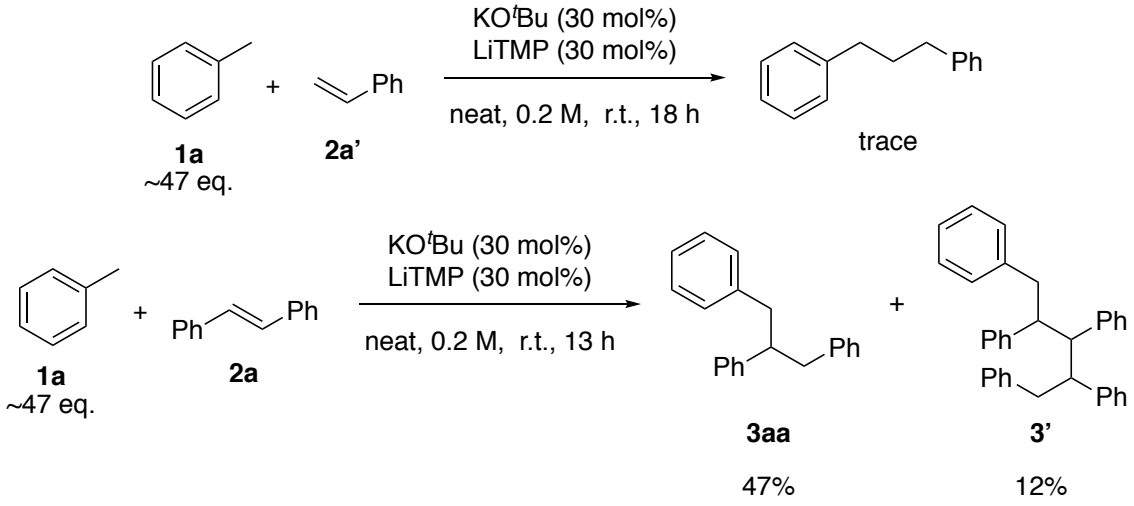


As shown above, reported reactions have some drawbacks of narrow scope, harsh condition and low yield; thus, it is worth developing more efficient Brønsted base-catalyzed addition reactions of alkylarenes with styrene derivatives.

2-2 Optimization of Reaction Conditions

The initial investigation began with a catalytic addition reaction of toluene **1a** with styrene **2'** as an electrophile in the presence of 30 mol% of KO^{t}Bu and LiTMP as a strong Brønsted base catalyst; however, only a trace amount of the desired product was observed, and oligomers derived from styrene were formed (**Scheme 2-2-1**, top). To suppress the oligomerization of styrene, sterically hindered β-phenyl styrene, called *trans*-stilbene **2a**, was subjected for the catalytic reaction to afford the desired adduct **3aa** in 47% yield, and also byproduct **3'** was observed in 12% yield (**Scheme 2-2-1**, bottom). It is noteworthy that there is no example of Brønsted base-catalyzed addition reactions using β-substituted styrene derivatives, as far as I know, probably due to steric hindrance of them.

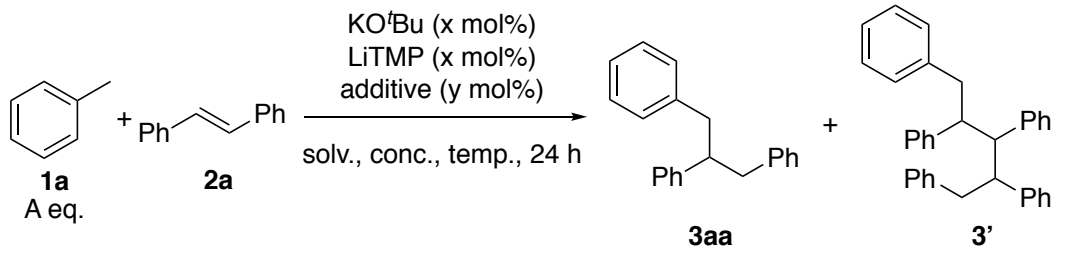
Scheme 2-2-1. Initial investigations



To improve the reactivity and the selectivity of the reaction, optimization of reaction conditions was conducted (**Table 2-2-1**). At first, 30 mol% of TMEDA (*N*,*N*,*N*′,*N*′-tetramethylethylenediamine) was added to the reaction as a ligand to enhance the reactivity, then the desired product **3aa** was obtained in 86% yield, and also the formation of byproduct **3'** was suppressed (entry 2). This enhancement of the reactivity and selectivity would be due to a deaggregation of the base catalyst.[30] The reaction in the presence of 10 mol% of catalysts proceeded smoothly to afford the product without any loss of reactivity (entry 3). Addition of 10 mol% of PMDTA (*N*,*N*,*N*′,*N*′′,*N*′′-pentamethyldiethylenetriamine) instead of TMEDA slightly improved both the yield and selectivity (entry 4). Next, in order to reduce the amount of toluene, several solvents were tested for the catalytic reactions (entries 5-7), then the reaction in CPME as a solvent gave the best selectivity between the product **3aa** and byproduct **3'**. The catalytic reaction at 0 ºC under concentrated condition (0.4 M) showed higher reactivity and selectivity (entry 8), and also the increasing the loading of PMDTA (20 mol%) was effective for the reaction

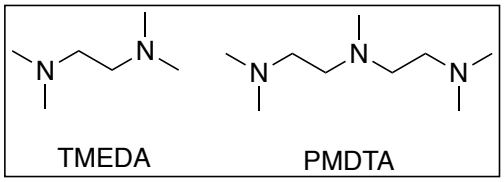
to afford the desired product in 98% yield probably because the deaggregation effect mentioned before was enhanced (entry 9). The reaction could be catalyzed by 5 mol% of KO^{t}Bu, LiTMP and 10 mol% of PMDTA under much higher concentration (0.8 M) to afford the desired product in 88% yield (entry 10). Therefore, the reaction condition in entry 10 was chosen as the optimal one.

Table 2-2-1. Optimization of reaction conditions



entry	A (eq.)	x (mol%)	additive	y (mol%)	solv.	conc. (M)	temp. (ºC)	3aa[a] (%)	3'[a] (%)
1[b]	~47	30	--	0	(neat)	0.2	r.t.	47	12
2[b]	~47	30	TMEDA	30	(neat)	0.2	r.t.	86	4
3	~47	10	TMEDA	10	(neat)	0.2	r.t.	86	4
4	~47	10	PMDTA	10	(neat)	0.2	r.t.	88	2
5	4.0	10	PMDTA	10	Heptane	0.2	r.t.	70	10
6	4.0	10	PMDTA	10	Et_2O	0.2	r.t.	44	6
7	4.0	10	PMDTA	10	CPME	0.2	r.t.	50	6
8	4.0	10	PMDTA	10	CPME	0.4	0	86	3
9	4.0	10	PMDTA	20	CPME	0.4	0	98	2
10	4.0	5	PMDTA	10	CPME	0.8	0	88	4

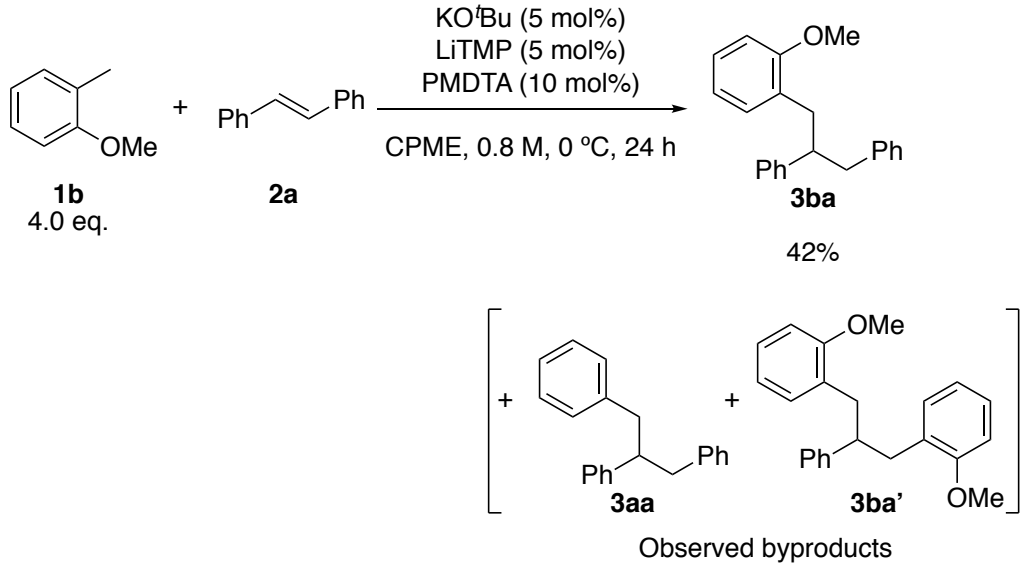
[a] Yield was determined by ^{1}H NMR analysis of the crude mixture. [b] Reaction time was 13 h.



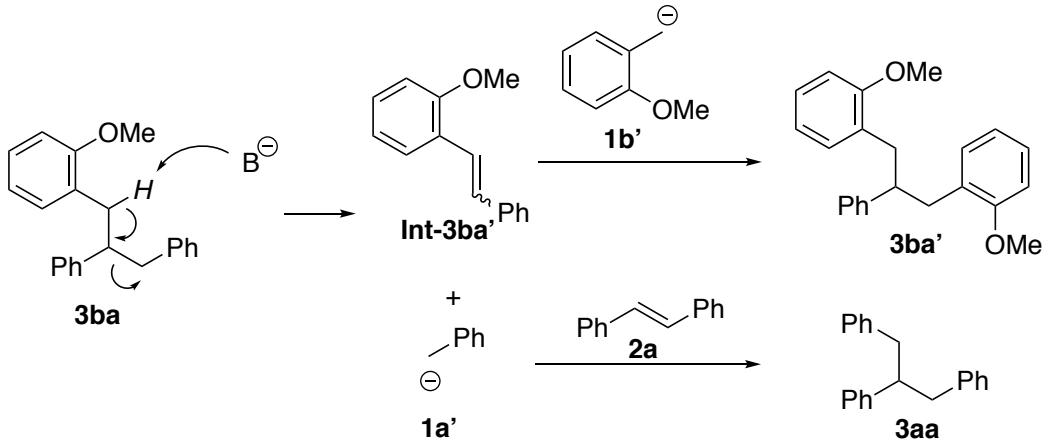
With this optimal reaction condition in hand, the catalytic addition reaction of *o*-methoxytoluene **1b** with **2a** was conducted. However, although **2a** was fully consumed, the desired product **3ba** was obtained in only 42% yield, and many kinds of byproducts were observed in the crude mixture of the reaction (**Scheme 2-2-2**). By ^{1}H NMR analysis of these byproducts, **3aa** and **3ba'** shown in **scheme 2-2-2** were found to be produced as main byproducts in the reaction of *o*-methoxytoluene. Assumed reaction mechanism of byproducts formation was shown in **scheme 2-2-3**. At first, deprotonations of the benzylic

hydrogens of *o*-methoxy aryl moiety of the products occurred, then the elimination took place to form benzyl anions of toluene **1a'** and *o*-methoxy aryl substituted stilbenes **Int-3ba'**. This substituted stilbenes **Int-3ba'** were attacked by second benzylic anions **1b'** which were produced by deprotonation of **1b** to form the byproducts **3ba'**. On the other hand, benzyl anions of toluene **1a'** reacted with another stilbenes **2a** to afford the byproduct **3aa**.[28b]

Scheme 2-2-2. Catalytic reaction of *o*-methoxytoluene **1b**

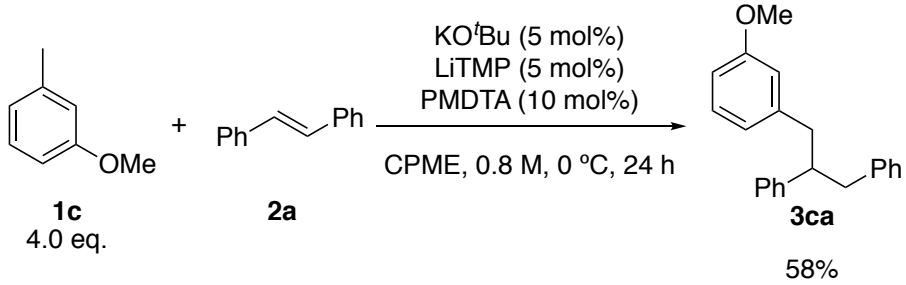


Scheme 2-2-3. Possible reaction mechanism of the byproducts formation



Similar phenomena were also observed in the catalytic reactions of *m*-methoxytoluene **1c** with **2a** to afford the products **3ca** in moderate yield (**Scheme 2-2-4**).

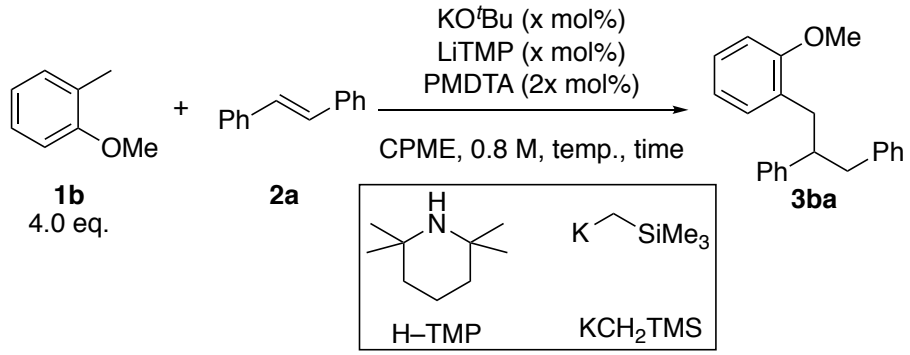
Scheme 2-2-4. Reaction of *m*-methoxytoluene



1c 4.0 eq. **2a** **3ca** 58%

To suppress the byproduct formation and improve the yield of the desired product, further optimization of reaction conditions using *o*-methoxytoluene **1b** as pronucleophiles was carried out (**Table 2-2-2**). First, the reaction of **1b** with **2a** was conducted in the presence of 10 mol% of KO^{t}Bu, LiTMP and 20 mol% of PMDTA as catalysts to afford the desired product in 32% yield, and many byproducts were formed as mentioned before (entry 1). The reaction without PMDTA did not give any product or byproducts because of low reactivity of the catalysts (entry 2). The reaction using NaO^{t}Bu instead of KO^{t}Bu also did not gave any desired product or byproduct probably because of low basicity of sodium-derived catalysts (entry 3). To suppress the deprotonation of benzylic hydrogens of the products, which might be a trigger of the byproduct formation shown in **scheme 2-2-3**, 20 mol% of H–TMP was added to the reaction, then the yield was improved to 44% (entry 4). Lower reaction temperature (–10 ºC) was also effective to suppress the byproduct formation to give the product in 57% yield. However, the byproduct formation was still not enough suppressed. Interestingly, the reaction using 10 mol% of alkyl potassium (KCH_2TMS)[31] instead of KO^{t}Bu and LiTMP gave the desired product in 79% yield (83% yield as isolated yield), and the formation of byproduct was suppressed (entry 6).

Table 2-2-2. Optimization of reaction conditions using **1b**

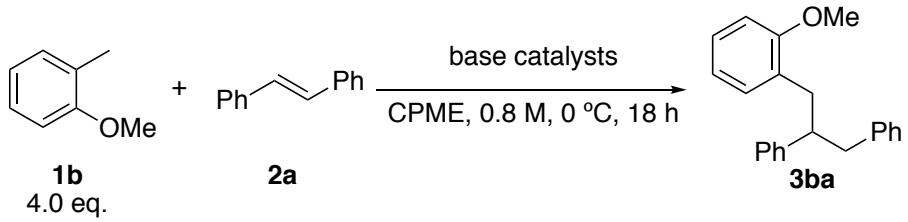


entry	x (mol%)	temp. (ºC)	time (h)	Yield[a] (%)
1	10	0	18	32
2[b]	5	0	24	trace
3[c]	5	0	24	trace
4[d]	10	0	18	44
5[d]	10	–10	18	57
6[e]	10	0	18	79 (83)[f]

[a] Yield was determined by ^{1}H NMR analysis of the crude mixture. [b] PMDTA was not added. [c] NaO^{t}Bu was used as a catalyst instead of KO^{t}Bu. [d] 20 mol% of H–TMP was added. [e] KCH_2TMS was used as a catalyst instead of KO^{t}Bu and LiTMP. [f] Isolated yield was shown in the parenthesis.

Next, further investigation about base catalysts was conducted (**Table 2-2-3**). The addition of 10 mol% of H–TMP to the reaction was not so much effective for the improvement of the yield (entry 3). On the other hand, in the presence of 10 mol% of KCH_2TMS, LiTMP and 20 mol% of PMDTA as base catalysts, lower yield of the desired product and enhanced byproduct formation were observed (entry 4). Similarly, in the presence of 10 mol% of KCH_2TMS, LiO^{t}Bu and 20 mol% of PMDTA as base catalysts, again lower yield of the desired product and enhanced byproduct formation were observed (entry 5). From these observations, it would be said that the presence of lithium cations in the reaction facilitated the byproduct formations, probably because the aggregation state of catalyst was altered by lithium cations, then the deprotonation of benzylic hydrogen of the product was accelerated to form byproducts via elimination of benzylic anions of toluene. Fortunately, it was found that, in the presence of only 2 mol% of KCH_2TMS and PMDTA, the reaction proceeded smoothly to afford the target product in 78% isolated yield (entry 6). Therefore, this reaction condition in entry 6 was chosen as the optimal one.

Table 2-2-3. Screening of base catalysts



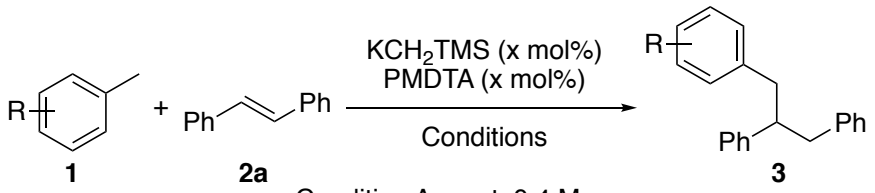
entry	base catalysts	Yield[a] (%)
1	KO^{t}Bu (10 mol%) LiTMP (10 mol%) PMDTA (20 mol%)	32
2	KCH_2TMS (10 mol%) PMDTA (10 mol%)	79
3	KCH_2TMS (10 mol%) H–TMP (10 mol%) PMDTA (10 mol%)	81
4	KCH_2TMS (10 mol%) LiTMP (10 mol%) PMDTA (20 mol%)	26
5	KCH_2TMS (10 mol%) LiO^{t}Bu (10 mol%) PMDTA (20 mol%)	25
6	KCH_2TMS (2 mol%) PMDTA (2 mol%)	86 (78)[b]

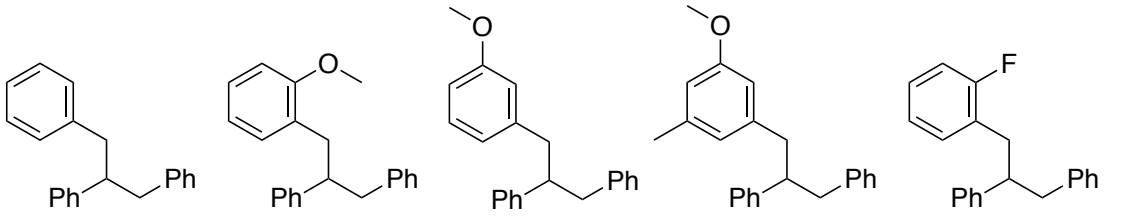
[a] Yield was determined by ^{1}H NMR analysis of the crude mixture. [b] Isolated yield was shown in the parenthesis.

2-3 Substrate Scope

The substrate scope for the catalytic addition reactions of alkylarenes with β-substituted styrene derivatives were conducted under the optimal reaction condition mentioned above. At first, various alkylarenes were subjected for the catalytic reactions with *trans*-stilbene **2a** (**Scheme 2-3-1**). For the reactions of relatively volatile and inexpensive alkylarenes such as toluene and xylenes, the reactions were conducted in neat condition (Condition A), and for the reactions of the other alkylarenes such as methoxytoluenes, CPME was used as a solvent (Condition B). The catalytic reaction of toluene **1a** with **2a** was conducted in the presence of 1 mol% of KCH_2TMS and PMDTA under condition A to afford the desired product **3aa** in 87% yield. The reaction of *o*-methoxytoluene **1b** proceeded under condition B to afford the product **3ba** in 78% yield. Similarly, the reaction of *m*-methoxytoluene **1c** proceeded smoothly in the presence 1 mol% of catalysts under condition B to afford the desired product **3ca** in 86% yield. Unfortunately, the reaction of *p*-methoxytoluene did not work well because of lower acidity of benzylic hydrogen of *p*-methoxytoluene. Then, di-substituted toluene was also tested for the reaction. While the reaction of 3,5-dimethylanisole **1d** showed sluggish reactivity compared to the reaction of *m*-methoxytoluene **1c**, the reaction of **1d** proceeded in the presence of 5 mol% of catalysts to give the desired product **3da** in 66% yield. Fluoro-substituted toluenes were also subjected for the reaction. Because of low nucleophilicity of benzyl anions derived from them and low durability of them under strongly basic conditions (Formation of benzyne or *ipso*-substitution would be possible.), higher catalyst loading (10 mol%) and lower reaction temperature (–10 ºC) were required for the reactions of them to afford the desired compounds **3ea** and **3fa** in 46% and 76% yield, respectively. The reactions of xylenes were conducted under Condition A. *o*- and *m*-xylene showed good reactivity for the reaction to afford the desired compounds **3ga** and **3ha** in 90% and 84% yield, respectively. While the reaction of *p*-xylene showed sluggish reactivity, higher reaction temperature (25 ºC) and prolonging reaction time (42 h) was effective to afford the product **3ia** in 64% yield. The reaction of *p*-isopropyltoluene showed also sluggish reactivity, then relatively high catalyst loading was required to give the desired product **3ja** in 58% yield. Ethylbenzene was also subjected for the reaction to afford the desired product **3ka** in 99% yield with moderate diastereoselectivity (67:33).

Scheme 2-3-1. Substrate scope with respect to pronucleophiles





Condition A
x = 1, 0 ˚C, 24 h

3aa 87%

Condition B
x = 2, 0 ˚C, 18 h

3ba 78%

Condition B
x = 1, 0 ˚C, 18 h

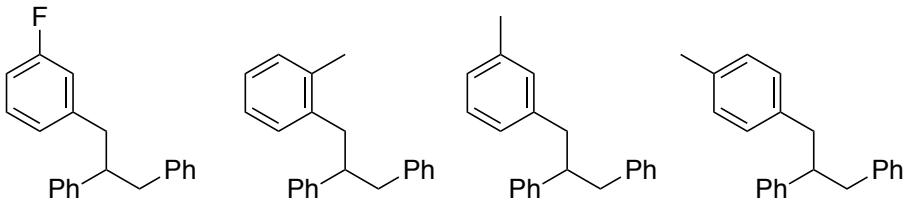
3ca 86%

Condition B
x = 5, 0 ˚C, 18 h

3da 66%

Condition B
x = 10, –10 ˚C, 24 h

3ea 46%



Condition B
x = 10, –10 ˚C, 24 h

3fa 76%

Condition A
x = 2, 0 ˚C, 24 h

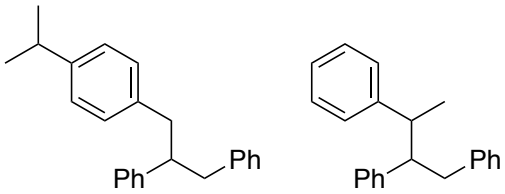
3ga 90%

Condition A
x = 1, 0 ˚C, 24 h

3ha 84%

Condition A
x = 2, 25 ˚C, 42 h

3ia 64%



Condition B
x = 5, 0 ˚C, 18 h

3ja 58%

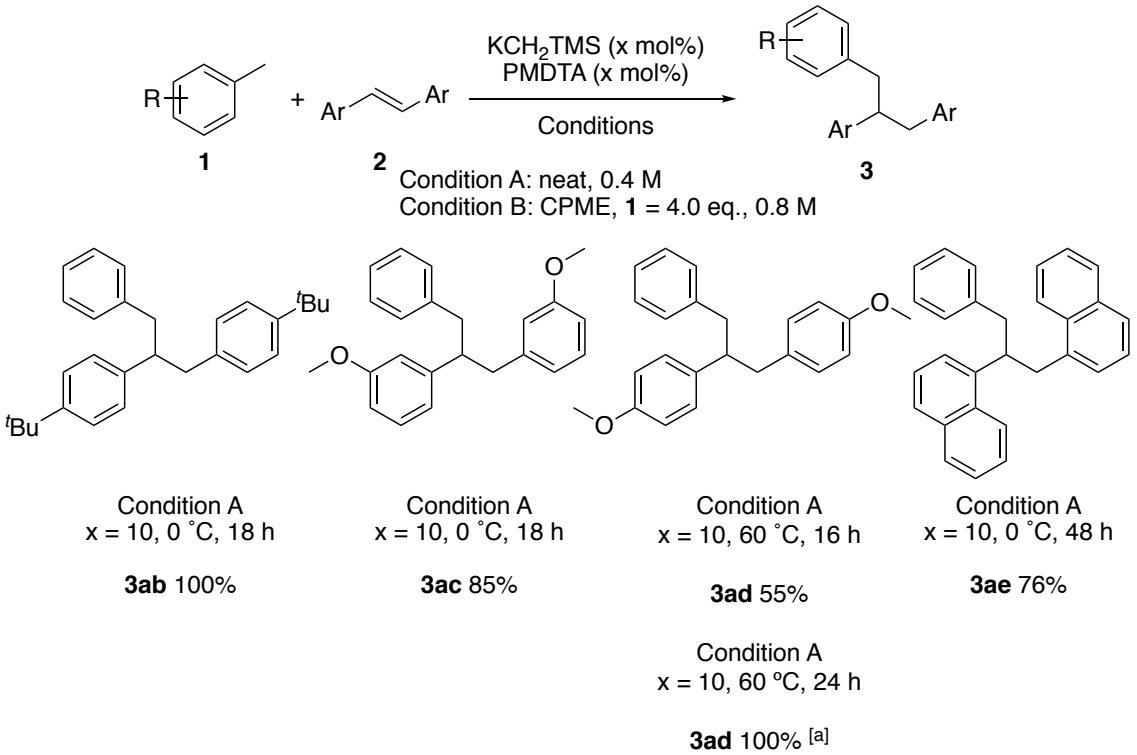
Condition A
x = 10, 0 ˚C, 24 h

3ka 99% dr 67:33

Next, substrate scope with respect to symmetrical stilbene derivatives was focused (**Scheme 2-3-2**). Under Condition A, the reactions of toluene **1a** with bis(*p*-^{t}Bu) and bis(*m*-methoxy) substituted stilbenes proceeded smoothly in the presence of 10 mol% of catalysts to afford the desired products **3ab** and **3ac** in 100% and 85% yield, respectively. On the other hand, bis(*p*-methoxy) stilbene **2d** showed much lower reactivity compared to the other electrophiles probably because of low electrophilicity of **2d.** Indeed, the

reaction of **2d** was conducted at 60 ºC to afford the desired product **3ad** in 55% yield. Fortunately, KO^{t}Bu and LiTMP as base catalysts instead of KCH_2TMS was effective for the reaction at high temperature to afford the product in almost quantitative yield. The reason was assumed that, at higher temperature, stability of reactive species produced by KO^{t}Bu and LiTMP was higher than that by KCH_2TMS. 1-Naphthyl substituted alkene **2e** exhibited sluggish reactivity due to low basicity of the reaction intermediate, then prolonging reaction time was needed to give the product **3ae** in 76% yield.

Scheme 2-3-2. Substrate scope with respect to symmetric electrophiles

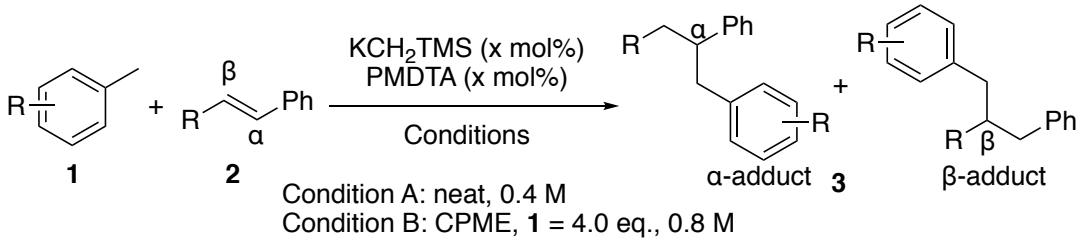


[a] KO^{t}Bu and LiTMP was used instead of KCH_2TMS.

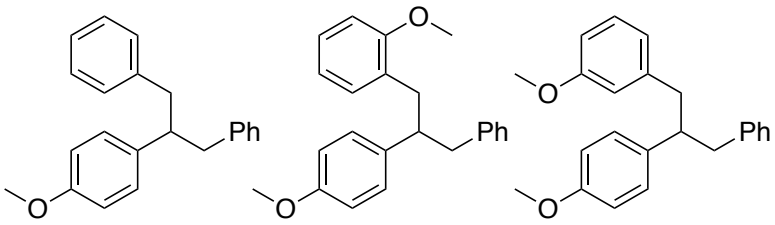
Next, substrate scope with respect to unsymmetrical electrophiles was investigated (**Scheme 2-3-3**). As for the reaction using unsymmetrical electrophiles, there were possible two regioisomers, α-adduct and β-adduct as shown in **Scheme 2-3-3**. The reaction of toluene **1a** with *p*-methoxy substituted stilbene **2f** was conducted to afford the desired product **3af** in 96% yield with high β selectivity (α∶β = 1:12). This high β selectivity was consistent with the reactivity difference between non-substituted stilbene **2a** and *p*-methoxy substituted stilbene **2d** as shown above (**Scheme 2-3-2**). The reaction of substituted toluene, *o*-methoxytoluene **1b** and *m*-methoxytoluene **1c** with **2f** were also conducted in CPME as solvent (Condition B) to afford the desired products **3bf** and **3cf** in 87% and 97% yield, respectively with high β selectivities. On the other hand, the reaction using *o*-methoxy substituted stilbene **2g** gave the product in 89% yield with moderate α selectivity (α∶β = 2.1:1), probably because of the coordination ability of *o*-

methoxy moiety or steric hindrance of it. The reaction using 1-naphthyl substituted styrene **2h** showed sluggish reactivity, but high α selectivity was observed. Not only stilbene derivatives, but also β-alkyl substituted styrene derivatives were also examined for the reaction. Because of low reactivity and existence of relatively acidic allylic hydrogens on the electrophile, higher reaction temperature was required for the reaction using ^{n}Pr substituted styrene **2i** as electrophiles to afford the product **3ai** in 33% yield with high β selectivity. As mentioned above, KO^{t}Bu and LiTMP as base catalysts instead of KCH_2TMS was effective for the reaction at high temperature to afford the product in 72% yield with high β selectivity. Similarly, the reaction using ^{i}Pr substituted styrene **2j** in the presence of 20 mol% of KO^{t}Bu and LiTMP instead of KCH_2TMS gave the product in 34% yield with high β selectivity. From these investigation, it was assumed that the regioselectivity could be attributed by the stability of the reaction intermediate.

Scheme 2-3-3. Substrate scope with respect to asymmetric electrophiles



Condition A: neat, 0.4 M
Condition B: CPME, **1** = 4.0 eq., 0.8 M



Condition A
x = 5, 0 ˚C, 24 h

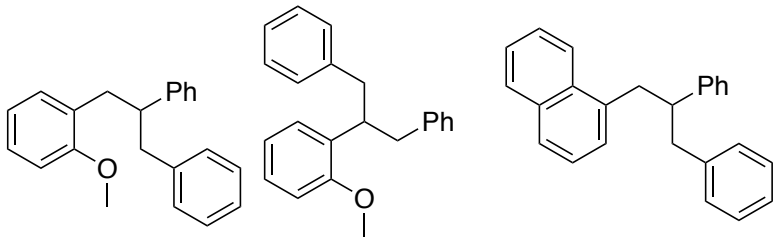
3af 96%, α:β = 1:12

Condition B
x = 5, 0 ˚C, 18 h

3bf 87%, α:β = 1:12

Condition B
x = 5, 0 ˚C, 18 h

3cf 97%, α:β = 1:10



3ba

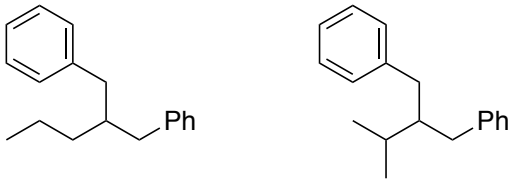
Condition A
x = 5, 0 ˚C, 24 h

89%, α:β = 2.1:1

3ag

Condition A
x = 10, 0 ˚C, 48 h

3ah 86%, α:β >20:1



Condition A
x = 20, 40 ˚C, 24 h

3ai 33%, α:β = 1:>20

Condition A
x = 10, 40 ˚C, 24 h

3aj 6%, α:β = 1:>20

Condition A
x = 20, 40 ˚C, 18 h

3aj 72%[a], α:β = 1:>20

Condition A
x = 20, 40 ˚C, 18 h

3aj 34%[a], α:β = 1:>20

[a] KO^{t}Bu and LiTMP was used instead of KCH_2TMS.

2-4 以下の節については、5年以内に雑誌等で刊行予定のため、非公開

2-7 Conclusion

The catalytic addition reactions of alkylarenes with alkenes have been developed by using a catalytic amount of alkyl potassium. It was found that β-substituted styrene derivatives were suitable electrophiles for strong base-catalyzed addition reactions of alkylarenes due to appropriate activation of C–C double bond and high basicity of the reaction intermediates. For the suppression of byproduct formation, alkyl potassium (KCH_2TMS) was effectively utilized for the reactions. Various substituted alkylarenes were applicable for the reactions to afford the desired hydrocarbons in moderate to high yields. The reactions using unsymmetrical electrophiles gave the products with moderate to high regioselectivities.

(5年以内に雑誌等に投稿予定のため、該当部分を一部略)

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Chapter 3

(本章については、5年以内に雑誌等で刊行予定のため、非公開)

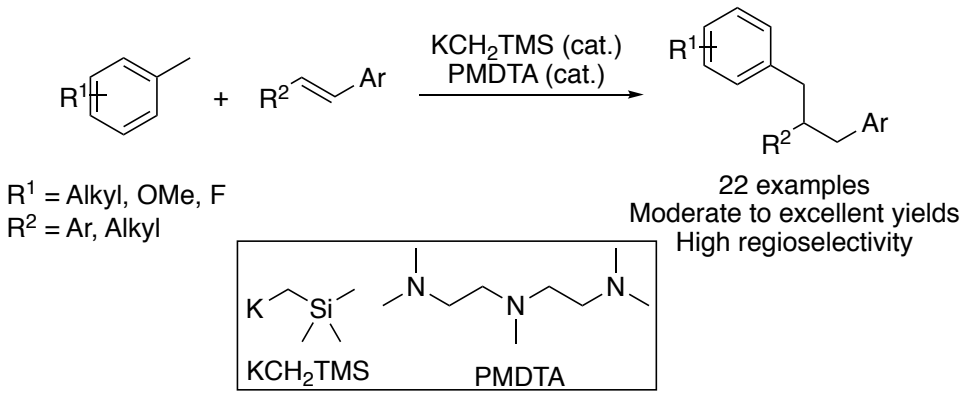
Summary

In my Ph.D. study, I have developed strong Brønsted base-catalyzed C–C bond forming reactions using less activated and unactivated alkenes as both electrophiles and pronucleophiles based on "Product base" strategy. By focusing on an inherent reactivity of a C–C double bond, I have achieved highly efficient and atom-economical, catalytic transformations of less activated substrates.

In Chapter 1, to find a mechanistic key point of the strong Brønsted base-catalyzed C–C bond forming reactions, several carbonyl compounds, which have different acidities, were reacted with several α,β-unsaturated carbonyl compounds, which have different electrophilicities, in the presence of catalytic amounts of KHMDS and 18-crown-6, and surveyed a relationship between combinations of substrates and reactivity. It was revealed that appropriate difference of the reactivity between pronucleophiles and electrophiles was crucial for the catalytic reactions. Specifically, when the acidity of the products was appropriately higher (4-6 as pK_a values) than that of the pronucleophiles, the catalytic reaction proceeded smoothly.

In chapter 2, I have investigated strong Brønsted base-catalyzed addition reactions of alkylarenes with less activated alkenes as electrophiles. For the catalytic reactions, the choice of strong base species was crucial to regulate both nucleophilicity and basicity of anionic intermediates. It was found that, in the presence of catalytic amounts of alkyl potassium (KCH_2TMS) and PMDTA as ligands, catalytic addition reactions of alkylarenes with β-substituted styrene derivatives proceeded to afford the desired materials in moderate to high yields with high regioselectivities. Several susbstrates bearing functional groups such as methoxy and fluoro group were found to be applicable substrates for the catalytic reactions (**Scheme 4-2**).

Scheme 4-2. Alkyl potassium-catalyzed addition reactions of alkylarenes with β-substituted styrene derivatives



From my Ph.D. study shown in this thesis, I have demonstrated a new possibility of highly atom economical, Brønsted base-catalyzed constructions of organic frameworks using inert compounds, especially inert alkenes.

(5 年以内に雑誌等で刊行予定のため、該当部分を一部略)

Experimental Section ~Chapter 1~

General Information

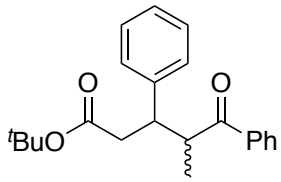
^{1}H, ^{13}C and ^{31}P NMR spectra were recorded with JEOL JNM-ECA500 and JNM-ECX600 spectrometers in $CDCl_3$ unless otherwise noted. Tetramethylsilane (TMS) served as internal standard (δ = 0 ppm) for ^{1}H NMR. $CDCl_3$ served as internal standard (δ = 77.0 ppm) for ^{13}C NMR. 80% H_3PO_4 served as internal standard (δ = 0) for ^{31}P NMR. IR spectra were measured with a JASCO FT/IR-4200 spectrometer. High-performance liquid chromatography was carried out using followed apparatuses; SHIMADZU LC-20AB (liquid chromatograph), SHIMADZU SPD-M20A (Photo diode array detector). Optical rotations were recorded on JASCO P-2100. Column chromatography was conducted on Silica gel 60N (spherical, neutral, Kanto Chem. Co., Inc.) and preparative thin-layer chromatography (PTLC) was carried out using Wakogel B-5F. Potassium bis(trimethylsilyl)amide (KHMDS) was purchased from Aldrich Co., Ltd.. 18-crown-6, **2a** and **2c** were purchased from Tokyo Chemical Industry Co., Ltd.. All solvents were distilled just before using in the presence of benzophenone and sodium. **2b**, **2d**, **2e**, **2f**, and **2g** were prepared form propionic anhydride and the corresponding alcohol or amines. **1a**, **1b** and **1c** were prepared form cinnamoyl chloride and the corresponding amide, alcohol and Grignard reagent, respectively. Unsaturated phosphonates **1d**, **1e**, **1f**, **1g**, **1h**, **1i**, and **1j** were prepared according to a reported method.[1] Chiral crown ethers **L1, L2, L3, L4, L5** and **L6** were synthesized from the corresponding BINOL-derivatives and the diols according to a literature.[2] Physical date of **L2** to **L6** were shown below. The yields of **3aa**,[3] **3ab**,[2] **3ba**,[2] **3bb**,[4] **3cb**[4] and **3cc**[4] were determined by ^{1}H HMR analysis of the crude mixture without isolation. The relative configuration of the products was assigned by an analogy of the 1,4-adducts of the previous study.[3]

Typical procedure of KHMDS/18-crown-6-catalyzed 1,4-addition reaction of ketone 2c with unsaturated ketone 1c (Table 1-1-1)

KHMDS (6.0 mg, 3.0 x 10^{-2} mmol) and 18-crown-6 (9.1 mg, 3.4 x 10^{-2} mmol) were placed in a dried 5 mL reaction tube with septa inside a glove box filled with argon. The tube was cooled to –40 °C, then toluene (0.6 mL) was added. The reaction mixture was stirred for 1 h at the same temperature for catalyst preparation. After that, ketone **2c** (48.3 mg, 0.36 mmol) was added to the reaction mixture by syringe, then unsaturated ketone **1c** (56.5 mg, 0.30 mmol), which was put in another dried tube inside a glove box, was added to the tube through cannula with extra toluene (0.5 mL). The whole mixture was stirred for 18 h at –40 ºC. The reaction was quenched with H_2O (1.0 mL) and extracted with DCM (10 mL) for three times. The combined organic layers were dried over anhydrous Na_2SO_4. After filtration and concentration under reduced pressure, the crude product was obtained. The crude product was purified by silica-gel PTLC (DCM-hexane)

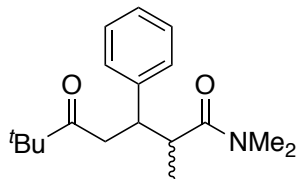
to afford the desired 1,4-adduct **3cc** in 98% yield (94.5 mg, 0.293 mmol, dr = 78:22).

***tert*-butyl 4-methyl-5-oxo-3,5-diphenylpentanoate (3bc, dr = 68:32)**; colorless oil;



HRMS (DART) calcd for $C_{22}H_{27}O_3$ $[M + H]^+$ 339.1960, found 339.1965; major isomer: ^{1}H NMR (600 MHz, $CDCl_3$) 8.01-8.00 (m, 2H), 7.59-7.18 (m, 8H), 3.77-3.75 (m, 1H), 3.55-3.53 (m, 1H), 2.64-2.60 (m, 1H), 2.48 (dd, 1H, *J* = 14.74, 10.77 Hz), 1.19 (s, 9H), 0.98 (d, 3H, *J* = 6.80 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 170. 7, 141.2, 136.8, 133.1, 18.7, 128.2, 128.1, 127.9, 126.7, 80.1, 45.5, 45.0, 40.4, 27.7, 16.6; minor isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.79-7.78 (m, 2H), 7.59-7.18 (m, 8H), 3.83-3.82 (m, 1H), 3.62-3.59 (m, 1H), 2.77 (dd, 1H, *J* = 14.74, 5.10 Hz), 2.64-2.60 (m, 1H), 1.24 (d, 3H, *J* = 6.80 Hz), 1.21 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 171.2, 136.7, 132.7, 128.4, 128.2, 128.0, 128.0, 126.5, 80.1, 46.0, 44.1, 38.1, 28.1, 14.7.

***N*,*N*,2,6,6-pentamethyl-5-oxo-3-phenylheptanamide (3ca, dr = 55:45)**; colorless oil;



HRMS (DART) calcd for $C_{18}H_{28}NO_2$ $[M + H]^+$ 290.2120, found 290.2121; major isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.28-7.13 (5H, m), 3.60 (1H, td, *J* = 8.59, 3.89 Hz), 3.09-2.97 (2H, m), 2.91 (3H, s), 2.81 (1H, dd, *J* = 17.18, 4.12 Hz), 2.76 (3H, s), 1.13 (3H, d, *J* = 6.87 Hz), 1.02 (9H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 175.0, 143.3, 128.2, 128.1, 126.3, 44.3, 42.5, 39.8, 37.2, 37.1, 35.5, 26.0, 16.5; minor isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.28-7.13 (5H, m), 3.50 (1H, td, *J* = 9.11, 3.89 Hz), 3.17-3.16 (1H, m), 3.09-2.97 (2H, m), 2.95 (3H, s), 2.94 (3H, s), 1.13 (3H, d, *J* = 6.87 Hz), 1.02 (9H, s), 0.95-0.94 (3H, m), 0.95 (9H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 175.3, 142.7, 128.2, 127.8, 126.4, 44.1, 44.1, 40.4, 40.0, 37.7, 35.6, 26.2, 14.3.

(5 年以内に雑誌等に刊行予定のため、該当部分を一部略)

Experimental Section ~Chapter 2~

General Information

^{1}H, ^{13}C and ^{19}F NMR spectra were recorded with JEOL JNM-ECA500 and JNM-ECX600 spectrometers in $CDCl_3$ unless otherwise noted. Tetramethylsilane (TMS) served as internal standard (δ = 0 ppm) for ^{1}H NMR, and $CDCl_3$ served as internal standard (δ = 77.0 ppm) for ^{13}C NMR. Benzotrifluoride (BTF, δ = –63.72) and C_6H_5F (δ = – 113.15 ppm) served as internal standard for ^{19}F NMR. IR spectra were measured with a JASCO FT/IR-4200 spectrometer. High-performance liquid chromatography was carried out using followed apparatuses; SHIMADZU LC-20AB (liquid chromatograph), SHIMADZU SPD-M20A (Photo diode array detector). Optical rotations were recorded on JASCO P-2100. Column chromatography was conducted on Silica gel 60N (spherical, neutral, Kanto Chem. Co.,Inc.) and preparative thin-layer chromatography (PTLC) was carried out using Wakogel B-5F. Potassium *tert*-butoxide (KO^{t}Bu) was purchased from Wako Pure Chemical Industrials, Ltd. Lithium 2,2,6,6-tetramethylpiperizide (LiTMP) was prepared according to a literature.[5] (Trimethylsilyl)methyl potassium (KCH_2TMS) was prepared according to a reported procedure.[6] *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) and *N*,*N*,*N*′,*N*′′,*N*′′-pentamethyldiethylenetriamine (PMDTA) were purchased from Tokyo Chemical Industry Co., Ltd. Heptane was purchased from Aldrich Co., Ltd.. Et_2O and cyclopentyl methyl ether (CPME) was purchased from Tokyo Chemical Industry Co., Ltd., and distilled just before use in the presence of benzophenone and sodium. Alkylarenes were purchased from Tokyo Chemical Industry Co., Ltd., and distilled with CaH. **2a'**, **2a** were purchased from Tokyo Chemical Industry Co., Ltd.. **2b,**[7] **2c,**[8] **2d,**[9] **2e,**[10] **2i,**[11] **2j,**[11] **4a,**[12] and **4b**[12] were synthesized according to literatures. **2f,**[13] **2g,**[14] and **2h**[15] were synthesized by typical Wittig reaction between corresponding aldehydes and benzyltriphenylphosphonium bromide. **4d** and **4e** were synthesized according to a literature.[16] **L1**,[3] **L3**,[17] **L4**[18] and **L5**[19] were synthesized according to literatures. **L2** was purchased from Aldrich Co., Ltd..

Typical procedure of catalytic addition reaction of alkylarene 1a with β-substituted styrene derivative 2a (Condition A, Table 2-3-1, reaction for 3aa)

KCH_2TMS (3.8 mg, 3.0 x 10^{-2} mmol) and alkene **2a** (540.4 mg, 3.0 mmol) were placed in a flame-dried 20 mL flask inside a glove box fulfilled with argon, and alkylarene **1a** (7.5 mL) and PMDTA (6.3 μL, 3.0 x 10^{-2} mmol) was subsequently added at –78 °C via well-dried syringe, and the whole mixture was stirred for 24 h at 0 °C. The reaction was quenched by adding water (2.0 ml) and extracted with DCM (20 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4. After filtration and concentration under reduced pressure, the crude product obtained was purified by flash column chromatography on silica gel (Hexane/DCM = 20:1) to afford the desired product **3aa**

(710.1 mg, 2.61 mmol, 87% yield).

Typical procedure of catalytic addition reaction of alkylarene 1b with β-substituted styrene derivative 2a (Condition B, Table 2-3-1, reaction for 3ba)

KCH_2TMS (3.8 mg, 3.0 x 10^{-2} mmol) and alkene **2a** (271.0 mg, 1.5 mmol) were placed in a flame-dried 10 mL flask inside a glove box fulfilled with argon, and CPME (0.75 ml), alkylarene **1b** (0.75 mL, 1.2 x 10 mmol, 4.0 eq.) and PMDTA (6.2 μL, 3.0 x 10^{-2} mmol) was subsequently added at –78 °C via well-dried syringe, and the whole mixture was stirred for 18 h at 0 °C. The reaction was quenched by adding water (2.0 ml) and extracted with DCM (20 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4. After filtration and concentration under reduced pressure, the crude product obtained was purified by PTLC (Hexane/DCM = 8:1 x 3) to afford the desired product **3ba** (351.6 mg, 1.16 mmol, 78% yield).

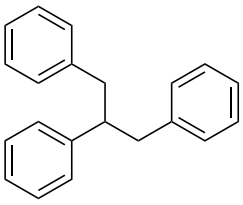
Typical procedure of catalytic addition reaction of alkylarene 1a with alkenyl silane 4d (Table 2-4-1, entry 4)

KO^tBu (3.4 mg, 3.0 x 10^{-2} mmol), LiTMP (4.4 mg, 3.0 x 10^{-2} mmol), 18-crown-6 (8.0 mg, 3.0 x 10^{-2} mmol) and alkenyl silane **4d** (109.0 mg, 3.0 x 10^{-1} mmol) were placed in a flame-dried 10 mL flask inside a glove box fulfilled with argon, and alkylarene **1a** (0.75 ml) was added at –78 °C via well-dried syringe, and the whole mixture was stirred for 18 h at 0 °C. The reaction was quenched by adding water (2.0 ml) and extracted with DCM (20 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4. After filtration and concentration under reduced pressure, the crude product obtained was purified by PTLC (Hexane/DCM = 5:1) to afford the desired product **5ad** (126.6 mg, 0.279 mmol, 93% yield).

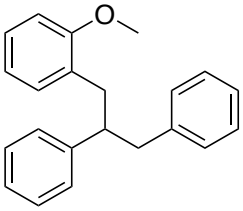
Typical procedure of catalytic asymmetric addition reaction of alkylarene 1c with β-substituted styrene derivative 2a (Table 2-5-1, entry 6)

KCH_2TMS (3.8 mg, 3.0 x 10^{-2} mmol) and alkene **2a** (54.3 mg, 3.0 x 10^{-1} mmol) were placed in a flame-dried 10 mL flask inside a glove box fulfilled with argon, and **L3** (11.0 mg, 3.3 x 10^{-2} mmol) was added as CPME solution (0.75 ml) at –78 °C via well-dried syringe. The reaction mixture was stirred for 15 min. at the same temperature. After that, alkylarene **1c** (146.6 mg, 1.2 mmol) was added, then the mixture was stirred for 18 h at 0 °C. The reaction was quenched by adding water (2.0 ml) and extracted with DCM (20 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4. After filtration and concentration under reduced pressure, the crude product obtained was purified by PTLC (Hexane/DCM = 3:1) to afford the desired product **3ca** (42.5 mg, 0.141 mmol, 47% yield).

propane-1,2,3-triyltribenzene (3aa); Colorless oil; IR (neat, cm^{-1}); 3061, 3027, 2924, 2853, 1601, 1495, 1449, 1075, 1031; HRMS (DART) calcd for $C_{21}H_{24}N_1$ $[M + NH_4]^+$ 290.19033, found: 290.19111; ^1H NMR ($CDCl_3$, 600 MHz): δ: 7.14-7.11 (6H, m), 7.06-7.03 (3H, m), 6.97 (2H, d, J = 8.25 Hz), 6.92 (4H, d, J = 8.25 Hz), 3.08-3.03 (1H, m), 2.90 (2H, dd, J = 13.74, 6.18 Hz), 2.83 (2H, dd, J = 13.75, 8.25 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ: 144.22, 140.45, 129.11, 128.08, 128.03, 127.88,126.10, 125.79, 49.87, 42.44.

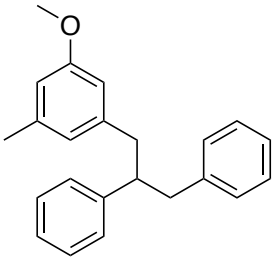


(3-(2-methoxyphenyl)propane-1,2-diyl)dibenzene (3ba); Colorless oil; IR (neat, cm^{-1}); 518, 601, 695, 749, 908, 1029, 1051, 1072, 1111, 1176, 1241, 1438, 1452, 1492, 1585, 1600; HRMS (DART) calcd for $C_{22}H_{23}O$ $[M + H]^+$ 303.17489, found: 303.17516.; ^1H NMR ($CDCl_3$, 600 MHz): δ: 7.14-7.09 (9H, m), 6.99 (2H, d, J = 7.94 Hz), 6.89 (1H, d, J = 7.37 Hz), 6.77-6.74 (2H, m), 3.71 (3H, s), 3.23-3.20 (1H, m), 3.02-2.99 (2H, m), 2.93-2.84 (2H, m); ^{13}C NMR (150 MHz, $CDCl_3$): δ: 157.57, 144.84, 140.82, 130.71, 129.09, 128.96, 127.89, 127.87, 127.03, 125.86, 125.85, 125.58, 120.04, 110.17, 55.14, 47.94, 42.33, 37.01.



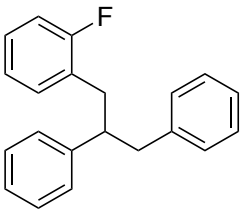
(3-(3-methoxyphenyl)propane-1,2-diyl)dibenzene (3ca); Colorless oil; IR (neat, cm^{-1}); 521, 546, 694, 739, 758, 772, 1042, 1072, 1152, 1260, 1436, 1452, 1465, 1488, 1583, 1600; HRMS (DART) calcd for $C_{22}H_{23}O$ $[M + H]^+$ 303.17489, found: 303.17370; HPLC analysis using Daicel Chiralpak OD-3 column (Hex/^{i}PrOH = 300/1, 0.7 mL/min, 210 nm, t_R = 32.7 min (major), 41.5 min (minor)); $[\alpha]_D$ = –0.684 (c 0.74, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz): δ: 7.13-7.08 (4H, m), 7.06-7.00 (3H, m), 6.97 (2H, d, J = 7.56 Hz), 6.92 (2H, d, J = 7.56 Hz), 6.59-6.58 (1H, m), 6.53 (1H, d, J = 7.56 Hz), 6.43 (1H, s), 3.59 (3H, s), 3.08-3.03 (1H, m), 2.91-2.79 (4H, m); ^{13}C NMR (150 MHz, $CDCl_3$): δ 159.29, 144.23, 142.04, 140.41, 129.11, 128.95, 128.09, 128.02, 127.88, 126.11, 125.79, 121.55, 114.74, 111.27, 55.01, 49.72, 42.45, 42.42.

(3-(3-methoxy-5-methylphenyl)propane-1,2-diyl)dibenzene (3da); Colorless oil; IR (neat, cm^{-1}); 494, 551, 612, 695, 739, 758, 781, 833, 925, 963, 1031, 1066, 1151, 1166, 1192, 1290, 1323, 1452, 1493, 1593; HRMS (DART) calcd for $C_{23}H_{25}O$ $[M + H]^+$ 317.19504, found: 317.19106; ^1H NMR ($CDCl_3$, 600 MHz): δ 7.14-7.01 (6H, m), 6.98 (2H, d, J = 7.94 Hz), 6.91 (2H, d, J = 7.94 Hz), 6.41 (1H, s), 6.37 (1H, s), 6.24 (1H, s), 3.58 (3H, s), 3.07-3.01 (1H, m), 2.90 (1H, dd, J = 6.61, 3.31 Hz), 2.84-2.75 (3H, m), 2.16 (3H, s); ^{13}C



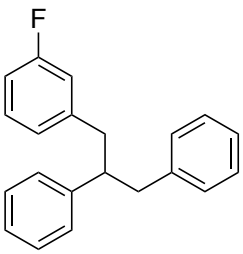
NMR (150 MHz, $CDCl_3$): δ 159.27, 144.34, 141.76, 140.44, 138.87, 129.10, 128.06, 127.99, 127.87, 126.06, 125.74, 122.49, 112.15, 111.69, 54.98, 49.62, 42.47, 42.31, 21.47.

3-(2-fluorophenyl)propane-1,2-diyl)dibenzene (3ea); Colorless oil; IR (neat, cm^{-1});



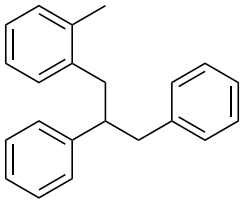
521, 601, 695, 752, 846, 1031, 1072, 1098, 1181, 1228, 1452, 1490, 1583, 1600; HRMS (DART) calcd for $C_{21}H_{23}FN$ $[M + NH_4]^+$ 308.18145, found: 308.17991; ^1H NMR ($CDCl_3$, 600 MHz): δ 7.12-7.10 (4H, m), 7.06-6.98 (5H, m), 6.93 (2H, t, J = 4.25 Hz), 6.88-6.83 (3H, m), 3.14-3.11 (1H, m), 2.99 (1H, dd, J = 6.61, 3.31 Hz), 2.92-2.89 (2H, m), 2.85-2.80 (1H, m); ^{13}C NMR (150 MHz, $CDCl_3$): δ 162.15 ($J_{C\text{-}F}$ = 245.35 Hz), 143.87, 140.26, 131.32 ($J_{C\text{-}F}$ = 5.98 Hz), 129.04, 128.07, 128.02, 127.75, 127.58 ($J_{C\text{-}F}$ = 7.18 Hz), 127.37 ($J_{C\text{-}F}$ = 15.56 Hz), 126.17, 125.80, 123.59 ($J_{C\text{-}F}$ = 3.59 Hz), 115.11 ($J_{C\text{-}F}$ = 22.73 Hz), 48.41, 42.47, 35.65.; ^{19}F NMR ($CDCl_3$, 465 MHz): δ = –119.10.

(3-(3-fluorophenyl)propane-1,2-diyl)dibenzene (3fa); Colorless oil; IR (neat, cm^{-1});



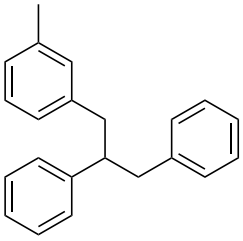
521, 548, 601, 626, 696, 744, 758, 778, 881, 909, 936, 959, 1031, 1072, 1139, 1249, 1452, 1486, 1588, 1602, 1615; HRMS (DART) calcd for $C_{21}H_{23}FN$ $[M + NH_4]^+$ 308.18145, found: 308.18183; ^1H NMR ($CDCl_3$, 600 MHz): δ 7.21-7.09 (7H, m), 7.04-7.00 (4H, m), 6.80 (1H, td, J = 8.50, 2.27 Hz), 6.74 (1H, d, J = 7.37 Hz), 6.67 (1H, d, J = 9.64 Hz), 3.13-3.10 (1H, m), 2.95-2.90 (4H, m); ^{13}C NMR (150 MHz, $CDCl_3$): δ 163.60 ($J_{C\text{-}F}$ = 246.56 Hz), 143.74, 143.05 ($J_{C\text{-}F}$ = 7.18 Hz), 140.18, 129.38 ($J_{C\text{-}F}$ = 8.38 Hz), 129.07, 128.17, 128.11, 127.77, 126.28, 125.91, 124.76 ($J_{C\text{-}F}$ = 2.39 Hz), 115.90 ($J_{C\text{-}F}$ = 20.35 Hz), 112.75 ($J_{C\text{-}F}$ = 20.35 Hz), 49.70, 42.56, 42.01; ^{19}F NMR ($CDCl_3$, 465 MHz): δ = –115.07.

(3-(*o*-tolyl)propane-1,2-diyl)dibenzene (3ga); Colorless oil; IR (neat, cm^{-1}); 454, 516,

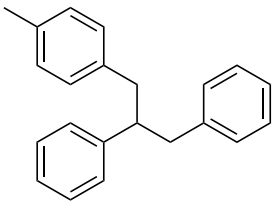


541, 562, 601, 695, 738, 759, 1029, 1072, 1452, 1493, 1600; HRMS (DART) calcd for $C_{22}H_{26}N$ $[M + NH_4]^+$ 304.20652, found: 304.20853; ^1H NMR ($CDCl_3$, 600 MHz): δ 7.21-7.10 (6H, m), 7.07-6.97 (7H, m), 6.86 (1H, d, J = 7.37 Hz), 3.08-2.94 (4H, m), 2.84 (1H, dd, J = 13.89, 8.22 Hz), 2.09 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$): δ 144.50, 140.58, 138.65, 136.16, 130.06, 129.91, 129.11, 128.09, 128.04, 127.78, 126.11, 125.90, 125.80, 125.46, 48.88, 42.34, 39.83, 19.28.

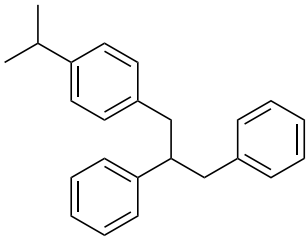
(3-(*m*-tolyl)propane-1,2-diyl)dibenzene (3ha); Colorless oil; IR (neat, cm^{-1}); 445, 518, 551, 601, 695, 739, 758, 772, 1031, 1072, 1452, 1493, 1602; HRMS (DART) calcd for $C_{22}H_{26}N$ $[M + NH_4]^+$ 304.20652, found: 304.20651; ^1H NMR ($CDCl_3$, 600 MHz): δ 7.20-7.03 (9H, m), 6.97 (2H, d, J = 7.94 Hz), 6.93 (1H, d, J = 7.37 Hz), 6.81-6.80 (2H, m), 3.15-3.09 (1H, m), 2.99-2.85 (4H, m) 2.24 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$): δ 144.36, 140.50, 140.36, 137.50, 129.95, 129.11, 128.05, 128.00, 127.90, 127.87, 126.54, 126.12, 126.06, 125.75, 49.77, 42.43, 42.34, 21.35.



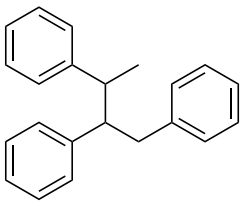
(3-(*p*-tolyl)propane-1,2-diyl)dibenzene (3ia); Colorless oil; IR (neat, cm^{-1}); 599, 696, 731, 746, 772, 908, 1076, 1029, 1452, 1495, 1509, 1596; HRMS (DART) calcd for $C_{22}H_{26}N$ $[M + NH_4]^+$ 304.20652, found: 304.20738; ^1H NMR ($CDCl_3$, 600 MHz): δ 7.12-7.02 (6H, m), 6.97-6.96 (2H, m), 6.91-6.89 (4H, m), 6.81 (2H, d, J = 7.94 Hz), 3.06-3.00 (1H, m), 2.91-2.78 (4H, m), 2.18 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$): δ 144.35, 140.50, 137.31, 135.16, 129.11, 128.95, 128.74, 128.05, 127.99, 127.89, 126.03, 125.73, 49.87, 42.40, 41.97, 20.98.



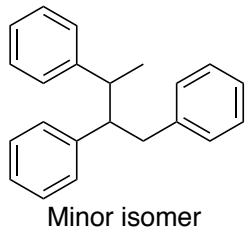
(3-(4-isopropylphenyl)propane-1,2-diyl)dibenzene (3ja); Colorless oil; IR (neat, cm^{-1}); 522, 548, 582, 695, 732, 758, 816, 1019, 1031, 1055, 1072, 1362, 1382, 1418, 1452, 1495, 1512, 1602; HRMS (DART) calcd for $C_{24}H_{27}$ $[M + H]^+$ 315.21128, found: 315.21292; ^1H NMR ($CDCl_3$, 600 MHz): δ 7.13-6.97 (10H, m), 6.89-6.87 (4H, m), 3.09-3.03 (1H, m), 2.92-2.97 (5H, m), 1.12 (6H, d, J = 6.80 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 146.26, 144.48, 140.51, 137.72, 129.09, 128.97, 128.06, 127.96, 127.88, 126.10, 126.03, 125.70, 49.66, 42.33, 42.00, 33.60, 24.01.



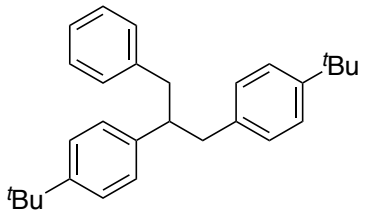
(butane-1,2,3-triyl)tribenzene (major diastereomer, 3ka-M); White solid; Mp: 92-93 ºC; IR (neat, cm^{-1}); 564, 696, 739, 772, 789, 795, 1395, 1452, 1495, 1509; HRMS (DART) calcd for $C_{22}H_{26}N$ $[M + NH_4]^+$ 304.20652, found: 304.20829; ^1H NMR ($CDCl_3$, 600 MHz): δ 7.36 (2H, t, J = 7.65 Hz), 7.30-7.20 (5H, m), 7.15-7.14 (1H, m), 7.06-7.00 (5H, m), 6.72 (2H, d, J = 7.37 Hz), 3.04-2.98 (1H, m), 2.93 (1H, dt, J = 10.34, 5.17 Hz), 2.80 (1H, dd, J = 13.32, 3.68 Hz), 2.62 (1H, dd, J = 13.32, 10.49 Hz), 1.02 (3H, d, J = 6.80 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ 146.55, 143.08, 140.88, 128.80, 128.57, 128.51, 127.99, 127.73, 127.61, 126.22, 126.08, 125.38, 55.64, 45.72, 41.15, 20.80.



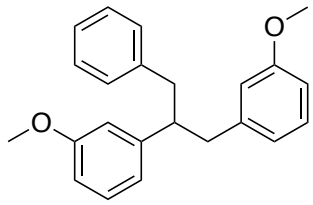
(butane-1,2,3-triyl)tribenzene (minor diastereomer, 3ka-m); Colorless oil; IR (neat, cm^{-1}); 498, 524, 542, 621, 694, 744, 761, 1031, 1069, 1375, 1450, 1493, 1602; HRMS (DART) calcd for $C_{22}H_{26}N$ $[M + NH_4]^+$ 304.20652, found: 304.20517; ^1H NMR ($CDCl_3$, 600 MHz): δ 7.10 (9H, m), 6.97 (4H, t, J = 7.65 Hz), 6.87 (2H, d, J = 6.80 Hz), 3.16-3.11 (3H, m), 2.91-2.86 (1H, m), 1.38 (3H, d, J = 6.24 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 144.85, 142.23, 140.78, 129.05, 129.00, 128.21, 127.93, 127.69, 127.43, 125.81, 125.79, 125.55, 54.38, 44.74, 38.71, 19.31.


Minor isomer

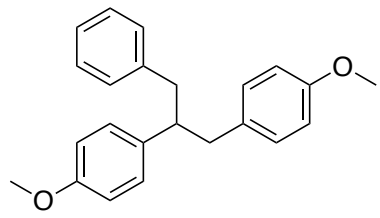
4,4'-(3-phenylpropane-1,2-diyl)bis(*tert*-butylbenzene) (3ab); White solid; Mp: 82-84 ºC; IR (neat, cm^{-1}); 698, 729, 746, 774, 789, 1395, 1453, 1495, 1509, 1596; HRMS (DART) calcd for $C_{29}H_{37}$ $[M + H]^+$ 385.28953. found: 385.29087; ^1H NMR ($CDCl_3$, 600 MHz): δ 7.15-7.12 (4H, m), 7.08-7.06 (2H, m), 7.03-7.00 (1H, m), 6.94-6.88 (6H, m), 3.08-3.03 (1H, m), 2.87-2.75 (4H, m), 1.20 (9H, s), 1.20 (9H, s); ^{13}C NMR (150 MHz, $CDCl_3$): δ 148.72, 148.46, 141.62, 140.73, 137.61, 129.14, 128.73, 127.92, 127.35, 125.62, 124.94, 124.92, 48.73, 42.10, 41.74, 34.31, 34.30, 31.39, 31.38.



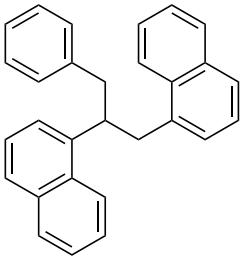
3,3'-(3-phenylpropane-1,2-diyl)bis(methoxybenzene) (3ac); Colorless oil; IR (neat, cm^{-1}); 474, 504, 571, 695, 741, 754, 776, 872, 1042, 1152, 1256, 1286, 1315, 1435, 1452, 1486, 1583, 1599; HRMS (DART) calcd for $C_{23}H_{25}O_2$ $[M + H]^+$ 333.18545. found: 333.18379; ^1H NMR ($CDCl_3$, 600 MHz): δ 7.24-7.21 (2H, m), 7.16-7.15 (3H, m), 7.05 (2H, d, J = 7.94 Hz), 6.72 (3H, d, J = 7.94 Hz), 6.67 (1H, d, J = 7.37 Hz), 6.63 (1H, s), 6.58 (1H, s), 3.74 (3H, s), 3.73 (3H, s), 3.19-3.13 (1H, m), 2.99-2.93 (4H, m); ^{13}C NMR (150 MHz, $CDCl_3$): δ 159.30, 159.27, 145.93, 141.99, 140.36, 129.08, 129.00, 128.96, 128.02, 125.79, 121.53, 120.26, 114.73, 113.72, 111.31, 111.22, 55.04, 55.00, 49.68, 42.32, 42.28.



4,4'-(3-phenylpropane-1,2-diyl)bis(methoxybenzene) (3ad); Colorless oil; IR (neat, cm^{-1}); 1610, 1584, 1511, 1459, 1298, 1178, 1107, 1036; HRMS (DART) calcd for $C_{23}H_{25}O_2$ $[M + H]^+$ 333.18545. found: 333.18418; ^1H NMR ($CDCl_3$, 600 MHz): δ 7.18-7.16 (2H, m), 7.11-7.10 (1H, m), 6.98 (2H, d, J = 6.80 Hz), 6.93 (2H, d, J = 8.50 Hz), 6.89 (2H, d, J = 8.50 Hz), 6.74-6.72 (4H, m), 3.73 (3H, s), 3.73 (3H, s), 3.06-3.01 (1H, m), 2.96-2.78 (4H, m); ^{13}C NMR (150 MHz, $CDCl_3$): δ 157.75, 157.63, 140.64, 136.35, 132.60, 129.99, 129.10, 128.72, 127.98, 125.68, 113.40, 113.39, 55.09, 55.06, 49.15, 42.52, 41.72.

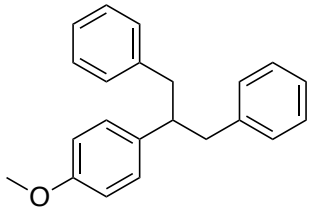


1,1'-(3-Phenylpropane-1,2-diyl)dinaphthalene (3ae); Colorless oil; IR (neat, cm^{-1});



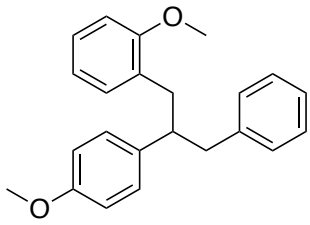
698, 729, 772, 908, 1395, 1452, 1495, 1029, 1596; HRMS (DART) calcd for $C_{29}H_{25}$ $[M + H]^+$ 373.19563; found: 373.19747; ^1H NMR ($CDCl_3$, 600 MHz): δ 7.79-7.77 (3H, m), 7.67 (2H, d, *J* = 8.50 Hz), 7.58 (2H, d, *J* = 7.94 Hz), 7.40 (4H, tt, *J* = 24.37, 10.11 Hz), 7.20-7.02 (8H, m), 4.34-4.32 (1H, m), 3.62-3.60 (1H, m), 3.44-3.42 (1H, m), 3.16-3.14 (2H, m); ^{13}C NMR (150 MHz, $CDCl_3$): δ 141.28, 140.33, 136.19, 133.79, 132.04, 129.24, 128.75, 128.65, 128.63, 128.10, 126.96, 126.65, 126.59, 125.96, 125.70, 125.43, 125.40, 125.24, 125.13, 125.10, 125.07, 123.57, 123.52, 122.62, 42.61, 41.08, 38.78.

(2-(4-methoxyphenyl)propane-1,3-diyl)dibenzene (3af); Colorless oil; IR (neat, cm^{-1});



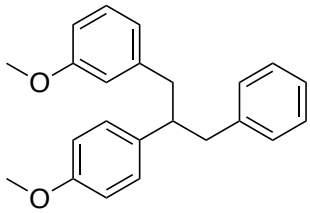
598, 696, 746, 772, 821, 908, 1031, 1029, 1109, 1176, 1243, 1300, 1395, 1452, 1495, 1510; HRMS (DART) calcd for $C_{22}H_{23}O$ $[M + H]^+$ 303.17489. found: 303.17435; ^1H NMR ($CDCl_3$, 600 MHz): δ 7.20-7.16 (4H, m), 7.13-7.11 (2H, m), 7.00-6.99 (4H, m), 6.95-6.94 (2H, m), 6.74-6.73, (2H, m), 3.74 (3H, s), 3.10-3.06 (1H, m), 2.95 (2H, dd, *J* = 6.61, 3.31 Hz), 2.86 (2H. dd. *J* = 13.32, 8.22 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 157.77, 140.56, 136.24, 129.11, 128.70, 128.01, 125.73, 113.42, 55.10, 48.99, 42.62.

1-methoxy-2-(2-(4-methoxyphenyl)-3-phenylpropyl)benzene (3bf); Colorless oil; IR



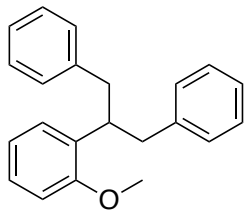
(neat, cm^{-1}); 546, 601, 698, 748, 824, 1031, 1105, 1176, 1239, 1438, 1492, 1510, 1585; HRMS (DART) calcd for $C_{23}H_{25}O_2$ $[M + H]^+$ 333.18545. found: 333.18666; ^1H NMR ($CDCl_3$, 600 MHz): δ 7.15-7.07 (4H, m), 6.99-6.93 (4H, m), 6.89 (1H, d, *J* = 7.37 Hz), 6.77-6.68 (4H, m), 3.70 (3H, s), 3.70 (3H, s), 3.20-3.14 (1H, m), 3.00-2.96 (2H, m), 2.87-2.83 (2H, m); ^{13}C NMR (150 MHz, $CDCl_3$): δ 157.59, 157.51, 140.89, 136.87, 130.70, 129.09, 129.02, 128.66, 127.83, 126.96, 125.51, 120.02, 113.23, 110.12, 55.11, 55.04, 47.04, 42.52, 37.13.

1-methoxy-3-(2-(4-methoxyphenyl)-3-phenylpropyl)benzene (3cf); Colorless oil; IR



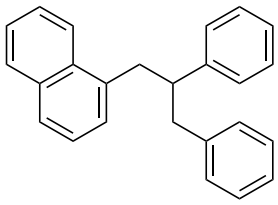
(neat, cm^{-1}); 599, 696, 774, 826, 908, 1029, 1078, 1029, 1243, 1395, 1452, 1510, 1582, 1596; HRMS (DART) calcd for $C_{23}H_{25}O_2$ $[M + H]^+$ 333.18545. found: 333.18535; ^1H NMR ($CDCl_3$, 600 MHz): δ 7.20-7.16 (2H, m), 7.11-7.09 (2H, m), 6.99-6.95 (4H, m), 6.73 (2H, d, *J* = 7.37 Hz), 6.66 (1H, d, *J* = 7.94 Hz), 6.60 (1H, d, *J* = 7.37 Hz), 6.52 (1H, s), 3.72 (3H, s), 3.68 (3H, s), 3.09-3.07 (1H, m), 2.94-2.92 (2H, m), 2.87-2.82 (2H, m); ^{13}C NMR (150 MHz, $CDCl_3$): δ 159.24, 157.77, 142.15, 140.49, 136.22, 129.10, 128.92, 128.68, 127.99, 125.72, 121.54, 114.75, 113.42, 111.13, 55.07, 54.97, 48.79, 42.62, 42.60.

(2-(2-methoxyphenyl)propane-1,3-diyl)dibenzene (3ag, mixture of the isomers);

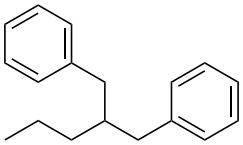


Colorless oil; IR (neat, cm^{-1}); 508, 601, 695, 748, 1029, 1052, 1109, 1241, 1288, 1452, 1492, 1585, 1600; HRMS (DART) calcd for $C_{22}H_{23}O$ $[M + H]^+$ 303.17489; found: 303.17493; ^1H NMR ($CDCl_3$, 600 MHz): δ7.14-6.69 (14H, m), 3.62 (3H, s), 3.23-3.22 (1H, m), 2.95-2.88 (4H, m); ^{13}C NMR (150 MHz, $CDCl_3$, detectable peaks): δ157.55, 140.90, 140.82, 130.71, 129.11, 129.09, 128.95, 127.89, 127.86, 127.03, 126.87, 125.86, 125.57, 120.32, 120.03, 110.66, 110.15, 55.34, 55.14, 47.93, 42.31, 40.72, 37.01.

1-(2,3-diphenylpropyl)naphthalene (3ah); Colorless oil; IR (neat, cm^{-1}); 432, 525, 562, 598, 695, 756, 776, 1029, 1072, 1395, 1452, 1493, 1509, 1598; HRMS (DART) calcd for $C_{25}H_{23}$ $[M + H]^+$ 323.17998. found: 323.18024; ^1H NMR ($CDCl_3$, 600 MHz): δ 7.81 (1H, d, *J* = 7.94 Hz), 7.70 (1H, d, *J* = 8.50 Hz), 7.64 (1H, d, *J* = 7.94 Hz), 7.45-7.37 (2H, m), 7.24-7.12 (7H, m), 7.05-7.03 (4H, m), 6.99 (1H, d, *J* = 6.24 Hz), 3.49 (1H, dd, *J* = 11.90, 3.97 Hz), 3.26-3.23 (2H, m), 3.04-3.03 (2H, m); ^{13}C NMR (150 MHz, $CDCl_3$): δ 144.67, 140.49, 136.36, 133.83, 131.90, 129.26, 128.74, 128.13, 128.09, 127.73, 127.33, 126.66, 126.15, 125.91, 125.65, 125.23, 125.13, 123.74, 48.97, 42.74, 39.66.



1-(2,3-diphenylpropyl)naphthalene (3ai); Colorless oil; IR (neat, cm^{-1}); 1601, 1495, 1452, 1376, 1031; HRMS (DART) calcd for $C_{18}H_{26}N_1$ $[M + NH_4]^+$ 256.20598; found: 256.20853; ^1H NMR ($CDCl_3$, 600 MHz): δ 7.27-7.25 (4H, m), 7.18-7.16 (2H, m), 7.13-7.12 (4H, m), 2.54 (4H, d, *J* = 6.24 Hz), 2.01-1.93 (1H, m), 1.38-1.34 (2H, m), 1.23-1.22 (2H, m), 0.83 (3H, t, *J* = 7.37 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 141.39, 129.18, 128.12, 125.64, 41.65, 40.16, 35.06, 19.68, 14.27.



(2-isopropylpropane-1,3-diyl)dibenzene (3aj); Colorless oil; IR (neat, cm^{-1}); 1602, 1494, 1456, 1365; HRMS (DART) calcd for $C_{18}H_{26}N_1$ $[M + NH_4]^+$ 256.20598; found: 256.20344; ^1H NMR ($CDCl_3$, 600 MHz): δ 7.26-7.24 (4H, m), 7.16-7.15 (2H, m), 7.11-7.10 (4H, m), 2.60 (2H, dd, *J* = 13.74, 6.90 Hz), 2.43 (2H, dd, *J* = 13.74, 7.56 Hz), 1.91-1.86 (1H, m), 1.72-1.67 (1H, m), 0.92 (6H, d, *J* = 7.56 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 141.88, 129.07, 128.16, 125.58, 48.26, 36.24, 27.49, 18.65.

(5 年以内に雑誌等に刊行予定のため、該当部分を一部略)

Experimental Section ~Chapter 3~

(5 年以内に雑誌等に刊行予定のため、非公開)

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Acknowledgment

I would like to express the deepest appreciation to my supervisor, Prof. Shū Kobayashi for his sincere encouragements and insightful suggestions. These helps have guided me for worthwhile and valuable study of chemistry.

I am deeply grateful to Dr. Yasuhiro Yamashita for constant encouragements and in-depth discussions. He also taught me how to be a good chemist, and how to live as a chemist.

Also I would like to thank to stuff members of our lab., Dr. Haruro Ishitani, Dr. Yuichiro Mori, Dr. Masaharu Ueno, Dr. Hiroyuki Miyamura, Dr. Woo-Jin Yoo, Dr. Tetsu Tsubogo, Dr. Zhu Lei, Dr. Tomohiro Yasukawa, Dr. Taku Kitanosono and Dr. Yuki Saito for their useful suggestions and helps.

I am cordially indebted to Dr. Hirotsugu Suzuki for his tremendous supports and advices. He taught me how to conduct experiments, how to discuss about chemistry, how to achieve a progress, how to live in the laboratory and more. Talking with him about not only chemistry but also other trifling and delightful things is helpful in daily lab. life.

I would like to express the deepest appreciations to Mr. Ryota Fukuyama and Mr. Tsubasa Hirata for their assistance.

I would also like to thank previous and current lab.1 members for their daily supports and helps. Discussions with them gave me hints for a progress in my study.

I also want to show my greatest appreciations to Mr. Satoshi Isshiki, Mr. Kohei Nishino, Mr. Masanori Aoki, and Mr. Tatsuhiro Tsukamoto for their sincere encouragements. I really enjoyed talking, playing softball, and football with them. We were the mightiest team for sports tournaments in history of our lab..

Also I want to thank all other members and secretaries of Kobayashi lab. for their supports and helps.

I want to show my gratitude to MERIT program and JSPS for financial supports.

Finally, I would like to offer my special thanks to my family and Miss. Miri Iwamura for their moral supports and warm encouragements.

Io Sato