Catalytic, Asymmetric Synthesis of β-Lactams with Cinchona Alkaloid Catalysts

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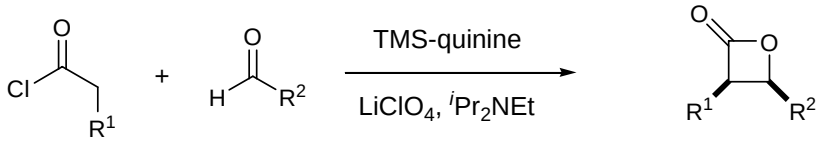
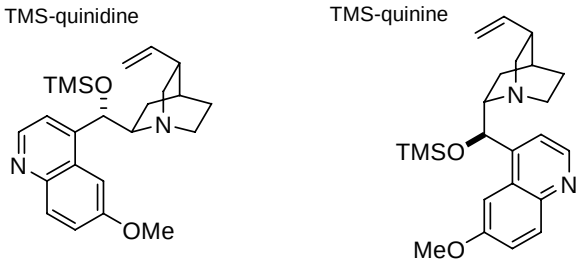
In 2004, our group found with TMS protected quinine and quinidine as catalysts, β-lactones can be synthesized with high diastereoselectivity and enantioselectivity by acyl-halide aldehyde cyclocondensation (AAC) reactions (Scheme I).

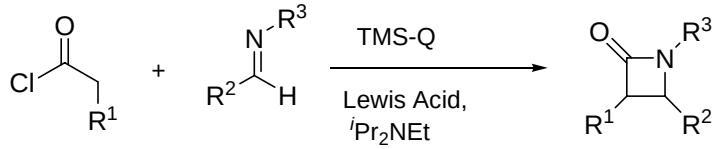


R^1=H, Me; R^2=C_6H_{11}, CMe_3, CH_2OBn, C_6H_5 84%-99% ee 90%-96% de



Scheme I. AAC reaction with alkaloid catalysts

Based on the success of AAC methodology in our group, we want to check the potential for the application of the same protocol in the asymmetric β-lactam synthesis (Scheme II). Instead of aldehyde, imines will be chosen as substrates for the [2+2] cycloaddition.

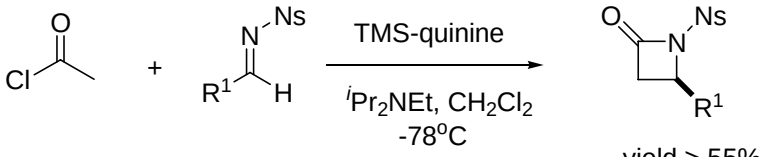


TMS-Q= TMS-Quinine/TMS-Quinidine

Scheme II. Hypothesized reaction for the synthesis of β–lactams

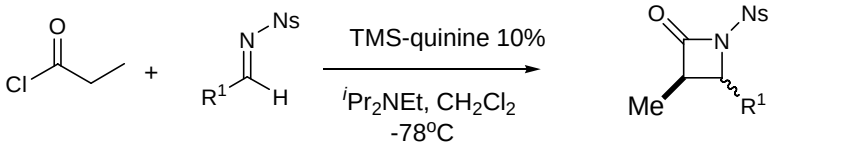
We want to know that with some activation group at nitrogen atom, whether we can get some active substrates. In addition, if the imine substrates are not very active, would Lewis acid provide sufficient activations to imines? If the substituted ketenes are substrates, what would the diastereoselectivity be?

The activation group at N atom was chosen as nitrobenzenesulfonyl group and the R^1 substituent can be aromatic groups (Scheme III). The yields and *ee* values were good.



Scheme III. Reaction between simple ketene and Ns-protected imine substrates

For the substituted ketenes, good diastereoselectivity wasn't achieved although the yields and *ee* values were still good (scheme IV).



Scheme IV. Reaction between methyl ketene and Ns-protected imine substrates

In this project, we extend the successful protocol in AAC chemistry to the asymmetric β–lactam synthesis. In our system, benzenesulfonyl group is proved to be a good choice of activation group. Because of the small energy difference in the transition state for the reaction between alkyl group substituted ketene and activated imine substrate, low diastereoselectivity was obtained.

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1.0 INTRODUCTION

1.1 BIOACTIVE β–LACTAM COMPOUNDS

Azetidin-2-one, also called β-Lactam, is a four member cyclic amide which was first synthesized by Staudinger in 1907.[1] Because of the discovery of penicillin in 1928 by Fleming and its structural confirmation by X-ray crystallography,[2] the bioactivity of β-lactam compounds has been investigated intensively.[3] Before 1970, penicillin and cephalosporins were the antibiotics that attracted most synthetic effort. Subsequently, many derivatives have been developed (Figure 1). Carbacephems are analogues of cephalosporins that are also used as antibiotics. The *trans* relationship between substituents at C_3 and C_4 in the β–lactam ring is different with the *cis* one in penicillin and cephalosporin. GV 104326, a tricyclic β-lactam (trinem), is a highly potent, broad-spectrum antibacterial agent which also contains the *trans* relationship. Recently, some β-lactams were found to be potential cholesterol absorption inhibitor.[4]

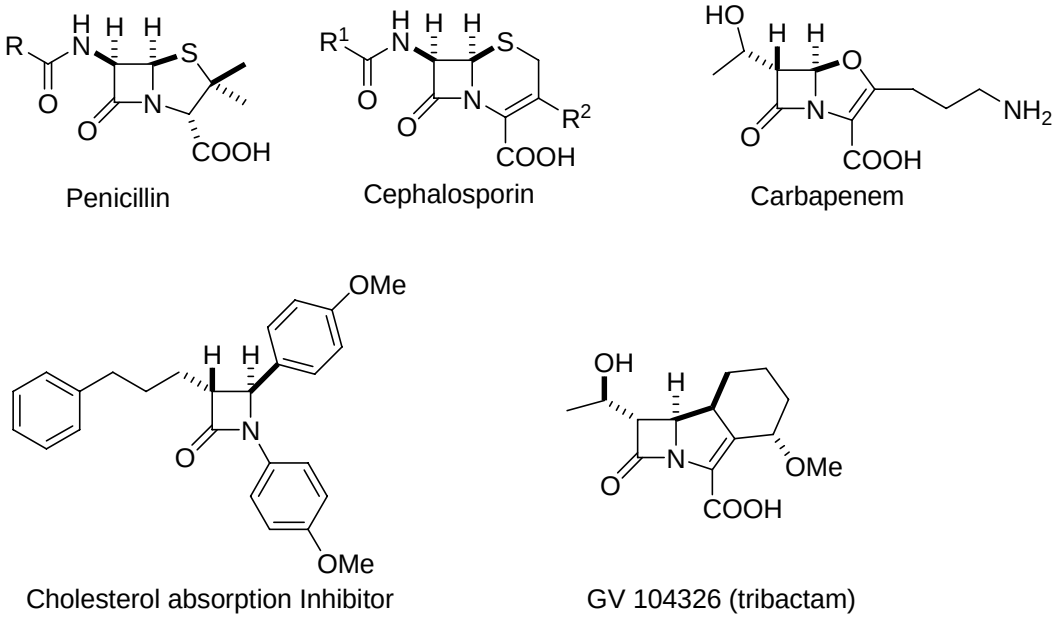
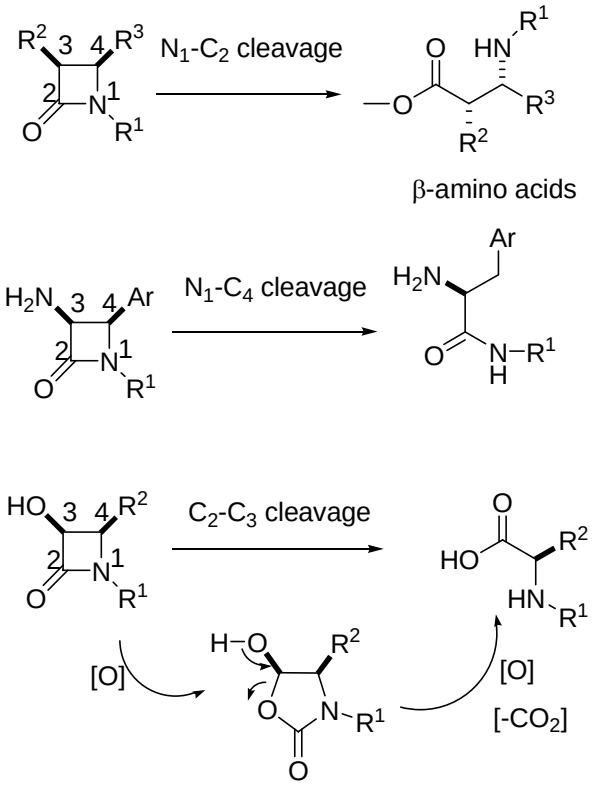


Figure 1 Bioactive β-lactam compounds

1.2 DERIVATIZATION OF β–LACTAM COMPOUNDS

In addition to their bioactivities, enatiomerically pure β-lactams are versatile building blocks for the synthesis of a variety of natural products, such as β-amino acids, oligopeptides, labeled peptides and azetidines.[5] Because of the β-lactams' highly strained four-member ring, the cleavage of any of the four bonds is possible (Scheme 1). The N_1-C_2 bond can be easily cleaved by nucleophiles (e.g. oxygen, nitrogen, and carbon) and get β-amino acid derivatives as products.[6] When R^2 is amino group and R^3 is aromatic group, palladium-catalyzed hydrogenolysis is a good way to break N_1-C_4 bond and get α–amino acid derived peptides.[5b] The ring-opening at C_2-C_3 bond of α–hydroxy β-lactams can also produce α–amino acid derivatives *via N*-carboxy α–amino acid anhydride (NCA) intermediates.[7] Selective cleavage of the C_3-C_4 bond is rare.



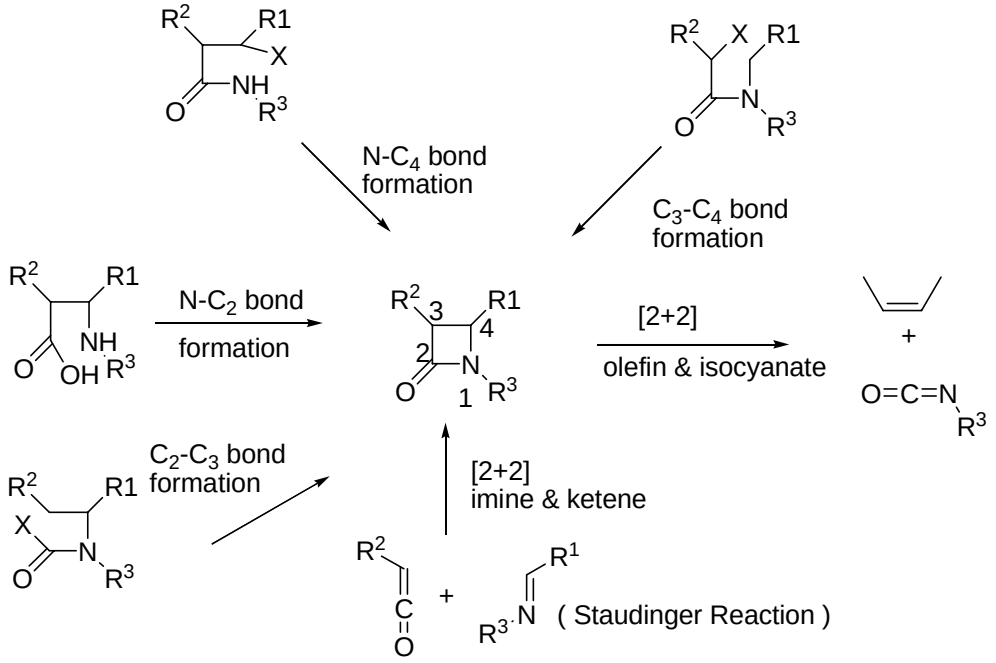
Scheme 1 Derivatization of β-lactams with bond cleavage

1.3 METHODS FOR THE SYNTHESIS OF β–LACTAM COMPOUNDS

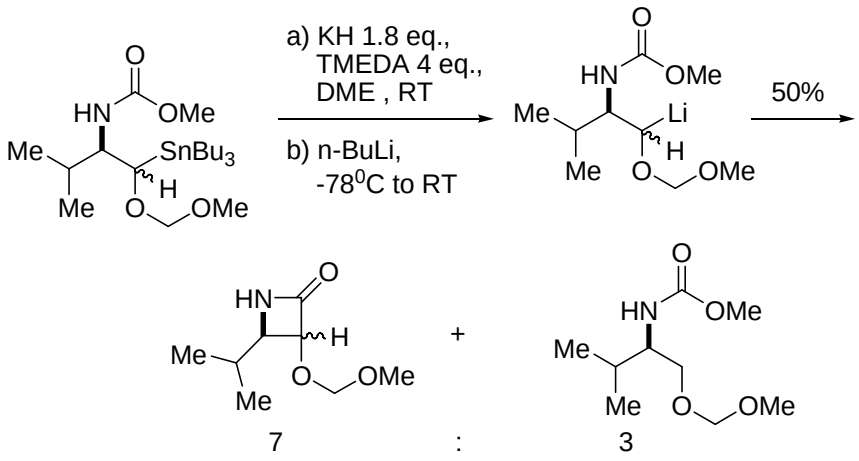
Inspired by the pharmacological applications of β-lactams and due to the limitations associated with their biosynthesis, chemical synthesis of this kind of compounds has attracted considerable attention over the last 80 years.[5a, 8] The strained four-member ring which constitutes the core structure of all β-lactam antibiotics is the main challenge point in the synthetic effort for synthesis of these compounds.

The four-member ring of β–lactam can be constructed by any of the four single-bond formations or by [2+2] cycloaddition (Scheme 2). The formation of the amide (N_1-C_2) bond is the most obvious approach and was utilized in the synthesis of penicillin.[9] In the four single-

bond constructions, C_2-C_3 bond formation was rare. One methodology involving a tributylstannane-mediated ring closure has been reported (Scheme 3).[10] Despite the poor yield, this method gave an alternative way to synthesize chiral β–lactam considering the starting material can be prepared from readily available β–amino acids. For the C_3-C_4 bond formation, in a simple sense, the C-C bond construction involves the formation of a nucleophilic center at C_3 and an electrophilic center at C_4, or vice versa.[11] The biosynthetic way of the β-lactam synthesis is mainly focused on the formation of C_4-N_1 bond.[12] A lot of approaches have been developed to construct this bond. The idea is the intramolecular displacement of a leaving group attached to C_4 with activated nitrogen (Figure 2).[13]



Scheme 2 Methods for β-lactam ring construction



Scheme 3 Formation of C_2-C_3 bond in the β–lactam ring

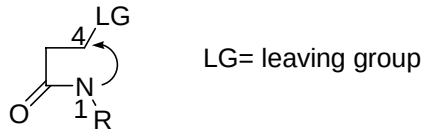
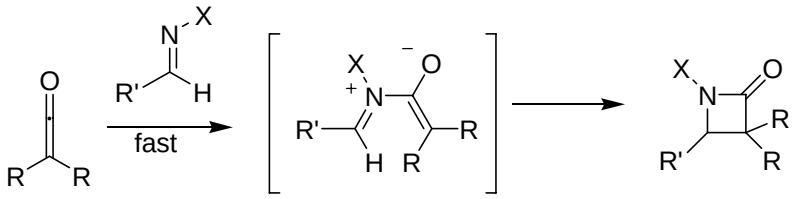


Figure 2 C_4-N_1 bond formation

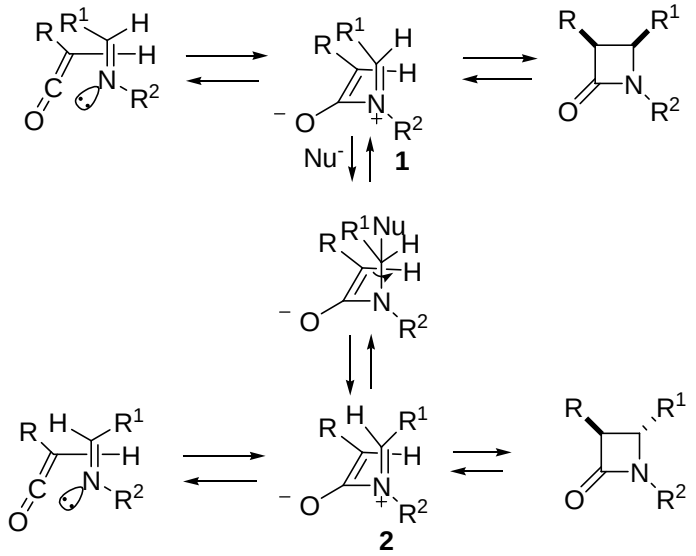
Compared with the single-bond construction approach of β–lactam synthesis, the ketene-imine cycloaddition which includes carbenoid insertion and the Staudinger reaction is more widely used.[8c, g] Due to the ready availability of both imines and ketenes, the Staudinger reaction has provided a useful and economical approach for the synthesis of β–lactams. In addition, the ketene-imine cycloaddition is more efficient, which constructs the β–lactam four-member ring in just one step reaction.

The mechanism for Staudinger reaction is that the electrophilic ketene is attacked by lone pair electrons of imine nitrogen and the zwitterionic enolate is formed. The following conrotatory ring closure forms the β-lactam (Scheme 4).[14] In most of cases, *cis* β-lactams are the major or the only products from *E*-imines. For this diastereoselectivity, some explanation has been established (Scheme 5).[15] Because the LUMO of the ketene carbonyl group is coplanar to the substituents of ketene (Figure 3), if the C=O bond is attacked by imines in an orthogonal

approach, thus an intermediate is generated in which the planes of the imine and the ketene should be perpendicular to each other. In addition, the attack of imine from the least hindered side is the most possible way for the formation of zwitterionic enolate. A conrotatory ring closure of the intermediate **1** will form the thermodynamically less stable *cis* β-lactam. For the cyclic imines, the formation of intermediate **2** will get the *trans* β-lactam. If the intermediate **1** was attacked by nucleophiles and the C=N bond was broken, the bond rotation will cause the formation of both intermediates **1** and **2**. Depending on the steric hindrance between R and R^1, the different value of *cis-trans* ratio will appear in Staudinger reaction. Additionally, the *cis* product can be isomerized to more stable *trans* one with strong base.[16]



Scheme 4 Mechanism for the Staudinger reaction



Scheme 5 Explanation for the diastereoselectivity

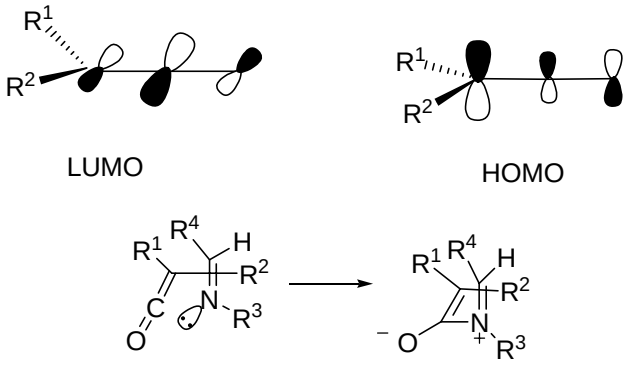
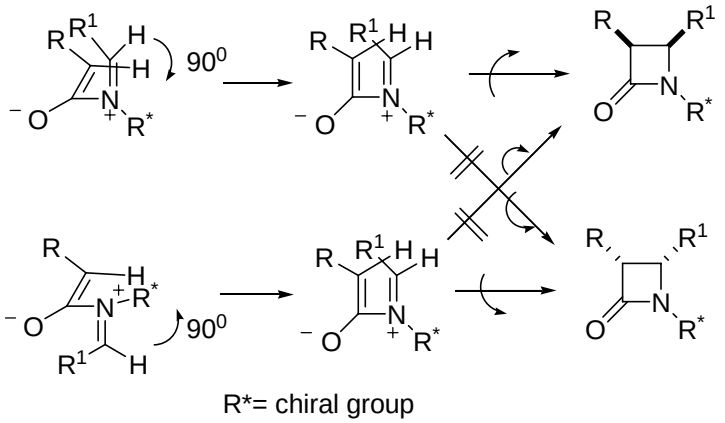


Figure 3. HOMO and LUMO of Ketene

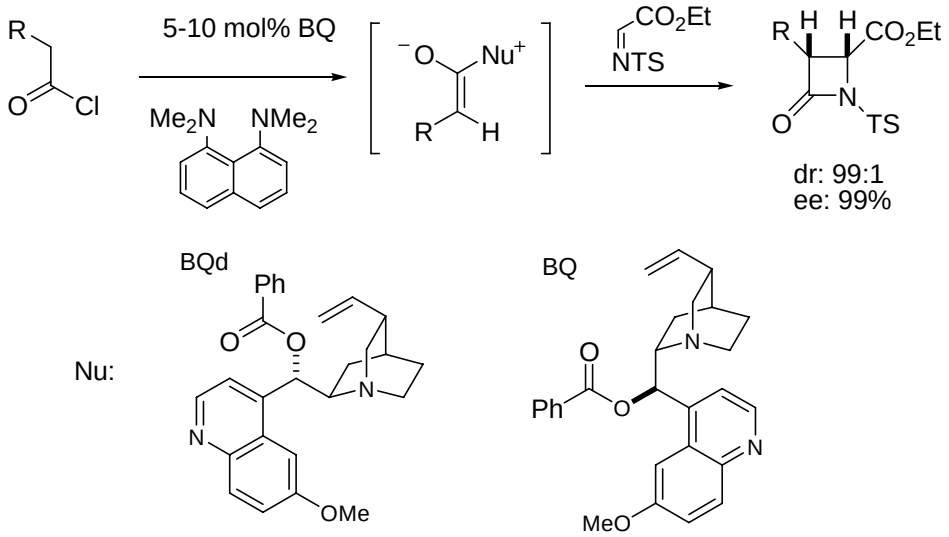
Generally, the asymmetric induction in the Staudinger reaction comes from the chiral imines or chiral ketenes, or both. The possible reason for the enantioselectivity is illustrated in Scheme 6. The imine can be placed on the top face or bottom face based on the substrate structure. Before the ring closure, the central C-N bond has to rotate toward an eclipsed arrangement. Based on the principle of least motion, the rotation will be only 90 degree. In order to avoid the interaction between the hydrogen of ketene and R^1 of the imine, the ring will be closed in only one direction. Thus, based on the substrate structure, one enantiomer will be preferred.



Scheme 6 Explanation for the asymmetric induction

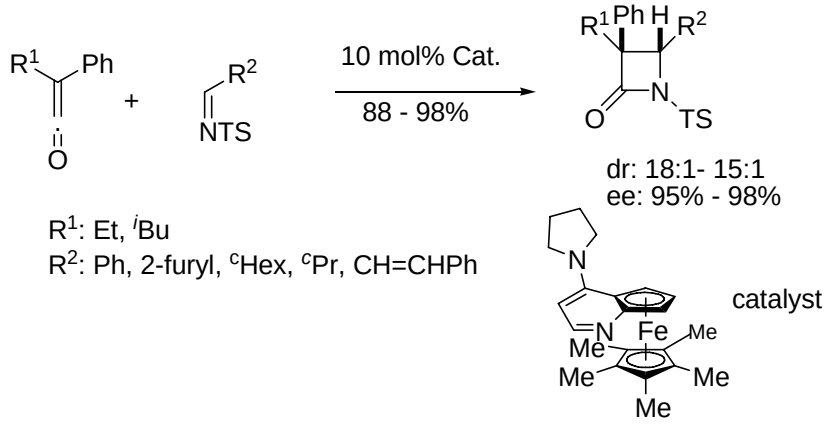
Although Staudinger reaction is widely used for β–lactam synthesis, most of the approaches are based on the use of chiral precursors, either imines or ketenes.[8g] In recent years, some asymmetric methods have been developed by Lectka and Fu's group.[17] Lectka's methodology is

based on the combined action of a pair of Brønsted bases (Scheme 7). The acyl chloride is dehydrochlorinated at low temperature by tertiary nucleophiles (e. g benzoylquinine). The resulting ketenes are trapped by the nucleophile and form chiral zwitterionic enolates which attack electrophilic imines and get β-lactams. The strong bases (e. g. "proton sponge") can form thermodynamically stable hydrochloride salt and reproduce the tertiary nucleophiles. So, the alkaloid catalysts are also called "proton shuttle". Due to the polarity reversal of ketenes and imines, this mechanism is different with the standard Staudinger reaction.

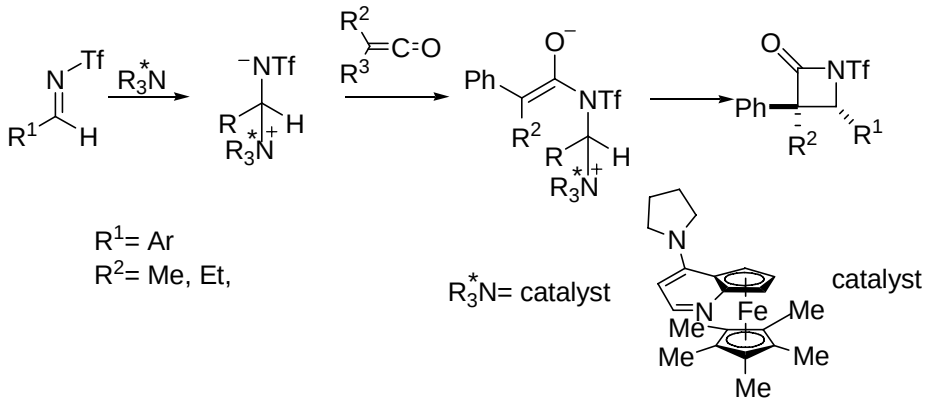


Scheme 7 Lectka's asymmetric synthesis of β–lactam compounds

Using planar-chiral azaferrocene heterocyclic compounds to activate ketenes, Fu found another efficient way to get *cis* β-lactams with high yields and enatioselecties (Scheme 8). Very recently, this group found when the protecting group of imines is switched from tosyl group to triflate, the diastereoselectivity is reversed.[18] The proposed explanation is that due to the strong electron withdrawing ability of Tf group, the nucleophilic catalyst will add to imines first. The resulting anion will attack ketene and form the enolate (Scheme 9). That is the reason for the reversed diastereoselectivity.

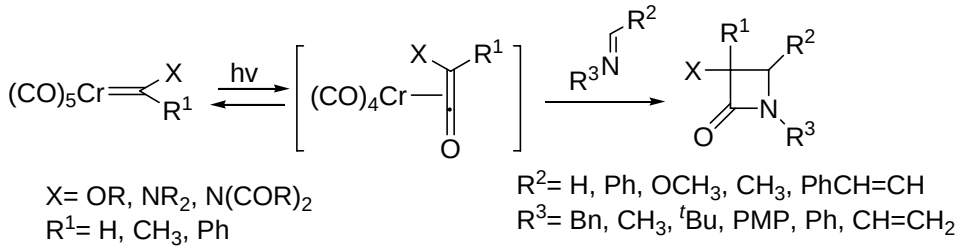


Scheme 8 Fu's β–lactam synthesis



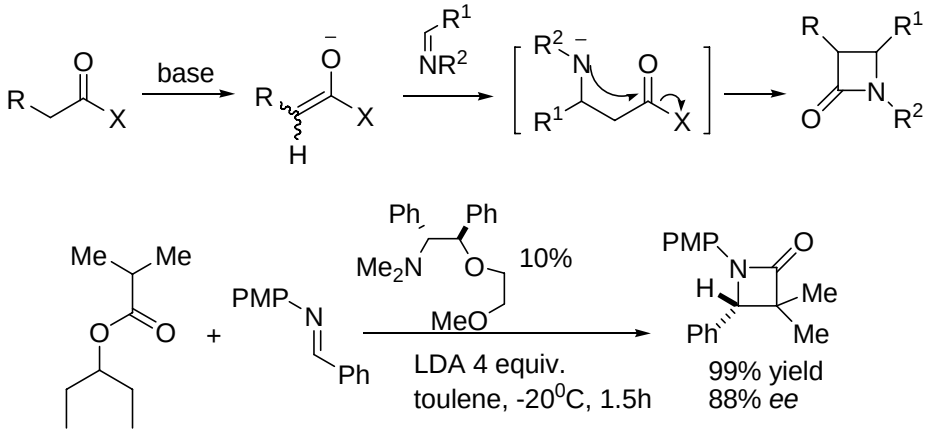
Scheme 9 Proposed Mechanism for the reversed diastereoselectivity

The carbenoid insertion method was developed by Hegedus' group.[8c] The chromium complex is prepared from chromium hexacarbonyl and organolithium reagents, which is air-stable and easily handled. Due to the strong electron withdrawing ability of $Cr(CO)_5$ group, the carbene carbon is quite electrophilic. Irradiated with visible light through Pyrex, one of the four *cis* CO groups is reversely inserted into the metal-carbon double bond. The resulting species has ketene-like reactivity and can react with imines, olefins, and carboxylic acid derivatives (Scheme 10).



Scheme10 Chromium carbene complexes for β-lactam synthesis

In addition to above methods, the ester enolate-imine condensation, also called Gilman-Speeter reaction, is another popular way for β–lactam synthesis (Scheme 11).[19, 8b] In 1997, Tomioka reported the first example of a direct catalytic enantioselective synthesis of β-lactam by using this method.[20] The active reagent is a ternary complex (comprising LDA, the ester enolate, and tridentate amino diether) which afforded β–lactam compounds in high yield and good *ee* value.



Scheme 11 Gilman-Speeter reaction in β–lactam synthesis

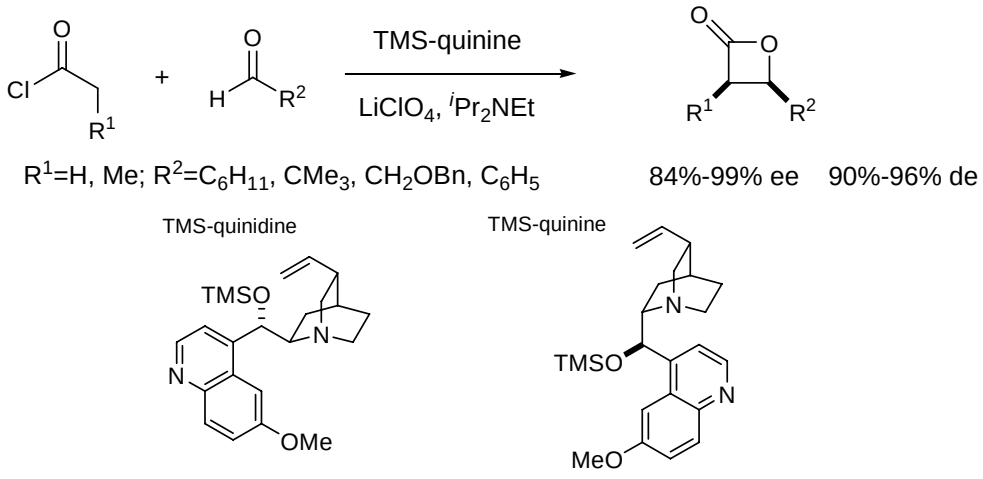
Although a lot of methods about the β–lactam synthesis have been developed since Staudinger's first synthesis in 1907, the catalytic and asymmetric version of this ketene-imine [2+2] cycloaddition is still rare. Considering our group's success in the synthesis of β-lactone,[21] we want to check whether we can extend the same idea to the β–lactam synthesis. The following questions are those we need to answer: Can we control the enatioselectivity with TMS-

Quinine/TMS-Quinidine catalysts and achieve high *ee* value? Can we obtain high diastereoselectivity if the substituted ketenes are used? Does the Lewis acid have the similar effect as in the AAC reaction? In the following chapter, I will discuss the research results in the β–lactam synthesis and try to answer these questions.

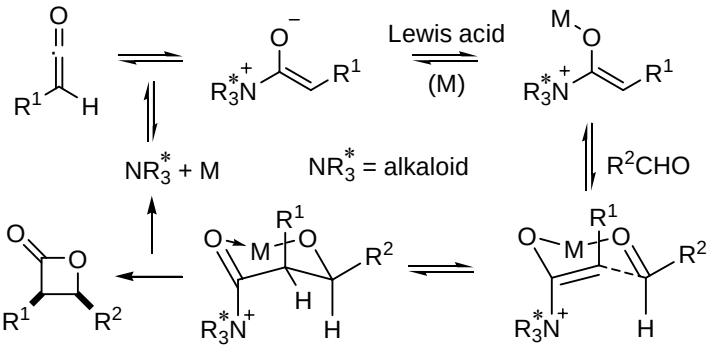
2.0 REACTION DEVELOPMENT AND DISCUSSION

2.1 BACKGROUND

In 2004, our group found with TMS protected quinine and quinidine as catalysts, β-lactones can be synthesized with high diastereoselectivity and enantioselectivity by acyl-halide aldehyde cyclocondensation (AAC) reactions (Scheme 12). With the appropriate choice of Lewis acids, the quench between catalysts which are Lewis bases and Lewis acids can be avoided. The Lewis acid additive is believed to activate both aldehyde and enolate and form a closed transition state, which facilitates β-lactones formation (Scheme 13).

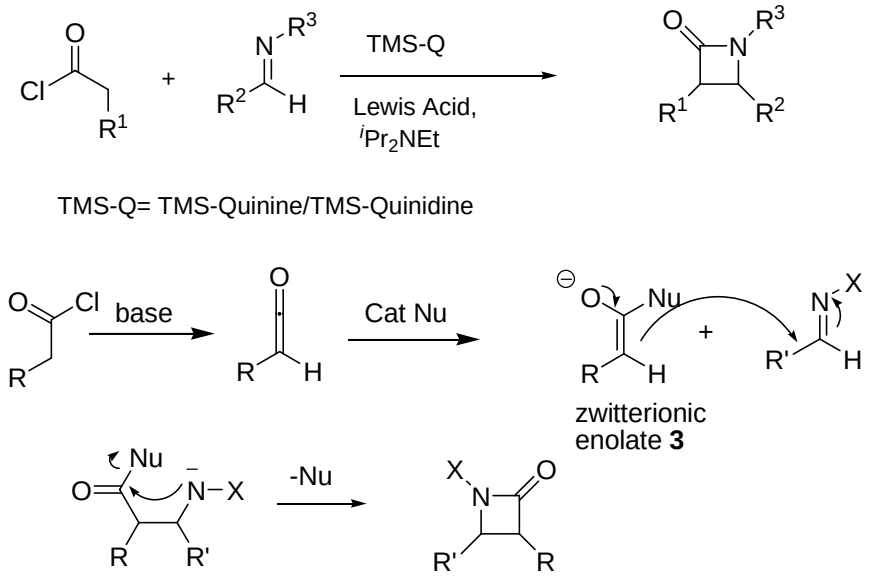


Scheme 12 AAC reaction with alkaloid catalysts



Scheme 13 Proposed mechanism for the **AAC** reaction

Based on the success of AAC methodology in our group, we want to check the potential for the application of the same protocol in the asymmetric β-lactam synthesis (Scheme 14). Similar as in AAC reactions, the ketene would be formed in *situ* and activated by cinchona alkaloid catalysts to form the zwitterionic enolate. Instead of aldehyde, imines will be chosen as substrates for the [2+2] cycloaddition. Compared with carbonyl compounds, due to the lower electronegativity of nitrogen atom, the LUMO of the C=N bond will be higher than the LUMO of the C=O bond. Thus, the C=N bond in imine substrate is less electrophilic (Figure 4). If imine substrates are activated and electrophilic enough (decreasing the LUMO), the enolate intermediate **3** will attack the electrophilic carbon atom and form the C-C bond much easier. The subsequent ring closure will form the 4-member β-lactam ring. This stepwise [2+2] cycloaddition is similar as the proposed mechanism in AAC chemistry.



Scheme 14 Hypothesized reaction way for the synthesis of β–lactams

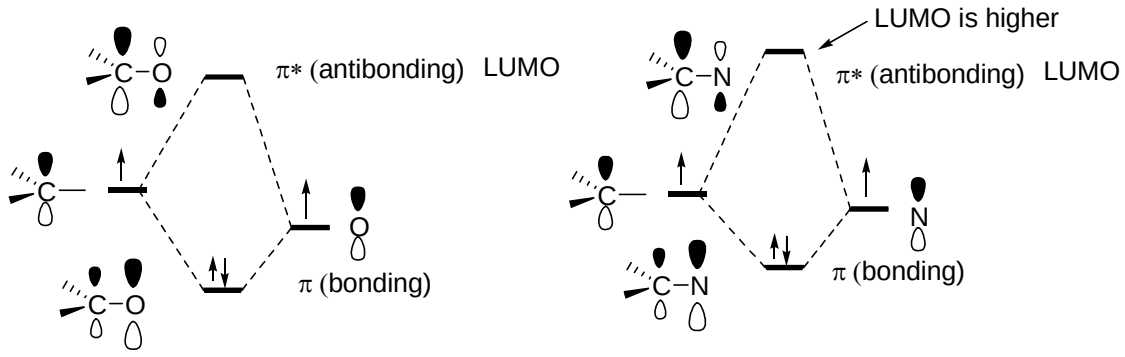


Figure 4. The LUMO of C=N and C=O bond

For the activation of imines, one way is to choose the electron withdrawing groups as substitution groups of imines and another way is to use Lewis acid to activate imines. In this project, we want to testify the hypothesized reaction way and explore the possible ways to activate the imine substrates. In Lectka's research, they used α–imino esters as substrates which have activation group attached to carbon atom. We want to know that if we add some activation group at nitrogen atom, whether we can get some active substrates. In addition, if the imine substrates are not very active, would Lewis acid provide sufficient activations to imines? If the

substituted ketenes are substrates, what would diastereoselectivity be? In the following section, I will try to answer these questions.

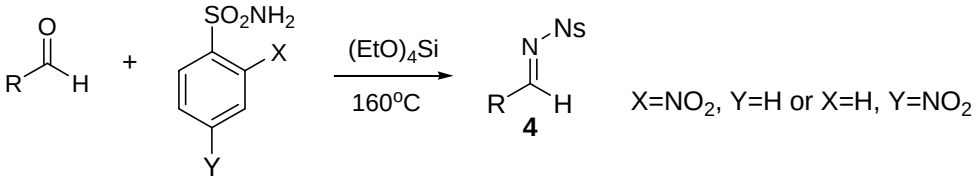
2.2 REACTION DEVELOPMENT AND DISCUSSION

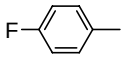
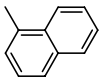
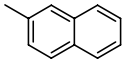
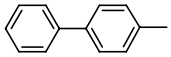
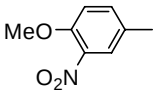
2.2.1 Choice of Substrates

2.2.1.1 Imine Substrates

In order to increase the electrophilicity of imine substrates, 2- and 4-nitrobenzenesulfonyl group were chosen as substitution groups at nitrogen atom. Benzenesulfonyl group is strongly electron-withdraw and the nitro group attached to the benzene ring will decrease the electron density at benzene ring further. In addition, Fukuyama has reported one mild way to deprotect this kind of protection group.[22] Considering the stabilizing effect of aromatic groups, they were chosen as the substitution group at carbon atom. In addition, the choice of aromatic group prevents the possible tautomerization between imine and enamine because there is no α–hydrogen can be deprotonated. In 2000, Ishigedani's group reported a way to prepare such kind of imines.[23] *N*-Alkylidenesulfonamides ($ArCH=NSO_2Ar'$) can be easily prepared by condensation of aromatic aldehyde ($ArCH=O$) with arenesulfonamides (H_2NSO_2Ar') in the presence of triethoxysilane, which acts as solvent and dehydrating reagent. The side product–ethanol is removed by Dean-Stark. After simple recrystalization, the pure product can be obtained. In addition, two unsaturated imines were prepared in the same way (Table 1).

Table 1 Imine substrates preparation

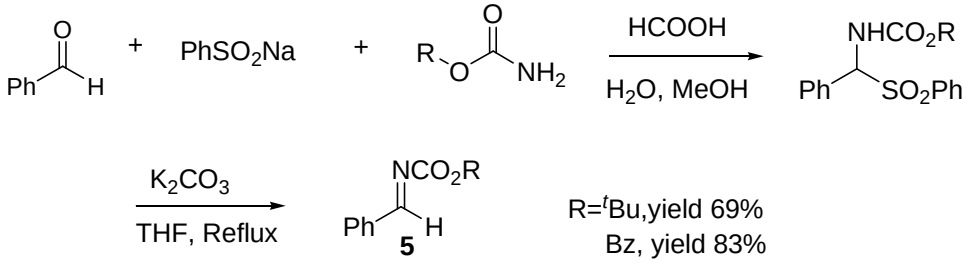


entry	R^1	substrate yield %
a		[a]75
b		[a]63
c		[a]51
d		78
e		71
f		64
g		51
h		72

[a]The Ns group in entry a-c was 1-sulfonyl-4-nitrobenzene. For the other entries, Ns group was 1-sulfonyl-2-nitrobenzene.

Considering the wide utilization of *t*-butyloxycarbonyl (Boc) and carbobenzyloxy (Cbz) group as amine protection groups, imine substrates with these groups attached to N atom were also prepared.[24] The condensation of benzyl aldehyde, sodium benzenesulfinate and cabamates

formed the corresponding sulfonamide sulfone, which was refluxed in THF in the presence of potassium carbonate. After filtration of the reaction mixture, the pure imines can be obtained (Scheme 15). Compared with the nosylate protected imines, Boc and Cbz groups have weaker electron withdrawing ability, which will decrease the electrophilicity of substrates and the addition of Lewis acid may be necessary.



Scheme 15 Procedure for imine substrate preparation

To check the substrate scope, some other imine substrates were also prepared according to the known procedure.[25] From **6a** to **6c**, the activation groups attached to N atom have decreased electron withdrawing ability. **6d** and **6e** are aliphatic imines, which can tautomerize to corresponding enamines. **6f** has a propargyl group and can be elaborated further.

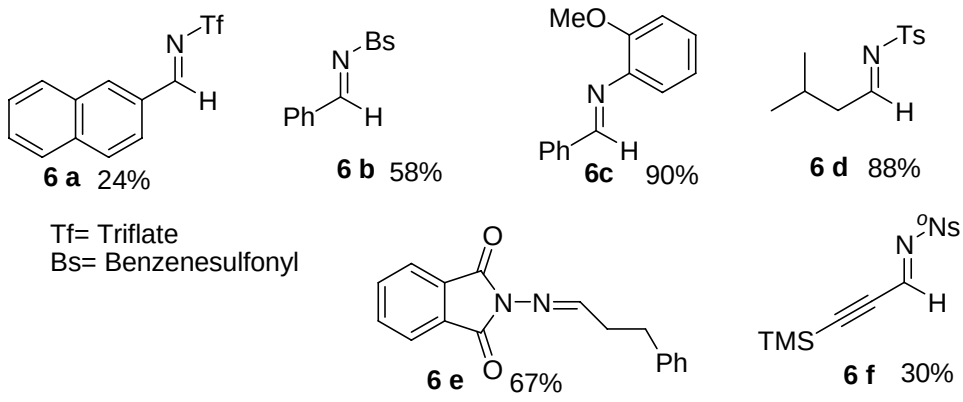


Figure 5. Some other imine substrates

2.2.1.2 Ketene Substrates

Simple and mono alkyl group substituted ketenes were chosen as substrate. Similar to the AAC chemistry, ketenes can be formed in *situ* by dehydrohalogenation of acetyl halide at low temperature.[26] With the slow addition of acyl chloride by syringe pump, the possible ketene dimerization is avoided because of the low concentration of ketene and low reaction temperature. Considering the increase steric hindrance with the larger alkyl group which will deteriorate the reaction, main effort was put on simple and methyl substituted ketenes.

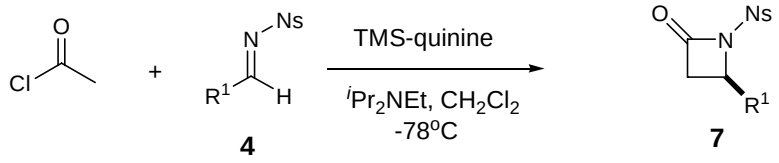
2.2.2 Results

2.2.2.1 Simple ketene and Ns-Imine Substrates

The imine substrate **4a** and simple ketene were chosen as starting point for the exploration of reaction condition. Based on the established AAC procedure, a test reaction was run. 10 mol% TMS-quinine and imine substrate were dissolved in CH_2Cl_2 and cooled to -78 ^{0}C . Acyl chloride was dissolved in CH_2Cl_2 and added to the reaction system slowly by syringe pump addition. The mixture was stirred -78 ^{0}C for 5 hours and then warmed to room temperature. The solid product was collected by filtration and washed with small amount of CH_2Cl_2. The yield was acceptable (65%) and the *ee* value was high (95%). If the workup procedure was changed to extraction, the *ee* value decreased to about 85%. It seems the β–lactam ring will be temporarily opened and cause the enatioselectivity erosion. Due to the strong electron withdraw ability of nitrobenzenesulfonyl group, without the addition of Lewis acid, the substrate was still activate enough. From this starting point, we want to fix the activation group as Ns group and then can explore the effect of substitution groups at C atom systematically. For aromatic groups, with the choice of substitution group at benzene ring, the electron density at C atom can be tuned. If the

electron withdrawing group is attached to the benzene ring, it will decrease the electron density in the aromatic ring and make the imine carbon atom more electrophilic. On the contrary, electing donating substituents on the benzene ring will increase the electron density and deactivate the imine substrates. We want to know: what is the scope of the substituents on the benzene ring? Is Lewis acid additive effective to activate the imine substrates? The results are summarized in Table 2. In entry b, the *para*-fluoro group is strongly electron withdrawing. Good yield (69%) and *ee* value (98%) were obtained. Similarly, in entry f, the *ortho*-chloro group is also very electron withdrawing and good result was also achieved (yield 80%, *ee* 96%). These two results indicate that with electron withdraw substituents on the benzene ring, the imine substrates are activated enough. For entry c to e, three conjugated aromatic substrates were tested. Because the conjugated bi-phenyl and naphthyl groups have the similar electrostatic property as phenyl group, we believe the reactivity will be also at the same level. The observed results confirmed this expectation (entry c, yield 87%, *ee* 99%; entry d, yield 57%, *ee* 99%; entry e, yield 80%, *ee* 99%). When the *para*-methoxy group was attached to the benzene ring, the increased electron density decreased the reactivity of the imine substrate. No product was observed even with the addition of Lewis acid (LiI, 3 eq.). In order to tune the electron density in the benzene ring, a nitro group was added to the *meta* position. Because of the strong electron withdrawing ability of nitro group, good result was gotten (entry g, yield 82%, *ee* 99%). It seems that electron donating substituents on the benzene ring are not tolerated in this reaction system. For entry h and i, the C=C bond is conjugated with aromatic ring and can also stabilize the carbon atom. But, the products are not as stable as other trials. The low yield is a result of the lost in the purification process (entry h); the racemic product is thought to be the result of self-epimerization of the furan ring (entry i).

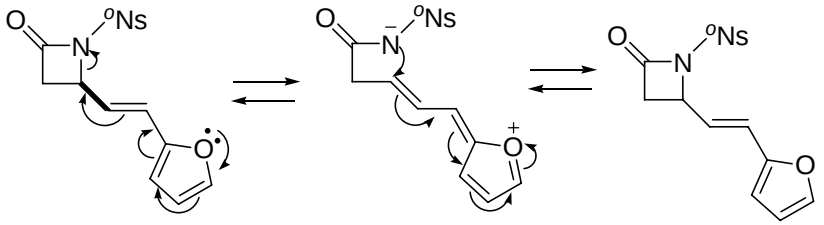
Table 2 Asymmetric Synthesis of β-lactams



entry	substrate	yield %	ee%[b]
[a]a	**4a**	65	[c] 95
[a]b	**4b**	69	[c] 98
[a]c	**4c**	87	[c,d]99
d	**4d**	57	[d] 99
e	**4e**	80	[d]99
f	**4f**	80	96
g	**4g**	82	99
h	**4h**	26	90
i	**4i**	72	---

[a] Entry a-c were Dr. Cheng Zhu's result. [b] Enantiomer excess ratio was determined by comparing two enantiomers retention time with HPLC. [c]The Ns group in entry a-c was 1-sulfonyl-4-nitrobenzene. For the other entries, Ns group was 1-sulfonyl-2-nitrobenzene. [d]The solvent was THF.

For the lost of chirality in entry i, the possible reason is that the electronrich 2-furyl substitution group will pump the lone pair electron of oxygen to furan ring. This electron transfer at the conjugate system causes the four-membered β–lactam ring temporally opened. Because the ring closure has no facial selectivity, the product is racemized (Scheme 16).



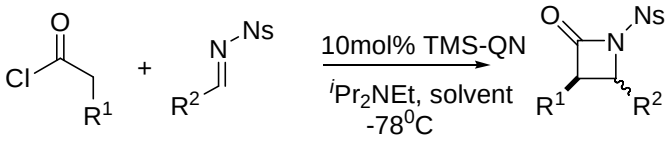
Scheme 16 Possible explanation for the racemization of entry i

2.2.2.2 Monosubstitued ketenes and Ns-Imine Substrates

With the successful cycloaddition reaction between simple ketene and Ns protected imines, we want to extend the reaction scope to substituted ketenes (Table 3). Although the reactivity was still good (entry a, h, i, j) for methyl ketenes, the satisfied diastereoselectivity didn't be achieved.

Due to the little low solubility in THF, the conversion was decreased for some trials (entry e, f, and g). The addition of Lewis acid seemed helpful for the reactivity but no increase for diastereoselectivity (entry a). Increased steric hindrance decreased the reactivity (entry c and d). Optimized condition for AAC reaction[27] also didn't function well (entry f).

Table 3 Reactions between Substituted Ketenes and Ns-imines

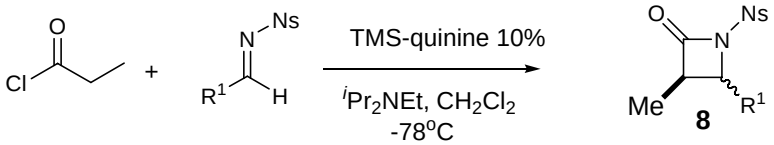


entry[b]	R^1	Imine	Solvent	Dr.[c]	% Conv.[c]
[a,d,e]a	Me	**4 a**	2:1 CH_2Cl_2:THF	1:1	100
[e]b	Me	**4 a**	2:1 CH_2Cl_2:THF	1.6:1	70
[e]c	Et	**4 a**	CH_2Cl_2	1.5:1	75
d	^{i}Pr	**4 c**	CH_2Cl_2	1:2	61
e	Me	**4 c**	2:1 CH_2Cl_2:THF	1:1	44
f	Me	**4 c**	9:1 CH_2Cl_2:DMF	1.2:1	75
[a]g	Me	**4 c**	2:1 CH_2Cl_2:THF	1.5:1	43
h	Me	**4 d**	CH_2Cl_2	1.5:1	100
i	Me	**4 e**	CH_2Cl_2	1.5:1	91
[d]j	Me	**4 c**	CH_2Cl_2	1:1.2	96

[a]$MgCl_2$ was added (a, 2eq.; g, 1 eq.). [b]Reaction time/temperature: a, overnight/-78^{0}C; b and c, overnight/-25^{0}C; d to j, 5 hours/-78^{0}C. [c] Diastereomer ratios and conversion were determined by ^{1}H NMR of crude product mixtures. Dr. ratio was *cis*:*trans*. [d] Some ee. values were checked: entry a, cis 99% and tran 94%; entry j, cis 34% and tran 98%. [e]These are Dr. Cheng Zhu's results.

Although the diastereoselectivity is not good, if the two diastereomers can be separated easily, the reaction will still be useful. So, several large scale (2 mmol) reactions are tried. The total yield for the two diastereomers is good and *ee* value for each diastereomers is also satisfactory (Table 4). The absolute configuration was confirmed by the crystals structure of **8 a**, which is exact same as we have expected.

Table 4 Asymmetric Synthesis of β-lactam with methyl substituted ketene



entry	Imine	yield %[a]	Separated yield %[b]	Dr. *cis:trans*[c]	ee %
a	**4 a**	86	*cis*:14%, *trans*:24%	1:1.4	*cis*:99 *trans*:98
b	**4 b**	88	*cis*:13%, *trans*:56%	1:1.1	*cis*:99 *trans*:98
c	**4 c**	66	---	1:2.3	*cis*:34 *trans*:98
d	**4 e**	67	*cis*:22%, *trans*:12%	1:0.9	*cis*:85 *trans*:99

[a]The yields were the combination yields of diastereomers. [b]The separated yield for each of the diastereomers included products from recrystalization and ISCO separation. Entry c can't get separated diastereomer. The difference between the two yields was accounted to unseparated mixtures and lost on the column. [c]The ratio was determined by comparing the integration value of two specific peaks in NMR spectra.

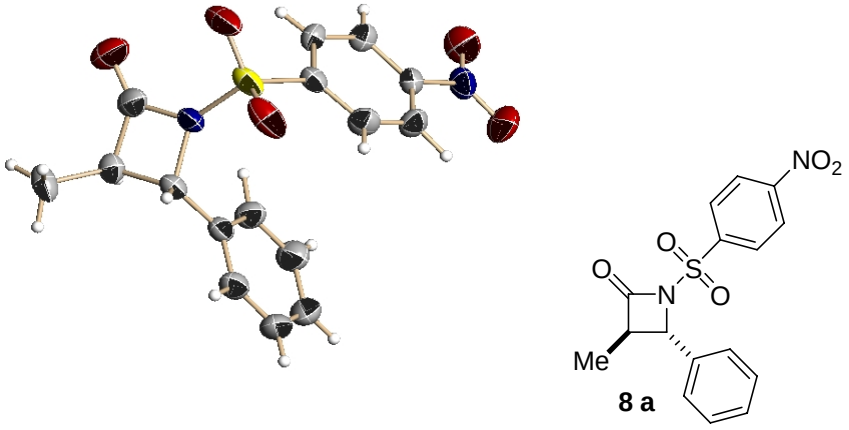


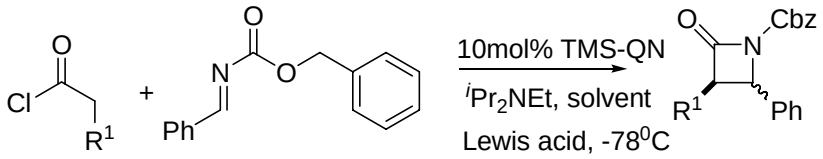
Figure 6. X-Ray Structure of **8a**

2.2.2.3 Ketenes and Cbz-Imine Substrates

Although the yields and *ee* values are satisfactory, the low diastereoselectivity of the reactions with methyl ketene is still a problem. Cheng got some potential results in previous tests with cbz protected imines. So, they were chosen as next target (Table 5). However, due to the weaker electron withdrawing ability of cbz group, there was no reaction under previous reaction condition. Considering the success of AAC reaction in our group, Lewis acid activation is a

possible way to increase the reactivity of substrates. With the appropriate choice of Lewis acid, the substrate reactivity did get some improvement (entry i, j). But, with the amount of Lewis acid increase, substrates began to decompose (entry b, c and h). Some transition metal salts were also tested as Lewis acid and no effect was found (entry d, e). The best diastereoselectivity was achieved with $LiClO_4$ as Lewis acid (entry k, 3:1; entry l, 6:1). For other trials, the ratio was lower than 1.5.

Table 5 Asymmetric β-lactam Synthesis with cbz protected imines



entry[a]	R^1	Lewis Acid	Solvent[b]	% Conv.[c]	% Dr.[c]
a	H	LiI, 1 eq.	10:1 CH_2Cl_2:Et_2O	23	--
b	H	LiI, 3 eq.	10:1 CH_2Cl_2:Et_2O	S.M. dec.	--
c	H	$LiClO_4$, 1 eq.	2:1 CH_2Cl_2:Et_2O	S.M. dec.	--
d	H	$Zn(OTf)_2$, 0.1 eq.	2:1 CH_2Cl_2:Et_2O	No RXN	--
e	H	$Yb(OTf)_3$,0.1 eq.	2:1 CH_2Cl_2:Et_2O	No RXN	--
f	H	$Mg(OTf)_2$,0.1 eq.	2:1 CH_2Cl_2:$E_{t2}O$	54	--
g	H	$Al(OTf)_3$,0.1 eq.	2:1 CH_2Cl_2:Et_2O	51	--
h	H	$Al(OTf)_3$, 1 eq.	2:1 CH_2Cl_2:Et_2O	S.M. dec.	--
i	H	$MgCl_2$, 1 eq.	2:1 CH_2Cl_2:Et_2O	73	--
j	H	LiOTf, 1 eq.	2:1 CH_2Cl_2:Et_2O	54	--
k	Me	$LiClO_4$, 1 eq.	2:1 CH_2Cl_2:Et_2O	77	3:1
l	Me	$LiClO_4$, 1 eq.	2:1 CH_2Cl_2:Et_2O	43	6:1
m	Me	LiI, 1 eq.	9:1 CH_2Cl_2:DMF	33	1:1
[d]n	Me	$LiClO_4$, 1 eq.	2:1 CH_2Cl_2:Et_2O	66	1:1
o	Me	$Mg(OTf)_2$,0.2 eq	2:1 CH_2Cl_2:Et_2O	7	1.2:1
p	Me	LiOTf, 1 eq.	2:1 CH_2Cl_2:Et_2O	No RXN	--
q	Me	$MgCl_2$,1 eq	2:1 CH_2Cl_2:Et_2O	S.M. dec.	--
r	Me	$Al(OTf)_3$, 1 eq.	2:1 CH_2Cl_2:Et_2O	<10	1:1

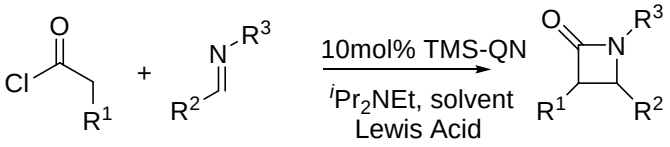
[a]Entry (a-c, k, l) were Dr. Cheng Zhu's result. [b]Reaction time/temperature: 14 hours/-78^{0}C, except entry l. For entry l, the temperature was -25^{0}C. [c]Diastereomer ratios and conversion were determined by ^{1}H NMR of crude product mixtures. Dr. ratio was *cis:trans*. [d]Me-QN was used as catalyst.

2.2.2.4 ketenes and Other Imine Substrates

From previous experiments, we know nosylate group can activate the imine substrates. In order to tune the electron density at C=N bond, imine substrates with the function groups having

different electron withdrawing ability were tested. In addition, some aliphatic imine substrates were also tested. The results are summarized in Table 6. When the activation group attached to N atom is Tf, the imine substrate is not very stable under reaction condition. Although Fu got good trans diastereoselectivity in his system,[18] no reaction was found in our trials. For entry b, c and f, benzenesulfonyl group can supply enough activation and get good reactivity for the substrates. In entry c, d and e, without sulfonyl group, the benzene ring can't make the C=N bond electrophilic enough. The *ortho* methoxy group increases the eletrondensity at benzene ring and decreases the reactivity of imine substrate further. With the addition of Lewis acid, there is still no reaction. Similar observation for entry g and h, the isoindoline-1, 3-dione unit in **6e** can't activate the C=N bond. For substrate **6f**, it is not very stable and only decomposed starting material was found. Based on the above data, we can see that benzene sulfonyl group is also a good choice as activation group in our system.

Table 6 Reactions between Ketenes and Other Imine Substrates



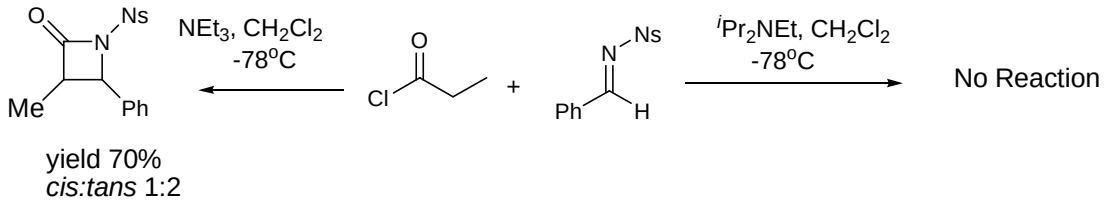
entry[a]	R^1	Imine	Solvent	Lewis Acid	% Conv[b]
a	Me	**6a**	CH_2Cl_2	---	No RXN
[a]b	H	**6b**	CH_2Cl_2	---	93
[a]c	Me	**6b**	2:1 CH_2Cl_2:Et_2O	$LiClO_4$, 1 eq.	79
[a]d	H	**6c**	2:1 CH_2Cl_2:Et_2O	$LiClO_4$, 1 eq.	No RXN
[a]e	H	**6c**	2:1 CH_2Cl_2:THF	$ZnCl_2$, 1 eq.	No RXN
[a]f	H	**6d**	CH_2Cl_2	---	72[c]
[a]g	H	**6e**	2:1 CH_2Cl_2:THF	$LiClO_4$, 1 eq.	No RXN
[a]h	H	**6e**	CH_2Cl_2	$ZnCl_2$, 1 eq.	No RXN
i	H	**6f**	CH_2Cl_2	---	No RXN

[a]These are Dr. Cheng Zhu's results. [b]Conversion was determined by ^{1}H NMR of crude product mixtures.. [c]This is the separated yield.

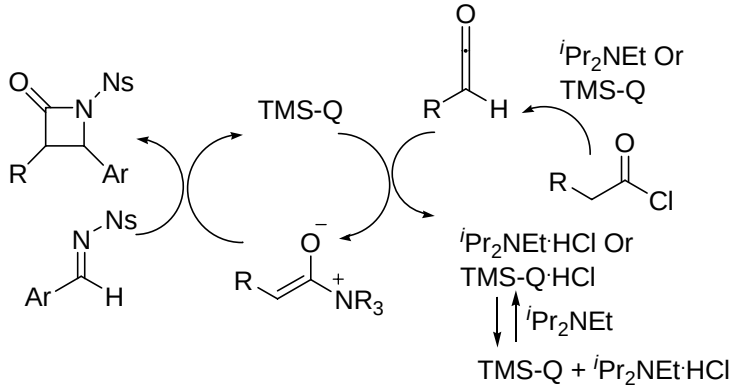
2.2.3 Discussion

2.2.3.1 Proposed Mechanism

Because of the extraordinary activity of simple ketene and mono-alkyl substituted ketenes, the lone pair electron of imine N atom will easily attack them even at low temperature. Just as previously mentioned, this is the first step of Staudinger reaction. In order to exclude this possible background reaction, some control experiments were also run (Scheme 17). Without the addition of alkaloid catalysts, NEt_3 and Hunig's base were added as base and nucleophile. Because of the steric hindrance of Hunig's base, which decreases the nucleophilicity, there was no reaction. On contrast, in situ formed ketene was attacked by nucleophilic NEt_3 and formed activated enolate. So, there should have no interference come from the ammonium salt. The possible mechanism is like this (Scheme 18). The ketene was in situ generated from acyl chloride through dehydrohalogenation reaction with Hunig's base. Then, it was attacked by chiral tertiary amine, which formed the zwitterionic intermediate. Due to the strong electron withdrawing ability of sulfonyl group, the nosylate protected imine was strongly electrophilic and attacked by the enolate quickly. The resulting intermediate did the conrotatory ring closure and released the catalyst. Based on Romo[26] and Lectka's[17b] observation, alkaloid catalyst can act as "proton shuttle" under reaction condition. It may dehydrohalogenate the acyl chloride and the salt will transfer the proton to the stronger base. Lectka reported that Hunig's base will compete with benzoylquinine as catalyst in reaction. In our system, such interference wasn't observed. In both of Lectka and Romo's system, the preferred solvent is toluene. The ammonium salt will precipitate and not interfere with the reaction in toluene. But the low solubility of substrates and catalyst in toluene will decrease the yield. In our system, polar solvent, such as THF, can be used.



Scheme 17 Control experiment

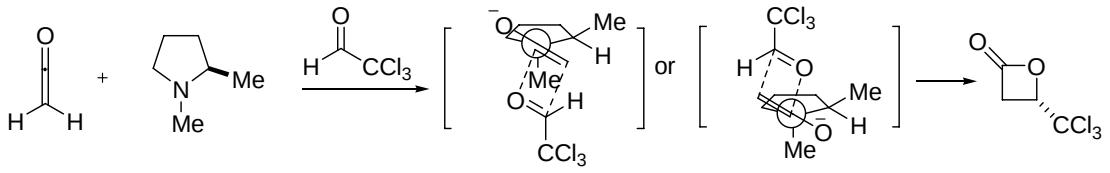


Scheme 18 Proposed Mechanism for β–lactam synthesis

2.2.3.2 Explanation for the Stereochemical Outcome

For the ketene-imine cycloaddition, the nosylate protected imine substrates are activated enough. Their reactivity is also verified by good yields (see Table 1, Table 3). For the high enantioselectivity achieved in reactions, it will be correlated to the distinguished structure of Cinchona alkaloid catalysts.

In 1982, Wynberg reported a ketene-chloral cycloaddition with quinidine as catalyst.[28] He proposed a model to explain the high enatioselectivity (scheme 19). In this model, he used 1, 2-dimethylpyrrolidine to take place quinidine. In the left TS, the chloral approaches the catalyst with the trichloromethyl group facing away from the methyl group of the catalyst to avoid steric strain. In the right TS, the CCl_3 group orients itself away from the ring methylene protons. From either TS, same product can be obtained. The author suggested that the chiral center adjacent to the nitrogen of quinuclidine part determines the chirality of product.



Scheme 19 Wynberg's stereochemical model

Although this model can partly explain the reaction, it is too simple to represent the unique structure of this kind of catalysts. Cinchona alkaloids are composed of two relatively rigid entities. One is an aromatic quinoline ring and the other is an aliphatic quinuclidine ring. They are connected by two C-C bonds. Although quinine and quinidine look like mirror images, they form a diastereomeric pair when the configuration at C_8 and C_9 are considered (Figure 7). Sometimes, they are called "pseudoenantiomers". In 1989, a detail conformational study of Cinchona alkaloids was reported by Wynberg's group.[29] Base on the data from NMR, molecular mechanic calculation and X-ray structure, four minimum energy conformations in solution were presented for quinidine (Figure 7). In two "open" conformations, the quinuclidine ring points away from the quinoline ring; in two "closed" conformations, the quinuclidine ring points toward the quinoline ring. The difference between two conformations in each category is the orientation of H_8 and H_9. In conformation 1, the orientation of two H atoms is almost anti relation; in conformation 2, a staggered orientation is formed.

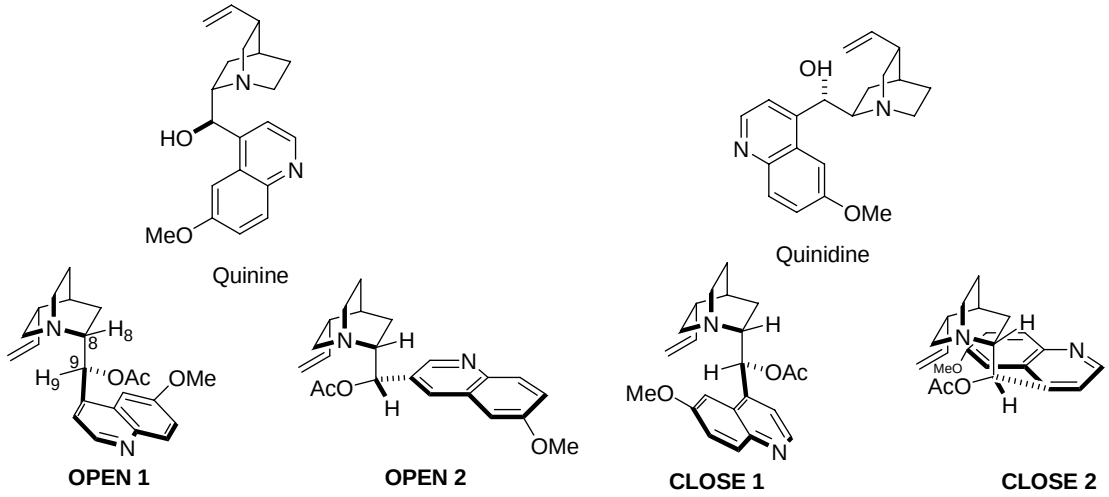


Figure 7. The four minimum energy conformations of quinidine

For the conformation of quinine and its derivatives, Wynberg proposed that if methoxy group is attached at C_9 position, the "close 1" conformation is preferred. In my calculation about the low energy conformation of TMS-quinine catalyst, the "open 2" conformation has the minimum energy (Figure 8).[30] In his research about the diastereoselectivity of the Mukaiyama aldol reaction, Heathcock[31] proposed that the enolate C=C bond antiperiplanar to the aldehyde C=O bond is the preferred transition state. Similarly, in the β–lactam synthesis, the imine C=N bond is also antiperiplanar to the enolate C=C bond, which can minimize the nonbonding interaction between nosylate group and quinoline ring of the catalyst. For the facial selectivity, enolate attacks the C=N bond from *re*-face will cause less strain of the transition state based on the data from calculation (Figure 9). Considering these two reasons, the high enatioselectivity can be explained.

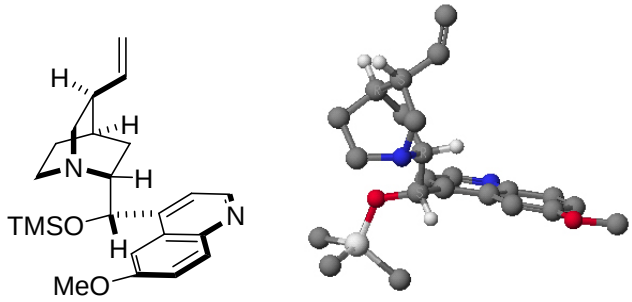


Figure 8. The minimum energy conformation of TMS-quinine catalyst

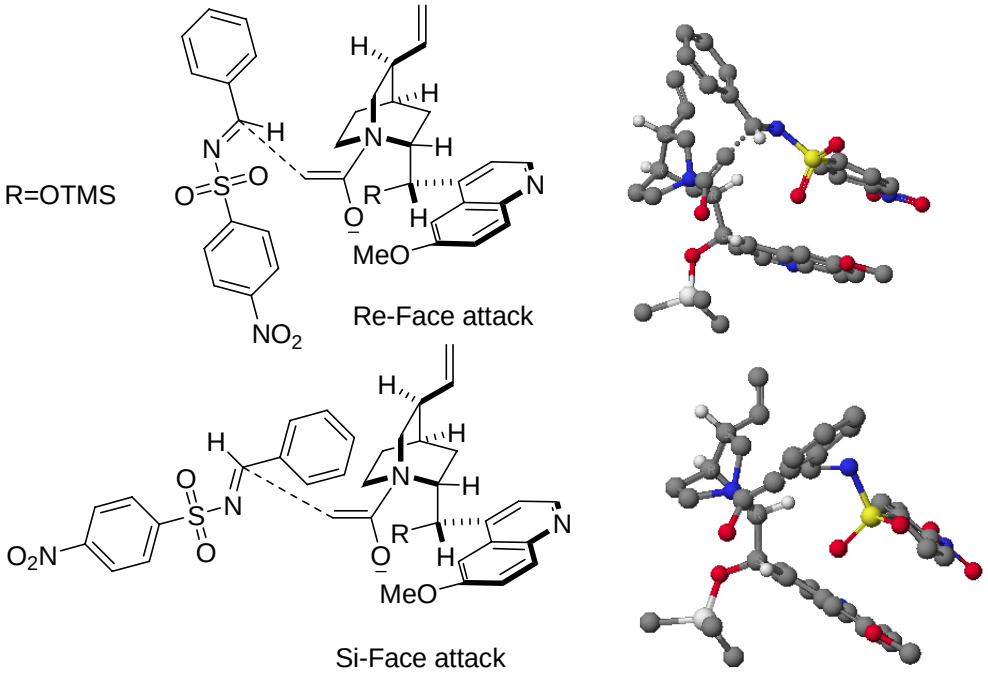


Figure 9. Explanation for stereochemical outcome

Just as mentioned previously, for methyl substituted ketene, the diastereoselectivity for the cycloaddition is not good. Although, for each diastereomer, the *ee* values are higher than 90%, the dr ration is only about 1:1. This can be explained by the models in Figure 10. From the result of calculation, the quinine moiety is preferably *trans* to the methyl substitution across the C=C bond. This makes the top face of the ketene C=C bond which is *re*-face is completely open to the imine electrophile. For the low diastereoselectivity, neither of the two faces of the imine

substrate can supply enough bias based on the data from the calculation. So, in order to increase the diastereoselectivity, we need to find a way to differentiate the steric environment around the C=N bond.

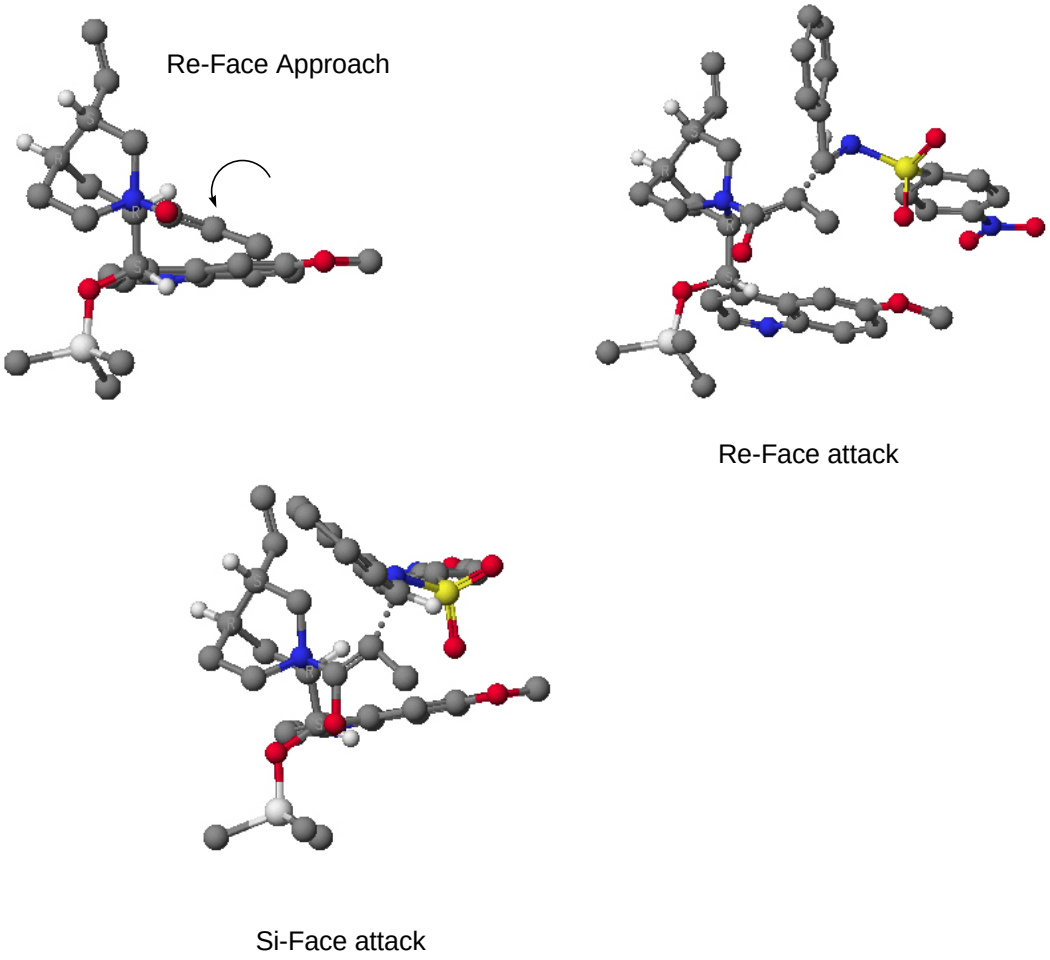
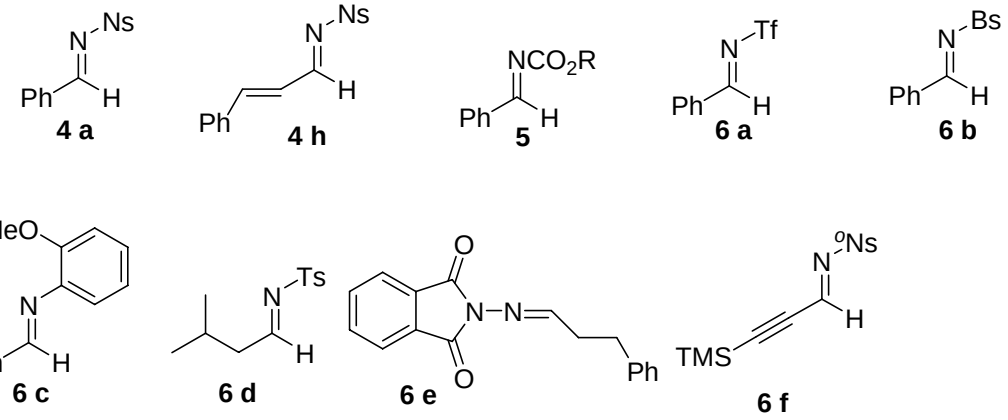


Figure 10. Explanation for the Enantioselectivity and Diastereoselectivity

2.2.3.3 Substitution group effect of imine substrate

From the experiment result, we can found that the properly activated imine substrate is very important for the success of β–lactam synthesis. If the activation group attached to N atom has too strong electron withdrawing ability, the imine is easily decomposed under the reaction condition (substrate **6a**). Benzenesulfonyl group is a good choice as activation group in our

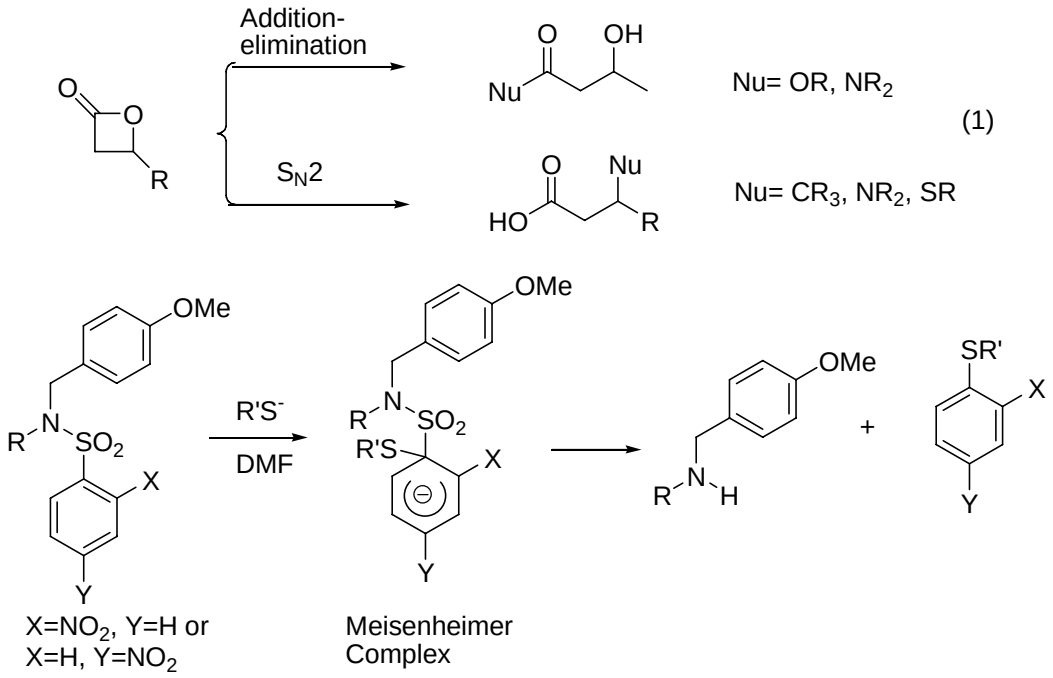
system. From Ns to Ts, although the electrophilic property of the imine substrate is decreased, good yields are still achieved. The decreased *ee* values can be contributed to the lower transition state difference (substrate **4, 6b, 6d**). When the C=N bond is more electronrich, the reactivity of imine decreases more (substrate **5, 6c, 6e**). With the addition of Lewis acid, the imine substrate **6** can be partly activated and get some conversion. For substrate **6c** and **6e**, there is no reaction at all even with Lewis acid activation. With the appropriate activation group at N atom, the substitution groups at C atom can be aryl group, alkyl group (substrate **4, 6d**). One exception is 4-methoxybenzyl group. No reaction was found for this substrate.



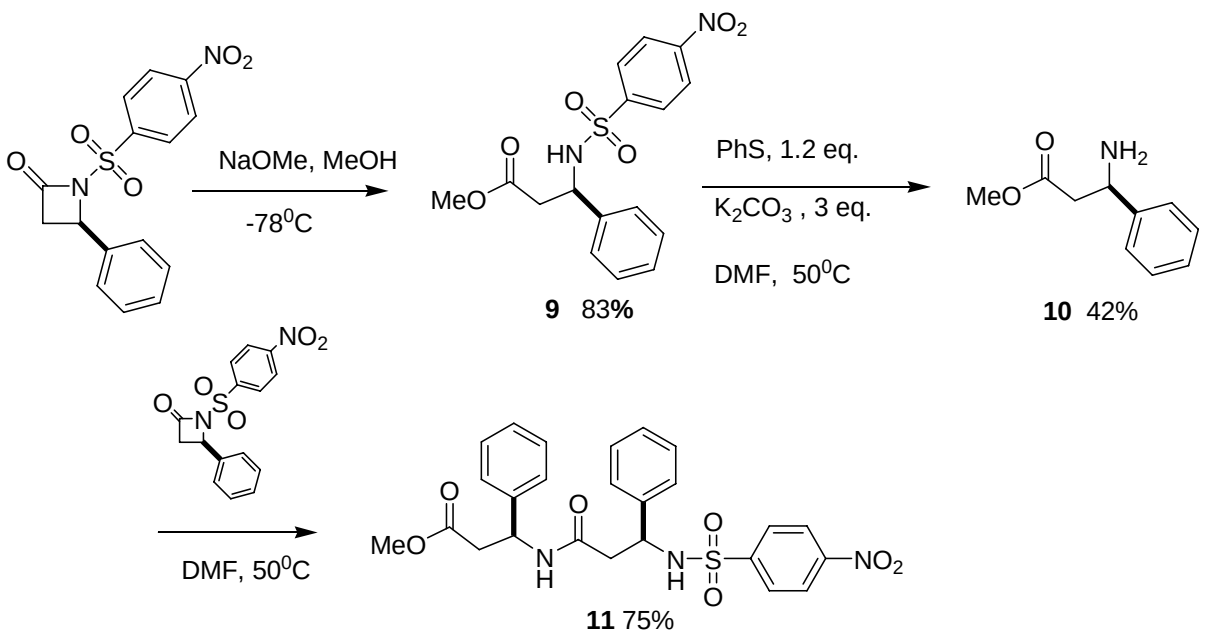
2.3 DERIVATIZATION OF β-LACTAM COMPOUNDS

With the optical pure β-lactam in hand, we wish to examine the possibility of derivatization of β-lactam compounds. Our group has developed some methods to open the β–lactone ring (eq 1).[32] Hard nucleophile, such as alkoxy group, will attack the carbonyl group of β–lactone. After the addition-elimination process, aldol product can be obtained. Soft nucleophile, such as mercapto group, will attack C_4 in a S_N2 fashion and get β–amino acids. Based on this observation, we want to extend this idea to the ring opening of β–lactam. Using some "hard

nucleophile", the 4-member ring can be opened at C_1 position and β–amino acid derivatives can be obtained. Originally, the standard Fukuyama's protocol was tried to remove the Ns group before the ring opening (Scheme 20).[22] Because the nucleophilic sulfur compounds which are used to form the Meisenheimer complexes with Ns group will also attack C_3 position of β–lactam and make starting material decomposed, successful deprotection is achieved only after the ring opening process. First, benzyl amine was tried and the ring opening process was successful. But, with two amide subunits in the structure, this compound was high polar and it was difficult to remove the nosylate group. We tried to use methoxy group to open the four member ring and then do the deprotection. This process was successful. After getting the amino ester, it was used to open another β-lactam ring, which was also successful (Scheme 21). So, we get a β-peptide from β-lactam. It is a starting point for the synthesis of useful β-peptide materials and a complement to the derivatization of β–lactone from AAC chemistry.



Scheme 20 Fukuyama's protocol for the deprotection of Ns group



Scheme 21 Derivatization of β–lactam compounds

2.4 CONCLUSION

In this project, we extend the successful protocol in AAC chemistry to the asymmetric β–lactam synthesis. With appropriate choice of activation group at N atom, the C=N bond of imine substrate can be electrophilic enough. The nucleophilic zwitterionic enolate formed from ketene-catalyst addition will attack the imine substrate quickly. In our system, benzenesulfonyl group is proved to be a good choice of activation group. Because of the small energy difference in the transition state for the reaction between alkyl group substituted ketene and activated imine substrate, low diastereoselectivity was obtained. If the electron withdrawing ability of activation group decreases, the reactivity of imine substrate is also decreased. The addition of Lewis acid has no obvious effect for increasing the reactivity of imine substrate.

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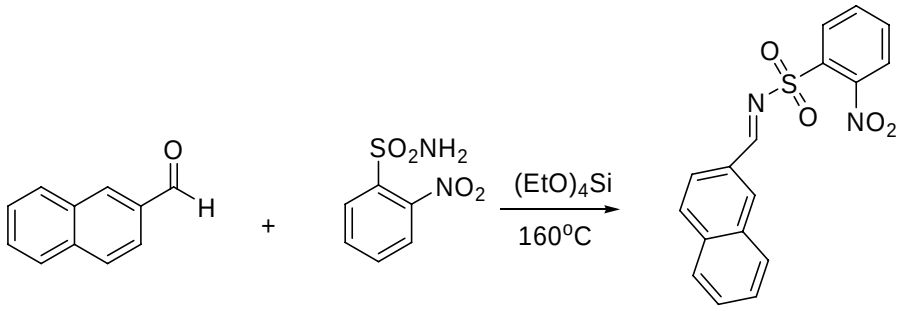
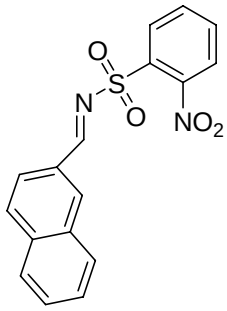
3.0 EXPERIMENTAL PROCEDURE

General Information: Optical rotations were measured on a Perkin-Elmer 241 digital polarimeter with a sodium lamp at ambient temperature and are reported as follows: $[\alpha]_\lambda$ (c g/100mL). Infrared spectra were recorded on a Nicolet Avatar 360 FT-IR spectrometer. NMR spectra were recorded on a Bruker Avance-300 (300 MHz) spectrometer with chemical shifts reported relative to residual $CHCl_3$ (7.27 ppm) for ^1H and $CDCl_3$ (77.23 ppm) for ^{13}C NMR spectra, CH_2Cl_2 (5.32 ppm) for ^1H and CD_2Cl_2 (54.00 ppm) for ^{13}C NMR spectra, DMSO (2.50 ppm) for ^1H and $(CD_3)_2SO$ (39.52 ppm) for ^{13}C NMR spectra. Analytical high performance liquid chromatography (HPLC) was performed on a Hewlett Packard 1100 liquid chromatograph equipped with a variable wavelength UV detector (deuterium lamp, 190-600 nm) using a Daicel Chiracel^{TM} AS-H column (250 x 4.6 mm) (Daicel Inc.) or Daicel Chiralpak^{TM} AD column (250 x 4.6 mm) (Daicel Inc.) and HPLC-grade isopropanol and hexanes as the eluting solvents. Unless otherwise stated, all reactions were carried out in dry glassware under a nitrogen atmosphere using standard inert atmosphere techniques for the manipulation of solvents and reagents. Anhydrous solvents (CH_2Cl_2, THF, diethyl ether and toluene) were obtained by passage through successive alumina and Q5 reactant-packed columns on a solvent purification system. Acetyl chloride and propyl chloride were purified according standard procedure. The other commercially available chemicals were directly used without further purification.

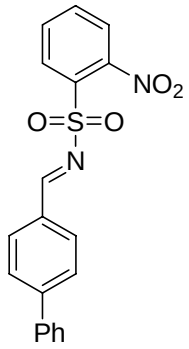
3.1 PREPARATION OF IMINE SUBSTRATES

General Procedure A: The general procedure is same as literature indicated.[22] A sulfonamide, an aldehyde (1.1 eq.), and tetraethyl orthosilicate (1.1 eq.) were combined in a flask with a Dean-Stark, and the mixture was heated at 160°C under nitrogen for 6h. After cooling to room temperature, the reaction mixture was dissolved in warm ethyl acetate, treated with *n*-hexane and allowed to stand at room temperature. The crystal were collected by filtration, washed with *n*-hexane, and dried.

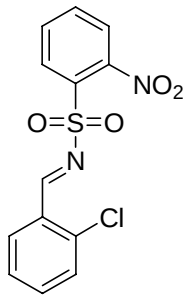




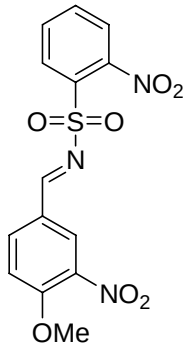
(E)-N-(naphthalen-2-ylmethylene)-2-nitrobenzenesulfonamide (4d): 2.02 g (10 mmol, 1.0 eq.) of sulfonamide, 1.72 g aldehyde (11 mmol, 1.1 eq.) and 2.45 ml (11 mmol, 1.1 eq.) of $(EtO)_4Si$ were heated in a flask equipped with a Dean-Stark apparatus for 6h. After cooling to ambient temperature, crystallization from EtOAc/hexane gave 2.64 g (78%) of the title compound as pale orange powder: mp 158-159°C; IR(KBr): 1587, 1570, 1535, 1366, 1163, 1055 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.24 (s, 1H), 8.44 (d, J = 6.3 Hz, 2H), 8.08 (dd, J = 8.6, 1.5 Hz 1H), 8.00 (d, J = 7.9 Hz, 1H), 7.94-7.89 (m, 2H), 7.85-7.79 (m, 3H), 7.70-7.58 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 154.8, 148.7, 137.4, 137.1, 134.7, 132.9, 132.7, 132.2, 132.1, 130.1, 129.8, 129.4, 128.3, 127.6, 124.9, 124.3; HRMS *m/z* calcd for $C_{17}H_{12}N_2O_4S$: 340.0518; found: 340.0512.



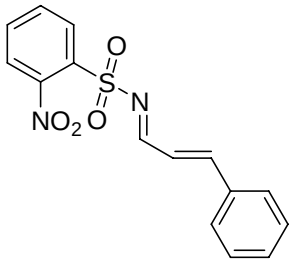
(E)-N-(biphenyl-4-ylmethylene)-2-nitrobenzenesulfonamide (4e): 4.04 g (20 mmol, 1.0 eq.) of sulfonamide, 3.83 g aldehyde (21 mmol, 1.05 eq.) and 4.91 ml (22 mmol, 1.1 eq.) of $(EtO)_4Si$ were heated in a flask equipped with a Dean-Stark apparatus for 6h. After cooling to ambient temperature, crystallization from EtOAc/hexane gave 5.19 g (71%) of the title compound as yellow powder: mp 159-161°C; IR(KBr): 1593, 1547, 1370, 1167, 1058 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 9. 15 (s, 1H), 8.30 (dd, J = 7.0, 1.9 Hz, 1H), 8.17 (d, J = 8.3, Hz 2H), 8.12-8.09 (m, 1H), 8.04-7.98 (m, 2H), 7.96-7.91 (m, 2H), 7.86-7.77(m, 2H), 7.54-7.42(m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.8, 148.0, 147.1, 138.4, 135.9, 133.4, 133.2, 132.6, 132.3, 131.2, 130.7, 129.7, 129.1, 128.9, 127.5, 127.3, 127.1, 125.0, 124.2; HRMS *m/z* calcd for $C_{19}H_{14}N_2O_4S$: 366.0674; found: 366.0672.



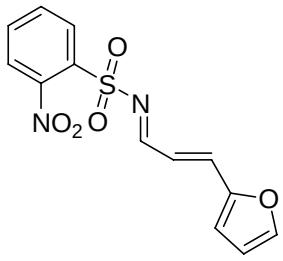
(E)-N-(2-chlorobenzylidene)-2-nitrobenzenesulfonamide (4f): 1.96 g (9.70 mmol, 1.0 eq.) of sulfonamide, 1.23 ml aldehyde (11 mmol, 1.1 eq.) and 2.45 ml (11 mmol, 1.1 eq.) of $(EtO)_4Si$ were heated in a flask equipped with a Dean-Stark apparatus for 6h. After cooling to ambient temperature, crystallization from EtOAc/hexane gave 2.00 g (64%) of the title compound as white needles: mp 167-168°C; IR(KBr): 1589, 1552, 1366, 1330,1164, 1122, 1057 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9. 58 (s, 1H), 8.40 (dd, J = 6.5, 2.9 Hz, 1H), 8.19 (d, J = 7.9, Hz 1H), 7.89-7.79 (m, 3H), 7.61-7.51 (m, 2H), 7.41-7.36 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 148.9, 139.9, 136.5, 135.0, 132.8, 132.3, 131.7, 130.9, 130.6, 129.8, 127.7, 125.1; HRMS *m/z* calcd for $(M^+ + H)$ $C_{13}H_{10}N_2O_4SCl$: 325.0050; found: 325.0058.



(E)-N-(4-methoxy-3-nitrobenzylidene)-2-nitrobenzenesulfonamide (4g): 1.97 g(9.75 mmol, 1.0 eq.) of sulfonamide, 1.99 g aldehyde(11 mmol, 1.1 eq.) and 2.45 ml (11 mmol, 1.1 eq.) of $(EtO)_4Si$ were heated in a flask equipped with a Dean-Stark apparatus for 6h. After cooling to ambient temperature, crystallization from CH_2Cl_2/hexane gave 1.80 g (51%) of the title compound as pale brown powder: mp 129-131°C; IR(KBr): 1597, 1538, 1364, 1326,1159, 1000 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.01 (s, 1H), 8.49 (d, J = 1.5 Hz, 1H), 8.41-8.36 (m, 1H), 8.34(dd, J=8.7, 1.3 HZ 1H), 7.87-7.76 (m, 3H), 7.26 (d, J=8.7 HZ 1H), 4.08(s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 158.1, 148.7, 140.4, 137.7, 135.1, 132.9, 132.3, 131.7, 128.5, 125.0, 124.7, 114.3, 57.4; HRMS *m/z* calcd for $C_{14}H_{11}N_3O_7S$: 365.0317; found: 365.0314.

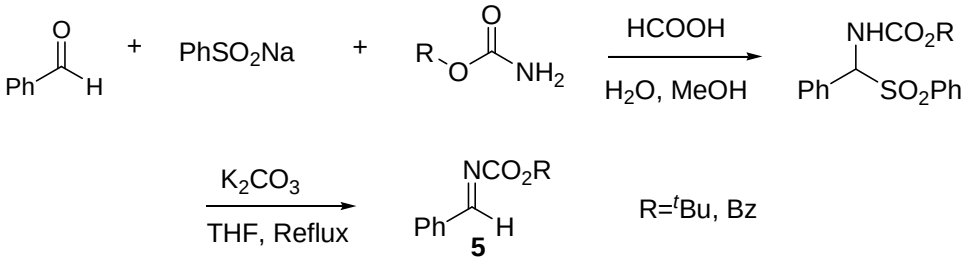


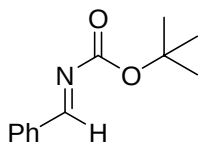
(E)-2-nitro-N-((E)-3-phenylallylidene)benzenesulfonamide (4h): 1.99 g(9.85 mmol, 1.0 eq.) of sulfonamide, 1.58 ml aldehyde(11 mmol, 1.1 eq.) and 2.45 ml (11 mmol, 1.1 eq.) of $(EtO)_4Si$ were heated in a flask equipped with a Dean-Stark apparatus for 6h. After cooling to ambient temperature, crystallization from EtOAc/hexane gave 2.23 g (72%) of the title compound as brown powder: mp 147-148°C; IR(KBr): 1579, 1540, 1362, 1321,1163, 1125, 1056 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.84(d, J = 9.5 Hz, 1H), 8.39-8.34 (m, 1H), 7.84-7.77 (m, 3H), 7.67 (d, J=15.7 HZ 1H), 7.63-7.60 (m, 2H), 7.51-7.43 (m, 3H), 7.07(dd, J = 15.7, 9.5 Hz 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 174.2, 157.0, 147.9, 135.7, 134.1, 133.1, 132.0, 131.2, 129.8, 129.2(2C), 129.1(2C), 124.9, 124.3; HRMS *m/z* calcd for $C_{15}H_{12}N_2O_4S$: 316.0518; found: 316.050.



(E)-N-((E)-3-(furan-2-yl)allylidene)-2-nitrobenzenesulfonamide (4i): 3.94 g(19.5 mmol, 1.0 eq.) of sulfonamide, 2.69 g aldehyde(22 mmol, 1.1 eq.) and 4.91 ml (22 mmol, 1.1 eq.) of $(EtO)_4Si$ were heated in a flask equipped with a Dean-Stark apparatus for 6h. After cooling to ambient temperature, crystallization from EtOAc/hexane gave 4.14 g (69%) solid compound. The solid was washed with 10 ml EtOAc and 1.76 g product was obtained. Later, 1.28 g solid was precipitated from the filtrate. The combined yield was 3.04 g (51%). The title compound is yellow powder: mp 148-149°C; IR(KBr): 1630, 1595, 1545, 1466, 1213, , 1164, 1122 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ8.73(d, J = 9.8 Hz, 1H), 8.38-8.33 (m, 1H), 7.84-7.75 (m, 3H), 7.62 (d, J=1.5 HZ 1H), 7.39 (d, J=15.4 HZ 1H), 6.92 (d, J=9.8 HZ 1H), 6.87(dd, J = 13.0, 6.5 Hz 1H), 6.58(dd, J = 3.5, 1.7 Hz 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 151.2, 148.7, 147.4, 140.5, 134.7, 132.8, 132.5, 132.2, 124.9, 122.1, 119.0, 113.7; HRMS *m/z* calcd for $C_{13}H_{10}N_2O_5S$: 306.0310; found: 306.0315.

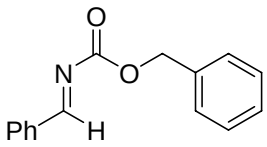
General Procedure B: The general procedure is same as literature indicated.[1] For the synthesis of **5b**, some modification was made. Because both of these two imines are known, full characterization isn't given.



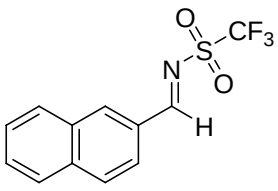


(E)-*tert*-butyl benzylidenecarbamate (5a): Sulfone product was prepared as follows: a mixture of benzaldehyde (5.3 g, 50 mmol), *t*-butyl carbamate (2.93 g, 25 mmol), sodium benzene sulfite (10.15 g, 62 mmol), and formic acid (2.3 g,

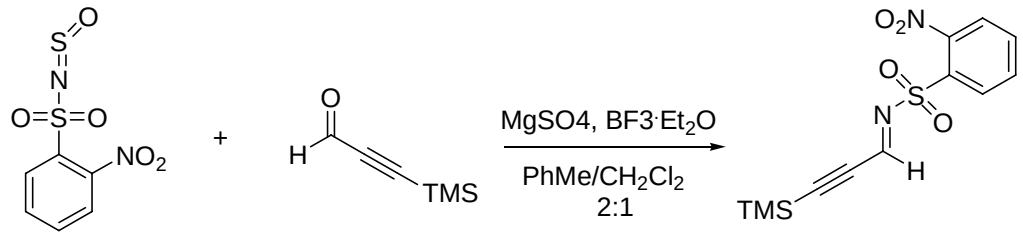
50 mmol) in 25 mL of methanol and 50 mL of water was stirred at room temperature for 21 h. The solid material was filtered, washed with water and ether, and then dried under reduced pressure to give 6.06 g (69%) of sulfone. A stirred mixture of 4.00 g (11.5 mmol) of sulfone and 9.40 g (68.0 mmol) of *dry* potassium carbonate in 134 mL of THF under argon was refluxed for 12 h. The mixture was then allowed to cool to room temperature and filtered through Celite, and the filtrate was concentrated to leave 2.36 g (100%) imine. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.94(s, 1H), 7.98-7.92 (m, 2H), 7.60-7.46 (m, 3H), 1.61(s, 9H).

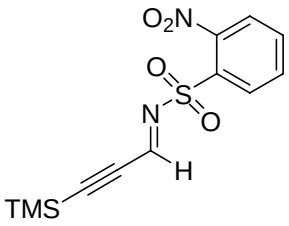


(E)-benzyl benzylidenecarbamate (5b): A mixture of benzaldehyde (2.12 g, 20 mmol), benzyl carbamate (3.02 g, 20 mmol), sodium benzene sulfite (3.61 g, 22 mmol) in 25 mL of fomic acid and 25 mL of water was stirred at room temperature for 14 h. The solid material was filtered, washed with water and ether, and then dried under reduced pressure to give 6.35 g (83 %) of sulfone. A stirred mixture of 6.35 g (16.64 mmol) of sulfone and 13.58 g (98.0 mmol) of *dry* potassium carbonate in 150 mL of THF under argon was refluxed for 12 h. The mixture was then allowed to cool to room temperature and filtered through Celite, and the filtrate was concentrated to leave 3.98 g (100%) imine. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.04(s, 1H), 8.02-8.00 (m, 2H), 7.57-7.33 (m, 8H), 5.42 (s, 2H).



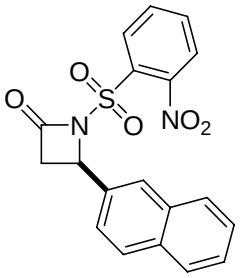
(E)-trifluoro-N-(naphthalen-2-ylmethylene)methanesulfonamide (6a): This compound was synthesized according to known procedure.[2] Because this is a known compound, full characterization isn't provided. ^{1}H NMR (300 MHz, $CDCl_3$) δ9.32 (s, 1H), 8.51 (s, 1H), 8.14 (dd, J = 8.6, 1.7 Hz 1H), 8.05 (d, J = 6.0 Hz 1H), 8.00 (d, J =8.8 Hz 1H), 7.96 (d, J = 8.2 Hz 1H), 7.76 (td, J = 6.9, 1.2 Hz 1H), 7.67 (td, J = 8.1, 1.2 Hz 1H).





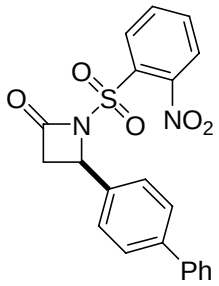
(E)-2-nitro-N-(3-(trimethylsilyl)prop-2-ynylidene)benzenesulfonamide (6f): This compound was synthesized according to known procedure.[3] A suspension of MgSO4 (0.7062 g, 5.87 mmol) in 10 ml toluene was added by a solution of *N*-Sulfinyl-*o*-nitrobenzenesulfonamide (0.2558 g, 1.03 mmol) in 5 ml dry CH_2Cl_2. After cooling to -30 ^{0}C, the aldehyde (0.2020 g, 1.6 mmol) and $BF_3{\cdot}Et_2O$ (1 mmol) were added subsequently. The solution was stirred for 3 hours. Then, the solvent was removed by high vacuum. The compound (95.3 mg, yield 30%) was recrystallized from CH_2Cl_2/Hexane as pale yellow needles. ^{1}H NMR (300 MHz, $CDCl_3$) δ8.40-8.36 (m, 1H), 8.29 (s, 1H), 7.87-7.80 (m, 3H), 0.28 (s, 9H).

3.2 SYNTHESIS OF β–LACTAM COMPOUNDS



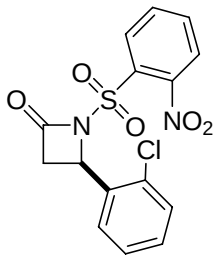
(R)-4-(naphthalen-2-yl)-1-(2-nitrophenylsulfonyl)azetidin-2-one (7d): To a solution of 0.0205 g (0.052 mmol, 0.05 eq.) of TMS-quinine and 0.376 g (1.1 mmol, 1.0 eq.) of imine in 10 ml of THF at -78°C was added 0.44 ml(2.5 mmol, 2.5 eq.) of *N, N*-diisopropylethylamine. Then, a solution of 0.142 ml (2.0 mmol, 2.0 eq.) of acetyl chloride in 0.5 ml THF was added over 2h via a syringe pump. After being stirred at -78°C for 5h, the reaction mixture was poured into 60 ml of CH_2Cl_2 and 15 ml of water. The organic layer was separated and subsequently washed with 10 ml saturated Na_2CO_3 solution and 10 ml of brine. The organic layers was dried (Na_2SO_4), filtered and concentrated in *vacuo*. Crystallization from CH_2Cl_2/hexane gave 0.240 g (57%) of the title

compound as pale yellow powder: mp 147-148°C; Separation of the enantiomers by Chiral HPLC(Daicel Chiralpak^{TM} AD column , flow rate 1.0 ml/min, 40% ^{i}PrOH, 60% hexane, Tr 17.0(R) and 15.1(S) min) provided the enantiomer ratio: (R) : (S) =99.5: 0.5(99% ee); $[\alpha]_D$ +252° (*c* 1.32, DMF); IR(KBr): 1812, 1547, 1367, 1173, 1137, 1043 cm^{-1}; ^{1}H NMR (300 MHz, CD_2Cl_2) δ7.89-7.74 (m, 5H), 7.70-7.59 (m, 2H), 7.55-7.49 (m, 2H), 7.44 (dd, J = 8.6, 1.5 Hz 1H), 7.39-7.34(m, 1H), 5.51(dd, J = 6.4, 3.5 Hz 1H), 3.67(dd, J =16.2, 6.4 Hz 1H), 3.27(dd, J = 16.2, 3.5 Hz 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.9, 147.2, 136.0, 133.8, 132.9, 132.7, 132.4, 130.7, 129.8, 128.5, 127.9, 127.5, 126.8, 126.6, 126.5, 124.7, 123.7, 57.9, 46.4; HRMS *m/z* calcd for $C_{19}H_{14}N_2O_5S$: 382.0613; found: 382.0623.

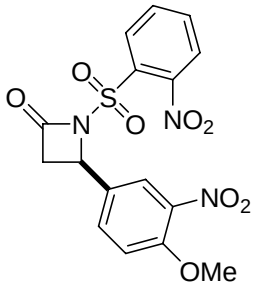


(R)-4-(biphenyl-4-yl)-1-(2-nitrophenylsulfonyl)azetidin-2-one (7e): To a solution of 0.0235 g (0.059 mmol, 0.05 eq.) of TMS-quinine and 0.373 g (1.02 mmol, 1.0 eq.) of imine in 10 ml of THF at -78°C was added 0.44 ml(2.5 mmol, 2.5 eq.) of *N, N*-diisopropylethylamine. Then, a solution of 0.142 ml (2.0 mmol, 2.0 eq.) of acetyl chloride in 0.5 ml THF was added over 2h via a syringe pump. After being stirred at -78°C for 5h, the reaction mixture was poured into 50 ml of EtOAc and 15 ml of water. The organic layer was separated and subsequently washed with 15 ml saturated Na_2CO_3 solution and 10 ml of brine. The organic layers was dried (Na_2SO_4), filtered and concentrated in *vacuo*. Crystallization from CH_2Cl_2/hexane gave 0.333 g (80%) of the title compound as pale yellow powder: mp 138-139°C; Separation of the enantiomers by Chiral HPLC(Daicel Chiralpak^{TM} AD column , flow rate 1.0 ml/min, 40% ^{i}PrOH, 60% hexane, Tr 25.4(R) and 22.5(S) min) provided the enantiomer ratio: (R) : (S) =99.5: 0.5(99% ee); $[\alpha]_D$ +338° (*c* 1.38, CH_2Cl_2); IR(KBr): 1808, 1546, 1376, 1171, 1120, 1047 cm^{-1}; ^{1}H NMR (300 MHz, CD_2Cl_2) δ7.92 (d, J = 7.8 Hz 1H), 7.73(d, J = 3.9 Hz 2H), 7.59-7.43 (m, 9H), 7.40-7.35(m, 1H),

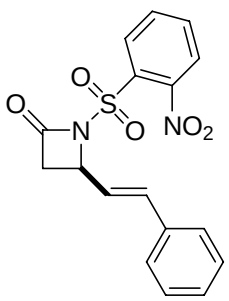
5.41(dd, J = 6.4, 3.5 Hz 1H), 3.63(dd, J =16.2, 6.4 Hz 1H), 3.22(dd, J = 16.2, 3.5 Hz 1H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 163.1, 147.9, 142.1, 140.2, 135.4, 135.2, 132.3, 132.0, 131.2, 129.0(2C), 127.8, 127.5(2C), 127.3(2C), 127.1(2C), 124.5, 57.9, 47.1; HRMS *m/z* calcd for $C_{21}H_{16}N_2O_5S$: 408.0780; found: 408.0774.



(R)-4-(2-chlorophenyl)-1-(2-nitrophenylsulfonyl)azetidin-2-one (7f): To a solution of 0.0431 g (0.109 mmol, 0.1 eq.) of TMS-quinine and 0.329 g (1.015 mmol, 1.0 eq.) of imine in 10 ml of CH_2Cl_2 at -78°C was added 0.44 ml(2.5 mmol, 2.5 eq.) of *N, N*-diisopropylethylamine. Then, a solution of 0.142 ml (2.0 mmol, 2.0 eq.) of acetyl chloride in 0.5 ml CH_2Cl_2 was added over 2h via a syringe pump. After being stirred at -78°C for 5h, the reaction mixture was poured into 50 ml of EtOAc and 15 ml of water. The organic layer was separated and subsequently washed with 15 ml saturated Na_2CO_3 solution and 10 ml of brine. The organic layers was dried (Na_2SO_4), filtered and concentrated in *vacuo*. Crystallization from $CHCl_3$/hexane gave 0.296 g (80%) of the title compound as white needles: mp 148-149°C; Separation of the enantiomers by Chiral HPLC(Daicel Chiralpak^{TM} AD column , flow rate 1.0 ml/min, 40% ^{i}PrOH, 60% hexane, Tr 10.0(R) and 8.7(S) min) provided the enantiomer ratio: (R) : (S) =98.0: 2.0(96% ee); $[\alpha]_D$ +467° (*c* 1.27, $CHCl_3$); IR(KBr): 1797, 1544, 1359, 1176, 1131, 1058 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ8.12 (dd, J = 7.8, 1.2 Hz 1H), 7.85-7.68 (m, 3H), 7.59-7.56(m, 1H), 7.41-7.38(m, 1H), 7.33-7.24(m, 2H), 5.80(dd, J = 6.6, 3.5 Hz 1H), 3.69(dd, J =16.2, 6.6 Hz 1H), 3.08(dd, J = 16.2, 3.5 Hz 1H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 163.5, 148.6, 136.2, 135.0, 133.1, 133.0, 132.8, 131.3, 130.6, 130.4, 128.0, 127.8, 125.1, 56.2, 47.0; HRMS *m/z* calcd for $C_{15}H_{11}N_2O_5SCl$: 366.0077; found: 366.0091.

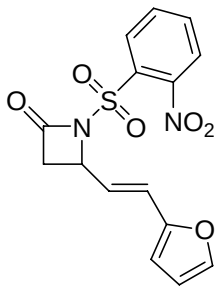


(R)-4-(4-methoxy-3-nitrophenyl)-1-(2-nitrophenylsulfonyl)azetidin-2-one (7g): To a solution of 0.0231 g (0.058 mmol, 0.1 eq.) of TMS-quinine and 0.189 g (0.518 mmol, 0.5 eq.) of imine in 10 ml of THF at -78°C was added 0.44 ml(2.5 mmol, 2.5 eq.) of *N, N*-diisopropylethylamine. Then, a solution of 0.142 ml (2.0 mmol, 2.0 eq.) of acetyl chloride in 0.5 ml CH_2Cl_2 was added over 2h via a syringe pump. After being stirred at -78°C for 5h, the reaction mixture was poured into 60 ml of CH_2Cl_2 and 10 ml of water. The organic layer was separated and subsequently washed with 15 ml saturated Na_2CO_3 solution and 10 ml of brine. The organic layers was dried (Na_2SO_4), filtered and concentrated in *vacuo*. Crystallization from CH_2Cl_2/hexane gave 0.172 g (82%) of the title compound as pale yellow powder: mp 84-86°C; Separation of the enantiomers by Chiral HPLC (Daicel Chiralpak^{TM} AD column , flow rate 1.0 ml/min, 40% ^{i}PrOH, 60% hexane, Tr 27.3(R) and 29.6(S) min) provided the enantiomer ratio: (R) : (S) =99.5: 0.5(99% ee); $[\alpha]_D$ +261° (*c* 1.78, $CHCl_3$); IR(KBr): 1802, 1537, 1366, 1284, 1173, 1128 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ8.15 (d, J = 7.4 Hz 1H), 7.90 (d, J=2.2 HZ, 1H), 7.84-7.68(m, 4H), 7.11 (d, J=8.7 HZ, 1H), 5.46(dd, J = 6.4, 3.4 Hz 1H), 3.97(s, 1 H), 3.64(dd, J =16.2, 6.4 Hz 1H), 3.15(dd, J = 16.2, 3.4 Hz 1H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 162.8, 153.6, 148.2, 139.8, 135.7, 132.7, 132.6, 132.5, 131.4, 129.2, 124.8, 124.2, 114.5, 57.1, 57.0, 46.9; HRMS *m/z* calcd for ($M+Na^+$) $C_{16}H_{13}N_3O_8SNa$: 430.0300; found: 430.0321.



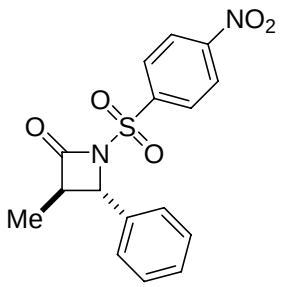
(R)-(E)-1-(2-nitrophenylsulfonyl)-4-styrylazetidin-2-one (7h): To a solution of 0.0437 g (0.11 mmol, 0.1 eq.) of TMS-quinine and 0.299 g (0.95 mmol, 1.0 eq.) of imine in 10 ml of CH_2Cl_2 at -78°C was added 0.44 ml(2.5 mmol, 2.5 eq.) of *N, N*-diisopropylethylamine. Then, a solution of 0.142 ml (2.0 mmol, 2.0 eq.) of acetyl chloride in 0.5 ml CH_2Cl_2 was added over 2h

via a syringe pump. After being stirred at -78°C for 5h, the reaction mixture was poured into 60 ml of CH_2Cl2 and 15 ml of water. The organic layer was separated and subsequently washed with 15 ml saturated Na_2CO_3 solution and 10 ml of brine. The organic layers was dried (Na_2SO_4), filtered and concentrated in *vacuo*. Crystallization from $CHCl_3$/hexane gave 0.088 g (26%) of the title compound as pale yellow needles: mp 108-110°C; Separation of the enantiomers by Chiral HPLC (Daicel Chiralpak^{TM} AD column , flow rate 1.0 ml/min, 40% ^{i}PrOH, 60% hexane, Tr 6.6(R) and 8.9(S) min) provided the enantiomer ratio: (R) : (S) =95: 5(90% ee); $[\alpha]_D$ +° (*c* 1.78, $CHCl_3$); IR(KBr): 1622, 1580, 1314, 1289, 1174, 1153, 1090 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ8.29 (d, J = 7.4 Hz 1H), 7.82-7.69(m, 3H), 7.40-7.28(m, 5H), 6.84(d, J=15.7 HZ 1H), 6.26(dd, J=15.7, 8.5 HZ 1H), 5.13(ddd, J =8.5, 6.3, 3.4 Hz 1H), 3.45(dd, J =16.1, 6.3 Hz 1H), 3.015(dd, J = 16.1, 3.4 Hz 1H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 163.2, 143.8, 136.4, 135.5, 135.3, 132.8, 132.6, 132.0, 128.9(2C), 127.1(2C), 125.0, 124.7, 58.3, 44.5; HRMS *m/z* calcd for $C_{17}H_{14}N_2O_5S$: 358.0623; found: 358.0625.



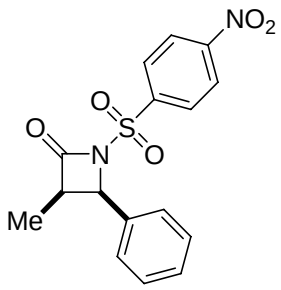
(E)-4-(2-(furan-2-yl)vinyl)-1-(2-nitrophenylsulfonyl)azetidin-2-one (7i): To a solution of 0.0443 g (0.11 mmol, 0.1 eq.) of TMS-quinine and 0.287 g (0.94 mmol, 1.0 eq.) of imine in 10 ml of CH_2Cl_2 at -78°C was added 0.44 ml(2.5 mmol, 2.5 eq.) of *N, N*-diisopropylethylamine. Then, a solution of 0.142 ml (2.0 mmol, 2.0 eq.) of acetyl chloride in 0.5 ml CH_2Cl_2 was added over 2h via a syringe pump. After being stirred at -78°C for 5h, the reaction mixture was poured into 60 ml of CH_2Cl2 and 15 ml of water. The organic layer was separated and subsequently washed with 15 ml saturated Na_2CO_3 solution and 10 ml of brine. The organic layers was dried (Na_2SO_4), filtered and concentrated in *vacuo*. Crystallization from $CHCl_3$/hexane gave 0.241 g (74%) of the title compound as yellow powder: mp 113-115°C; IR(KBr): 1703, 1543, 1368,

1249, 1180, 1151, 1126, 998 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ8.47-8.43(m, 1H), 7.79-7.75(m, 3H), 7.42(dd, J=1.8, 0.8 HZ 1H), 6.43(d, J=3.2 HZ 1H), 6.36(dd, J=3.2, 1.8 HZ 1H), 6.21(ddd, J =9.4, 5.9, 3.2 Hz 1H), 6.02(d, J=5.9 HZ 1H), 5.98(ddd, J =7.7, 5.6, 2.2 Hz 1H), 3.39(dd, J=21.1, 2.2 HZ 1H), 3.04(ddd, J=21.1, 5.6, 0.8 HZ 1H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 150.9, 143.6, 135.5, 134.9, 133.2, 132.1, 124.7, 124.6, 123.0, 110.8, 109.1, 54.9, 34.7; HRMS *m/z* calcd for $C_{15}H_{12}N_2O_6S$: 348.0416; found: 348.0416.

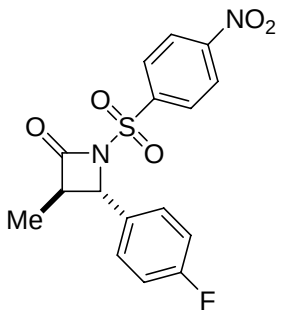


(3R,4S)-3-methyl-1-(4-nitrophenylsulfonyl)-4-phenylazetidin-2-one (8a): To a solution of 0.0865 g (0.22 mmol, 0.1 eq.) of TMS-quinine and 0.578 g (1.99 mmol, 1.0 eq.) of imine in 15 ml of CH_2Cl_2 at -78°C was added 0.88 ml(5.0 mmol, 2.5 eq.) of *N, N*-diisopropylethylamine. Then, a solution of 0.350 ml (4.0 mmol, 2.0 eq.) of acetyl chloride in 1.0 ml CH_2Cl_2 was added over 2h via a syringe pump. After being stirred at -78°C for 14h, the reaction mixture was poured into 50 ml of EtOAc and 15 ml of water. The organic layer was separated and subsequently washed with 15 ml saturated Na_2CO_3 solution and 10 ml of brine. The organic layers was dried (Na_2SO_4), filtered and concentrated in *vacuo*. Crystallization from CH_2Cl_2/hexane gave 0.593 mg (86%) of the mixture of two diastereomers as pale yellow powder. Carefully recrystalization from CH_2Cl_2/hexane gave 81.6 mg (11.8%) title compound as pale yellow prisms. The mother liquid was removed organic solvent in *vacuo*. The resulting mixture of diastereomers was separated by ISCO (15-30% 6min, 30% 15 min, EtOAc/Hexane), which gave 0.084 g (12%) title compound as pale yellow powder. mp 160-161 °C; Separation of the enantiomers by Chiral HPLC (Daicel Chiracel^{TM} AS-H column , flow rate 0.5 ml/min, 50% ^{i}PrOH, 50% hexane, Tr 22.1 (S) and 26.8 (R) min) provided the enantiomer ratio: (R): (S) =95.5: 4.5 (91 % ee); $[\alpha]_D$ -97° (*c* 0.80, DMF);IR(KBr): 1806, 1535, 1368, 1351, 1168, 1138, 1106, 1084, 740 cm^{-1}; ^1H NMR (300 MHz,

$CDCl_3$) δ8.25(d, J=9.1 Hz 2H), 7.85(d, J=9.1 Hz 2H), 7.40-7.32 (m, 3H), 7.20-7.16 (m, 2H), 4.73 (d, J=2.9 HZ 1H), 3.29(qd, J =7.5, 3.2, Hz 1H), 1.44(d, J=7.4 HZ, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 167.7, 151.2, 144.6, 135.9, 129.7, 129.3 (2C), 129.1 (2C), 127.3 (2C), 124.7 (2C), 65.9, 55.2, 12.7; HRMS *m/z* calcd for $C_{13}H_{10}N_2O_4S$: 291.0440; found:291.0438.

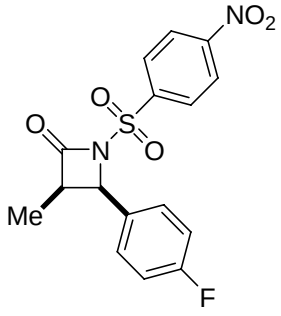


(**3R,4R)-3-methyl-1-(4-nitrophenylsulfonyl)-4-phenylazetidin-2-one (8a'**): The rest mixture of diastereomers was separated by ISCO. 0.098 g (14%) title compound was gained as pale yellow powder: mp 144-146 °C; Separation of the enantiomers by Chiral HPLC (Daicel Chiracel^{TM} AS-H column , flow rate 0.5 ml/min, 50% ^{i}PrOH, 50% hexane, Tr 22.0 (R) and 37.9 (S) min) provided the enantiomer ratio: (R) : (S) =99.5: 0.5 (98 % ee); $[\alpha]_D$ +144° (*c* 0.51, DMF); IR(KBr): 1798, 1533, 1368, 1350, 1180, 1136, 1086, 1051, 739 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ8.36(d, J=8.6 Hz 2H), 8.05(d, J=8.6 Hz 2H), 7.38-7.32 (m, 3H), 7.14-7.11 (m, 2H), 5.29 (d, J=6.8 HZ 1H), 3.71(qd, J =14.8, 7.3, Hz 1H), 0.83 (d, J=7.7 HZ, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 167.9, 151.4, 144.6, 133.8, 129.7, 129.4 , 129.0, 127.6, 124.9, 62.0, 51.1, 9.6; HRMS *m/z* calcd for $C_{13}H_{10}N_2O_4S$: 291.0440; found:291.0438.



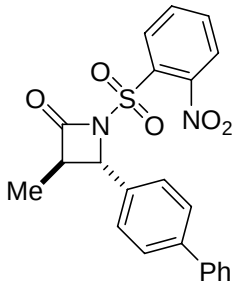
(3R,4S)-4-(4-fluorophenyl)-3-methyl-1-(4-nitrophenylsulfonyl)azetidin-2-one (8b): To a solution of 0.0888 g (0.22 mmol, 0.1 eq.) of TMS-quinine and 0.774 g (2.51 mmol, 1.0 eq.) of imine in 15 ml of CH_2Cl_2 at -78°C was added 0.88 ml (5.0 mmol, 2.5 eq.) of *N, N*-diisopropylethylamine. Then, a solution of 0.350 ml (4.0 mmol, 2.0 eq.) of acetyl chloride in 1.0 ml CH_2Cl_2 was added over 2h via a syringe pump. After being stirred at -78°C for 14h, the reaction mixture was poured into 50 ml of EtOAc and 15 ml of water. The organic layer was separated and subsequently washed with 15 ml saturated Na_2CO_3

solution and 10 ml of brine. The organic layers was dried (Na_2SO_4), filtered and concentrated in *vacuo*. Crystallization from CH_2Cl_2/hexane gave 0.447 g (49%) of the title compound as pale yellow powder. The mother liquid was remove the solvent in *vacuo* and recrystallized from CH_2Cl_2/hexane, which gave 0.356 g mixture of diastereomers. The mixture was separated by ISCO (5-15% 5 min, 15-25% 5 min, 25% 12 min, EtOAc/Hexane). Another 0.064 g (7%) title compound was obtained. mp 162-163 °C; Separation of the enantiomers by Chiral HPLC (Daicel Chiracel™ AS-H column , flow rate 0.5 ml/min, 50% ^{i}PrOH, 50% hexane, Tr 23.4 (R) and 28.8 (S) min) provided the enantiomer ratio: (R) : (S) =99: 1 (98 % ee); $[\alpha]_D$ -136° (*c* 0.84, DMF); IR(KBr): 1806, 1609, 1535, 1512, 1367, 1350, 1236, 1168, 1084, 893, cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ8.30 (d, J=8.8 Hz, 2H), 7.88 (d, J=8.8 Hz, 2H), 7.26-7.21 (m, 2H), 7.08-6.99 (m, 2H), 4.69(d, J=3.3 HZ 1H), 3.27 (qd, J =7.4, 3.3 Hz 1H), 1.36 (d, J=7.7 HZ, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 167.5, 165.0, 161.7, 151.7, 144.4, 131.8, 129.1, 129.0, 128.9 (2C), 124.7 (2C), 116.3, 116.0, 65.0, 55.2, 12.5; HRMS *m/z* calcd for $C_{16}H_{13}N_2O_5S$: 364.0529; found:364.0532.

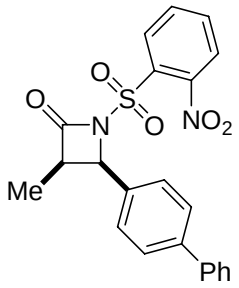


(3R,4R)-4-(4-fluorophenyl)-3-methyl-1-(4-nitrophenylsulfonyl)azetidin-2-one (8b'): The mixture was separated by ISCO and obtained 0.120 g (13%) title compound as pale yellow powder. mp 164-165 °C; Separation of the enantiomers by Chiral HPLC(Daicel Chiracel™ AS-H column , flow rate 0.5 ml/min, 50% ^{i}PrOH, 50% hexane, Tr 20.2 (R) and 25.4 (S) min) provided the enantiomer ratio: (R) : (S) =99.5 : 0.5 (99 % ee); $[\alpha]_D$ +209° (*c* 0.82, DMF); IR(KBr): 1801, 1608, 1534, 1512, 1369, 1309, 1231, 1179, 1135, 857 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ8.39 (d, J=9.0 Hz, 2H), 8.10 (d, J=9.0 Hz, 2H), 7.18-7.13 (m, 2H), 7.09-7.02 (m, 2H), 5.27 (d, J=6.8 HZ, 1H), 3.68 (qd, J =7.7,

6.8 Hz, 1H), 0.82 (d, J=7.7 HZ, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 167.6, 164.8, 161.5, 151.3, 144.3, 129.7, 129.3 (2C), 129.2 (2C), 124.8, 116.0, 115.7, 116.0, 61.1, 50.9, 9.5; HRMS *m/z* calcd for $C_{16}H_{13}N_2O_5S$: 364.0529; found:364.0532.



(3R,4S)-4-(biphenyl-4-yl)-3-methyl-1-(4-nitrophenylsulfonyl)azetidin-2-one (8d): To a solution of 0.0861 g (0.22 mmol, 0.1 eq.) of TMS-quinine and 0.730 g (2.0 mmol, 1.0 eq.) of imine in 15 ml of CH_2Cl_2 at -78°C was added 0.88 ml (5.0 mmol, 2.5 eq.) of *N, N*-diisopropylethylamine. Then, a solution of 0.350 ml (4.0 mmol, 2.0 eq.) of acetyl chloride in 1.0 ml CH_2Cl_2 was added over 2h via a syringe pump. After being stirred at -78°C for 14h, the reaction mixture was poured into 50 ml of EtOAc and 15 ml of water. The organic layer was separated and subsequently washed with 15 ml saturated Na_2CO_3 solution and 10 ml of brine. The organic layers was dried (Na_2SO_4), filtered and concentrated in *vacuo*. Crystallization from CH_2Cl_2/hexane gave 0.561 g (66%) of the mixture of diastereomers as pale yellow powder. The mixture was separated by ISCO (5-15 % 5 min, 15-30 % 5 min, 30 % 12 min, EtOAc/Hexane). 0.105 g (12.4 %) title compound was obtained as pale yellow powder: mp 150-152 °C; Separation of the enantiomers by Chiral HPLC(Daicel Chiralpak^{TM} AD column , flow rate 1.0 ml/min, 40% ^{i}PrOH, 60% hexane, Tr 12.2 (R) and 14.5 (S) min) provided the enantiomer ratio: (R) : (S) =99.5: 0.5 (99 % ee); $[\alpha]_D$ -215° (*c* 1.00, DMF); IR(KBr): 1798, 1542, 1377, 1124, 1055, 845 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, J=7.5 Hz, 1H), 7.82-7.75 (m, 2H), 7.67-7.53 (m, 6H), 7.50-7.37 (m, 4H), 5.06 (d, J=3.2 HZ, 1H), 3.39 (qd, J =7.4, 3.3 Hz, 1H), 1.47 (d, J=7.4 HZ, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.0, 142.2, 140.3, 135.3, 135.1, 132.7, 132.4, 131.7, 129.0 (2C), 127.8 (2C), 127.2 (2C), 127.1 (2C), 124.6, 66.3, 55.5, 12.6; HRMS *m/z* calcd for $C_{22}H_{18}N_2O_5S$: 422.0936; found:422.0934.



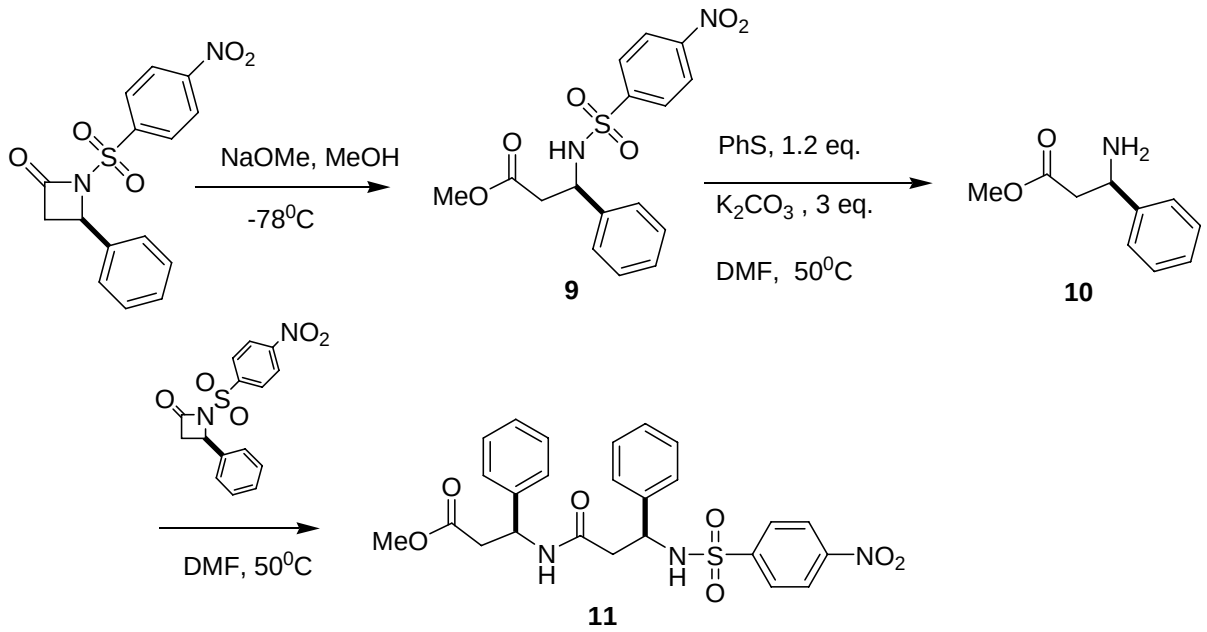
(3R,4R)-4-(biphenyl-4-yl)-3-methyl-1-(2-nitrophenylsulfonyl)azetidin-2-one (8d'): The mixture of diastereomers was separated by ISCO (5-15 % 5 min, 15-30 % 5 min, 30 % 12 min, EtOAc/Hexane). 0.186 g (22.1 %) title compound was obtained as pale yellow powder: mp 156-158 °C; Separation of the enantiomers by Chiral HPLC (Daicel Chiralpak^{TM} AD column , flow rate 1.0 ml/min, 40% ^{i}PrOH, 60% hexane, Tr 20.9 (R) and 13.1 (S) min) provided the enantiomer ratio: (R) : (S) =92.5: 7.5 (85 % ee); $[\alpha]_D$ +338° (*c* 1.07, DMF); IR(KBr): 1802, 1543, 1370, 1174, 1129, 852 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (d, J=7.4 Hz, 1H), 7.84-7.76 (m, 3H), 7.61-7.57 (m, 4H), 7.49-7.34 (m, 5H), 5.66 (d, J=6.7 HZ, 1H), 3.81 (qd, J =7.6, 3.8 Hz, 1H), 0.96 (d, J=7.6 HZ, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 148.0, 141.5, 140.2, 135.2, 132.9, 132.8, 132.4, 131.5, 128.8 (2C), 127.6, 127.4 (2C), 127.3 (2C), 127.0 (2C), 124.5, 62.6, 50.6, 9.7; HRMS *m/z* calcd for $C_{22}H_{18}N_2O_5S$: 422.0936; found:422.0934.

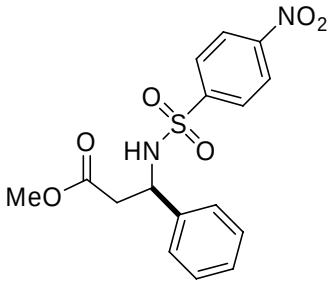
Table 1. Crystal data and structure refinement for **8a**.

Identification code	xu1110s	
Empirical formula	C16 H14 N2 O5 S	
Formula weight	346.35	
Temperature	200(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 8.4942(5) Å	α= 90°.
	b = 7.0841(4) Å	β= 92.3830(10)°.
	c = 13.1341(8) Å	γ= 90°.
Volume	789.64(8) Å^3	
Z	2	
Density (calculated)	1.457 Mg/m^3	
Absorption coefficient	0.235 mm^{-1}	

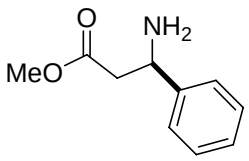
F(000)	360
Crystal size	0.45 x 0.21 x 0.16 mm^3
Theta range for data collection	1.55 to 32.49°.
Index ranges	-12<=h<=12, -10<=k<=10, -19<=l<=18
Reflections collected	10445
Independent reflections	5341 [R(int) = 0.0179]
Completeness to theta = 32.49°	98.0 %
Absorption correction	Sadabs
Max. and min. transmission	0.9634 and 0.9018
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5341 / 1 / 274
Goodness-of-fit on F^2	1.110
Final R indices [I>2sigma(I)]	R1 = 0.0494, wR2 = 0.1217
R indices (all data)	R1 = 0.0541, wR2 = 0.1255
Absolute structure parameter	0.05(6)
Largest diff. peak and hole	0.500 and -0.160 e.$Å^{-3}$

3.3 DERIVATIZATION OF β-LACTAM



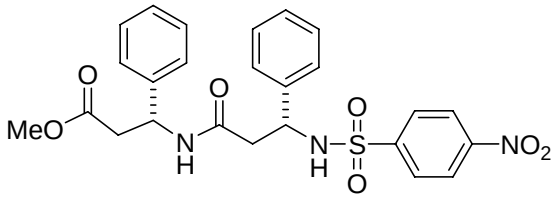


(R)-methyl-3-(4-nitrophenylsulfonamido)-3-phenylpropanoate (9): To a solution of 0.182 g (3.4 mmol, 1.7 eq.) of NaOMe in 6 ml of MeOH at -78°C was added 0.664 g (2 mmol) of lactam in a mixture of 4ml CH_2Cl_2 and 2 ml MeOH dropwisely. After being stirred at -78°C for 1.5 hours, the reaction mixture was poured into 60 ml of CH_2Cl_2 and 15 ml of water. The organic layer was separated and subsequently washed with 10 ml of brine. The organic layers was dried (Na_2SO_4), filtered and concentrated in *vacuo*. Then, it was purified by chromatography(40% EtOAC/Hexane) and gave 0.604 g (83%) of the title compound as pale yellow powder: mp 138-140°C; Separation of the enantiomers by Chiral HPLC (Daicel Chiracel^{TM} OD-H column , flow rate 1.0 ml/min, 10% ^{i}PrOH, 90% hexane, Tr 53.4 (R) and 45.9 (S) min) provided the enantiomer ratio: (R) : (S) =95.7: 4.3(83% ee); $[\alpha]_D$ +38.3°(*c* 1.15, DMF); IR(KBr): 1717, 1609, 1522, 1435, 1350, 1207, 1166, 1092, 1071cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12(d, J=9.0 HZ, 2H), 7.78(d, J=9.0 HZ, 2H), 7.20-7.11(m, 3H), 7.09-7.04(m, 2H), 6.27(d, J=3.2 HZ 1H), 4.86(m 1H), 3.63(S, 3H), 2.85(d, J=6.2 HZ, 1H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 149.9，146.6，138.7，128.9(2C)，128.5(2C), 128.4 ， 126.7(2C) ， 124.1(2C, 55.1, 52.3 ， 41.3; HRMS *m/z* calcd for $C_{16}H_{16}N_2O_6SNa$ ($M+Na^+$): 387.0521; found: 387.0627.



(R)-methyl-3-amino-3-phenylpropanoate (10): A mixture of **10** (100.8 mg, 0.278 mmol) and K_2CO_3 in 2ml DMF was added PhSH (36.8 mg, 0.333 mmol). The mixture was stirred at 50°C for 5 hours. Then, the mixture was cooled to room temperature. Then, 3 ml saturated $NaHCO_3$ solution was added. The mixture was diluted with 15 ml Et_2O and the separated organic phase was washed with H_2O (4*2 ml). The aqueous phase was washed with 20 ml CH_2Cl_2. The organic layers was dried (Na_2SO_4),

filtered and concentrated in *vacuo*. Then, it was purified by chromatography(50% EtOAC/Hexane) and gave 20.8 mg (42%) of the title compound. Because this compound is known,[4] full characterization wasn't given. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.23 (m, 5H), 4.44 (d, J= 8.9, 6.7 Hz, 1H), 3.69 (s, 2H), 2.72-2.63 (m, 2H), 1.87 (br, 2H).



R)-methyl-3-((R)-3-(4-nitrophenylsulfonamido)-3-phenylpropanamido)-3-phenylpropanoate (11): A mixture of 52.0 mg of lactam(0.157 mmol, 1 eq.) and 33.2 mg of amino ester(0.185 mmol, 1.2 eq.) in 3ml of DMF at 50°C was stirred for 4 hours. The mixture was cooled to room temperature. The organic solvent was removed in *vacuo*. The concentration was purified by chromatography(40% EtOAC/Hexane) and gave 60.3 mg (75%) of the title compound as white needles: mp 67-69°C; Separation of the enantiomers by Chiral HPLC(Daicel Chiralpak^{TM} AD column , flow rate 1.0 ml/min, 40% ^{i}PrOH, 60% hexane, Tr 30.9 (R) provided the enantiomer ratio: (R) : (S) =99.5: 0.5 (> 99% ee); $[\alpha]_D$ +41°; IR(KBr): 3299, 1735, 1647, 1531, 1438, 1350, 1165, 1093, 1064cm^{-1}cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01(d, J=8.6 HZ, 2H), 7.71(d, J=8.5 HZ, 2H), 7.31-7.21(m, 4H), 7.13-7.02(m, 6H), 6.88-6.86(m, 1H), 5.30(dd, J=13.9, 6.1HZ, 1H), 4.84(dd, J=12.5, 6.1HZ, 1H), 3.55(S, 3H), 2.81-2.62(m, 4H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 169.6, 149.7, 146.8, 140.0, 139.1, 129.0(2C), 128.7(2C), 128.4(2C), 128.1, 128.0, 126.9(2C), 126.3(2C), 123.9(2C), 55.8, 52.1, 49.9, 43.1, 39.6; HRMS *m/z* calcd for $C_{25}H_{25}N_3O_7SNa$ ($M+Na^+$):534.1311; found: 534.1305.

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