学位論文

（要約）

Development of Strong Brønsted Base-catalyzed Addition Reactions of Weakly Acidic Compounds via Product Base
(生成物の塩基性に着目した強塩基触媒による低酸性化合物の付加反応の開発)

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化学専攻

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Development of Strong Brønsted Base Catalyzed Addition Reactions Using Poorly Acidic Amides, Esters and Alkylarenes *via* Product Base

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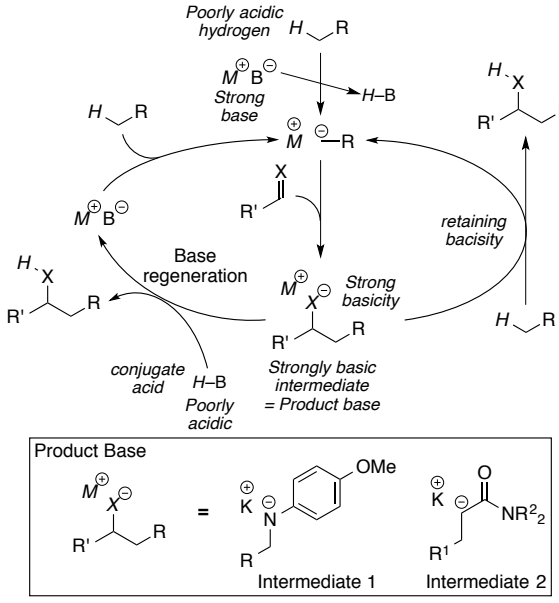
Introduction

Catalytic carbon-carbon (C–C) bond forming reactions are one of the most fundamental and promising methods for construction of complex organic molecules. Especially, Brønsted base catalyzed C–C bond forming reactions are very useful from the viewpoint of atom economy because the reactions proceed under simple proton transfer conditions. Up to now, many kinds of the catalytic reactions including asymmetric variants of it have been reported. Although there are many examples using relatively acidic nucleophiles such as nitromethane, only few reports to use poorly acidic nucleophiles have been investigated. A problem of the reactions using poorly acidic nucleophiles in Brønsted base catalyzed reactions is inactivity of a hydrogen of the pronucleophiles under mild basic conditions, and only strong Brønsted base species such as LDA can accomplish efficient deprotonation of the poorly acidic hydrogen. However, examples of strong Brønsted base catalyzed reactions have been rarely reported to date because the reactions have a problem in the catalytic cycle. The problem is that a base regeneration step hardly proceeds in the catalytic cycle due to poor acidity of a conjugated acid and weak basicity of a reaction intermediate, and the reaction gives the desired product theoretically in a stoichiometric manner. Thus, the most reliable methods for the formation of C–C bond from the poorly acidic compounds is to employ a stoichiometric amount of strong Brønsted base as a mediator of deprotonating appropriate hydrogen. In order to improve the atom-economy of the reactions using the poorly acidic compounds, we focused on basicity of the reaction intermediate. If a strongly basic reaction intermediate (= product base) appeared after nucleophilic addition, the product base could deprotonate the hydrogen of the conjugated acid or poorly acidic hydrogen in the next nucleophile. Previously, we designed the product base to have strongly basic amide part, and have I investigated catalytic Mannich-type reactions of simple esters *via* the intermediate 1 in my master thesis. In my PhD. thesis, I focused on development of new electrophiles that give strongly basic product base and catalytic reactions using poorly acidic pronucleophiles.



Scheme 1. Plausible Catalytic Cycle of Strong Brønsted Base Catalyzed Reaction

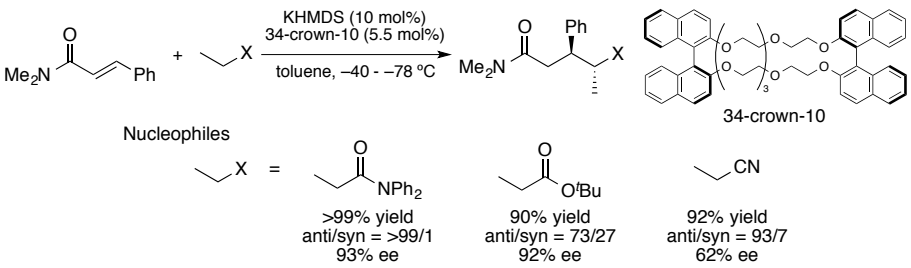
1. Catalytic Asymmetric 1,4-Addition Reactions of Amides and Esters

Carbonyl moieties are contained in wide range of natural products and pharmaceuticals, and it is very important to introduce them stereoselectively. Aldehydes and Ketones are well known carbonyl nucleophiles under proton transfer conditions, and asymmetric variant of them have been developed broadly. On the other hand, the examples of amides and ester have rarely appeared to date because of poor acidities of a α-hydrogen of these carbonyl compounds. As far as we know, there is only one report of catalytic reaction using simple amide as a nucleophile reported by our group previously. However, the available nucleophiles are limited to ketone and amide, and the enantioselectivity of the reaction was moderate. Thus, I focused on a general method to accomplish catalytic asymmetric reactions using poorly acidic carbonyl and related compounds, amides, esters and alkylnitriles.

First of all, I designed the catalytic reactions using poorly acidic amides. A key to the catalytic reactions was

strongly basic reaction intermediate. In this time, I focused on α,β-unsaturated carbonyl compounds as new candidates of electrophiles because the basicity of the reaction intermediate, metal enolate, could be determined the structure of the carbonyl moiety. As the results of the electrophile screening, only α,β-unsaturated amide gave the desired product in high yield in the catalytic 1,4-addtion reactions using poorly acidic amides.

Then, I tried to develop catalytic asymmetric 1,4-addition reactions using amides. As I mentioned above, I already reported racemic variant of it. The enantioselective reactions could be possible if a catalytic amount of a chiral ligand that is coordinated to metal center was introduced in the reactions. Consequently, I found a chiral macro crown ether, (*R, R*)-Binaphtho-34-crown-10, and KHMDS catalyst system gave the desired 1,4-adduct in excellent yield with excellent diastereo- and enantioselectivities after screening of chiral crown ether, and the system could be applicable to various kind of α,β-unsaturated amide including aliphatic amide with keeping stereoselectivities. In addition, other poorly acidic carbonyl and related compounds, ester and nitrile, was also good pronucleophiles of the catalytic asymmetric 1,4-addition reactions to afford the desired adduct in high yield with good to excellent stereoselectivities. The amide moieties of the desired 1,4-adduct were converted to other functional groups selectively, and the 1,4-adduct was good starting materials of intermediates of natural compounds. The catalyst system could accomplish first example of catalytic asymmetric 1,4-addition reactions of amide.



Scheme 2. Catalytic Asymmetric 1,4-Addition Reactions of Poorly Acidic Carbonyl and Related Nucleophiles

Next, I was interested in the structure of binaphtho-34-crown-10 and KHMDS catalyst system. This catalyst system showed interesting properties about ratio of the binaphtho-34-crown-10 and KHMDS. The catalyst system showed same reactivities and stereoselectivities between 1:1 and 1:2 ratio of binaphtho-34-crown-10 and KHMDS. Judging from these same results, I anticipated the catalyst structure as 1:2 complex of binaphtho-34-crown-10 and KHMDS, and I tried several studies to clarify this expectation. However, results of dynamic ^{1}H NMR and MALDI MS suggested that the structure of the complex be 1:1 complex of binaphtho-34-crown-10 and KHMDS. In addition, crystallographic structure of the 1:2 mixture also indicated 1:1 complex. Thus, the structure of the complex would be 1:1 complex both in solution and crystal.

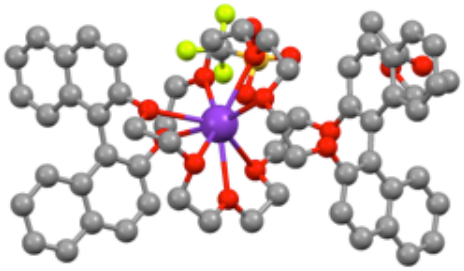


Figure 1. X-ray Crystallographic Structure of KOTf-Binaphtho-34-Crown-10 Complex

Conclusion

I have developed strong Brønsted base catalyzed reactions using poorly acidic nucleophiles by utilizing the strongly basic reaction intermediates (product base). In the catalytic reactions of carbonyl and related compounds, I accomplished highly stereoselective reactions using binaphtho-34-crown-10 as a chiral ligand. The product base can broaden the possibility of the catalytic reactions using poorly acidic compounds.

(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)

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Development of Strong Brønsted Base-catalyzed Addition Reactions of Weakly Acidic Compounds via Product Base

Abbreviations

acac	acetylacetonate
Ac	acetyl
Ar	aryl
B	base
BINOL	1,1'-bi-2-naphthol
Boc	*tert*-butoxycarbonyl group
BOX	bis(oxazoline)
Bu	butyl
CAN	cerium ammonium nitrate
cod	1,5-cyclooctadiene
CPME	cyclopentyl methyl ether
Cy	cyclohexyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DIA	diisopropylamide
DMSO	dimethyl sulfoxide
dr	diastereomer ratio
ee	enantiomeric excess
E	electrophile
Et	ethyl
EWG	electron-withdrawing group
FG	functional group
HMDS	hexamethyldisilazide
i	iso
LA	Lewis acid
LAB	lithium aminoborohydride
LDA	lithium dimethylamide
M	metal
m	*meta*
MS	molecular sieves
Me	methyl
n	normal
Nu	nucleophile
o	*ortho*
OMP	*o*-methoxyphenyl
p	*para*
PAP	proazaphosphatrane
Ph	phenyl
Phen	1,10-phenantholorine

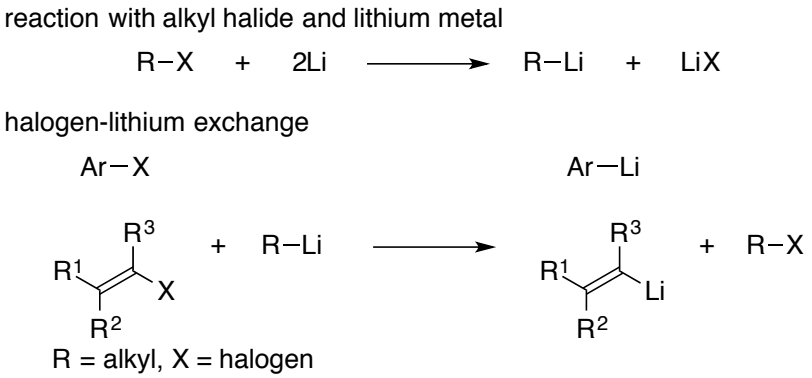
PMP	*p*-methoxyphenyl
Pr	propyl
rt	room temperature
t	tertiary
TBME	tert-butyl methyl ether
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMEDA	tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperazide
TMS	trimethylsilyl
Ts	tosyl

Introduction

Carbanion Formation

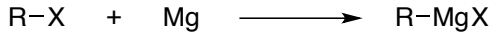
A carbanion, which has a negative charge on a carbon atom, is a very useful intermediate for construction of carbon–carbon (C–C) bond.[1] Generally, carbanions participate in C–C bond formation as nucleophiles, and the amount of the carbanion affects efficiency of the C–C bond formation. Therefore, smooth carbanion formation is a key to achieve the highly efficient reactions.

Nowadays, we can employ various carbanion species as commercial sources such as alkyl lithium reagents, Grignard reagents, and so on. Alkyl lithium reagents, which are the most common organometallic compounds in organic synthesis, are sometimes employed as nucleophiles.[1,2] A common preparation method of alkyl lithium reagents is a reaction between an alkyl halide and lithium metal, and the formed alkyl lithium species is stored in a hydrocarbon solvent or an ether solvent due to its high reactivity (**Scheme 0-1**, top scheme).[3] In addition, alkyl lithium reagents are useful for formation of other organolithium reagents *via* halogen-lithium exchange, deprotonation, and so on. Especially, halogen-lithium exchange can produce aryl and alkenyl lithiums from corresponding aryl and alkenyl halides (**Scheme 0-1**, bottom scheme), and these reagents expand variation of lithium nucleophiles.[4]



Scheme 0-1. Preparation of Organolithium Reagents

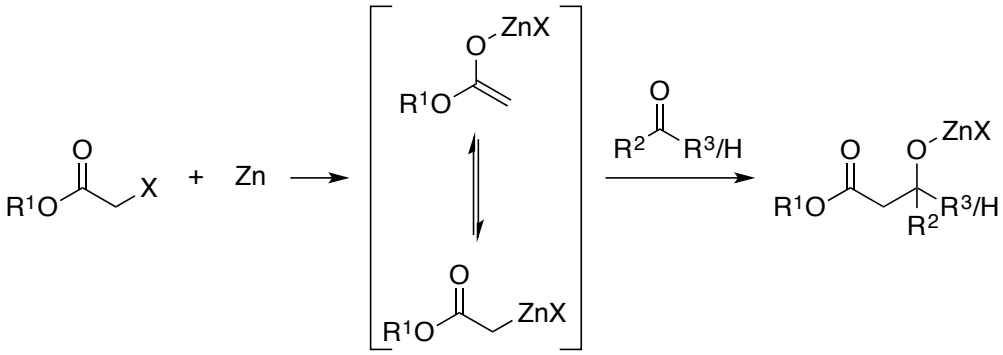
Grignard reagents, which were discovered by Victor Grignard in 1900[5], are also famous metallic carbanion species.[1,2a,2b,4b,6] Typically, the reagents are prepared from an alkyl halide and magnesium metal in an ether solvent *via* single electron transfer (**Scheme 0-2**), and various kinds of Grignard reagents are commercially available now. Use of Grignard reagent is the easiest and the most promising method for construction of C–C bond.



Scheme 0-2. Preparation of Grignard Reagents

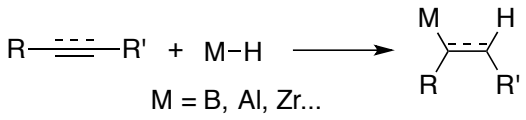
Reformatsky reaction, which gives a *β*-hydroxy ester form an *α*-halo ester and a

ketone, or an aldehyde, also forms a metallic carbanion equivalent as an intermediate *in situ*.[1,7] In the reaction, a mixture of zinc metal and an α-halo ester provides a zinc enolate, and subsequent addition of a ketone or an aldehyde to the mixture gives a corresponding *β*-hydroxy ester (**Scheme 0-3**). In general, reactivity of the zinc enolate is lower than the corresponding lithium or magnesium enolate, but higher functional group tolerance can be achieved. Recently, other metals such as Sm, Cr, and so on are also applicable to the reactions.[7]



Scheme 0-3. Reformatsky Reactions

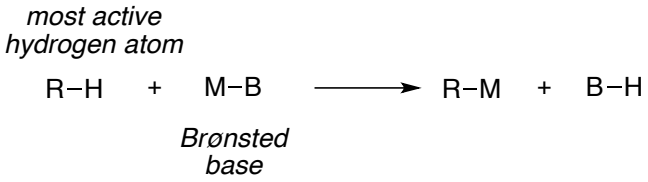
Although those organometallic reagents are very useful for the C–C bond formation, they always requires pre-installation of halogen atoms in the corresponding pronucleophiles. Hydrometalation is one example of metallic carbanion formation without use of halogenated starting materials.[1,8] Generally, hydrometalation requires an alkene or an alkyne as a pronucleophile, and it reacts with a metal hydride to afford an alkyl or a vinyl carbanion that is a nucleophile in a following step (**Scheme 0-4**). Various kinds of metal hydrides are used for the carbanion formation, and B, Al, Zr, and so on, are well-known metal hydride species. However, the hydrometalation always requires introduction of double or triple bond in the pronucleophile structure, and available starting materials are limited.



Scheme 0-4. Hydrometalation

Deprotonation is one solution to avoid the pre-functionalization of pronucleophiles such as introduction of a halogen atom, an alkene.[1,9] In deprotonation, a carbanion species is formed *via* abstraction of a hydrogen atom in the presence of a Brønsted base species (**Scheme 0-5**). Therefore, the carbanion formation *via* deprotonation is said to be step and atom economical compared to other carbanion formations. Generally, deprotonation is controlled by a pK_a value. That is, the most

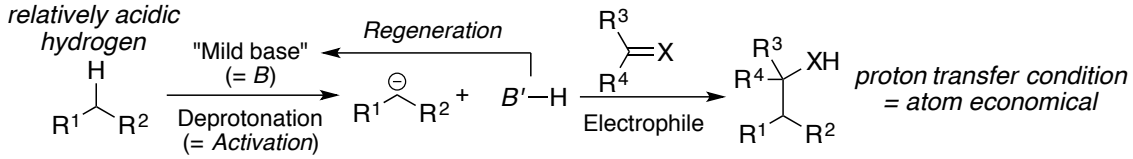
acidic hydrogen atom was deprotonated firstly, and the pK_a value of the hydrogen atom should be sufficiently low to be deprotonated.



Scheme 0-5. Deprotonation

All C–C bond formations *via* carbanion intermediates inherently form co-products derived from the corresponding additives (metal, base, and so on). Therefore, atom economy of the C–C bond formation *via* carbanion intermediate is not good especially when a stoichiometric amount of additive is used. Thus, reducing amounts of the additives are inevitable to improve the atom economy.

Base-catalyzed C–C bond formations have been widely developed to date (**Scheme 0-6**).[10,11,12] However, available pronucleophiles are limited in the catalytic reactions, and almost all examples are conducted by using relatively acidic pronucleophiles. On the other hand, most promising and reliable C–C bond formation using weakly acidic pronucleophiles is using a stoichiometric amount of strong Brønsted bases (**Figure 0-1**).[9]



Scheme 0-6. Base-catalyzed C–C Bond Formation

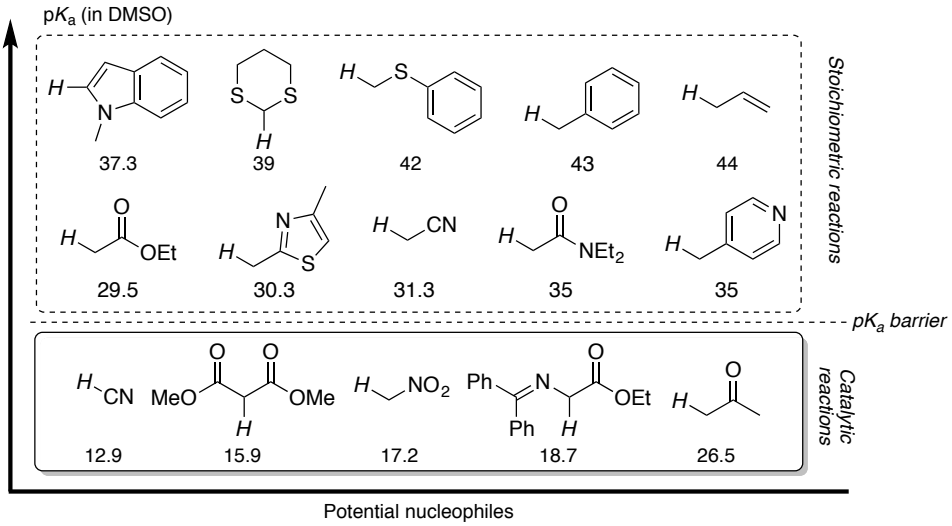
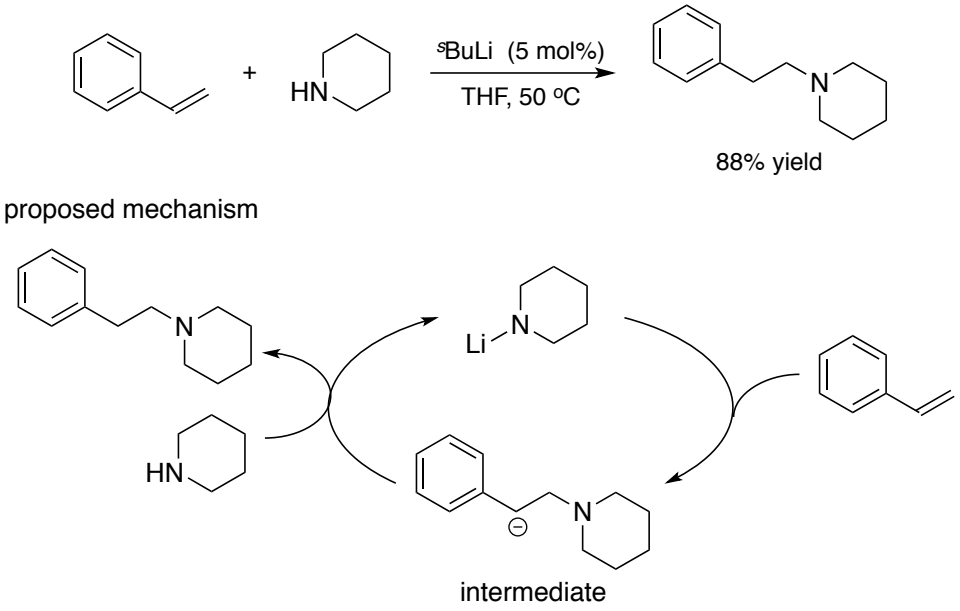


Figure 0-1. Potential Pronucleophiles

Strong Brønsted Base-catalyzed Reactions

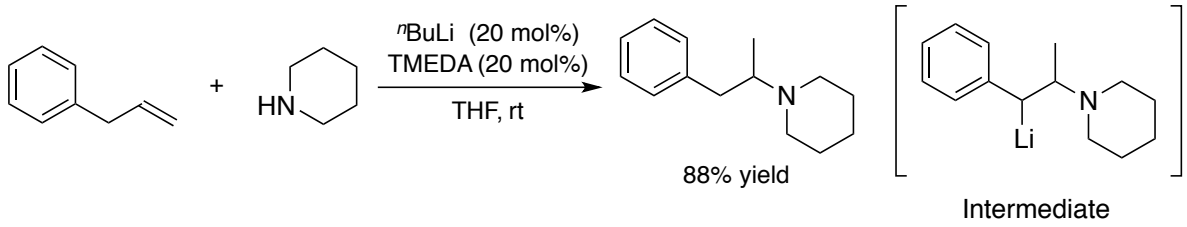
Strong Brønsted bases, which can deprotonate weakly acidic pronucleophiles, usually are required more than a stoichiometric amount for the efficient reactions. This is because the acidity of corresponding conjugate acids of the strong Brønsted base is very low, and the low acidity prevents base regenerations in the catalytic cycle (See **Chapter 1-2**). On the other hand, several strong Brønsted base-catalyzed reactions have been reported to date despite the catalyst regeneration problem.[13]

In 1972, Falk *et al.* achieved hydroamination of aryl olefins with the catalytic amount of ^{n}BuLi (**Scheme 0-7**).[13b] In the reaction, lithium dialkylamide derived from ^{n}BuLi and corresponding amine *in situ* reacted with aryl olefins to afford the desired adducts in moderate to high yields. Catalytic turnover of the reaction was achieved by forming strongly basic benzyl anion intermediate that deprotonated a hydrogen atom of the next dialkylamine.



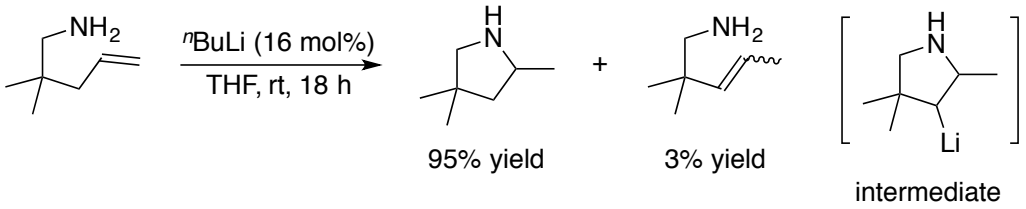
Scheme 0-7. Strong Brønsted Base-catalyzed Hydroamination Using Styrene

Beller *et al.* reported ^{n}BuLi catalyzed domino-isomerization-hydroamination reactions using allylbenzene in 2000 (**Scheme 0-8**).[13f] In first step of the reaction, BuLi isomerized allylbenzene to form *β*-methyl styrene. The *β*-methyl styrene reacted with a lithium amide that was formed *in situ* to afford the desired adducts in high yields with high regioselectivities. The same intermediate, a benzyl anion, regenerated the lithium amide in situ, and only the catalytic amount of the strong Brønsted base catalyzed the reactions well.



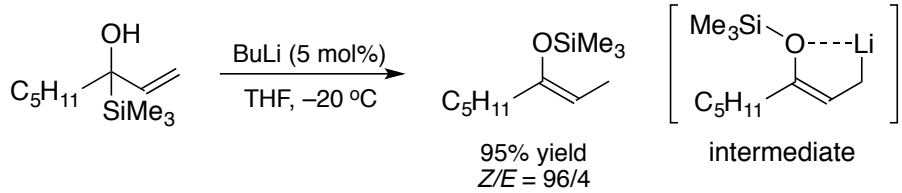
Scheme 0-8. Strong Brønsted Base-catalyzed Hydroamination Using Allyl Benzen

Strong Brønsted base-catalyzed intramolecular hydroamination was also reported. Ates *et al.* accomplished catalytic hydroaminations using unactivated alkenes in the presence of ^{n}BuLi catalyst (**Scheme 0-9**).[13d] The unactivated alkene was attacked by the *in situ*-formed lithium amide, and cyclized amines, piperidine and piperadine, were obtained efficiently. In this case, the strongly basic reaction intermediate was alkyl lithium species that deprotonate a hydrogen atom of a primary amine.



Scheme 0-9. Strong Brønsted Base-catalyzed Intramolecular Hydroamination

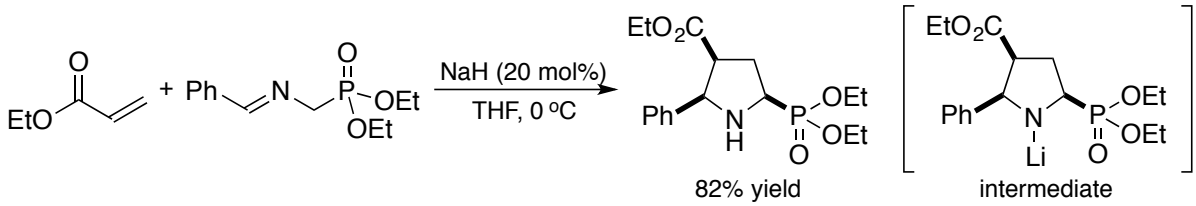
Isomerization reactions were also achieved with strong Brønsted base catalysts. In 1984, Kuwajima *et al.* demonstrated ^{n}BuLi-catalyzed rearrangements of 1-(trimethylsilyl)allylic alcohols (**Scheme 0-10**).[13c] In the reaction, Brook rearrangement gave an allyl anion from a lithium alkoxide, and isomerization of the allylic part then proceeded to afford the silyl enol ethers in high yields. A key intermediate of the reaction would be an allylic anion on the terminal position, and the intermediate was sufficiently basic to deprotonate the next alcohol.



Scheme 0-10. Strong Brønsted Base-catalyzed Rearrangement of 1-(Trimethylsilyl)allylic Alcohol

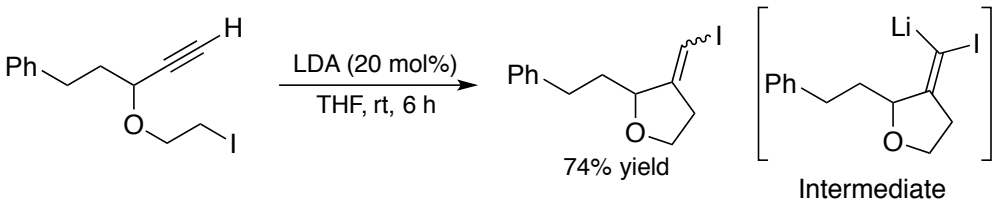
Cyclization is also a good candidate of the strong Brønsted base-catalyze reaction. For example, Dehnel *et al.* have developed sodium hydride-catalyzed cyclization reactions using Schiff bases of α-aminophosphonates (**Scheme 0-11**).[13h] Deprotonated Schiff base reacted with acrylate to afford a sodium dialkylamide, a strongly basic

reaction intermediate. The reaction intermediate smoothly deprotonate a hydrogen atom of the next Schiff base, and the reaction proceeded catalytically.



Scheme 0-11. Strong Brønsted Base-catalyzed Cyclization of Schiff Bases of α-Aminophosphonates

Harada *et al.* have investigated LDA-catalyzed intramolecular cycloisomerization reactions (**Scheme 0-12**).[13i] An alkynyl lithium was converted to a vinyllithium intermediate *via exo*-cyclization, and the vinyllithium worked as a strong Brønsted base to deprotonate a hydrogen atom of the next alkyne.



Scheme 0-12. Strong Brønsted Base-catalyzed Intramolecular Cyclization of Alkyne

Although several examples of strong Brønsted base-catalyzed reactions have been reported to date, the applicable substrates are limited. A key of the catalytic reactions is basicity of the reaction intermediates. If the strongly basic reaction intermediate could be formed in various kinds of catalytic reactions, it would broaden generality of the strong Brønsted base-catalyzed reactions using weakly acidic pronucleophiles. Therefore, I focused on strong Brønsted base-catalyzed reactions by utilizing a strongly basic reaction intermediate.

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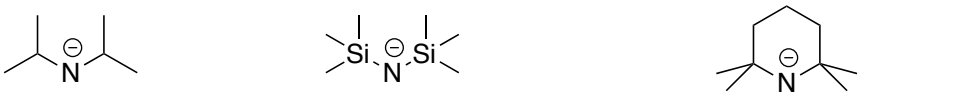
Chapter 1 Development of Catalytic Asymmetric 1,4-Addition Reactions Using Poorly Acidic Carbonyl and Related Compounds

1-1 Background

Alkali-metal secondary amide

Alkali-metal secondary amides are one of the most widespread reagents in synthetic organic chemistry.[1] These amides are well-known as strong Brønsted base species as with alkyllithium and alkali-metal hydride, and commonly used to form polarized C–M bonds via deprotonation.[2] Generally, the alkali-metal secondary amides have sterically hindered substituents on the nitrogen atoms, and the deprotonation is much favored compared to nucleophilic addition. In addition, alkali-metal secondary amides are much soluble in hydrocarbon solvents, and handling of them is easier than other strong Brønsted bases. Thus, the alkali-metal secondary amides are usually chosen as an appropriate strong Brønsted base species for the purpose of deprotonation.



diisopropylamide (DA) | 1,1,1,3,3,3,-hexamethyldisilazide (HMDS) | 2,2,6,6-tetramethylpiperazide (TMP)

Figure 1-1-1. Structure of Alkali-metal Secondary Amides

Diisopropylamide (DIA), 1,1,1,3,3,3-hexamethyldisilazide (HMDS), 2,2,6,6-tetramethylpiperazide (TMP) are common structures as the amide parts (**Figure 1-1-1**), and structures and aggregation states of the alkali-metal secondary amides in a solid state have been widely investigated to date.[3,4,5] In general, these structures and aggregation states are influenced by existence of Lewis base donors such as tetrahydrofuran (THF) and tetramethylethylenediamine (TMEDA). For example, aggregation states of alkali-metal HMDSs, which are most studied alkali-metal secondary amides, are different in the presence or absence of the Lewis base donors. LiHMDS exists as a cyclic trimer in a solid state when any Lewis base donor is absent (left in **Figure 1-1-2**).[3a,b] Addition of THF deaggregates the trimer, and a symmetrical cyclodimer is formed (middle in **Figure 1-1-2**).[3c] More Lewis basic donor, TMEDA, supports formation of mononuclear species by chelating to the lithium cation by two nitrogen atoms of TMEDA (right in **Figure 1-1-2**).[3d]

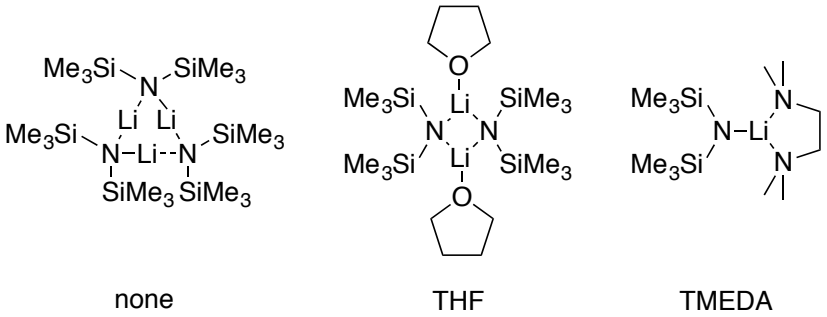


Figure 1-1-2. Aggregation States of LiHMDS in Solid State

Although NaHMDS also changes its aggregation state by the existence of the Lewis base donors, the whole structures are completely different from LiHMDS. NaHMDS exist as a polymer[3e] or a cyclic trimer[3f,g] without solvation support (left in **Figure 1-1-3**), and THF converts the structure from the trimer to a cyclodimer with one or two THF (middle in **Figure 1-1-3**).[3h,i] TMEDA and NaHMDS complex exist as a polymer of dimers, that is, the cyclodimer of NaHMDS is connected by TMEDA in a polymer fashion (right in **Figure 1-1-3**).[3j]

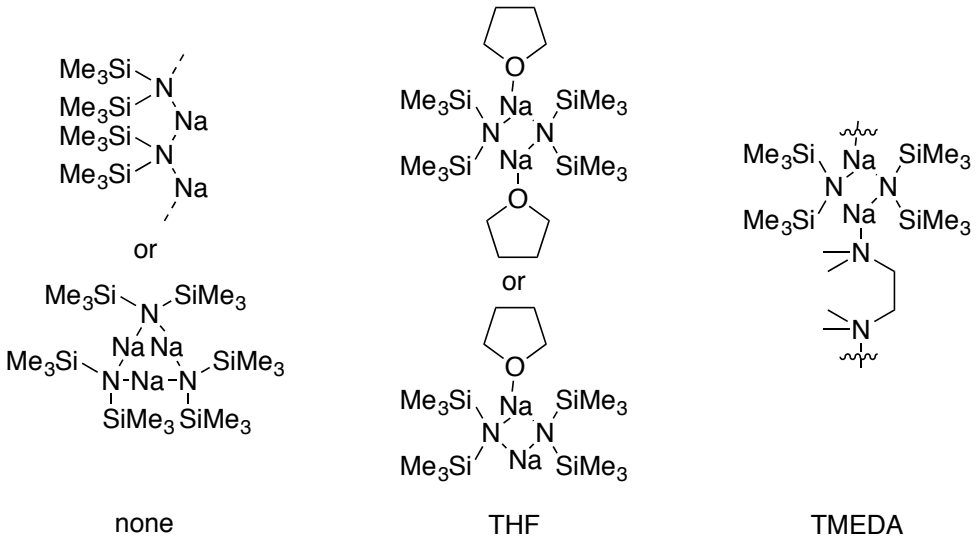


Figure 1-1-3. Aggregation States of NaHMDS in Solid State

Although the structures of LiHMDS and NaHMDS have been well reported, a X-ray single crystallographic structure of KHMDS with THF or TMEDA has not been reported yet, and only an aggregation state with no solvation is known. The structure of KHMDS without any solvation is a cyclodimer aggregation state (**Figure 1-1-4**),[3k,l] and distance of the K–N bond attached to the same potassium atom is slightly different. The properties of alkali-metal secondary amides, especially basicity, are different from each aggregation states and structures, and the basicity would be tunable by adjusting solvents and Lewis base donors.

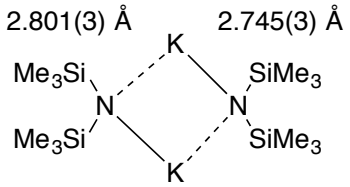


Figure 1-1-4. Aggregation States of KHMDS without Solvation in Solid State

The basicity of alkali-metal secondary amides is the most important factor to evaluate their deprotonating abilities and utilities. Although various factors such as choice of alkali-metal, solvent effect, its aggregation state, and so on affect the deprotonating ability, the simplest and the most direct way to determine the basicity is modification of structure of the amide anion part. The basicity of the amide anions roughly correlates with acidity of the corresponding conjugated acids, and more weakly acidic conjugated acid provides more strongly basic alkali-metal secondary amide anions. Although the acidity can be influenced by an analysis method, solvent, temperature, and so on, a general tendency of the acidity cannot change (**Table 1-1-1**).[6] The most strong basic amide anion would be TMP among typical amide anions, and the pK_a value of the conjugate acid is around 37. DIA shows almost same or lower pK_a values, and the basicity of DIA is considered to be almost the same or slightly weak compared to TMP. The basicity of HMDS would be much lower than TMP and DIA, and the difference is at least 5 in pK_a order. The basicity difference is derived from electronic and steric effects of the alkali-metal secondary amides, and the lowest basicity of HMDS among them is explained by anion stabilization effect of silicon atoms. A wide range of basicity can be realized the alkali-metal secondary amides, and changing the amide anion part is the most simple way to adjust the basicity.

Table 1-1-1. Acidity of Secondary Amines[1b]

TMP	DIA	HMDS	Method
37.3	35.7	29.7	^{13}C NMR spectroscopy in THF[6a,b]
37.9	34.4	–	^{1}H NMR spectroscopy in THF[6c]
35.53	35.41	24.37	Calculated value in THF[6d]

Weakly acidic carbonyl and related compounds

Carbonyl compounds are among the most important and fundamental building blocks in pharmaceuticals and natural products, and studies of the carbonyl compounds have long history.[7] α-Carbanion formation of the carbonyl compounds is well-known phenomena, and this carbanion formation is a key to functionalize the α-position of carbonyl compounds.[8] Base species are usually used for accelerating the reaction rate of the α-functionalization of the carbonyl compounds because equilibrium between the carbonyl compound and their corresponding enolate is shifted to form much amount of the enolate. When the acidity of the carbonyl compounds is very low, addition of

strong Brønsted base species are inevitable for the formation of the enolate because the enolates are much less favored in the equilibrium compared to the corresponding carbonyl compounds under non-basic conditions. Therefore, the reactions using weakly acidic carbonyl compounds such as simple amides and esters without any activating group at the α-position always needs strong Brønsted base species. However, the strong Brønsted base is usually required more than a stoichiometric amount for the smooth reactions[9,10] because of stability of the corresponding conjugated acid, and there are few examples of base-catalyzed reactions using simple amides or esters (**Figure 1-1-5**).[11]

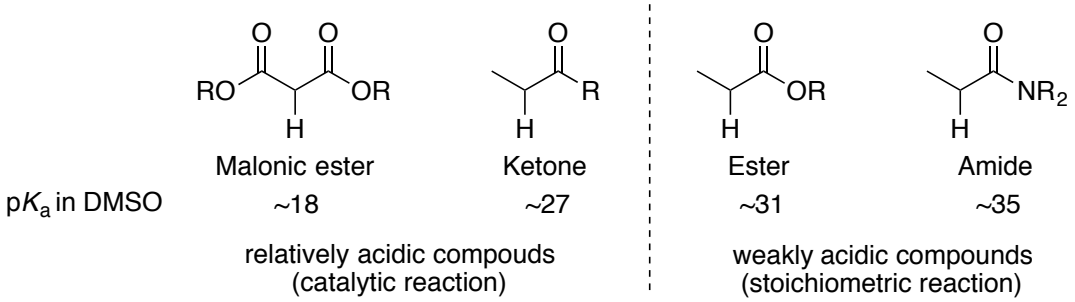
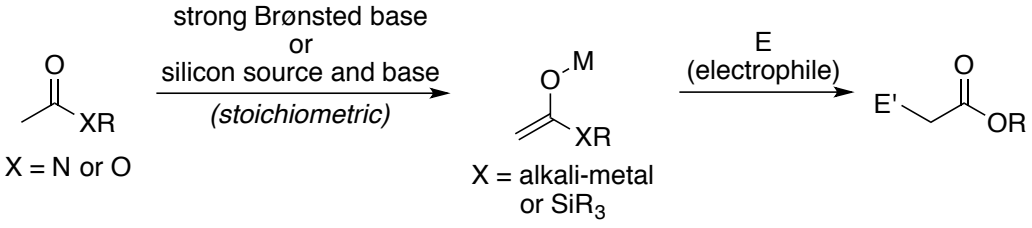


Figure 1-1-5. Representative Carbonyl Pronucleophiles and Their Acidity[12]

Catalytic direct reactions using simple esters and amides are very challenging topics even now. In traditional methods, these pronucleophiles have been activated by deprotonation with a stoichiometric amount of strong Brønsted base[9] or by formation of an isolable silicon enolate with a stoichiometric amount of silicon source[10] (**Scheme 1-1-5**), and these methods are not atom economical.



Scheme 1-1-5. Traditional Reactions Using Esters and Amides

Recently, ester equivalents, which have the same oxidation state as esters and amides, have been developed, and their catalytic reactions are achieved (**Figure 1-1-6**).[13] In general, additional functional group of the ester equivalents is a key to activate the α-hydrogen atoms by changing an electronic property α-C–H bond, and the acidity of them is enhanced.

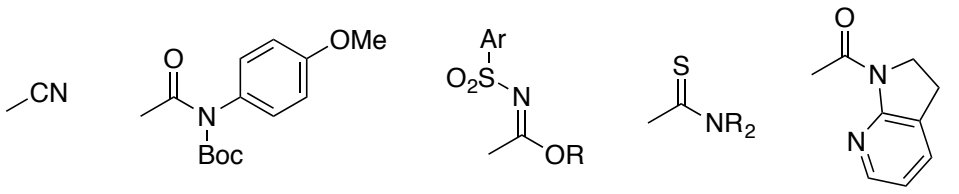
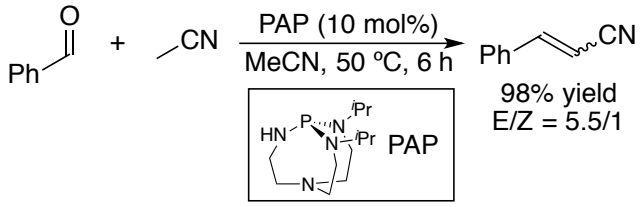


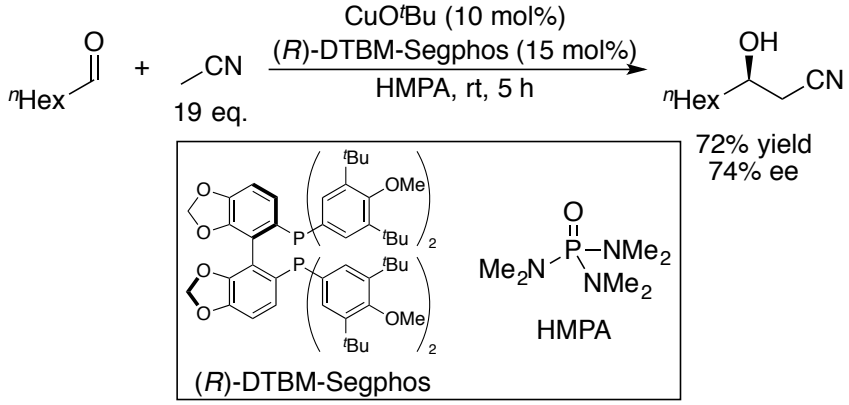
Figure 1-1-6. Ester Equivalents[13]

Verkade *et al.* demonstrated first example of catalytic reactions using acetonitrile in 1998 (**Scheme 1-1-6**).[13a] In the reactions, acetonitrile reacted with aldehyde in the presence of an organo-superbase catalyst, proazaphosphatrane (PAP), to afford the desired α,β-unsaturated nitriles in high yields.



Scheme 1-1-6. Catalytic Aldol Condensation of acetnitrile

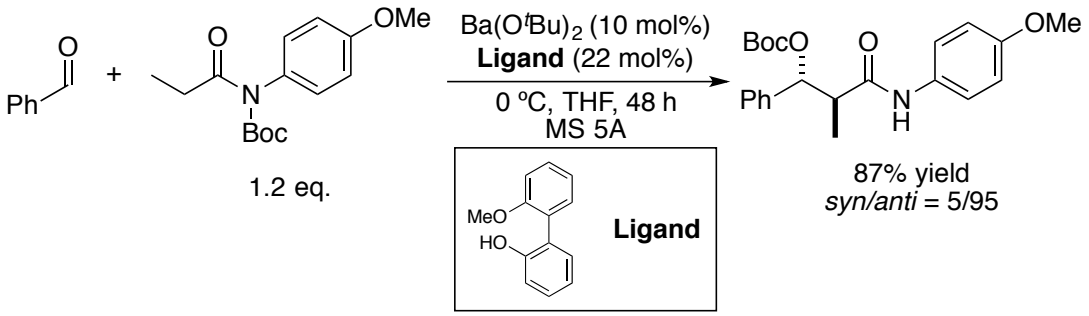
First example of the asymmetric variants was reported in 2005 (**Scheme 1-1-7**).[13f] Kanai and Shibasaki *et al.* achieved catalytic asymmetric cross aldol-type reactions by using CuO^tBu catalyst. A bisphosphine ligand, (*R*)-DTBM-Segphos, controlled the stereoselectivities to afford the desired adduct with moderate to good enantioselectivities. Although several catalytic reactions using alkylnitriles have been developed to date, examples of the successful enantioselective reactions were limited.



Scheme 1-1-7. Catalytic Asymmetric Aldol-type Reaction of acetnitrile

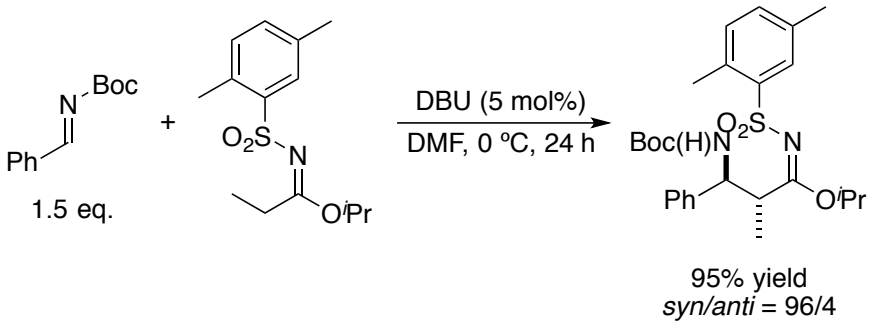
In 2006, our group reported catalytic aldol reactions using (*N*-Boc)acylanisidide in the presence of Ba(O^tBu)$_2$ (**Scheme 1-1-8**).[13g] The reaction proceeded with *anti*-selectivity, and initial trial of asymmetric reaction implied possibility of

enantioselective reactions. The amide part of the product was converted to carboxylic acid in the presence of $NaNO_2$.



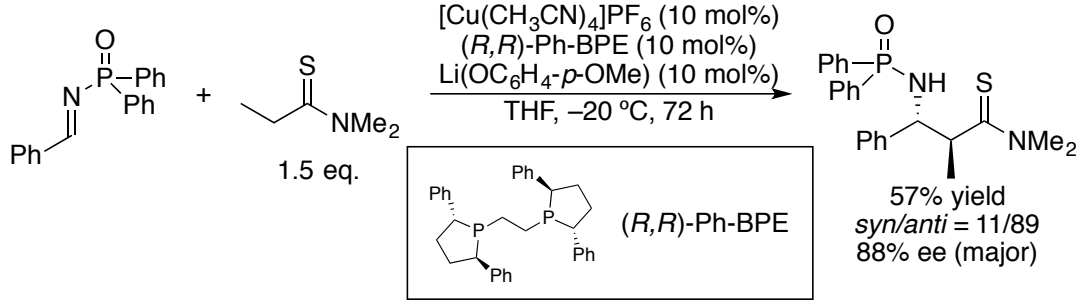
Scheme 1-1-8. Catalytic Aldol Reaction Using (*N*-Boc)propioanisidide

Our group also investigated catalytic Mannich-type reactions using sulfonyl imidates as pronucleophiles in 2008 (**Scheme 1-1-9**).[13i] The sulfonyl imidates, which acidity was adjusted by an additional functional group on the nitrogen atom, were deprotonated by DBU smoothly, and the desired Mannich-type reactions proceeded with *anti*-selectivities. The sulfonyl imidate parts were converted to an ester under mild basic conditions whereas harsh conditions are required in the presence of acid.



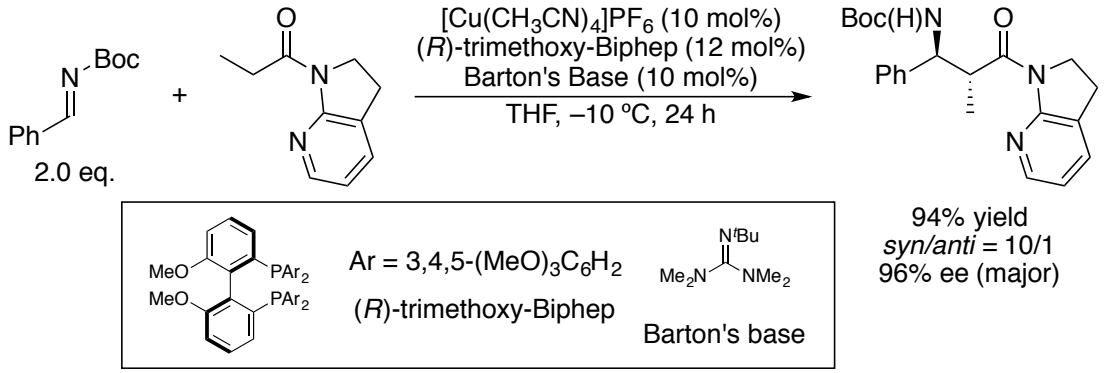
Scheme 1-1-9. Catalytic Mannich-type Reaction Using Sulfonyl Imidate

Kumagai and Shibasaki *et al.* were focused on interaction between a thioamide and a soft Lewis acid for activation of an α-hydrogen atom, and they have developed catalytic asymmetric Mannich-type reactions using thioamides in the presence of a Cu(I) catalyst (**Scheme 1-1-10**).[13j] Addition of a chiral phosphine ligand controlled not only diastereoselectivities but also enantioselectivities well, and highly stereoselective reactions were achieved. The thioamide moiety was transformed various kinds of other functional groups such as thioester, amide and amine.



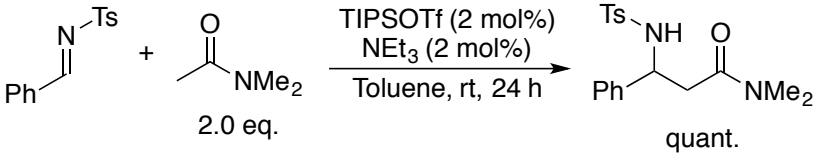
Scheme 1-1-10. Catalytic Mannich-type Reaction Using Thioamide

Recently, the same group has investigated 7-azaindole amides as ester equivalents. In the first report of the amides, they introduced an electron-withdrawing group at the α-position, and coordination of a Cu(I) catalyst to the electron-withdrawing group and the nitrogen atom on the azaindoline helped to form distorted amide structure.[13l] The distorted amide structure diminished amide conjugation, and acidity of the α-hydrogen atom was enhanced. On the basis of the concept, they reported catalytic asymmetric aldol reactions using 7-azaindole amides. However, acidity of the α-position was also elevated by introduction of electron-withdrawing group, and the amides were not simple ester equivalents. More recently, the amide without any activating group at the α-position was investigated in catalytic asymmetric Mannich-type reactions (**Scheme 1-1-11**).[13o] They found that Cu(I) catalyst was coordinated to the nitrogen atom on the azaindole and oxygen atom of the carbonyl part, and the coordination would lead to the similar situations of the amides with an electron-withdrawing group. Finally, the 7-azaindole amides reacted with *N*-Boc imine well to afford the desired product in high yields with high stereoselectivities. The azaindole amide parts were also easily converted to other functional group such as an aldehyde, a carboxylic acid, and so on. Although these ester equivalents were successfully achieved catalytic reactions with high stereoselectivities, the ester equivalent parts always needed several steps for their conversion and preparation. Thus, direct use of the simple amides and esters are more favorable from the viewpoint of sustainable chemistry.



Scheme 1-1-11. Catalytic Mannich-type Reaction Using 7-Azaindole Amide

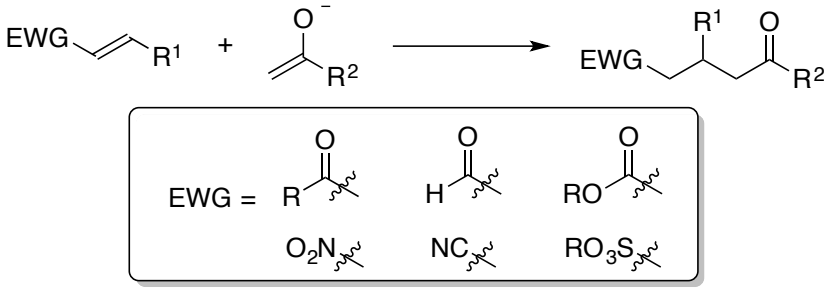
In 2011, catalytic Mannich-type reactions using simple amides appeared (**Scheme 1-1-12**).[11a] The catalyst of the reaction was triisopropylsilyl triflate (TIPSOTf) and Et_3N, and N-Si bond would be cleaved when the catalyst was regenerated. The asymmetric variant was also conducted by using a Cu catalyst and bisphosphine ligand, and the desired 1,4-adduct was obtained with moderate enantioselectivity. Although this is the first example of the catalytic Mannich-type reactions using simple amides, only the simple amides and ketones could be employed as pronucleophiles, and an ester and a thioester were not applicable. Therefore, catalytic reactions using weakly acidic carbonyl compounds have many limitations even now, and more general methods to activate these pronucleophiles are highly required.



Scheme 1-1-12. Catalytic Mannich-type Reaction Using Simple Amides

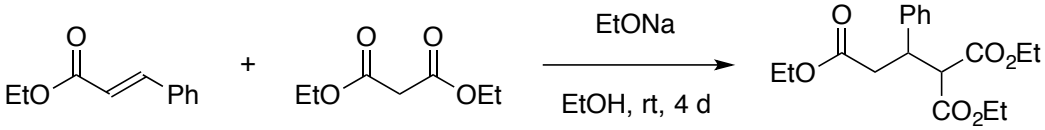
1,4-Addition Reactions

1,4-Addition reactions, which are nucleophilic conjugate addition reactions to the *β*-position of electrophiles, are the most successful and promising methods to provide *β*−functionalized products.[7] Generally, these reactions required electron-deficient alkenes or alkynes as a good electrophile, and various kinds of functional groups can be introduced on the alkenes or alkynes theoretically. In addition, these reactions usually proceed with perfect atom economy when the reactions are conducted under proton transfer conditions.[8] Therefore, 1,4-addition reactions under the proton transfer conditions are one of the most ideal reactions to prepare various kinds of *β*-functionalized products efficiently (**Scheme 1-1-13**).[14]



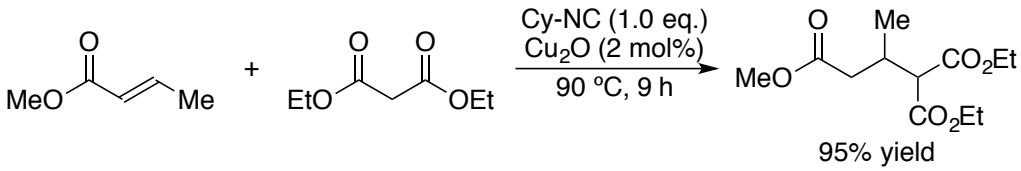
Scheme 1-1-13. General Scheme of 1,4-Addition Reaction

Arthur Michael found that diethyl malonate reacted with ethylcinnamate in the presence of EtONa, and this was the first example of a 1,4-addtion reaction using a carbon nucleophile (**Scheme 1-1-14**).[15] Nowadays, the 1,4-addition reactions using carbon nucleophiles are called as Michael reaction based on his name.



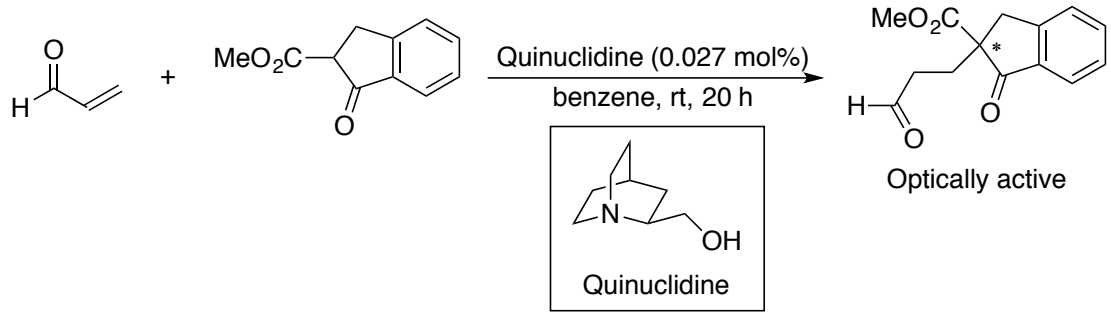
Scheme 1-1-14. First Example of 1,4-Addition Reaction Using Carbon Nucleophile

After the Michael's work, various kinds of 1,4-addition reactions have been reported. The first report of transition metal-catalyzed 1,4-addition reaction appeared in Saegusa's work in 1972.[16] They treated active pronucleophiles such as malonates with methyl acrylate, acrylonitrile, and ethyl propionate with Cu_2O and cyclohexyl isocyanide (CyNC) complex (**Scheme 1-1-15)**.



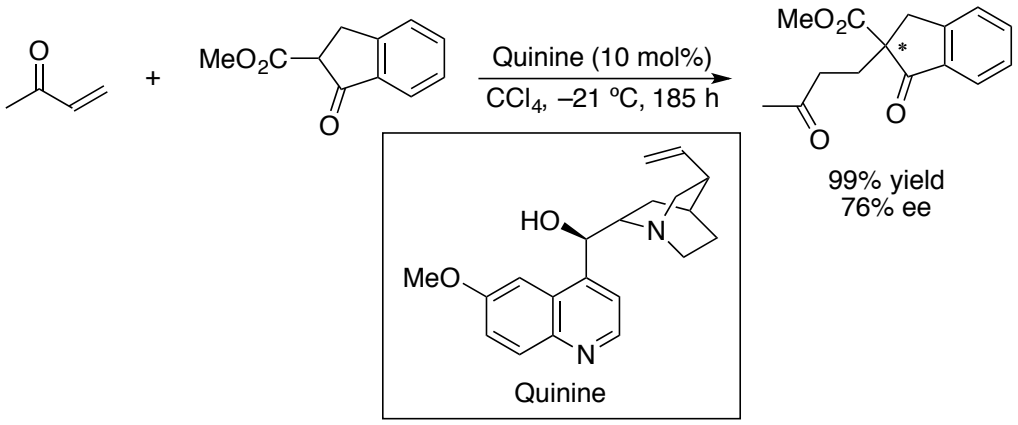
Scheme 1-1-15. Transition Metal Catalyzed 1,4-Addition Reaction

The first report of catalytic asymmetric 1,4-addition reactions using chiral catalyst appeared in 1973 (**Scheme 1-1-16**). Långström and Bergson demonstrated the asymmetric 1,4-addtion reaction of 2-carboxy-1-indanone by using chiral alcohol as a catalyst.[17] Unfortunately, they did not measure the accurate enantioselectivity of the product, and they claimed the enantioselection by only measuring optical rotation of the product.



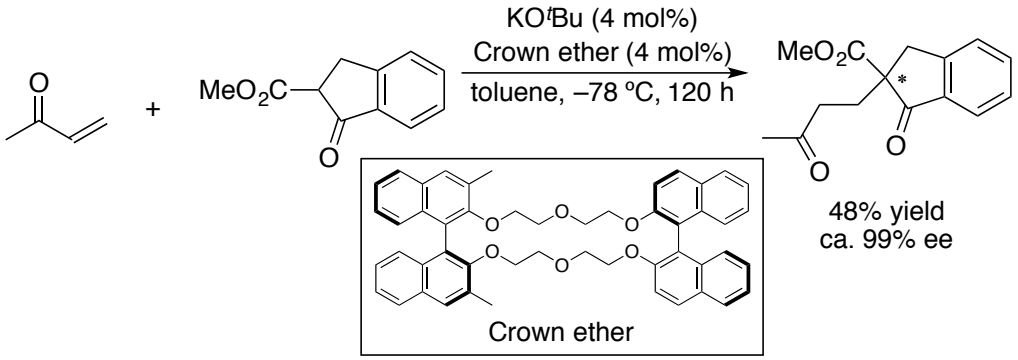
Scheme 1-1-16. Catalytic 1,4-Addition Reaction Using Quinuclidine Catalyst

On the other hand, Wynberg and Helder reported catalytic asymmetric 1,4-addition reactions with a quinine catalyst, and this was the first example of the asymmetric variant to determine the enantiomeric excess of the product (**Scheme 1-1-17**).[18] The quinine catalyst showed possibility of the enantioselective reactions, and the desired products were obtained with good enantioselectivity.



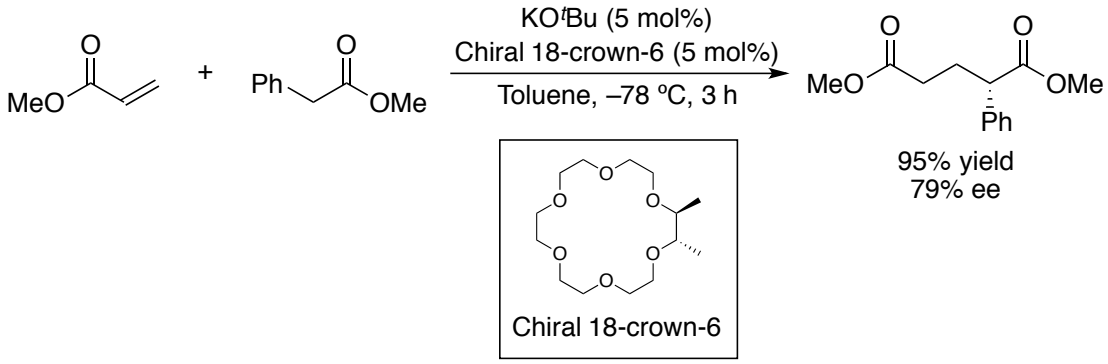
Scheme 1-1-17. Catalytic 1,4-Addition Reaction Using Quinine Catalyst

Cram *et al.* investigated the same catalytic asymmetric reaction as the Wynberg and Helder's work by using potassium KO^{t}Bu and a chiral crown ether ligand (Scheme 1-1-18).[19a] Although they achieved highly enantioselective reaction, the substrate was limited to methyl vinyl ketone, and another electrophile, methyl acrylate, gave the desired product with moderate enantioselectivity.



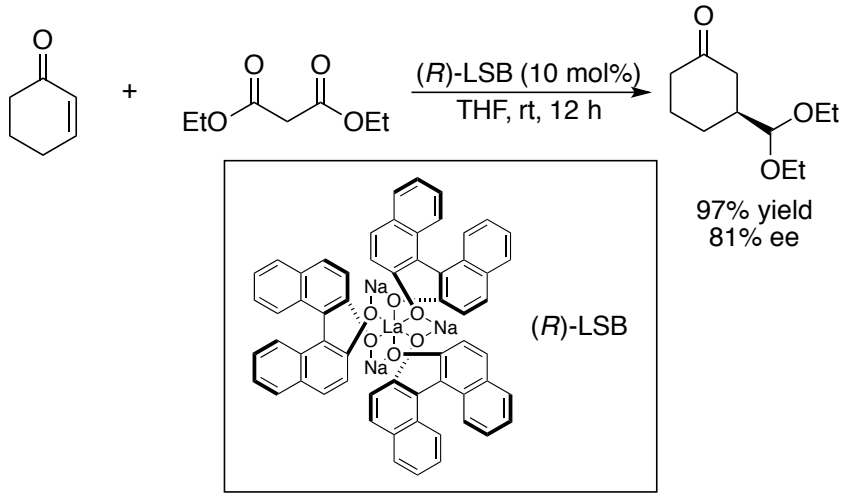
Scheme 1-1-18. Catalytic 1,4-Addition Reaction Using KO^{t}Bu and Chiral Crown Ether Catalyst

The combinations of alkali-metal alkoxides and chiral crown ethers were effective catalysts for catalytic asymmetric 1,4-addition reactions, and several highly enantioselective reactions were accomplished.[19] For example, Koga *et al.* developed catalytic asymmetric 1,4-addition reactions of methyl phenylacetate by using KO^{t}Bu and a simple chiral crown ether.[19b] In the reaction, dimethyl 18-crown-6 was a good ligand to control enantioselectivities of the products, and moderate to good enantioselectivities were observed.



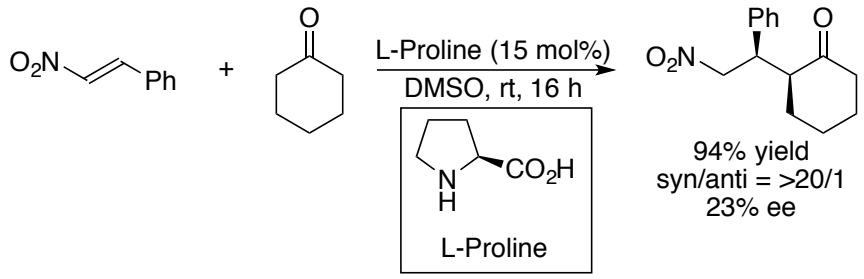
Scheme 1-1-19. Catalytic 1,4-Addition Reaction Using KO^{t}Bu and Chiral Crown Ether Catalyst

In 1995, Shibasaki *et al.* reported catalytic asymmetric 1,4-addition reactions of malonates using a heterobimetallic multifunctional catalyst.[20] The catalyst, lanthanum -sodium-(*R*)-Binol complex ((*R*)-LSB), acted as both a Brønsted base and a Lewis acid, and the enantioselectivities of the reactions were controlled well.



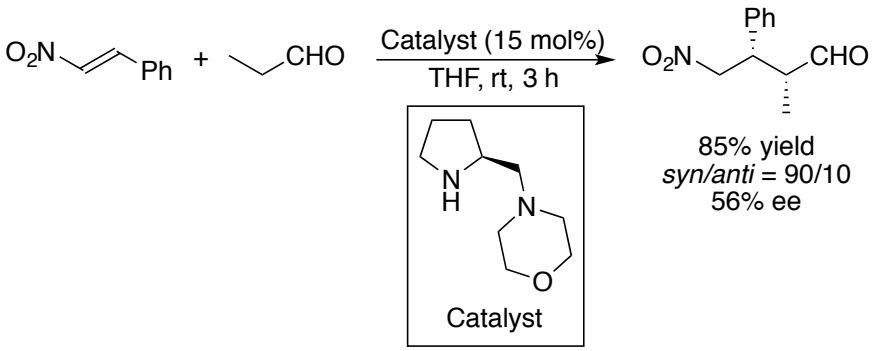
Scheme 1-1-20. Catalytic 1,4-Addition Reaction Using LSB

Enamine-catalyzed 1,4-addition reactions are also important for controlling the enantioselectivities. In 2001, List *et al.* reported proline-catalyzed asymmetric 1,4-addition reactions of unmodified ketones (**Scheme 1-1-21**).[21] Although this was the first example of the enamine-catalytic reactions, the enantioselectivity was poor.



Scheme 1-1-21. Catalytic 1,4-Addition Reaction Using Proline Catalyst

In the same year, Barbas III *et al*. also has investigated catalytic asymmetric 1,4-addition reactions of aldehydes using a catalyst derived from proline (**Scheme 1-1-22**).[22] In this case, the catalyst controlled the stereoselectivities well, and good to high diastereoselectivities and moderate to good enantioselectivities were achieved. Nowadays, many kinds of enamine-catalyzed reactions are available and usually achieve highly stereocontrolled reactions.



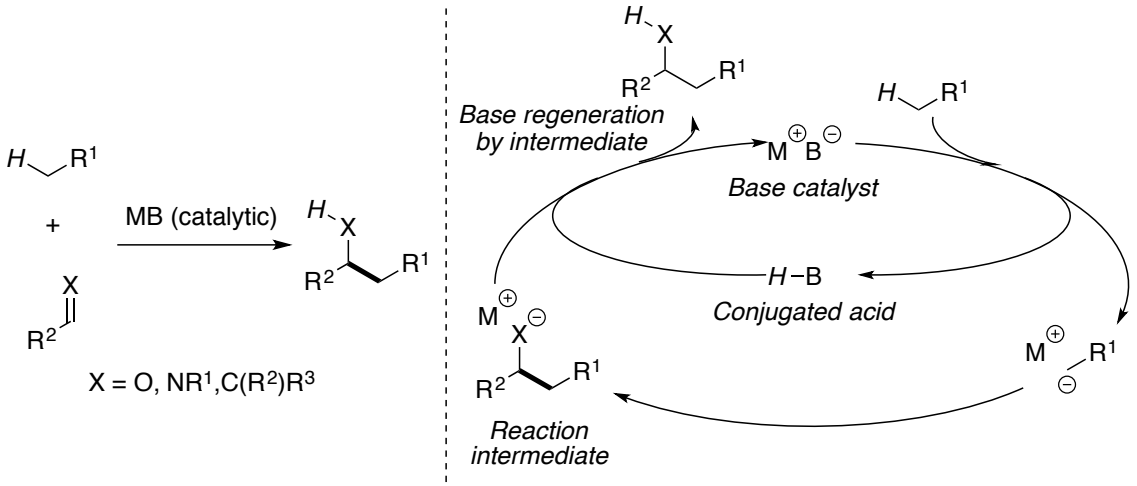
Scheme 1-1-22. Catalytic 1,4-Addition Reaction Using Proline-derived Catalyst

Nowadays, catalytic asymmetric 1,4-addition reactions have been widely developed. However, examples of using weakly acidic carbonyl compounds such as simple esters and amides as pronucleophiles are limited even now.

1-2 Concept of Strong Brønsted Base-Catalyzed Reactions

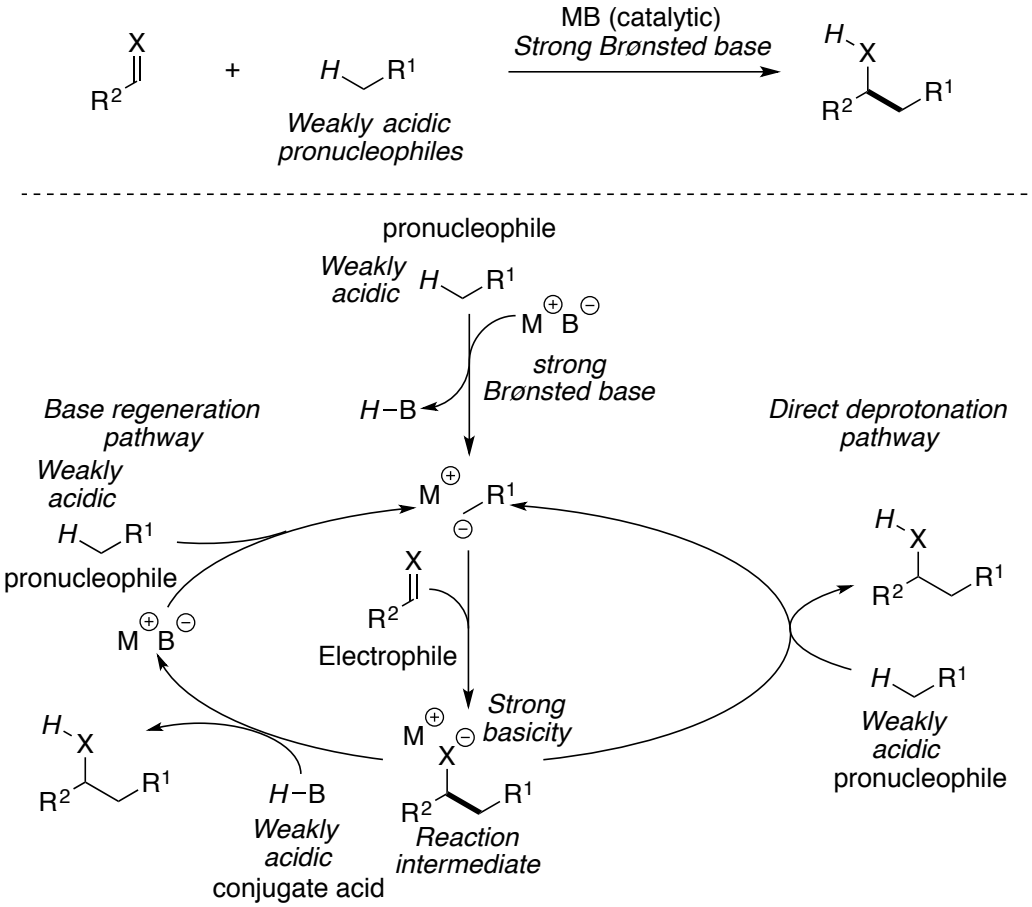
Brønsted base-catalyzed carbon-carbon (C–C) bond forming reactions are one of the most fundamental and successful methods for construction of complex molecules in organic synthesis.[7] In general, the reactions proceed under proton transfer conditions, which do not change a sum of molecular weights between start and end point of the reactions, and the excellent atom economy is achieved due to this nature.[8] However, successful examples of the reactions are limited to those using only relatively acidic pronucleophiles,[23] and weakly acidic pronucleophiles are said to be difficult to be used in the reactions.[11]

One approach for the reactions of the weakly acidic pronucleophiles is to use strong Brønsted base catalysts. However, they have a critical issue for their catalytic turnover, and it is considered to be very difficult to achieve strong Brønsted base-catalyzed reactions without designing catalytic cycles. In fact, very few examples of them have been accomplished to date, and almost all cases require special substrates or harsh conditions.[24] A key of the catalytic turnover issue is inefficient regeneration of the base species under the strong Brønsted base-catalyzed conditions. In a typical Brønsted base-catalyzed reactions, the base catalysts are regenerated from the corresponding conjugate acid, and the regeneration is caused by a reaction intermediate that is formed after C–C bond formation (**Scheme 1-2-1**). Whereas both the conjugate acid and the reaction intermediate are formed even in the strong Brønsted base-catalyzed reactions, basicity of the intermediate is not sufficiently strong to deprotonate the conjugated acid. Thus, I hypothesized that if the intermediates were designed to possess adequately strong Brønsted basicity to regenerate the base catalyst, the strong Brønsted base-catalyzed reactions would be achieved without any special condition (**Scheme 1-2-2**, Base regeneration pathway). As another reaction pathway, direct deprotonation of the next pronucleophile promoted by the reaction intermediates would be considered when acidity of the pronucleophile is equal to or higher than the conjugated acid (**Scheme 1-2-2**, Direct deprotonation pathway).[11b] In both pathways, strongly basic reaction intermediates (= product base) play a key role for the efficient catalytic turnover in the strong Bronsted base-catalyzed reactions.

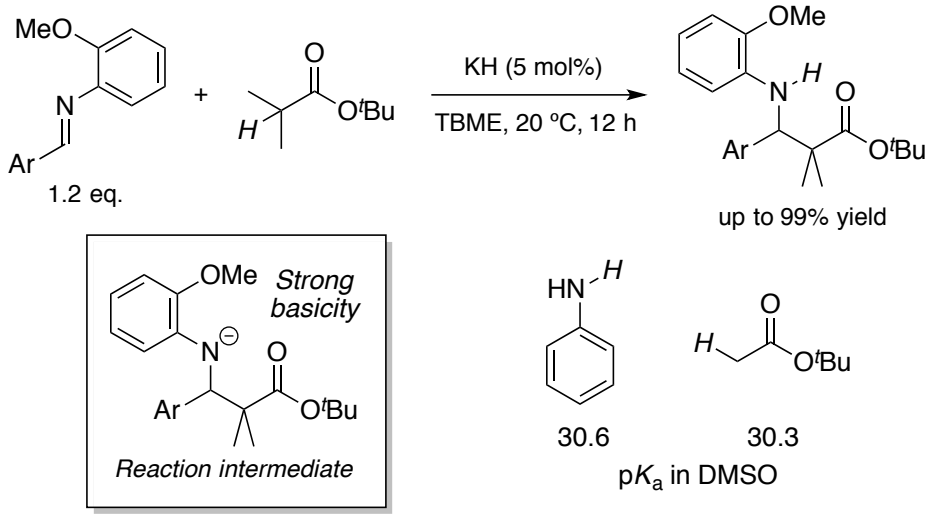


Scheme 1-2-1. Catalytic Cycle of Typical Brønsted Base-Catalyzed Reactions (Base Regeneration Mechanism)

Based on the hypothesis of the product base, I have developed catalytic Mannich-type reactions using simple esters without any activating group at the *α*-positions.[11b] In the reactions, potassium hydride (KH) was employed as a strong Brønsted base catalyst to fix the catalytic cycle to the direct deprotonation pathway. The key reaction intermediates were designed to form aryl amide anion species because acidity of anilines, which were conjugate acids of arylamides, were almost same as those of esters (pK_a in DMSO; aniline: 30.6 vs *tert*-butyl acetate: 30.3[12]), and basicity of the arylamides was sufficiently strong to deprotonate the next esters directly. Thus, *N*-*o*-methoxyphenyl (OMP), which was removed by oxidative cleavage using ceric ammonium nitrate (CAN), etc., was introduced as a protecting group of the imines. It was found that the Mannich-type reactions of esters proceeded well in the presence of only a catalytic amount of KH when the *N*-OMP imines were used as electrophiles (**Scheme 1-2-3**). In addition, the *N*-OMP imines were applicable to other weakly acidic carbonyl and related pronucleophiles such as simple amides and alkylnitriles. The successful examples of the Mannich-type reactions indicated that a concept of the product base could be applicable to various kinds of reactions. However, only aryl imines were available to this concept at this stage, and expansion of kinds of applicable electrophiles were needed to demonstrate utilities of this concept. Therefore, I focused on investigation of new catalytic reactions using weakly acidic pronucleophiles based on this concept in my PhD. course.



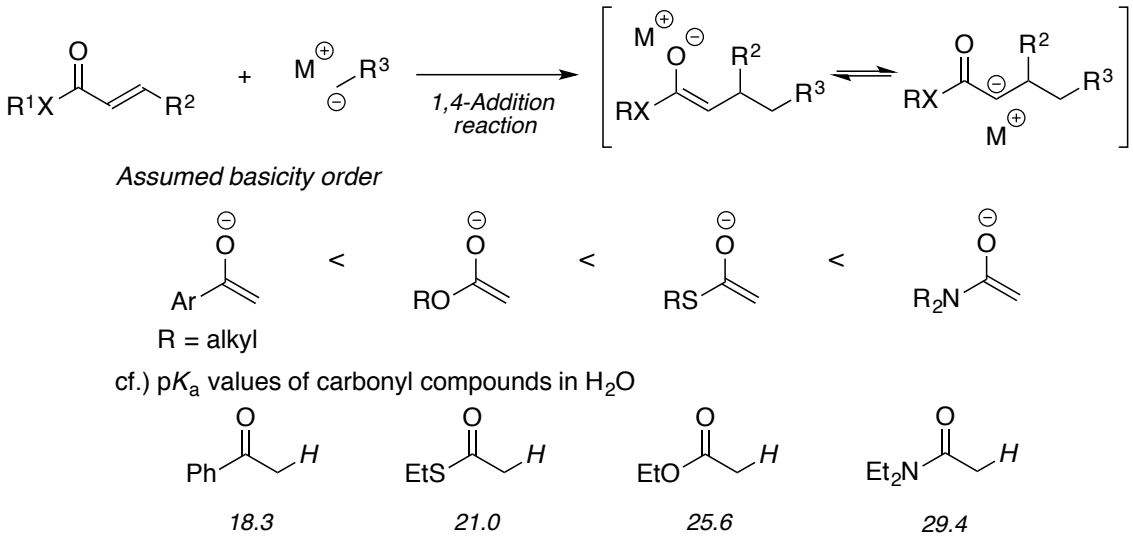
Scheme 1-2-2. Catalytic Cycle of Strong Brønsted Base-Catalyzed Reactions



Scheme 1-2-3. Catalytic Mannich-type Reactions Using Simple Esters

1-3 Reaction Design

Initially, catalytic reactions using simple amides were designed based on the concept of the product base. A key to achieve the catalytic turnover was to form a strongly basic reaction intermediate in the catalytic cycle. As candidates of such kinds of electrophiles, *α,β*-unsaturated carbonyl compounds, which gave metal enolate anions after a 1,4-addition step, were selected because basicity of the enolate anions were electronically tunable by choosing appropriate carbonyl moieties. In my hypothesis, basicity of enolate anions would roughly correlate with acidity of *α*-hydrogen atoms of the corresponding carbonyl compounds. Thus, metal enolate anions derived from weakly acidic carbonyl compounds should have strong basicity (**Scheme 1-3-1**).

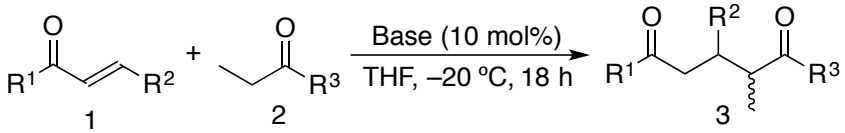


Scheme 1-3-1. Reaction Intermediates of 1,4-Addition Reactions

On the basis of the concept of the product base, catalytic 1,4-addition reactions of *N,N*-dimetylpropionamide (**2a**) were conducted with several cinnamate derivatives in the presence of a catalytic amount of KH (**Table 1-3-1**). Whereas chalcone (**1a**), *S-tert*-butylthio cinnamate (**1b**) and methyl cinnamate (**1c**) did not react at all or reacted sluggishly with propionamide **2a** (Entries 1–3), only *N,N*-tetramethylenecinnamamide (**1d**) gave the desired 1,4-adduct **3da** in high yield (Entry 4). It was likely that basicity of the reaction intermediate would correlate with acidity of the corresponding carbonyl compounds. That is, only an amide enolate moiety would possess sufficiently strong basicity to deprotonate a *α*-hydrogen atom of propionamide **2a** due to low acidity of the corresponding simple amide moiety (**Scheme 1-3-1**). Thus, optimization of the reaction conditions was continued using cinnamamide **1d** in the presence of catalytic amounts of metal amides. Screening of a metal cation part indicated that $KN(SiMe_3)_2$ (KHMDS) was the best alkaline metal amide catalyst compared to other metal amides (Entries 7 vs 5, 6). A poor yield of LiHMDS would be related to its low basicity and

aggregation state due to relatively high Lewis acidity of lithium cation (Entry 5). The sizes of alkaline metal cations seemed to affect diastereoselectivities judging from results of the reactions using NaHMDS and KHMDS (Entries 6 vs 7). In the racemic reactions, the 1,4-addition steps would proceed in 8 membered transition states, and a large metal cation was considered to stabilize the transition state.[9a] Sterically hindered propionamide, *N,N*-diphenylpropionamide (**2b**), improved the diastereoselectivity probably due to enhancement of *E/Z* ratio of the nucleophilic enolate (Entry 8). Finally, it was found that the catalytic reactions proceeded well with 1.2 equivalents of propionamide **2b** (Entry 9), and almost the same reactivity and diastereoselectivity were observed when *N,N*-dimethylcinnamamide (**1e**) was employed as an electrophile (Entry 10).

Table 1-3-1. Catalytic 1,4-Addition Reactions of Amides



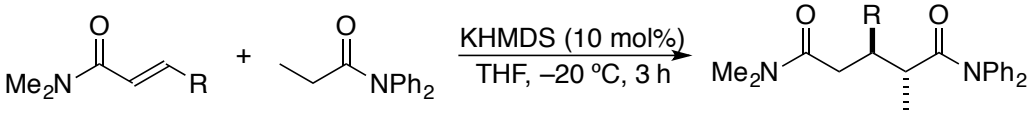
Entry	1	2	Base	Yield (%)	*anti*/*syn*
1[b]	**1a**	**2a**	KH	0	–
2[b]	**1b**	**2a**	KH	<5	–
3[b]	**1c**	**2a**	KH	0	–
4[b]	**1d**	**2a**	KH	quant.	90:10
5	**1d**	**2a**	LiHMDS	9	65:35
6	**1d**	**2a**	NaHMDS	quant.	77:23
7	**1d**	**2a**	KHMDS	97	90:10
8	**1d**	**2b**	KHMDS	97	98:2
9 [c,d]	**1d**	**2b**	KHMDS	86	98:2
10 [c,d]	**1e**	**2b**	KHMDS	87	98:2

1a: R^1 = Ph, R^2 = Ph; **1b:** R^1 = OMe, R^2 = Ph; **1c:** R^1 = S^{t}Bu, R^2 = Ph; **1d:** R^1 = N-$(CH_2)_4$-, R^2 = Ph; **1e:** R^1 = NMe_2, R^2 = Ph; **2a:** R^3 = NMe_2; **2b:** R^3 = NPh_2. [a] Reaction conditions (unless otherwise noted): **1** (0.400 mmol), **2** (0.800 mmol), base catalyst (0.0400 mmol), THF, –20 °C, 18 h. [b] The reaction was conducted at 20 °C. [c] Compound **2b** (1.2 equiv) was used. [d] Reaction time: 3 h.

The substrate generality was then surveyed under the optimized reaction conditions (**Table 1-3-2**). Positions of a methyl substituent on the terminal aromatic ring of *α,β*-unsaturated amides did not influence the diastereoselectivities (Entries 1–3). *α,β*-Unsaturated amides bearing electron-donating and withdrawing groups on the aromatic rings reacted with propionamide **2b** smoothly (Entries 4, 5). When sterically hindered aromatics, 1- and 2- naphthyl groups, were introduced on the terminal position, the desired reactions proceeded efficiently without decrease of the diastereoselectivities

(Entries 6, 7). KHMDS was not good catalyst for the catalytic reactions with *N,N*-dimethylcrotonamide (**1g)**, which afforded a dimer of the electrophile **1g** without any formation of the desired 1,4-adduct (**3bg**). Probably, acidity of a γ-hydrogen atom of crotonamide **1g** was higher than that of propionamide **2b**, and deprotonation of the γ-hydrogen atom proceeded prior to the α-hydrogen atom of the propionamide. To suppress the side reaction, NaHMDS was chosen as a base catalyst instead of KHMDS. Fortunately, the catalytic reaction proceeded smoothly without formation of any side product when a catalytic amount of NaHMDS was employed (Entry 8). In this investigation, it was found that a wide range of α,β-unsaturated amides were applicable to the catalytic 1,4-addition reactions of simple propionamides.

Table 1-3-2. Substrate Generality of Catalytic 1,4-Addition Reactions[a]



1 **2b** 1.2 eq. **3**

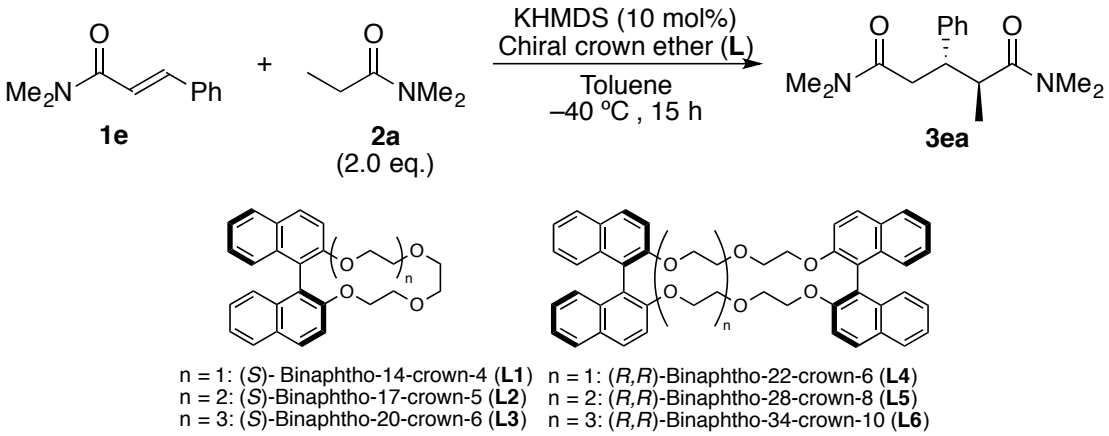
Entry	R	Yield (%)	*anti/syn*
1	*p*-MeC_6H_4 (**1f**)	89	99/1
2	*m*-MeC_6H_4 (**1g**)	quant.	99/1
3	*o*-MeC_6H_4 (**1h**)	84	99/1
4	*p*-$MeOC_6H_4$ (**1i**)	86	98/2
5	*p*-ClC_6H_4 (**1j**)	91	98/2
6	1-Naphthyl (**1k**)	quant.	99/1
7	2-Naphthyl (**1l**)	quant.	99/1
8[b]	Me (**1m**)	83	98/2

[a] Reaction conditions (unless otherwise noted): **1** (0.400 mmol), **2** (0.480 mmol), KHMDS (0.0400 mmol), THF, –20 °C, 3 h. [b] NaHMDS was used as base catalyst instead of KHMDS.

1-4 Optimizations of Asymmetric Reaction Conditions

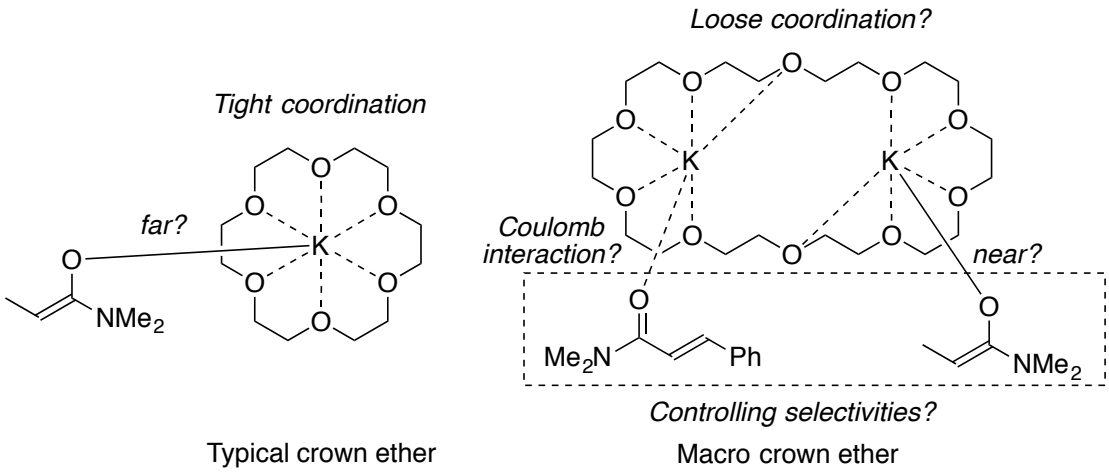
Investigation of asymmetric variants of the 1,4-addtion reactions was then started. First of all, chiral crown ethers were screened for modifying chiral environments around the potassium cation (**Table 1-4-1**).[19] Typical binaphtho crown ethers, binaphtho-14-crown-4 (**L1**), binaphtho-17-crown-5 (**L2**), binaphtho-20-crown-6 (**L3**) and binaphtho-22-crown-6 (**L4**), did not construct suitable chiral environments (Entries 1-4). In those cases, a key to control the stereoselectivity would be only steric factors around the potassium enolate anion formed, and the cinnamamide probably approached to the enolate without any interaction with the potassium cation. In addition, distance between the enolate anion and the potassium cation was considered to be long because ether chains of the chiral ligands tightly coordinated and protected the cation, and the chiral environment around the cation would not affect the near enolate anion. On the basis of the hypothesis, I focused on macro crown ethers as chiral ligands. I think macro crown ethers would coordinate to a potassium cation loosely compared to small ring size crown ethers, and two potassium cations in the crown ethers could control positions of the cinnamamide and the enolate if the cavity size was enough big to contain two potassium cations (**Scheme 1-4-1**). Thus, a chiral macro crown ether, binaphtho-34-crown-10 (**L6**), was synthesized in 4 steps, and the 1,4-addition reaction was conducted by using 2:1 ratio of KHMDS and **L6** due to making a 2:1 complex. Gratifyingly, the catalyst system afforded the desired 1,4-adduct with high enantioselectivity (Entry 6). On the other hand, a little smaller ring size binaphtho crown ether, 28-crown-8 (**L5**), decreased the enantioselectivity compared to **L6** (Entry 5).

Table 1-4-1. Ligand Screening[a]



Entry	L (mol%)	Yield (%)	*anti*/*syn*	*ee* (%)
1	**L1** (11)	86	98:2	60[b]
2	**L2** (11)	77	92:8	8[b]
3	**L3** (11)	86	91:9	41[b]
4	**L4** (11)	90	91:9	3
5	**L5** (5.5)	86	96:4	50
6[c]	**L6** (5.5)	quant.	93:7	88

[a] Reaction conditions (otherwise noted): **1e** (0.400 mmol), **2a** (0.800 mmol), toluene, –40 °C, 15 h, catalyst prepared from KHMDS and **L**. [b] Absolute configuration of the product is opposite. [c] The reaction time was 4 h.

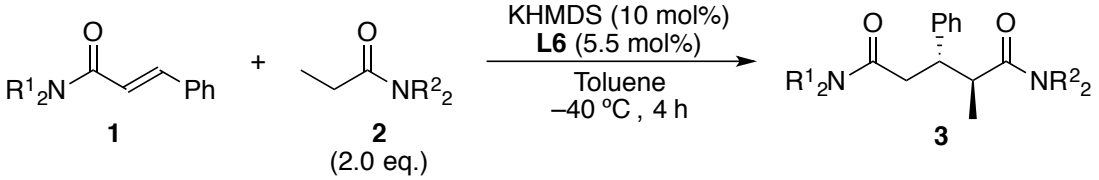


Scheme 1-4-1. Concept of Macro Crown Ethers

Effect of substituents on nitrogen atoms of both nucleophiles and electrophiles were surveyed (**Table 1-4-2**). *α,β*-Unsaturated amides with various alkyl substituents were screened, and it was found that *N,N*-dimethylcinnamamide (**1e**) was an appropriate

electrophile to afford the desired 1,4-adduct with highest diastereoselectivity (Entries 1, 2). In the screening of the nucleophile, diphenylpropionamide **2b** improved diastereo- and enantioselectivity slightly compared to dimethylpropionamide **2a** (Entry 3). In following optimization, *N,N*-dimethylcinnamamide (**1e)** and *N,N*-diphenylpropionamide (**2b)** was employed as optimal substrates.

Table 1-4-2. Substituent Effects[a]

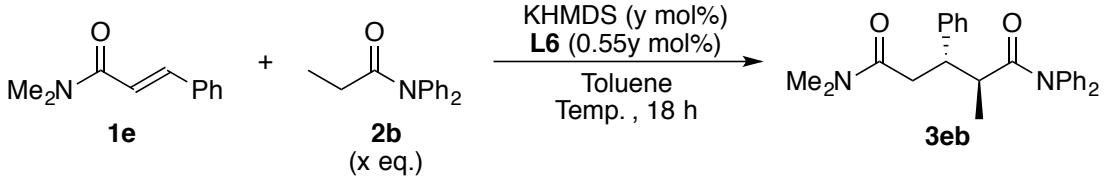


Entry	NR^1_2	R^2	Yield (%)	*anti*/*syn*	*ee* (%)
1	NMe_2 (**1e**)	Me (**2a**)	quant.	93/7	88
2	$N(CH_2)_4$ (**1d**)	Me (**2a**)	quant.	98/2	84
3[b]	NMe_2 (**1e**)	Ph (**2b**)	quant.	>99/1	90

[a] Reaction conditions (otherwise noted): **1** (0.400 mmol), **2** (0.800 mmol), toluene, –40 °C, 4 h, catalyst prepared from KHMDS and **L6**. [b] The reaction time was 15 h.

Optimization of the reaction conditions was conducted (**Table 1-4-3**). Interestingly, the amount of propionamide **2b** affected the enantioselectivity slightly (Entries 1 vs 2). Probably, an excess amount of the propionamide would affect the chiral environment around the potassium cation due to its coordination. The reaction proceeded smoothly even at –78 ºC with improving enantioselectivity (Entry 3). It was likely that catalyst loading was a key to reproduce the result, and a reproducibility issue happened when 8.0 mol% of KHMDS and 4.4 mol% of **L6** were employed (Entry 4). The problem would be caused by an adventitious amount of water, which deactivated the strong Brønsted base catalyst. To omit the possibility, a dehydrating agent, MS 4A, was added to the reaction mixture, and the result was in good agreement with another trial (Entry 5). In addition, an addition of MS 4A in the reaction mixture slightly improved the reactivity (Entries 4 vs 5). Finally, it was found that the catalytic asymmetric reactions proceeded smoothly with excellent stereoselectivities in the presence of 5 mol% of KHMDS and 2.8 mol% of binaphtho-34-crown-10 **L6** (Entry 6).

Table 1-4-3. Optimization of Reaction Conditions[a]



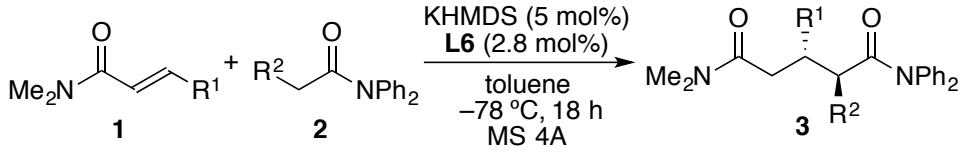
Entry	x	y	Temp. (ºC)	Conc. (M)	Yield (%)	*anti*/*syn*	*ee* (%)
1[b]	2.0	10	–40	0.2	quant.	>99/1	90
2[b]	1.2	10	–40	0.2	quant.	>99/1	93
3	1.2	10	–78	0.2	quant.	>99/1	98
4	1.2	8.0	–78	0.2	7, 64[c]	>99/1[d]	93, 98[c]
5[e]	1.2	8.0	–78	0.2	86, 88[c]	>99/1[d]	97, 98[c]
6[e]	1.2	5.0	–78	0.4	96	>99/1	98
7[e]	1.2	4.0	–78	0.4	29	>99/1	98

[a] Reaction conditions (otherwise noted): **1** (0.400 mmol), **2** (0.800 mmol), toluene, –40 °C, 4 h, catalyst prepared from KHMDS and **L6**. [b] The reaction time was 15 h. [c] The reaction was repeated under the same conditions. [d] Same diastereoselectivities were observed in both trials. [e] MS 4A was added to the reaction mixture.

1-5 Substrate Generality

The substrate scope was then investigated under the optimized reaction conditions (**Table 1-5-1**). The reactions of *α,β*-unsaturated amide bearing *ortho*-, *meta*- and *para*-tol groups as the terminal aromatic rings gave the desired 1,4-adduct in high yields with excellent stereoselectivities (Entries 1–3). Introduction of an electron-donating substituent on the electrophile slightly decreased the reactivity, and elevating the temperature and the catalyst loading were needed to obtain high yield. These modifications did not decrease the stereoselectivities dramatically (Entry 4). On the other hand, an electron-withdrawing substituent, chloro- or bromo-, on the aromatic ring did not influence both the reactivities and the stereoselectivities (Entries 5, 6). An electron-rich heteroaromatic, 2-furyl, was also a good substituent to afford the desired product with complete stereoselectivities (Entry 7). A sterically hindered aromatic group, 1-naphthyl, also did not affect both the reactivity and the stereoselectivities (Entry 8). On the other hand, the substrate bearing another sterically hindered aromatic, 2-naphthyl, had a problem about its solubility in toluene at –78 ºC, and increasing the solvent amount and the reaction temperature were required. Although the bulky group needed slightly hard reaction conditions compared to the optimal ones, high level of stereocontrol was achieved even in the different conditions (Entry 9). Then, aliphatic *α,β*-unsaturated amides were surveyed as electrophiles. Fortunately, *N,N*-dimethylcrotonamide (**1m**) reacted with propionamide **2b** with much suppression of side reactions different from the racemic ones (Entry 10, and see **Table 1-3-2**, Entry 8). A key of the suppression was more acidic hydrogens of pronucleophile **2b** than those of **2a**, and it enhanced a reaction rate of the desired deprotonation. The substrates bearing other aliphatic substituents, isopropyl, isobutyl and cyclohexyl, on the terminal positions also worked well as electrophiles to give the desired adducts without formation of any side product (Entries 11–13). Finally, an amide pronucleophile with a one carbon extended alkyl chain, butyroamide (**2c**), was used in the catalytic reaction, and it was found that a length of the alkyl chains also did not affected the yield and stereoselectivities (Entry 14).

Table 1-5-1. Substrate Generality of Catalytic Asymmetric 1,4-Addition Reactions of Simple Amides[a]



Entry	R^1	**2**	Yield (%)	*anti*/*syn*	*ee* (%)
1[b]	*o*-MeC_6H_4 (**1f**)	**2b**	91	>99:1	98
2	*m*-MeC_6H_4 (**1g**)	**2b**	92	>99:1	97
3[c]	*p*-MeC_6H_4 (**1h**)	**2b**	99	>99:1	96
4[c,d]	*p*-$MeOC_6H_4$ (**1i**)	**2b**	95	>99:1	98
5	*p*-ClC_6H_4 (**1j**)	**2b**	90	>99:1	96
6	*p*-BrC_6H_4 (**1n**)	**2b**	95	>99:1	96
7	2-Furyl (**1o**)	**2b**	93	>99:1	95
8	1-Naphthyl (**1k**)	**2b**	97	>99:1	98
9[c,e,f,g]	2-Naphthyl (**1l**)	**2b**	93	>99:1	93
10[e,h]	Me (**1m**)	**2b**	>99	>99:1	96
11[c,e]	^{i}Pr (**1p**)	**2b**	90	>99:1	98
12[c]	^{i}Bu (**1q**)	**2b**	89	>99:1	97
13[c]	Cy (**1r**)	**2b**	89	>99:1	98
14[c]	Ph (**1d**)	**2c**	94	>99:1	94

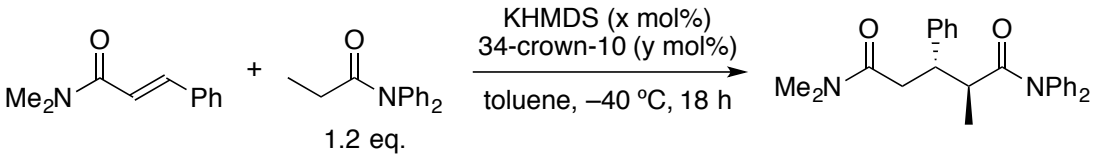
2c: $R^2 = C_2H_5$. [a] Reaction conditions (unless otherwise noted): 1 (0.400 mmol), 2 (0.480 mmol), toluene, MS 4A, –78 °C, 18 h, catalyst prepared from KHMDS (0.0200 mmol) and L4 (0.0112 mmol). [b] Reaction time was 30 h. [c] Reaction was conducted at –60 °C. [d] 8 mol% KHMDS and 4.4 mol% L4 were used. [e] 10 mol% KHMDS and 5.5 mol% L4 were used. [f] Concentration was 0.1 M. [g] Reaction was conducted without MS 4A. [h]2.0 equiv. 1 and 1.0 equiv. 2 were used.

1-6 Catalyst Structure

As use of chiral macro crown ether ligands has been scarcely reported in asymmetric reactions, I was interested in structure of the catalyst. In my investigation, binaphtho-34-crown-10 (**L6)** was designed to capture two potassium cations in its cavity. However, there is no experimental information about the structure at this stage. Thus, I started to conduct several experiments to elucidate it.

First of all, effect of base-ligand ratios was surveyed with fixing the amount of the base species (**Table 1-6-1**). When the reaction was carried out in a 2:1 ratio of KHMDS and **L6**, almost the same yield and stereoselectivities were observed compared to the 1:1 mixture (Entries 1, 2). On the other hand, enantioselectivities of the 3:1, 4:1 and 5:1 mixtures were apparently different from the 1:1 and 2:1 mixtures whereas results of these three were almost the same. (Entries 3-5). Although these same enantioselectivities in entries 1 and 2 looked like contrary to existence of a racemic pathway by free KHMDS (Entry 6), it could be explained by a slower reaction rate of the racemic pathway than the corresponding asymmetric pathway (The asymmetric reactions were completed within 4 h; see **Table 1-4-2**). If the racemic pathway were too slow to change the stereoselectivities, the enantioselectivity gap between the 2:1 and 3:1 mixtures would be explained by structure difference of the active species between these two.

Table 1-6-1. Catalytic Asymmetric 1,4-Addition Reactions of A Diphenylamide in Various Ratios of KHMDS-Ligand[a]



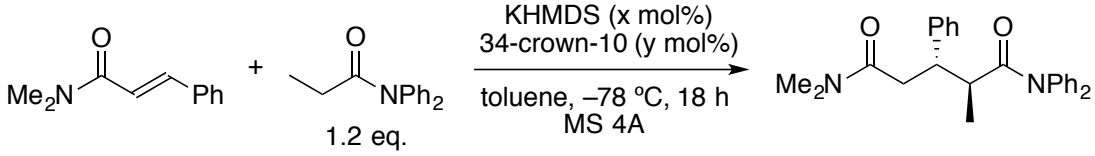
Entry	x	y	Yield (%)	*anti/syn*	ee (%)
1	10	10	98	>99/1	93
2	10	5.0	97	>99/1	92
3	10	3.3	96	>99/1	85
4	10	2.5	92	>99/1	83
5	10	2.0	97	>99/1	85
6	5.0	0	83	>99/1	-

[a] Reaction conditions (otherwise noted): **1** (0.400 mmol), **2** (0.380 mmol), toluene, –40 °C, 18 h, catalyst prepared from KHMDS and **L6**.

Although the enantioselectivity gap between the 2:1 and 3:1 ratios of KHMDS and **L6** was interesting, I only focused on the structure of the active species in the 2:1 mixture because the optimal base-ligand ratio was 2:1. To gain more information about the structure of the 2:1 mixture, the reactivities were compared in different

base-ligand ratio with fixing the amount of **L6** to 3.3 mol% (**Table 1-6-2**). If the 2:1 and 1:1 mixture formed a 2:1 complex of KHMDS and **L6**, higher reactivities would be observed in the 2:1 mixture than the 1:1 mixture due to a higher amount of the active species (3.0 mol% of active species in Entry 1 vs 1.5 mol% of active species in Entry 2). When the reaction were conducted with the 2:1 mixture, a higher reactivity was observed than the 1:1 mixture (Entries 1 and 2). In addition, the background reaction was completely suppressed at –78 ºC (Entry 3). That is, an additional racemic product was not formed by free KHMDS. The results were consistent with my hypothesis, and it was likely that structures of the 1:1 and the 2:1 mixture would be a 2:1 complex of KHMDS and **L6**.

Table 1-6-2. Catalytic Asymmetric 1,4-Addition Reactions of A Diphenylamide with Various Ratios of KHMDS-Ligand[a]



Entry	x	y	Yield (%)	*anti/syn*	ee (%)
1	6.0	3.3	quant.	>99/1	98
2	3.0	3.3	88	>99/1	98
3	3.0	0	NR	–	–

[a] Reaction conditions (otherwise noted): **1** (0.400 mmol), **2** (0.480 mmol), toluene, –78 °C, 18 h, catalyst prepared from KHMDS and **L6**.

To gain more insights into the structure, X-ray single crystallographic analysis was conducted. Firstly, I tried to obtain a single crystal of a KHMDS-**L6** mixture in a 2:1 ratio. However, several trials were not successful to get the single crystal. Probably, instability of KHMDS against moisture would be problematic. Thus, potassium sources were changed to more stable ones, which had weakly basic counter anions. After many trials, it was found that a mixture of potassium triflate (KOTf) and **L6** in a 2:1 ratio gave the single crystal by treating it in hexane-ethyl acetate mixed solvent system. X-ray crystallographic analysis of the crystal indicated that the crystal was composed by a 1:1 ratio of KOTf and **L6** (**Figure 1-6-1**). Although the analysis suggested that the most stable structure of the mixture was the 1:1 complex in a solid state, it was contrary to the observations that the desired 1,4-addition reactions with the 2:1 mixture proceeded faster than the 1:1 mixture without decay of enantioselectivities.

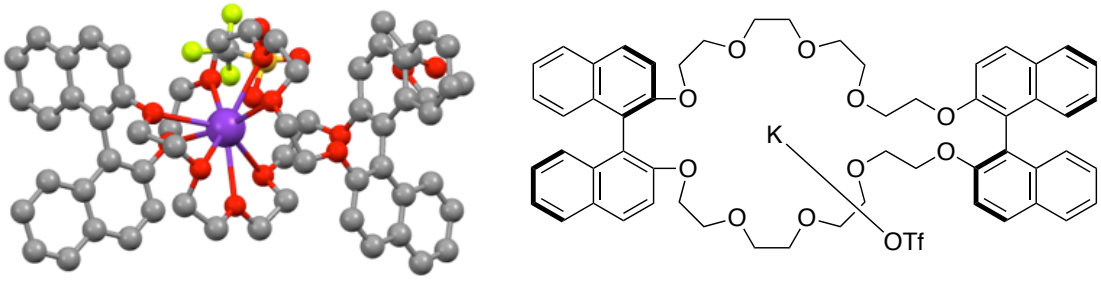


Figure 1-6-1. X-ray Crystallographic Structure of KOTf–Binatpho-34-crown-10 (**L6**) Complex

I further conducted dynamic ^{1}H NMR and MALDI-TOF MS analysis of the mixture. In the ^{1}H NMR analysis at 0 ºC, chemical shifts of ether hydrogen atoms that were positioned next to BINOL oxygen atom (**Figure 1-6-2**, H_a) was gradually moving by changing the KHMDS–L6 ratio from 0:1 to 2:1 (**Figure 1-6-2**, Left). The gradual shift change implied that fast equilibrium existed in a solution state at 0 ºC. Thus, the study was conducted at –60 ºC to distinguish the species under equilibrium. In the 1:1 mixture, a ca. 2.5:1 ratio of KHMDS-**L6** complex and free **L6** were observed. Peaks of the free **L6** disappeared and only the KHMDS-**L6** complex was observed when KHMDS and **L6** were mixed at a 2:1 ratio. These results suggested that the complex of KHMDS and **L6** was formed under equilibrium conditions, and the equilibrium moved towards the 1:1 complex by increasing the amount of KHMDS against **L6** (**Figure 1-6-3**). The formation of the 1:1 complex was also supported in an analysis of MALDI-TOF MS to show peaks of 928 mass/charge, and the value was same as a sum of **L6** and a potassium cation. Therefore, active species of the 2:1 mixture were considered to be a 1:1 complex of KHMDS and **L6** in the solution state.

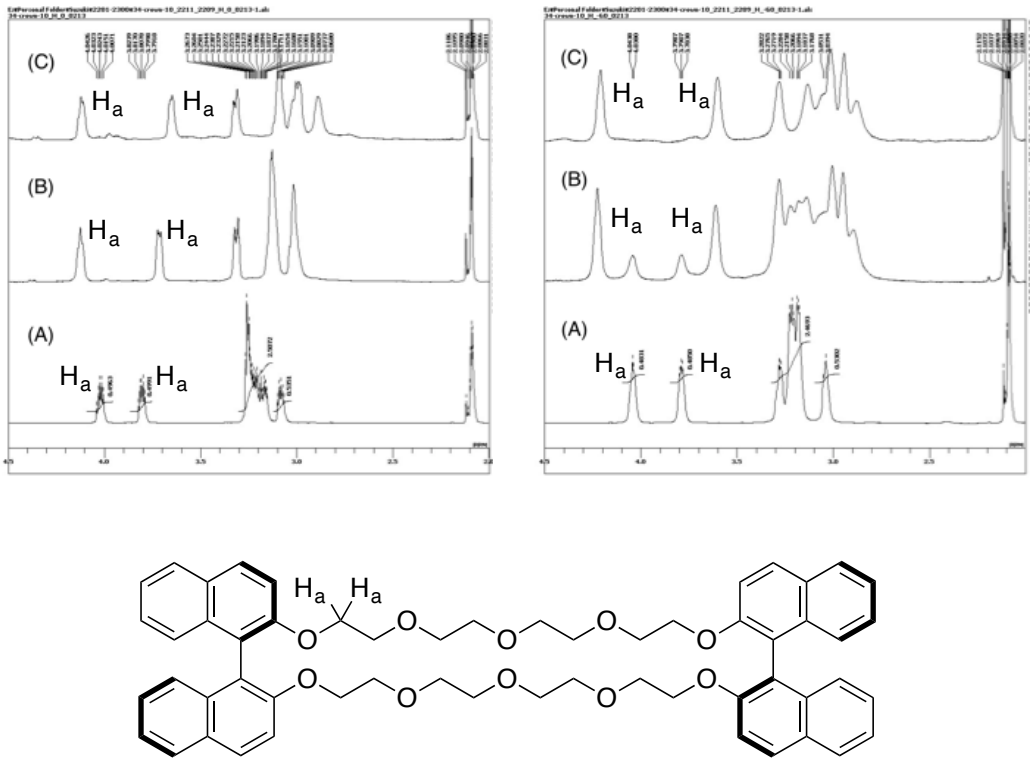


Figure 1-6-2. Dynamic ^{1}H NMR Analysis of the KHMDS–Binaphtho-34-crown-10 (**L6**) Mixture; Left: at 0 ºC in toluene, Right: at –60 ºC in toluene, (A): only **L6**, (B): 1:1 mixture of KHMDS and **L6**, (C): 2:1 mixture of KHMDS and **L6**.

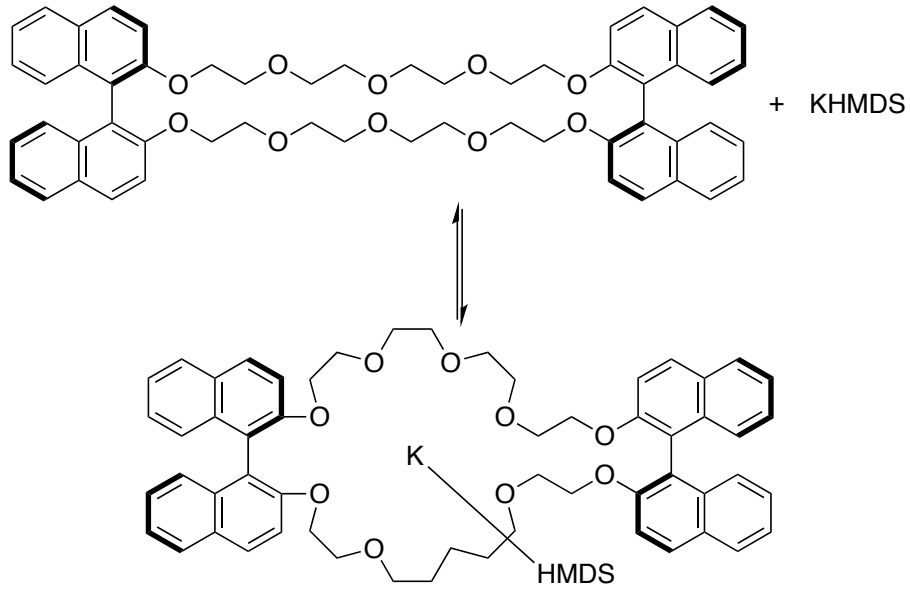


Figure 1-6-3. Equilibrium of KHMDS and **L6**

1-7 Reaction Mechanism and Transition State

As written in the previous sections, the catalytic asymmetric 1,4-addition reactions of simple amides were designed to keep strong basicity in the catalytic cycle by forming strongly basic reaction intermediates (See **Section 1-2**). Under the optimized reaction conditions, two different pathways, base regeneration and direct deprotonation pathways, would be considered after formation of the reaction intermediates whereas the 1,4-addition step, that is a chiral induction step, would be common (**Figure 1-7-1**). In the base regeneration pathway, an acidic hydrogen atom of H–HMDS was deprotonated by amide enolate intermediate **3-K** that was formed after the 1,4-addition step (**Figure 1-7-1** Left cycle). On the other hand, the direct deprotonation pathway proceeded *via* deprotonation of the next propionamide **2** by the intermediate **3-K** directly to regenerate the potassium enolate **2-K** (**Figure 1-7-1** Right cycle). Although it was difficult to distinguish these pathways by experiments, the major pathway would be assumed judging from acidities of H–HMDS and propionamides. A hydrogen atom of the H-HMDS is much acidic than a α-hydrogen atom of the propionamide (pK_a in DMSO; H-HMDS: 31, propionamide: 35[12]), and, judging from these values, the favored pathway would be the base regeneration one.

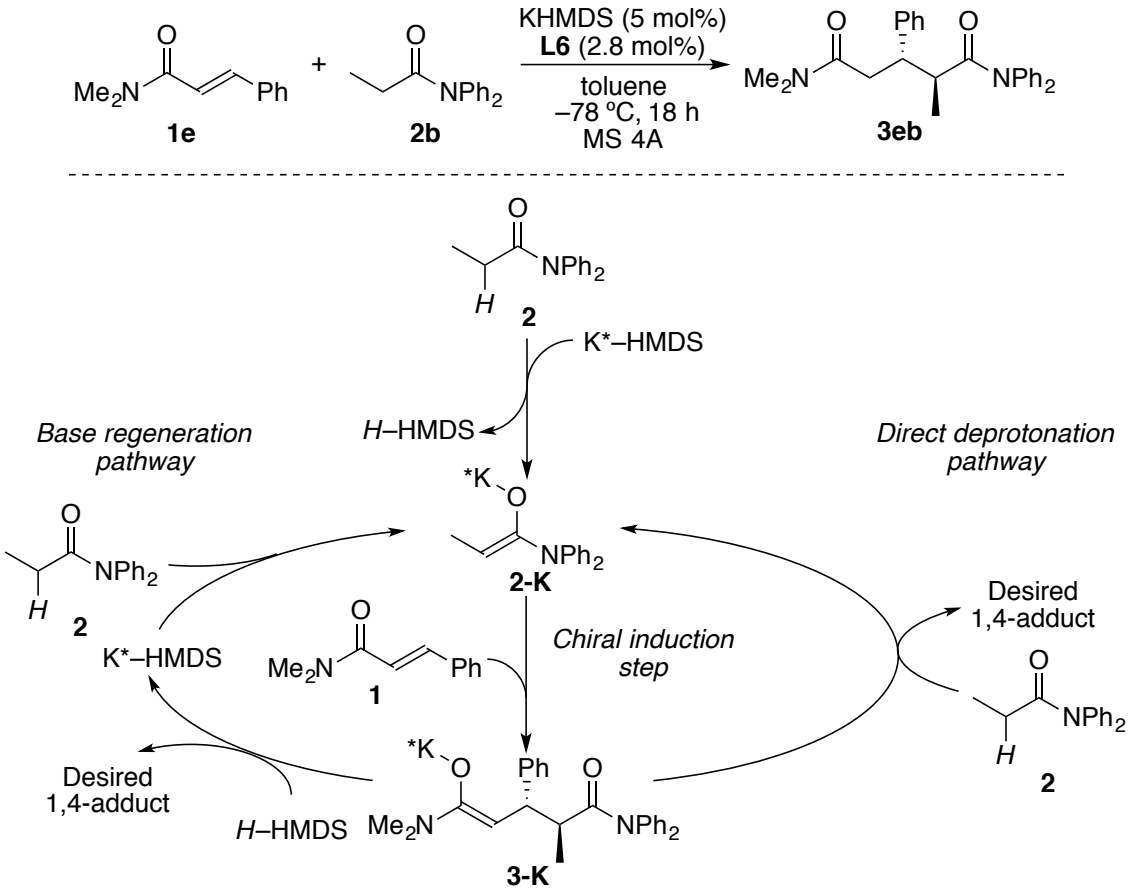
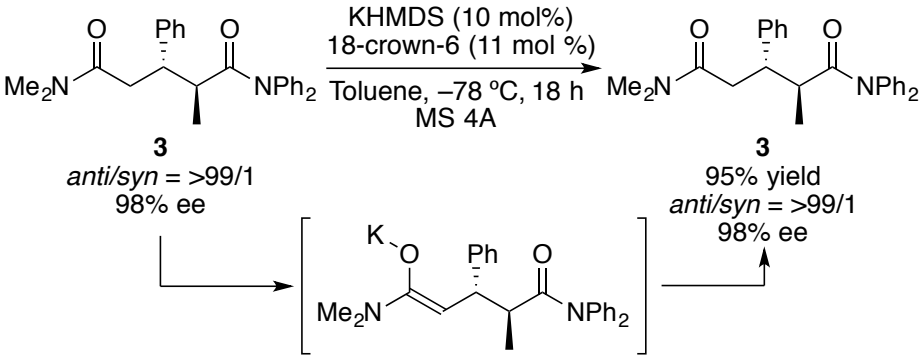


Figure 1-7-1. Proposed Reaction Mechanism.

In the reaction, the intermediate would be unstable because it was designed to possess strong basicity, and it was considered that the backward reaction, that gave a cinnamamide **1** and an amide enolate **2-K** from the intermediate **3-K**, would proceed. To clarify the process, the 1,4-adduct **3eb** was put in the presence of KHMDS and 18-crown-6 under the optimized reaction conditions (**Scheme 1-7-1**) because KHMDS, sterically bulky strong Brønsted base, favored to deprotonate a α-hydrogen atom of the sterically vacant dimethylamide moiety than the diphenylamide moiety (kinetic conditions), and the reaction intermediate **3-K** was reproduced under the racemic conditions. In the racemic conditions, starting product **3eb** was almost recovered, and no cinnamamide **1e** and propionamide **2b** were detected. In addition, the stereoselectivities did not change at all. (**Scheme 1-7-1**). The results indicated that no backward reaction proceeded once the intermediate **3-K** was formed. Thus, the intermediate **3-K** only deprotonate the hydrogen atom of H-HMDS without its backward reaction. This stability of the reaction intermediate, which was likely to be derived from energy difference between alkene and alkane, would be a key for the catalytic reactions.



Scheme1-7-1. Checking Backward Reactions

Then, origin of the stereoselectivities was considered. Excellent stereoselectivities would be explained based on two factors, *E/Z* ratio of the amide enolate **2-K** and a transition state of its nucleophilic addition step. *E/Z* ratio of substituted enolates has been studied well for a long time, and it is reported that propionamides usually favor formations of Z-enolates.[25] To clarify the *E/Z* ratio under the optimized reaction conditions, direct observation of the catalyst and propionamide **2b** mixture was tried by ^{1}H NMR analysis. However, only peaks of the catalyst and propionamide **2b** were observed, and no amide enolate **2-K** was observed. This is probably because acidities of the H–HMDS and the propionamide were much different, and a very small amount of the enolate **2-K** was formed. Thus, it would be difficult to determine the *E/Z* ratio by experimental results, and a major isomer of the enolate **2-K** was assumed by theoretical models. The *E/Z* selectivities were determined in the deprotonation step, and two possible deprotonation pathways, a 6-membered cyclic transition state and an open transition state, existed. Although Lewis acidic metal cations such as a lithium cation were required for the rigid 6-membered cyclic transition state generally, the potassium cation was not Lewis acidic cation and was covered with the crown ether in the asymmetric reactions. Thus, it was considered that these factors would prevent the base and the propionamide forming the rigid 6-membered cyclic transition state (**Figure 1-7-2**),[26] and the propionamide would be deprotonated *via* an open transition state. In the open transition state, the methyl group of the propionamide was likely to be fixed in less sterically hindered positions, and the transition state gave the Z-enolate (**Figure 1-7-3**, top figure). Based on the model, the Z-enolate seemed to be formed after the deprotonation.

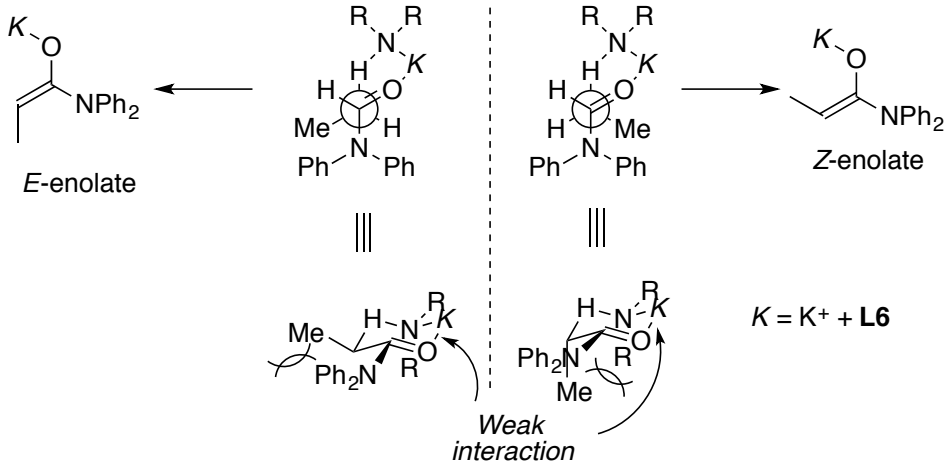


Figure 1-7-2. 6-Membered Cyclic Transition State for Deprotonation Step

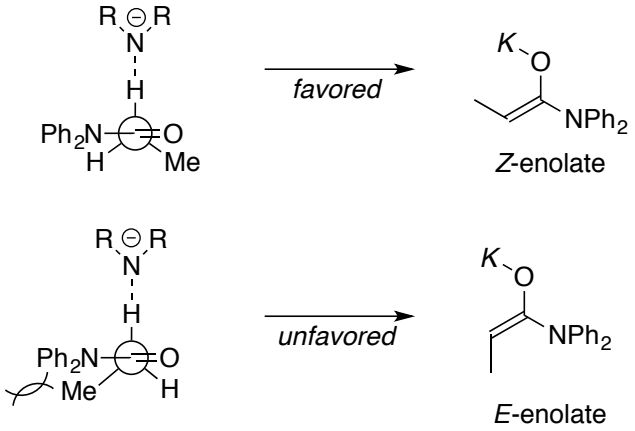


Figure 1-7-3. Open Transition State for Deprotonation Step

I considered a transition state of the 1,4-addition step when Z-enolate **2-K** was formed.[9a] To gain an insight into the transition state, the reaction mixture was observed in ^{1}H NMR analysis because the reaction intermediate should retain in the reaction mixture if there was no proton source. However, no intermediate **2-K** was observed in the analysis, and only the protonated 1,4-adduct **3** was observed probably due to the same reasons mentioned above. Thus, the transition state was assumed only by information of X-ray crystallography of KOTf and **L6** (**Figure 1-6-1**). A position of the amide enolate **2-K** considered to be put in parallel with helices of the ether chains due to steric reasons. Bulky nitrogen substituents of the propionamide **2** would favor direction towards naphthyl rings of **L6** because the direction was vacant compared to direction of ether chains (**Figure 1-7-3** Right transition state). The oxygen atom of the cinnamamide seemed to be directed towards the potassium cation due to coulomb interaction between the oxygen atom and the cation, and the alkenyl moiety of the cinnamamide would prevent the ether parts same as the reason of direction of the propionamide. If the direction of these substrates is fixed as mentioned above, the

desired absolute and relative configurations could be achieved. However, it is very difficult to assume the transition state exactly due to flexibility of the macro crown ether and difficulty of the direct observation.

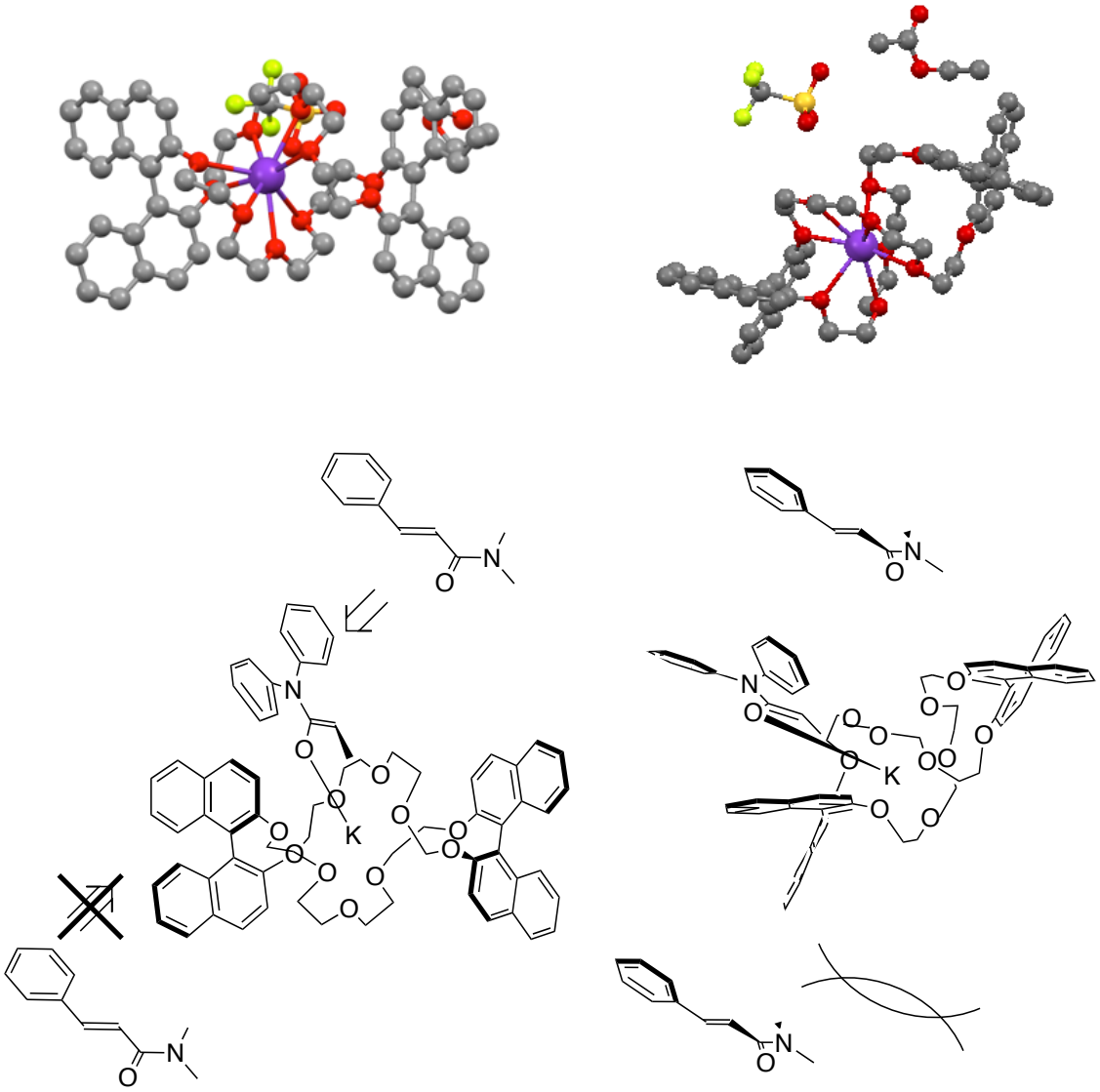
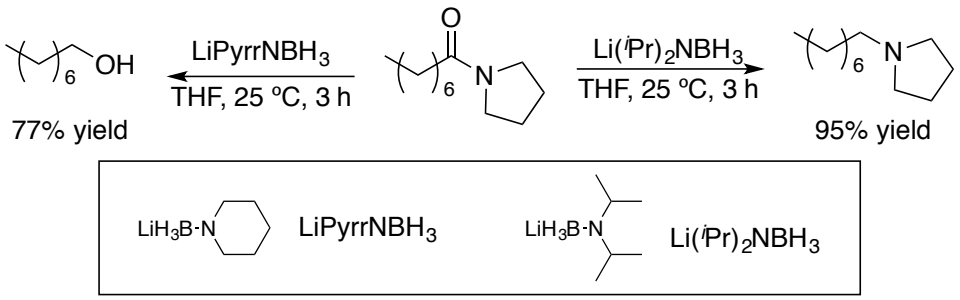


Figure 1-7-4. Assumed Transition State of the 1,4-Addition Step; Left: side view, Right: top view.

1-8 Transformations of 1,4-Adducts

To demonstrate utilities of the obtained 1,4-adduct, transformations of the amide moieties were investigated. First of all, reduction of one of the amides was conducted using lithium aminoborohydride (LAB) reagents.[27] The LABs are known as relatively stable reducing agents compared to $LiAlH_4$, and they can achieve selective reductions. For example, amides are converted to alcohols or amines selectively by using LAB, and the selectivities are generally determined by a steric factor of the each amino group in the LABs (**Scheme 1-8-1**). In this investigation, LAB reagent with small substituents, lithium dimethylaminoborohydride ($LiMe_2NBH_3$), was used as a reductant due to obtaining alcohol selectively.

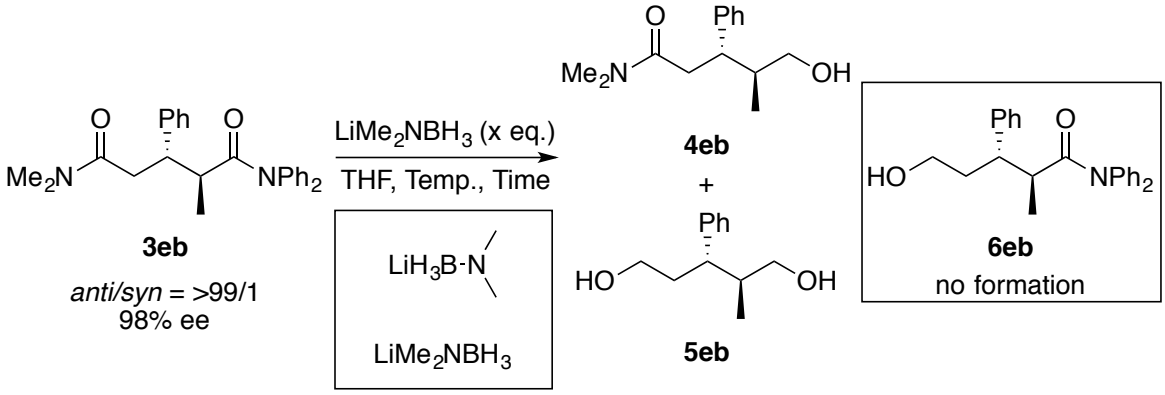


Scheme 1-8-1. Selective Reduction of Amide by LABs

An amide reduction of the 1,4-adduct was conducted with a stoichiometric amount of $LiMe_2NBH_3$ in THF (**Table 1-6-1**). First of all, 1.1 equivalents of $LiMe_2NBH_3$ were employed as a reductant, and the major product was dimethylamide-alcohol **4eb** (Entry 1). Although a small amount of diol **5eb** was obtained under the reaction conditions, another monoalcohol, diphenylamide-alcohol (**6eb**), was not observed. This observation indicated that a reduction rate of the diphenylamide moiety was faster than that of dimethylamide moiety probably due to a property of a more electrophilic C=O bond of the diphenylamide moiety. This result encouraged me to achieve selective reductions of diamide **3eb**. To suppress the over reduction, the amount of the reductant was decreased to 1.0 equivalent. The yield of dimethylamide-alcohol **4eb** was improved slightly, but a small amount of diol **5eb** was also gotten even under those conditions (Entry 2). Then, temperature effect was examined. When the reductant was added at room temperature, almost the same result was obtained as Entry 1 (Entry 3). On the other hand, the reactivity was dramatically dropped at lower temperature, and the reaction was not completed even for 24 h (Entry 4). To improve the reactivity at 0 ºC, a superstoichiometric amount of the reductant was added to the reaction mixture. Gratifyingly, a satisfactory yield of dimethylamide-alcohol **4eb** was achieved with much suppression of diol **5eb** formation (Entry 5). The optimized reaction conditions were applied to optically active diamide

3eb, and desired dimethylamide-alcohol **4eb** was obtained without any loss of the enantioselectivity (Entry 6). Thus, it was found that the diphenylamide moiety of **3ea** was selectively reduced to the corresponding alcohol in the presence of $LiMe_2NBH_3$.

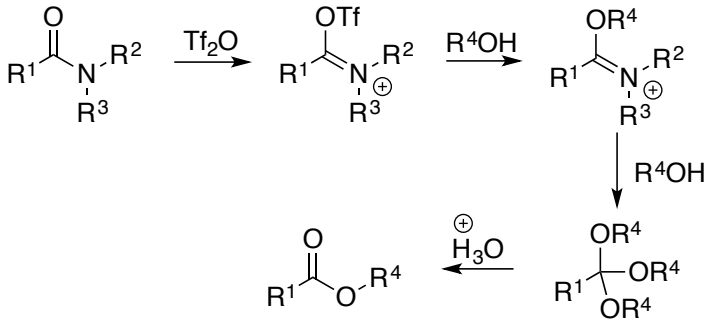
Table 1-8-1. Selective Reduction of Diphenylamide by $LiMe_2NBH_3$[a]



Entry	x	Time (h)	Temp. (ºC)	**4aa** Yield (%)	*anti/syn*	ee (%)	**5aa** Yield (%)	*anti/syn*
1[b]	1.1	5	–20→rt	54	>99/1	–	<5	
2[b]	1.0	5	–20→rt	67	>99/1	–	<5	
3[b]	1.1	5	rt	51	>99/1	–	<5	
4[b]	1.1	24	0	34	>99/1	–	10	>99/1
5[b]	1.1	4	0	81	>99/1	–	6	>99/1
6	1.1	4	0	88	>99/1	98	<5	

[a] Reaction conditions (unless otherwise noted): **3eb** (0.200 mmol), $LiMe_2NBH_3$ (1.00 mmol), THF. [b] Racemic **3eb** was used as a starting material.

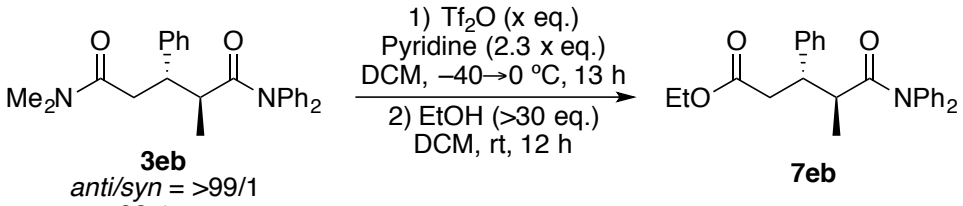
A selective conversion of the dimethylamide moiety was then investigated. To achieve the selective conversion, difference between the dimethylamide and the diphenylamide was considered. One major difference between these amides is electronic properties of the nitrogen atoms. In general, alkyl groups are considered to be electron-donating groups, and electron density of the nitrogen atoms of the alkylamides is higher than those of the diarylamides. Namely, dimethylamides can form an imidate intermediate faster than the diphenylamides due to a strong electron donating ability of the nitrogen atom. Thus, if the transformation of the product proceeds via the imidate intermediate, the dimethylamide moiety would be converted to other functional groups selectively. Based on this hypothesis, an esterification of the amide with triflic anhydride (Tf_2O) was chosen because the reaction would proceed via the imidate intermediate (**Scheme 1-8-2**).[28]



Scheme 1-8-2. Esterification of Amide by Alcohol with Tf_2O

Firstly, the esterification reaction was conducted under reported conditions (1.3 equivalents of Tf_2O),[28] but the reactivity was very low (**Table 1-6-2**, Entry 1). Although the conversion of diamide **3eb** was very low, only desired ester **6eb** was obtained selectively. Then, an excess amount of Tf_2O was used to improve the yield of ester **6eb**, and a selective transformation of diamide **3eb** to ester **6eb** was accomplished in high conversion of **3eb** (Entry 2). The transformation did not affect the stereoselectivities at all when optical active **3eb** was used as a starting material (Entry 3).

Table 1-8-2. Esterification of Dimethylamide[a]



3eb
anti/syn = >99/1
98% ee

7eb

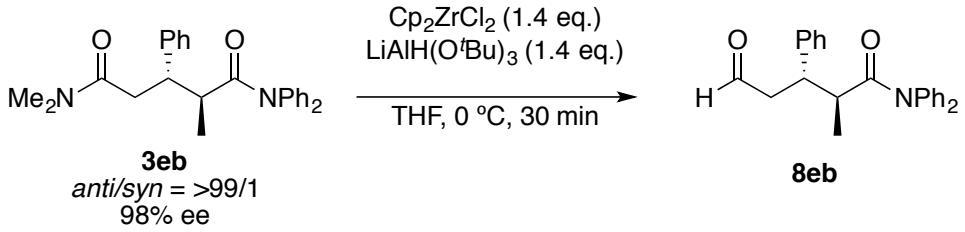
Entry	x	Yield (%)	*anti/syn*	ee (%)
1[b]	1.3	18	>99/1	–
2[b]	10	89	>99/1	–
3	10	83	>99/1	98

[a] Reaction conditions (unless otherwise noted): **3eb** (0.200 mmol), Tf_2O (2.00 mmol), Pyridine (4.60 mmol), DCM. [b] Racemic **3eb** was used as a starting material.

Finally, a reduction of **3eb** was investigated with *in situ*-formed Schwartz's reagent because the dimethylamide moiety of **3eb** would be transformed to aldehyde selectively due to a stronger Lewis basicity of the dimethylamide moiety (**Table 1-8-3**).[29] The reduction was conducted by using a mixture of Cp_2ZrCl_2 and $LiAlH(O^tBu)$, that gave Schwartz's reagent ($Cp_2ZrCl(H)$) in situ, under reported conditions. The in situ formed Schwartz's reagent reduced the dimethylamide moiety selectively in high yield (Entry 1), and the reaction proceeded with maintaining the

stereoselectivities (Entry 2). Thus the dimethylamide moiety was also selectively converted to other functional groups by using Tf_2O or Swartz's reagents.

Table 1-8-3. Reduction of Dimethylamide[a]



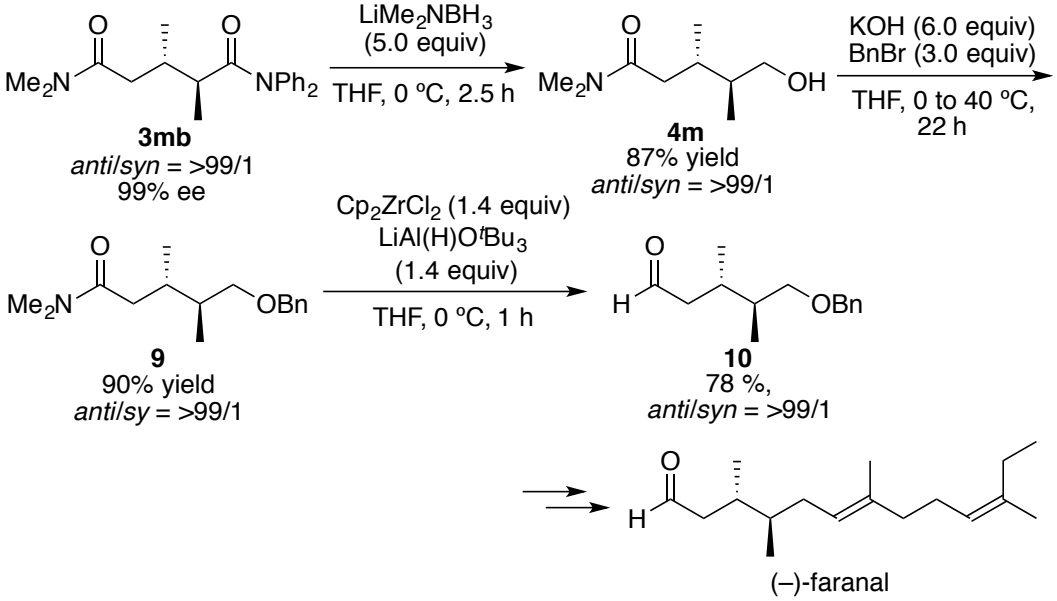
Entry	Yield (%)	*anti/syn*	ee (%)
1[b]	82	>99/1	–
2	78	>99/1	98

[a] Reaction conditions: **3eb** (0.200 mmol), Cp_2ZrCl_2 (0.280 mmol), $LiAlH(O^tBu)_3$ (0.280 mmol), THF, 0 ºC, 30 min. [b] Racemic **3eb** was used as a starting material.

1-9 Formal Synthesis of Natural Products

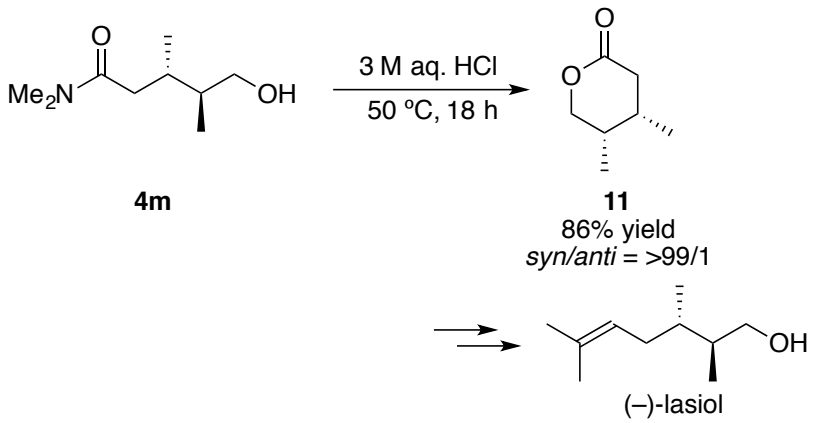
The obtained 1,5-dicarbonyl compounds can be transformed to natural compounds or pharmaceuticals within several steps because the carbonyl moieties were converted to various kinds of functional groups, alcohol, ester and aldehyde, easily. Thus, I planed to conduct formal syntheses of natural compounds from the products obtained in the asymmetric reactions.

An intermediate of (–)-faranal, which was a pheromone of ants, was synthesized stereoselectively from diamide **3mb** (**Scheme 1-9-1**). In the first step of the synthesis, the diphenylamide moiety of **3mb** was reduced by $LiMe_2NBH_3$ to afford dimethylamide-alcohol **4m** in high yield with maintaining stereoselectivities. The alcohol moiety of **4m** was then protected with benzyl group under basic conditions, a following reduction of the dimethylamide by Schwartz's reagent gave intermediate **10**. Intermediate **10** can be converted to (–)-faranal by following literature known procedures.[30a] Intermediate **10** was synthesized more efficiently than previous method without any formation of byproducts.[30a]



Scheme 1-9-1. Formal Synthesis of (–)-Faranal

Dimethylamide-alcohol **4m** was also an intermediate of another natural compound, (–)-lasiol (**Scheme 1-9-2**). Dimethylamide-alcohol **4m** was cyclized under acidic conditions in 1 step, and the intermediate of (–)-lasiol **11** was obtained in high yield without any loss of the stereoselectivities. Intermediate **11** can be also transformed to (–)-lasiol in several steps by following literature known procedures.[31]

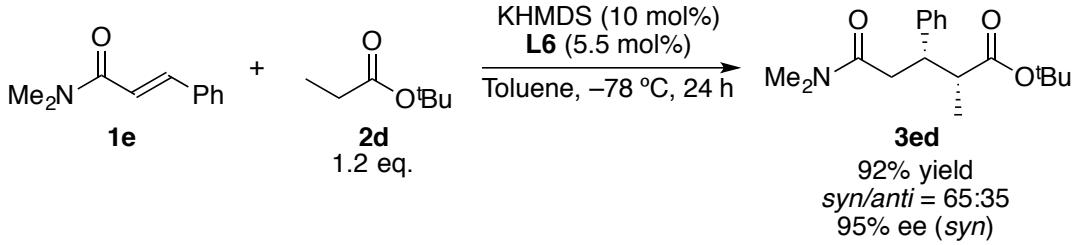


Scheme 1-9-2. Formal Synthesis of (–)-Lasiol

1-10 Catalytic Asymmetric 1,4-Addition Reactions of Simple Ester, Nitrile

Since applications of potassium–chiral macro crown ether complex to asymmetric catalysis were very rare (to the best of my knowledge, this is the first case), I was interested in abilities of the complex for enantioselection. Thus, I focused on catalytic asymmetric 1,4-addition reactions of weakly acidic carbonyl or related compounds that were rarely used in the catalytic reactions.

First of all, a simple ester was selected as a weakly acidic pronucleophile because structures of an amide and an ester were similar, and highly stereoselective reactions were expected (**Scheme 1-9-1**).[9] When *tert*-butyl propionate (**2d**) was employed as a nucleophile, the reaction proceeded smoothly with excellent enantioselectivities. However, the *syn* adduct was obtained as a major product, and the selectivity itself was moderate different from the reactions using propionamides. Probably, the moderate diastereoselectivity would be derived from a moderate *E/Z* ratio of a corresponding ester enolate anion. To the best of my knowledge, this is the first example of a catalytic asymmetric reaction of simple ester.[32]



Scheme 1-10-1. Catalytic Asymmetric 1,4-Addition Reactions of Simple Esters

An alkylnitrile was one of the most difficult pronucleophiles in asymmetric reactions due to small size of the nitrile moiety.[13a,b,d-f,33] Actually, acetonitrile was sometimes used in catalytic asymmetric aldol reactions, but the enantioselectivities were moderate in most cases. In addition, there is no example of catalytic asymmetric 1,4-addition reaction of alkylnitrile. Thus, I started to develop catalytic asymmetric 1,4-addition reactions using propionitrile. (**Scheme 1-9-2**). It was found that propionitrile (**2e)** reacted with cinnamamide **1e** well to afford the desired adduct in high yield with high diastereoselectivity and moderate enantioselectivity.[34] In the reaction, the amount of the nitrile was very important to suppress a side reaction. The side reaction was considered to be double Michael addition, which proceeded via addition of the reaction intermediate to cinnamamide **1e**. Thus, use of an excess amount of the nitrile help the deprotonation step by the reaction intermediate prior to the over 1,4-addition by the reaction intermediate.

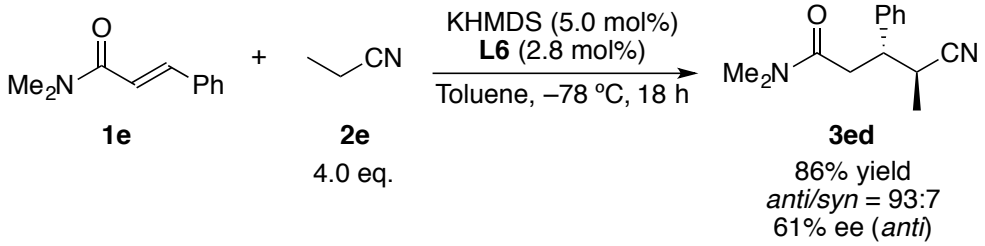


Table 1-10-2. Catalytic Asymmetric 1,4-Addition Reactions of Propionitrile

(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)

In those investigations, I found that several weakly acidic pronucleophiles were applicable to the catalytic asymmetric 1,4-addition reactions with good to excellent stereoselectivities.

1-11

本節については、5 年以内に雑誌等で刊行予定のため、非公開。

1-12 Conclusion

In this section, I succeeded in the investigation of catalytic asymmetric 1,4-addition reactions using weakly acidic carbonyl or related compounds based on the concept of the product base.

I have investigated catalytic 1,4-addition reactions of simple amides.[38] A key to the catalytic turnover of the reactions was a choice of the electrophile. The *α*,*β*-Unsaturated amide was a good electrophile that provided strongly basic reaction intermediate *in situ* (= *product base*), and the strong basicity of the product base facilitated the catalyst regeneration or the deprotonation of the next pronucleophile.

Asymmetric variants of the reactions were also exploited based on the concept of the product base. It was found that combination of KHMDS and a macrocyclic crown ether, binaphtho-34-crown-10 (**L6**), could control the stereoselectivity well to afford the desired products with complete diastereoselectivities and excellent enantioselectivities. The structure of the electrophiles did not affect the stereoselectivities, and a wide range of the *α*,*β*-unsaturated amides gave the desired products with excellent stereoselectivities.

The active species of the KHMDS-**L6** mixture was considered to be 1:1 complex of KHMDS and **L6** judging from several experiments, and higher reactivity of the 2:1 mixture than 1:1 mixture could be explained by difference of the amount of the active species. Although single crystallographic X-ray analysis clearly indicated that the structure of the catalyst was helices in a solid state, the structure in a solution state were unclear at this stage.

The amide moieties of the desired product were converted to other functional groups selectively. The transformation was applied to the formal synthesis of natural compounds.

The KHMDS-**L6** catalyst system could be applicable to various kinds of catalytic asymmetric 1,4-addition reactions using weakly acidic carbonyl and related compounds. *tert*-butyl propionate gave the desired compound with moderate diastereoselectivity and high enantioselectivity.[32] On the other hand, propionitrile[34] afforded the desired products with high diastereoselectivities and good enantioselectivities.

(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)

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Chapter 2

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。

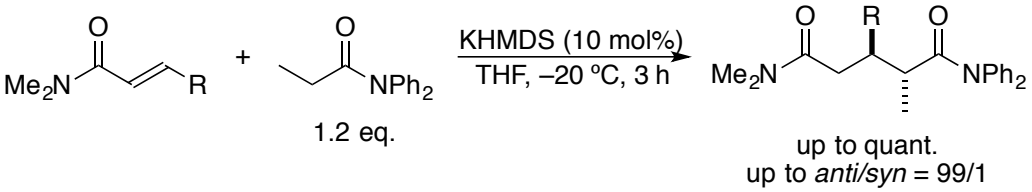
Chapter 3

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。

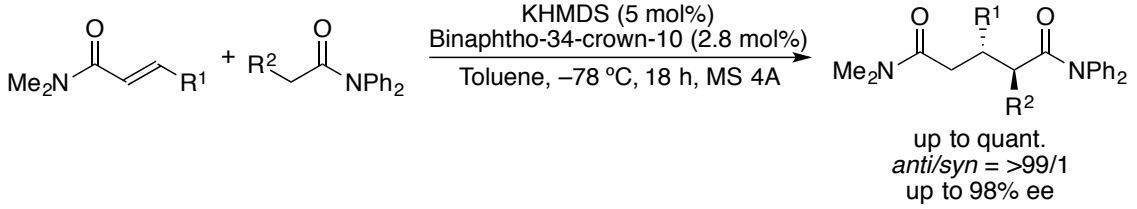
4 Summary

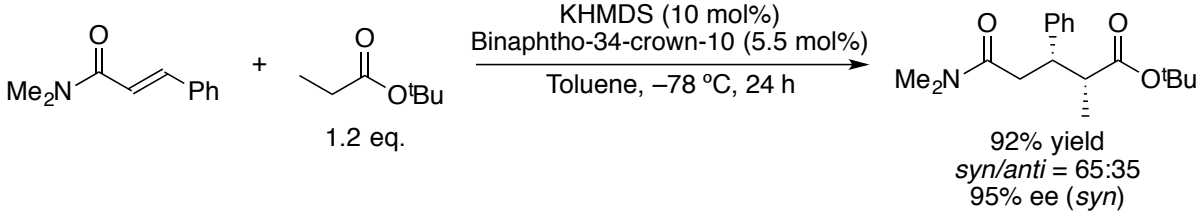
I have developed strong Brønsted base-catalyzed addition reactions of weakly acidic compounds *via* product base. A key of all my works is basicity of reaction intermediates, and two electrophiles, an *α,β*-unsaturated amides and a *N*-*tert*-butyl imine, are selected to provide the strongly basic reaction intermediates (= product base).

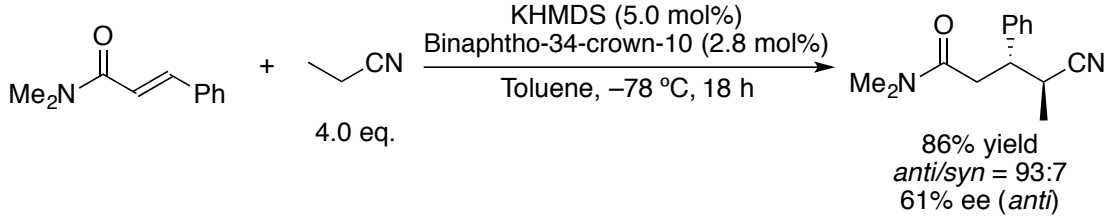
In chapter 1, I have investigated catalytic 1,4-addition reactions using simple amides. In the reaction, *α,β*-unsaturated amides were chosen as electrophiles due to strong basicity of the corresponding reaction intermediates, amide enolates, and it was found that various kinds of *α,β*-unsaturated amides were applicable to the catalytic reactions.

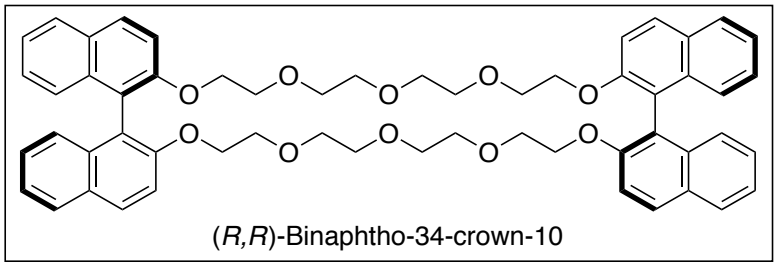


I also found that a macrocyclic crown ether ligand controlled stereoselectivities of the catalytic reactions. A KHDMS-binaphtho-34-crown-10 catalyst afforded the desired adducts in high yields with complete diastereoselectivities and very high enantioselectivities. In addition, the catalyst system also achieved catalytic asymmetric 1,4-addition reactions using *tert*-butyl propionate, propionitrile.

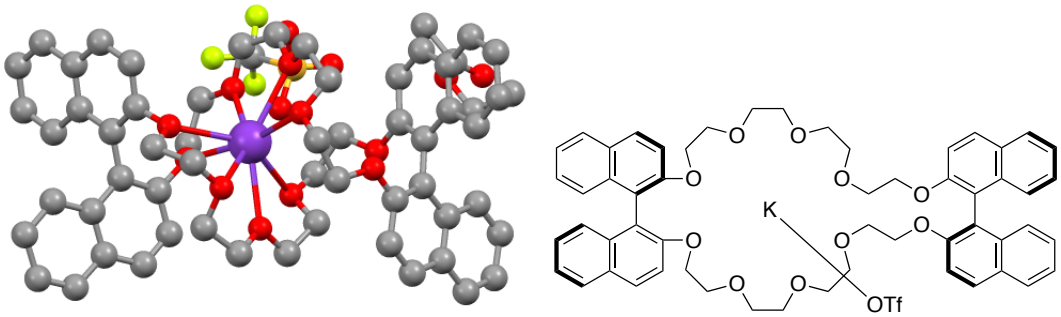








Several experiments revealed that structure of the catalyst system was considered to form a 1:1 complex of KHMDS and binaphtho-34-crown-10. Although I assumed a transition state of the reactions based on single X-ray crystallography structure of the catalyst, the exact transition state is still vague because of difficulty of elucidation of the exact catalyst structure in a solution state, and further investigation is needed to determine it.



In this chapter, I succeeded to develop the first examples of catalytic asymmetric 1,4-addition reactions of simple amides, an ester, an alkylnitrile.

(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)

Experimental Section ~Chapter 1~

1. General

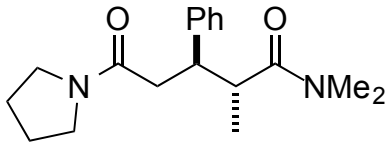
Melting points were measured with Büchi Melting Point D-545, and the values were uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on JEOL JNM-ECA500 and JNM-ECX600 spectrometers in $CDCl_3$ unless otherwise noted. Tetramethylsilane (TMS) served as internal standard (δ= 0) for ^{1}H NMR, and $CDCl_3$ served as internal standard (δ= 77.0) for ^{13}C NMR. IR spectra were measured using 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. MALDI-TOF MS were measured by SHIMADZU Kratos Axima-CFR. 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), sodium bis(trimethylsilyl)amide (NaHMDS), lithium bis(trimethylsilyl)amide (LiHMDS) were purchased from Aldrich Co., Ltd. All metal HMDS were sublimated and stored in glove box. Potassium hydride (KH) was purchased from Kanto Chem. Co., Inc. as mineral oil dispersion and was washed with anhydrous hexane several times and dried under reduced pressure inside a glove box before use. (*S*)-Binaphtho-14-crown-4 (**L1**) and (*S*)-Binaphtho-20-crown-6 (**L3**) were purchased from Wako Pure Chemical Industries, Ltd. (*S*)-Binaphtho-17-crown-5 (**L2**),[1] (*R,R*)-binaphtho-22-crown-6 (**L4**)[2] and (*R,R*)-binaphtho-28-crown-8 (**L5**)[3] was prepared by following a literature. THF and toluene were distilled just before using in the presence of benzophenone and sodium. Propionamide and butyramide were prepared from propionyl chloride and corresponding amine in the presence of pyridine. *tert*-Butyl propionate was prepared from propionic anhydride and *tert*-butyl alcohol in a typical procedure. Propionitrile was purchased from Tokyo Chemical Industry Co., Ltd., and distilled before use. *N,N*-Dimethyl ethanesulfonamide was prepared from ethanesulfonyl chloride and dimethylamine hydrochloride in the presence of pyridine as the typical procedure. Chalcone and Methyl cinnamate were purchased from Tokyo Chemical Industry Co., Ltd. and recrystallized before use. *α,β*-Unsaturated thioester was synthesized by HWE reactions following literature.[4] *α,β*-Unsaturated amides were prepared from corresponding *α,β*-unsaturated acid chlorides and amine. CHCA (α-cyano-4-hydroxy-cinnamic acid) was purchased from Aldrich.

2.1 Typical experimental procedure of KH-catalyzed 1,4-addition reaction of *N,N*-dimethyl propionamide (Table 1-3-1, Entry 4)

KH (4.0 mg, 0.10 mmol) and *N*-cinnamoylpyrrolidine **1d** (200.5 mg, 0.996 mmol) were added in a flame-dried 10 mL flask inside a glove box fulfilled with argon, and THF (2.5 mL) was added at 20 ºC. After 10 minutes stirring,

N,N-dimethylpropionamide **2a** (206.4 mg, 2.041 mmol) was added to the reaction mixture. The whole mixture was stirred for 18 h at the same temperature. The reaction was quenched by water, and the mixture was extracted with DCM (10 mL x 3). The organic layers were combined and dried over anhydrous Na_2SO_4. After filtration and concentration under reduced pressure, the crude product obtained was purified by silica-gel column chromatography (hexane-ethyl acetate) to afford the desired adduct (299.9 mg, >99% yield).

***N*,*N*,2-trimethyl-5-oxo-3-phenyl-5-(pyrrolidin-1-yl)pentanamide** (**3da**): yellow oil;

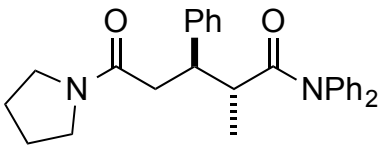


^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.29-7.15 (5H, m), 3.61 (1H, td, *J* = 8.25, 4.81 Hz), 3.35-3.22 (5H, m), 2.96-2.74 (7H, m), 2.66 (1H, dd, *J* = 15.12, 8.94 Hz), 1.82-1.69 (4H, m), 1.18 (3H, d, *J* = 6.9 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 175.1, 169.8, 143.1, 128.2, 128.1, 127.7, 126.3, 46.5, 45.4, 43.9, 40.0, 37.2, 35.8, 35.4, 25.9, 24.2, 14.5; IR(neat, cm^{-1}); 3466, 2971, 2876, 1630, 1494, 1452; HRMS (Dart) calcd for $C_{18}H_{27}N_2O_2$ [M + H]$^+$ 303.2073, found 303.2062.

2.2 Typical experimental procedure of KHMDS-catalyzed 1,4-addition reaction of *N*,*N*-diphenyl amide (Table 1-3-1, Entry 9)

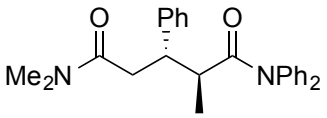
KHMDS (8.0 mg, 0.040 mmol), *N*-cinnamoylpyrrolidine (79.8 mg, 0.396 mmol) and *N,N*-diphenyl propionamide (110.6 mg, 0.491 mmol) were added in a flame-dried 5 mL reaction tube inside a glove box fulfilled with argon. The tube was cooled to –20 ºC then THF (2.0 mL) was added. The whole mixture was stirred for 3 h at the same temperature. The reaction was quenched by water and the mixture was extracted with DCM (10 mL x 3). The organic layers were combined and dried over anhydrous Na_2SO_4. After filtration and concentration under reduced pressure, the crude product obtained was purified by silica-gel PTLC (hexane-ethyl acetate) to afford the desired adduct (145.3 mg, 86% yield).

2-methyl-5-oxo-*N*,*N*,3-triphenyl-5-(pyrrolidin-1-yl)pentanamide (**3db**); colorless oil;

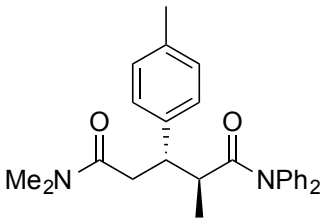


^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.40-7.15 (8H, m), 7.06 (5H, d, *J* = 6.8 Hz), 6.73 (2H, d, *J* = 7.4 Hz), 3.71 (1H, td, *J* = 9.5, 4.3 Hz), 3.35-3.21 (3H, m), 3.16-3.11 (1H, m), 2.91 (1H, dd, *J* = 9.1, 6.2 Hz), 2.70 (1H, dd, *J* = 15.0, 4.3 Hz), 2.48 (1H, dd, *J* = 15.3, 9.6 Hz), 1.81-1.64 (4H, m), 1.30 (3H, d, *J* = 6.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 175.2, 169.6, 142.8, 142.7, 129.4, 128.5, 128.5, 128.4, 127.9, 127.5, 126.6, 126.6, 126.5, 125.8, 46.4, 45.4, 45.1, 42.5, 36.9, 25.8, 24.1, 15.5; IR(neat, cm^{-1}); 3466, 2973, 2874, 1629, 1433, 1379, 1259, 1078; HRMS (Dart) calcd for $C_{28}H_{31}N_2O_2$ [M + H]$^+$ 427.2386, found 427.2369.

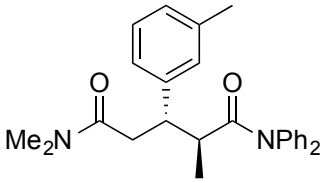
(2*S*,3*S*)-*N*^{5},*N*^{5},2-trimethyl-*N*^{1},*N*^{1},3-triphenylpentanediamide (**3eb**); colorless solid; Mp: 171-173 ºC; HPLC analysis using Daicel Chiralpak AD-H column (Hex;^{i}PrOH = 80:20, 1.0 mL/min, 254 nm, t_R = 47.4 min (Major), 41.9 min (minor)); $[\alpha]_D$=–170.65 (c 1.87, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.41-7.04 (13H, m), 6.75 (2H, d, *J* = 7.6 Hz), 3.68 (1H, td, *J* = 9.5, 4.4 Hz), 2.89-2.72 (8H, m), 2.58 (1H, dd, *J* = 15.1, 9.6 Hz), 1.29 (3H, d, *J* = 6.9 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 175.3, 171.3, 142.9, 142.9, 129.5, 128.7, 128.7, 128.6, 128.5, 128.1, 127.6, 126.7, 126.6, 126.0, 45.2, 43.0, 37.3, 35.4, 35.4, 15.5; IR(neat, cm^{-1}); 3464, 3061, 3029, 2969, 2933, 1640, 1492, 1378, 1264, 1141; HRMS (Dart) calcd for $C_{26}H_{29}N_2O_2$ $[M + H]^+$ 401.2229, found 401.2228.



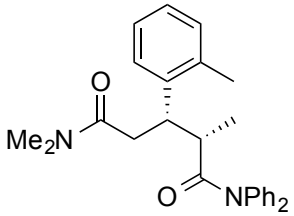
(2*S*,3*S*)-*N*^{5},*N*^{5},2-trimethyl-*N*^{1},*N*^{1}-diphenyl-3-(*p*-tolyl)pentanediamide (**3fb**); colorless oil; $[\alpha]_D$=263.37 (c 0.47, $CHCl_3$); HPLC analysis using Daicel Chiralpak AD-H column (Hex;^{i}PrOH = 80:20, 1.0 mL/min, 254 nm, t_R = 35.8 min (Major), 41.5 min (minor)); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.40-7.33 (3H, m), 7.18 (t, 2H, J = 7.2 Hz), 7.07 (5H, d, *J* = 8.3 Hz), 6.92 (2H, d, *J* = 7.6 Hz), 6.77 (2H, d, *J* = 7.6 Hz), 3.64 (1H, td, *J* = 8.9, 4.1 Hz), 2.88-2.79 (7H, m), 2.73 (1H, dd, *J* = 15.1, 4.1 Hz), 2.56 (1H, dd, *J* = 15.1, 9.6 Hz), 2.32 (3H, s), 1.26 (3H, d, *J* = 6.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 175.3, 171.3, 142.8, 139.7, 135.9, 129.4, 128.6, 128.6, 128.6, 128.5, 128.2, 127.5, 126.6, 125.9, 44.6, 42.9, 37.2, 35.3, 35.2, 21.0, 15.2; IR(neat, cm^{-1}); 3459, 2935, 1659, 1492, 1377, 1264, 1142; HRMS (Dart) calcd for $C_{27}H_{31}N_2O_2$ $[M + H]^+$ 415.2386, found 415.2397.



(2*S*,3*S*)-*N*^{5},*N*^{5},2-trimethyl-*N*^{1},*N*^{1}-diphenyl-3-(*m*-tolyl)pentanediamide (**3gb**); colorless oil; $[\alpha]_D$=205.17 (c 5.01, $CHCl_3$); HPLC analysis using Daicel Chiralpak AD-H column (Hex;^{i}PrOH = 80:20, 1.0 mL/min, 254 nm, t_R = 43.7 min (Major), 33.7 min (minor)); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.38-7.31 (m, 3H), 7.16 (t, 3H, J = 7.6 Hz), 7.07-6.98 (m, 4H), 6.88 (d, 1H, *J* = 7.6 Hz), 6.79-6.77 (m, 3H), 3.64 (td, 1H, *J* = 9.5, 4.4 Hz), 2.89-2.77 (m, 7H), 2.70 (dd, 1H, *J* = 15.1, 4.1 Hz), 2.56 (dd, 1H, *J* = 15.1, 9.6 Hz), 2.31 (s, 3H), 1.28 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 175.4, 171.4, 142.8, 142.8, 137.3, 129.4, 129.1, 128.6, 128.6, 128.0, 127.6, 127.4, 126.7, 126.0, 125.6, 125.5, 45.2, 43.0, 37.3, 35.4, 35.2, 21.4, 15.4; IR(neat, cm^{-1}); 3445, 1738, 1638, 1491, 1375, 1217; HRMS (Dart) calcd for $C_{27}H_{31}N_2O_2$ $[M + H]^+$ 415.2386, found 415.2379.

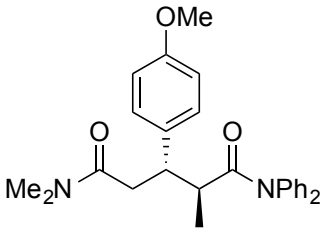


(2*S*,3*S*)-*N*^{5},*N*^{5},2-trimethyl-*N*^{1},*N*^{1}-diphenyl-3-(*o*-tolyl)pentanediamide (**3hb**); colorless oil; $[\alpha]_D$=233.43 (c 0.21, $CHCl_3$); HPLC analysis using Daicel Chiralpak AD-H column (Hex;^{i}PrOH = 80:20, 1.0 mL/min, 254 nm, t_R = 12.7 min (Major), 8.4

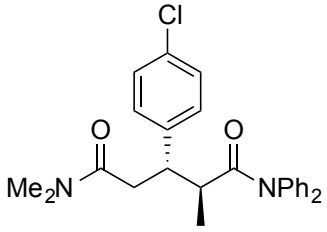


min (minor)); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.39-7.30 (m, 3H), 7.16-7.04 (m, 8H, *J* = 6.6 Hz), 6.88-6.87 (m, 1H), 6.58 (d, 2H, *J* = 7.6), 3.93 (td, 1H, *J* = 10.0, 4.1 Hz), 2.93-2.88 (m, 1H), 2.75 (d, 6H, *J* = 15.1 Hz), 2.69 (dd, 1H, *J* = 15.1, 4.1 Hz), 2.52 (dd, 1H, *J* = 15.1, 9.6 Hz), 2.41 (s, 3H), 1.36 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 175.4, 171.3, 142.9, 142.8, 141.6, 137.8, 130.3, 129.3, 128.5, 128.4, 127.3, 126.8, 126.7, 126.2, 125.8, 125.3, 42.3, 40.4, 37.2, 36.5, 35.3, 19.8, 16.4; IR(neat, cm^{-1}); 3460, 3063, 2970, 1648, 1492, 1376, 1265, 1143; HRMS (Dart) calcd for $C_{27}H_{31}N_2O_2$ $[M + H]^+$ 415.2386, found 415.2394.

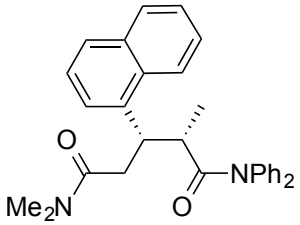
(2*S*,3*S*)-3-(4-methoxyphenyl)-*N*^{5},*N*^{5},2-trimethyl-*N*^{1},*N*^{1}-diphenylpentanediamide (**3ib**); yellow oil; $[\alpha]_D$=240.07 (c 0.53, $CHCl_3$); HPLC analysis using Daicel Chiralpak OD-H column (Hex;^{i}PrOH = 90/10, 1.0 mL/min, 254 nm, t_R = 61.5 min (Major), 52.8 min (minor)); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.39-7.34 (m, 3H), 7.19 (t, 2H, *J* = 8.3 Hz), 7.10-7.05 (m, 3H), 6.97 (d, 2H, *J* = 8.3 Hz), 6.82-6.79 (m, 4H), 3.79 (s, 3H), 3.62 (td, 1H, *J* = 9.5, 4.4 Hz), 2.86-2.79 (m, 7H), 2.72 (dd, 1H, *J* = 14.8, 4.5 Hz), 2.53 (dd, 1H, *J* = 15.1, 10.3 Hz), 1.27 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 175.5, 171.4, 158.3, 142.9, 135.0, 129.5, 129.4, 128.7, 128.6, 127.7, 127.7, 126.7, 126.0, 113.5, 55.3, 44.4, 43.1, 37.4, 35.5, 15.5; IR(neat, cm^{-1}); 3446, 2935, 1644, 1512, 1492, 1379, 1249, 1143; HRMS (Dart) calcd for $C_{27}H_{31}N_2O_3$ $[M + H]^+$ 431.2335, found 431.2350.



(2*S*,3*S*)-3-(4-chlorophenyl)-*N*^{5},*N*^{5},2-trimethyl-*N*^{1},*N*^{1}-diphenylpentanediamide (**3jb**); yellow oil; $[\alpha]_D$=197.57 (c 0.81, $CHCl_3$); HPLC analysis using Daicel Chiralpak AD-H column (Hex;^{i}PrOH = 70:30, 1.0 mL/min, 254 nm, t_R = 30.5 min (Major), 58.9 min (minor)); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.40-7.35 (m, 3H), 7.27-7.19 (m, 4H), 7.11-6.99 (m, 5H), 6.80 (d, 2H, *J* = 7.6 Hz), 3.67 (td, 1H, *J* = 8.9, 4.1 Hz), 2.88-2.73 (m, 8H), 2.53 (dd, 1H, *J* = 15.5, 10.0 Hz), 1.27 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 175.1, 170.9, 142.7, 142.7, 141.6, 132.3, 129.9, 129.7, 128.8, 128.5, 128.2, 127.8, 126.6, 126.1, 44.4, 42.8, 37.3, 35.5, 35.1, 15.4; IR(neat, cm^{-1}); 3463, 2970, 2936, 1659, 1492, 1379, 1265, 1144; HRMS (Dart) calcd for $C_{26}H_{28}Cl_1N_2O_2$ $[M + H]^+$ 435.1839, found 435.1860.

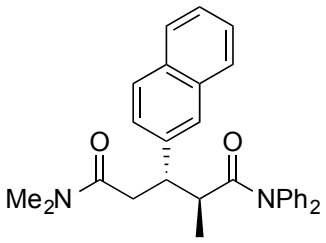


(2*S*,3*S*)-*N*^{5},*N*^{5},2-trimethyl-3-(naphthalen-1-yl)-*N*^{1},*N*^{1}-diphenylpentanediamide (**3kb**); colorless oil; $[\alpha]_D$=184.39 (c 4.79, $CHCl_3$); HPLC analysis using Daicel Chiralpak AD-H column (Hex;^{i}PrOH = 80:20, 1.0 mL/min, 254 nm, t_R = 24.3 min (Major), 16.2 min (minor)); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.86 (s, 1H), 7.78 (d, 1H, *J* = 8.3 Hz), 7.69 (d, 1H, *J* = 8.3 Hz), 7.42-7.35 (m, 6H), 7.14-6.99 (m, 6H), 6.60 (s, 2H),



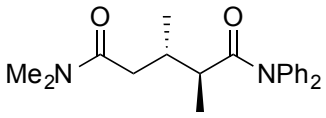
4.66 (s, 1H), 3.17 (s, 1H), 3.01 (dd, 1H , J = 15.5, 5.2 Hz), 2.76 (d, 7H, J = 42.6 Hz), 1.24 (d, 3H, J = 6.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 175.3, 171.4, 142.9, 133.8, 133.8, 131.8, 129.6, 128.8, 128.7, 128.5, 128.4, 127.6, 127.5, 127.1, 126.7, 126.1, 125.8, 125.4, 124.8, 124.1, 41.7, 37.2, 35.5, 35.3, 29.2, 15.4; IR(neat, cm^{-1}); 3460, 3047, 2970, 2935, 1658, 1492, 1378, 1265, 1144; HRMS (Dart) calcd for $C_{30}H_{31}N_2O_2$ $[M + H]^+$ 451.2386, found 451.2383.

(2*R*,3*R*)-*N*^{5},*N*^{5},2-trimethyl-3-(naphthalen-2-yl)-*N*^{1},*N*^{1}-diphenylpentanediamide

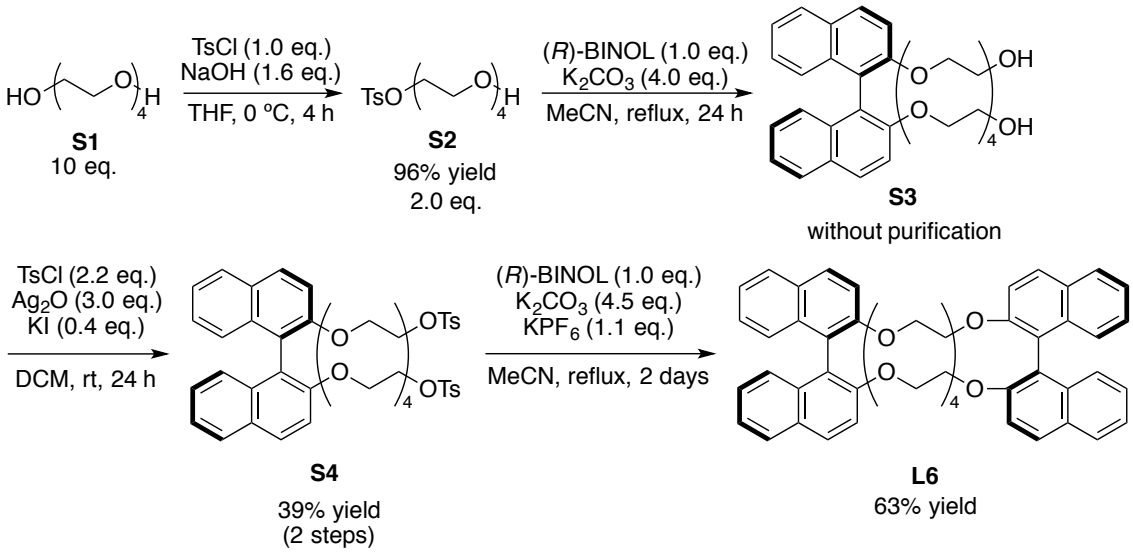


(**3lb**); colorless oil; $[\alpha]_D$=–108.50 (c 0.69, $CHCl_3$); HPLC analysis using Daicel Chiralpak AD-H column (Hex;^{i}PrOH = 80:20, 1.0 mL/min, 254 nm, t_R = 128.7 min (Major), 118.1 min (minor)); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.80 (1H, d, J = 7.6 Hz), 7.74 (2H, t, J = 9.3 Hz), 7.46-7.36 (6H, m), 7.20 (1H, dd, J = 8.3, 1.4 Hz), 7.09-6.94 (5H, m), 6.67 (2H, d, J = 7.6 Hz), 3.87 (1H, td, J = 9.3, 4.6 Hz), 3.03-2.98 (1H, m), 2.85-2.68 (8H, m), 1.32 (3H, d, J = 6.9 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 175.3, 171.2, 142.9, 142.7, 140.7, 133.2, 132.5, 129.5, 128.7, 128.6, 127.7, 127.6, 127.6, 127.5, 126.6, 126.5, 125.9, 125.9, 125.4, 45.2, 43.0, 37.3, 35.4, 35.5, 35.3, 15.5; IR(neat, cm^{-1}); 3464, 3058, 2934, 1658, 1492, 1378, 1267, 1142; HRMS (Dart) calcd for $C_{30}H_{31}N_2O_2$ $[M + H]^+$ 451.2386, found 451.2363.

(2*S*,3*S*)-*N*^{5},*N*^{5},2,3-tetramethyl-*N*^{1},*N*^{1}-diphenylpentanediamide (**3ob**); colorless solid; Mp: 120-124 ºC; $[\alpha]_D$=–111.58 (c 0.30, $CHCl_3$); HPLC analysis using Daicel Chiralpak AD-H column (Hex;^{i}PrOH = 90:10, 1.0 mL/min, 254 nm, t_R = 26.1 min (Major), 44.1 min (minor)); ^{1}H NMR (600 MHz , $CDCl_3$) δ: 7.41-7.17 (m, 10H), 2.97 (d, 6H, J = 44.7 Hz), 2.67 (dd, 1H, J = 15.1, 9.6 Hz), 2.58-2.54 (m, 1H), 2.45-2.40 (m, 1H), 1.98 (dd, 1H, J = 15.1, 9.5 Hz)1.14 (d, 3H, J = 6.9 Hz), 0.96 (d, 3H, J = 6.9 Hz); ^{13}C NMR (150MHz, $CDCl_3$) δ: 176.3, 172.3, 143.0, 129.9, 128.9, 128.8, 127.9, 127.9, 126.7, 126.1, 41.9, 37.5, 36.5, 35.5, 33.1, 18.5, 14.1; IR(neat, cm^{-1}); 3480, 3061, 3037, 2966, 2935, 1665, 1492, 1381, 1268, 1147; HRMS (Dart) calcd for $C_{21}H_{27}N_2O_2$ $[M + H]^+$ 339.2073, found 339.2080.



3. Preparation of (*R*,*R*)-binaphtho-34-crown-10 (L6)



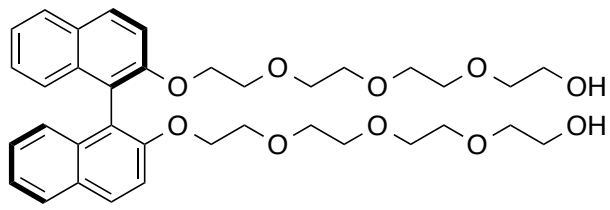
Synthesis of monotosylate S2

Monotosylate **S2** was synthesized following literature.[5]

Synthesis of (*R*)-BINOL-diol S3[6]

Monotosylate **S2** (10.31 g, 29.59 mmol), (*R*)-BINOL (4.17 g, 14.6 mmol) and K_2CO_3 (7.93 g, 57.4 mmol) were placed in a flame-dried 300 mL flask that was fulfilled with argon and anhydrous MeCN (160 mL) was added. The reaction mixture was stirred for 24 h under reflux conditions, and then the flask was cooled to room temperature. The reaction mixture was filtered through Celite, and the filtrate was evaporated under reduced pressure. The crude product **S3** obtained was used in the next reaction without further purification (9.75 g).

(R_a)-2,2'-(((((((([1,1'-binaphthalene]-2,2'-diylbis(oxy))bis(ethane-2,1-diyl))bis(oxy))bis(ethane-2,1-diyl))bis(oxy))bis(ethane-2,1-diyl))bis(oxy))bis(ethan-1-ol) (**S3**);

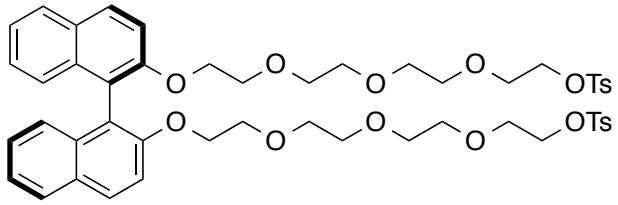


colorless oil; $[\alpha]_D$=24.6 (c 0.31, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.93 (d, 2H, *J* = 8.9 Hz), 7.85 (d, 2H, *J* = 8.3 Hz), 7.42 (d, 2H, *J* = 8.9 Hz), 7.33-7.30 (m, 2H), 7.22-7.20 (m, 2H), 7.14 (d, 2H, *J* = 8.3 Hz), 4.14-4.07 (m, 4H), 3.68 (t, 4H, *J* = 4.5 Hz), 3.58-3.54 (m, 8H), 3.48-3.46 (m, 8H), 3.22 (t, 4H, *J* = 4.47), 3.16-3.14 (m, 2H), 3.10-3.08 (m, 2H), 2.86 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 154.2, 134.0, 129.3, 129.2, 127.8, 126.2, 125.4, 123.6, 120.4, 120.4, 115.6, 72.4, 70.4, 70.3, 70.1, 69.9, 69.5, 61.6; IR(neat, cm^{-1}); 2922, 2870, 1507, 1353, 1328, 1266, 1244, 1128, 1092; HRMS (ESI) calcd for $C_{36}H_{46}NaO_{10}$ $[M + Na]^+$ 661.2989, found 661.2994.

Synthesis of (*R*)-BINOL-ditosylate S4

(*R*)-BINOL-diol **S3** (9.75 g, 15.3 mmol), TsCl (6.62 g, 34.7 mmol), Ag_2O (10.85 g, 46.82 mmol) and KI (1.02 g, 6.14 mmol) were placed in a flame-dried 300 mL flask that was fulfilled with argon, and DCM (150 mL) was added. The reaction mixture was stirred for 24 h at room temperature. After stirring, the mixture was filtered through silica gel, and the filtrate was evaporated under reduced pressure to give a crude product. The crude product was purified by silica-gel column chromatography (hexane-ethyl acetate) to afford the desired product **S4** (5.30 g, 39 % yield (2 steps)).

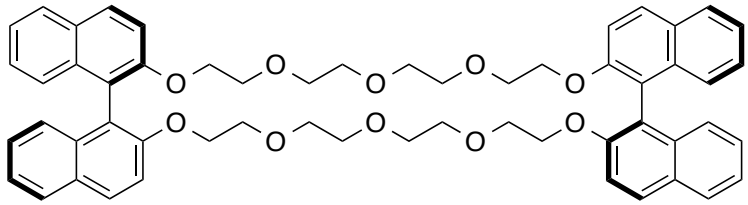
(R_a)-(((((((([1,1'-binaphthalene]-2,2'-diylbis(oxy))bis(ethane-2,1-diyl))bis(oxy))bis(ethane-2,1-diyl))bis(oxy))bis(ethane-2,1-diyl))bis(oxy))bis(ethane-2,1-diyl) bis(4-methylbenzenesulfonate) (**S4**); colorless oil; $[\alpha]_D$=13.41 (c 0.25, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.92 (d, 2H, *J* = 8.9 Hz), 7.84 (d, 2H, *J* = 8.3 Hz), 7.77 (d, 4H, *J* = 8.3 Hz), 7.41 (d, 2H, *J* = 8.9 Hz), 7.30 (dd, 6H, *J* = 7.6, 4.8 Hz), 7.20-7.17 (m, 2H), 7.13 (d, 2H, *J* = 8.3 Hz), 4.11 (t, 4H, *J* = 4.8 Hz), 4.09-4.07 (m, 4H), 3.61 (t, 4H, J = 4.8 Hz), 3.47-3.43 (m, 8H), 3.38-3.38 (m, 4H), 3.17-3.16 (m, 4H), 3.13-3.11 (m, 2H), 3.07-3.05 (m, 2H), 2.40 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 154.2, 144.7, 134.0, 132.8, 129.7, 129.3, 129.2, 127.9, 127.7, 126.2, 125.4, 123.6, 120.3, 115.5, 70.5, 70.3, 70.3, 70.1, 69.8, 69.5, 69.2, 68.5, 21.5; IR(neat, cm^{-1}); 2921, 2871, 1594, 1507, 1454, 1356, 1267, 1246, 1176, 1134, 1096; HRMS (ESI) calcd for $C_{50}H_{58}NaO_{14}S_2$ $[M + Na]^+$ 969.3166, found 969.3185.



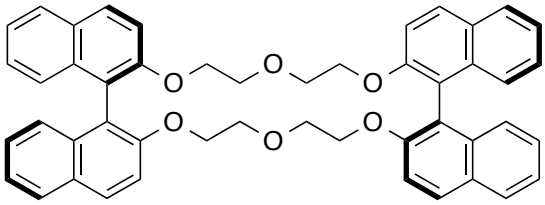
Synthesis of (*R,R*)-34-crown-10 (L6)[7]

(*R*)-BINOL-ditosylate **S4** (4.23 g, 4.47 mmol), (*R*)-BINOL (1.28 g, 4.47 mmol), K_2CO_3 (2.80 g, 20.3 mmol) and KPF_6 (0.90 g, 4.9 mmol) were placed in a flame-dried flask that was fulfilled with argon, and MeCN (300 mL) was added. The reaction mixture was stirred for 48 h under reflux conditions. After that, the mixture was cooled to room temperature and filtered through Celite. The filtrate was evaporated under reduced pressure, and DCM (100 mL) was then added. The DCM solution was washed with 1 M HCl (50 mL x 3), 1 M NaOH (50 mL x 2) and brine (100 mL). The organic layer was dried over anhydrous Na_2SO_4. After filtration and concentration under reduced pressure, the crude product obtained was purified by silica-gel column chromatography (hexane-ethyl acetate) to afford the desired product **L6** (2.50 g, 63 % yield). The product was dried for 5 h at 80 ºC under reduced pressure to remove a trace amount of water.

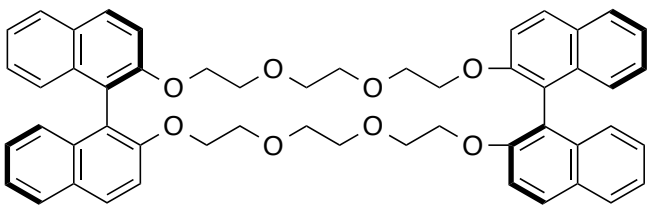
8,9,11,12,14,15,17,18,33,34,36,37,39,40,42,43-hexadecahydrotetranaphtho[2,1-*e*$_1$:1',2'-*g*$_1$:2'',1'''-*n*:1''',2'''-*p*][1,4,7,10,13,18,21,24,27,30]decaoxacyclotetratriacontine (**L6**); colorless solid; Mp 62-64 ºC; $[\alpha]_D$=–105.50 (c 0.22, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.91 (d, 4H, *J* = 8.9 Hz), 7.84 (d, 4H, *J* = 8.2 Hz), 7.44 (d, 4H, *J* = 8.9 Hz), 7.30 (t, 4H, *J* = 7.2 Hz), 7.20 (t, 4H, *J* = 7.6, 4.8 Hz), 7.13 (d, 4H, *J* = 8.2 Hz), 4.15-4.11 (m, 4H), 4.04-4.01 (m, 4H), 3.53-3.49 (m, 4H), 3.41-3.38 (m, 4H), 3.30-3.17 (m, 16H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 154.4, 134.0, 129.4, 129.2, 127.8, 126.2, 125.4, 123.6, 120.5, 115.9, 70.6, 70.4, 69.8, 69.7; IR (neat, cm^{-1}); 3056, 3007, 2872, 1620, 1592, 1507, 1328, 1268, 1244, 1130, 1090, 983, 869, 808, 749, 667; HRMS (ESI) calcd for $C_{56}H_{56}NaO_{10}$ $[M + Na]^+$ 911.3771, found 911.3769.



12,13,15,16,31,32,34,35-octahydrotetranaphtho[2,1-*h*:1',2'-*j*:2'',1'''-*s*:1''',2'''-*u*][1,4,7,12,15,18]hexaoxacyclodocosine (**L4**); white solid; Mp 128-132 ºC; $[\alpha]_D$ = 160.11 (c 0.50, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.94 (4H, d, J = 8.94 Hz), 7.86 (4H, d, J = 8.25 Hz), 7.31-7.30 (8H, m), 7.18 (4H, t, J = 7.56 Hz), 7.07 (4H, d, J = 8.94 Hz), 3.93-3.90 (4H, m), 3.83-3.80 (4H, m), 3.27-3.25 (4H, m), 3.15-3.13 (4H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 154.1, 134.1, 129.3, 129.1, 127.7, 126.2, 125.5, 123.6, 120.4, 115.4, 69.4, 69.2; IR (neat, cm^{-1}); 3057, 3008, 2929, 2874, 1621, 1592, 1507, 1355, 1328, 1269, 1133, 1088, 985, 869, 807, 750; HRMS (ESI) calcd for $C_{48}H_{40}NaO_6$ $[M + Na]^+$ 735.2723, found 735.2709.



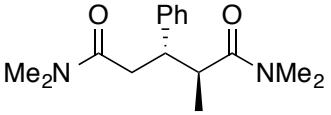
8,9,11,12,14,15,30,31,33,34,36,37-dodecahydrotetranaphtho[1,2-*a*$_1$:2',1'-*k*:1'',2''-*m*:2''',1'''-*y*][1,4,7,10,15,18,21,24]octaoxacyclooctacosine (**L5**); white solid; Mp 88-91 ºC; $[\alpha]_D$ = 141.60 (c 0.51, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.92 (4H, d, J = 8.94 Hz), 7.84 (4H, d, J = 8.25 Hz), 7.43 (4H, d, J = 8.94 Hz), 7.31-7.30 (4H, m), 7.19-7.18 (4H, m), 7.11 (4H, d, J = 8.25 Hz), 4.12-4.08 (4H, m), 3.98-3.95 (4H, m), 3.48-3.44 (4H, m), 3.37-3.33 (4H, m), 3.16 (8H, ddd, J = 12.54, 7.73, 3.26 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 154.5, 134.1, 129.5, 129.2, 127.8, 126.2, 125.5, 123.7, 120.8, 116.3, 70.5, 69.8, 69.8; IR (neat, cm^{-1}); 3056, 3007, 2922, 2873, 1621, 1592, 1507, 1328, 1267, 1244, 1129, 1089, 807, 750, 666; HRMS (ESI) calcd for $C_{52}H_{48}NaO_8$ $[M + Na]^+$ 823.3247, found 823.3246.



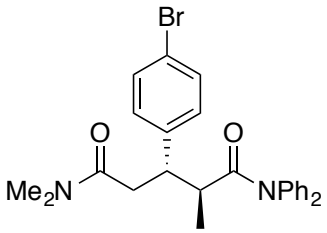
4. Experimental procedure of a catalytic asymmetric 1,4-addition reaction of *N,N*-diphenyl amide (Table 2, Entry 8)

KHMDS (4.0 mg, 0.020 mmol), (*R*)-34-crown-10 (**L6**) (9.8 mg, $1.1x10^{-2}$ mmol) and MS4A (50 mg) were placed in a flame-dried 10 mL flask inside a glove box fulfilled with argon. The flask was cooled to 0 ºC, then toluene (0.3 mL) was added. The reaction mixture was stirred for 1 h at the same temperature. After stirring, the flask was cooled to –78 ºC. To the catalyst preparation flask was added *N,N*-dimethyl cinnamamide **1e** (70.5 mg, 0.402 mmol) and *N,N*-diphenyl propionamide **2b** (108.0 mg, 0.479 mmol) that were placed in a flame-dried tube under argon atmosphere through cannula by using extra toluene (0.7 mL). The whole mixture was stirred for 18 h at –78 ºC. The reaction was quenched by water, and the mixture was extracted with Et_2O (10 mL x 3). The organic layers were combined and dried over anhydrous Na_2SO_4. After filtration and concentration under reduced pressure, the crude product obtained was purified by silica-gel PTLC (hexane-ethylacetate) to afford the desired adduct **3eb** (153.8 mg, 96 % yield).

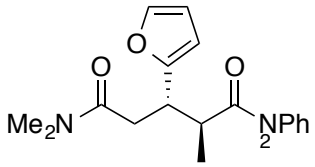
(2*S*,3*S*)-*N*^{1},*N*^{1},*N*^{5},*N*^{5},2-pentamethyl-3-phenylpentanediamide (**3ea**)[8]; white solid; Mp: 100-101 ºC; $[\alpha]_D$=–24.19 (c 3.03, $CHCl_3$); HPLC analysis using Daicel Chiralpak OD-H column (Hex;^{i}PrOH = 80:20, 1.0 mL/min, 210 nm, t_R = 29.4 min (Major), 22.8 min (minor));^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.29-7.15 (m, 5H), 3.59 (td, 1H, *J* = 8.4, 4.6 Hz), 3.19-3.15 (m, 1H), 2.92 (d, 6H, J = 33.7), 2.84-2.72 (m, 8H), 1.17 (d, 3H, *J* = 6.9); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 175.0, 171.3, 143.0, 128.1, 127.6, 126.4, 43.9, 40.4, 37.2, 37.2, 35.4, 35.3, 34.0, 14.2.



(2*S*,3*S*)-3-(4-bromophenyl)-*N*^{5},*N*^{5},2-trimethyl-*N*^{1},*N*^{1}-diphenylpentanediamide (**3nb**); colorless solid; Mp: 85-87 ºC; $[\alpha]_D$=146.50 (c 1.73, $CHCl_3$); HPLC analysis using Daicel Chiralpak AD-H column (Hex;^{i}PrOH = 70:30, 1.0 mL/min, 254 nm, t_R = 32.6 min (Major), 64.4 min (minor)); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.40-7.33 (m, 5H), 7.18 (t, 2H, *J* = 6.9 Hz), 7.08-7.03 (m, 3H), 6.95 (d, 2H, *J* = 8.2 Hz), 6.8 (d, 2H, *J* = 7.55 Hz), 3.66 (td, 1H, *J* = 9.44, 3.9 Hz), 2.86-2.71 (m, 8H), 2.51 (dd, 1H, *J* = 15.45, 10.0 Hz), 1.27 (d, 3H, *J* = 6.87 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ:174.7, 170.5, 142.4, 141.9, 130.8, 130.0, 129.4, 128.5, 128.2, 128.2, 127.6, 126.3, 125.8, 120.0, 44.3, 42.4, 37.0, 35.2, 34.8, 15.2; IR(neat, cm^{-1}); 3061, 2970, 2935, 1664, 1491, 1379, 1265; HRMS (Dart) calcd for $C_{26}H_{28}BrN_2O_2$ $[M + H]^+$ 481.1314, found 481.1298.

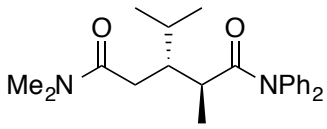


(2*S*,3*S*)-3-(furan-2-yl)-*N*^{5},*N*^{5},2-trimethyl-*N*^{1},*N*^{1}-diphenylpentanediamide (**3ob**); colorless oil; $[\alpha]_D$=87.43 (c 1.42, $CHCl_3$); HPLC analysis using Daicel Chiralpak AD-3 column (Hex;^{i}PrOH = 75:25, 1.0 mL/min, 254 nm, t_R = 41.7 min (Major), 46.6 min (minor)); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.38-7.23 (m, 6H), 7.09 (d, 5H, *J* = 15.8 Hz),



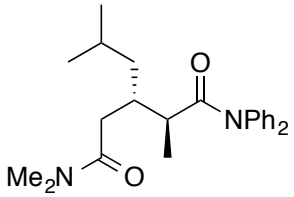
6.29 (s, 1H), 6.03 (d, 1H, *J* = 3.4 Hz), 3.83 (td, 1H, *J* = 8.6, 4.6 Hz), 2.99-2.83 (m, 7H), 2.72-2.62 (m, 2H), 1.21 (d, 3H, J = 6.9 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 175.0, 171.0, 155.9, 142.8, 142.7, 140.6, 129.6, 128.7, 128.5, 127.7, 126.6, 126.0, 110.4, 106.5, 41.1, 38.4, 37.1, 35.5, 32.7, 14.9; IR(neat, cm^{-1}); 3071, 2970, 2935, 1665, 1492, 1380, 1266; HRMS (Dart) calcd for $C_{24}H_{27}N_2O_3$ $[M + H]^+$ 391.2022, found 391.2021.

(2*S*,3*R*)-3-isopropyl-*N*^{5},*N*^{5},2-trimethyl-*N*^{1},*N*^{1}-diphenylpentanediamide (**3pb**);



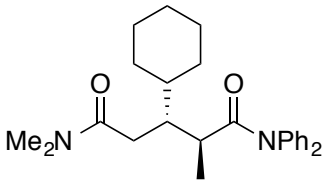
colorless oil; $[\alpha]_D$=110.11 (c 2.65, $CHCl_3$); HPLC analysis using Daicel Chiralpak AD-H column (Hex;^{i}PrOH = 80:20, 1.0 mL/min, 254 nm, t_R = 6.1 min (Major), 8.6 min (minor)); ^{1}H NMR (600 MHz , $CDCl_3$) δ: 7.47-7.13 (m, 10H), 3.02-2.96 (m, 7H), 2.62 (dd, 1H, *J* = 16.5, 4.1 Hz), 2.46-2.42 (m, 1H), 2.09 (dd, 1H, *J* = 16.5, 6.2 Hz), 1.48-1.42 (m, 1H), 1.03 (d, 3H, *J* = 6.9 Hz), 0.69 (d, 3H, *J* = 6.9 Hz), 0.41 (d, 3H, *J* = 6.2 Hz); ^{13}C NMR (150MHz, $CDCl_3$) δ: 176.2, 172.7, 143.1, 142.8, 129.4, 129.1, 128.6, 127.5, 126.9, 125.9, 41.1, 37.0, 37.0, 35.6, 31.0, 30.4, 20.2, 19.7, 11.3; IR(neat, cm^{-1}); 3061, 2961, 2874, 1647, 1492, 1377, 1267; HRMS (Dart) calcd for $C_{23}H_{31}N_2O_2$ $[M + H]^+$ 367.2386, found 367.2389.

(2*S*,3*S*)-3-isobutyl-*N*^{5},*N*^{5},2-trimethyl-*N*^{1},*N*^{1}-diphenylpentanediamide (**3qb**); colorless



oil; $[\alpha]_D$=176.87 (c 0.37, $CHCl_3$); HPLC analysis using Daicel Chiralpak AD-H column (Hex;^{i}PrOH = 90/10, 1.0 mL/min, 254 nm, t_R = 7.8 min (Major), 8.5 min (minor)); ^{1}H NMR (600 MHz , $CDCl_3$) δ: 7.39-7.15 (m, 10H), 2.98 (d, 6H, *J* = 43.3 Hz), 2.90-2.87 (m, 1H), 2.77 (dd, 1H, *J* = 16.2, 4.5 Hz), 2.55-2.54 (m, 1H), 2.00 (q, 1H, *J* = 8.0 Hz), 1.12-1.02 (m, 6H), 0.72 (d, 3H, *J* = 6.19 Hz), 0.56 (d, 3H, *J* = 6.19 Hz) ; ^{13}C NMR (150MHz, $CDCl_3$) δ: 176.1, 172.4, 143.2, 142.9, 129.6, 128.9, 128.7, 127.6, 126.9, 126.0, 42.3, 37.9, 37.2, 35.5, 33.4, 33.1, 24.9, 23.1, 21.9, 11.2; IR(neat, cm^{-1}); 3061, 2952, 2870, 1665, 1593, 1492, 1378, 1265; HRMS (Dart) calcd for $C_{24}H_{33}N_2O_2$ $[M + H]^+$ 381.2542, found 381.2545.

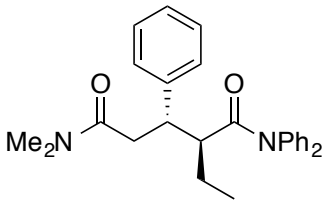
(2*S*,3*R*)-3-cyclohexyl-*N*^{5},*N*^{5},2-trimethyl-*N*^{1},*N*^{1}-diphenylpentanediamide (**3rb**);



colorless oil; $[\alpha]_D$=–70.51 (c 0.27, $CHCl_3$); HPLC analysis using Daicel Chiralpak AD-H column (Hex;^{i}PrOH = 80:20, 1.0 mL/min, 254 nm, t_R = 5.7 min (Major), 11.0 min (minor)); ^{1}H NMR (600 MHz , $CDCl_3$) δ: 7.42 (d, 4H, *J* = 18.6 Hz), 7.31-7.25 (m, 5H), 7.14 (s, 1H), 3.02-2.96 (m, 7H), 2.60 (dd, 1H, *J* = 16.8, 3.8 Hz), 2.49 (s, 1H), 2.11 (dd, 1H, *J* = 16.5, 6.2 Hz), 1.64 (d, 1H, *J* = 13.1 Hz), 1.53 (d, 1H, *J* = 11.7 Hz), 1.46 (d, 1H, *J* = 11.7 Hz), 1.39 (d, 1H, *J* = 12.4 Hz), 1.27 (d, 1H, *J* = 12.4 Hz), 1.13-0.94 (m, 7H), 0.79-0.73 (m, 1H), 0.31-0.25 (m, 1H) ; ^{13}C NMR (150MHz, $CDCl_3$) δ: 176.5, 172.8, 143.2, 142.8, 129.4, 129.1, 128.7,

127.6, 127.0, 125.9, 40.4, 40.0, 37.1, 36.6, 35.7, 31.0, 30.2, 29.9, 26.4, 26.2, 26.2, 11.5; IR(neat, cm^{-1});3464, 3061, 2926, 2851, 1664, 1492, 1377, 1266, 1150; HRMS (Dart) calcd for $C_{26}H_{35}N_2O_2$ $[M + H]^+$ 407.2699, found 407.2680.

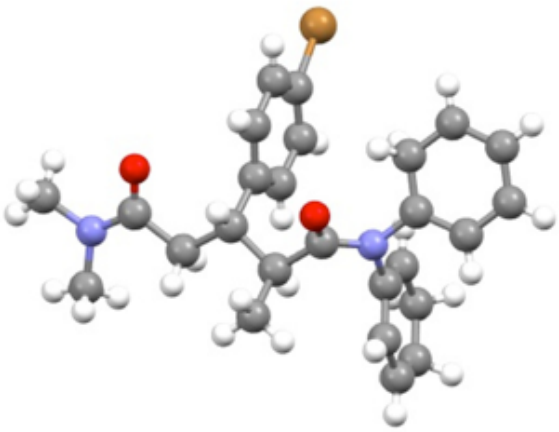
(2*S*,3*S*)-2-ethyl-*N*^{5},*N*^{5}-dimethyl-*N*^{1},*N*^{1},3-triphenylpentanediamide (**3ec**); colorless oil;

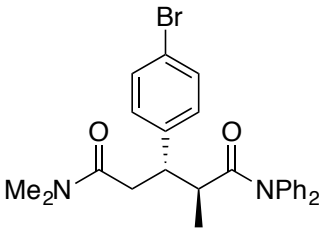


$[\alpha]_D$=–11.86 (c 0.68, $CHCl_3$); HPLC analysis using Daicel Chiralpak AD-H column (Hex;^{i}PrOH = 80:20, 1.0 mL/min, 254 nm, t_R = 27.2 min (Major), 13.1 min (minor)); ^{1}H NMR (600 MHz , $CDCl_3$) δ: 7.40-7.07 (m, 13H), 6.92 (d, 2H, *J* = 7.6 Hz), 3.84-3.80 (m, 1H), 2.96-2.67 (m, 9H), 1.87-1.82 (m, 1H), 1.47-1.43 (m, 1H), 0.96 (t, 3H, *J* = 7.6 Hz) ; ^{13}C NMR (150MHz, $CDCl_3$) δ: 174.1, 171.3, 142.9, 142.6, 129.5, 129.3, 128.7, 128.0, 128.0, 127.7, 126.7, 126.3, 126.0, 126.0, 49.4, 42.7, 37.1, 35.4, 33.0, 21.4, 12.1; IR(neat, cm^{-1});3063, 3030, 2965, 2933, 1662, 1492, 1384, 1287; HRMS (Dart) calcd for $C_{27}H_{31}N_2O_2$ $[M + H]^+$ 414.2386, found 414.2377.

5. Structure of compound 3nb

Absolute configuration of diamide **3nb** was determined by X-ray single crystal structure analysis of the product obtained in the asymmetric reaction using (*S*,*S*)-binaphtho-34-crown-10 (in our typical reactions on the tables 2 and 3, (*R*,*R*)-binaphtho-34-crown-10 was used as a chiral ligand) after recrystallization in hexane-ethyl acetate mixed solvent system. The data have been deposited with the Cambridge Crystallographic Data Centre under the organic and organometallic compounds as entry CCDC 1032790. Flack parameter is 0.98, that means the opposite enantiomer is correct structure in the reaction using (*S*,*S*)-binaphtho-34-crown-10.

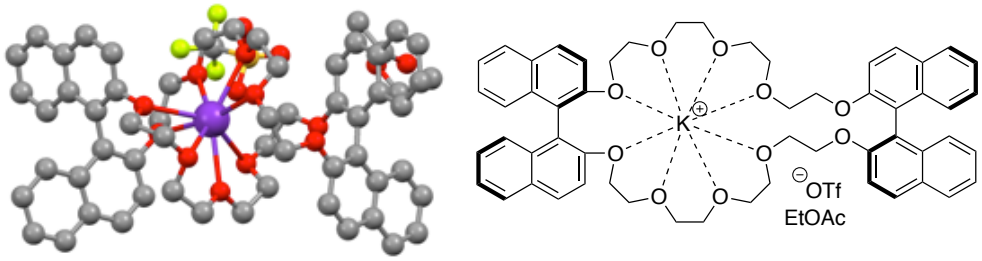




6. The X-ray structure of the binaphtho-34-crown-10 (L4)–KOTf complex

Binaphtho-34-crown-10 (**L6**, 17.8 mg, 20.0 μmol) and KOTf (7.5 mg, 40 μmol) were placed in a sample tube, and toluene (1.0 mL) was added. The mixture was stirred for 1 h at room temperature, and then filtered to remove precipitation. After

filtration, the filtrate was evaporated under reduced pressure and an oily residue was obtained. It was dissolved in ethyl acetate (0.4 mL), and the whole was put at room temperature under hexane vapor atmosphere. After 1 week, small colorless crystals appeared and were collected by filtration. The data have been deposited with the Cambridge Crystallographic Data Centre under the organic and organometallic compounds as entry CCDC 1032789.

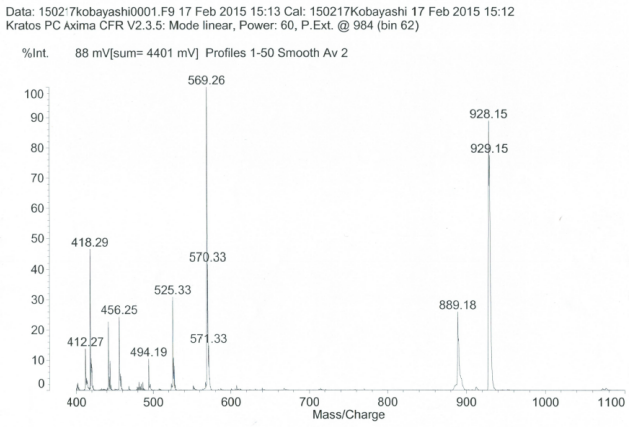


7. NMR analysis of the catalyst solution

KHMDS (11.4 mg, 5.71 x 10^{-2} mmol) and binaphtho-34-crown-10 (**L6**, 24.8 mg, 2.79 x 10^{-2} mmol) were placed in a flame-dried tube with septa inside a glovebox fulfilled with argon. The tube was cooled to –78 ºC and then toluene-d_8 (1.0 mL) was added. The mixture was stirred at –78 ºC for 1 h. After stirring, the mixture was transferred to a well-dried NMR tube inside a glove box. ^{1}H NMR analysis was conducted at –60 ºC and 0 °C.

8. MALDI-TOF MS analysis of the catalyst solution

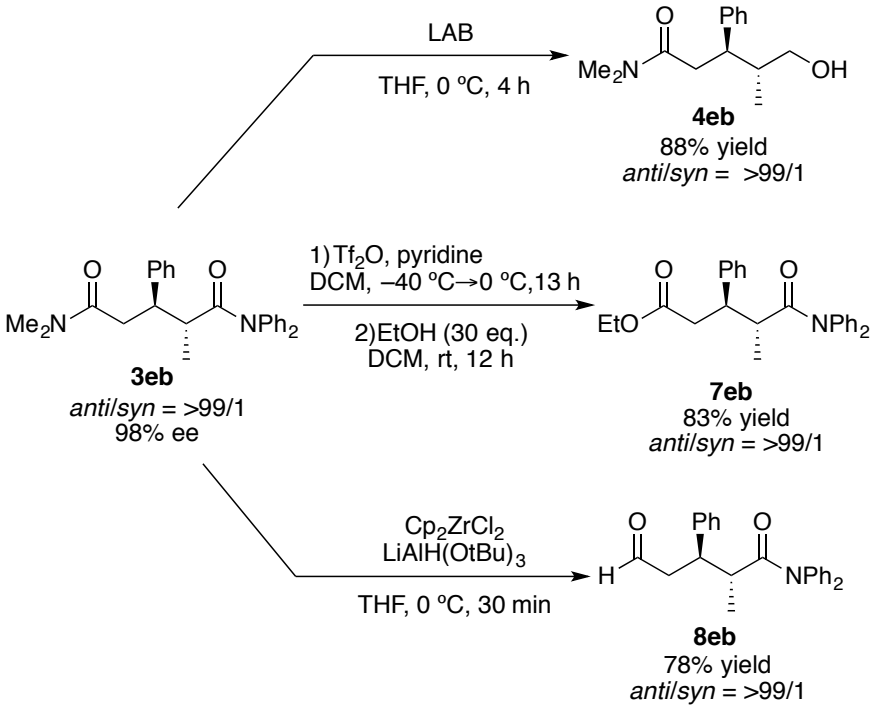
KHMDS (8.1 mg, 4.1 x 10^{-2} mmol) and binaphtho-34-crown-10 (**L6**, 17.5 mg, 1.97 x 10^{-2} mmol) were placed in a flame-dried tube with septa inside a glovebox fulfilled with argon. The tube was cooled to –78 ºC then toluene (1.0 mL) was added. The mixture was stirred at –78 ºC for 1 h. After stirring, MALDI-TOF MS measurement was conducted. CHCA (10 mg/mL in 1:1 mixture of acetonitrile/0.1% TFA aq.) was used as a matrix of the measurement. The signal of the **K-L6** complex (1:1) was observed. Calibration was conducted by using PEG (Polyethylene glycol).



9. Experimental procedure of checking backward reaction (Scheme 1-7-1)

Diamide **3eb** (143.8 mg, 0.3590 mmol, *anti/syn* = >99/1, 98% ee), KHMDS (8.8 mg, 4.4 x 10^{-2} mmol) and 18-crown-6 (11.4 mg, 4.32 x 10^{-2} mmol) and MS4A (50 mg) were placed in a flame-dried 10 mL flask inside a glove box fulfilled with argon. The flask was cooled to −78 ºC, then toluene (1.0 mL) was added. The reaction mixture was stirred for 18 h at the same temperature. The reaction was quenched by water, and the mixture was extracted with DCM (10 mL x 3). The organic layers were combined and dried over anhydrous Na_2SO_4. After filtration and concentration under reduced pressure, the crude product obtained was purified by silica-gel PTLC (hexane-ethylacetate) to afford the desired adduct **3eb** (137.0 mg, 0.3421 mmol).

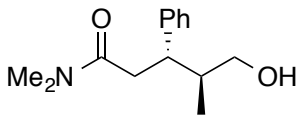
10. Transformation of Product



Transformation of amide 3eb into alcohol 4eb

Diamide **3eb** (39.1 mg, 9.76 x 10^{-2} mmol) was placed in a flame-dried 10 mL flask inside a glove box fulfilled with argon. The flask was cooled to 0 ºC, then lithium dimethyaminoborohydride (LAB, 1 M in THF, 0.5 mL, 1.0 mmol) was added. The reaction mixture was stirred for 4 h at same temperature. After stirring, the reaction mixture was quenched by slow addition of 1 M HCl and then extracted with DCM (10 mL x 5). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration and concentration under reduced pressure, the crude product obtained was purified by silica-gel PTLC (hexane-ethyl acetate) to afford the desired alcohol **4eb** (20.2 mg, 88 % yield, 96% ee).

(3*S*,4*S*)-5-hydroxy-*N*,*N*,4-trimethyl-3-phenylpentanamide (**4eb**); colorless oil; $[\alpha]_D$=-

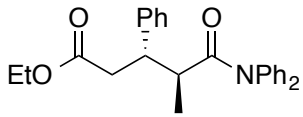


–281.26 (c 0.23, $CHCl_3$); HPLC analysis using Daicel Chiralpak AD-H column (Hex;^{i}PrOH = 90:10, 1.0 mL/min, 210 nm, t_R = 18.0 min (Major), 15.2 min (minor)); ^{1}H NMR (600 MHz , $CDCl_3$) δ: 7.31-7.19 (m, 5H), 3.48 (dd, 1H, *J* = 13.1, 5.5 Hz), 3.38 (dd, 1H, *J* = 11.7, 5.5 MHz), 3.29 (dd, 1H, *J* = 11.7, 8.3), 2.94 (d, 6H, *J* = 41.2), 2.84 (dd, 1H, *J* = 15.8, 7.6 MHz), 2.64 (dd, 1H, *J* = 15.8, 5.5 MHz), 2.05-2.01 (m, 1H), 0.84 (d, 3H, *J* = 6.9 MHz); ^{13}C NMR (150MHz, $CDCl_3$) δ: 172.6, 144.0, 128.2, 128.2, 126.2, 65.9, 42.2, 40.8, 37.4, 35.7, 34.2, 13.1; IR(neat, cm^{-1}); 3416, 2927, 1630, 1495, 1454, 1400; HRMS (Dart) calcd for $C_{14}H_{21}N_1O_2$ $[M + H]^+$ 236.1651, found 236.1640.

Transformation of amide 3eb into ester 7eb

Diamide **3eb** (42.1 mg, 0.105 mmol) was placed in a flame-dried 10 mL flask inside a glove box fulfilled with argon and DCM (0.5 mL) was added. The flask was cooled to –40 ºC, and then pyridine (185 μL, 2.30 mmol) and Tf_2O (168 μL, 1.00 mmol) were added. The reaction mixture was gradually heated from –40 ºC to 0 ºC over 2 h. The reaction mixture was then stirred for 11 h at 0 ºC. After stirring, EtOH (0.5 mL) was added to the flask. The reaction mixture was stirred at room temperature for 12 h and was quenched by 1 M HCl and then extracted with Et_2O (10 mL x 3). The combined organic layers were washed with 1 M HCl and sat. $NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4. After filtration and concentration under reduced pressure, the crude product obtained was purified by silica-gel PTLC (hexane-ethylacetate) to afford the desired ester **7eb** (34.9 g, 83 % yield, 97% ee).

ethyl (3*S*,4*S*)-5-(diphenylamino)-4-methyl-5-oxo-3-phenylpentanoate (**7eb**); white

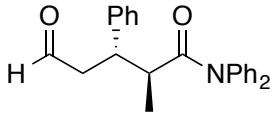


solid; Mp: 100-102 ºC; $[\alpha]_D$=+17.00 (c 0.35, $CHCl_3$); HPLC analysis using Daicel Chiralpak AD-3 column (Hex;^{i}PrOH = 75:25, 1.0 mL/min, 254 nm, t_R = 13.9 min (Major), 24.4 min (minor)); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.35-6.74 (m, 15H), 3.92 (q, 2H, *J* = 6.9 Hz), 3.56 (td, 1H, *J* = 10.1, 4.8 MHz), 2.81-2.76 (m, 2H), 2.44 (dd, 1H, *J* = 15.1, 10.3 MHz), 1.29 (d, 3H, *J* = 6.9 MHz), 1.02 (t, 3H, *J* = 7.2 Hz) ; ^{13}C NMR (150MHz, $CDCl_3$) δ: 175.1, 171.9, 142.6, 142.0, 129.4, 128.6, 128.5, 128.4, 128.4, 128.1, 127.6, 126.9, 126.5, 126.0, 60.2, 45.4, 43.3, 37.5, 15.8, 13.9; IR(neat, cm^{-1}); 3061, 3031, 2979, 1733, 1668, 1593, 1492, 1377, 1261; HRMS (Dart) calcd for $C_{26}H_{28}N_1O_3$ $[M + H]^+$ 402.2069, found 402.2056.

Transformation of amide 3eb into aldehyde 8eb

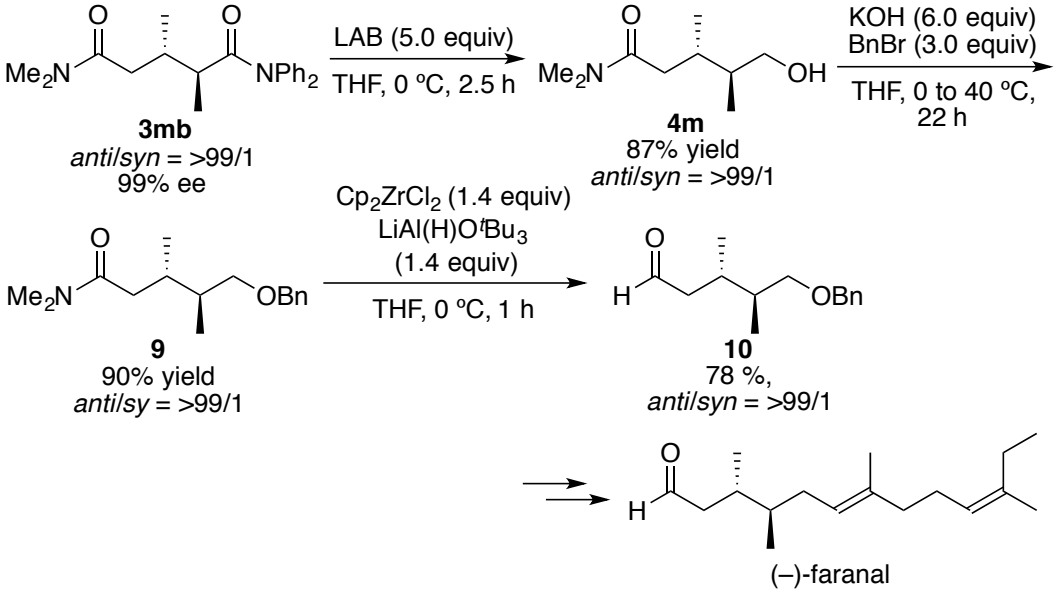
Diamide **3eb** (40.8 mg, 0.102 mmol) and Cp_2ZrCl_2 (42.5 mg, 0.145 mmol) were placed in a flame-dried 10 mL flask inside a glove box fulfilled with argon, and THF (0.36 mL) was added. The flask was cooled at 0 ºC, then LiAl(H)O*t*Bu$_3$ (1 M in THF, 140 μL, 1.4 mmol) was added. The reaction mixture was stirred for 30 min at the same

temperature. After stirring, the reaction mixture was quenched by addition of 1 M HCl and then extracted with DCM (10 mL x 5). The combined organic layers were washed with brine (20 mL) and dried over anhydrous Na_2SO_4. After filtration and concentration under reduced pressure, the crude product obtained was purified by silica-gel PTLC (hexane-ethylacetate) to afford the desired alcohol **8eb** (28.3 mg, 78 % yield, 98% ee).



(2*S*,3*S*)-2-methyl-5-oxo-*N*,*N*,3-triphenylpentanamide (**8eb**); colorless oil; $[\alpha]_D$=–30.40 (c 0.31, $CHCl_3$); HPLC analysis using Daicel Chiralpak AD-H column (Hex;^{i}PrOH = 90:10, 1.0 mL/min, 254 nm, t_R = 18.9 min (Major), 20.9 min (minor));^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.56 (t, 1H, *J* = 1.1 Hz), 7.34-7.08 (m, 11H), 6.85-6.78 (m, 4H), 3.67 (td, 1H, *J* = 9.9, 4.7 Hz), 2.86-2.77 (m, 2H), 2.63-2.56 (m, 1H), 1.27 (d, 3H, *J* = 6.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 201.5, 174.9, 142.5, 141.8, 129.5, 128.7, 128.5, 128.5, 128.4, 128.4, 127.8, 127.2, 126.5, 126.1, 45.8, 43.5, 43.3, 15.9; IR(neat, cm^{-1}); 3061, 3030, 2970, 2825, 2723, 1721, 1666, 1492, 1377, 1263; HRMS (Dart) calcd for $C_{24}H_{24}N_1O_3$ $[M + H]^+$ 358.1807, found 358.1789.

Formal synthesis of (-)-faranal

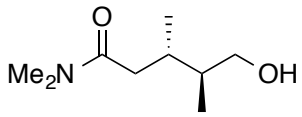


Synthesis of alcohol 4m

Diamide **3mb** (66.8 mg, 0.197 mmol) was placed in a flame-dried 10 mL flask inside a glove box fulfilled with argon. The flask was cooled to 0 ºC, then LAB (1 M in THF, 1.0 mL, 1.0 mmol) was added. The reaction mixture was stirred for 2 h at the same temperature. After the stirring, the reaction mixture was quenched by slow addition of conc. HClaq. and then extracted with chloroform (10 mL x 5). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration and concentration under reduced pressure, the crude product obtained was purified by

silica-gel column chromatography (chloroform-methanol) to afford the desired alcohol **4m** (29.7 mg, 87 % yield).

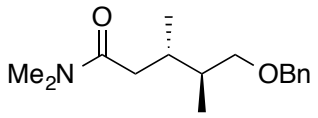
(3*S*,4*S*)-5-hydroxy-*N*,*N*,3,4-tetramethylpentanamide (**4m**); colorless oil; ^{1}H NMR (600 MHz , $CDCl_3$) δ: 3.59-3.28 (m, 3H), 3.00 (d, 6H, *J* = 46.7 MHz), 2.46-2.39 (m, 2H), 2.07 (dt, 1H, *J* = 18.1, 4.1 MHz), 1.80-1.75 (m, 1H), 0.99 (d, 3H, *J* = 6.9 Hz) , 0.78 (d, 3H, *J* = 6.9 Hz) ; ^{13}C NMR (150MHz, $CDCl_3$) δ: 173.6, 65.5, 39.9, 37.4, 35.7, 35.0, 29.3, 18.8, 11.7; IR(neat, cm^{-1}); 3393, 2959, 2879, 1626, 1406, 1264, 1152, 1048; HRMS (Dart) calcd for $C_9H_{20}N_1O_2$ $[M + H]^+$ 174.1494, found 174.1486.



Synthesis of benzyl ether 9

Alcohol **4m** (30.3 mg, 0.175 mmol) and pulverized KOH (58.8 mg, 1.05 mmol) were placed in a well-dried 10 mL flask that was fulfilled with argon, and THF was added (2.0 mL). Benzyl bromide (62.4 μL, 0.525 mmol) was then added to the reaction mixture, and the whole was stirred for 18 h at room temperature. After that, temperature of the reaction mixture was elevated to 40 ºC. The mixture was stirred for 4 h, and was quenched by water and extracted with DCM (10 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration and concentration under reduced pressure, the crude product obtained was purified by silica-gel PTLC (hexane-ethyl acetate) to afford the desired benzyl ether **9** (41.3 mg, 90 % yield).

(3*S*,4*S*)-5-(benzyloxy)-*N*,*N*,3,4-tetramethylpentanamide (**9**); colorless oil; ^{1}H NMR (600 MHz , $CDCl_3$) δ: 7.35-7.26 (m, 5H), 4.48 (s, 2H), 3.44 (dd, 1H, *J* = 9.3, 7.2 Hz), 3.31 (dd, 1H, *J* = 8.9, 6.2 Hz), 2.93 (d, 6H, *J* = 7.6 Hz), 2.43 (dd, 1H, *J* = 14.4, 4.1 Hz), 2.20-2.18 (m, 1H), 2.10 (dd, 1H, *J* = 14.4, 9.6 Hz), 1.86 (dt, 1H, *J* = 12.6, 5.3 Hz) , 0.94-0.91 (m, 6H) ; ^{13}C NMR (150MHz, $CDCl_3$) δ: 138.6, 128.3, 128.3, 127.5, 127.4, 73.6, 73.0, 37.7, 37.4, 37.0, 35.4, 32.3, 16.8, 14.1; IR(neat, cm^{-1}); 2959, 2917, 2876, 2850, 1638, 1456, 1397; HRMS (Dart) calcd for $C_{16}H_{26}N_1O_2$ $[M + H]^+$ 264.1964, found 264.1954.

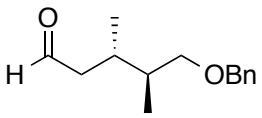


Synthesis of aldehyde 10

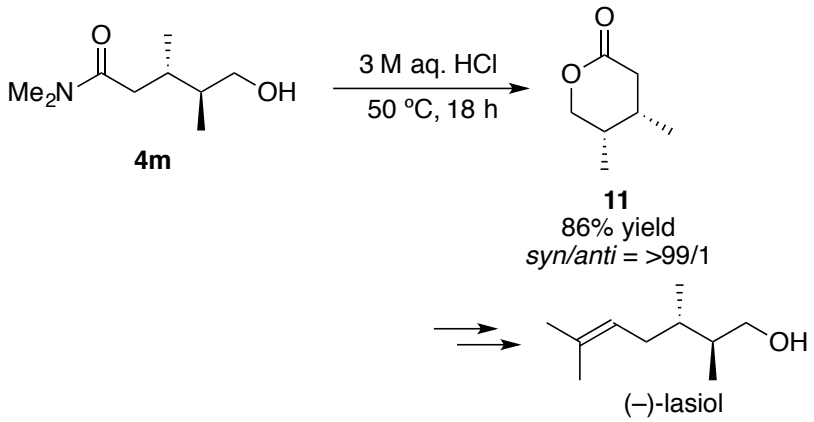
Benzyl ether **9** (27.4 mg, 0.104 mmol) and Cp_2ZrCl_2 (42.7 mg, 0.146 mmol) were placed in a flame-dried 10 mL flask inside a glove box fulfilled with argon, and THF (0.5 mL) was added. The flask was cooled at 0 ºC, then LiAl(H)O*t*Bu$_3$ (1 M in THF, 146 μL, 1.46 mmol) was added. The whole was stirred for 30 min at the same temperature. After stirring, the reaction mixture was quenched by 1 M HCl and then extracted with DCM (10 mL x 5). The combined organic layers were washed with brine (20 mL) and dried over anhydrous Na_2SO_4. After filtration and concentration under reduced pressure, the crude product obtained was purified by silica-gel PTLC

(hexane-ethyl acetate) to afford the desired alcohol **10** (17.8 mg, 78 % yield).

(3*S*,4*S*)-5-(benzyloxy)-3,4-dimethylpentanal (**10**)[9]; colorless oil; $[\alpha]_D$=+15.5 (c 0.13, $CHCl_3$), lit $[\alpha]_D$=+14.7 (c 1.4, $CHCl_3$)[7]; ^{1}H NMR (400 MHz , $CDCl_3$) δ: 9.72 (s, 1H), 7.37-7.26 (m, 5H), 4.48 (d, 2H), 3.38-3.30 (m, 2H), 2,47 (dd, 1H, *J* = 4.6, 16.5 Hz), 2.30-2.46 (m, 1H), 2.17 (ddd, 1H, 1.83, 9.16, 16.0 Hz), 1.87-1.81 (m, 1H), 0.96-0.77 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 203.3, 138.4, 128.4, 127.6, 127.6, 73.2, 73.0, 47.3, 37.8, 29.4, 17.6, 13.5.



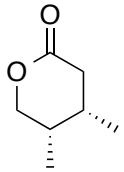
Formal synthesis of (-)-lasiol



Synthesis of lactone 11

Alcohol **4m** (20.9 mg, 0.121 mmol) was placed in a flame-dried 10 mL flask, and 3 M aq. HCl (8.0 mL) was added. The whole solution was stirred at 50 ºC for 18 h. After stirring, the reaction mixture was cooled to room temperature, and then extracted with chloroform (10 mL x 5). The combined organic layers were washed with brine (10 mLx2) then dried over anhydrous Na_2SO_4. After filtration and concentration under reduced pressure, the crude product obtained was purified by silica-gel PTLC (hexane-diethyl ether) to afford the desired lactone **11** (13.4 mg, 86 % yield).

(4*S*,5*S*)-4,5-dimethyltetrahydro-2*H*-pyran-2-one (**11**); colorless oil; $[\alpha]_D$=–39.0 (c 0.27, MeOH), lit $[\alpha]_D$=+46.6 (c 1.85, MeOH)[11]; ^{1}H NMR (600 MHz , $CDCl_3$) δ: 4.23 (dd, 1H, *J* = 11.7, 4.1 MHz), 4.07 (dd, 1H, *J* = 11.0, 6.9 MHz), 2.55 (dd, 1H, *J* = 17.9, 6.2 MHz), 2.25 (dd, 1H, *J* = 17.9, 7.6 MHz), 2.11-2.07 (m, 1H), 2.01 (dq, 1H, *J* = 14.4, 3.6 Hz), 0.94-0.90 (m, 6H); ^{13}C NMR (150MHz, $CDCl_3$) δ: 170.8, 73.4, 36.4, 31.1, 29.9, 15.8, 11.5.

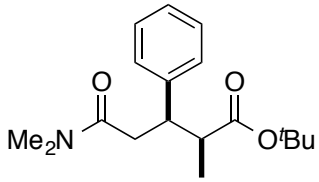


11. Catalytic asymmetric 1,4-additon reactions using simple ester, nitrile and sulfonamide

Typical procedure of catalytic asymmetric 1,4-addition reaction of ^{t}Bu propionate

KHMDS (7.9 mg, 4.0 x 10^{-2} mmol) and **L6** (19.8 mg, 2.23 x 10^{-2} mmol) were placed in a dried 10 mL flask inside a glove box filled with argon. The flask was cooled to –78 ˚C, then toluene (0.7 mL) was added. The reaction mixture was stirred for 1 h at the same temperature for catalyst preparation. After that, ^{t}Bu propionate (**2d**, 64.1 mg, 0.492 mmol) was added to the reaction mixture by syringe, then *N,N*-dimethylcinnamamide (**1e**, 70.0 mg, 0.400 mmol), which was put in another dried tube inside a glove box, was added to the reaction mixture through cannula with extra toluene (1.5 mL). The whole mixture was stirred for 24 h at –78 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 (Hexane-Ethyl acetate) to afford the desired 1,4-adduct **3ed** (*syn*-form, 73.7 mg, 0.241 mmol; *anti*-form, 39.3 mg, 0.129 mmol).

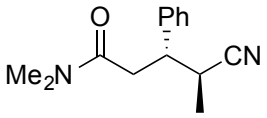
***tert*-butyl 5-(dimethylamino)-2-methyl-5-oxo-3-phenylpentanoate (3ed);** colorless oil; *Syn*-form: HPLC analysis using Daicel Chiralpak AD-3 column (Hex/^{i}PrOH = 95/5, 1.0 mL/min, 210 nm, t_R = 22.1 min (major), 16.4 min (minor)); $[\alpha]_D$ = –13.77 (c 0.23, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.29-7.18 (m, 5H), 3.38 (td, 1H, *J* = 10.1, 4.4 Hz), 2.85 (s, 3H), 2.78 (s, 3H), 2.74 (dd, 1H, *J* = 14.8, 10.0 MHz), 2.67-2.61 (m, 2H), 1.46 (s, 9H), 0.93 (d, 3H, *J* = 6.9 Hz): minor δ: 7.26-7.16 (m, 5H), 3.41 (td, 1H, *J* = 9.1, 5.4 Hz), 2.81 (s, 3H), 2.79 (s, 3H), 2.77-2.73 (m, 2H), 2.66 (dd, 1H, *J* = 15.1, 8.9 MHz), 1.23 (d, 3H, *J* = 6.9 Hz), 1.18 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 175.1, 170.8, 141.8, 128.2, 128.1, 126.6, 80.4, 46.1, 45.2, 37.9, 37.2, 35.2, 28.0, 16.0; IR (neat, cm^{-1}); 2976, 2932, 1723, 1649, 1495, 1455, 1395, 1367, 1259, 1149, 849, 763, 701, 665; HRMS (DART) calcd for $C_{18}H_{28}NO_3$ $[M + H]^+$ 306.2069, found 306.2054; *Anti*-form: HPLC analysis using Daicel Chiralpak OD-3 column (Hex/^{i}PrOH = 95/5, 0.7 mL/min, 210 nm, t_R = 18.7 min (Major), 16.3 min (minor)); $[\alpha]_D$ = –17.03 (c 0.19, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.26-7.16 (m, 5H), 3.41 (td, 1H, *J* = 9.1, 5.4 Hz), 2.81 (s, 3H), 2.79 (s, 3H), 2.77-2.73 (m, 2H), 2.66 (dd, 1H, *J* = 15.1, 8.9 MHz), 1.23 (d, 3H, *J* = 6.9 Hz), 1.18 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 174.3, 171.3, 142.4, 128.3, 128.0, 126.5, 79.9, 45.7, 45.4, 37.2, 36.6, 35.4, 27.6, 15.7; IR (neat, cm^{-1}); 2976, 2933, 1724, 1648, 1494, 1455, 1395, 1367, 1253, 1150, 849, 761, 701, 664; HRMS (DART) calcd for $C_{18}H_{28}NO_3$ $[M + H]^+$ 306.2069, found 306.2061.



Typical procedure of catalytic asymmetric 1,4-addition reaction of propionitrile

KHMDS (4.1 mg, 2.1 x 10^{-2} mmol) and **L6** (9.7 mg, 1.1 x 10^{-2} mmol) were placed in a dried 10 mL flask inside a glove box filled with argon. The flask was cooled to –78 ˚C, then toluene (1.0 mL) was added. The reaction mixture was stirred for 1 h at the same temperature for catalyst preparation. After that, propionitrile (**2e**, 111 μL, 1.60 mmol) and *N,N*-dimethylcinnamamide (**1e**, 70.1 mg, 0.400 mmol), which were put in another dried tube inside a glove box, were added to the flask through cannula with extra toluene (2.0 mL). The whole mixture was stirred for 18 h at –78 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 (Hexane-Ethyl acetate) to afford the desired 1,4-adduct **3ee** (77.6 mg, 0.337 mmol).

(3*S*,4*S*)-4-cyano-*N*,*N*-dimethyl-3-phenylpentanamide (3ee, *anti*/*syn* = 93/7);



colorless oil; *Anti*-form: HPLC analysis using Daicel Chiralpak AD-3 column (Hex/^{i}PrOH = 95/5, 0.7 mL/min, 210 nm, t_R = 23.1 min (3*R*,4*R*), 36.8 min (3*S*,4*S*)); ^{1}H NMR (600 MHz, $CDCl_3$) δ:7.29-7.17 (m, 5H), 3.33-3.27 (m, 2H), 2.95 (s, 3H), 2.94-2.91 (m, 1H), 2.88 (s, 3H) 2.65 (dd, 1H, *J* = 16.5, 4.1 Hz), 1.07 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ:169.9, 139.0, 128.4, 128.2, 127.4, 121.6, 43.4, 36.9, 36.9, 35.3, 29.7, 16.3; *Syn*-form: ^{1}H NMR (600 MHz, $CDCl_3$, detectable peaks) δ:7.29-7.17 (m, 5H), 3.40-3.36 (m, 1H), 2.86 (s, 3H), 2.83-2.82 (m, 1H), 2.78 (s, 3H), 1.16 (d, 3H, *J* = 7.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ:169.7, 140.3, 128.5, 127.6, 127.2, 121.9, 44.5, 36.9, 36.3, 35.2, 31.0, 16.3; IR (neat, cm^{-1}); 3485, 2937, 2238, 1646, 1496, 1455, 1404, 1265, 1147; HRMS (DART) calcd for $C_{14}H_{19}N_2O$ $[M + H]^+$ 231.1497, found 231.1490.

(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)

Experimental Section ~Chapter 2~

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。

Experimental Section ~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。

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