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**Enantioselective organocatalyzed aza-Morita-Baylis-Hillman and
formal [n+2] cycloaddition reactions of ketimines**

A Doctoral Thesis
Submitted to the Department of Chemistry
Graduate School of Science
Osaka University

By
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Synthetic Organic Chemistry
The Institute of Scientific and Industrial Research (ISIR)
August, 2014

Dedicated to my parents, the driving force of my life.

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Abbreviations

Ac	acetyl
anhyd.	anhydrous
aq.	aqueous or water solution
Ar	aryl
atm.	atmosphere
β -ICD	β -isocupreidine
BINOL	1,1'-bi-2, 2'-naphthol
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
Bz	benzoyl
cat.	catalyst or catalytic amount of
COSY	correlation spectroscopy
CPME	cyclopentylmethyl ether
⁶ Hex or Cy	cyclohexyl
d	days
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DEA	diethylamine
DIBAL	diisobutylaluminium hydride
DMAP	4-(dimethylamino)pyridine
DMP	Dess-Martin periodinane
dr	diastereomeric ratio
<i>E</i>	entgegen
EDG	electron donating group
ee	enantiomeric excess
eq	equivalent
ESI-MS	electrospray ionization mass spectrometry
Et	ethyl
EVK	ethyl vinyl ketone
EWG	electron withdrawing group
Fc	ferrocenyl
FMO	frontier molecular orbital
FG	functional group
Fig.	figure

FT-IR	Fourier transform infrared spectroscopy
GPC	gel permeation chromatography
h	hour
HFIPA	1,1,1,3,3,3-hexafluoroisopropyl acryl ester
HMBC	heteronuclear multiple bond correlation
HMQC	heteronuclear multiple quantum correlation
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
IBX	2-iodoxybenzoic acid
INADEQUATE	incredible natural abundance double quantum transfer experiment
INEPT	insensitive nuclei enhanced by polarization transfer
IPA	isopropyl alcohol
<i>J</i>	coupling constant
KHMDS	potassium hexamethyldisilazide
LA	Lewis acid
LAH	lithium aluminium hydride
LB	Lewis base
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
liq.	liquid
LUMO	lowest unoccupied molecular orbital
MBH	Morita-Baylis-Hillman
Me	methyl
Mes	mesityl (2,4,6-trimethylphenyl)
min	minute
MO	molecular orbital
MOM	methoxymethyl
m.p.	melting point
Ms	mesyl (methanesulfonyl)
MS	molecular sieve
MTBE	methyl <i>tert</i> -butyl ether
MVK	methyl vinyl ketone
M.W.	molecular weight
μW	microwave
NBS	N-bromosuccinimide
NCS	N-chlorosuccinimide
NIS	N-iodosuccinimide
NMR	nuclear magnetic resonance

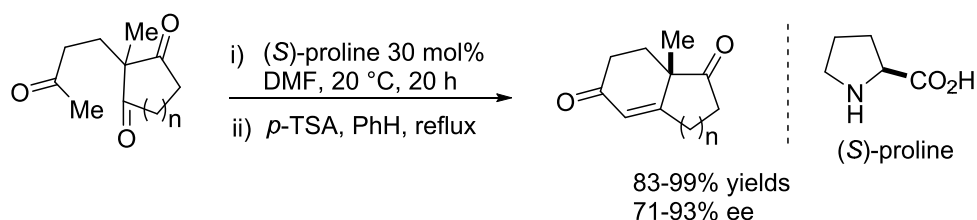
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
Np	naphthyl
NR or n.r.	no reaction
Ns	nosyl (nitrosobenzenesulfonyl)
Nu or Nuc	nucleophile
ORTEP	Oak Ridge Thermal Ellipsoid Program
PG	protecting group
Ph	phenyl
Ph-H	benzene
Piv	pivaloyl
PMP	<i>para</i> -methoxyphenyl
PPA	polyphosphoric acid
ppm	parts per million
ⁱ Pr	isopropyl
Proton-sponge	1,8-Bis(dimethylamino)naphthalene
P.T.	proton transfer
PTC	phase-transfer-catalyst
PTSA	<i>p</i> -toluenesulfonic acid
Py	pyridine
quant.	quantitative
R	alkyl
<i>R</i>	rectus
<i>rac</i>	racemic
RCM	ring-closing metathesis
RDS	rate-determining step
R _f	perfluoroalkyl group
R _f	retention factor in chromatography
Rochelle salt	potassium sodium tartrate
ROESY	rotating frame nuclear Overhauser effect spectroscopy
ROM	ring-opening metathesis
rt	room temperature
<i>S</i>	sinister
s	seconds
SET	single electron transfer

(<i>R</i>)-SITCP	(11a <i>R</i>)-(+)-5,6,10,11,12,13-Hexahydro-5-phenyl-4H-diindeno[7,1- <i>cd</i> :1',7'- <i>ef</i>] phosphine
SOMO	single occupied molecular orbital
SPRIX	spiro bis(isoxazoline)
TBAB	tetrabutylammonium bromide
TBS	<i>tert</i> -butyldimethylsilyl
TBHP	<i>tert</i> -butylhydroperoxide
TEA	triethylamine
TEMPO	2,2,6,6-tetramethylpiperidinyloxy
temp.	temperature
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	<i>N,N,N',N'</i> -tetramethylethylenediamine
TMG	1,1,3,3-tetramethylguanidine
TMS	tetramethylsilyl or tetramethylsilane
Ts	<i>para</i> -toluenesulfonyl
TS	transition state
UV	ultraviolet
<i>vic</i>	vicinal
Weinreb amide	<i>N,O</i> -dimethylhydroxamic acids
XRD	x-ray diffraction
xyl or xylyl	3,5-dimethylphenyl
y.	yield
Z	benzyloxycarbonyl
Z	zusammen

Chapter 1

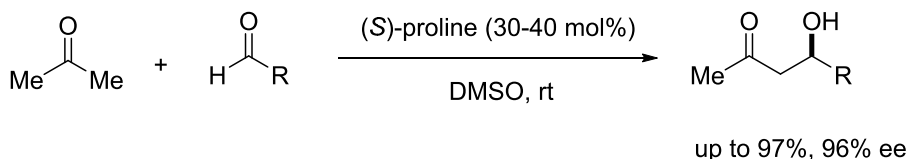
Background

Synthesis of enantiopure compounds represents one of the most attractive and challenging fields in organic synthesis.^[1] Complementary to the traditional metal-mediated asymmetric synthesis,^[2] and inspired by the enzymatic labor in Nature, the use of simple and small organic compounds as catalyst has gained more and more applications in current organic synthesis.^[3] Coined and defined in 2000 by W. C. MacMillan,^[4] *organocatalysis* has had a fast developing owing to their in general important advantages such as: non-toxic, usually stable under aerobic conditions, commercially available or easy synthesized, reactions conducted under mild conditions, among others.^[3]

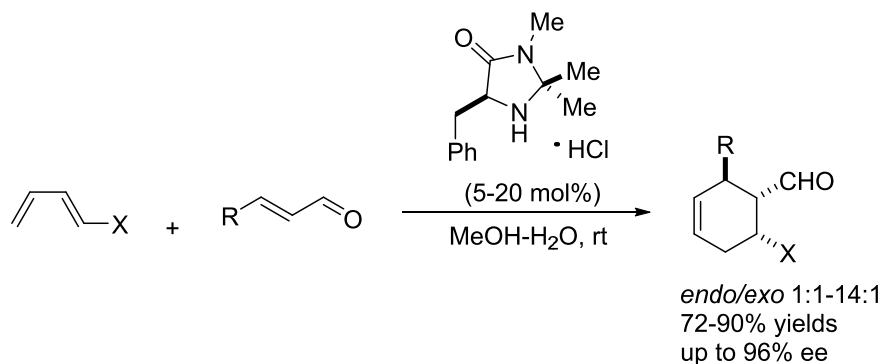


Scheme 1.- Pioneering example of organocatalysis promoted by (*S*)-proline.

Historically, the discovery of organocatalysis can be dated to the late of 1950s with the report of Pracejus on the preparation of (-)- α -phenyl methylpropionate in 74% ee by using an alkaloid-type tertiary amine.^[5] However, high yield and high enantioselectivity was first observed on the (*S*)-proline promoted Robinson annulation, up to 93% ee, thereby considered one of the frameworks of organocatalysis (Scheme 1).^[6] The process involving aldol reaction and known as Hajos-Parris-Eder-Sauer-Wiechert reaction provides access to some key intermediates for the synthesis of natural products. Identified as potential versatile catalyst, in 2000 List and Barbas applied (*S*)-proline on the aldol reaction achieving results comparable in terms of enantioselectivities to those obtained by using metal-containing catalyst (Scheme 2).^[7]



Scheme 2.- Asymmetric aldol reaction catalyzed by (*S*)-proline.



Scheme 3.- Asymmetric Diels-Alder cycloaddition catalyzed by imidazolidinone catalyst.

MacMillan reported secondary amine catalyst to activate enals *via* iminium ion for the synthesis cyclohexenyl ring systems by Diels-Alder reaction with notably enantioselectivity levels (Scheme 3).^[4] Thus, the concept of iminium ion activation together with the proline aldol research described by List and Barbas set the bases for the emerging organocatalysis generation.

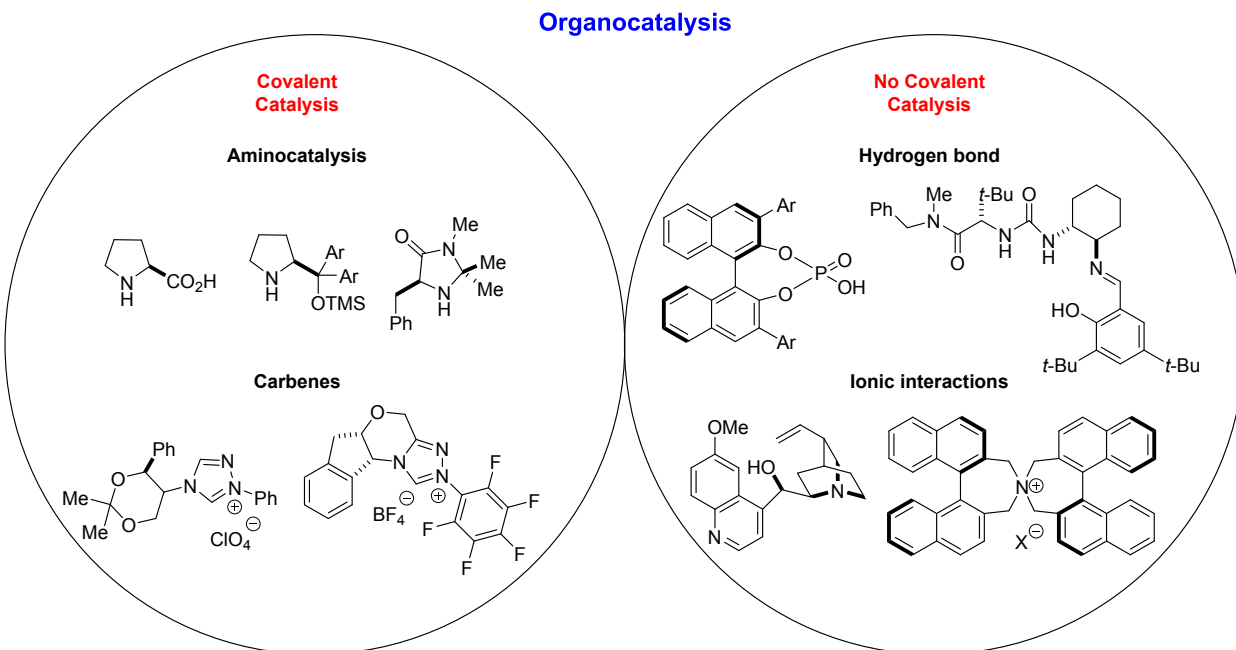


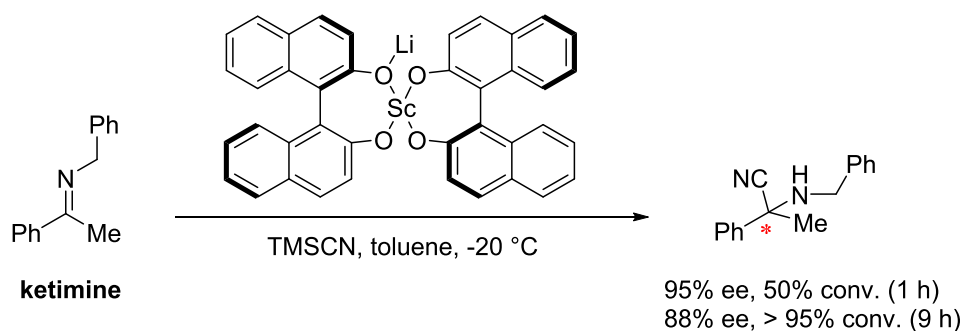
Figure 1.- General classification of the activation mode in organocatalysis.

The fast development of organocatalysis has allowed it to be recognized as an independent synthetic area. The organocatalysts have two main functions; they can activate the electrophile or the nucleophile (or both in the case of bifunctional catalysis), or they create an asymmetric environment that is responsible for setting the chirality of the product.

Based on the interaction or activation, organocatalysts can be classified into two big groups as covalent or non-covalent catalysts (Figure 1). In covalent catalysis, a covalent bond between the organocatalyst and the substrate is formed. In this category, aminocatalysis^[8] and carbenes^[9] are included. In the case of non-covalent interactions between the substrate and the catalyst, the activation of the substrate occurs *via* hydrogen bonds^[10] (*e.g.*, thioureas,^[11] squaramides^[12] and phosphoric acids^[13]) or ionic interactions (*e.g.*, chiral bases such as cinchona alkaloids^[14] and phase-transfer-catalysts^[15]).

Catalytic formation of tetrasubstituted carbon stereogenic centers

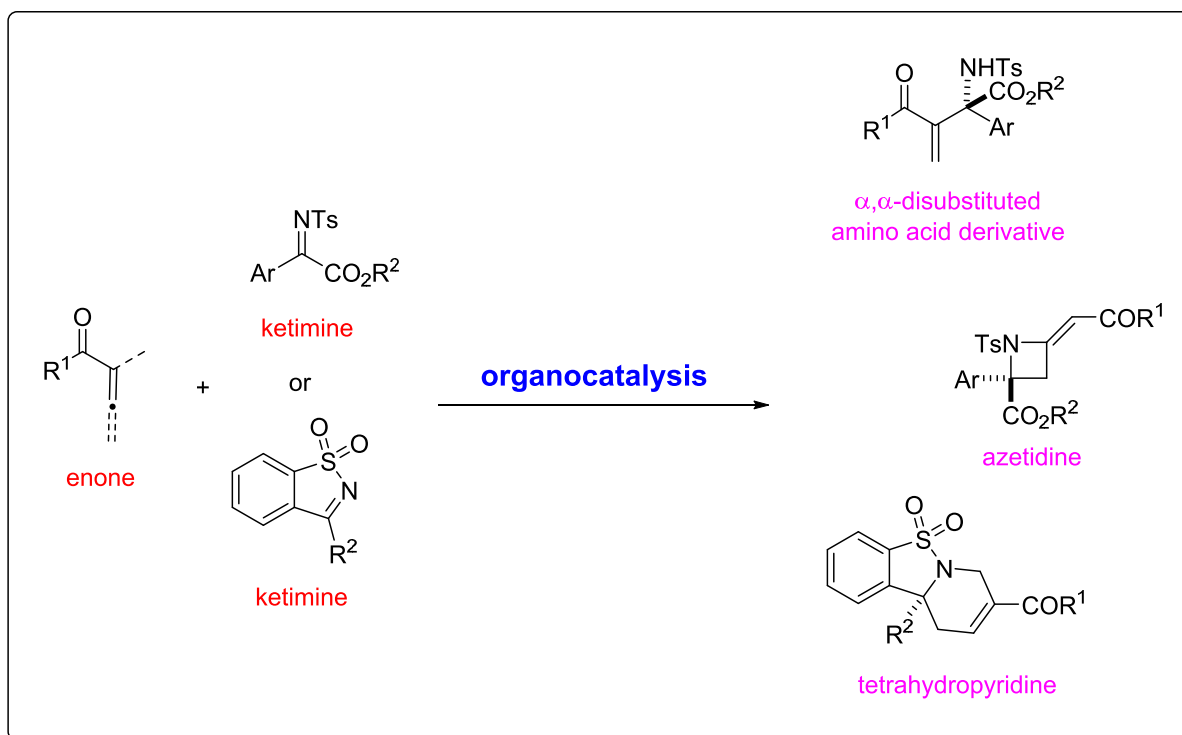
Preparation of enantiopure compounds bearing a tertiary stereogenic center in academia and industry has reached very good levels by applying the large variety of available methods including chiral auxiliaries, ligands or catalysis.^[16] However, synthesis of biologically relevant molecules bearing a tetrasubstituted stereogenic center still remains as challenging field.^[17]



Scheme 4.- Asymmetric addition of TMSCN to ketimines.

The straightforward method to create tetrasubstituted carbon centers is through the nucleophilic addition. Several groups were involved on the addition of silyl enolates to ketones where a chelating ketone was coordinated to different metal complexes to yield high levels of stereoselectivity.^[18] Similarly, it was envisioned the synthesis of amines on a tetrasubstituted carbon center by the corresponding nucleophilic addition to ketimines. The Strecker reaction represents an important transformation which provides access to α -disubstituted amino acids derivatives. Vallée reported the first examples of metal-catalyzed asymmetric additions of TMSCN or HCN catalyzed by titanium-based complexes, and more successfully with chiral heterobimetallic scandium complex (Scheme 4).^[19] In a subsequent series of publications Shibasaki described the use of gadolinium complexes affording high enantioselectivities, up to 98% ee.^[20]

This work



Scheme 5.- Enantioselective synthesis of relevant structures bearing a tetrasubstituted stereogenic carbon center.

Although generation of compounds bearing a tetrasubstituted carbon center has been partially developed by using metallic-complexes,^[17-21] there is great concern about the use of metal-containing catalyst, especially for the synthesis of compounds with potential application in the pharmaceutical industry. In this work, I have developed a series of strategies involving organocatalysis for the synthesis of several important compounds possessing a chiral tetrasubstituted carbon center in high enantioselectivities (Scheme 5).

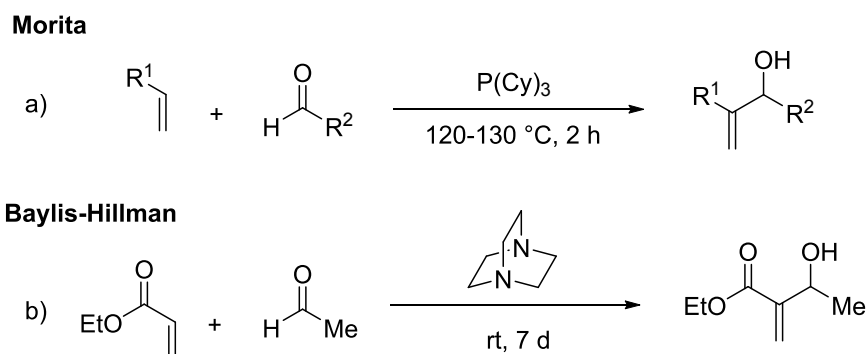
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Chapter 2

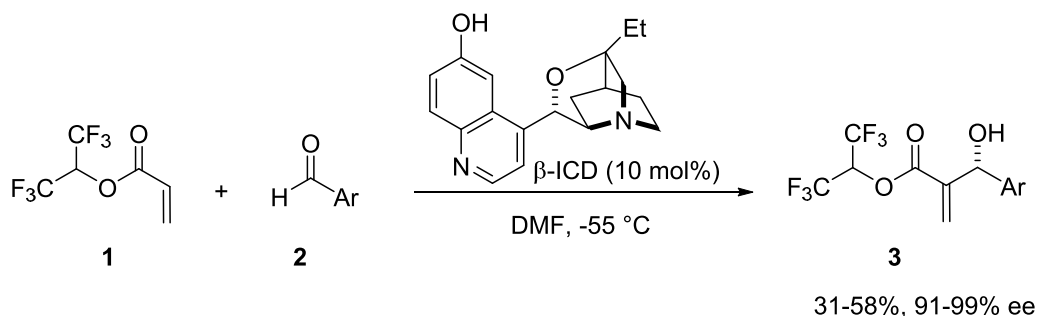
Aza-Morita-Baylis-Hillman (aza-MBH) reaction of ketimines

The Morita-Baylis-Hillman (MBH) reaction is known to be one of the most efficient C-C bond forming reactions between electron-deficient alkenes with aldehydes, allowing access to highly functionalized allylic alcohols with atom economy in straightforward manner.^[1] The reaction was first reported in 1968 by Morita and co-workers (Scheme 1a).^[2]

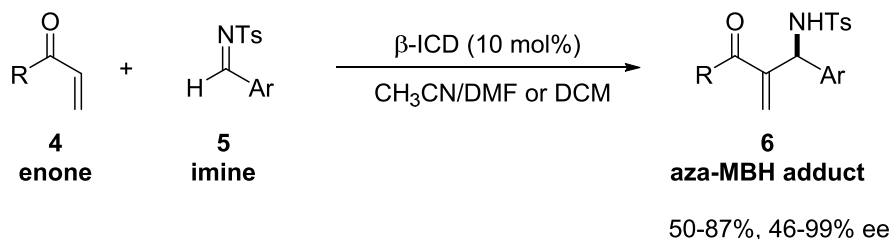


Scheme 1.- Morita-Baylis-Hillman (MBH) reaction.

Unfortunately, this phosphine-promoted transformation suffered from low yields and it was neglected for a while. In 1972 a German patent indicating similar transformation under tertiary amine catalysis was reported (Scheme 1b).^[3] Owing to its synthetic importance, several groups were involved on the study of the reaction mechanism and the development of different methods to expand the scope of MBH reaction by using metal and metal-free protocols.^[1] Among these, the introduction of β -ICD (β -isocupreidine) by Hatakeyama and Iwabuchi represented an important step through the development of asymmetric MBH reaction. They reported the addition of acrylates to a variety of aromatic and aliphatic aldehydes for the formation of MBH-adducts up to 99% ee (Scheme 2).^[4] The use of that

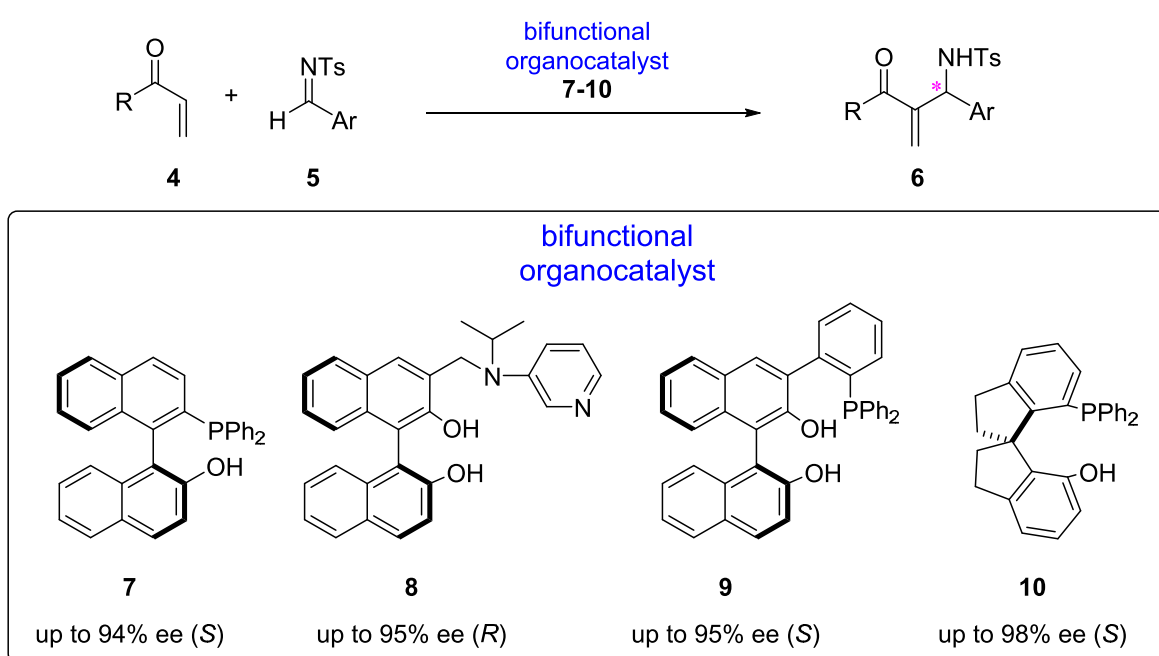


Scheme 2.- Asymmetric MBH reaction of aldehydes and HFIPA catalyzed by β -ICD.



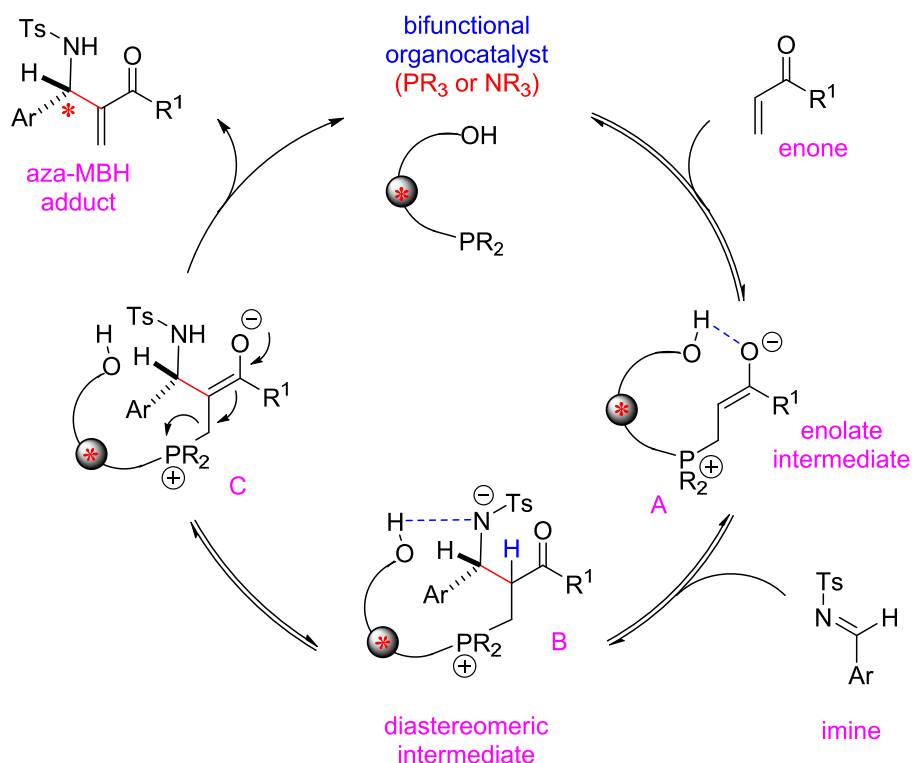
Scheme 3.- Asymmetric aza-MBH reaction catalyzed by β -ICD

particular substrate 1,1,1,3,3,3-hexafluoroisopropyl acryl ester (HFIPA) displayed an almost 200-fold rate acceleration compared to methyl acrylate, under identical reaction conditions. The same organocatalyst showed high activity on the corresponding reaction of enone **4** and imine **5**, aza-MBH reaction, for the enantioselective synthesis of allylic amines as reported by Shi in 2002 (Scheme 3).^[5]



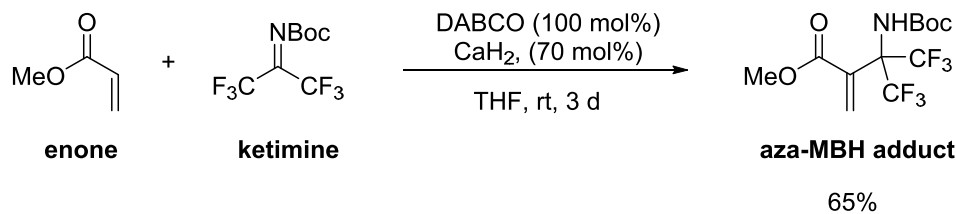
Scheme 4.- Chiral bifunctional organocatalyst for aza-MBH reaction.

As demonstrated by our group and others,^[6] BINOL and SPINOL-based bifunctional chiral organocatalysts (phosphines or tertiary amines) among other systems, have been found to work exceptionally well on the aza-MBH reaction of aldimines (Scheme 4). The general accepted mechanism is illustrated in Scheme 5.^[1,4-7] Michael addition of chiral Lewis base (LB) organocatalyst generates the formation of an enolate intermediate **A**. Using a brønsted acid would help to enhance the stability of this intermediate through hydrogen bonding



Scheme 5.- Reaction mechanism of aza-MBH reaction.

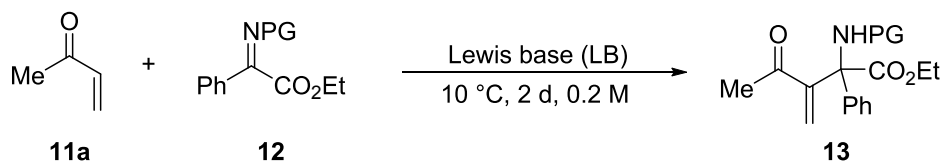
donation. The second step involves the aldol type addition to the electrophile, in this case aldimine, generating thus a new C-C bond (intermediate **B**). This is also the enantioselectivity- determining step. As described on the intermediate **B**, complexity on the enantioselective discrimination arises from the fact that two different possible diastereomeric intermediates can be generated. To avoid steric interactions, catalyst would prefer to approach *via* the less congested face of the substrate, locating the bulky group far from the approaching site. The next step is a proton transfer to generate **C**. Finally, a retro-Michael step delivers the enantioenriched aza-MBH adduct with concurrent regeneration of the organocatalyst to complete the catalytic cycle. It is clear that in the case of one of the substituents on aldimine is an aryl group and the other hydrogen, the transition state generally favors location of aryl group far from the catalyst backbone decreasing steric hindrance, thereby increasing the possibility to obtain higher enantioselectivity.



Scheme 6.- Achiral aza-MBH reaction of ketimines.

Although several examples on the enantioselective aza-MBH reaction of aldimines are reported in literature,^[1,4-7] the corresponding process using ketimines as substrates (where hydrogen in imine is replaced for a different substituent), which eventually would provide access to a multifunctional allylic amines bearing a tetrasubstituted carbon center, remained undisclosed. The only example found in literature was reported in 2001 by Burger.^[8] A very activated bis-trifluoromethyl ketimine was reacted with acrylate in presence of a stoichiometric amount of DABCO delivering aza-MBH adduct in moderate yield (Scheme 6).

Table 1.- Achiral LB catalyzed aza-MBH reaction of **11a** with **12**.

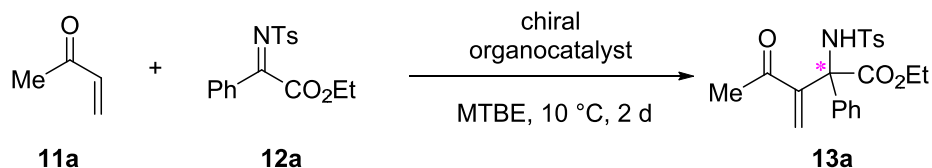


Entry	Lewis base	PG	Solvent	Yield %
1	DMAP	Ts	DCM	10
2	DABCO	Ts	DCM	7
3	DBU	Ts	DCM	trace
4		Ts	DCM	trace
5	PPh ₃	Ts	DCM	74
6	PPh ₃	Ts	(CH ₂ Cl) ₂	70
7	PPh ₃	Ts	CHCl ₃	54
8	PPh ₃	Ts	toluene	80
9	PPh ₃	Ts	THF	34
10	PPh ₃	Ts	Et ₂ O	50
11	PPh ₃	Ts	MTBE	96
12	PPh ₃	PMP	MTBE	NR

Conditions: **11a** (0.12 mmol), **12** (0.04 mmol), LB (10 mol%). PG = Protecting group. NR = No reaction.

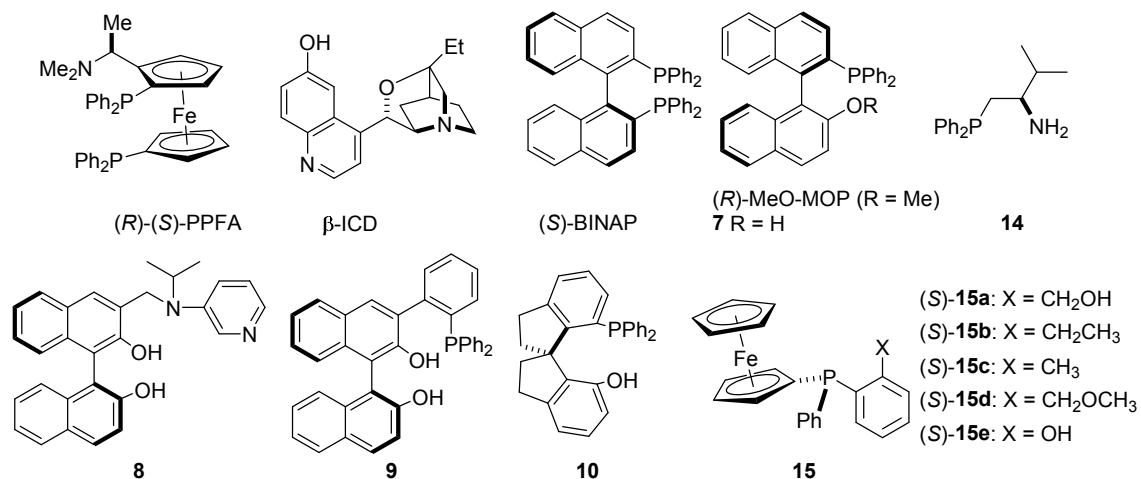
With the aim of developing a method for construction of α,α -disubstituted amino acid derivatives bearing a chiral tetrasubstituted carbon center, ester-containing ketimine was selected as a model substrate. The reaction was initially explored with achiral Lewis bases (Table 1). Amine type catalyst such as DABCO and DMAP provided poor yields of the aza-MBH adduct accompanied with decomposition of ketimine (entries 1,2). Trace amount of

Table 2.- Enantioselective aza-MBH reaction of **11a** with ketimine **12a**.



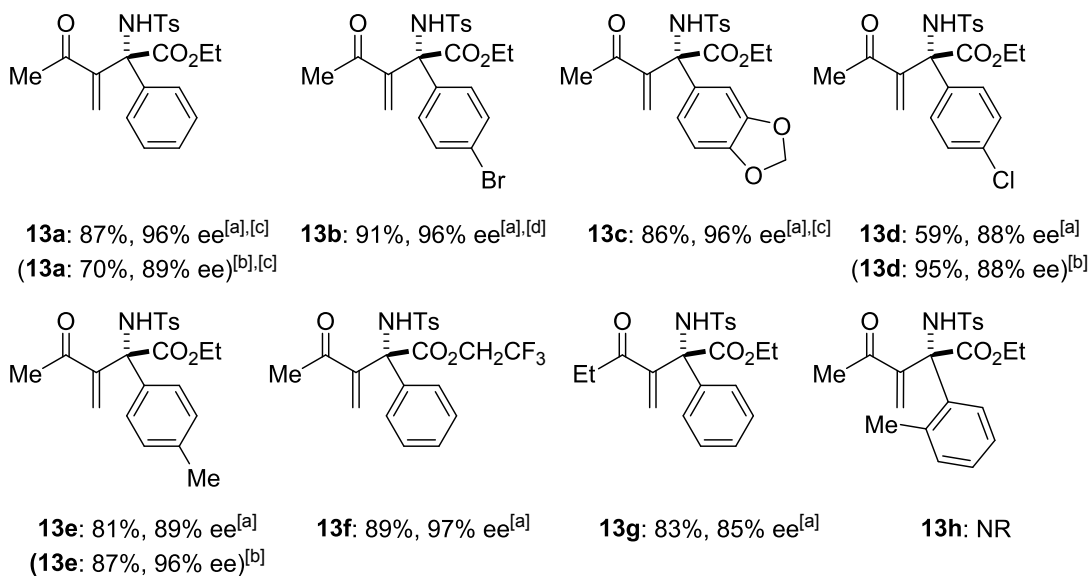
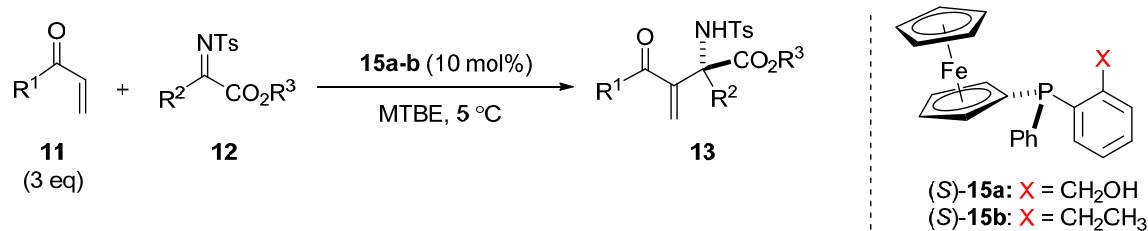
Entry	Chiral organocatalyst	Yield %	ee %
1	(<i>R</i>)-(<i>S</i>)-PPFA	trace	--
2	β -ICD	trace	--
3	(<i>S</i>)-BINAP	trace	--
4	(<i>R</i>)-MeO-MOP, (<i>R</i>)-7	trace	--
5	(<i>R</i>)-14	29	0
6	(<i>S</i>)-8, (<i>S</i>)-10	trace	--
7	(<i>S</i>)-9	25	38
8	(<i>S</i>)-15a	87	96
9	(<i>S</i>)-15b	70	89
10	(<i>S</i>)-15c	42	15
11	(<i>S</i>)-15d	52	17
12	(<i>S</i>)-15e	trace	--

Conditions: **11a** (0.12 mmol), **12a** (0.04 mmol), chiral organocatalyst (10 mol%).



product was observed by using DBU or 2-phenyl-2-imidazolidine (entries 3,4). Gratifyingly, the reaction proceeded smoothly under PPh₃ catalysis, affording the racemic α,α -disubstituted amino acid derivative in 74% yield (entry 5). Further screening improved the yield up to 96% chemical yield by using *t*-BuOMe (MTBE) as solvent (entry 11). No reaction was observed when PMP was used as protecting group (entry 12).

Next, various chiral catalysts such as (*R*)-(*S*)-PPFA, β -ICD, (*S*)-BINAP, (*R*)-MeO-MOP, and compounds (*R*)-**7**, (*S*)-**8-10**, were tested as shown in Table 2. Some of them, which are known to mediate the enantioselective MBH-type processes.^[1,4-7,9] showed no activity with ketimine **12a** (entries 1-4, 6). Chiral organocatalyst (*R*)-**14** possessing highly nucleophilic phosphine led to racemic product (entry 5). The acid-base organocatalyst (*S*)-**9**^[6f] promoted the reaction to give **13a** in 25% yield and 38% ee (entry 7). During the screening process, P-chirogenic^[10] organocatalysts were found to promote the aza-MBH reaction. Thus, the ferrocenyl P-chirogenic organocatalyst (*S*)-**15a** promoted the reaction in

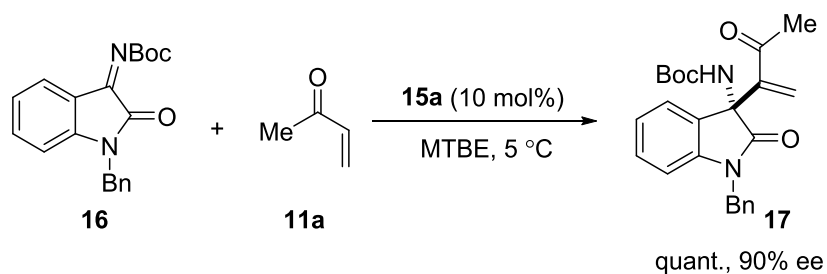


[a] (*S*)-**15a** was used. [b] (*S*)-**15b** was used. [c] Performed at 10 °C. [d] 20 mol% was used. NR = No reaction.

Scheme 7.- Substrate scope catalyzed by P-chirogenic organocatalyst.

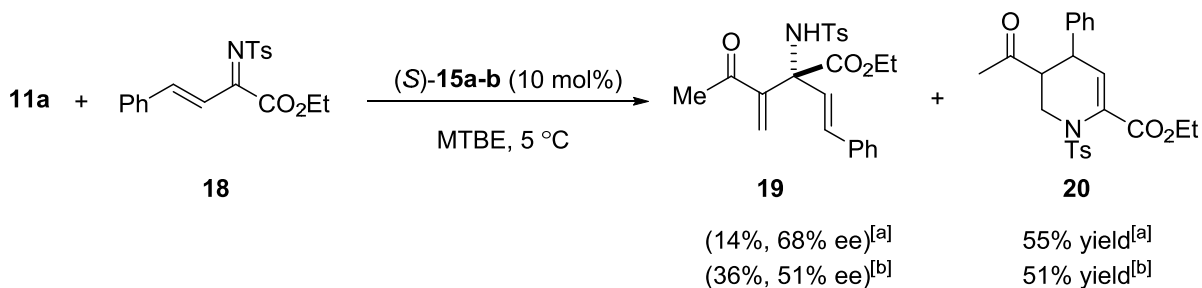
87% yield with 96% ee (entry 8), whereas (*S*)-**15c** with methyl and (*S*)-**15d** with methoxymethyl as *ortho*-substituents exhibited low asymmetric inductions (entries 10, 11). No catalytic activity was observed when (*S*)-**15e** bearing an *ortho*-hydroxy substituent was used (entry 12). Since the organocatalyst (*S*)-**15b** having an ethyl substituent afforded **13a** with high enantioselectivity (entry 9), the steric effect of the hydroxymethyl group or the ethyl substituent on the catalyst (*S*)-**15a** and (*S*)-**15b** respectively, would be important to promote the reaction with high enantiocontrol.

With the optimized conditions, substrate scope was studied (Scheme 7). Moderate to high enantioselectivities were obtained irrespective of the electronic nature of the substituent on the aromatic ring (entries **13a** to **13e**). Replacing ethyl ester for trifluoroethyl ester delivered the aza-MBH adduct in higher enantioselectivity, 97% ee (entry **13f**). The reaction was not restricted to MVK (methyl vinyl ketone), but also ethyl group was successfully introduced (entry **13g**). However, the reaction was sensitive to sterically demanding *ortho*-substituted substrates, resulting in no reaction (entry **13h**).



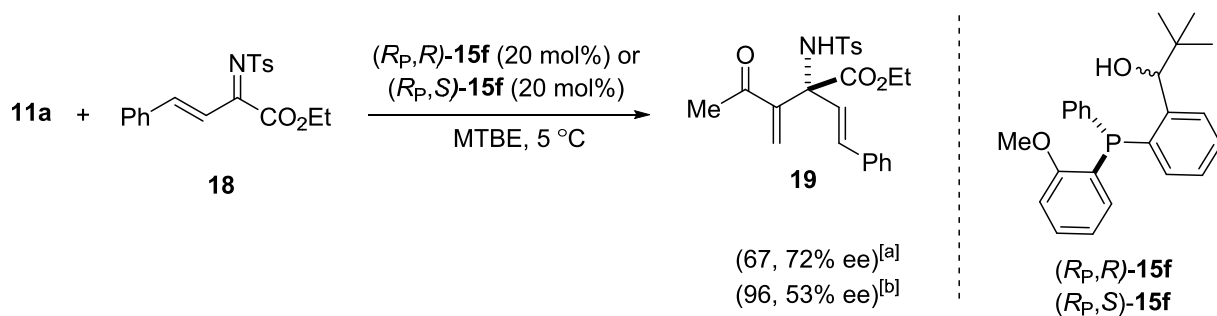
Scheme 8.- aza-MBH reaction of isatin-derived ketimine **16**.

Cyclic isatin-derived ketimine was also found to be suitable substrate, affording the desired product **17** in 90% ee (Scheme 8). Applying catalyst (*S*)-**15a** and (*S*)-**15b** to α,β -unsaturated ketimine **18** delivers the desired aza-MBH product in low yield and moderate enantioselectivities, along with the formation of tetrahydropyridne **20**,^[11] generated through a



[a] (*S*)-**15a** was used. [b] (*S*)-**15b** was used.

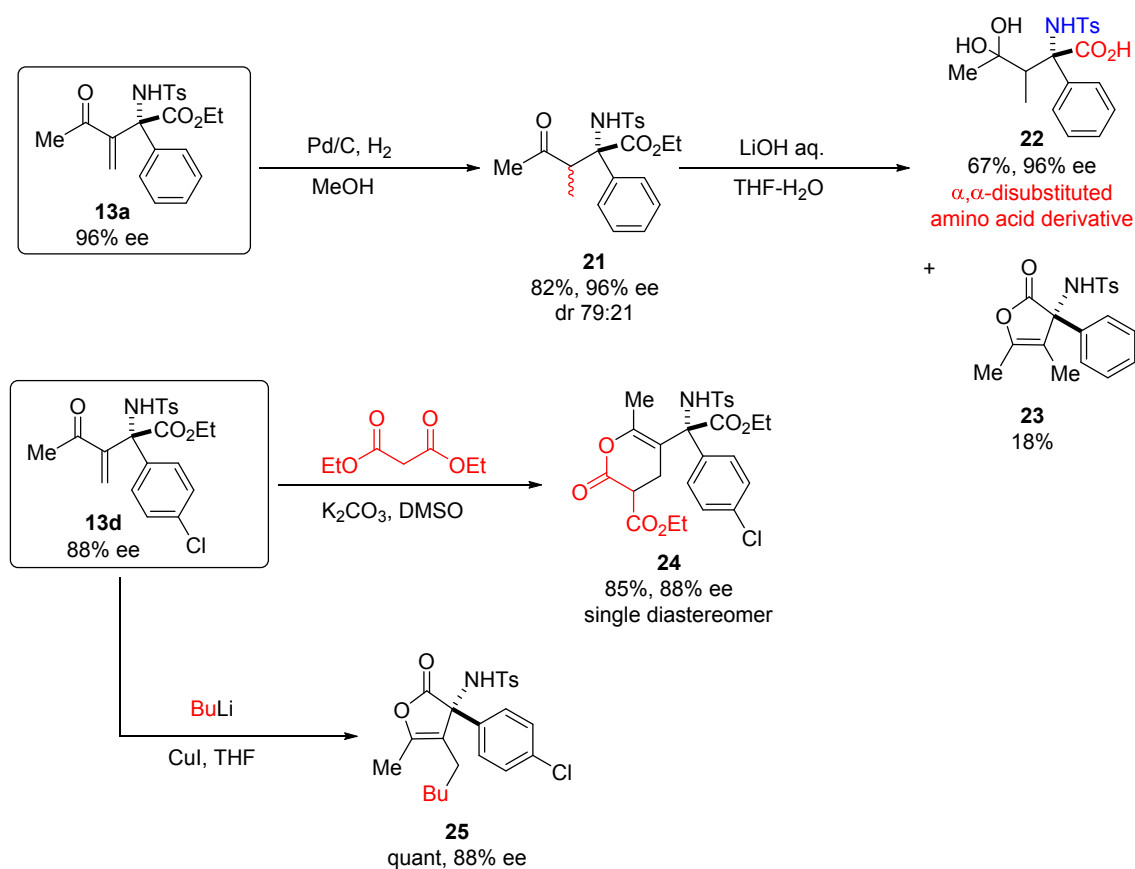
Scheme 9.- aza-MBH reaction of α,β -unsaturated ketimine **18** using (*S*)-**15a-b**.



[a] $(R_P,R)-15f$ was used. [b] $(R_P,S)-15f$ was used.

Scheme 10.- aza-MBH reaction of α,β -unsaturated ketimine **18** using catalyst **15f**.

[4+2] cyclization process (Scheme 9). The reaction was then explored with more bulky catalysts. Using P-chirogenic organocatalysts $(R_P,R)-15f$ and $(R_P,S)-15f$ were found to give the aza-MBH adduct **19** in moderate yield and moderate enantioselectivities (Scheme 10).



Scheme 11.- Synthetic transformations of aza-MBH adducts **13**.

To demonstrate the synthetic utility of highly functionalized aza-MBH products **13**, a variety of transformations were performed (Scheme 11). The α -methyl ketone **21** was obtained in good yield by 1,4-conjugated reduction of **13a** using Pd/C under H₂ without over reduction. Amino acid derivative **22** can be easily obtained after 2 steps, reduction and hydrolysis, accompanied by a five-membered ring byproduct **23**, starting from **13a**. Furthermore, Michael addition of BuLi with CuI or diethylmalonate with K₂CO₃ to **13d** produced the cyclic products **24** and **25** *via* sequential 1,4-addition/lactonization with over 85% yields, respectively.

Note:

By the same time of the report of our research, and independently, the groups of Shi and Chen have reported enantioselective aza-MBH reaction of ketimines using different catalysts and different substrates to those described here.^[12]

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Chapter 3

Formal [2+2] cycloaddition reaction of ketimines

Chiral azetidines constitutes an important class of N-containing four-membered heterocycles incorporated in natural products, and recently also applied as a chiral ligand for

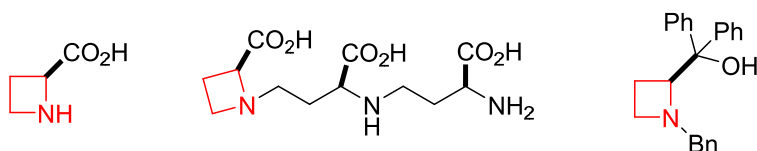
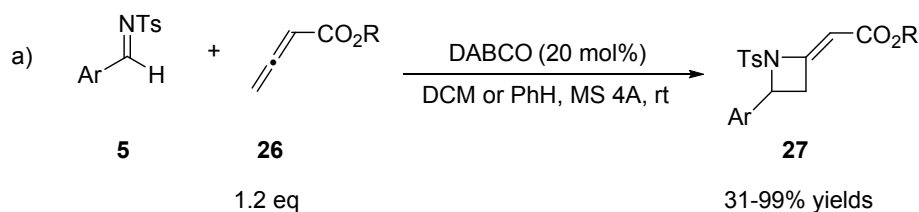


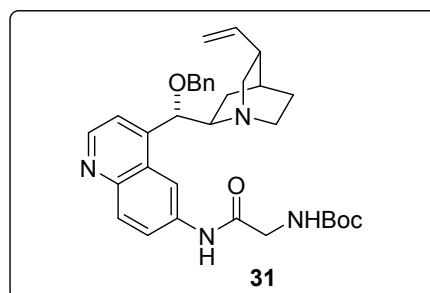
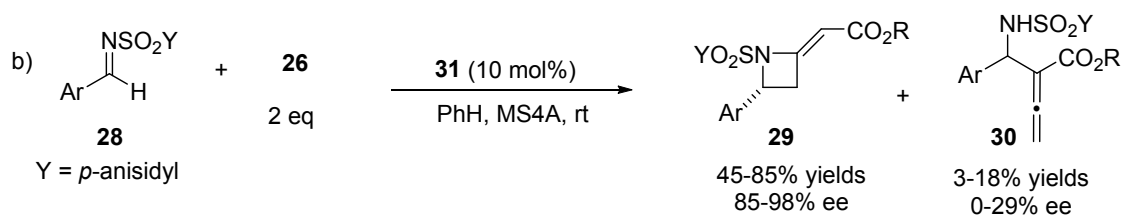
Figure 1. - Presence of azetidine in biologically important compounds.

asymmetric transformations.^[1] The general approach for their preparation normally involves a large sequence of linear steps delivering the heterocycles in low yields.^[2] More efficient route

Achiral

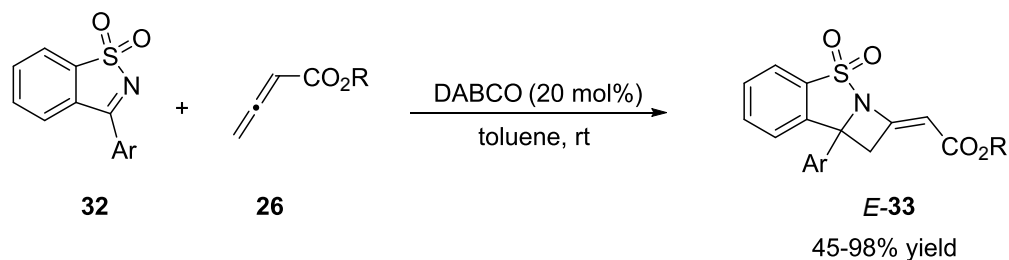


Chiral



Scheme 1. - Formal [2+2] cycloaddition of aldimines with allenolates.

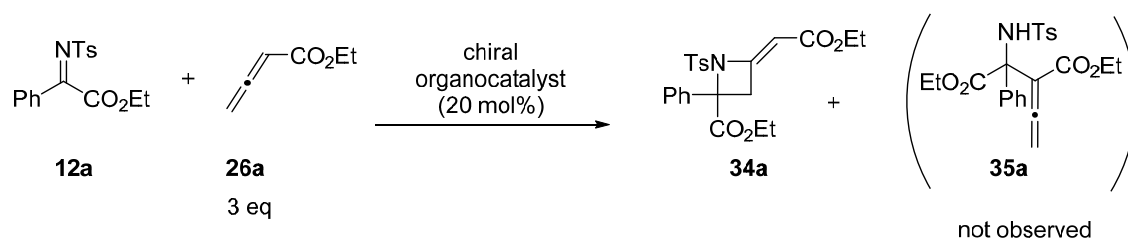
to azetidines is through [2+2] cycloaddition reaction.^[3] In an attempt to extend the scope of aza-Morita-Baylis-Hillman reaction to a different α,β -unsaturated enones, Shi and co-workers



Scheme 2.- Achiral formal [2+2] cycloaddition of ketimines with allenates.

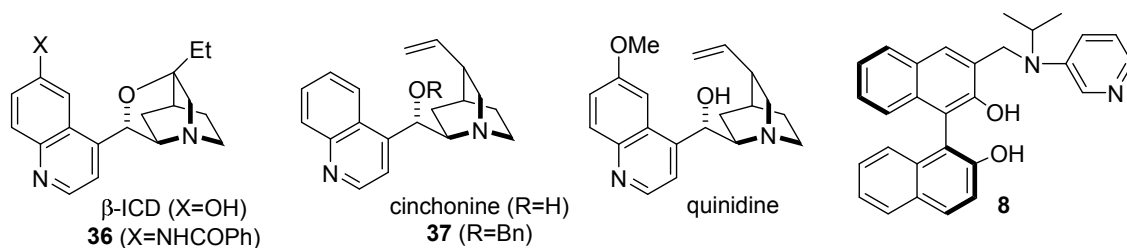
identified generation of azetidines in the reaction with aldimines and 2,3-butadienote by using DABCO as catalyst *via* formal [2+2] cycloaddition process (Scheme 1a).^[4] The corresponding asymmetric protocol was later developed by Masson and Zhu by using an

Table 1.- Catalyst screening for formal [2+2] cycloaddition of ketimines with allenates.

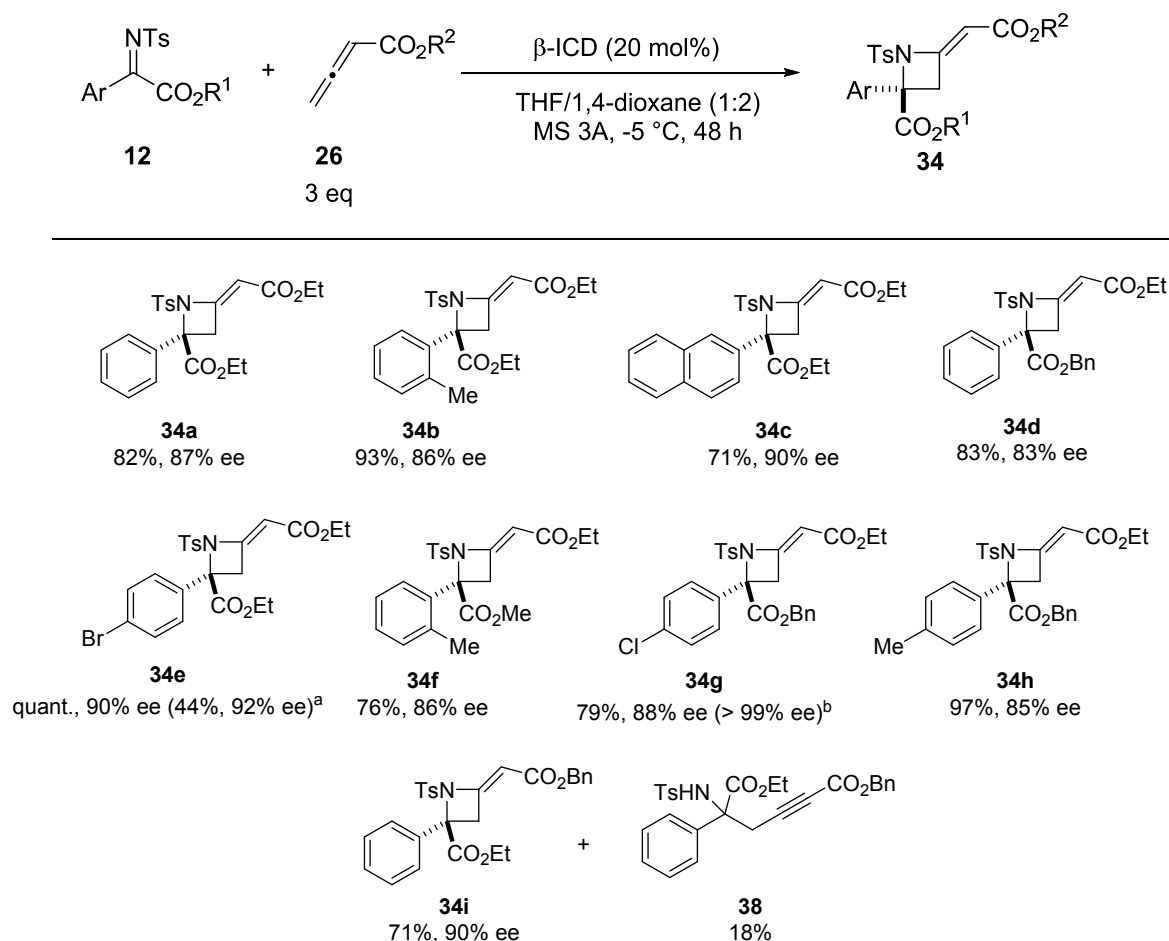


Entry	Organocatalyst	Solvent	T (°C)	t (h)	Yield % ^[a]	ee %
1	DABCO	THF	25	96	43	--
2	DMAP	THF	25	96	20	--
3	DBU	THF	25	96	0	--
4	β -ICD	THF	25	24	42	80
5	β -ICD	1,4-dioxane	25	24	58	82
6	β -ICD	DCM	25	24	36	66
7	β -ICD	toluene	25	24	28	80
8	β -ICD	THF	0	24	45	84
9	β -ICD	THF/1,4-dioxane (1:1)	0	24	49 (69) ^b	89(87) ^b
10	β -ICD	THF/1,4-dioxane (1:2)	-5	48	82 ^b	87 ^b
11	36	THF/1,4-dioxane (1:1)	0	24	10(trace) ^c	65(nd) ^c
12	37	THF/1,4-dioxane (1:1)	0	24	23	59
13	cinchonine, quinidine or 8	THF/1,4-dioxane (1:1)	0	24	0	--

[a] Determined by ¹H-NMR. [b] MS 4Å was added. [c] 20 mol% of 2-naphthol was added. nd: Not determined.



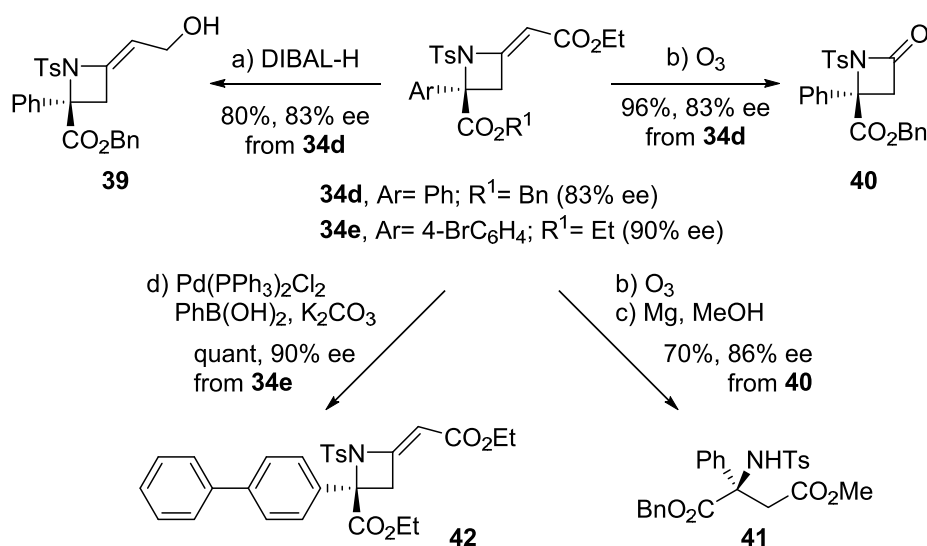
alkaloid-type tertiary amine organocatalyst (Scheme 1b).^[5] It is important to notice that in the case of Masson and Zhu report, they observed the competitive formation of aza-MBH-adduct **30** as minor byproduct, affecting the yield of the desired azetidine. In 2012, the group of Ye has reported the achiral synthesis of azetidines bearing a tetrasubstituted carbon center *via* formal [2+2] cycloaddition of cyclic ketimines (Scheme 2).^[6] Interestingly, although they tried to develop the enantioselective process, they were not able to observe any formation of



[a] At -20 °C. [b] After a single recrystallization.

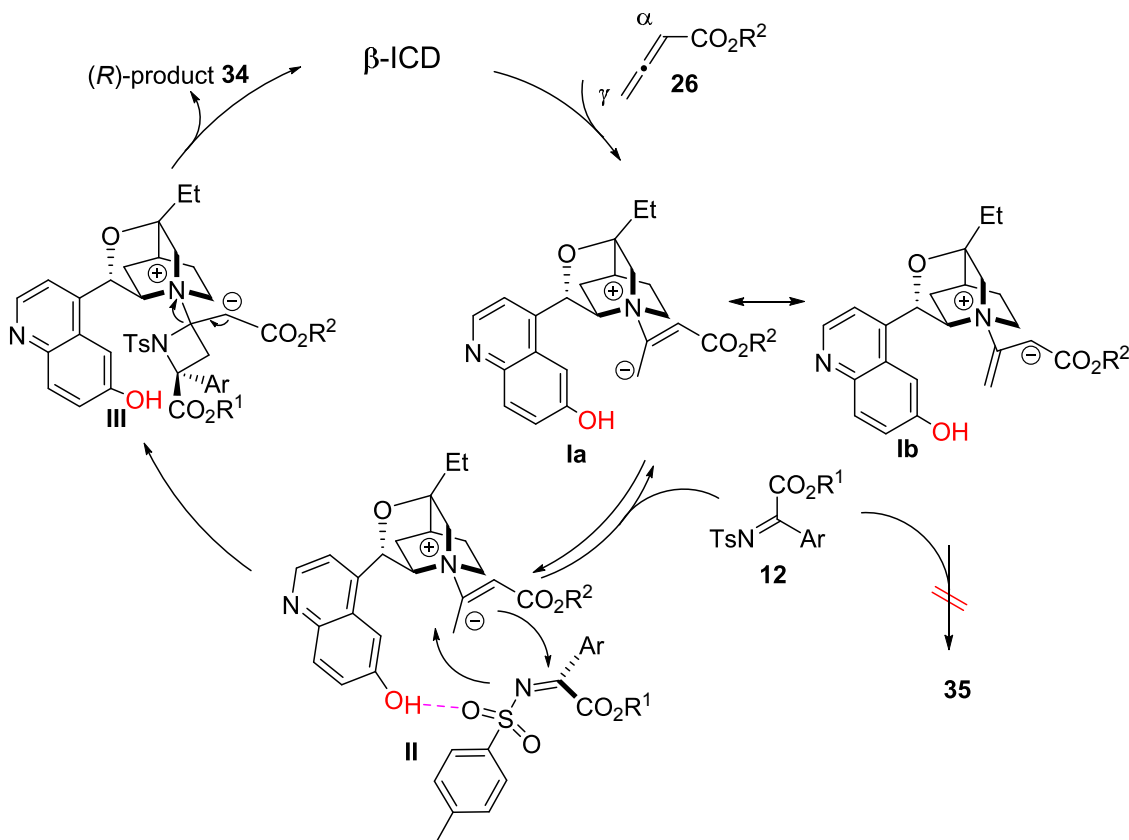
Scheme 3.- Substrate scope catalyzed of formal [2+2] cycloaddition catalyzed by β -ICD.

azetidine when using chiral organocatalysts. Interested in establish an enantioselective method, reaction using acyclic ketimine **12a** was explored. Among the achiral organocatalyst tested, DABCO was superior delivering azetidine in 43% yield (entries 1-3). Next, various chiral amine catalyst were applied. β -Isocupreidine (β -ICD), acid-base organocatalyst known to mediate MBH-processes,^[7] afforded **34a** in moderate yield with 80% ee (entry 4). Using 1,4-dioxane or lowering the reaction temperature (entries 5, 8) had a positive effects on the chemical yield and enantioselectivities. Furthermore, the mixed solvent of THF/1,4-dioxane (1:1 ratio) achieved good outcomes in terms of enantioselectivity (entry 9). Applying amide-type analogous β -ICD **36** (in presence or absence of naphthol),^[8] cinchonine, organocatalyst **37**, quinine or organocatalyst **8**,^[9] exhibited low or no activity (entries 11-13). Notably, neither formation of aza-MBH adduct **35a** nor the *Z*-configuration of azetidine **34a** was observed in any reaction; however, α -ketoester was formed due to partial hydrolysis of ketimine. To suppress the decomposition, molecular sieves (MS 4A) were added to reaction. The addition of MS 4A improved the chemical yield maintaining high enantioselectivity (entry 9). Further optimization allowed the optimal condition with a mixed solvent THF/1,4-dioxane (1:2) at -5 °C in the presence of MS 3A (Scheme 3, **34a**). Under the optimal conditions, highly *E*-selective and (*R*)-configured azetidines **34** were obtained in good to excellent yields with high enantioselectivities (83-92% ee) irrespective of the electronic nature of substituent groups on the aromatic ring. Single recrystallization of azetidine **34g** afforded optically pure azetidine (> 99% ee). Using benzyl-ester allenolate (CO₂Bn) delivers azetidine in 71% chemical yield and 90% ee, however, it came accompanied by formation of byproduct **38** in 18% yield. Absolute configuration was indirectly deduced by comparison with a literature reported compound (see supplementary section).

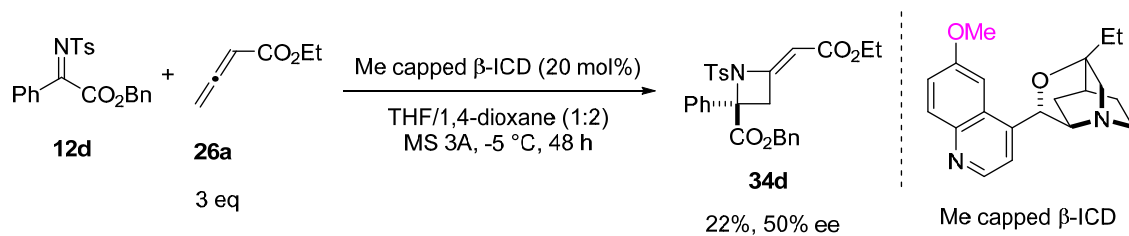


Scheme 4.- Synthetic transformations of azetidine (*R*)-**34**.

To demonstrate the synthetic utility of highly functionalized azetidines **34**, various transformations were performed (Scheme 4). Allyl alcohol **39** was obtained by DIBAL-H reduction of **34d**. β -Lactam **40** was synthesized in 96% yield by oxidation with O_3 . Subsequently, treatment of lactam **40** with Mg/MeOH cleaved the amide bond to provide acyclic α,α -disubstituted amino acid derivative **41** in good yield. Finally, **34e** could react with phenylboronic acid *via* Suzuki-Miyaura cross-coupling to quantitatively give biphenyl compound **42**.



Scheme 5.- Our proposed reaction mechanism.



Scheme 6.- Formal [2+2] cycloaddition of **12d** with **26a** using methyl capped β -ICD.

The proposed mechanism of [2+2] cycloaddition is shown in scheme 5. Addition of β -ICD to allenolate **26** affords the resonance-stabilized zwitterionic intermediate **I**, which could react with ketimine **12** according to two different pathways. Addition of the γ -carbanion to **12** would yield intermediate **II**, which upon 4-*exo*-trig cyclization would give intermediate **III**. To avoid steric interactions between the aryl substituent of ketimine and the quinoline backbone in the catalyst, the reaction using β -ICD would favor product with (*R*)-configuration. Finally, azetidine **34** is formed upon fragmentation of **III**, with concurrent regeneration of catalyst. In contrast, formation of aza-MBH compound **35** through the addition of the α -carbanion **Ib** to ketimine is not supported probably because of the steric hindrance in the ketimine. To gain insights into the enantioselective induction step, an additional experiment with modified catalyst was performed (Scheme 6). By using a methyl capped β -ICD organocatalyst resulted in low activity and low enantioselectivity, implying the important role of hydroxyl unit in the catalyst. Based on this result, we hypothesized that the oxygen on the sulfonyl group in the ketimine would be activated by OH group in β -ICD through hydrogen bond. Although, coordination with the oxygen in the carbonyl group on the ketimine cannot be ruled out. Further calculations studies using computational chemistry are necessary to better understand the transition state involved in the present mechanism.

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Chapter 4

Formal [4+2] cycloaddition reaction of ketimines

Functionalized tetrahydropyridines represent an important motif largely found in many pharmaceuticals and natural products (Figure 1).^[1] Among the different approaches

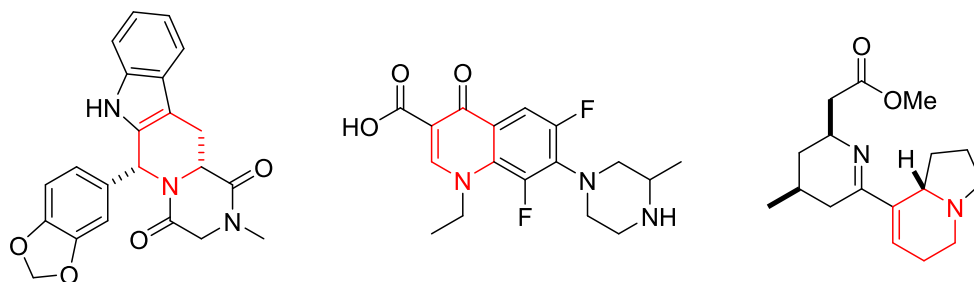
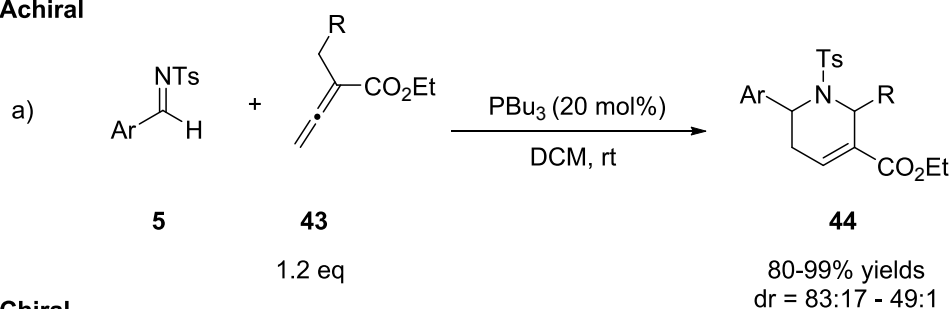


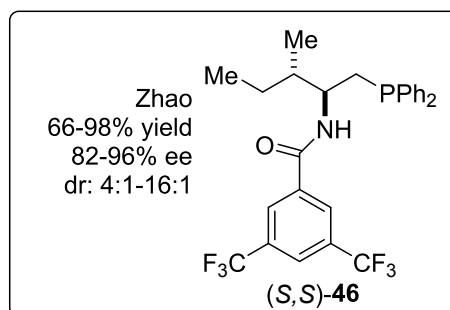
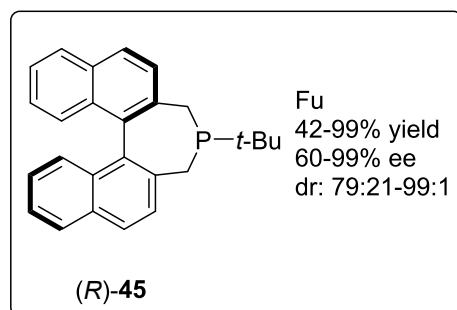
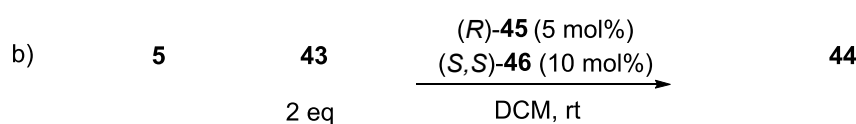
Figure 1.- Biologically active tetrahydropyridine-containing compounds.

reported in literature, [4+2] cycloaddition reaction constitutes the more straightforward method for their construction.^[2] Since the pioneering report in 2003 by Prof. Kwon and her

Achiral

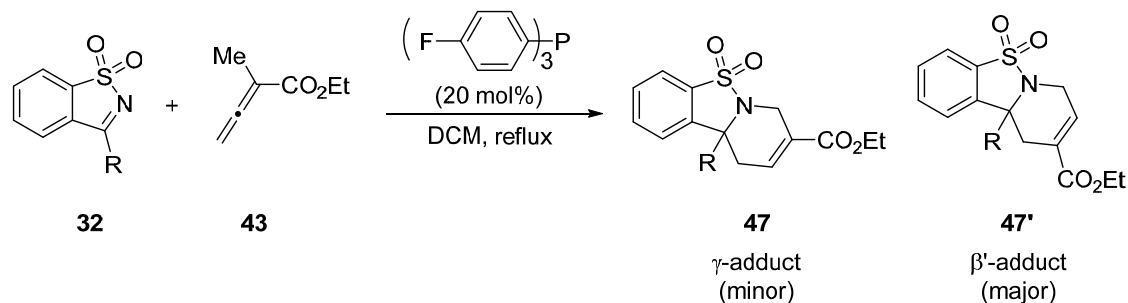


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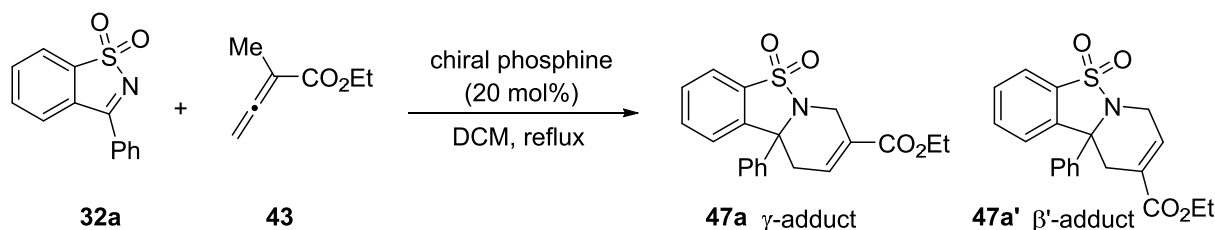
Scheme 1.- Formal [4+2] cycloaddition of aldimines with allenoates.

co-workers on the preparation of tetrahydropyridine from aldimines and allenates promoted by PBu_3 , Lewis base (LB) organocatalysis was recognized as an important route to synthesize this family of heterocycles (Scheme 1a).^[3] The corresponding asymmetric transformation was later developed by using a binaphthyl-based C_2 -symmetric mono-phosphine and an amino



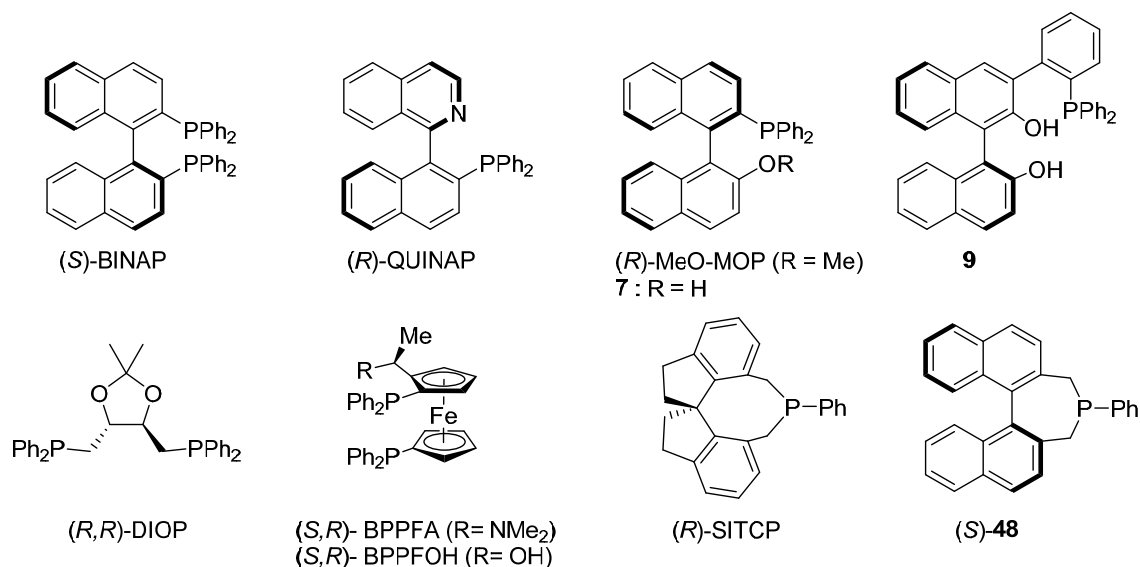
acid-based bifunctional phosphine by Fu and by Zhao's groups, respectively (Scheme 1b).^[4] However, despite of the importance of tetrahydropyridines bearing a tetrasubstituted stereogenic carbon center in areas such as medicinal chemistry,^[1] the asymmetric preparation of these systems remained elusive for long time. In 2012, Ye's group described the synthesis

Table 1.- Catalyst screening for formal [4+2] cycloaddition of ketimines with allenates.

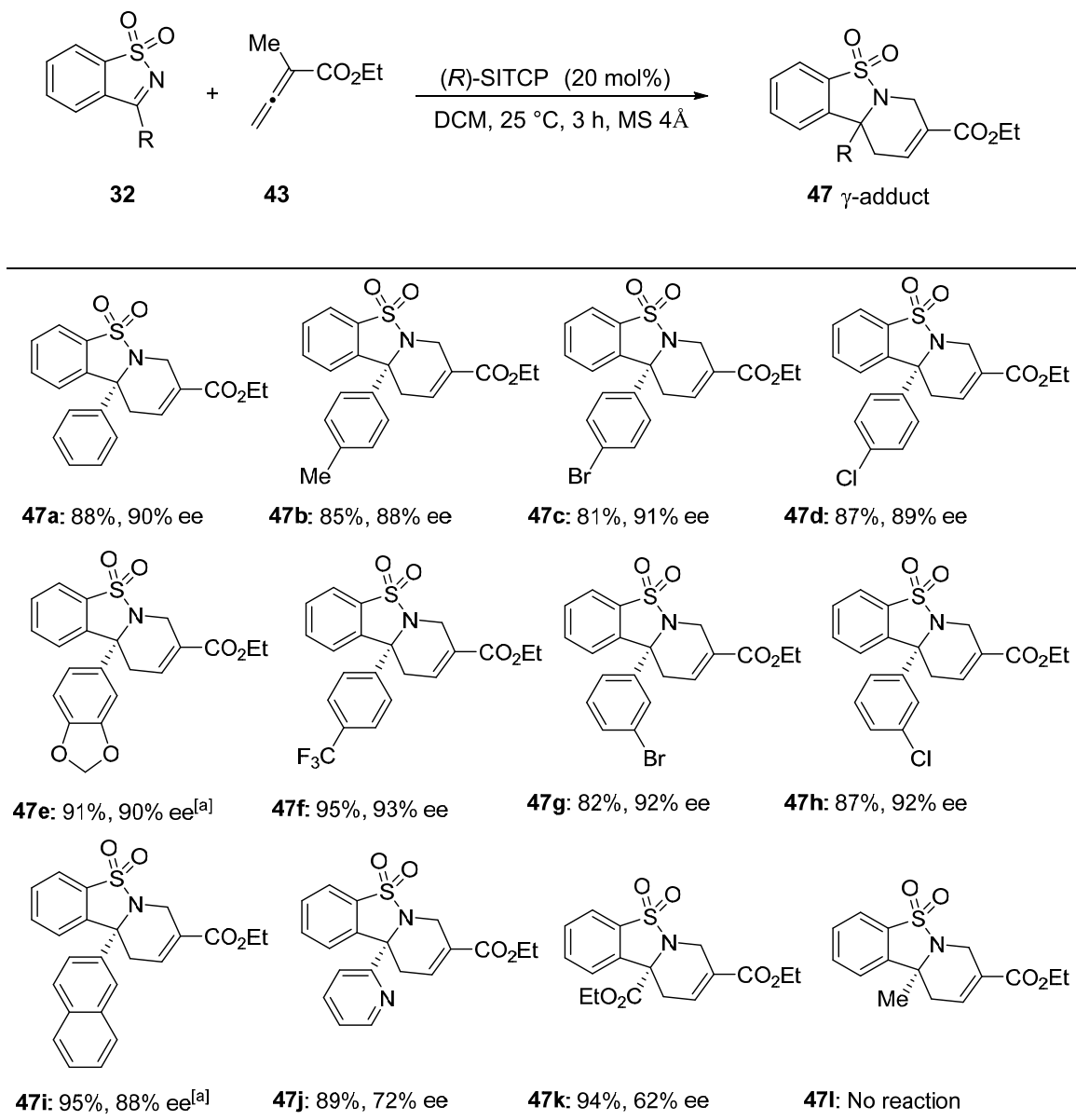


Entry	Chiral phosphine	t (h)	T (°C)	Ratio 47:47' ^[a]	Total yield ^[b]	ee of 47 (%)	ee of 47' (%)
1	(<i>S</i>)-BINAP	24	reflux	--	no reaction	--	--
2	(<i>R</i>)-QUINAP	24	reflux	--	no reaction	--	--
3	(<i>R</i>)-MeO-MOP, (<i>R</i>)-7, (<i>S</i>)-9	24	reflux	--	no reaction	--	--
4	(<i>R,R</i>)-DIOP	24	reflux	1.3:1	35	55	11
5	(<i>S,R</i>)-BPPFA	24	reflux	1:2.1	34	70	6
6	(<i>S,R</i>)-BPPFOH	24	reflux	1:2.8	23	84	9
7	(<i>R</i>)-SITCP	3	25	5:1	83	86	8
8 ^[c]	(<i>R</i>)-SITCP	3	25	> 20:1	88	90	--
9 ^[c]	(<i>S</i>)-48	3	25	> 20:1	81	80	--

[a] Determined by ¹H-NMR. [b] ¹H-NMR (1,3,5-trimethoxybenzene as internal standard). [c] MS 4Å was added.



of tetrahydropyridines bearing a tetrasubstituted carbon center by using a saccharin-derived cyclic ketimines and catalyzed by an electron-deficient triaryl phosphine (Scheme 2).^[5] They were able to obtain in moderate to excellent selectivity the thermodynamically favored β' -adduct in good yields (55-75%). Towards the development of an enantioselective process, formal [4+2] cycloaddition of ketimines was initially explored with different phosphines (Table 1). Triaryl phosphines (BINAP, QUINAP, (R)-Me-MOP, catalyst (R)-7 and (S)-9) were found to be inactive in the present transformation (entries 1-3). Shifting to a monomethyl or/and ferrocenyl-containing phosphines, a stimulating enantioselectivity value was observed (55-84% ee), although in low yield and low regioselectivity (entries 4-6). Interestingly, spiro-type organocatalyst (R)-SITCP^[6-8] was found to promote with high enantioselectivity and modest regioselectivity the formal [4+2] cycloaddition reaction (entry 7). Further optimization revealed the use of MS 4 Å to have a markedly effect as additive to deliver exclusively the formation of the γ -adduct in 88% yield and 90% ee (entry 8). Evaluation of the corresponding binaphthyl-type monophosphine provided the desired compound in similar regioselectivity but slightly lower yield and enantioselectivity (entry 9). Decreasing the catalyst loading affected both regioselectivity and enantioselectivity (supplementary section). The substrate scope was then evaluated under the obtained optimized reaction conditions (Scheme 3). High regioselectivity and high enantioselectivity was observed independently of the electronic nature of the substituted groups on the aromatic ring (entries **47a-h**). Bulky 2-naphthyl group was also tolerated (**47i**). 2-pyridin ring and an ester group were also successfully introduced, although with lower enantioselectivity (entries **47j** and **47k**). The reaction of alkyl-substituted ketimine **32i** did not afford any cycloadduct; however it resulted in the recovery of the starting material even at increased reaction temperatures and prolonged reaction times. The absolute configuration was determined by



[a] Stirred for 8 hours.

Scheme 3.- Substrate scope catalyzed by (*R*)-SITCP.

single X-ray crystallographic analysis of tetrahydropyridine **47c** (Figure 2).^[9] Absolute configuration of **47a-b** and **47d-k** was tentatively assigned by comparison of their optical rotation.

Based on the observed results and related literature reports,^[3,4,5b] the reaction mechanism is believed to proceed as illustrated in Scheme 4. The addition of phosphine organocatalyst to α -methyl acrylate **43** triggers the generation of reactive zwitterionic species **I**. Electronrich and nucleophilic monoaryl-phosphine leads to formation of kinetically

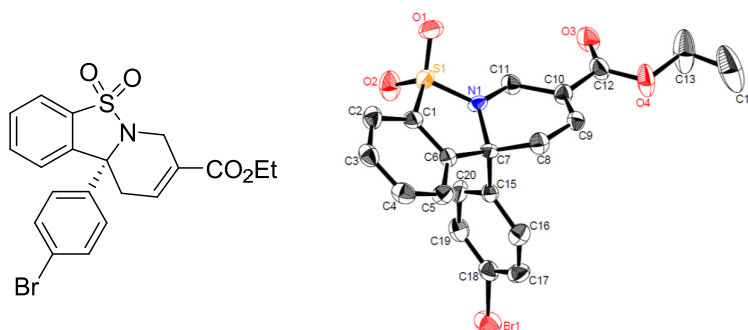
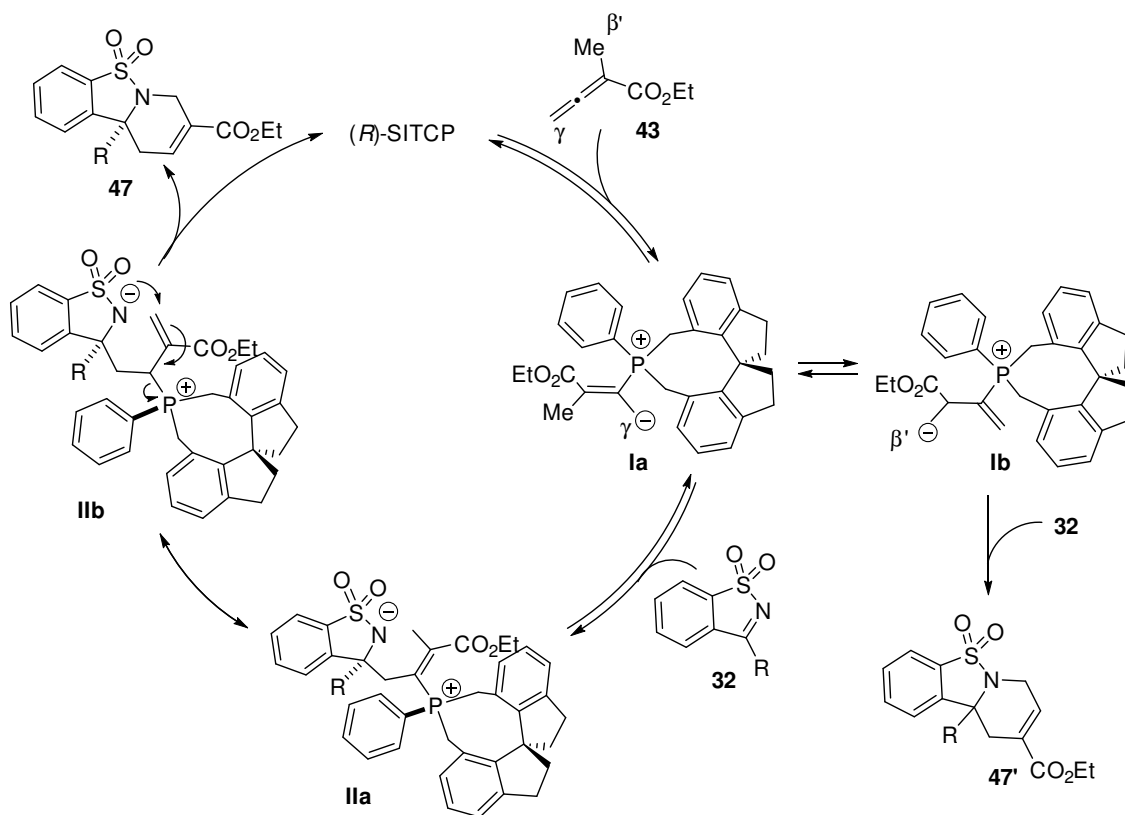


Figure 2.- Drawing ORTEP of tetrahydropyridine **47c**.

favored γ -addition to ketimine **32** through intermediate **Ia**. Once intermediate **II** is generated, intramolecular cyclization affords the tetrahydropyridine **47** with concomitant regeneration of the catalyst. To avoid steric interactions between the R substituent in the ketimines and phenyl substituent on the catalyst, the present system using (*R*)-SITCP favor the formation of (*R*)-tetrahydropyridine **47a-i** or (*S*)-**47j-k**. Proton source from H₂O or 2-naphthol^[10] could assist the generation of **Ib**, and consequently the formation of β' -tetrahydropyridine **47'**.



Scheme 4.- Proposed reaction mechanism.

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- [7] (*R*) or (*S*)-SITCP is commercially available from Sigma-Aldrich and Strem.
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- [9] CCDC No. 964567 ((*R*)-**47c**) contains the supplementary crystallographic data. This data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
- [10] An addition of Brønsted acid such as 2-naphthol (20 mol%) led to drastically dropping of reaction rate and stereoselectivities; after 24 h, 50% total yield of products **47a** and **47a'** (**47a**:**47a'** = 1:1.2) were obtained in 19% ee for **47a** and 11% ee for **47a'**, respectively.

Chapter 5

Synthesis of cyclobutane by formal [2+2] cycloaddition reaction of tetrasubstituted alkenes

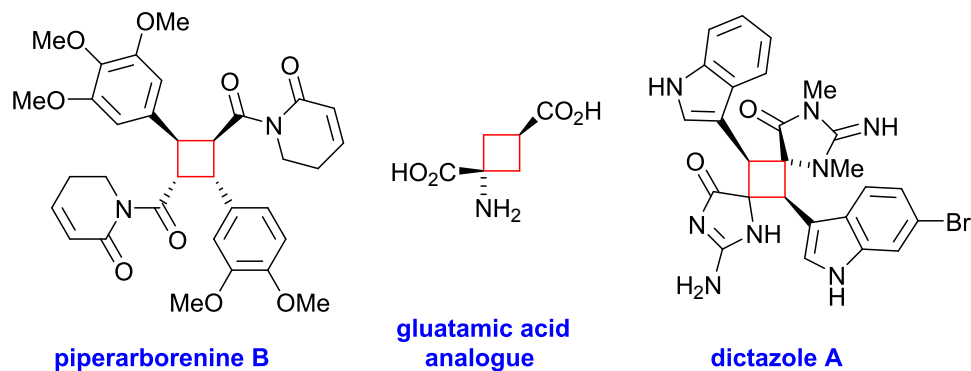
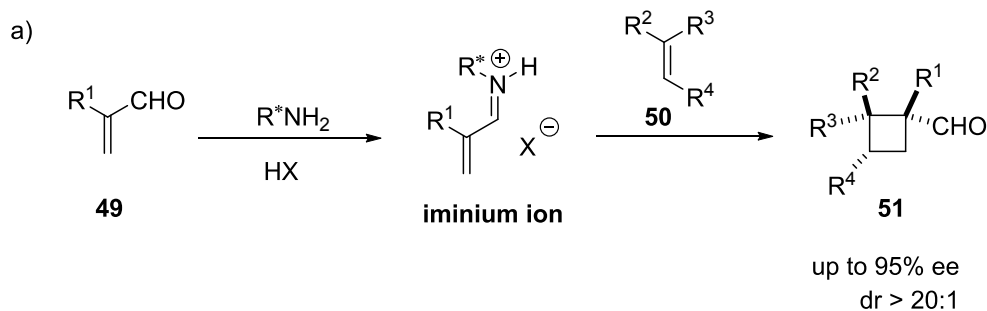


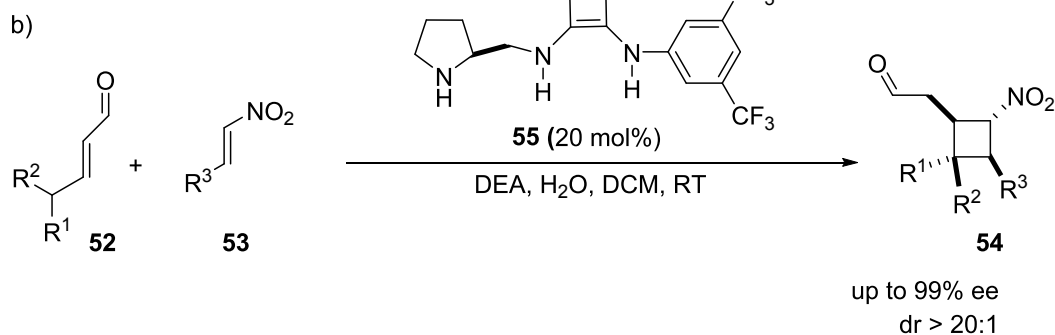
Figure 1.- Cyclobutane-containing biologically active compounds.

Four-membered rings are important structural motifs frequently present in bioactive natural products and pharmaceutical agents.^[1] This interesting constraint ring has also been recently studied in the field of catalysis. Murakami^[2] and Cramer^[3] have presented a variety

Iminium



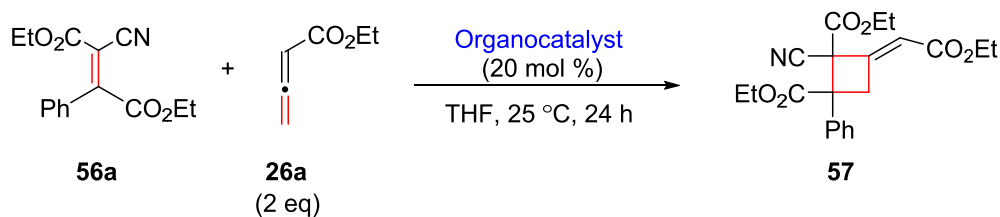
Dienamine



Scheme 1.- Organocatalytic formal [2+2] cycloaddition reaction.

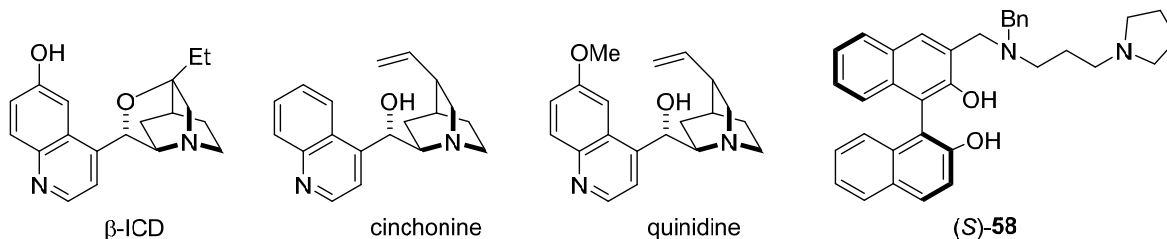
of synthetic applications by making use of the high reactivity on the C-C bond. However, most of the existing methods only give access to racemic cyclobutanes, and only a few reports of asymmetric metal-catalyzed reactions have been documented.^[4] Organocatalysis, particularly aminocatalysis, has shown their potential by a couple of reports on the asymmetric synthesis. Ishihara and co-workers reported an enantioselective [2+2] cycloaddition of unactivated alkenes **50** and α -acyloxyacroleins **49** under iminium catalysis (Scheme 1a).^[5] Blackmond,^[6a,b] and Seebach, Hayashi and their co-workers,^[6c] contributed on the study of Michael addition of aldehydes and nitroalkenes for the identification by NMR of the formation of an unexpected cyclobutane intermediate derived from a formal [2+2] cycloaddition. Inspired by these precedents reports, Jørgensen and co-workers^[7] designed a novel bifunctional catalyst **55** for the remote activation of α,β -unsaturated aldehydes **52** and nitroalkenes **53** under the concept of dienamine activation (Scheme 1b).

Table 1.- Catalyst screening for formal [2+2] cycloaddition reaction of **56a** with **26a**.

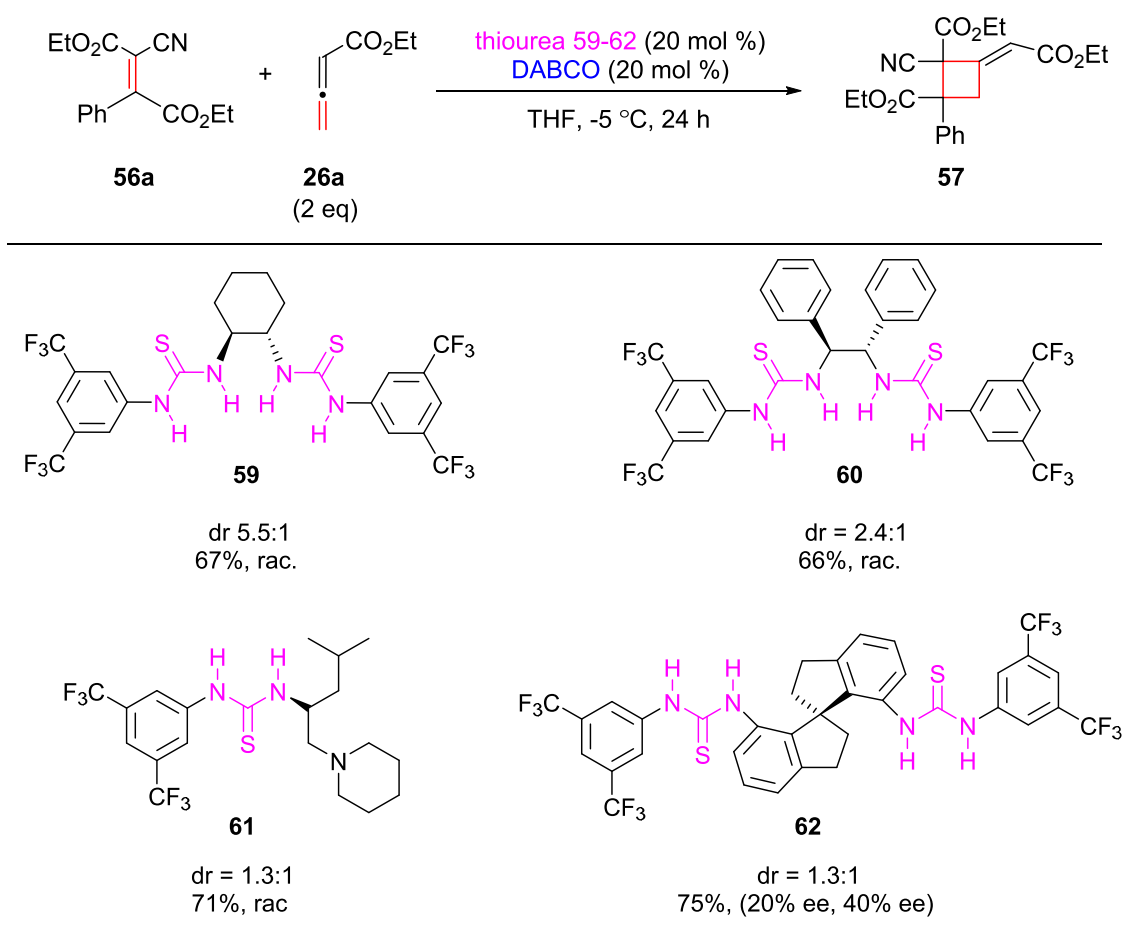


Entry	Organocatalyst	Yield %	dr % ^[a]	ee %
1	DMAP	0	--	--
2	DABCO	65	> 20:1	--
3	DBU	0	--	--
4	TMG	0	--	--
5^[b]	β -ICD	0	--	--
6^[b]	cinchonine	0	--	--
7^[b]	quinidine	0	--	--
8^[b]	(<i>S</i>)- 58	0	--	--

[a] Determined by ¹H-NMR. [b] Stirred for 24 h under reflux. TMG = 1,1,3,3-tetramethylguanidine.



With the aim of expanding the allenolate chemistry by using organocatalysis,^[8] enantioselective synthesis of cyclobutane was studied. Formal [2+2] cycloaddition was explored with an electron-deficient tetrasubstituted alkene **56a** in presence of different organocatalysts (Table 1). The initial exploration of achiral Lewis base shown DMAP, DBU, and TMG to be inactive on the cycloaddition (entries 1,3,4). Satisfyingly, the reaction in presence of DABCO afforded formation of the 4-member ring system in moderate yield and high diastereoselectivity (entry 2). Next, chiral organocatalysts were evaluated. Surprisingly, reaction in presence of alkaloid-type, including β -ICD, or BINOL-based organocatalysts, did not promote formal [2+2] cycloaddition even under reflux reaction conditions (entries 5-8), probably due to a steric hindrance.



Scheme 2.- Thiourea co-catalyst asymmetric cyclobutane synthesis.

Asymmetric induction by using achiral Lewis base and co-catalyst chiral thiourea has been reported by different groups.^[9] Formal [2+2] cycloaddition was thus explored in a co-catalytic system of DABCO and chiral thioureas (Scheme 2). Bis-thiourea and thiourea

59-61 delivers formation of cyclobutane in similar moderate yields, however enantioselective induction was not observed, affording compound **57** in racemic form. Developed by our group, a more rigid SPIRO-derived bistiourea **62** showed moderated enantioselective induction on cyclobutane synthesis, up to 40% ee.

With the promising results observed by using co-catalyzed DABCO and spiro-based bistiourea **62**, we are currently trying to improve the above results. It is believed that a modification on the spiro compound, perhaps introducing a bulky substituent, may increase the enantioselectivity on the cyclobutane compound.

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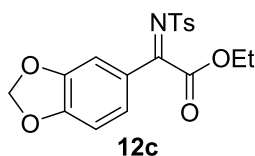
Supplementary section

Chapter 2.

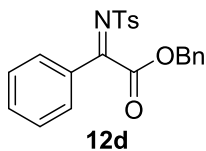
Preparation of ketimines **12**

A solution of the corresponding keto ester (1.25 eq), *p*-toluenesulfonamide (1.0 eq.), and triethylamine (1.0 eq) in CH₂Cl₂ was cooled to 0 °C. To this mixture was added a solution of TiCl₄ (1.0 eq.) in CH₂Cl₂ under N₂. The mixture was stirred at 0 °C for 30 min. and then warmed to ambient temperature and stirred for 1 h. The mixture was then quenched with sat. NaHCO₃ and extracted three times with DCM. The combined organic phases were washed with brine, dried over Na₂SO₄, and concentrated. The resulting residue was purified by SiO₂ column chromatography (15% EtOAc/hexane) or GPC (CHCl₃ only) to afford **12**.

REPRESENTATIVE DATA



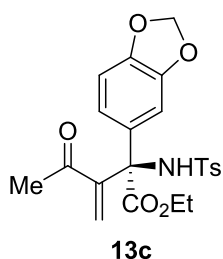
12c: yellow oil (58%); ¹H-NMR (CDCl₃) δ 7.91 (d, 2H, *J* = 8.2 Hz), 7.39 (d, 1H, *J* = 1.4 Hz), 7.35-7.32 (m, 3H), 6.83 (d, 1H, *J* = 8.2 Hz), 6.06 (s, 2H), 4.55 (q, 2H, *J* = 7.3 Hz), 2.43 (s, 3H), 1.47 (t, 3H, *J* = 7.3 Hz); ¹³C-NMR (CDCl₃) δ 166.2, 164.9, 153.7, 148.6, 144.5, 136.0, 129.7, 127.8, 127.9, 125.8, 108.5, 102.4, 63.2, 21.7, 14.0; HRMS (ESI) calcd for C₁₈H₁₇NO₆SNa 398.0674 [(M+Na)⁺], found *m/z* = 398.0670; IR (KBr): ν 3086, 2987, 1743, 1600, 1318, 1248, 1155 cm⁻¹.



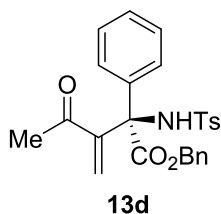
12d: yellow solid (65%); ¹H-NMR (CDCl₃) δ 7.90 (d, 2H, *J* = 8.2 Hz), 7.77 (d, 2H, *J* = 7.3 Hz), 7.57 (t, 1H, *J* = 7.3 Hz), 7.52 (d, 1H, *J* = 2.3 Hz), 7.50 (d, 1H, *J* = 1.4 Hz), 7.44-7.37 (m, 5H), 7.31 (d, 2H, *J* = 8.2 Hz), 5.52 (s, 2H), 2.43 (s, 3H); ¹³C-NMR (CDCl₃) δ 166.8, 164.7, 144.8, 135.5, 134.8, 134.2, 131.3, 129.9, 129.7, 129.1, 129.0, 128.9, 128.7, 128.2, 68.9, 21.7; HRMS (ESI) calcd for C₂₂H₁₉NO₄SNa, *m/z* = 416.0932 [(M+Na)⁺], found *m/z* = 416.0927; IR (KBr): ν 3061, 2952, 1741, 1594, 1332, 1158 cm⁻¹.

General procedure for enantioselective aza-MBH reaction of **11** and **12**.

To a solution of organocatalyst (*S_p*)-**15** (10-20 mol%), *N*-tosylketimine **12** (0.040 mmol) in MTBE (0.2 mL) was added enone (0.12 mmol, 3.0 eq.). The reaction mixture was stirred at 5-10°C, and was stirred until the reaction reached completion determined by TLC analysis. After purification via column chromatography, product **13** was obtained.



13c: pale yellow oil (86%); ¹H-NMR (CDCl₃) δ 7.50 (d, 2H, *J* = 8.2 Hz), 7.28 (dd, 1H, *J* = 2.3, 1.8 Hz), 7.20 (d, 2H, *J* = 7.8 Hz), 7.15 (d, 1H, *J* = 1.8 Hz), 6.79 (d, 1H, *J* = 8.2 Hz), 6.45 (s, 1H), 6.41 (s, 1H), 6.33 (s, 1H), 5.97 (d, 1H, *J* = 1.8 Hz), 5.96 (d, 1H, *J* = 1.4 Hz), 4.07 (qd, 1H, *J* = 12.4, 7.3 Hz), 4.04 (qd, 1H, *J* = 12.4, 7.3 Hz), 2.39 (s, 3H), 1.74 (s, 3H), 1.10 (t, 3H, *J* = 7.3 Hz); ¹³C-NMR (CDCl₃) δ 196.8, 170.4, 147.6, 147.2, 144.2, 142.9, 138.5, 135.6, 130.5, 129.0, 127.8, 122.9, 109.4, 107.4, 101.4, 67.3, 62.6, 24.6, 21.4, 13.7; HRMS (ESI) calcd for C₂₂H₂₃NO₇SNa, *m/z* = 468.1092 [(M+Na)⁺], found *m/z* = 468.1080; enantiomeric excess: 41%, determined by HPLC (Chiralcel OD-H, hexane/2-propanol = 10/1, flow rate 1.0 ml/min, 25°C, 230 nm) minor peak: *t_R* = 32.2 min, major peak: *t_R* = 22.4 min; [α]_D²¹ = +47.6 (*c* 0.21, CHCl₃); IR (KBr): ν 3328, 1733, 1680, 1503, 1393, 1228, 1161 cm⁻¹.



13d: pale yellow oil (98%); ¹H-NMR (CDCl₃) δ 7.73-7.71 (m, 2H), 7.50 (d, 2H, *J* = 8.4 Hz), 7.35-7.33 (m, 3H), 7.27-7.26 (m, 3H), 7.20 (d, 2H, *J* = 8.8 Hz), 7.07-7.05 (m, 2H), 6.53 (s, 1H), 6.39 (s, 1H), 6.28 (s, 1H), 5.00 (d, 1H, *J* = 12.4 Hz), 4.96 (d, 1H, *J* = 11.9 Hz), 2.39 (s, 3H), 1.70 (s, 3H); ¹³C-NMR (CDCl₃) δ 197.0, 170.4, 144.1, 142.9, 138.6, 136.6, 135.7, 134.6, 129.1, 128.9, 128.4, 128.3, 128.2, 127.8, 127.8, 68.3, 67.6, 24.5, 21.4; HRMS (APCI) calcd for C₂₆H₂₅NO₅SH, *m/z* = 464.1531 [(M+H)⁺], found *m/z* = 464.1529; enantiomeric excess: 41%, determined by HPLC (Chiralpak AS-H, hexane/2-propanol = 65/35, flow rate 0.5 ml/min, 25°C, 219 nm) minor peak: *t_R* = 28.9 min, major peak: *t_R* = 19.0 min; [α]_D²¹ = +3.1 (*c* 3.2, CHCl₃); IR (KBr): ν 3289, 1737, 1681, 1448, 1330, 1225, 1164 cm⁻¹.

Chapter 3.

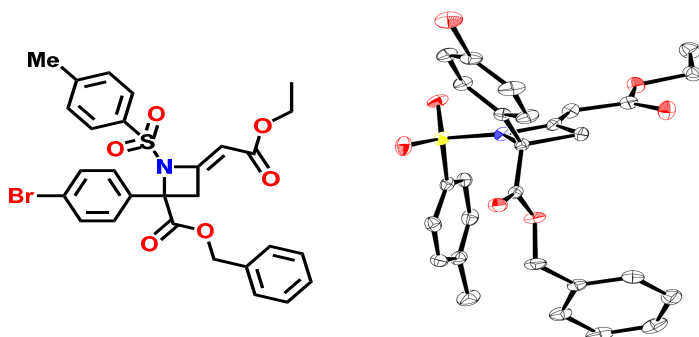


Figure S3. ORTEP drawing of racemic **34e**.

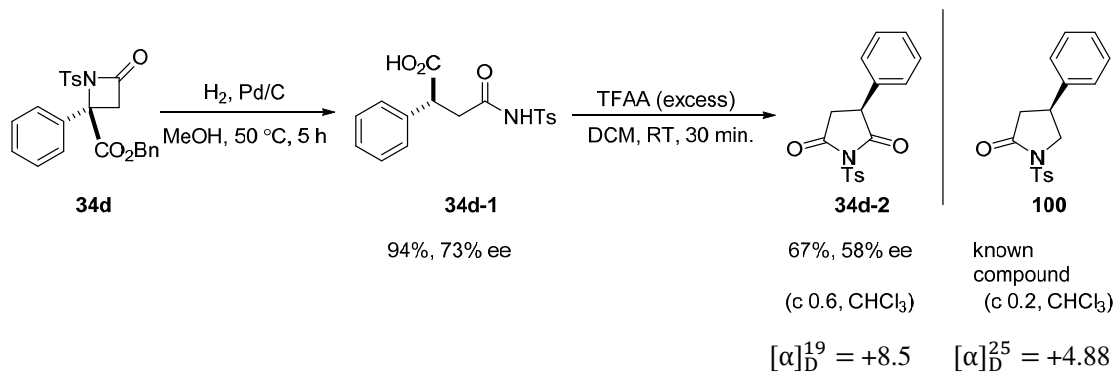


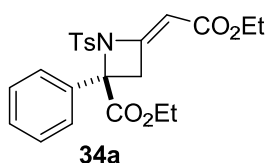
Table S3. Indirect determination of absolute configuration on azetidine **34**.

Compound **100** is a reported compound:

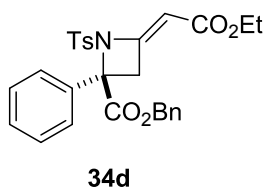
M. K. Ghorai and D. P. Tiwari, *J. Org. Chem.* **2010**, *75*, 6173.

General procedure for enantioselective formal [2+2] cycloaddition of ketimines with allenates

To a solution of β -ICD (20 mol%), *N*-tosylketimine **12** (0.060 mmol) and powdered molecular sieves 3A (20 mg) in 0.3 mL of THF/1,4-dioxane mixture (1:2) at -5 °C, allenate **26** (0.12 mmol, 3.0 equiv) was added under nitrogen atmosphere. The reaction mixture was stirred at -5 °C until the reaction reached completion determined by TLC analysis. The crude product was filtered with EtOAc in a short column of silica and purified via column chromatography (hexane/EtOAc) to obtain the corresponding compound **34**.



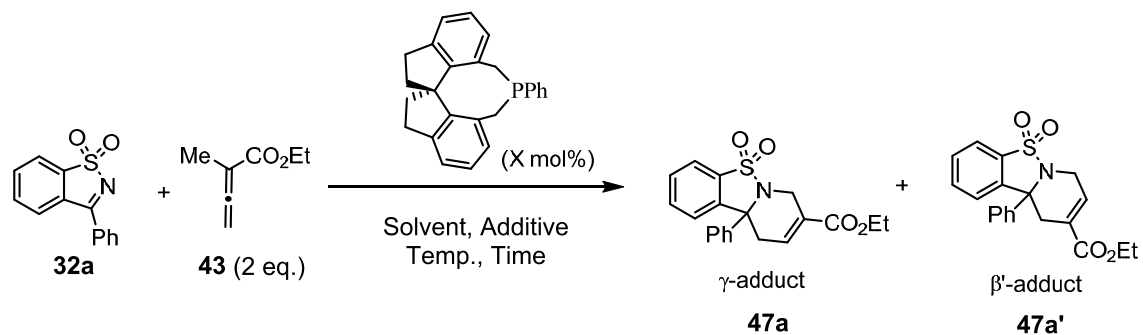
34a: pale yellow oil (82%); $^1\text{H-NMR}$ (CDCl_3) δ 7.45-7.32 (m, 7H), 7.17 (d, 2H, $J = 8.2$ Hz), 5.69 (t, 1H, $J = 1.8$ Hz), 4.34 (qd, 1H, $J = 11.0, 7.3$ Hz), 4.29 (qd, 1H, $J = 11.0, 7.3$ Hz), 4.14 (q, 2H, $J = 7.3$ Hz), 3.68 (d, 2H, $J = 1.8$ Hz), 2.39 (s, 3H), 1.31 (t, 3H, $J = 7.3$ Hz), 1.27 (t, 3H, $J = 7.3$ Hz); $^{13}\text{C-NMR}$ (CDCl_3) δ 169.4, 167.2, 156.2, 144.5, 135.9, 134.7, 129.4, 129.2, 128.6, 127.5, 127.2, 93.4, 77.6, 62.6, 59.8, 41.6, 21.6, 14.4, 14.0; HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{25}\text{NO}_6\text{SNa}$, $m/z = 466.1295$ [$\text{M}+\text{Na}$] $^+$, found $m/z = 466.1297$; IR (KBr): ν 2925, 1739, 1708, 1656, 1366, 1167, 1088 cm^{-1} ; enantiomeric excess: 87%, determined by HPLC (Chiralpak AD, hexane/2-propanol = 4/1, flow rate 1.0 mL/min, 25 °C, 260 nm) minor peak: $t_R = 11.5$ min, major peak: $t_R = 25.9$ min; $[\alpha]_D^{23} = +26.0$ (c 0.6, CHCl_3).



34d: pale yellow oil (83%); $^1\text{H-NMR}$ (CDCl_3) δ 7.41 (d, 2H, $J = 8.2$ Hz), 7.38-7.29 (m, 10H), 7.13 (d, 2H, $J = 8.2$ Hz), 5.69 (t, 1H, $J = 1.8$ Hz), 5.30 (d, 1H, $J = 12.4$ Hz), 5.25 (d, 1H, $J = 12.4$ Hz), 4.13 (q, 2H, $J = 7.3$ Hz), 3.69 (dd, 1H, $J = 16.5, 1.8$ Hz), 3.64 (dd, 1H, $J = 16.5, 1.8$ Hz), 2.38 (s, 3H), 1.26 (t, 3H, $J = 7.3$ Hz); $^{13}\text{C-NMR}$ (CDCl_3) δ 169.3, 167.1, 156.0, 144.5, 135.8, 134.8, 134.6, 129.4, 129.2, 128.61, 128.58, 128.5, 128.3, 127.5, 127.2, 93.6, 77.6, 68.0, 59.8, 41.5, 21.6, 14.4; HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{27}\text{NO}_6\text{SNa}$, $m/z = 528.1451$ [$\text{M}+\text{Na}$] $^+$, found $m/z = 528.1451$; IR (KBr): ν 2926, 1741, 1708, 1657, 1366, 1167, 1090 cm^{-1} ; enantiomeric excess: 83%, determined by HPLC (Chiralpak AD, hexane/2-propanol = 9/1, flow rate 1.0 mL/min, 25 °C, 260 nm) minor peak: $t_R = 26.5$ min, major peak: $t_R = 51.3$ min; $[\alpha]_D^{25} = +19.0$ (c 0.3, CHCl_3).

Chapter 4.

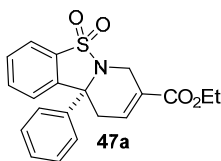
Table S1. Optimization for the enantioselective organocatalyzed formal [4+2] cycloaddition of ketimines.



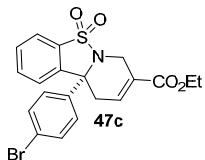
Entry	Solvent	T (°C)	X	Additive	t (h)	Ratio of 47a:47a'	Yield of 47a (%)	ee of 47a (%)
1	toluene	25	20	No	24	2.2:1	47	61
2	THF	25	20	No	24	---	low conversion	---
3	<i>t</i> -BuOMe	25	20	No	24	---	low conversion	---
4	CHCl ₃	25	20	No	24	3.5:1	60	73
5	DCM	25	20	No	3	5:1	69	86
6	DCM	35	20	No	3	10:1	79	87
7	DCM	15	20	No	24	8.3:1	79	89
8	DCM	25	20	MS 4A	3	>20:1	88	90
9	DCM	25	20	2-naphthol (20 mol%)	24	1:1.2	23	19
10	DCM	25	10	MS 4A	3	14.3:1	82	84

General procedure for enantioselective formal [4+2] cycloaddition of **32** with **43**.

To a solution of spiro monophosphine catalyst (*R*)-**SITCP** (20 mol%), cyclic ketimine **32** (0.02g, 0.060 mmol) and powdered molecular sieves 4A (20 mg) in 0.3 mL of anhydrous DCM at 25 °C, allenolate **43** (2.0 equiv) was added under nitrogen atmosphere. The reaction mixture was stirred at 25 °C until the reaction reached completion determined by TLC analysis. The crude product was filtered with EtOAc through a short column of silica gel and purified *via* column chromatography (hexane/EtOAc) to obtain the corresponding compound **47**.



47a: 88% yield; colorless oil; ¹H-NMR (CDCl₃) δ 7.89-7.87 (m, 1H), 7.55-7.52 (m, 2H), 7.40-7.31 (m, 5H), 7.21-7.19 (m, 1H), 7.10-7.07 (m, 1H), 4.56 (m, 1H), 4.17 (qd, 1H, *J* = 10.1, 7.3 Hz), 4.15 (qd, 1H, *J* = 10.1, 7.3 Hz), 3.62-3.53 (m, 1H), 3.46 (ddd, 1H, *J* = 18.3, 6.4, 2.3 Hz), 2.75-2.66 (m, 1H), 1.27 (t, 3H, *J* = 7.3 Hz); ¹³C-NMR (CDCl₃) δ 164.3, 143.4, 137.8, 135.1, 133.2, 132.6, 129.3, 129.1, 128.6, 127.5, 126.9, 123.9, 121.6, 63.4, 61.0, 35.7, 32.9, 14.1; HRMS (ESI) calcd for C₂₀H₁₉NO₄SNa, *m/z* = 392.0927 [(M+Na)⁺], found *m/z* = 392.0928; IR (KBr): ν 2982, 1710, 1658, 1492, 1295, 1256, 1175, 738, 575 cm⁻¹; enantiomeric excess: 90%, determined by HPLC (Chiralpak IA, hexane/2-propanol = 4/1, flow rate 1.0 mL/min, 25 °C, 220 nm) minor peak: *t_R* = 11.4 min, major peak: *t_R* = 14.7 min; [α]_D²³ = -278.7 (*c* 0.7, CHCl₃, 90% ee).



47c: 81% yield; white solid; m.p. 46-48 °C; ¹H-NMR (CDCl₃) δ 7.90-7.88 (m, 1H), 7.58-7.53 (m, 2H), 7.48 (d, 2H, *J* = 8.2 Hz), 7.25 (d, 2H, *J* = 8.2 Hz), 7.20-7.17 (m, 1H), 7.08-7.06 (m, 1H), 4.56 (m, 1H), 4.20 (qd, 1H, *J* = 10.1, 7.3 Hz), 4.16 (qd, 1H, *J* = 10.1, 7.3 Hz), 3.59-3.52 (m, 1H), 3.40 (ddd, 1H, *J* = 18.3, 6.4, 2.3 Hz), 2.74-2.67 (m, 1H), 1.28 (t, 3H, *J* = 7.3 Hz); ¹³C-NMR (CDCl₃) δ 164.2, 142.7, 137.0, 134.7, 133.3, 132.7, 132.3, 129.6, 128.8, 127.7, 123.8, 122.9, 121.7, 63.0, 61.1, 35.7, 32.8, 14.1; HRMS (ESI) calcd for C₂₀H₁₈BrNO₄SNa, *m/z* = 470.0032 [(M+Na)⁺], found *m/z* = 470.0036; IR (KBr): ν 2927, 1714, 1660, 1446, 1291, 1257, 1170, 757, 511 cm⁻¹; enantiomeric excess: 91%, determined by HPLC (Chiralpak AD-H, hexane/2-propanol = 7/1, flow rate 1.0 mL/min, 25 °C, 230 nm) minor peak: *t_R* = 34.4 min, major peak: *t_R* = 39.5 min; [α]_D²⁵ = -151.0 (*c* 0.5, CHCl₃, 91% ee).

Chapter 5.

General procedure for synthesis of cyclobutane by formal [2+2] cycloaddition of tetrasubstituted alkenes

To a solution of DABCO (20 mol%), tetrasubstituted alkene **56** (0.073 mmol) and chiral bistiourea **62** (20 mol%) in 0.4 mL of THF at -5 °C, allenolate **26a** (0.146 mmol, 2.0 equiv) was added under nitrogen atmosphere. The reaction mixture was stirred at -5 °C until the reaction reached completion determined by TLC analysis. The crude product was filtered with EtOAc in a short column of silica and purified via column chromatography (hexane/EtOAc) to obtain the corresponding compound **57**.

Conclusions

Several organocatalytic processes were developed. P-chirogenic organocatalyst gives access to multifunctional allylic amines in high enantioselectivity. Alkaloid-type tertiary amine β -ICD afforded four-membered nitrogen-containing azetidines in high yields and high enantioselectivity. A spiro type phosphine was successfully applied on the regio- and enantioselective synthesis of tetrahydropyridine compounds. Finally, a combination of achiral Lewis base and chiral bistiourea allows access to cyclobutane in moderate enantioselectivity and diastereoselectivity under organocatalytic reaction conditions.

A variety of molecules were prepared in enantioselective manner by using chiral organocatalysis. Synthetically useful compounds bearing a tetrasubstituted stereogenic carbon center were in most cases applied as a chiral building blocks for further elaboration of important compounds such as α,α -disubstituted amino acids derivatives.

List of publications

- S. Takizawa, **F. A. Arteaga**, Y. Yoshida, M. Suzuki, H. Sasai, *Asian J. Org. Chem.* **2014**, 3, 412.
- S. Takizawa, **F. A. Arteaga**, Y. Yoshida, M. Suzuki, H. Sasai, *Org. Lett.* **2013**, 15, 4142.
- S. Takizawa, E. Rémond, **F. A. Arteaga**, Y. Yoshida, V. Sridharan, J. Bayardon, S. Jugé, H. Sasai, *Chem. Commun.* **2013**, 49, 8392.

Related publications

- S. Takizawa, **F. A. Arteaga**, K. Kishi, S. Hirata, H. Sasai, *Org. Lett.* **2014**, *in press*, DOI:10.1021/ol501855m.
- S. Hirata, K. Tanaka, K. Matsui, **F. A. Arteaga**, Y. Yoshida, S. Takizawa, H. Sasai, *Tetrahedron: Asymmetry* **2013**, 24, 1189.
- S. Takizawa, **F. A. Arteaga**, Y. Yoshida, J. Kodera, Y. Nagata, H. Sasai, *Dalton Trans.* **2013**, 42, 11787.

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