

**ASYMMETRIC SYNTHESIS OF NITROGEN CONTAINING BIOACTIVE
COMPOUNDS VIA THE UTILIZATION OF ENANTIOPURE *p*-
TOLUENESULFINIMINES**

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ABSTRACT

Asymmetric Synthesis of Nitrogen-Containing Bioactive Compounds via the Utilization of Enantiopure *p*-Toluenesulfinimines

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Doctor of Philosophy

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Doctoral Advisory Committee Chair: Prof. Rodrigo B. Andrade, Ph.D.

The research objective of this thesis research was to develop new methods for the asymmetric synthesis of amine derivatives using *p*-toluenesulfinimines. Enantiopure sulfinimines are versatile chiral building blocks for the asymmetric synthesis of alkaloids. Sulfinimines were prepared by the condensation of (*S*)- or (*R*)-*p*-toluenesulfinamide with aldehydes and ketones in good to excellent yields, which were prepared from the commercially available Anderson reagent.

The first research project was the development of a new method for the preparation of enantiopure *anti*- α -alkyl β -amino ketones and was accomplished by the stereoselective α -alkylation of enolates of sulfinimine derived β -amino esters. The *anti*- α -alkyl β -amino esters were transformed to their corresponding Weinreb amides by reacting with lithium dimethyl hydroxyl amine without epimerization. Reactions of the Weinreb amides with Grignard and organolithium reagents afforded the corresponding *anti*- α -alkyl β -amino ketones in modest yields and high optical purity. The modest yields are the results of competition between addition and reduction of the Weinreb amide. *anti*- α -Alkyl β -amino ketones are important chiral building blocks for the

asymmetric synthesis of nitrogen-containing biologically active molecules, such as pyrrolidines, piperidines and other alkaloids.

To further illustrate the utility of sulfinimine –derived enantiopure *N*-sulfinyl *anti*- α -alkyl β -amino ketones, they was applied to the asymmetric synthesis of the unknown *anti*-C5, C6 derivative of 2,3,4,6-tetrasubstituted indolizidine 221-T. The key step in the synthesis was the stereoselective construction of the piperidine ring of the 5,6,8-*tri*-substituted indolizidine and was realized via the use of an acid-catalyzed intramolecular Mannich cyclization. The indolizidine was readily transformed in to the key intermediate 7-hydroxyl-2,3,4,6-tetrasubstituted indolizidine in high stereoselectivity and yield. Changing the sequence of chemical operation steps avoided the production of the side product β -pyrrole ketone. Reduction of the intermediate piperdinone, followed by ring-closing metathesis and reductive catalytic hydrogenation afford the bicyclic indolizidine with overall 76% yield of 3 steps.

The C-2 branched cocaine analogs are thought to have varied bioactivities and potent therapeutical uses compared to other positions of substituted cocaine analogs. However, reports on the synthesis of such analogs are few. The first example of preparation of a cocaine analog having a dimethylphosphonate group at the C-2 position was reported. The key step in forming the required isoxazolidine intermediate, which controls the required *cis*-stereochemistry at C-2 and C-3, was a novel microwave induce stereoselective [3 + 2] intramolecular cycloaddition of an α,β -unsaturated pyrrolidine nitrene. The use of the microwave irradiation techniques significantly reduce the time required for isoxazolidine formation from 96 hours to five hours.

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CHAPTER 1

ASYMMETRIC SYNTHESIS OF β -AMINO KETONES AND *syn*- α - SUBSTITUTED β -AMINO KETONES

1.1. Introduction

Enantiopure β -amino ketones belong to an important class of nitrogen-containing compounds which have a unique structure.¹ Although not existing commonly in nature, several natural products have this structural unit including valachine, a natural occurring alkaloid isolated from Chilean barberry *Berberis valdiviana* Phil.,² anatoxin-A, which is a bicyclic alkaloid and cyantoxin a compound which exhibits acute neurotoxicity.³ In addition, kopsanone, which belongs to the *Kopsia* alkaloid family, also has the β -amino ketone unit, and is currently the subject of many synthetic studies (Figure 1.1).⁴

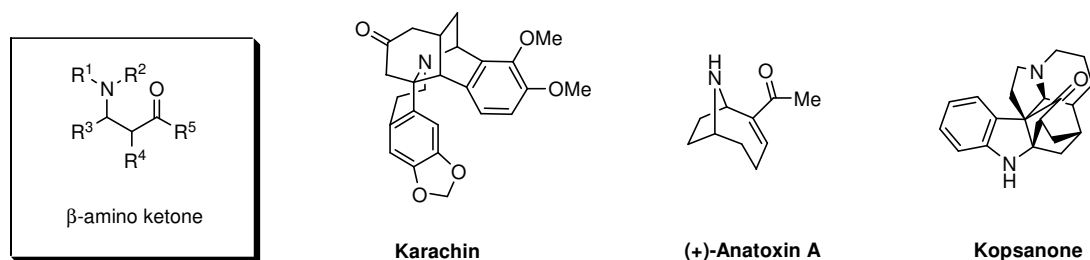


Figure 1.1

Moreover, β -amino ketones are also widely found in pharmaceutical products. For example, Moban (Molindone), a therapeutic antipsychotic developed by the Endo Pharmaceutical Co., is used in the treatment of schizophrenia.⁵ Falicain, found in nose drops, antimicrobial and stomatological lotions, has the β -piperidinoethyl-4-propoxyphenylketone structure (Figure 1.2).⁶ Be-2254 an adrenergic α -antagonist also

incorporates the β -amino ketone moiety, and is used in the treatment of hypertension, vasospasm and pheochromocytoma.⁷

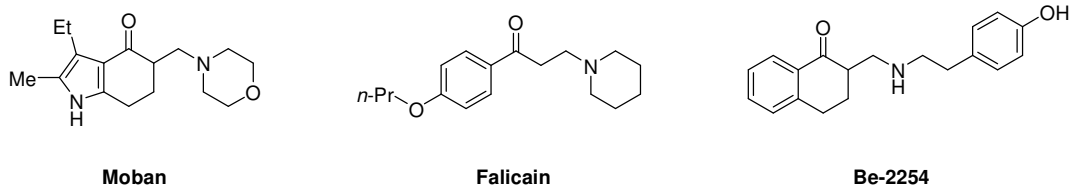


Figure 1.2

Furthermore, enantiopure β -amino ketones have emerged as versatile chiral building blocks for the asymmetric synthesis of alkaloids and other nitrogen-containing bioactive products. There are many reports of its application in the synthesis of piperidine and indolizidine alkaloids.⁸ The piperidine and indolizidine heterocycles and their derivatives are ubiquitous building blocks for the synthesis of pharmaceuticals and fine chemicals. In addition, β -amino ketones can be readily converted into a range of valuable derivatives (Figure 1.3). For example, β -amino ketones are useful chiral building blocks for Wittig-type condensations.⁹ Reduction or addition of organometallic reagents to the keto moiety transforms them to 1,3-amino alcohols,¹⁰ a widely used building block. β -Amino acids, synthetic challenging amino acids, can be prepared via the Baeyer-Villiger oxidation of β -amino ketones and subsequent hydroxylation.¹¹

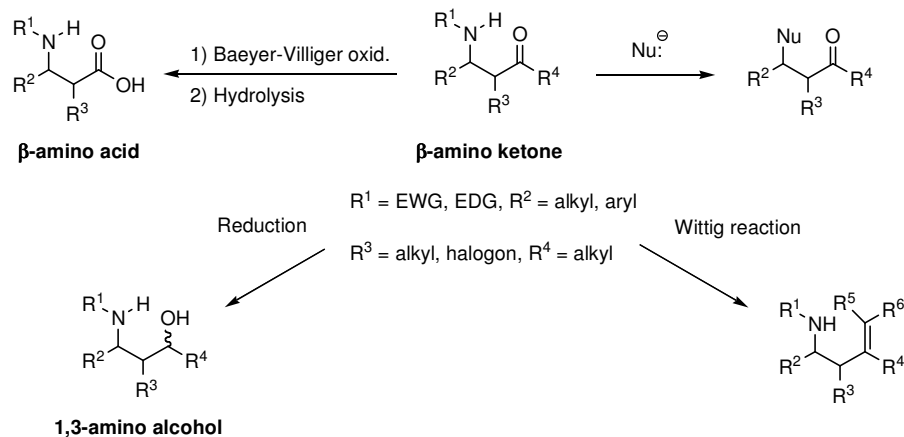


Figure 1.3

α -Substituted β -amino ketones are a subclass of β -amino ketones, which also have numerous synthetic applications in the synthesis of bioactive natural products.¹² Given the significance of β -amino ketones and α -substituted β -amino ketones, it is not surprising that their synthesis and applications have become an important endeavor in recent years (Figure 1.4). Numerous methodologies have emerged, and most of the work prior to 2012 has been reviewed.¹³

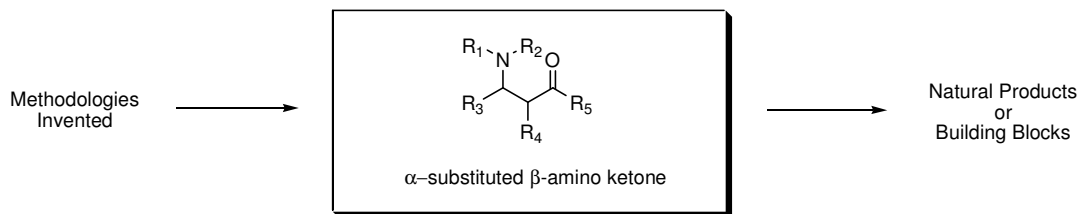


Figure 1.4

One of the most widely used methods for the synthesis of β -amino ketones and α -substituted β -amino ketones is the Mannich reaction (Figure 1.5).¹⁴ The Mannich reaction utilizes an enolate or an enol as the nucleophilic component that reacts with an

imine or iminium ion to give the β -amino ketone or α -substituted β -amino ketones.

Imine or iminium ions are formed by condensation of an amine with an aldehyde.¹⁵

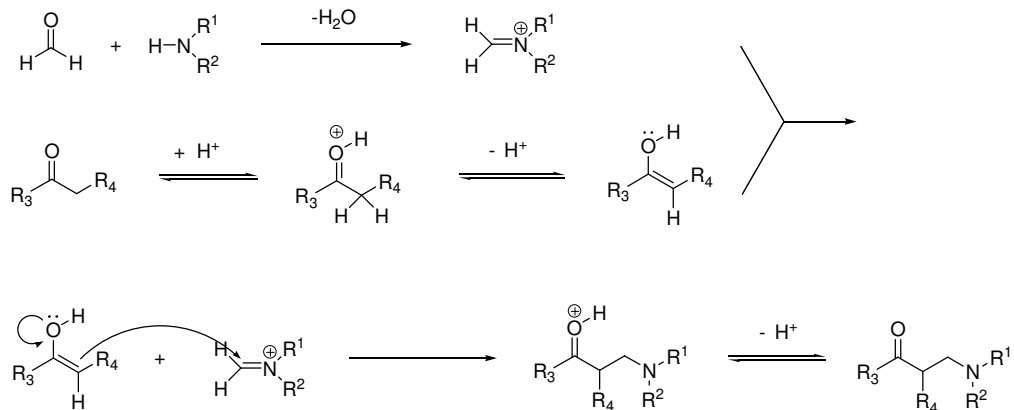


Figure 1.5

Progress has been made in the preparation of enantiopure β -amino ketone via the organo-catalyzed Mannich reaction¹⁶ and the use of enantiopure sulfinimines in Mannich type reactions (Figure 1.6).^{17,18} However, from a practical point of view, the organo-catalyzed Mannich reaction has limitations which cannot provide a general method for the synthesis of β -amino ketone. These limitations include moderate stereoselectivity, low conversion rates in reactions with aliphatic imines, and high loading of the catalyst.

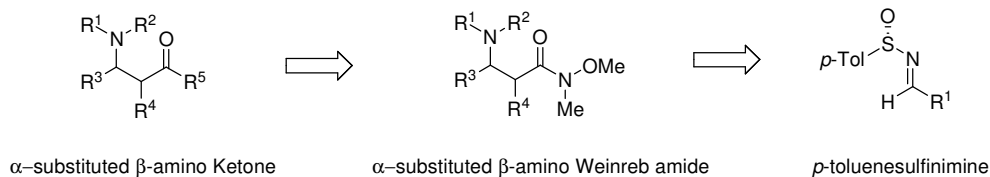


Figure 1.6

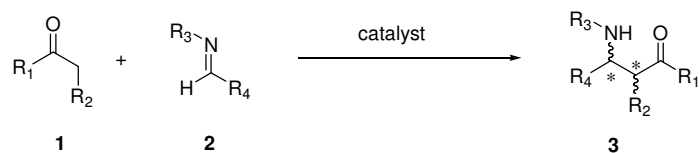
Fortunately, the use of sulfinimine chemistry and *N*-sulfinyl β -amino Weinreb amides not only overcomes these limitations (Figure 1.6.), but also expands the range of

different β -amino ketones that can be prepared.¹⁷ Using this methodology, aliphatic, aryl, vinyl and heterocyclic substituted β -amino ketones can be prepared with good to excellent yields and selectivity. In addition, reacting chiral *N*-phosphonyl imines with ketone derived enolates becomes another supplemental method to the *N*-sulfinimine chemistry.¹⁹ At the same time, some other methods like aza-Michael addition²⁰ and 1,3-dipolar cycloaddition²¹ have emerged as efficient approaches to prepare these compounds. Enantiopure β -amino ketones can also be prepared via enzymatic kinetic resolution.²²

This chapter focuses on the properties, the preparation of β -amino ketones and *syn*- α -substituted β -amino ketones.²³⁻²⁵ Furthermore, their application in the synthesis of building blocks and natural alkaloids is introduced.²⁶

1.2. Preparation of β -amino ketones via Mannich type addition of enolate addition to imines

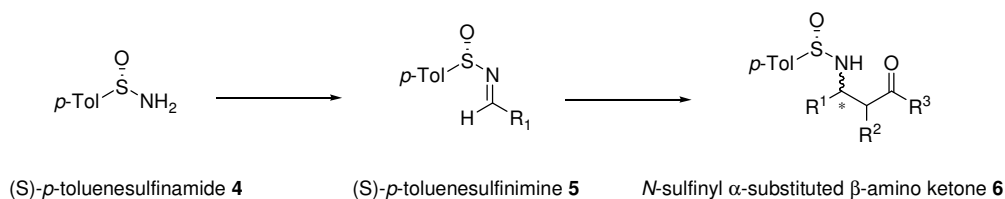
In the classical Mannich reaction, the enolates are key synthetic intermediates for the synthesis of diverse alkaloids and building blocks.^{27,28} Different kinds of enolates and their equivalents including metal enolates,²⁹ ketene silyl acetals³⁰, enol silyl ethers,³¹ and others, have been used.^{32,33} Their application to the asymmetric synthesis of enantiopure β -amino ketones via nucleophilic addition to imines **2** has been extensively studied (Scheme 1.1).³⁴ With the development of the catalytic asymmetric Mannich reaction, both metal-based and metal-free catalysis have been used as rate accelerating and stereo-directing reagents to prepare enantiopure β -amino ketones **3**.^{30,35}



Metal catalyst = ML_n , L = chiral ligands
 Non-metal catalyst = proline, proline-derivative, bifunctional acid et. al

Scheme 1.1

Moreover, Davis et al. developed enantiopure *p*-toluenesulfinimines **5**, which are prepared from *p*-toluenesulfinamides **4**, are excellent electrophiles for various enolates and their equivalents addition.³⁶ They have been extensively utilized for the asymmetric synthesis of enantiopure β -amino ketones **6** (Scheme 1.2).³⁷



Scheme 1.2

1.2.1. Preparation of enantiopure β -amino ketones via metal-catalyzed ketone enolate Mannich additions

The Mannich reaction is an effective method to prepare chiral β -amino ketones, since two adjacent stereocenters are constructed in a single step with concomitant carbon-carbon bond formation.³⁸ The first asymmetric Mannich reactions involved the addition of preformed enolates and enamines to the activated imines using stoichiometric amounts of chiral auxiliaries.³⁹ With the development of methods available for catalytic

asymmetric syntheses, metal-catalyzed asymmetric Mannich reaction was afforded initially.^{40,41}

Shibasaki and co-workers disclosed the first report of a catalytic asymmetric Mannich reaction by using ketones.⁴² In their study, the application of the cooperative catalysis of heterobimetallic AlLi bis(*R*)-binaphthoxide complex **8** (*R*-ALB) and La(OTf)₃·*n*H₂O was conducted,⁴³ which function as both a Lewis acid and a Bronsted base (Figure 1.7).

The direct enantioselective Mannich-type reactions of ketones were not previously reported, because of their low reactivity and the difficulty in controlling over-addition of ketone enolate to product ketones. In the one-pot three-component experiment, propiophenone (**9**), *para*-formaldehyde (**10**), and pyrrolidine (**11**) were reacted in the presence of catalytic amount of (*R*)-LaLi₃tris(binaphthoxide) **7** (*R*-LLB) (Scheme 1.3).

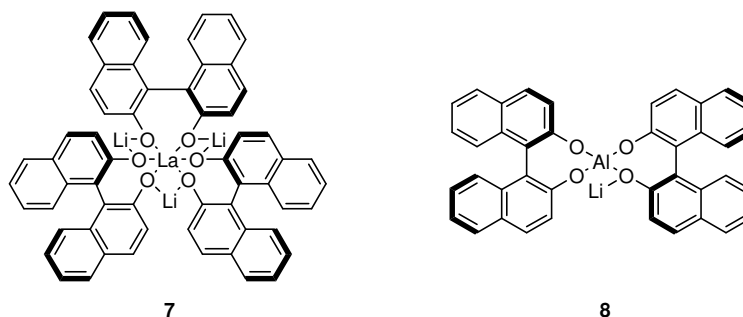
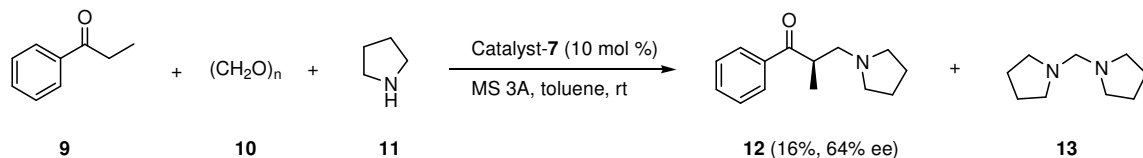


Figure 1.7

The reaction proceeded at rt with 3A⁰ molecular sieves as the dehydrating agent, affording the corresponding α -methyl β -amino ketone **12** in 64% e.e. (Scheme 1.3).⁴² However, the yield of the Mannich product **12** was only 16%. The low yield is caused by

the competing Mannich reaction between paraformaldehyde (**10**) and two molecules of pyrrolidine (**11**) which leads to the formation of dipyrrolidinomethane **13**.



Scheme 1.3

To inhibit the condensation of paraformaldehyde (**10**) with pyrrolidine (**11**), aminomethyl ether **15** was used as an alternative electrophile to the *in situ* formed imine cation. When reacting phenyl ketone **14a** with aminomethyl ether **15**, catalyst (*R*)-ALB **8** (10 mol %) gave 12% yield of product α -substituted β -amino ketone **16a** with a slight enantioselectivity of 25%. However, when heterobimetallic complex ALLibis(binaphthoxide) (**8**) (ALB) was combined with $\text{La}(\text{OTf})_3 \cdot n\text{H}_2\text{O}$, the reaction gave an improved yield to 65% and enantioselectivity to 40% (Table 1.1, entry 1). Under these optimized conditions, other aryl ketones were subject to the Mannich addition reacting with aminomethyl ether **15**. As shown in the table below (Table 1.1), all the β -amino aryl ketones **16a-e** were obtained in moderate to good yields and with a range of 31-44% e.e..

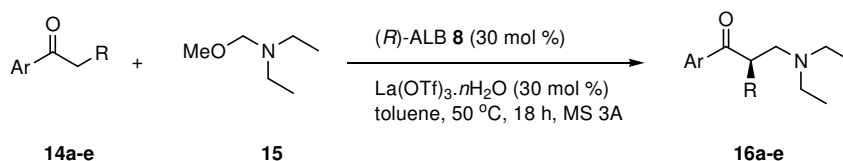


Table 1.1 (*R*)-ALB **12** catalyzed ketone derived asymmetric Mannich reaction.⁴²

Entry	Ar	Aryl ketone	R	Product	Yield (%)	ee (%)
1	Ph	14a	CH ₃	16a	65	40
2 ^a	Ph	14b	C ₂ H ₅	16b	69	34
3	<i>p</i> -MeOC ₆ H ₄	14c	CH ₃	16c	76	31
4	2-naphthyl	14d	CH ₃	16d	61	44
5	6-MeO-2-naphthyl	14e	CH ₃	16e	69	44

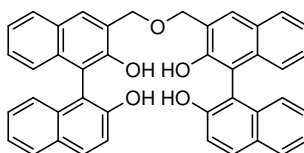
^a aminomethyl ethers **15** was added over 36 h.

In conclusion, the first direct ketone derived catalytic asymmetric Mannich reaction was developed using the cooperative catalysis of heterobimetallic complex (ALB) **8** and La(OTf)₃·*n*H₂O. More importantly, this method paved the way of further asymmetric synthesis of β-amino ketone via metal-based catalyst.

1.2.2. Metal-catalyzed preparation of enantiopure α-hydroxyl β-amino ketone

In 2003, Shibasaki et al. reported a ketone derived direct asymmetric Mannich reaction by using Et₂Zn/linked-BINOL complex **17** as the catalyst (Figure 1.7).⁴⁴ Prior to the utilization of this catalyst in Mannich reaction, the diethylzinc catalyst was investigated as a catalyst in direct asymmetric *syn*-selective aldol reactions and Michael reactions. In those reactions with aryl hydroxyketones as the donors, the Et₂Zn/linked-BINOL complex **17** exhibits high selectivities.⁴⁵ In the Mannich reactions between various *N*-protected imines, hydroxyaceto-2-methoxyphenone **19**, and Et₂Zn/linked-

BINOL complex **17**, it revealed that *N*-diphenylphosphinoyl (Dpp)-protected imines were the most promising imines with regard to stereoselectivity. As summarized (Table 1.2), the present asymmetric zinc catalysis was applicable to various aryl, alkyl, heterocyclic imines **18a-l**.



(*S,S*)-Linked BINOL Ligand **17**

Figure 1.8

All reactions were performed with catalytic amounts of complex **17** (1 mol %), Et₂Zn (4 mol %) and MS 3A°. The excellent enantioselectivities were obtained within a range of 98% to 99.5%, especially with imines derived from α -nonenolizable aldehydes. Imines derived from various substituted aromatic aldehydes **18a-18j** afforded corresponding α -hydroxyl β -amino aryl ketones **20a-j** with high *anti*-selectivity, where the d.r. ranged from 94:6 to 98:2 (Table 1.2, entries 1-10). Furthermore, *ortho*-substituents on the aromatic rings resulted in almost exclusive formation of the *anti*-adducts, both of which have d.r. equal to or higher than 98:2 (Table 1.2, entry 2, 8). Imine **18k** derived from α,β -unsaturated aldehyde gave a less *anti*-selectivity, but the diastereoselectivity of d.r. 81:19 was improved at a lower temperature (Table 1.2, entry 12). Aliphatic *cyclo*-propyl imine **18l** provided Mannich adduct in a high ee of 99%, but together with a modest *anti*-selectivity of 80:20 (Table 1.2, entry 13).

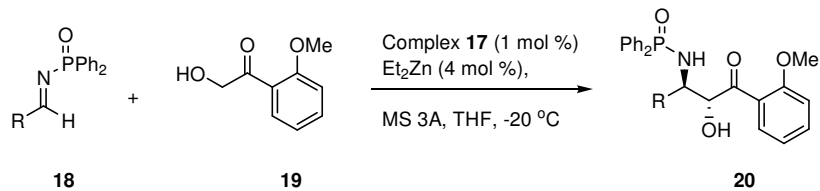


Table 1.2 Direct catalytic asymmetric Mannich reaction with a Et₂Zn/(S,S)-linked-BINOL.⁴⁴

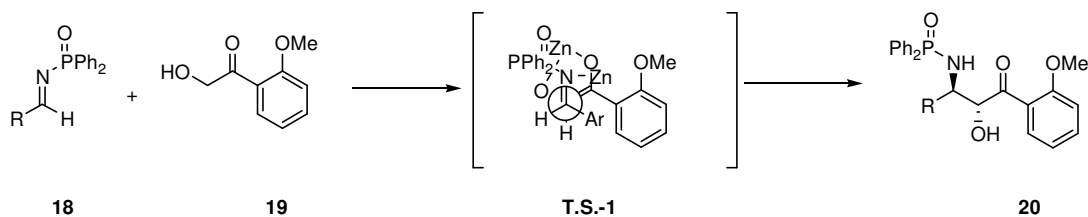
entry	R	Linked-BINOL	product	Temp. (°C)	Time (h)	Yield ^b (%)	d.r. ^c (<i>anti/syn</i>)	ee (%) (<i>anti</i>)	
1	4-MeC ₆ H ₄	18a	1	20a	-20	9	98	96/4	98
2	2-MeC ₆ H ₄	18b	1	20b	-20	6	99	>98/2	99
3	C ₆ H ₅	18c	1	20c	-20	6	98	96/4	99
4	4-MeOC ₆ H ₄	18d	1	20d	-20	6	97	95/5	99
5	4-NO ₂ C ₆ H ₄	18e	1	20e	-20	9	96	97/3	98
6	4-ClC ₆ H ₄	18f	1	20f	-20	4	97	97/3	98
7	4-BrC ₆ H ₄	18g	1	20g	-20	4	97	95/5	98
8	1-naphthyl	18h	1	20h	-20	6	97	98/2	>99.5
9	2-naphthyl	18i	1	20i	-20	7	95	94/6	99
10	2-furyl	18j	1	20j	-20	7	98	96/4	>99.5
11	(<i>E</i>)-cinnam	18k	1	20k	-20	4	98	76/24	>99.5
12	(<i>E</i>)-cinnam	18k	1	20k	-30	7	97	81/19	>99.5
13	<i>Cyclo</i> -propyl	18l	1	20l	-30	5	98	80/20	99
14	2-Me-C ₆ H ₄	18b	0.25	20b	-20	6	99	>98/2	99

^a 2 equiv of **18** was used. For less soluble imines, THF/CH₂Cl₂ mixed solvent was used. ^b Isolated yield. ^c Determined by the ¹H NMR of the crude mixture. ^d 1.28 g of **18 b** was used.

To demonstrate the practical utility, this catalytic Mannich reaction was performed on a gram scale with as little as 0.25 mol % of BINOL **17**. After 6 h reaction, Mannich product **20b** was afforded in a yield of 99%, over 98:2 d.r. and an e.e. of 99%

(Table 1.2, entry 14). The commercial availability of both Et_2Zn solution and linked-BINOL **17** also makes the present system advantageous from a practical viewpoint.⁴⁶

Interestingly, it was found that the *anti*-diastereoselectivity induced by Et_2Zn /linked-BINOL complex **17** in Mannich reaction is opposite to the reported aldol reaction, which gave the *syn*-diastereoselectivity by using the same catalyst.⁴⁷ Because the absolute configurations at the α -position of both the *aldol*- and the Mannich-products are identical ($2R$), the facial selection of the Zn-enolate generated from **19** should be same (*Si*-face shielding), and the electrophiles should approach in a different manner in these two reactions. It was reasoned that *anti*-selectivity in the present Mannich-type reaction could result from the diphenylphosphinoyl (Dpp) group, which is a bulky group on the imine nitrogen. To avoid steric repulsion between the Dpp group and the methoxyl group on the phenyl ring, Mannich reaction would proceed via the transition states **TS-1** as shown below, preferentially affording *anti*-product **20** (Scheme 1.5).

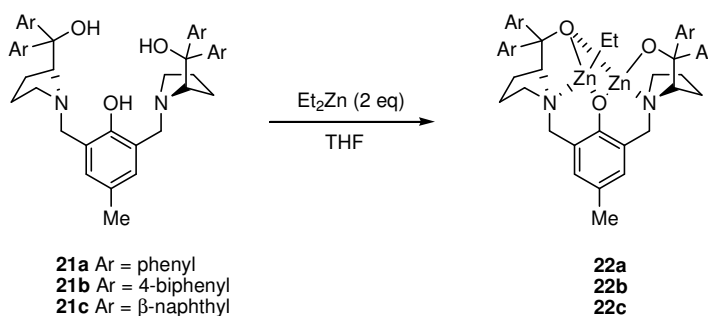


Scheme 1.5

At the same time, Trost and co-workers report another type of dinuclear zinc catalyzed asymmetric Mannich reaction to generate α -hydroxyl β -amino ketones.⁴⁸ Crown compounds were utilized together with the dinuclear zinc catalyst in the Mannich reaction, which provided higher catalytic efficiency compared to other structural

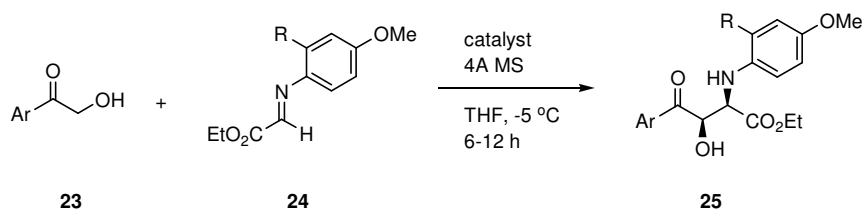
complexes. Experimental results demonstrated that the crown-design provided a good chiral recognition and gave a facile product-catalyst exchange which solved the problems of product inhibition.

The development of this metal-catalyzed Mannich reaction originally stems from the results from the analogous aldol reaction.⁴⁹ The dinuclear zinc catalysts **22a-c** are generated *in situ* by mixing *tri*-hydroxyl ligand **21a-c** with 2 equivalent of diethylzinc in THF (Scheme 1.6).⁵⁰



Scheme 1.6

Reacting hydroxyacetophenone **23** and glyoxalate imine **24a** in the presence of dinuclear zinc catalyst **22a** gave a high yield of the amino alcohol adduct **25**, which has a good diastereoselectivity favoring the *syn* adduct and an excellent enantioselectivity (Table 1.3, entry 1). In the process of optimizing the reaction conditions including monitoring the different substitutions on the nitrogen, it was found that more bulky 2-methyl-4-methoxy aniline derivatives afforded the products with better yields and stereoselectivities (Table 1.3, entries 2-6). Interestingly, lower catalyst load (2.5 mol %) in the same reaction of hydroxyacetophenone **23a** and imine **24** led to an increase in both the diastereo- and enantio-selectivity (Table 1.3, entry 2).



Scheme 1.7

Moreover, ligand effect was observed in the use of biphenyl ligand **22b**, product *syn*- amino alcohol **25** was produced with an increase in d.r. (12:1) and yield (92%) (Table 1.3, entry 3). Based on this result, the biphenyl complex **22b** was then adopted as the standard catalyst for the glyoxalate series Mannich addition. The electron-rich aromatic hydroxyl ketones **23b-e** required higher catalyst loads (5 mol %) while low load of (2.5 mol %) catalyst resulted in no reaction (Table 1.3, entries 5-8). 4-Methoxy hydroxyl ketone **23b** has a dramatic drop of the *syn:anti* diastereoselectivity to 2:1 (Table 1.3, entry 5).

Table 1.3 Additions of α -hydroxyl acetophenone **23** to glyoxyalate imines **24**.⁴⁸

Entry ^a	Ketone (Ar =)	Imine 24 (R =)	Cat.	Yield 25 ^b (%)	d.r. ^c	e.e. ^d (%)	
1 ^e	C ₆ H ₅	23a	H	22a	76	6.5:1	95
2 ^f				22a	79	8:1	>98
3 ^f	C ₆ H ₅	23a	CH ₃	22b	92	12:1	>99
4 ^{f,g}				22a	97	8.6:1	98
5	4-MeO-C ₆ H ₄	23b	CH ₃	22a	75	2:1	94
6	3-MeO-C ₆ H ₄	23c	CH ₃	22b	59	7:1	98
7	2-MeO-C ₆ H ₄	23d	CH ₃	22b	81	>20:1	>99

Table 1.3, continued

8	2-furyl	23e	CH ₃	22b	81	8:1	>99
^a All reactions are as in eq 1 using a 2:1 ratio of hydroxyketone to imine using 5 mol % catalyst unless noted otherwise. ^b See ref 5. ^c Determined by ¹ H NMR spectroscopy on the crude mixture. ^d Determined by chiral HPLC on a Chiracel OD or AD column. ^e 10 mol % catalyst. ^f 2.5 mol % catalyst. ^g Hydroxyketone-to-imine ratio 1.1:1 in the presence of 3.7 mol % Ph ₃ PS.							

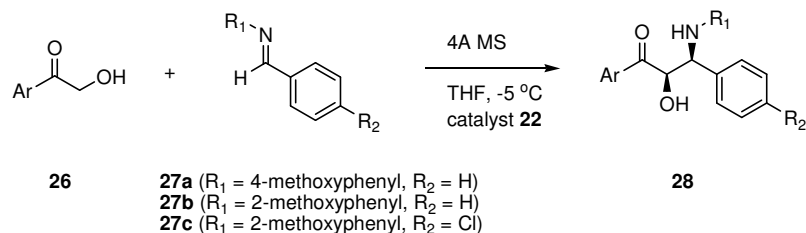
The *meta*-methoxy hydroxyl ketone **23c** regained the diastereoselectivity, which is a 7:1 d.r., 98% e.e. and a moderate yield of 59% (Table 1.3, entry 6). Importantly, in the case of *ortho*-methoxy hydroxyl ketone **23d**, a complete diastereo- and enantioselectivity were afforded, which has an over 20:1 d.r. and the e.e. higher than 99% (Table 1.3, entry 5). In addition, heteroatomic ketone 2-hydroxyacetylfuran (**23e**) catalyzed by dizinc complex **22b** affording the desired *syn*-amino alcohol adduct with comparable selectivities as the parent acetophenone **23a** (Table 1.3, entry 8).

As the continuing investigation of reaction conditions, aldimines **27** derived from aromatic aldehydes were examined under the standard conditions (Scheme 1.8, Table 1.4). The phenyl ligand derived catalyst **22a** accelerated the reaction of α -hydroxy ketone **26a** and imine **27a** to give the product with a moderate *syn:anti* ratio of 1.7:1 but excellent enantioselectivity of 99% in both diastereomers (Table 1.4, entry 1). Changing catalyst to β -naphthyl ligand derived **22c**, a strong ligand effect was still observed which has a more than doubled *syn:anti* diastereoselectivity of 4.3:1 (Table 1.4, entry 2).

Reacting with the α -hydroxyacetophenone (**26a**), both aldimine 2-methoxyphenyl **27b** and **27c** gave a dramatic increase in diastereoselectivity (>15:1) in the presence of phenyl ligand derived catalyst **21a** or β -naphthyl catalyst **22a** (Table 1.4, entries 1-6). Similarly, the same electronic effects were also observed in aldimines **27a-c**

as for glyoxalate imines. *para*-Chloro imine **27c** gave a dramatic rate increase without detecting any adverse effect on stereocontrol (Table 1.4, entry 5). Furthermore, the electron-rich aromatic ketones **26b-c** showed excellent diastereo- and enantioselectivities with aldimine **27c** although longer reaction times were needed (Table 1.4, entries 7-8).

The increased diastereoselectivity can be rationalized through a bidentate binding model with the *ortho*-substituted derivative. The two-point binding of the imine through the nitrogen and methoxy helps rigidify the dynamic nature of the imine-Lewis acid complex.⁵¹ The increased rigidity should prevent the *E/Z* isomerization for the carbon-nitrogen double bond, which may account for the low d.r. in the case of aldimine **27a** (Table 1.4, entry 1).


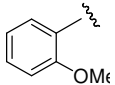



Scheme 1.8

Table 1.4 Additions of α -hydroxyl ketone **26** to glyoxalate imines **27a-c**.⁴⁸

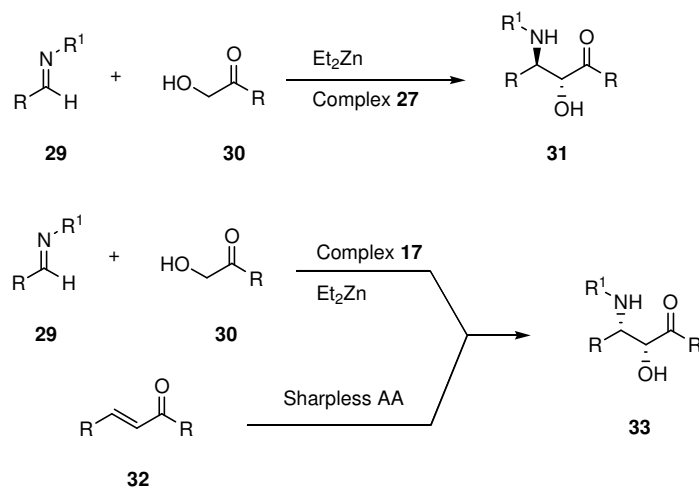
Entry ^a	Ketone (Ar)	Imine	Catalyst	Yield 28 ^b (%)	d.r. ^c (<i>syn/anti</i>)	e.e. ^d (%)
1	26a 	27a	22a	61	1.7:1	99
2		27a	22c	64	4.3:1	99
3		27b	22a	66	>15:1	>99
4		27b	22c	70	>15:1	99

Table 1.4, continued

5			27c	22a	90	>15:1	>99
6			27c	22c	87	>15:1	>99
7	26b		27c	22a	68	>15:1	>98
8	26c		27c	22a	74	>15:1	99

^aAll reactions are using a 2:1 ratio of hydroxyketone to imine using 5 mol % catalyst unless noted otherwise. ^b Products have been fully characterized. ^c Determined by ¹H NMR spectroscopy on the crude mixture. ^d Determined by chiral HPLC on a Chiralcel OD or AD column. ^e Hydroxyketone-to-imine ratio 1.1:1 in the presence of 7.5 mol % Ph₃AsO. ^f 5 mmol scale.

In summary, the application of dinuclear zinc catalysts afforded moderate to good diastereoselectivities and enantiomeric excess. Trost's and Shibasaki's zinc complexes are complementary in selectivity and provide new routes to either *syn*-1,2-amino alcohol **33** or *anti*-1,2-amino alcohol **31**, respectively. Besides that, the dinuclear zinc complex-catalyzed Mannich reactions can be considered as a regiospecific alternative to the Sharpless asymmetric aminohydroxylation reaction.^{52,53}

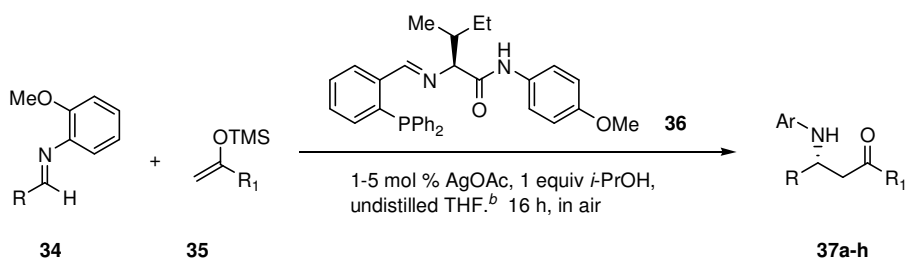


Scheme 1.9

1.2.3. Metal-catalyzed enol silyl ether Mannich reaction

Metal-catalyzed asymmetric Mannich addition has made advanced developments so far. However, reactions of the less nucleophilic enol ethers with imines have not been fully investigated. Notable progress has been made on the metal-catalyzed asymmetric additions of related nucleophilic silyl ketene acetals to activated aryl imines.⁵⁴⁻⁵⁶ It is therefore feasible to develop an efficient enantioselective metal-catalyzed processes which are fitful to enol ethers and similar activated imines, such as those derived from glyoxylates.

Hoveyda et al. reported the Ag-catalyzed asymmetric additions of silyl enol ethers to aryl, alkyl, alkenyl, and alkynyl imines.⁵⁷ β -Amino ketones **37a-h** were obtained with high yields and optical purities (up to >98% e.e.) in the presence of AgOAc (1-5 mol %) and the *iso*-Leu-derived phosphine **36** (1-5 mol %). Moreover, all the silver catalyzed transformations were performed in the air with undistilled solvents.



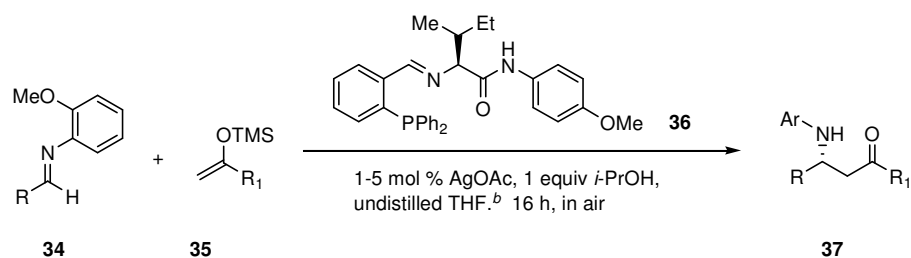
Scheme 1.10

Previous studies reported that chiral phosphine **36** and AgOAc maintained an ability to catalyze the cycloaddition between arylimines and Danishefsky diene with good to excellent yields and selectivities.⁵⁸ The catalyzing ability of the silver salt and

phosphine **36** represented in the intramolecular reaction with TMS enol ether and aryl imines would promote the intermolecular Mannich reaction between imines **34** derived from aromatic and heterocyclic aldehydes and TMS enol ethers **35**.

Experimental results showed that all the reactions are prompted efficiently (Table 1.4). Besides that, it was observed that addition of 1 equivalent of *i*-PrOH in reaction leads to a high conversion rate, which was also found in the intramolecular cycloaddition.⁵⁸ A possible reason could be that reaction involved a shuttling shift of Me₃Si group from oxygen atom to nitrogen atom and *i*-propanol accelerates this process by helping to release the final product β -amino ketone from the Ag cation.

In the case of the *non*-substituted phenyl imine (**34a**), as well as *para*- and *meta*-substituted phenyl groups bearing electron-rich or electron-deficient aryl imines (Table 1.5, entries 3-12), AgOAc-catalyzed reactions afforded the desired β -amino ketones in good to excellent enantioselectivities (86-98% ee). Electron-poor imines are more reactive such that their transformations can be effected at lower temperatures, giving rise to improved optical purities. Reactions of the electron-rich substrates (Table 1.5, entries 3-4) are more selective when carried out in toluene (**37b** is obtained in 82% ee in THF). Catalytic asymmetric reactions of the more sterically demanding imines that bear an *ortho* substituent (Table 1.5, entries 13-14) proceed efficiently but with lower asymmetric induction (74-80% ee). Heterocyclic imines also participate in facile and enantioselective additions (Table 1.5, entries 15-16).



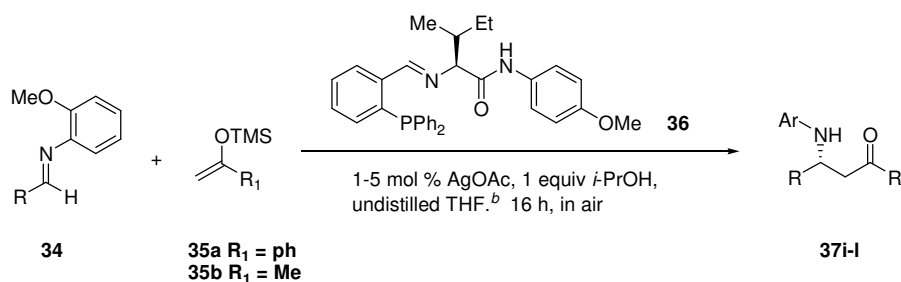
Scheme 1.10

Table 1.5 Ag-catalyzed enantioselective Mannich reactions of silyl ethers **35** with aryl imines **34**.⁵⁷

Entry	R	R ₁	36 , AgOAc (mol %)	T (0 °C)	Yield (%) ^b	ee (%) ^c
1	Ph	34a Ph	35a 3	-10	54	94
2	Ph	34a Me	35b 5	-10	65	92
3	<i>p</i> -MeOC ₆ H ₄	34b Ph	35a 5	22	61	96
4	<i>p</i> -MeOC ₆ H ₄	34b Me	35b 5	22	71	90
5	<i>p</i> -NO ₂ C ₆ H ₄	34c Ph	35a 3	-5	88	92
6	<i>p</i> -NO ₂ C ₆ H ₄	34c Me	35b 5	-10	91	92
7	<i>p</i> -ClC ₆ H ₄	34d Ph	35a 1	4	84	96
8	<i>p</i> -ClC ₆ H ₄	34d Me	35b 5	-10	79	90
9	<i>m</i> -NO ₂ C ₆ H ₄	34e Ph	35a 3	-10	97	86
10	<i>m</i> -NO ₂ C ₆ H ₄	34e Me	35b 3	-5	96	86
11	2-naphth	34f Ph	35a 3	-5	88	98
12	2-naphth	34f Me	35b 3	-5	94	92
13	<i>o</i> -BrC ₆ H ₄	34g Ph	35a 5	4	70	80
14	<i>o</i> -BrC ₆ H ₄	34g Me	35b 5	4	46	76
15	2-furyl	34h Ph	35a 3	4	84	86
16	2-furyl	34h Me	35b 3	4	78	90

^a Reaction in THF except entries 3 and 4 which were run in toluene. ^b Isolated yields. ^c By chiral HPLC.

Except that it is applicable in active aryl imines, the Ag-catalyzed method can also be applied to alkenyl imines (**34i-k**, Table 1.6), alkynyl imines (**34l**, Table 1.6) and alkyl imines (**34m-o**, Table 1.6).^{40,59} A range of unsaturated β -amino ketones listed below (**37i-l**, Table 1.6) were prepared in synthetically useful yields and high enantioselectivities. The corresponding reactions involving aliphatic imines (**34m-o**, Table 1.6),⁴⁰ can be carried out through a three-component process that affords the desired amines (**37m-o**, Table 1.6) in good enantioselectivities (92-94% ee). However, the isolated yields are relatively low, which are likely due to the instability of the aliphatic imine substrates. It should be noted that the equivalent of water released through *in situ* formation of the aliphatic imines obviates the need for the use of *i*-propanol.

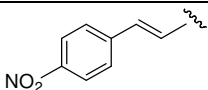
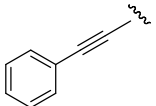


Scheme 1.11

Table 1.6 Ag-catalyzed enantioselective Mannich reactions of silyl ethers **35** with unsaturated imines **34**.⁵⁷

Entry	R	R_1	36 , AgOAc		T (0 °C)	Yield (%) ^b	ee (%) ^c	
				(mol %)				
1		i	Ph	35a	1	4	51	90
2		i	Me	35b	1	4	77	89
4		j	Me	35b	5	22	47	90

Table 1.6, continued

5		k	Ph	35a	3	-5	>98	92
6		k	Me	35b	3	-5	74	90
7		l	Ph	35a	1	4	93	92
8		l	Me	35b	3	-5	91	88
9	<i>n</i> -C ₁₀ H ₂₁	M	Me	35b	5	4	60	92
10	Cy	N	Me	35b	5	4	53	94
11	<i>i</i> -Bu	o	Me	35b	5	4	41	94

^a Reactions in THF except entries 3 and 4. ^b Isolated yields. ^c By chiral HPLC.

In summary, AgOAc and chiral phosphine catalyzed Mannich reaction of enol silyl ethers with imines afforded the optically active β -amino ketones with high enantioselectivity. Because of the wide range of substituted imines and silyl enol ethers, the silver catalyzed protocol should have a broad utility in the synthesis of β -amino ketones and its related biologically active molecules.⁶⁰

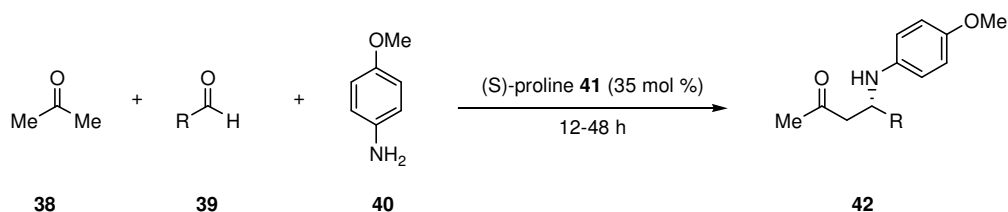
1.3. Preparation of enantiopure β -amino ketones via the organocatalytic asymmetric Mannich reaction

The first amino acid-catalyzed stereoselective Robinson annulation was discovered in early 1970s,⁶¹ since then there has been no intensive research on this concept. Even though the annulation reaction is frequently used in synthesis, it was not until three decades later that it was demonstrated that amino acids and their derivatives can function as catalysts for direct asymmetric C-C bond formation.⁶²

Recent advances made in the development of metal-free organocatalytic asymmetric reactions have received much attention.⁶³⁻⁶⁵ Those developments in this area have had a profound effect on the Mannich reaction with the use of proline, chiral pyrrolidines, *Cinchona* alkaloid-derived catalysts, and so on. Until now, the use of those small molecules as catalysts has become a powerful strategy in the construction of chiral building blocks and natural products.⁶⁶

1.3.1. One-Pot Three-Component Mannich Reaction: Proline catalyzed reaction

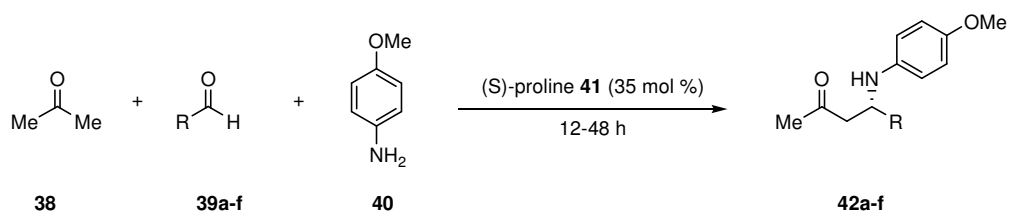
Asymmetric organocatalysis of Mannich-type reaction was first realized in the Hajos-Parrish-Eder-Sauer-Wiechert reaction.^{61,67} The basis of this type of reaction is the facile *in situ* generation of enamines, which function as the chiral enolate equivalents made from ketones or aldehydes.⁶⁸ List and co-workers reported the first preparation of chiral β -amino ketone via organocatalytic Mannich reaction catalyzed by chiral amine (Scheme 1.12).⁶⁹



Scheme 1.12

The design of this reaction was built on proline-catalyzed asymmetric aldol reactions⁷⁰ and Kobayashi's work on three-component Mannich reactions.⁷¹ It was found that after stirring L-proline, *p*-nitrobenzaldehyde (**39**), and *p*-anisidine (**40**) in

acetone/DMSO mixed solvent for 12 h, corresponding Mannich product **42a** was formed with a good enantioselectivity but a moderate yield (Table 1.7, entry 1). Low yield of product **42a** was caused by formation of the Aldol addition product and the condensation between *p*-anisidine (**40**) and aldehyde **39**. A similar result was observed with 2-naphthaldehyde **39b**, which gave the product β -amino ketone **42b** in good enantioselectivity (96% ee), albeit in modest yield (35%) (Table 1.7, entry 2). However, when changing aldehydes to aliphatic aldehydes, all aldehydes **39c-f** produced their corresponding β -amino ketones **42c-f** in good to excellent yields (56% to 90%) and ee's of up to 93% (Table 1.7, entries 3-6). These results demonstrated that less reactive aliphatic aldehydes prevent the aldol addition of the enamines and reduced the condensation between aldehyde and *p*-anisidine (**40**), which lead to a high yield of Mannich product.


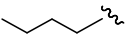
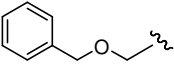



Scheme 1.13

Table 1.7 Products from the proline-catalyzed asymmetric three-component Mannich reaction.⁶⁹

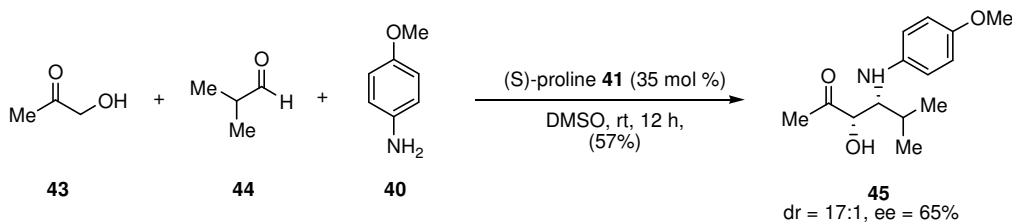
Entry	Aldehyde	R	Product	Yield (%)	ee (%)
1	39a		42a	50	94
2	39b		42b	35	96

Table 1.7, continued

3	39c		42c	90 (87)	93 (91)
4	39d		42d	74	73
5	39e		42e	82	75
6	39f		42f	56	70

^a PMP = *p*-methoxyphenyl. ^b The ee's of products **42a-f** were determined by chiral-phase HPLC analysis using Chiralpak AD and AS columns (Daicel Chemical Industries, Ltd.) with hexane/2-propanol mixtures as eluents. ^c Reactions in DMSO/acetone 4:1. ^d Reactions in pure acetone. ^e Reaction in CHCl₃/acetone 4:1.

Moreover, ketones other than acetone can also furnish the desired Mannich products in good yields and enantioselectivities. For example, in the reaction of α -hydroxyacetone **43**, *iso*-butyraldehyde **44** and *p*-anisidine (**40**), *syn*-amino alcohol **45** was formed within 12 h as the only regioisomer in good enantioselectivity (65% ee) and stereoselectivity (*syn:anti* = 17:1) (Scheme 1.14). Although e.e. values need to be improved, the α -hydroxyacetone Mannich reaction could also complement the Sharpless asymmetric aminohydroxylation^{66,72} for the construction of chiral amino alcohols.⁷³



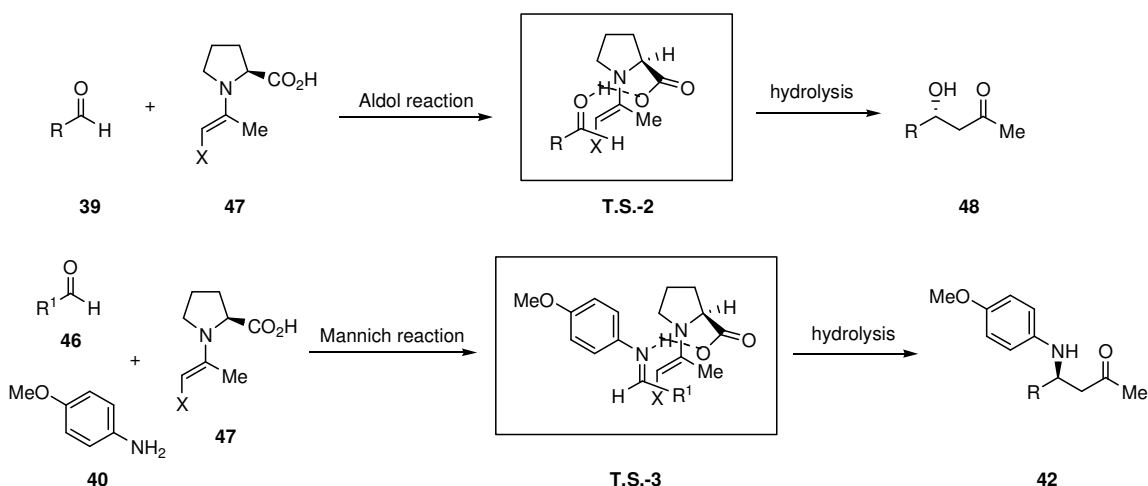
Scheme 1.14

Proline is commercially available in both enantiomeric forms and it can be recovered from reaction via filtration. Beside that, the PMP (*p*-methoxyphenyl) group

can be removed smoothly via oxidative conditions.⁷⁴ These advantages make the proline-catalyzed asymmetric synthesis of β -amino ketones a highly efficient method.

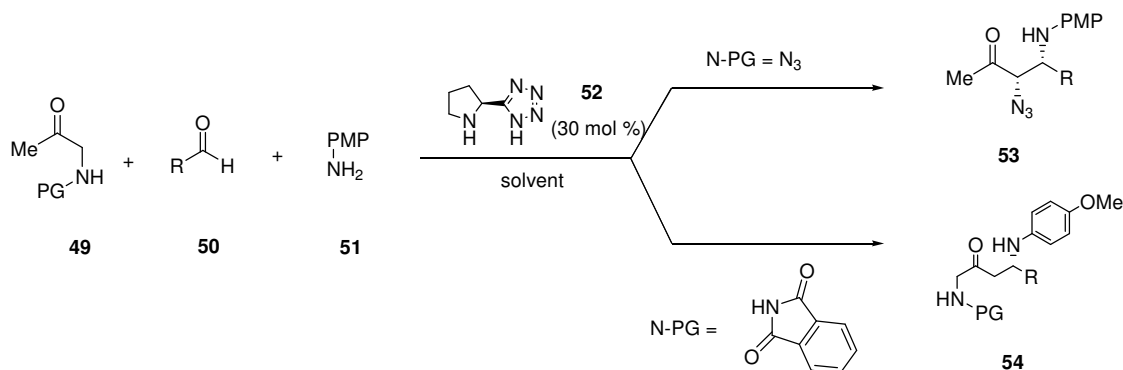
X-Ray analysis of the above Mannich products' structure established the *syn*-diastereoselectivity of the reaction. However, this is apparently opposite to the proline-catalyzed aldol reaction, which has *anti*-diastereoselectivity (Scheme 1.15).⁷⁵ One proposed explanation is that in Aldol reaction enamines **47** typically generate a *re*-facial attack on the aldehyde **39**, whereas Mannich products **48** are normally formed through a *si*-face attack on an imine.

Although it is known that imines made from aldehyde **46** and *p*-anisidine (**40**) may undergo (*E*)/(*Z*) isomerization, and (*Z*)-imines are present in low equilibrium concentrations. It is assumed that (*E*) configurations are adopted by both proline-enamine and imine in transition state (T.S.-3).⁷⁶ The *si*-face of the imine is selectively attacked by enamine **47** directed by the carboxylic acid protonation to its lone pair. The enamine attacks to the *re*-face of imine would result in unfavorable interaction between the pyrrolidine and phenyl ring. Computational studies using density functional theory (B3LYP/6-31G*) supported this mechanism, from which the predicted enantioselectivity excess is consistent with experimental results.⁷⁷



Scheme 1.15

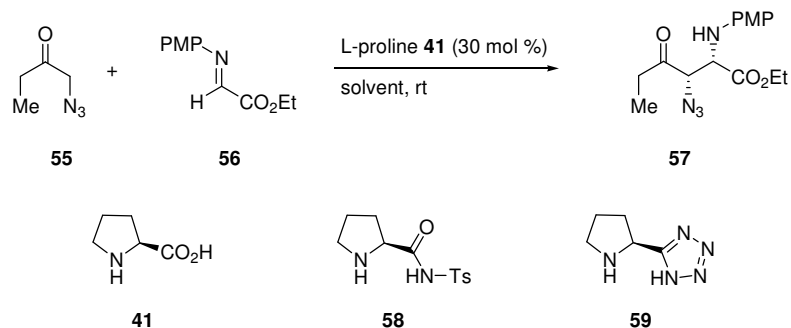
Although α -hydroxyl ketones have been employed in catalytic synthesis of α -hydroxyl β -amino ketones, the utilization of α -amino ketones was not reported due to their instability in reaction. In 2006, Barbas and co-workers described the use of α -azido ketone and α -amino ketone in the asymmetric synthesis of α -azido β -amino ketones and α' -amino β -amino ketones (Scheme 1.16).⁷⁸



Scheme 1.16

Initial study was made on the reaction of *p*-methoxyphenyl (PMP) protected α -imino ethyl glyoxylate **56** with azidobutanone **55** using a catalytic amount of L-proline

41 in DMSO. The Mannich reaction was completed within 48 h at rt, which gave the Mannich adduct 1,2-diamino ketone **57** in 84% yield and over 92% e.e.. However, a low diastereoselectivity is obtained which has the ratio of *syn:anti* equal to 51:49 (Table 1.8, entry 1). When changing the solvent to DMF and cooling the reaction to 4 °C, reaction diastereoselectivity improved, but elongated time is needed to complete the reaction (Table 1.8, entry 2). Changing solvent to 2-propanol increased the both reactivity and enantioselectivity, but decreased the diastereoselectivity (Table 1.8, entry 3).



Scheme 1.17

Table 1.8 Effect of various catalysts and solvents on the organocatalytic asymmetric synthesis of 1,2-azidoamines.⁷⁸

Entry ^a	Catalyst	Solvent	Time (h)	Yield (%)	<i>syn/anti</i>	e.e. (<i>syn/anti</i>)
1	41	DMSO	48	84	51/49	92/98
2	41	DMF,	187	82	92/8	96/99
3	41	IPA, 4 °C	24	80	89/11	99/99
4	58	DMSO	24	80	56/44	79/69
5	59	DMSO	4	93	94/6	98/70
6	59	DMF	6	90	82/18	75/88
7	59	DMF, 4 °C	39	92	91/9	97/65
8	59	NMP	6	88	84/16	85/86

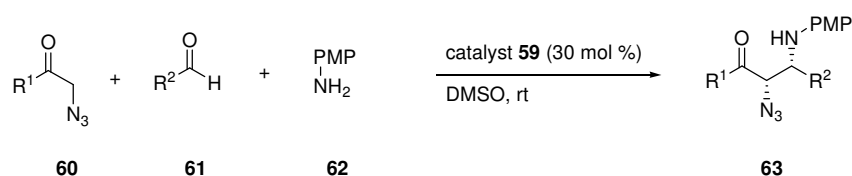
Table 1.8, continued

9	59	NMP, 4 °C	40	90	91/9	97/90
10	59	IPA, 4 °C	24	90	95/5	99/99
11	59	DCM	120	93	83/17	90/43
12	59	CH ₃ CN	72	84	78/22	72/45
13	59	dioxane	31	80	78/22	91/22
14	59	Toluene	95	76	76/24	89/16
15	59	[bmin]BF ₄	48	83	78/22	73/44

^a ee was determined by chiral HPLC analysis. *Syn/anti* ratio was based on ¹H NMR. Stereochemistry was assigned on the basis of previous Mannich reactions.

The L-proline derivative sulfonamide **58** and tetrazole **59** were then tested as catalysts. Compared with proline, these catalysts are stronger acids which have been used previously in enamine-based organocatalysis.^{79,80} The reaction was completed in DMSO within 24 h with catalyst **58**, but poor diastereoselectivity was obtained (Table 1.8, entry 4). When tetrazole **59** was used the reaction was completed within 4 h in DMSO with a good diastereo- and enantio-selectivity (Table 1.8, entry 5). Then tetrazole **59** was used as the standard catalyst, and various solvents were screened (Table 1.8, entries 5-15). Among the solvents examined, DMSO was found to be the most effective in terms of reaction time, yield, diastereo- and enantio- selectivities. IPA, DMF and NMP provided good diastereo- and enantio- selectivity at 4 °C, but a longer reaction time is needed. Comparatively, reaction rates were much slower in DCM, CH₃CN, 1,4-dioxane, toluene, and ionic liquid [1-butyl-3-methylimidazolium]BF₄, in which modest yields, diastereo- and enantio- selectivities were afforded.

Under the optimized conditions, the next study was on the three-component Mannich reactions using different α -azido ketones, amines and aldehydes (Table 1.9). The reaction of α -azido acetone **60a** was complete within 30 min, whereas α -azido acetophenone **60b** required 40 h for completion. Reaction with benzyloxyacetaldehyde **61c** and carbohydrate-derived aldehydes **61e** regioselectively afforded the α -azido β -amino ketone **63c-e**, and all of these products have a good range of diastereoselectivities (*syn/anti* = 70:30 to 91:9) and enantioselectivities (82% - 99% e.e.).

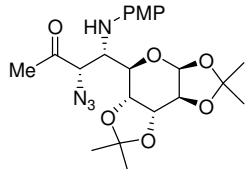


Scheme 1.18

Table 1.9 Mannich reactions for the synthesis of various 1,2-azidoamines.⁷⁸

Entry	product	Time (h)	Yield (%)	<i>syn/anti</i>	ee (<i>syn/anti</i>)
1	 $\text{Me}-\text{C}(=\text{O})-\text{CH}(\text{N}_3)-\text{CH}(\text{CO}_2\text{Et})-\text{NH}-\text{PMP}$ 63a	0.5	96	91/9	99/99
2	 $\text{Ph}-\text{C}(=\text{O})-\text{CH}(\text{N}_3)-\text{CH}(\text{CO}_2\text{Et})-\text{NH}-\text{PMP}$ 63b	40	87	88/12	99/64
3	 $\text{Me}-\text{C}(=\text{O})-\text{CH}(\text{N}_3)-\text{CH}(\text{OBn})-\text{NH}-\text{PMP}$ 63c	0.5	83	80/20	85/29
4	 $\text{Me}-\text{C}(=\text{O})-\text{CH}(\text{N}_3)-\text{CH}(\text{OBn})-\text{NH}-\text{PMP}$ 63d	6	80	85/15	82/79

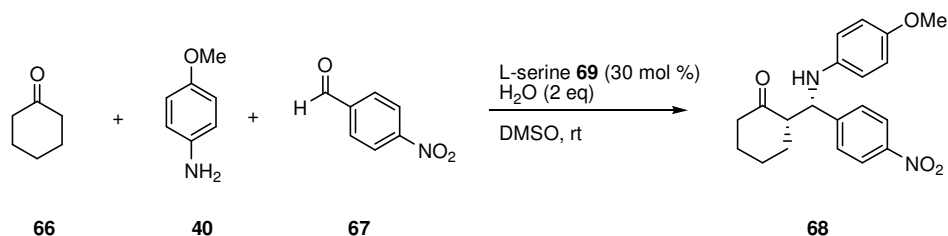
Table 1.9, continued

5		63e	36	60	70/30	--
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After that, a phthaloyl-protected α -amino ketone, phthalimidoacetone **64** was subject to the similar three-component Mannich reaction (Table 1.10). Catalyst **59** in DMSO was used under optimized reaction conditions. Reaction of preformed ethyl glyoxalate imine at rt provided its regiospecific product α' -amino β -amino ketone **65a** in 86% yield and 64% e.e. Lowering the reaction temperature to 4 °C improved the e.e. value; DMF gave a 90% e.e., whereas NMP provided 91% e.e. (Table 1.10, entries 2-3). When the *p*-nitrobenzaldehyde derived imine was reacted under the three component Mannich reaction, similar to product **65a**, the highest e.e. of 97% was obtained in NMP at 4 °C (Table 1.10, entry 7).

In contrast to α -azidoketones **60** that provided 1,2-diamine derivatives or α -azido β -amino ketones exclusively, phthalimidoacetone **64** produced only the 1,4-diamine ketone or α' -amino β -amino ketone derivatives. Unlike the results obtained using tetrazole catalyst **59**, with L-proline **41** and tosylate proline **58** as catalysts, phthalimidoacetone derived Mannich product **65a-b** are only formed in trace amounts, while L-proline **41** lead to the formation of cycloaddition side product.⁸¹

In the synthesis of chiral β -amino ketone via amino acid-catalyzed Mannich reactions, proline and proline derivatives have shown high efficiency as catalysts. However, acyclic amino acids and acyclic chiral amines had not been intensively investigated until Cordova and co-workers reported their results (Scheme 1.20).⁸³

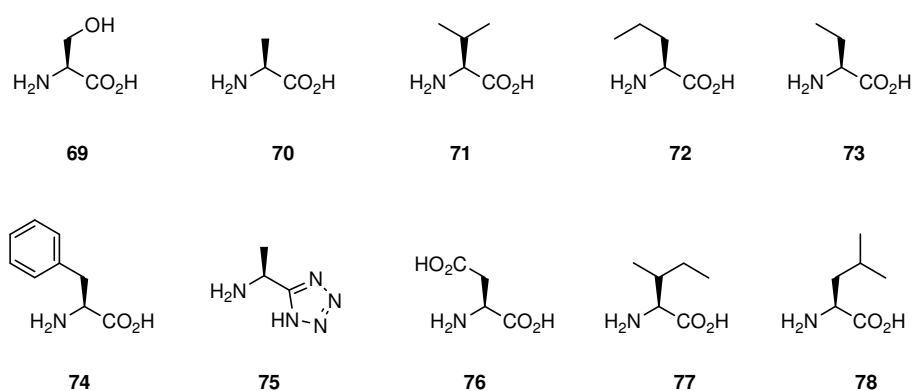


Scheme 1.20

Stirring cyclohexanone (**66**), *p*-anisidine (**40**), *p*-nitrobenzaldehyde (**67**), and L-serine **69** in H₂O/DMSO gave *syn*- α -substituted β -amino ketone **68** in a 60% yield with a diastereoselectivity of *syn:anti* ratio 6:1 and a 94% e.e. (Scheme 1.21). In comparison, proline catalyzed the formation of **68** in a 50% yield with a lower *syn:anti* ratio 2:1 d.r. and 84% e.e.. Low yields of both these reactions were caused by the formation of trace amounts of the aldol addition products.

Furthermore, various chiral acyclic amines and amino acids were used as catalysts for this asymmetric Mannich reaction (Table 1.11). When aliphatic amino acid (*S*)-alanine (**70**) was used in the reaction, β -amino ketone **68** was formed in 42% yield with a diastereoselectivity of *syn:anti* ratio 3:1 and 98% e.e. (Table 1.11, entry 7). Yield was increased to 68% after extending the reaction time to 48 h, but a loss of e.e. to 86% was obtained (Table 1.11, entry 5). To improve the yield by increasing the nucleophilicity of the amine, one equivalent of dicyclohexyl amine was added. However, it led to a loss of

diastereoselectivity. Moreover, other aliphatic amino acids L-serine (**69**), L-valine (**71**), L-isoleucine (**78**), and L-leucine (**77**) were also tested as the catalysts, which gave the product **68** with diastereoselectivities in a range of *syn:anti* ratio of 2:1 to 6:1 and enantioselectivities 91-94% e.e.. Besides that, it was observed that addition of small amounts of water slightly improved the yield. Previous related studies revealed that addition of water accelerates the reaction which improves the yield naturally.⁸⁴



Scheme 1.21.

Table 1.11 Examples of screened amino acids for the catalytic asymmetric three-component Mannich reaction.⁸³

Entry	Catalyst	Time (h)	Yield (%)	d.r.	ee (%)
1	69	48	60	6:1	94
2	69	48	60	2:1	98
3	70	24	32	3:1	90
4	70	14	30	3:1	>99
5	70	48	68	3:1	86
6	70	24	27	3:1	90
7	70	14	42	3:1	98
8	70	48	40	2:1	99

Table 1.11, continued

9	71	48	65	2:1	91
10	72	48	60	3:1	82
11	73	48	61	4:1	85
12	74	48	75	2:1	79
13	75	12	74	3:1	94
14	75	12	89	3:1	94
15	76	48	82	3:1	58
16	77	48	38	6:1	93
17	78	48	18	3:1	91

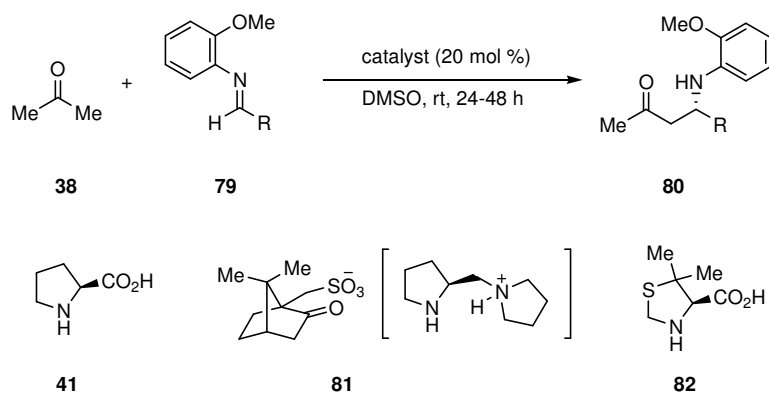
^a In a typical experiment, the catalyst (30 mol %) was added to a mixture of ketone **66** (1.5 mmol), *p*-anisidine (0.45 mmol), and *p*-nitrobenzaldehyde (0.5 mmol) and H₂O (1 mmol) in DMSO (2.0 mL). ^b Isolated yield of the pure aldol products after silica gel column chromatography based on the amine component. ^c Syn/anti ratio as determined by NMR analysis. ^d Determined by chiral-phase HPLC analyses. ^e 1 equiv. of dicyclohexyl amine was added. ^f 5 equiv. of water were added. ^g No water was added. ^h 10 equiv. of the ketone was used.

When chiral amine **75** was tested in the reaction, β -amino ketone **68** was obtained with a 89% yield, a d.r. of *syn:anti* ratio of 6:1 and a 94% e.e. (Table 1.11, entry 14). The use of tetrazole derivative **75** improved the catalyst solubility, which increased the catalytic efficiency as well. In this case, the highest efficiency was obtained when no water was added. The investigation of acyclic amino acid or amine catalyzed Mannich reaction dramatically expanded the catalyst structure. The possible employment of a whole range of amino acids would be raised, which provides the synthesis of enantiopure β -amino ketone more versatile methods.^{85,86}

1.3.3. Preparation of β -Amino Ketones via Mannich Reaction by using Aldimines and Ketones.

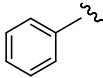


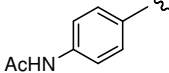


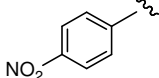


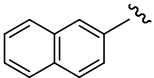

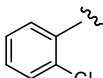
In previous studies of three-component proline-catalyzed asymmetric synthesis of β -amino ketone, ketone and proline derived enamines added stereoselectively to the *in situ* formed imine from aldehyde and aryl amine. According to the wide range of commercially available and easily made imines,⁸⁷ the direct catalyzed reaction between enamine and preformed imines will become a highly attractive research area.

During the discovery of the one-pot three-component Mannich reaction, Barbas and co-workers performed the asymmetric Mannich reaction of acetone (**38**) with a variety of aldimines.⁸⁸ The mixture of acetone (**38**) and *N*-*p*-methoxyphenyl (PMP) aldimines **79a-e** was catalyzed by amino acids and their derivatives in the solvent of DMSO. In the screen for the addition of acetone (**38**) to *N*-*p*-methoxyphenyl (PMP) aldimines **79a-e** with 20 mol % of catalysts **41**, **81** and **82**, all these catalysts afforded the β -amino ketones **80a-e** in modest yields (Table 1.12). It was observed that compared to other catalysts **41** and **81**, catalysts **82** gave a higher enantioselectivity of 80% e.e. when the *para*-nitrophenyl imine **79c** reacted with acetone (Table 1.12, entry 8).



Scheme 1.22

Table 1.12 Aldimine derived organocatalytic synthesis of β -Amino ketones.⁸⁸

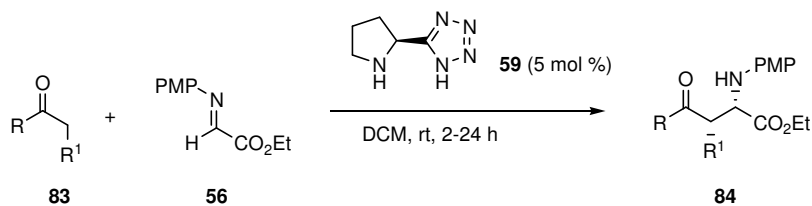
Entry	R	Catalyst	Yield (%)	ee (%)	
1		79a	81	43	2
2		82	45	15	
3		81	50	67	
4		79b	41	48	51
5		82	48	60	
6		81	40	55	
7		79c	41	50	40
8		82	48	80	
9		81	32	25	
10		79d	41	42	86
11		82	56	88	
12		79e	82	47	75

Although proline and its derivatives have proved to be highly enantioselective in the aldimine-derived Mannich reaction, the formation of the product always required highly polar solvents such as DMSO due to the low solubility of proline in other solvents. A high solubility of the catalyst would improve the catalytic efficiency correspondingly.

Ley et al. reported the Mannich addition of ketones to *p*-methoxyphenyl (PMP) α -amino ethyl glyoxalate (**56**) catalyzed by 5-pyrrolidin-2-yltetrazole (**59**).⁸⁰ This new organocatalyst has significant advantage over its parent analog L-proline in that it can be used in non-polar solvents without loss of enantioselectivity.⁸⁹ Furthermore, the scope of this reaction was expanded to other cyclic and acyclic ketones such as 3-pentanone and

cyclohexanone. All these aliphatic ketones afforded Mannich products in excellent stereoselectivities.

When both cyclic ketones **83a**, **83b** and acyclic ketones **83c**, **83d** were subject to the organocatalyzed addition to *N*-PMP-iminoglyoxylate (**56**), all the products **84a-d** were formed with 99% e.e. but moderate yields (Table 1.13, entries 1-4). α -Fluoro acetone **83e** was converted to its corresponding product β -amino ketone **84e** with a low yield of 31% and a slight e.e. of 14% (Table 1.13, entry 5). This result demonstrated that low yield of product **84e** was caused by the slow rate, which is mainly due to the formation of a biphasic mixture between the DCM and fluorous phases. Almost quantitative yield was observed when acetone **83f** was reacted, which also led to an enantioselectivity of over 99% e.e. (Table 1.13, entry 7). The reaction to form β -amino ketone **84g** was performed in neat acetone, which simplifies the purification into the evaporation of the solvent after filtration of reaction mixture through a short pad of silica.

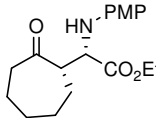
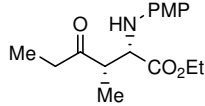
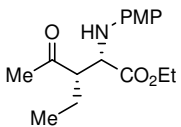
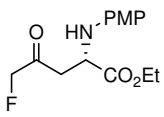
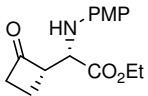
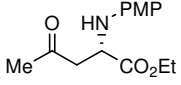


Scheme 1.23

Table 1.13 Tetrazole-catalyzed addition of ketones **83** to *N*-PMP-ethyl iminoglyoxylate **56**.⁸⁰

Entry	Product	Time (h)	Yield (%) ^a	d.r. (<i>syn/anti</i>) ^b	ee (%) ^c
1	 84a	2	65	>19:1	>99

Table 1.13, continued

2		84b	8	59	>19:1	>99
3		84c	16	63	>19:1	>99
4		84d	8	72	>19:1	>99
5		84e	24 ^d	31	--	14
6		84f	24	74	>19:1	94
7		84g	8	99 ^e	--	>99

^a Based on isolated product. ^b Determined by ¹H NMR spectroscopy. ^c Determined by chiral HPLC. ^d Reaction stopped after 24 h at 55% conversion. ^e Reaction performed at acetone.

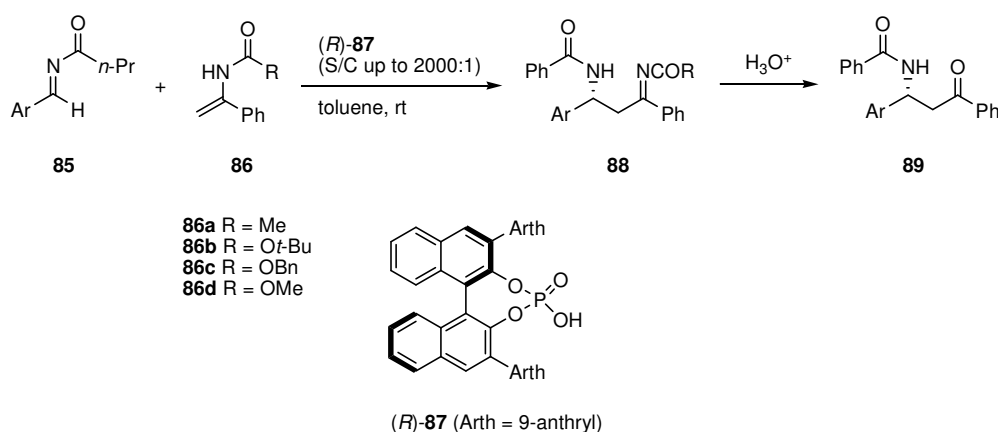
Tetrazole catalyst **59** has shown a high ability in catalyzing Mannich addition of ketones to *N*-PMP protected α -imino ethyl glyoxalate in non-polar solvents. This represents an attractive alternative to L-proline, which avoids the use of DMSO and reduces the amount of catalyst without compromising enantioselectivity. Except that, due to its reactivity and exclusive (*E*) geometry, the *N*-PMP-imine has become a typical electrophile in Mannich addition.⁹⁰⁻⁹²

1.3.4. Bifunctional Bronsted Acid Activation of the Mannich Reaction

Most of the organocatalysts discussed have focused on activation of the carbon nucleophilicity by formation of an enamine intermediate and its nucleophilic attack onto the preformed imine. Few investigations have been made so far into the improvement of the electrophility of the imine. Although electrophilic activation of a substrate by Bronsted acid has been a classical approach to promote reaction, the development of effective asymmetric Bronsted acid transformation in Mannich reaction has been relatively limited.^{93,94}

1.3.4.1. Chiral Bronsted Acid Catalyzed Mannich Reaction

Although organocatalysts have proven to be highly diastereoselective in the Mannich reaction, one critical drawback of this methodology is the inadequate catalytic efficiency.^{95,96} Most of those reactions are performed at the substrate-to-catalyst (S/C) molar ratio of 10 or less to achieve sufficient yields without loss of stereoselectivity. Terada and co-workers reported a high substrate-to-catalyst (S/C) molar ratio reaction with chiral Bronsted acid (*R*)-**87** as the catalyst.⁹⁷



Scheme 1.24

Starting with *N*-benzoylimines **85** and enamides **86a-d**, after stirring at rt in toluene, β -aminoimine **88a-d** was obtained in high yields and good enantioselectivities (Scheme 1.24). The optimized reaction conditions permit an imine-to-catalyst molar ratio up to 2000 to afford the corresponding products with high enantioselectivities.

Results were listed in the table (Table 1.14), the S/C ratio was first set to 50:1 (2 mol % catalyst amount) when using the binaphthol-derived monophosphoric acid (*R*)-**87** as the catalyst. Reaction was finished with a yield of 77% and a 69% e.e. in DCM (Table 1.14, entry 1). The yields and enantioselectivities were determined after hydrolysis of imine adducts **88** to β -aminoketones **89** under HBr in MeOH work-up conditions. Among the different solvents tested, toluene was the best with respect to both yield and enantiomeric excess (Table 1.14, entries 1-4).

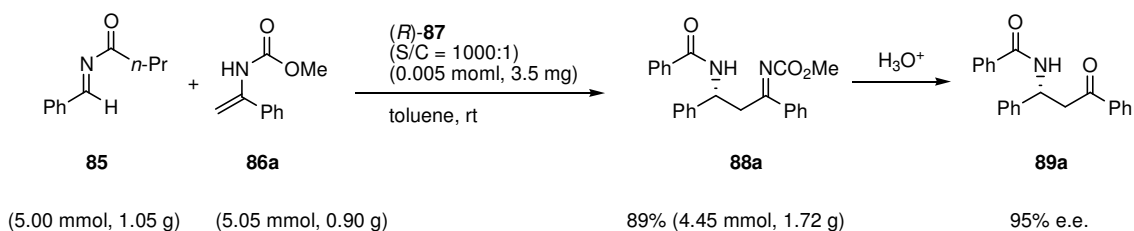
When enamide **86a** and various enecarbamates **86b-d** were subject to the reaction conditions with benzoylimine **85** in toluene, a dramatic steric effect was observed with different alkoxy substituted enecarbamates. The enantioselectivity increased with decreasing size of the alkoxy moiety, which followed the order of e.e. *t*-BuO **86b** < BnO **86c** < MeO **86d** reaching 95% ee in the reaction with the smallest methyl carbamate **86d** (Table 1.14, entry 7). Lowering the reaction temperature and catalyst loading still achieved a comparable level of product formation (Table 1.14, entries 8-11). In these cases, the enantioselectivities and the yields were maintained at an equally high level. Most importantly, it should be emphasized that the reaction can be performed without considerable loss of enantioselectivity, even when the S/C ratio was increased to as much as 2000:1 (0.05 mol % catalyst amount) (Table 1.14, entry 11).

Table 1.14 Chiral Bronsted acid-catalyzed reaction of imine **85** with an enamide **86a** and enecarbamates **86b-d**.⁹⁷

Entry	86	S/C	(mol %)	Solvent	Time (h)	Yield (%)	ee (%)
1	86a	50:1	2	DCM	0.5	77	69
2	86a	50:1	2	DCE	0.5	61	70
3	86a	50:1	2	Et ₂ O	0.5	71	80
4	86a	50:1	2	toluene	0.5	90	86
5	86b	50:1	2	toluene	1	94	60
6	86c	50:1	2	toluene	1	55	83
7	86d	50:1	2	toluene	1	85	95
8 ^e	86d	50:1	2	toluene	1	76	96
9	86d	1000:1	0.1	toluene	2	64	95
10	86d	1000:1	0.1	toluene	5	82	95
11	86d	2000:1	0.05	toluene	5	85	93

^a Unless otherwise noted, all reactions were carried out with 0.10 mmol of 2 (Ar = Ph) and 0.12 mmol of 3 in a 0.1 M solution at rt. ^b Molar ratio of imine 2/catalyst 1. ^c Yield of the isolated product of 5 after hydrolysis of 4. ^d Enantiomeric excess was determined by chiral HPLC analysis. ^e Reaction performed at 0 °C.

The high S/C process was further evaluated by performing a large-scale experiment on the preparation of β -aminoimine **88a** (Scheme 1.14). It is noteworthy that only an amount of 3.5 mg of (*R*)-**87** was sufficient to yield 1.7 g of the β -aminoimine product **88a** with high conversion rate (89% yield) of this reaction. Product β -amino ketone **89a** was obtained with a 95% e.e. after hydrolysis of its precursor β -aminoimine **88a**, which demonstrated a high stereoselectivity of the gram scale catalytic reaction.



Scheme 1.25

A highly efficient enantioselective aza-ene-type reaction of *N*-benzoyl-imine with enecarbamates has been developed. The present method provides a practical route to synthetically useful enantiopure β -amino ketone. Furthermore, the formed intermediate β -amino-imine derivatives can be readily transformed into 1,3-diamines via reduction, of which derivatives are of highly synthetic and biological importance.^{98,99}

1.3.4.2. Chiral Bronsted Acid-Base Combined Salt Catalyzed Mannich

Reaction

A chiral organic salt which consists of a Bronsted acid and a Bronsted base is one of the most promising catalysts in asymmetric syntheses.^{100,101} In general, the acid-base combinations have several advantages over single-molecule catalysts, with regard to flexibility in the design of their combined salts. Chiral ammonium sulfonates¹⁰² and ammonium phosphonates¹⁰² are typical examples of these organocatalysts with enantioselective properties. 2,2'-Disubstituted 1,1'-binaphthyl compounds are some of the most used structures in this type of chiral organocatalysts.^{103,104}

However, these compounds often require bulky substituents at the 3,3'-positions to achieve high enantioselectivity in asymmetric catalysis. In contrast, chiral 1,1'-binaphthyl-2,2'-disulfonic acid (BINSA **90**) is a more promising chiral Bronsted acid

catalyst, since both the Bronsted acidity and bulkiness can be easily controlled by complexation with achiral amines without changing the substitutions at the 3,3'-position in a binaphthyl skeleton (Figure 1.9).^{105,106}

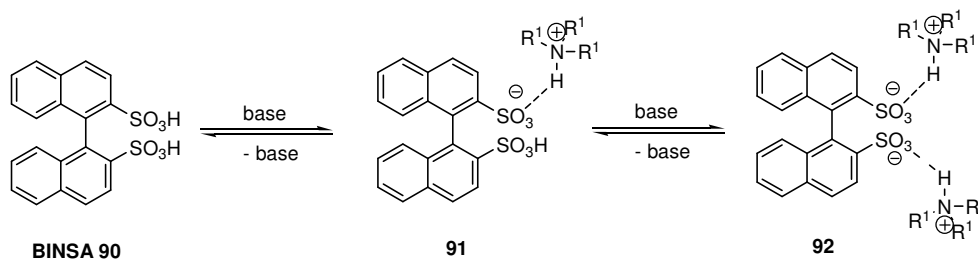
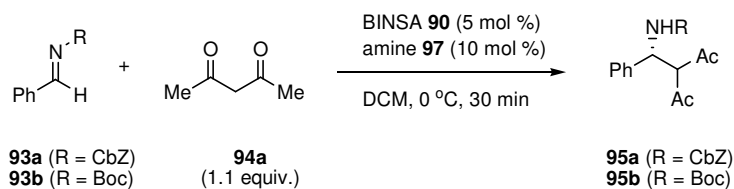


Figure 1.9

In 2008, Ishihara et al. reported a practical synthesis of chiral BINSA **90** and applied this stereoselective catalysis in the Mannich reaction of making β -amino ketone by using 2,6-diarylpyridine as the combined salts.¹⁰⁷ The first reaction was examined between *N*-Cbz-phenylaldimine (**93a**) and acetylacetone (**94**) (Table 1.15) in DCM at 0 °C. Addition of 5 mol % of BINSA **90** led to the formation of product **95** with an only 17% e.e. (Table 1.15, entry 1). After that, the chiral BINSA **90** and achiral amine combined salts were examined as the chiral Bronsted acid-base catalysts. Addition of pyridine, 2-phenylpyridine, and 2,6-lutidine all gave product **95a** in low yield owing to the insolubility of the corresponding salts (Table 1.15, entries 2-4). In comparison, 2,6-di-*tert*-butylpyridine improved the enantioselectivity up to 76% e.e. (Table 1.15, entry 5). Moreover, when BINSA **90** was combined with 2,6-diphenylpyridine, a homogeneous catalyst was formed *in situ*, which was found to be highly effective to afford **95a** in a 74% yield and 92% e.e. (Table 1.15, entry 6). Similarly, when *N*-Boc-phenylaldimine

93b was subject to the standard reaction condition, adduct *N*-Boc- β -amino ketone **95b** was obtained in 83% yield with 85% e.e. (Table 1.15, entry 7).



Scheme 1.26

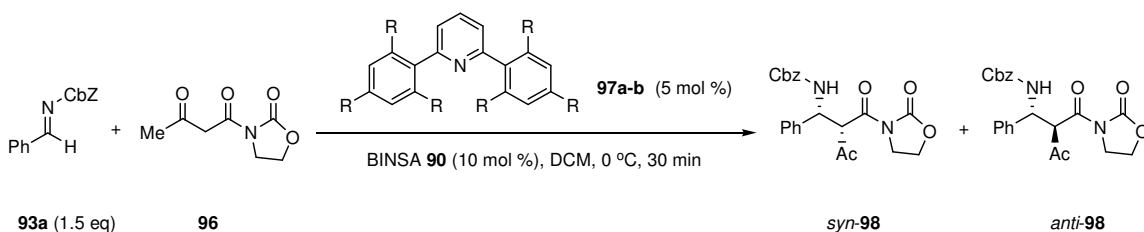
Table 1.15 Ammonium salts of **90** as Tailor-made catalysts.¹⁰⁷

Entry ^a	Imine	Amine 97	Product	Yield (%)	ee (%)
1	93a	--	95a	81	17
2	93a	C ₅ H ₅ N	95a	8	5
3	93a	2-Ph- C ₅ H ₅ N	95a	11	10
4	93a	2,6-Me ₂ -C ₅ H ₃ N	95a	19	0
5	93a	2,6- <i>t</i> -Bu ₂ -C ₅ H ₃ N	95a	32	76
6	93a	2,6-Ph ₂ -C ₅ H ₃ N (97a)	95a	74	92
7	93b	2,6-(1,3,5-trimethyl-Ph) ₂ -C ₅ H ₃ N (97b)	95b	83	85

^a Acetylacetone **7a** was added at 0 °C over 1 h, and the resultant mixture was stirred for 30 min.

Based on the above results, this chiral combined ammonium salt **90.97a₂** was utilized in the reaction of *N*-Cbz-phenylaldimine (**93a**) and ketoester equivalent 3-acetoacetyl-2-oxazolidinone (**96**) (Scheme 1.27). However, the optimized chiral ammonium salt **90.97a₂** was not effective in promoting this asymmetric Mannich reaction, α -substituted β -amino ketone **98** was obtained in 86% yield but with low diastereoselectivities and enantioselectivities. In contrast, when 2,6-dimesitylpyridine (**97b**) was used in place of 2,6-diphenylpyridine (**97a**), the enantioselectivity of *syn*-

diastereomer **98** increased to 93% e.e., while *anti*-diastereomer **98** gave a 90% e.e.. In this way, suitable chiral ammonium salts could be easily tailor-made for different reactions, which made it possible to avoid preparing single-molecule catalysts in advance, thus offering a quick solution to the optimization problem.



97a (R = H): 86% (*syn:anti* = 53:47), 72% ee (*syn*) and 20% ee (*anti*)

97b (R = Me): 81% (*syn:anti* = 60:40), 93% ee (*syn*) and 90% ee (*anti*)

Scheme 1.27

In summary, BINSA was found to be a highly effective chiral Bronsted acid that could be combined with an achiral Bronsted base to catalyze the asymmetric Mannich reaction. Moreover, it was believed that BINSA would become a powerful chiral auxiliary that could trigger a new frontier in acid-base chemistry in asymmetric catalyses.

1.4. Introduction to Chiral *p*-Toluenesulfinimine and *p*-Toluenesulfinamide

Chiral amines are present in a large majority of bioactive alkaloids and heterocyclic compounds. Consequently, the asymmetric synthesis of enantiopure amine containing compounds represents an important endeavor in the discovery and production of new bio-related reagents. In the past four decades, an ever increasing collection of methods based upon the chiral amine reagents *p*-toluenesulfinamides and *p*-toluenesulfinimines have become some of the most extensively used synthetic approaches for the synthesis of bioactive compounds (Figure 1.10).¹⁰⁸

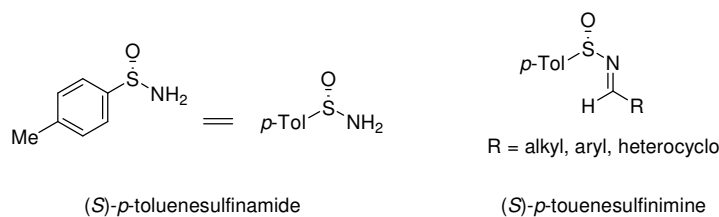


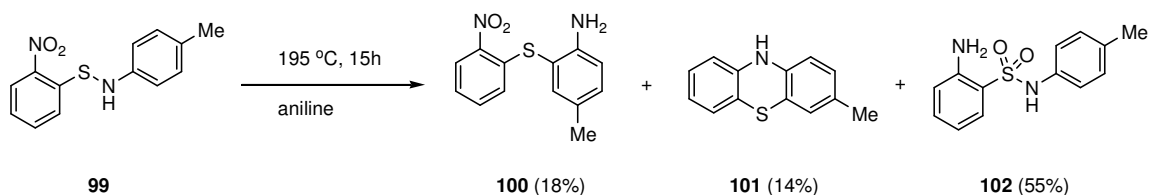
Figure 1.10

1.4.1. Brief Introduction to Sulfur-Nitrogen Chemistry.

Compounds containing the sulfur-nitrogen bond are of considerable importance both from a practical as well as a theoretical standpoint. These compounds have been reported to be useful as antiradiation drugs, antioxidants and accelerators in the vulcanization of rubber. In the last forty years, the chemistry of sulfur-nitrogen compounds has received intensive investigation, but it still retains the capacity to confound the chemists.¹⁰⁹ In nature, sulfur-nitrogen compounds are regularly found with unexpected structures and properties. One of the most remarkable compounds is the polysulfurnitride, which has metallic properties, even though it contains only nonmetallic elements.¹¹⁰

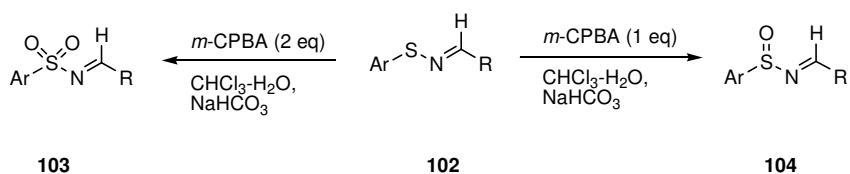
Sulfur-nitrogen compounds that contain sulfur and coordinate nitrogen are usually classified as sulfur imides,¹¹¹ thionyl imides (*S* IV),¹¹² sulfuryl imides (*S* VI)¹¹² and thiazenes (*S* IV or VI).¹¹³ The strength of sulfur-nitrogen bonds in these compounds are greatly affected by factors, such as steric interactions, lone pair electron repulsion and p-d π bonding.¹¹⁴ The variability in these effects would lead to different sulfur-nitrogen bond energy, which gives the varied thermal stabilities of sulfur nitrogen compounds.

To investigate these sulfur-nitrogen compounds' thermal stability, Davis and co-workers first performed studies focused on the mechanisms of the thermal rearrangements of sulfenamides (sulfur imides) (Scheme 1.28),¹¹⁵ about which little was known at that time. Interestingly, it was observed that after heating of sulfenamide **99** at 195 °C, 2'-amino-2-nitrodiphenyl sulfide (**100**) and 3-methylphenothiazine (**101**) were produced, along with the major product 2-aminobenzenesulfon-*p*-toluidine (**102**) in 55% yield. A possible reason for the formation of the sulfonamide was that *o*-nitro group could transfer its oxygen atom onto the adjacent sulfur group.^{116,117}



Scheme 1.28

Similar oxidation was observed in the oxidation of sulfenimines.¹¹⁸ When 2 equivalents of *m*-chloroperbenzoic acid (*m*-CPBA) was used, the sulfonimine was produced in which two oxygen atoms are transferred from the peroxides to the aryl sulfur group. Significantly, when only one equivalent of the oxidation was used, selective oxidation of the sulfenimine gave the corresponding sulfinimine **104** in excellent yield (Scheme 1.29).



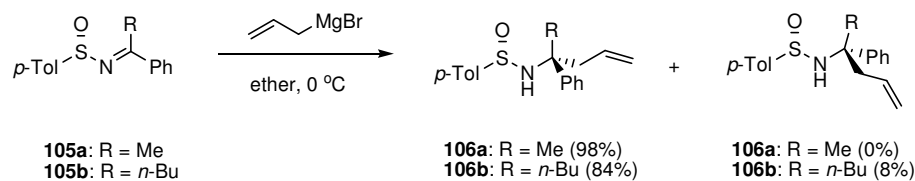
Scheme 1.29

Compared with sulfenimines, sulfinimine **104** was relatively stable and preferred the (*E*) configuration of the single isomer while the sulfenimine **102** was a mixture of *E/Z* isomers.¹¹⁹ Enhanced stability may be attributed to an attractive interaction between the sulfinyl oxygen and the proton on the imino carbon. Sulfenimines have proven to be compounds with most of their reactions occurring at the S-N rather than the C-N bond.¹²⁰ By contrast, the sulfinyl group in sulfinimine greatly activates the C-N double bond for nucleophilic addition.

1.4.2. Enantiopure sulfinimines

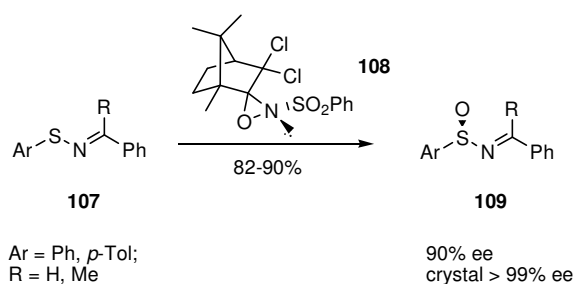
Racemic sulfinimines were first discovered by Davis et al. in 1974.¹¹⁸ Burger and co-workers reported the synthesis of racemic sulfinimines by reacting sulfinamide with hexafluoroacetone.¹²¹ The first optically active sulfinimines were prepared by Cinquini and co-workers by the reaction of Grignard reagents and benzonitrile, then followed by addition of (-)-menthyl (*S*)-*p*-toluenesulfinate.¹⁰⁸ The sulfinimine compounds were obtained with an inversion of chirality at sulfur, of which absolute configurations were assigned on that basis.

As part of a study on sulfinimine chemistry, the investigation in the enantioselective addition reaction of chiral *N*-sulfinyl ketimines were reported by Hua et al.¹²² Treatment of sulfinyl ketimines **105** with allylmagnesium bromide gave the sulfinamide (*R*)-**106** with excellent stereoselectivity and can be converted into optically pure amines, β - and γ -amino acids readily (Scheme 1.30). These results demonstrated that as a chiral auxiliary the sulfinyl group displays a unique reactivity and stereoselectivity in directing nucleophilic addition.



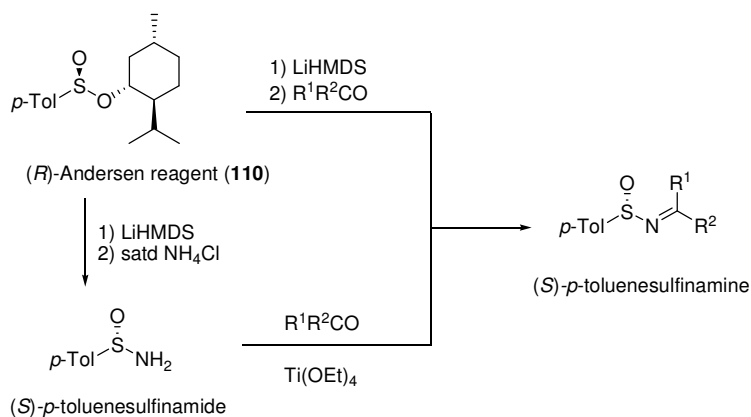
Scheme 1.30

Davis et al. reported a general approach for the synthesis of chiral sulfinimines in both enantiomeric forms.¹²³ The method involves the asymmetric oxidation of sulfenimines derived from aldehydes with (+)- or (-)- Davis oxaziridine¹²⁴ **108** (Scheme 1.31). The sulfinimines were isolated in 85-95% yield and 88-90% e.e., further crystallization of the crude sulfinimines improved the e.e. to >97%.



Scheme 1.31

Since it was impractical to prepare enantiopure sulfinimines by asymmetric oxidation of sulfenimines with oxaziridines, Davis and co-workers devised a more practical one-pot method using the Andersen reagent (+)- or (-)-menthyl *p*-toluenesulfinate (**110**). Treatment of (*R*)-Andersen reagent (**110**) with LiHMDS in the presence of various aldehydes, the corresponding enantiopure *p*-toluenesulfinimines (R¹ = H) were isolated in good to excellent yields (Scheme 1.32).¹²⁵ However, this one-pot procedure was only general for aldehydes and separation of the menthol by-product was problematic.



Scheme 1.32

A more innovative method developed by Davis et al. is the condensation of *p*-toluenesulfinamide with aldehydes and ketones using the mild Lewis acid dehydrating reagent Ti(OEt)_4 .¹²⁶ This sulfinimine preparation method can be utilized with diverse aldehydes and ketones, and nowadays it is demonstrated to be remarkably general, affording sulfinimine in high yield and enantiomeric purity (Scheme 1.32).

The discovery of sulfinimines provides a general solution to the problem of addition of organometallic reagents to chiral imines. In the structure of sulfinimine, the electron-attracting sulfinyl group activates the $\text{C}=\text{N}$ bond for nucleophilic addition. The chiral sulfinyl auxiliary also exerts powerful and predictable stereodirecting effects, which results in addition of organometallic reagents to sulfinimines with high diastereoselectivities. The sulfinyl group in the product sulfinamide is easily removed under comparatively mild conditions.

1.4.3. Enantiopure *p*-toluenesulfinamides

Enantiopure *p*-toluenesulfinimines have been used in the synthesis of a large number of chiral amine derivatives, it is therefore important to develop practical methods for the synthesis of enantiomeric *p*-toluenesulfinamide. The synthesis and isolation of enantiomerically pure *p*-toluenesulfinamine was first reported by Davis and co-workers in 1997.¹²⁷ Treatment of the (*R*) and (*S*) menthyl *p*-toluenesulfinate (Andersen reagent) with LiHMDS followed by aqueous workup afforded both the (*S*) and (*R*) forms of *p*-toluenesulfinamides. This method has become a highly practical procedure for producing enantiopure *p*-toluenesulfinamides. Since then, different types of sulfinamide derivatives have been reported. Ellman developed *tert*-butanesulfinamide^{128,129} and (*S*)-(+)-2,4,6-trimethylphenylsulfinamide was prepared by Senanayake^{130,131} and has significantly expanded the utilization of sulfinimine chemistry. By far, *p*-toluenesulfinamide and *tert*-butanesulfinamide are the most convenient reagents for the preparation of chiral sulfinimines. Both sulfinamides are commercially available in both *R* and *S* forms. Some other sulfinamides are listed below (Figure 1.11).

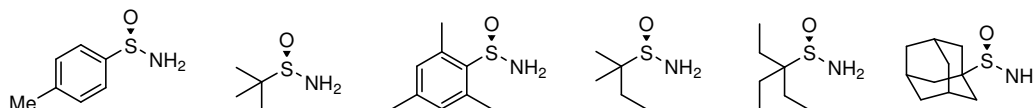


Figure 1.11

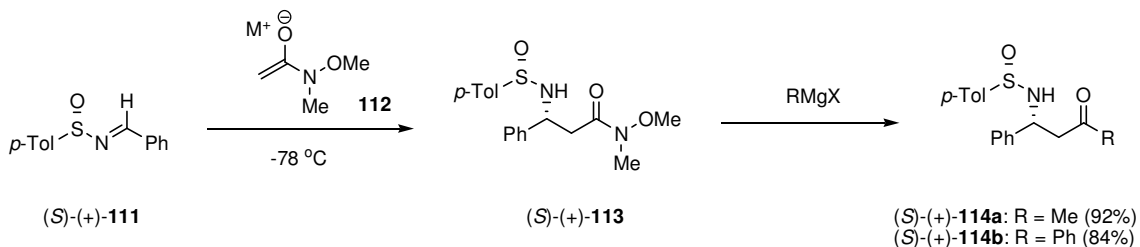
1.4.4. Preparation of enantiopure β -amino ketones from *p*-toluenesulfinimines.

The wide utility of *p*-toluenesulfinimines in the highly diastereoselective asymmetric syntheses of amine derivatives has been reviewed.^{132,133} Among the various

synthetic applications starting from Davis sulfinimine (*p*-toluenesulfinimine), one of the most valuable utilizations is the extension of sulfinimine to the preparation of chiral β -amino ketone.

1.4.4.1. Preparation of β -amino ketone from β -amino Weinreb amides.

Davis and co-workers reported the first synthesis of chiral β -amino ketones (+)-**114** by reacting organometallic reagents with *N*-sulfinyl β -amino Weinreb amide (+)-**113**, prepared by addition of the potassium enolate of *N*-methoxy-*N*-methylacetamide (**112**) to *p*-toluenesulfinimine (+)-**111** (Scheme 1.33).¹³⁴ Weinreb amides which were introduced by Nahm and Weinreb in 1980s,¹³⁵ are valuable carbonyl equivalents and are widely used for the synthesis of carbonyl compounds.¹³⁶

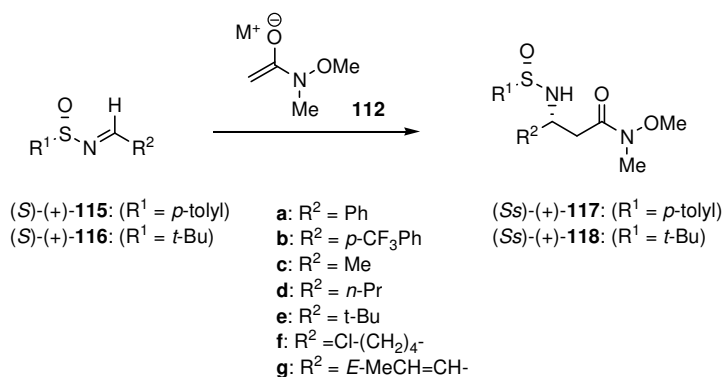


Scheme 1.33

In the process of preparing *N*-sulfinyl β -amino Weinreb amide **117**, **118**, all these products are formed in moderate to good diastereoselectivities and yields (Scheme 1.34, Table 1.16). *N*-*p*-Toluenesulfinylimines (S)-(+)-**115** gave better yields and higher diastereoselectivities than the corresponding *N*-(*tert*-butylsulfinyl)imines (S)-(+)-**116** (Table 1.16, entries 3, 6-11, 12-14). It was observed that the diastereomeric Weinreb amides **118**, derived from the sulfinimine **116**, could not be separated by chromatography.

For *p*-toluenesulfinimine (S)-(+)-**115**, corresponding product *N*-sulfinyl β-amino Weinreb amide (Ss)-(+)-**117** was obtained with best yields and highest diastereo-selectivities when the potassium enolate of *N*-methoxy-*N*-methylacetamide **112** was reacted in THF.

Furthermore, most of the β-amino Weinreb amides **117** were made with diastereoselectivities better than 98%.



Scheme 1.34

Table 1.16 Synthesis of β-amino Weinreb amides **117** and **118** from sulfinimines and *N*-methoxy-*N*-methylacetamide at -78 °C.¹³⁷

entry	sulfinimine		Base	Weinreb	dr (% de) ^a	Yield (%) ^c
	R ¹	R ²		amide		
1	115a	<i>p</i> -tolyl	Ph	LiHMDS (THF)	(+)- 117a	79:21 (58) ^b
2	115a	<i>p</i> -tolyl	Ph	NaHMDS (THF)	(+)- 117a	82:18 (64)
3	115a	<i>p</i> -tolyl	Ph	KHMDS (THF)	(+)- 117a	85:15 (70) 65 ^d
4	115a	<i>p</i> -tolyl	Ph	KHMDS (PhMe)	(+)- 117a	51:49 (2)
5	115a	<i>p</i> -tolyl	Ph	KHMDS (Et ₂ O)	(+)- 117a	54:46 (8)
6	115b	<i>p</i> -tolyl	<i>p</i> -CF ₃ Ph	KHMDS (THF)	(+)- 117b	77:23 (54) ^e
7	115c	<i>p</i> -tolyl	Me	KHMDS (THF)	(+)- 117c	92:8 (84) 52
8	115d	<i>p</i> -tolyl	<i>n</i> -Pr	KHMDS (THF)	(+)- 117d	99:1 (98) 68
9	115e	<i>p</i> -tolyl	<i>t</i> -Bu	KHMDS (THF)	(+)- 117e	99:1 (98) 68

Table 1.16, continued

10	115f	<i>p</i> -tolyl	Cl-(CH ₂) ₄	KHMDS (THF)	(+)- 117f	99:1 (98)	76
11	115g	<i>p</i> -tolyl	<i>E</i> -MeCH=CH-	KHMDS (THF)	(+)- 117g	99:1 (98)	82
12	116a	<i>t</i> -Bu	Ph	KHMDS (THF)	(+)- 118a	52:48 (4) ^e	
13	116d	<i>t</i> -Bu	<i>n</i> -Pr	KHMDS (THF)	(+)- 118d	86:14 (72) ^e	
14	116e	<i>t</i> -Bu	<i>t</i> -Bu	KHMDS (THF)	(+)- 118e	88:12 (76) ^e	

^a Determined by ¹H NMR of the crude reaction mixture unless otherwise noted. ^b Estimated by isolation of the two diastereoisomers. ^c Isolated yield of major diastereoisomer. ^d Isolated by fractional crystallization. ^e Inseparable mixture of diastereoisomers.

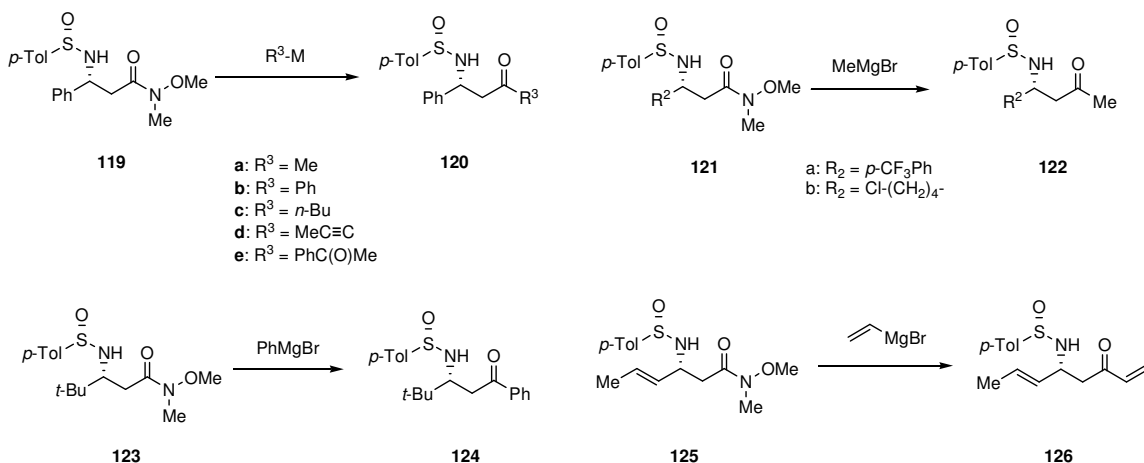
The exceptions were products derived from sulfinimines prepared from aromatic aldehydes, **115a** (R² = Ph), **115b** (R² = *p*-CF₃Ph) and **115c** (R² = Me), where the maximum d.e. values were 70%, 54% and 84%, respectively (Table 1.16, entry 3, 6 and 7). The absolute stereochemistry of the major diastereoisomers for enolate additions to sulfinimines (*S*)-**115** and (*S*)-**116** was determined to be *R* by independent syntheses. The addition of organometallic reagents to the C-N double bond of sulfinimines is assumed to have the six-membered chairlike transition states where the metal ion, Li⁺, Na⁺, or Zn²⁺ is coordinated to the sulfinyl oxygen.¹³⁸ The experimental results obtained are in agreement with this chelation-control transition-state hypothesis. However, it was not anticipated that the potassium enolate of *N*-methoxy-*N*-methylacetamide gave better diastereoselectivities than either the lithium or sodium enolates (Table 1.16, entries 1-3), because potassium ions are generally thought to be poorer coordinating ions than lithium or sodium.

The subsequent step was reacting the prepared *N*-sulfinyl β-amino Weinreb amides **117**, **118** with various organometallic reagents to give corresponding *N*-sulfinyl β-amino ketones (Scheme 1.35, Table 1.17). It was found that 5 equivalents of the

organometallic reagent afforded the best yields and shortest reaction times.

Methylmagnesium bromide reacted with amide **119**, **121a** and **121b** afforded the corresponding methyl ketones **120a**, **122a** and **122b**, respectively, in good yield (Table 1.17, entries 1, 10-11). Phenylmagnesium bromide with amide **119** and **123** gives the phenyl ketones **120b**, **124** in 84% and 88% yields (Table 1.17, entries 4 and 12).

In comparison, Grignard reagents are generally more efficient than lithium reagents in giving high yields of *N*-sulfinyl β -amino ketone (Table 1.17, entry 1, 3, 4-5), although *n*-butyllithium with amide **119** afforded *n*-butyl ketone **120c** in 88% yield (Table 1.17, entry 6). Reactions were usually complete within 1-2 h, except that amide **119** with 1-propynylmagnesium bromide required 12 h for reaction. It afforded alkynyl ketone **120d** in a 95% yield (Table 1.17, entry 8-9).



Scheme 1.35

Table 1.17 Synthesis of *N*-sulfinyl β -amino ketones from β -amino Weinreb amides and organometallic reagents.¹³⁷

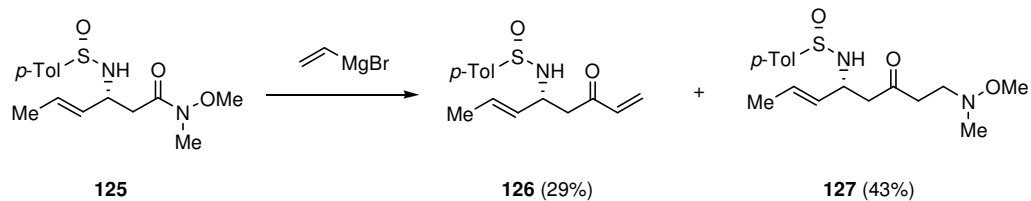
entry	Weinreb amide (R^2)	R^3 (eq)	conditions	product	yield (%)
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Table 1.17, continued

1	Ph	119	MeMgBr (5)	THF, 2.5, -78 to rt	120a	92 (Me)
2			MeMgBr (3)	THF, 2.5, -78 to rt	120a	67 (Me)
3			MeLi (5)		120a	60 (Me)
4			PhMgBr (5)	THF, 2.5, -78 to rt	120b	84 (Ph)
5			PhLi (5)	THF, 1.0, -78 to rt	120b	49 (Ph)
6			<i>n</i> -BuLi (8)	THF, 0.5, -78	120c	88 (<i>n</i> -Bu)
7			MeC≡CMgBr (5.0)	THF, 2.5, -78 to rt	120d	72 (MeC≡C)
8			MeC≡CMgBr (5.0)	THF, 12, -78 to rt	120d	95 (MeC≡C)
9			PhC(O)Me	LDA	120e	
10	<i>p</i> -CF ₃ Ph	121a	MeMgBr (5)	THF, 2.5, -78 to rt	122a	63 (Me)
11	Cl-(CH ₂) ₄ -	121b	MeMgBr (5)	THF, 0.5, -78 to rt	122b	77 (Me)
12	<i>t</i> -Bu	123	PhMgCl (5)	THF, 2.5, -78 to rt	124	88 (Ph)
13	<i>E</i> -MeCH=CH-	125	CH ₂ =CHMgBr (10)	THF, 0.5, 0 ^a	126	29 (CH ₂ =CH-)
				THF, 0.5, 0 ^a	127	43 (CH ₂ =CH-)
14				THF, 0.5, 0 ^b	126	56 (CH ₂ =CH-)

^a Quenched by addition of aqueous saturated NH₄Cl to the reaction mixture. ^b Quenched by addition of the reaction mixture to 5:1 H₂O:HOAc.

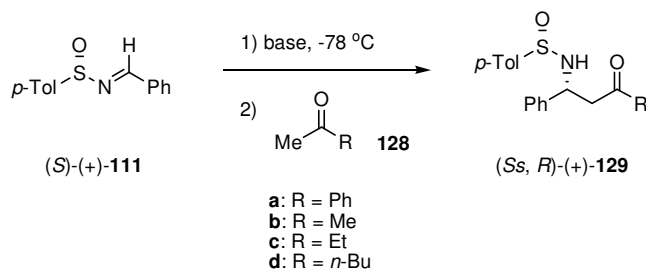
Reaction of unsaturated Weinreb amide **125** with vinylmagnesium bromide only gave ketone **126** in 29% yield (Table 1.17, entry 13),¹³⁹ and β-(*N*-methoxy-*N*-methyl)aminoethyl ketone **127** was formed as a major product (Scheme 1.36). The reason for the low yields was that the liberated *N,O*-dimethylhydroxylamine anion reacts rapidly with product **126** in a Michael type addition. Quenching the reaction with a mixture of H₂O:HOAc (5:1) minimized the formation of side product **127**, which led to an improvement in yield of the product **126** to 56%. The mechanism of adding acetic acid solution is still not clear, but it is more likely that the *N,O*-dimethylhydroxylamine nucleophilicity is reduced that could prevent the formation of product **127**.¹⁴⁰



Scheme 1.36

1.4.4.2. Preparation of β -amino ketones from methyl ketone enolates.

Davis et al. disclosed that nonracemic β -amino ketone (+)-**129** could be prepared by direct reaction of potassium enolates of methyl ketones with sulfinimines (+)-**111** (Scheme 1.37).¹⁴¹ The enolates of methyl ketone were generated from reacting ketones **128**, such as acetophenone (**128a**), acetone (**128b**), 2-butanone (**128c**), and 2-hexanone (**128d**) with the appropriate bases and then (*S*)-(+)-*p*-toluenesulfinimine **111** solution was added at $-78\text{ }^\circ\text{C}$. All obtained results are summarized below (Table 1.18).



Scheme 1.37

Table 1.18 Addition of Methyl Ketone Enolates to Sulfinimine (*S*)-(+)-**111** at $-78\text{ }^\circ\text{C}$.¹³⁴

Entry	Ketone (R =)	Base	Solvent	product	Yield ^a (% de) ^b
1	Ph 128a	LDA	THF	(<i>Ss, R</i>)-(+)- 129a	53 (>96)
2		LiHMDS	THF		59 (>96)
3		NaHMDS	THF		<10

Table 1.18, continued

4			KHMDS	THF		95 (>96)
5	Me	128b	NaHMDS	THF	(<i>Ss, R</i>)-(+)- 129b	<10
6			KHMDS	THF		40 (62)
7			KHMDS	Et ₂ O		72 (70)
8	Et	128c	KHMDS	Et ₂ O	(<i>Ss, R</i>)-(+)- 129c	90 (90)
9	<i>n</i> -Bu	128d	KHMDS	THF	(<i>Ss, R</i>)-(+)- 129d	65 (80)
10			KHMDS	Et ₂ O		83 (90)

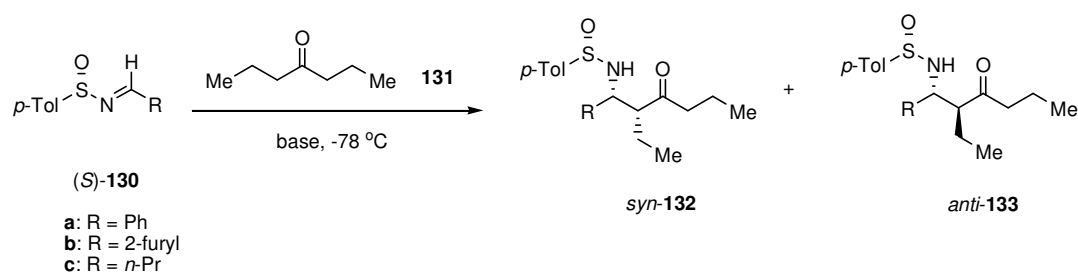
^a Isolated yield of major diastereoisomer. ^b Determined from the ¹H NMR of the crude reaction mixture.

Screened reaction conditions revealed that the potassium enolate of the methyl ketone **128a** afford the highest yield and diastereoselectivity (Table 1.18, entry 4). In this KHMDS/ether reaction condition, the absolute stereochemistry of the newly created stereocenter was established as R by comparison of the rotation of product **129a** with an authentic sample.¹³⁴ Although the lithium enolate of acetophenone (**128a**) gave the ketone **129a** with high d.e. >96%, the yields were modest (Table 1.18, entries 1-2). While changing the enolate metal cation to sodium, reaction produced a complex of mixtures (Table 1.18, entries 3). Furthermore, improved yields and diastereoselectivities were observed when changing the solvent from THF to ether (Table 1.18, entries 6-7 and 9-10).

1.4.4.3. Preparation of enantiopure *syn* α -substituted β -amino ketone from *p*-toluenesulfinimines.

Before the utilization of prochiral enolate addition to the *p*-toluenesulfinimine, methods for the asymmetric synthesis of α -substituted β -amino ketones had not been

described. Similar investigation was performed on asymmetric synthesis of *syn*- and *anti*- α , β -diamino esters by addition of protected glycine enolates to *p*-toluenesulfinimines.^{142,143} Building on these supporting results and new ideas, Davis et al. devised a more direct method for the preparation of *syn*- α -substituted β -amino ketones. This procedure involved the addition of the metal enolate derived from 4-heptanone (**131**) to *p*-toluenesulfinimines (*S*)-**130** (Scheme 1.38).¹⁴⁴



Scheme 1.38

In the typical experiment, the *p*-toluenesulfinimines (*S*)-**130a** was added to the preformed sodium enolate of 4-heptanone (**131**) at $-78\text{ }^{\circ}\text{C}$, two products α -substituted β -amino ketones *syn*-**132a** and *anti*-**133a** were isolated in 66% and 21% yield, respectively (Table 1.19, entry 1). The best selectivities were observed for the lithium enolate in ether, with 1.5 and 3.0 equivalents of the lithium enolate of 4-heptanone (**131**); the ratios of **132a**:**133a** were 9:1 and 18:1, respectively (Table 1.19, entries 9-10).

Table 1.19 Addition of the enolate of 4-heptanone (**131**) to *p*-toluenesulfinimine (*S*)-**130** at $-78\text{ }^{\circ}\text{C}$.¹⁴⁴

Entry ^a	sulfinimine		solvent	enolate		<i>syn</i> : <i>anti</i> ^e (% yield) ^f
	130 (R =)	Base		<i>E,Z</i> ^{b,c} 131 (equiv) ^d	132a : 133a	
1	130a (Ph)	NaHMDS	Et ₂ O	3.5:1 (1.5)	132a : 133a	3:1 (66):(21)
2			Et ₂ O			3:1 (55):(18)

Table 1.19, continued

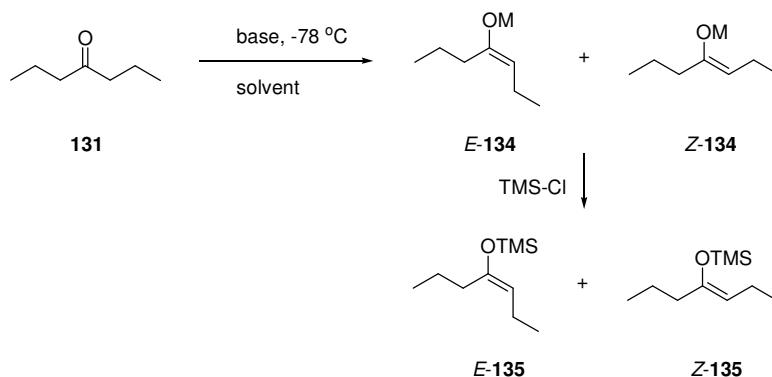
3			Et ₂ O	3.5:1 (0.9)		3:1 (36)
4			Et ₂ O	(1.5)		1:1 (44):(44)
5			THF	1:45 (1.5)		2:1 (55):(24)
6		KHMDS	Et ₂ O	4:1 (1.5)		2:3 (34):(50)
7			THF	1:2.5 (1.5)		6:5 (52):(40)
8			PhMe	(1.5)		2:1 (48)
9		LiHMDS	Et ₂ O	15:1 (1.5)		9:1 (35)
10			Et ₂ O	12:1 (3.0)		18:1 (71)
11			THF	1:2.5 (1.5)		6:1 (21)
12	130b (2-furyl)	NaHMDS	Et ₂ O	3.5:1 (1.5)	132b:133b	3:1 (62):(20)
13		LiHMDS	Et ₂ O	15:1 (3.0)		15:1 (64)
14	130c (<i>n</i> -Pr)	NaHMDS	Et ₂ O	3.5:1 (1.5)	132c:133c	3:1 (65):(21)
15		LiHMDS	Et ₂ O	15:1 (3.0)		12:1 (67)
16		LiHMDS	Et ₂ O	15:1 (3.0)		10:1 (78):(8)
17		LiHMDS	THF	1:2.5 (1.5)		4:1 (20)

^a Sulfinimine transferred to the enolate unless otherwise noted. ^b *E:Z* ratio of the enolate was determined by trapping experiments. ^c The % THF, from the LiHMDS solution, in ether was approximately the same. ^d Equivalents of enolate. ^e Determined by ¹H NMR on the crude reaction mixtures. ^f Isolated yields of major and minor isomers. ^g 4-Heptanone was added to **11a** and the base. ^h HMPA, 1.5 equiv added. ⁱ The % THF in Et₂O was approximately 3 times greater. ^j The preformed enolate added to the sulfinimine.

These same trends were observed in the reactions of the lithium enolate of **131** with *p*-toluenesulfinimines 2-furyl substituted **130b** and *n*-Pr substituted **130c**. The major isomer *syn*-**132b** and *syn*-**132c** were isolated in 64% and 67% yields, respectively (Table

1.19, entries 13 and 15). An alternative procedure involved adding the lithium enolate of **131** to the *p*-toluenesulfinimine *n*-Pr substituted **130c**, which increased the yield of the major product *syn*-**132c** to 78%, while it resulted in decreased selectivity (Table 1.19, entry 16). The assignment of the absolute stereochemistry for the β -amino ketones *syn*-**132** and *anti*-**133** was determined by conversion of the enantiomer of *syn*-**132c** to a natural alkaloid (-)-**223A**.¹⁴⁴

Previous studies by Heathcock and others on the aldol reaction demonstrated that there is a strong correlation between the enolate geometry and the stereochemistry of the aldol product.^{145,146} In the investigation of 4-heptanone (**131**) enolate geometries, trapping the enolates **134** generated via LiHMDS, NaHMDS and KHMDS with TMSCl at -78 °C gave the corresponding (*E*)- and (*Z*)-enol silanes (*E*)-**135**, (*Z*)-**135**, respectively (Scheme 1.39).¹⁴⁷



Scheme 1.39

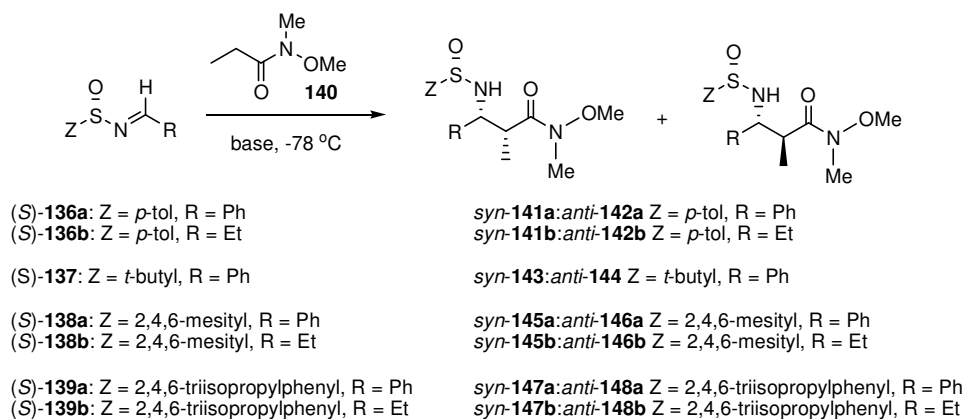
The (*Z*)-enolate (**Z-134**) was favored in THF, and sodium enolate gave a higher *Z:E* ratio of 45:1 in THF compared with lithium and potassium enolates (Table 1.19, entry 5, 7 and 11). Significantly, it was observed that diethyl ether provided a dramatic increase in the selectivity for the formation of (*E*)-enolate (**E-134**). In contrast to the

sodium and potassium enolates, the lithium enolate generated from LiHMDS gave the highest *E:Z* ratio of 15:1, which afforded α -substituted β -amino ketones *syn:anti* ratio in a range from 9:1 to 18:1 (Table 1.19, entries 10, 13, 15 and 16). The solvent effect in the formation ratio of enolates (*E*)-**134** and (*Z*)-**134** was explained via Ireland transition model.^{148,149}

Methods for the asymmetric synthesis of α -substituted β -amino ketones that are required for the synthesis of architecturally complex piperidine alkaloids via the Mannich cyclization protocol are limited. This methodology was applied in the asymmetric synthesis of indolizidine **223A**, which provide the precursor of the key step intramolecular Mannich cyclization.

1.4.4.4. Preparation of enantiopure *syn*- α -substituted β -amino ketone from *p*-toluenesulfinimines and prochiral Weinreb Amide Enolates.

Davis and co-workers disclosed the most direct way for preparing α -substituted β -amino Weinreb amide via the addition of a prochiral Weinreb amide enolate **140** to *p*-toluenesulfinimine **136-139**.¹⁵⁰ All the results recorded are listed below (Scheme 1.40, Table 1.20). Experimental results revealed that good stereo-induction as observed for the formation of the *syn*- α -methyl β -amino Weinreb amides *syn*-**141a** and *syn*-**141b**, regardless of the base (Table 1.20, entries 1-4 and 6). Optimum results were noted when LiHMDS was used with THF (Table 1.20, entries 1 and 6). However, all four diastereoisomers were detected which can not be separated by conventional chromatography.



Scheme 1.40

Table 1.20 Synthesis of α -substituted β -amino Weinreb amides at -78 °C.¹⁵⁰

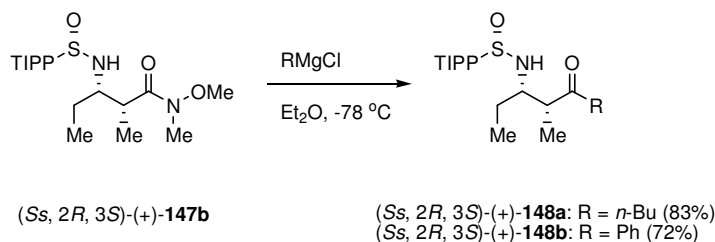
Entry	Z	R	Base ^a	Solvent	Yield (%) ^b
					d.r. (<i>syn</i> : <i>anti</i>) ^c
1	136a	Ph	LiHMDS	THF	99 (87:13:<1:trace)
2			LiHMDS	THF:Et ₂ O (1:1)	35 (93:7:trace)
3			NaHMDS	THF	67 (91:6:3:0)
4			NaHMDS	Et ₂ O	99 (73:17:9:1)
5			KHMDS	THF	NR
6	136b	Et	LiHMDS	THF	67 (75:11:10:4)
7	137	Ph	LiHMDS	THF	NR
8	138a	Ph	LiHMDS	THF	99 (96:4:0:0)
9	138b	Et	LiHMDS	THF	72 (80:17:3:0)
10	139a	Ph	LiHMDS	THF	74 (92:5:3:0)
					<i>syn</i> - 147a , 68 ^d
11	139b	Et	LiHMDS	THF	95 (4:1:0:0)
					<i>syn</i> - 147b , 76%
					<i>anti</i> - 148b , 19% ^d

^a Ratio of base to **8**. ^b Combined yield of diastereoisomers that were not separable unless otherwise noted.
^c Determined by ¹H NMR on the crude reaction mixture. ^d Isolated yields.

This phenomenon was occasionally observed in the addition of carbanion species to sulfinimines and it can be solved by changing the size of *N*-sulfinyl group.¹⁵¹ Similar work was reported by Senanayake et al. that for the addition of Grignards to diverse sulfinimines, the stereoselection improves as the steric size of the *N*-sulfinyl moiety increases.¹⁵² Guided by this idea, the prochiral enolate of **140** was added to sulfinimines (*S*)-**137**, (*S*)-**138** and (*S*)-**139** where the *N*-sulfinyl group was *tert*-butyl, 2,4,6-mesityl and 2,4,6-triisopropylphenyl, respectively. It was found that addition of the lithium enolate of **140** to *tert*-butanesulfinimine (*S*)-**137** resulted in no reaction and sulfinimine (*S*)-**137** was recovered (Table 1.20, entry 7). A possible reason could be that the large size of the *tert*-butyl moiety inhibits the addition of the bulky Weinreb amide enolate. When the *N*-sulfinyl group on the sulfinimine was changed into the less bulky *N*-(2,4,6-mesitylsulfinyl) and the *N*-(2,4,6-triisopropylphenylsulfinyl) groups, (*S*)-**138** and (*S*)-**139** gave similar results similar as those of (*S*)-**136**, with the *syn*-isomers **145a,b** and **147a,b** predominating (Table 1.20, entries 8-11). Importantly, the *N*-(2,4,6-triisopropylphenylsulfinyl)-amides *syn*-**147a** and *syn*-**147b** were isolated in 68% and 76% yield, respectively (Table 1.20, entries 10 and 11).

The absolute configuration of the α -substituted β -amino Weinreb amide (+)-**147b** was determined by conversion to products of known stereochemistry. These results establish that the major diastereomer formed in the addition of prochiral lithium enolate of **140** to sulfinimines **136-139** has the *syn* stereochemistry. Reaction of 5 equiv of *n*-butyl and phenylmagnesium chloride with (*S*_s, 2*R*, 3*S*)-(+)-**147b** gave the corresponding *syn*- α -methyl β -amino ketones (+)-**148a** and (+)-**148b** in 83% and 72% yields, respectively (Scheme 1.41). More than that, the above experiments demonstrated a high

configuration stability of this α -substituted β -amino Weinreb amides, which was exhibited in the chemical transformations.



Scheme 1.41

In addition to prochiral enolate of Weinreb amides, addition of the prochiral enolates of esters,¹⁵³ glycine esters,^{142,143} α -bromoesters,¹⁵⁴ ketones,¹⁴⁴ and Boc-protected- α -hydroxy esters¹⁵⁵ to *p*-toluenesulfinimines gave *syn*- α -substituted β -amino carbonyl derivatives as the major product. This stereoselectivity could be rationalized by the addition of the *E*-enolate species to the *p*-toluenesulfinimine via a six-membered chairlike transition states. As in the case of Weinreb amide enolate addition to sulfinimines, transition state TS-1 well explained the formation of the major *syn*-2,3-disubstituted amide (Figure 1.12).

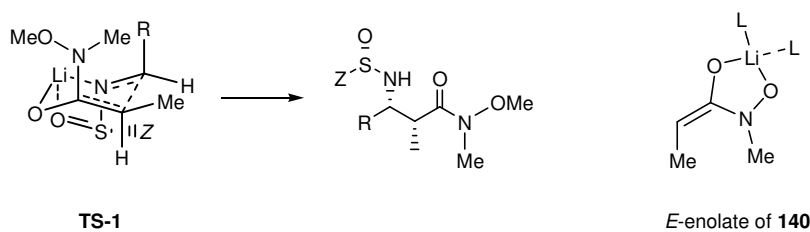


Figure 1.12

It is more likely that the lithium enolate of Weinreb amide exists in a (*E*)-conformation in the transition state, even though it is arguable that lithium enolates of

amides usually prefer (*Z*)-geometry due to less A^{1,3} interaction in contrast to (*E*)-form.¹⁵⁶ Since A^{1,3} interaction is the major effect in the unchelated form, some other intramolecular effects should prevail over the not important A^{1,3} interaction in the chelated form, which makes the (*E*)-geometry of enolate **140** a favored conformation.¹⁵⁷

In summary, of four possible diastereoisomers the *syn*- α -substituted β -amino Weinreb amides are the major products observed in the addition of lithium prochiral Weinreb amide enolates to sulfinimines. These new sulfinimine-derived chiral building blocks are important precursors of *syn*- α -substituted β -amino acids, aldehydes, and ketones on hydrolysis, reduction and reaction with Grignard reagents, respectively.

CHAPTER 2

PREPARATION OF *anti*- α -SUBSTITUTED β -AMINO KETONE FROM *p*-TOLUENESULFINIMINE

2.1. Introduction

Enantiopure α -substituted β -amino ketones have emerged as versatile chiral building blocks for the asymmetric synthesis of natural products and nitrogen-containing bioactive compounds.^{158,159} Their utilities in asymmetric synthesis make the development of methods for the synthesis of *syn* and *anti*- α -substituted β -amino ketones of considerable importance.^{160,161} The asymmetric synthesis of *syn*- α -substituted β -amino ketones has been a rapidly growing field, as discussed in the previous chapter.¹⁶² However, to the best of knowledge, there are no reports of the synthesis of enantiopure *anti*- α -substituted β -amino ketones (Figure 2.1). It is therefore important to develop a method to facilitate the synthesis of *anti*- α -substituted β -amino ketones.

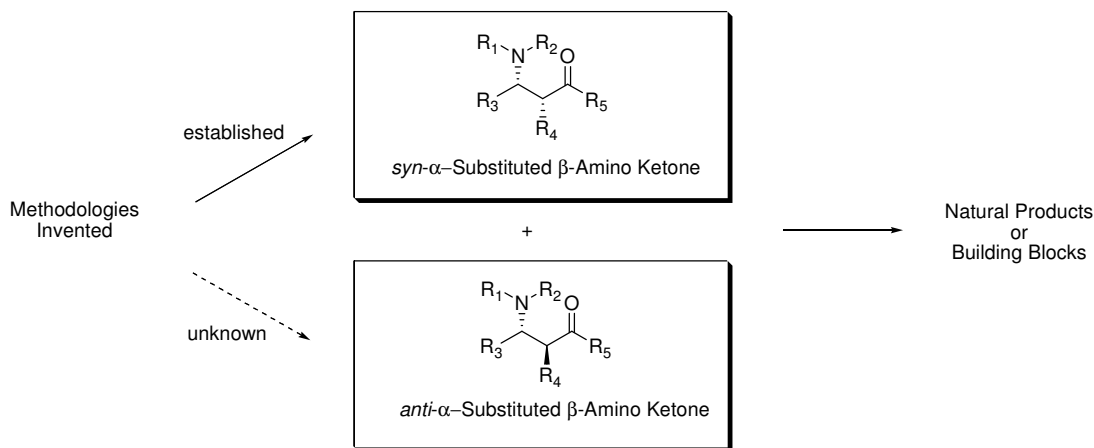
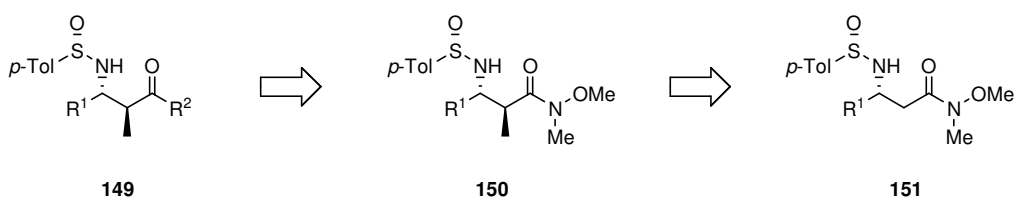


Figure 2.1

2.2. Proposed synthetic methodology

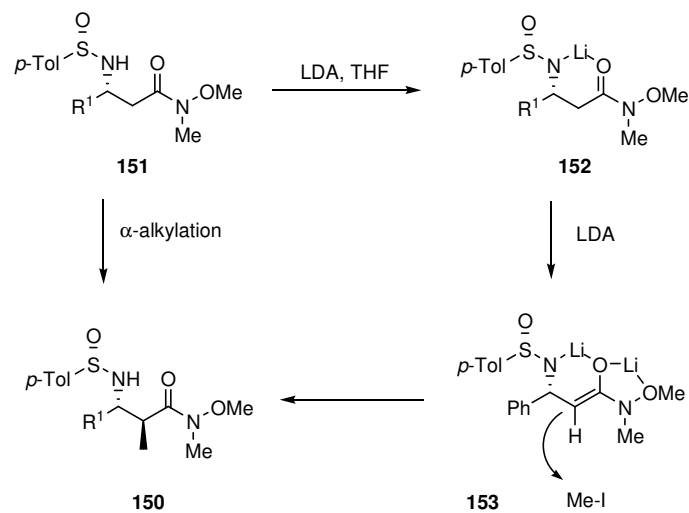
Previous studies reported that Grignard reagents reacting with the *syn*- α -substituted β -amino Weinreb amides afforded the corresponding *syn*- α -substituted β -amino ketones in excellent yield without epimerization at the α -position.¹⁵⁹ Conceptually, the addition of Grignard reagents or lithium reagents to the *anti*- α -substituted β -amino Weinreb amides would represent a general route to the corresponding *anti*- α -substituted β -amino ketones (Scheme 2.1).



Scheme 2.1

Initially the proposal was that a rigid bicyclic structure **153** would be formed after treatment of β -amino Weinreb amide **151** with 2 equivalents of base (Scheme 2.2). After the NH proton was removed, the nitrogen anion will coordinate with the metal cation, which will also coordinate to carbonyl group oxygen to form a six-member ring **152**. A subsequent equivalent of base will remove the α -carbon proton; the formed amide enolate could bond to metal cation and the methoxy group oxygen to build the five-member ring **153**. It was expected that the chirality element of the β -carbon and that of the *N*-sulfinyl group would reinforce each other to direct the electrophile attack from the β face of the enamide to give the *anti*- α -substituted β -amino Weinreb amide as the major product. Addition of Grignard or lithium reagent to the *anti*- α -substituted β -amino

Weinreb amide **150** would afford chiral *anti*- α -substituted β -amino ketone **149** (Scheme 2.2).



Scheme 2.2

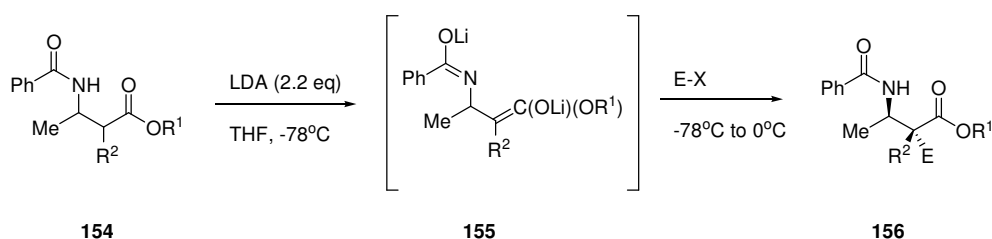
2.3. Background

The key step in the above approach is the diastereoselective alkylation of *N*-sulfinyl β -amino Weinreb amide, which has not been described. However, similar α -alkylation of *N*-protected β -amino esters has been reported to occur with good to excellent levels of diastereoselectivity affording the *anti*- α -alkylation product in high yields.¹⁶³⁻¹⁶⁶ In addition, the *N*-sulfinyl β -amino Weinreb amide could be prepared by the reaction of *N*-sulfinyl β -amino ester with lithium *N,O*-dimethylhydroxylamine.¹⁶⁷

2.3.1. α -Alkylation of racemic β -amino esters

Seebach et al. first reported the α -alkylation of β -amino esters in 1980s.¹⁶³

Racemic *N*-benzoyl-3-aminobutanoates **154** were deprotonated with 2.2 equivalent of LDA in THF at $-75\text{ }^{\circ}\text{C}$; methyl *N*-benzoyl-3-aminobutanoate **155** were then alkylated with excess electrophiles to give the racemic *anti*- α -alkyl β -amino methyl esters **156** (Scheme 2.3).



Scheme 2.3

All the products **156** were obtained with moderate to high yields and stereoselectivities. The results are summarized in Table 2.1. α -Alkylation of ethyl *N*-benzoyl-3-aminobutanoate **154a** with methyl iodide gave *anti*- α -methyl ethyl *N*-benzoyl-3-aminobutanoate **156a** in a 73% yield and a *anti:syn* ratio 4:1 (Table 2.1, entry 1). Changing the electrophile from methyl iodide to a more bulky ethyl iodide led to a higher *anti:syn* diastereomeric ratio of 13:1 in 38% yield (Table 2.1, entry 2). When methyl *N*-benzoyl-3-aminobutanoate (**154b**) was subject to the standard reaction condition, a higher diastereomeric ratio of 16:1 was obtained, and the product was obtained with a 73% yield (Table 2.1, entry 4).

When benzaldehyde was added as the electrophile, both the methyl ester **154a** and the ethyl ester **154b** were alkylated with moderate yields and diastereoselectivities (Table

2.1, entry 3 and 8). The highest selectivity was achieved when the α -ethyl *N*-benzoyl-3-aminobutanoate **154b** was reacted with benzyl bromide (Table 2.1, entry 9).

Table 2.1 α -alkylation of the racemic β -amino esters **154**.

Entry ^a	R ¹	ester	R ²	Product	E-X	Yield (%)	d.r. (<i>anti:syn</i>)
1	Et	154a	H	156a	MeI	73	4:1
2	Et	154a	H	156b	EtI	38	13:1
3	Et	154a	H	156c	PhCHO	44	3:1
4	Me	154b	H	156d	MeI	45	4:1
5	Me	154b	H	156e	EtI	73	16:1
6	Me	154b	H	156f	AllylBr	70	31:1
7	Me	154b	H	156g	BnBr	70	36:1
8	Me	154b	H	156h	PhCHO	60	5:1
9	Me	154b	Et	156i	BnBr	80	99:1

^a The selectivities with all the products were determined by GC and NMR (¹H and ¹³C).

The listed products' absolute configuration was determined by conversion into known products. Reduction of the methylated product **156a** with LAH and subsequent cyclization with phosgene produced the cyclic urethane **157** of *trans* configuration (Figure 2.2), which was determined by ¹H NMR (Table 2.1, entry 1).^{168,169} Hydrolysis of the ester **156h** to acid and subsequent cyclization with benzenesulfonylchloride afforded the β -lactone **158**. Elimination of CO₂ from β -lactone **158** gave the product the *trans*-alkene **159** that has a coupling constant *J* (HC=CH) 16 Hz.¹⁷⁰

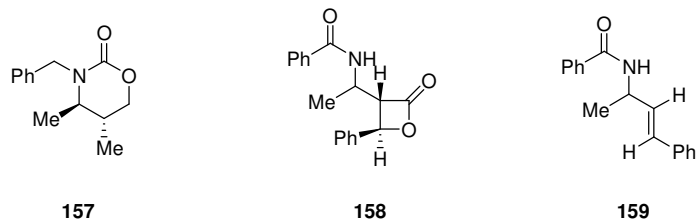
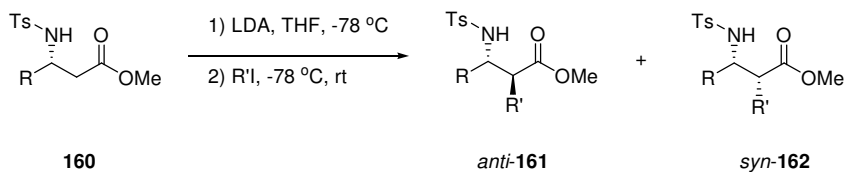


Figure 2.2

These formed alkylated esters can be readily converted to other valuable structures, such as peptides, β -lactams and heterocycles.¹⁷¹⁻¹⁷³ However, starting with racemic amino esters, all the alkylated products were obtained as a mixture of enantiomers.

2.3.2. α -Alkylation of enantiopure β -amino esters

Wang et al. utilized Seebach's LDA/alkyl halide methodology as standard reaction conditions, and the α -substitution of a series of enantiopure *N*-tosyl β -amino methyl esters **160** was explored (Scheme 2.4).¹⁷⁴ The chiral β -amino methyl esters were prepared from L-alanine and L-phenylalanine with high optical purity.¹⁷⁵ *N*-Tosyl β -amino methyl esters **160** were deprotonated with 2.2 equivalents of LDA followed by the addition of the alkyl halide. These results are summarized in Table 2.2.



Scheme 2.4

Table 2.2 α -Alkylation of *N*-tosyl β -amino methyl esters.

Entry ^a	R	Methyl ester 160	R'	Product	d.r. (<i>syn:anti</i>)	Yield (%)
1	Me	160a	Me	161a	95:5	88
2	Me	160a	PhCH ₂	161b	95:5	47
3	Me	160a	Allyl	161c	>95:5	71
4	PhCH ₂	160b	Me	161d	91:9	82
5	PhCH ₂	160b	PhCH ₂	161e	75:25	51

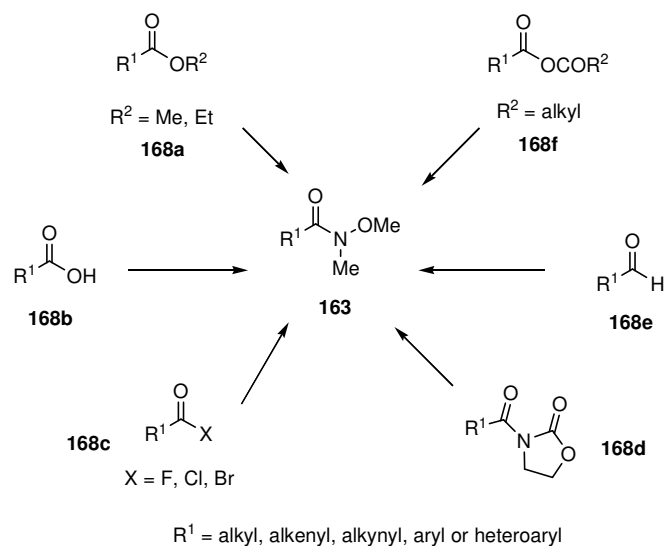
^a Diastereomers ratio was calculated based on ¹H NMR and ¹³C NMR.

Reacting the lithium enolate of methyl butanoate **160a** with methyl iodide gave the *anti*-**161a** with a 19:1 *anti:syn* diastereomeric ratio and 88% yield (Table 2.2, entry 1). When benzyl iodide and allyl iodide were added as the electrophiles, the diastereomeric ratio was maintained, but the yield dropped (Table 2.2, entry 2-3). Reaction of the β -benzyl methyl ester **160b** with methyl iodide led to a similar *d.r.* 91:9 and a yield of 82%. Unexpectedly, when the enolate of **160b** (R = PhCH₂) was treated with benzyl iodide at -78 °C, the *anti*-methyl ester **161e** was produced with only a moderate *d.r. anti:syn* 3:1 and 51% yield (Table 2.2, entry 5).

2.3.3. Conversion of methyl esters to Weinreb amides

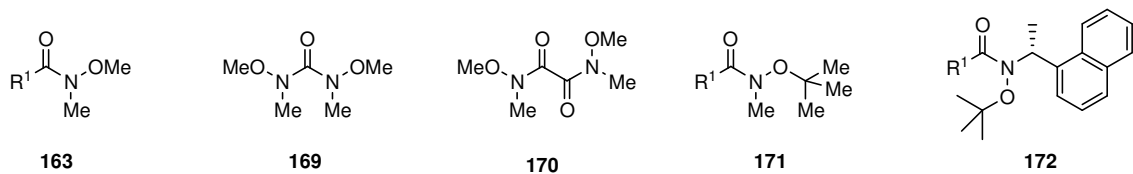
N-Methoxy-*N*-methylamides, popularly called Weinreb amides, were discovered in 1981 by Weinreb and Nahm.¹⁷⁶ Nowadays, the Weinreb amide serves as an excellent acylating agent for organolithium or organomagnesium reagents and it has become a robust equivalent for an aldehyde group.¹⁷⁷⁻¹⁷⁹

2.3.3.1. Brief introduction to Weinreb amides



Scheme 2.6

Moreover, the unique property of Weinreb amides attracted many structural variations (Figure 2.3). Those variations expanded the functionalities of this species utilized in the nucleophilic addition. Weinreb amides and their derivatives are used in Wittig reactions,¹⁸⁷ remote functionalization,¹⁸⁸ serving as carbonyl¹⁸⁹ and α -diketone synthons.¹⁹⁰



R¹ = alkyl, alkenyl, alkynyl, aryl or heteroaryl

Figure 2.3

Interestingly, Davies et al. designed chiral auxiliary **172** which combined the functionalities of Weinreb amides and Myers' pseudoephedrine auxiliary (Figure 2.4). Derivative **173** acts as a chiral Weinreb amide, allowing asymmetric enolate alkylation

afford amides **174** with high diastereoselectivity. Subsequent reaction with LiAlH₄ or methyl lithium affords the corresponding enantiopure ketones or aldehydes, respectively.¹⁹¹

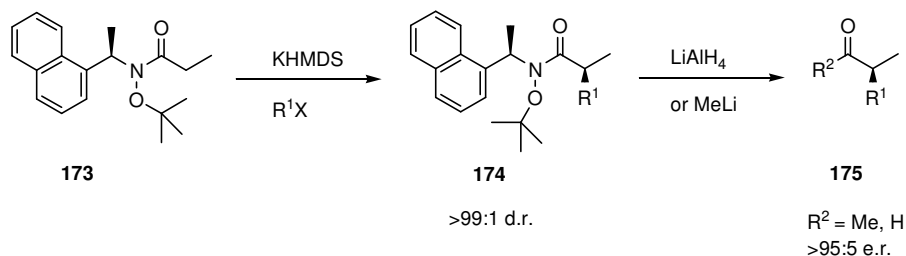
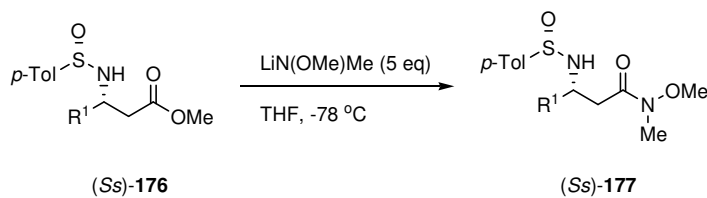


Figure 2.4

2.3.3.2. Preparation of β -amino Weinreb amides from β -amino esters.

It has been discussed that addition of the enolate of acetamide **112** to *p*-toluenesulfinimines **115** gave the enantiopure β -amino Weinreb amides **117** readily. Davis et al. reported that *N*-sulfinyl β -amino Weinreb amides **177** can be prepared in good yields by treating methyl *N*-sulfinyl β -amino carboxylates (*Ss*, *R*)-**176** with 5 equivalents of lithium *N,O*-dimethylhydroxylamine (Scheme 2.7, Table 2.3).¹⁶⁷ Various substituted β -amino methyl esters were transformed into the corresponding Weinreb amides **177a-e** with moderate to good yields. These results are summarized in Table 2.3. It was found that the β -amino stereocenter in **176a-e** is not affected by strong basic reaction conditions. The absolute stereochemistry of all the amides **177a-e** was established as *R*. The *N*-sulfinyl methyl ester **176** was prepared by addition of the sodium enolate of methyl acetate in ether to (*R*)-*p*-toluenesulfinimine depending on the chirality of the sulfur stereocenter, which affords the *R* isomer exclusively.



Scheme 2.7

Table 2.3 Synthesis of β -amino Weinreb amides from *N*-sulfinyl β -amino methyl esters and lithium *N,O*-dimethylhydroxylamine at -78 $^\circ\text{C}$ in THF.

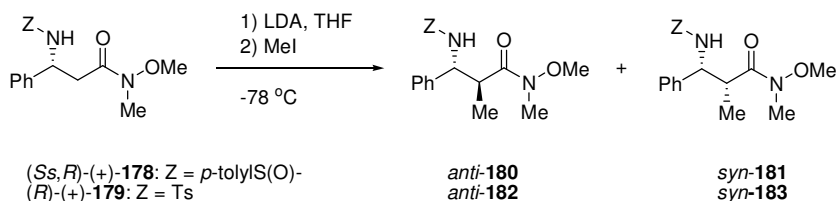
Entry		β -amino ester		LiN(OMe)Me	Product amide	Yield (%)
		R ¹	R ²			
1	176a	<i>p</i> -tolyl	Ph	5	177a	78
2		<i>p</i> -tolyl	Ph	3		61
3	176b	<i>p</i> -tolyl	<i>p</i> -CF ₃ Ph	5	177b	54
4	176c	<i>p</i> -tolyl	Me	5	177c	66
5	176d	<i>p</i> -tolyl	<i>t</i> -Bu	5	177d	68
6	176e	<i>p</i> -tolyl	<i>E</i> -MeCH=CH-	5	177e	82

2.4. Present study

Guided by the proposed strategy, the chirality elements of the β -carbon and the *N*-sulfinyl group would reinforce each other to direct the electrophile attack from the β face of the enamide to give high *anti*-stereoselectivity. Experiments were performed on the direct α -alkylation of *N*-sulfinyl β -amino Weinreb amide.¹⁹² The *N*-sulfinyl β -amino Weinreb amides were prepared from the precursor *p*-toluenesulfinimines or were prepared from its corresponding *N*-sulfinyl β -amino methyl ester which was also derived from *p*-toluenesulfinimine.

2.4.1. α -Alkylation of β -amino Weinreb amide

Weinreb amide (*Ss*, *3R*)-(+)-**178** was treated at -78 °C in THF with 2.4 equiv of LDA, then methyl iodide (3.0 equiv) was added slowly. After 1 h, the reaction was quenched with satd. aqueous NH₄Cl to give both *anti*-(*Ss*, *2S*, *2R*)-(+)-**180** and *syn*-(*Ss*, *2R*, *3R*)-(+)-**181** β -amino Weinreb amides in a 1:1 *anti:syn* ratio (Table 2.4, entry 1). Addition of LiCl to the preformed enolate improved the *anti:syn* ratio to 2:1, which correspondingly led to the product *anti*-amide **180** with an increased yield of 46% (Table 2.4, entry 2). The *anti*-**180** structure was determined by ¹H, ¹³C NMR, IR and HMRS, and the absolute stereochemistry was established via comparison with its *syn*-isomer *syn*-**181**, which is known. Conversion of its structural analog into known compounds further confirmed the *anti*- relative configuration, which will be discussed in section 2.4.2..¹⁹³



Scheme 2.8

Table 2.4 Alkylation of β -amino Weinreb amide enolates at -78 °C.

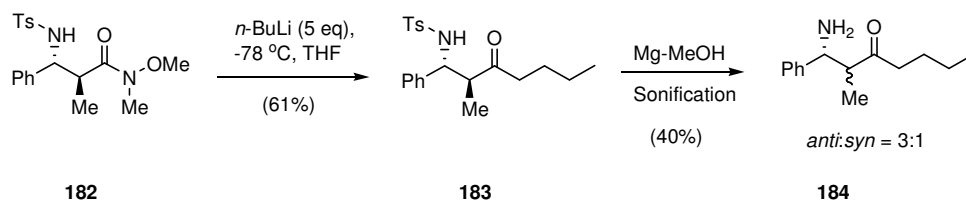
entry	Z	Conditions	<i>anti:syn</i> 2:3	Yield (%)
1	178a (<i>p</i> -tolylS(O)-)	--	1:1	19
2	178a (<i>p</i> -tolylS(O)-)	LiCl (10)	2:1	46 ^{a,b}
3	179b (TS)	--	3:1	16

Table 2.4, continued

4	179b (TS)	LiCl (10)	12:1	37 ^c
^a Determined by ¹ H NMR on the crude reaction mixture. ^b Combined yield of inseparable <i>anti:syn</i> isomers. ^c Isolated yield of pure diastereoisomer.				

The above result for the α -alkylation of *N*-sulfinyl β -amino Weinreb amide is not consistent with the original expectation. To clarify which chirality element, the β -carbon stereocenter or the *N*-sulfinyl chirality predominates in directing the attack of the electrophile, it is necessary to perform the alkylation with the *N*-tosyl β -amino Weinreb amides **179**. *N*-Tosyl amides **179** were prepared from the *N*-sulfinyl β -amino Weinreb amide **178** via oxidation by *m*-CPBA.¹⁹⁴ It was found that when *N*-tosyl amide **179a** was alkylated under the standard reaction conditions, a moderate *anti:syn* 3:1 d.r. and 16% yield was obtained (Table 2.4, entry 3). Significantly, use of LiCl improved the *anti:syn* to 12:1 which afforded *anti*-**182** in 37% isolated yield (Table 2.4, entry 4).¹⁹⁵ The *anti*-**182** structure was determined by ¹H, ¹³C NMR and IR which will be discussed in section 2.4.4. Oxidation of *N*-sulfinyl *anti*-Weinreb amide *anti*-**180** with *m*-CPBA gave spectral properties identical to the tosyl amide **182**.

Before trying to optimize the yield of the alkylation product *anti*-**182**, it was necessary to determine whether it would react with Grignard and lithium reagents without epimerization at the α -center. Surprisingly, reaction of *anti*-amide **182** with 5 equivalents of methyl magnesium bromide resulted in no reaction (Scheme 2.9). However, with 5 equivalents of *n*-butyllithium, a 61% yield of the *anti*-*n*-butyl ketone **183** was obtained without any epimerization being detected.



Scheme 2.9

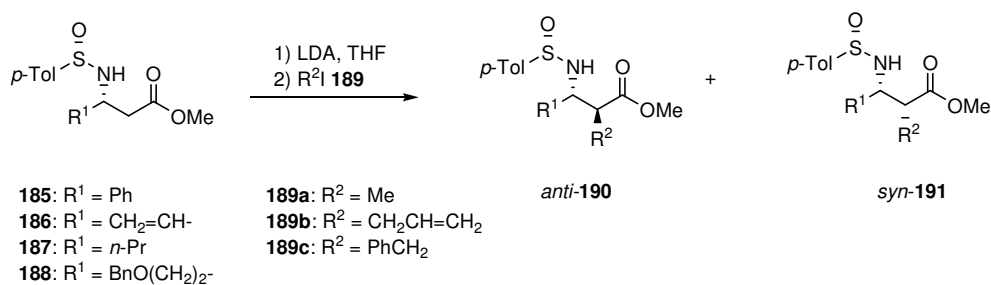
Removal of the *N*-tosyl group in *anti*-ketone **183** was next explored. While a number of methods are available for removal of *N*-tosyl amine groups, such as sodium naphthalide,¹⁹⁶ Na/NH₃,¹⁹⁷ and HBr/HOAc,¹⁹⁸ the harshness of these conditions would be incompatible with enolizable ketones such as *anti*-ketone **183**. Cleavage of arenesulfonamides by reduction with Mg-MeOH under ultrasonic conditions is reported to be tolerant of carbonyl groups.¹⁹⁹ However, sonication of *anti*-ketone **183** under optimal conditions gave only the β-amino ketone **184** with an inseparable 3:1 mixture of isomers in poor yield.

2.4.2. α-Alkylation of *N*-sulfinyl β-amino methyl esters

Previous studies had shown that *N*-sulfinyl *syn*-α-substituted β-amino Weinreb amides react with Grignard and lithium reagents to give good yields of the corresponding ketones and the *N*-sulfinyl group was easily removed under mild acid conditions.¹⁵⁹ No epimerization at the α-position was observed. Since the selectivity for α-alkylation of *N*-sulfinyl β-amino Weinreb amide enolates was poor (Table 2.4, entries 1-2), it was anticipated that alkylation of the *N*-sulfinyl β-amino ester enolates would give better diastereoselectivity. Then α-alkylated β-amino esters were readily transformed to the

corresponding Weinreb amides by reaction with lithium *N,O*-dimethylhydroxy amine as discussed earlier.

Under the same condition for *N*-sulfinyl Weinreb amides (Scheme 2.10), treatment of methyl ester-**185** with 2.4 equiv of LDA at -78 °C followed by addition of 3.0 equiv of MeI resulted in a mixture of *anti*-**190a** and *syn*-**191a** in a 2:1 ratio (Table 2.5, entry 1). Importantly, the *anti*:*syn* diastereoselectivity improved to 7:1 on the addition of 10 equivalent of LiCl (Table 2.5, entry 2).



Scheme 2.10

Table 2.5 Alkylation of *N*-sulfinyl β-amino esters using LDA in THF.

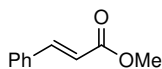
entry	R ¹ =	R ² =	LiCl ^d	Temp (°C)	<i>anti</i> -ester	<i>anti</i> : <i>syn</i> ^b	Yield (%) ^c
1	185: Ph	Me		-78	190a	2:1	NA
2		Me	10	-78 to -50	190a	7:1	80 ^d
3		allyl	10	-50	190b	96:4	64 ^d
4		BnCH ₂	10	-50	190c	96:4	72 ^d
5	186: vinyl	Me	10	-50	190d	89:11	88
6		allyl	10	-50	190e	91:9	76
7		BnCH ₂	10	-50	190f	>99:1	82

Table 2.5, continued

8	187 : <i>n</i> -Pr	Me	10	-50	190g	>99:1	82
9	188 : BnO(CH ₂) ₂	Me	10	-78	190h	>99:1	62

^a Equivalents of added LiCl. ^b Isomer ratio determined by ¹H NMR on the crude reaction mixture. ^c Combined yield of *anti:syn* isomers. ^d (*E*)-methyl cinnamate **192**, 5-10% was isolated.

As expected, alkylation of the enolate of **185** with allyl iodide **189b** and benzyl iodide **189c** afforded the corresponding α -substituted derivatives (+)-*anti*-**190b** and (+)-*anti*-**190c** with better yields and excellent selectivities (Table 2.5, entries 3-4). These results could be explained in terms of more bulky electrophiles having a steric preference compared with small size molecules in *anti*-addition. In each of these examples, (*E*)-methyl cinnamate (**192**) (Scheme 2.11) was produced in a range of 5-10% yield that was caused by an elimination of one molecule of *p*-toluenesulfinamide from the β -amino ester **185** (Table 2.5, entries 2-4). (*E*)-Methyl cinnamate (**192**) is a known compound,²⁰⁰ and the side product separated in alkylation has the same spectral properties as an authentic sample. Alkylations of the enolate of *N*-sulfinyl β -amino ester derivatives (+)-**186**, (+)-**187**, and (+)-**188** gave similar high *anti:syn* diastereoselectivities, together with moderate to good yields (Table 2.5, entries 5-9). However, with none of these examples was it possible to isolate *anti*-ester **190** and *syn*-ester **191** by column chromatography.



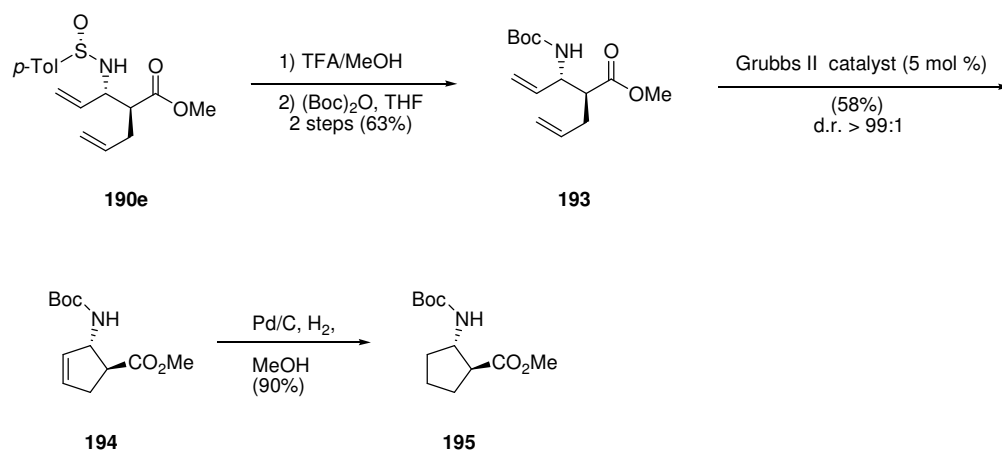
(*E*)-methyl cinnamate **192**

Scheme 2.11

2.4.3. Assignment of stereochemistry

Earlier studies suggested that the major isomer formed in the alkylation of *N*-sulfinyl β -amino ester enolates was the *anti*-isomer, since *anti* selectivity has been observed in the α -alkylation of β -amino esters (Scheme 2.10).²⁰¹ To confirm the stereochemical assignment of α -alkylation, the alkylation product was converted to a compound of known absolute stereochemistry. This method not only verified the *anti*-stereochemistry, but illustrated the utility of *anti*- α -substituted β -amino esters as valuable new chiral building blocks.

Removal of the *N*-sulfinyl group in (+)-**190e** and replacement with a Boc group gave the amino diene (-)-**193** in 63% yield for two steps (Scheme 2.12). The amino diene (-)-**193** and Grubbs II catalyst in DCM was stirred at rt to give *anti*-cyclopentene β -amino ester (+)-**194** in 58% yield as a single isomer. Subsequent hydrogenation with palladium on carbon led to a 90% yield of cyclic *trans*- β -amino methyl ester **195**. The optical rotation of ester **195** was in accordance with the literature value,¹⁹³ which firmly established the absolute configuration of the product and the stereochemistry of α -alkylation was defined as *anti*.



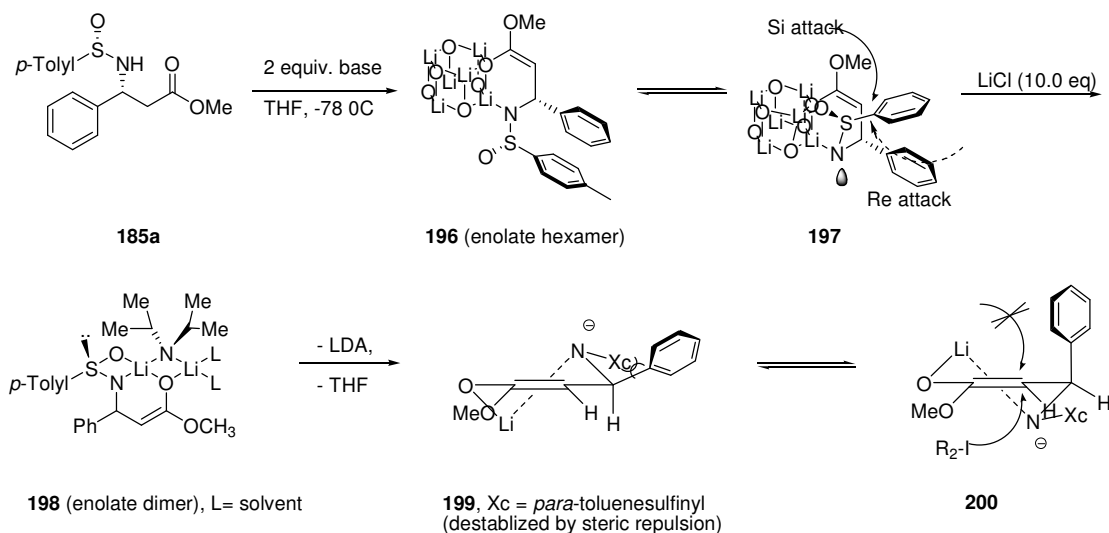
Scheme 2.12

Additionally, cyclic β -amino acid derivatives are important building blocks for the synthesis of natural products and β -peptides.²⁰² The synthesis of cyclic β -amino ester (+)-**195** is highly efficient, five steps with a 25% overall yield from β -amino ester (+)-**190e**. In comparison, (+)-**195** was previously prepared from (*S*)-methionine in 9 steps, with a 12% overall yield.¹⁹³ Moreover, the enantiopure cycloalkenyl (+)-**194** could be readily functionalized, which makes this structural modification of chiral cyclic β -amino acids derivatives a convenient method.

2.4.4. Mechanism of α -Alkylation of β -amino methyl esters.

Most of the alkylated esters were obtained with good yields and diastereoselectivities, and with *anti*-diastereoselection. These results can be interpreted as consistent with the chelation of the lithium ion between enolate oxygen and the deprotonated amino group (Scheme 2.13).²⁰³ When *N*-sulfinyl β -amino methyl ester **185a** was subjected to two equivalents of bases, the generated dianion enolate is proposed

to form a hexamer aggregate **196** in solution. The hexamer **197** is believed to show little difference between the *si* face and *re* face attack probably due to some known co-effects of the *N*-sulfinyl group and the rigid hexamer.

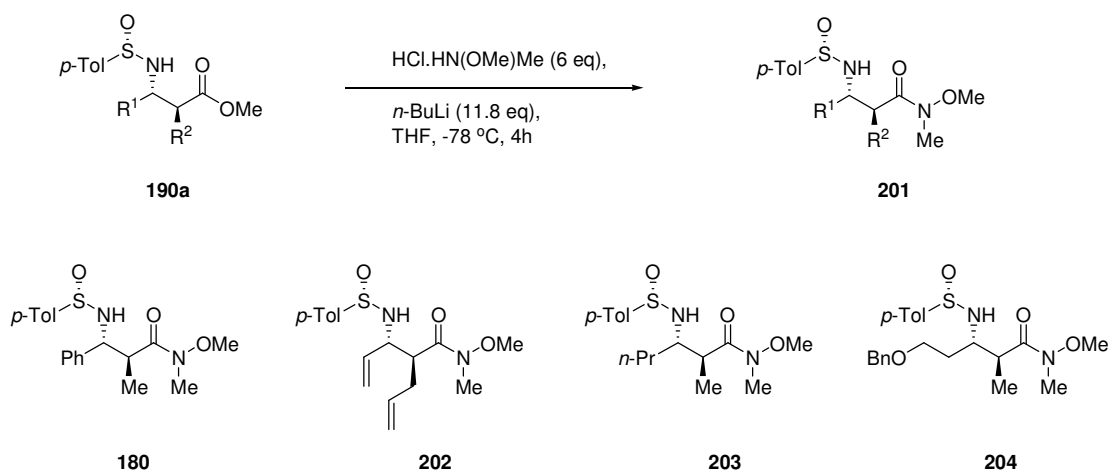


Scheme 2.13

Related mechanistic studies suggest that the addition of LiCl would lead to the decomposition of the enolate hexamer **197** into the dimer **198**.¹⁹⁵ After losing one molecule of LDA, it is proposed that the monomer would exist in equilibrium with half chair structures **199** and **200**. The intramolecular steric repulsion might destabilize the conformation **199**, which would favor structure **200**. Based on models of enolate **200**, the phenyl group is in a pseudo-axial position and would sterically direct the electrophile to attack at the α-carbon from the α-face of the formed bicyclic structure, which affords the major alkylation product with *anti* selectivity. Experimental results demonstrated that more bulky substituents at the β-amino carbon and larger electrophiles result in higher *anti*-selectivities, supporting this mechanistic hypothesis.

2.4.5. Conversion of α -substituted β -amino methyl esters to Weinreb amides.

α -Alkylation of β -amino ester enolate derivatives have demonstrated that good levels of *anti:syn* selectivity can be achieved (Table 2.5). However, in none of these examples could the *anti*-isomers be separated by column chromatography. Fortunately, it was found that the corresponding Weinreb amides were readily separable.¹⁵⁹ It is therefore necessary to convert all of the *anti*- α -alkyl β -amino methyl esters to the corresponding Weinreb amides. Treatment of the 7:1 *anti:syn* mixture of β -amino ester (+)-**190a** with 6 equivalents of LiN(OMe)Me at -78 °C gave a 75% yield of *anti*- α -methyl β -amino Weinreb amide (+)-**201** (Scheme 2.14). Importantly, (+)-**201** was obtained as a single isomer with spectral properties identical with an authentic sample.¹⁵⁹



Scheme 2.14

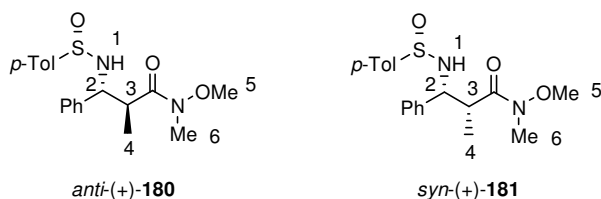
Table 2.6 Synthesis of *anti*- α -substituted β -amino Weinreb amides from corresponding methyl esters.

Entry	Ester	R ¹	R ²	<i>anti</i> -Amide	Yield (%)
1	190a	Ph	Me	180	75

Table 2.6, continued

2	190e	Vinyl	Allyl	202	81
3	190g	<i>n</i> -Pr	Me	203	84
4	190h	BnO(CH ₂) ₂	Me	204	83

In general the *anti*- α -protons in these Weinreb amides appear upfield compared to the *syn* isomers and this observation could be used to determine the relative configuration of these Weinreb amides.¹⁵⁹ For example, *anti*-(+)-**201** has the α -proton resonating at δ 4.49 ppm whereas the α -proton of the *syn* isomer is at δ 4.74 ppm (Scheme 2.15, Table 2.7). Similar results were found for the conversion of α -substituted β -amine esters **202**, **203** and **204** to their corresponding Weinreb amides where single isomers were obtained.

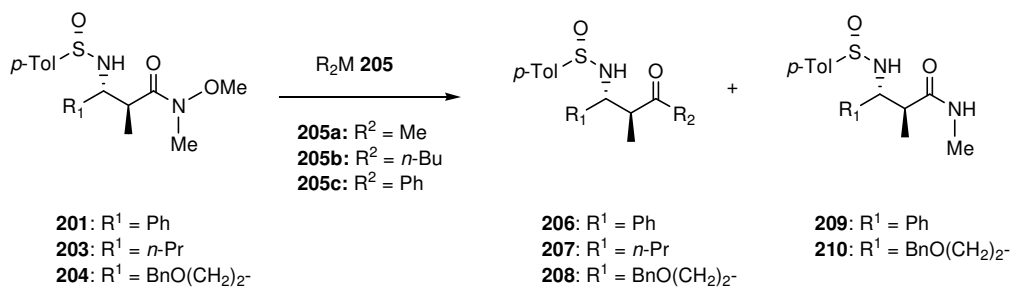
**Scheme 2.15****Table 2.7** ¹H NMR comparison of *anti*-(+)-amide **180** and *syn*-(+)-amide **181**.

entry	H	<i>anti</i> -(+)- 180 (ppm)	<i>syn</i> -(+)- 181 (ppm)
1	-NH	5.92 (bd, $J = 6.8$ Hz, 1H)	5.13 (d, $J = 3.2$ Hz, 1H)
2	-CH	4.49 (t, $J = 6.4$ Hz, 1H)	4.74 (m, 1H)
3	-CH	2.97 (m, 1H)	3.2 (m, 1H)
4	-CH ₃	1.12 (d, $J = 6.8$ Hz, 3H)	1.04 (d, $J = 7.2$ Hz, 3H)
5	-OCH ₃	2.24 (s, 3H)	2.34 (s, 3H)
6	-NCH ₃	3.0 (s, 3H)	3.02 (s, 3H)

2.4.6. Synthesis of α -alkyl β -amino ketones from Weinreb amides.

With the chiral α -alkyl β -amino Weinreb amides in hand, the next objective is to convert them into the corresponding α -alkyl β -amino ketones. Results of the addition of Grignard and lithium reagents to *anti*- α -methyl β -amino Weinreb amides are given below (Scheme 2.16, Table 2.8).

Addition of 10 equiv of methylmagnesium bromide to Weinreb amide (+)-**201** at -78 °C in THF resulted in no reaction (Table 2.8, entry 1). Even after warming to 0 °C for 1 h, none of the desired product **206a** was detected and the Weinreb amide (+)-**201** was recovered in good yield and recycled. Interestingly, when MeMgBr was added at a temperature of 0 °C, a better yield of 95% (+)-**206a** was obtained (Table 2.8, entry 2). Unexpectedly reaction of Weinreb amide (+)-**201** with either *n*-butylmagnesium chloride or *n*-butylmagnesium bromide at 0 °C failed to give *n*-butyl ketone **206b** (Table 2.8, entries 3-4). Various reaction conditions were screened, including warming the reaction to 25 °C, addition of LiCl,²⁰⁴ CeCl₃,²⁰⁵ and HMPA,²⁰⁶ however, none of these modifications had any affect in increasing the yields, and the Weinreb amides were recovered in all cases (Table 2.8, entry 5).



Scheme 2.16

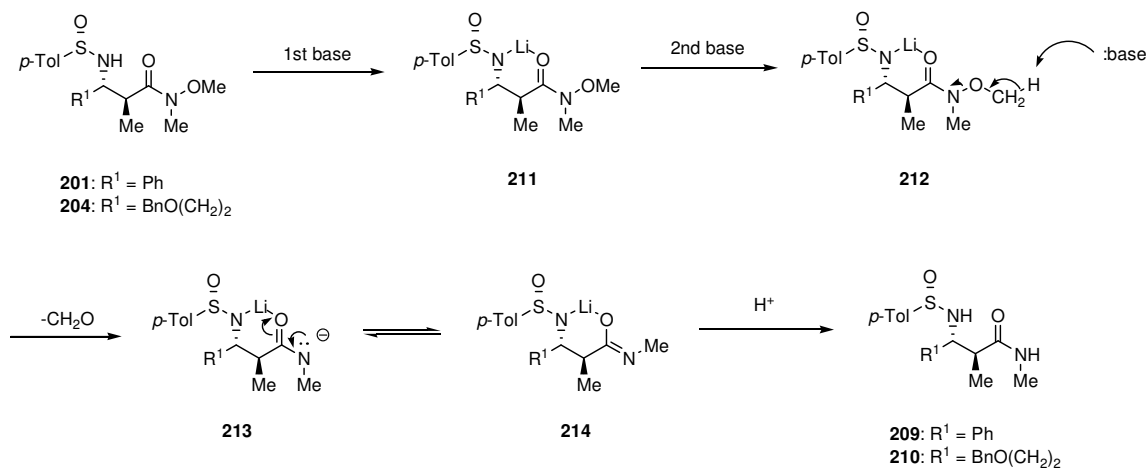
Table 2.8 Synthesis of β -amino ketones from β -amino Weinreb amides in THF for 2 h.

entry	(R ¹ =)	<i>anti</i> -amide	RM (equiv)	Temp (°C)	Product	Yield (%) ^a
1	Ph	201	MeMgBr (10)	-78	206a	no reaction
2			MeMgBr (10)	0	206a	95
3			<i>n</i> -BuMgCl (10)	0	206b	no reaction
4			<i>n</i> -BuMgBr (10)	0	206b	no reaction
5			<i>n</i> -BuMgBr (10)	0 to 25	206b	no reaction
6			<i>n</i> -BuLi (5)	-78	206b	34
7			<i>n</i> -BuLi (10)	-78	206b	38
8			<i>n</i> -BuLi (5)	-50	206b	38
9			MeLi (5)	-50	206a	73
10			PhLi (5)	-50	206c	61
11	<i>n</i> -Pr	203	MeLi (5)	-50	207a	33
12			MeMgBr (10)	0	207a	no reaction
13	BnO(CH ₂) ₂	204	<i>n</i> -BuMgCl (10)	24	208b	no reaction
14			MeLi	-50	208a	45
15			MeMgBr (10)	0	208a	no reaction
16			<i>n</i> -BuLi (5)	-78	208b	25
17			<i>n</i> -BuLi (5)	-50	208b	40

^a Isolated yield of pure diastereoisomer. ^b Ratio of products determined by ¹H NMR. ^c 5-10% yield.

When the organometallic reagent was changed to *n*-butyllithium, the desired product, *n*-butyl ketone (+)-**206b**, was formed in only 34% yield (Table 2.8, entry 6). Furthermore, a mixture of the reduced amide (+)-**209** and the unreacted starting material (+)-**201** was obtained. Reduced amides such as *anti*-amide (+)-**209**, are often observed in reactions of Weinreb amides with highly basic reagents and they are thought to be formed

via an E₂ pathway with formation of formaldehyde.²⁰⁷ As for *anti*-amide (+)-**201**, intermediate **211** has the possibility of being reduced by the organometallic reagent to lose one molecule of formaldehyde, which leads to the formation of the amide anion **213** (Scheme 2.17). Subsequent protonation of the resulting intermediate would produce the reduced amide **209**.



Scheme 2.17

Increasing the amount of *n*-BuLi improved the conversion rate of the Weinreb amide (+)-**201**, but it also resulted in an increase of the reduced amide (+)-**209** (Table 2.8, entry 7). The optimum reaction conditions of adding 5 equivalent of *n*-BuLi at -50 °C in THF afforded the *anti*-ketone (+)-**206b** and the reduced amide (+)-**209** in 38% and 33 % yield, respectively (Table 2.8, entry 8). Attempts to modify the reaction by varying the temperature, reaction time and amount of *n*-BuLi or addition of additives such as LiCl, CeCl₃, all failed to give any better results. Interestingly, when MeLi and PhLi were treated with *anti*-amide **201**, better yields were observed in formation of the corresponding ketones; i.e. a 73% yield of methyl ketone (+)-**206a** and a 61% yield of

phenyl ketone (+)-**206c** (Table 2.8, entries 9-10). Under these conditions, none of the reduced amide (+)-**209** was detected. Product **206a-c** structures were established via the use of ^1H NMR, ^{13}C NMR and IR by comparison with the spectral properties of *N*-sulfinyl β -amino methyl ester **190a**.

When other *anti*- α -methyl β -substituted Weinreb amides (+)-**203** and (+)-**204** were reacted with MeLi and *n*-BuLi using the optimized conditions, it was observed that the corresponding *anti*- α -methyl β -amino ketones (+)-**207a**, (+)-**208a** and (+)-**208b** were produced with low to modest yields in a range of 33-45% (Table 2.8, entries 11, 14 and 17). Unexpectedly, methylmagnesium bromide failed to react with either of these amides (Table 2.8, entries 12 and 15).

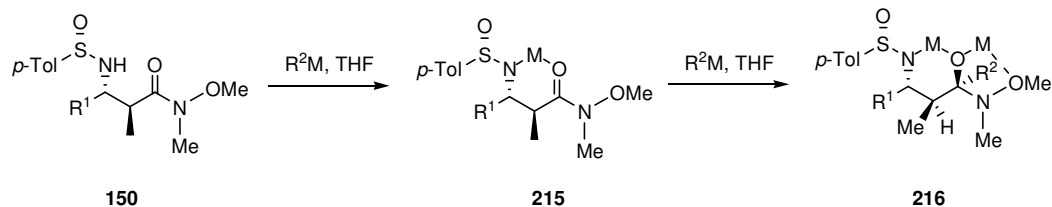
In none of the examples listed in Table 2.8 was epimerization at the α -carbon detected. A possible reason is that the *p*-tolyl *N*-sulfinyl group has an ability of stabilizing anions at the nitrogen atom. The nitrogen anion prevents the second base attacking the α -proton of the amide to form a dianion, since a dianion structure is highly energetic and thermodynamically unfavorable.

2.4.7. Mechanistic Considerations.

The results for the addition of Grignard reagents and lithium reagents to *anti*- α -methyl β -amino Weinreb amides are puzzling. While MeMgBr reacts with *N*-sulfinyl *anti*- α -methyl β -amino Weinreb amide (+)-**201** ($\text{R}^1 = \text{Ph}$ -) to give an excellent yield of the methyl ketone (+)-**206a** (Table 2.8, entry 2), it failed to add to the corresponding *N*-

tosyl derivative *anti*-(+)-**182** or with Weinreb amides (+)-**203** ($R^1 = n\text{-Pr}$) and (+)-**204** ($R^1 = \text{BnO}(\text{CH}_2)_2\text{-}$) derived from *N*-alkyl sulfinimines (Scheme 2.16, Table 2.8). On the other hand, lithium reagents react readily with these Weinreb amides (+)-**201**, (+)-**203** and (+)-**204** to give the corresponding ketones, which gives low to moderate yields due to the competition between the addition and the reduction of Weinreb amides. By contrast the corresponding *N*-sulfinyl *syn*- α -methyl β -amino Weinreb amides give excellent yields of the corresponding ketones with lithium and Grignard reagents and reduction was not observed.

It is reasonable to assume that addition of an organometallic reagent R^2M to the β -amino Weinreb amides results first in deprotonation of the acidic *N*-sulfinyl proton to give species **215** (Scheme 2.18). Deprotonation of the *N*-sulfinyl amides derived from the sulfinimines has often been used to explain the exceptional protecting group ability of the *N*-sulfinyl group in sulfinimine chemistry.²⁰⁸ Species **215** is probably formed as a complex mixture of aggregates resulting from both *intra*- and intermolecular chelation. It is proposed that formation of the tetrahedral intermediate **216** results from addition of the organometallic reagent R^2M to the carbonyl group of amide **215** from the least hindered direction. For steric reasons this should be more favorable in the *syn*- α -substituted β -amino Weinreb amide than in the *anti*-derivative. Dimeric lithium acetylide is reported to react with Weinreb amides via a monosolvated monomer-based transition state to form the tetrahedral intermediate.¹⁸¹ In a study of displacements at the nitrogen atom of lithioalkoxyamides by organometallic reagents, lithium reagents were more reactive than Grignard reagents which is consistent with our findings.²⁰⁹



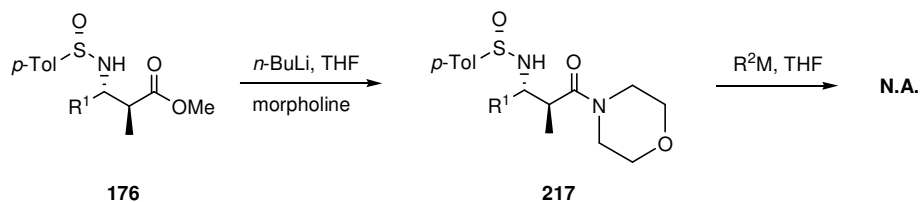
Scheme 2.18

2.4.8. *N*-Sulfinyl β -amino morpholine amide

Given the limited compatibility and low conversion rate of *anti-N*-sulfinyl α -substituted β -amino Weinreb amides to ketones, it is important to design a more general method for the synthesis of the ketones. Recent studies report that carboxylic acid derived morpholine amides are useful nucleophilic acylation reagents and an alternative to reagent Weinreb amides in ketone synthesis.^{210,211}

N-sulfinyl *anti*- α -substituted β -amino morpholine amide **217** was prepared by addition of *N*-lithiomorpholine to *N*-sulfinyl *anti*- α -substituted β -amino methyl ester **176** affording the *N*-sulfinyl *anti*- α -substituted β -amino morpholine amide in 76% yield. Epimerization at the α -carbon stereocenter was not detected. However, reaction of amide **217** with MeMgBr gave none of the desired methyl ketone **206a**. All attempts to prepare **206b** by reaction modification including addition of HMPA, solvent screening of THF, Et₂O and temperature adjustments from -78 to 25 °C failed to produce ketones (Scheme 2.19, Table 2.9). Although it was reported that the less basic but higher oxophilic organocerium species reacted with morpholine amides to form ketone in good yields,²¹²

addition of MeLi in the presence of CeCl₃ to morpholine amide **217** failed to give the desired ketone **206a** (Table 2.9, entry 8).



Scheme 2.19

Table 2.9 Synthesis of β -amino ketones from β -amino morpholine amides.

Entry	Organometallic reagent (eq.)	Additive	Temp (°C)	Solvent	Yield (%) ^a
1	MeMgBr (5)	--	-78	THF	N.A.
2	MeMgBr (5)	--	-20	THF	N.A.
3	MeMgBr (5)	--	25	THF	N.A.
4	MeMgBr (5)	CeCl ₃	25	THF	N.A.
5	MeMgBr (5)	HMPA	25	THF	N.A.
6	MeMgBr (5)	--	25	Et ₂ O	N.A.
7	MeLi (5)	--	25	THF	N.A.
8	MeLi (5)	CeCl ₃	25	THF	N.A.

^a Isolated yield of *anti*- α -methyl β -amino ketone **206a**.

Previous studies reported that an important limitation to the use of morpholine amides in ketone synthesis is their susceptibility to steric hindrance of both the organometallic reagents and the starting amides. This largely steric argument could be used to interpret some findings here, but is undoubtedly much more complex.

In summary, the first asymmetric synthesis of the *anti*- α -substituted β -amino Weinreb amides and their corresponding ketones is reported. This was accomplished by reaction of lithium dimethylhydroxylamine with *N*-sulfinyl *anti*- α -substituted β -amino esters. Alkylation of *N*-sulfinyl β -amino Weinreb amide enolates resulted in poor diastereoselectivities. Grignard reagents do not react with *N*-sulfinyl *anti*- α -substituted β -amino Weinreb amides perhaps for steric reasons. However, lithium reagents react with these Weinreb amides affording the corresponding ketones in low to moderate yields because addition of the lithium reagent competes with reduction of the Weinreb amide.

CHAPTER 3

TOTAL SYNTHESIS OF (5*S*, 6*R*, 8*S*, 9*R*)-5,9 *Z*-INDOLIZIDINE 221T FROM *N*-SULFINYL *anti*- α -METHYL β -AMINO KETONES

3.1. Introduction

Nitrogen-containing saturated heterocyclic systems are important core structures due to their presence in many natural products.²¹³ Indolizidine is one of these heterocyclic compounds forming the central bicyclic core of the indolizidine alkaloids, which are usually isolated from the skin of amphibians (Figure 3.1).^{214,215} Many of these indolizidine alkaloids display significant biomedical activity, such as inhibition of nicotine acetylcholine receptors²¹⁶ or binding affinity for the human δ -opioid receptor.²¹⁷ These biological activities have made indolizidine alkaloids the promising candidates for control of Alzheimer's disease, schizophrenia and Parkinson's disease.

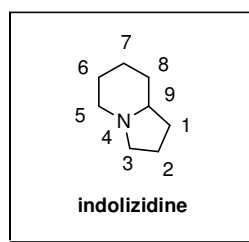


Figure 3.1

During the past decades, indolizidine ring systems have become the targets of many synthetic efforts due to the interesting biological activities and limited sources from nature.^{218,219} Initially, this group of alkaloids included the 3,5- and 5,8-disubstituted indolizidines as well as the structurally more complex pumiliotoxins and allopumiliotoxins (Figure 3.2). In 1997, Daly and co-workers reported the first isolation

of the *tri*-substituted indolizidine alkaloid **223A** along with three higher homologues, extracted from the Panamanian population of the frog *Dendrobates pumilio* Schmidt.²²⁰

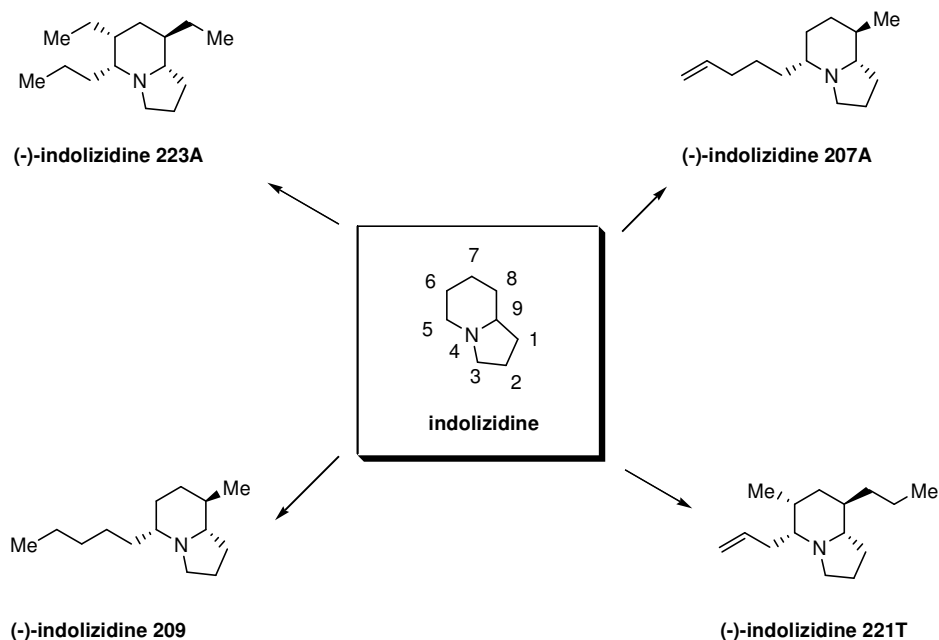


Figure 3.2

However, this alkaloid depicted by Daly and co-workers did not represent the real absolute configuration of indolizidine **223A**. Due to the microgram amounts of indolizidines separated from natural sources, the structure of indolizidine **223A** bearing 5,6,8-*tri*-substituents was initially defined as structure **218**, which was characterized merely on the basis of GC-MS, GC-FTIR and ¹H NMR data.

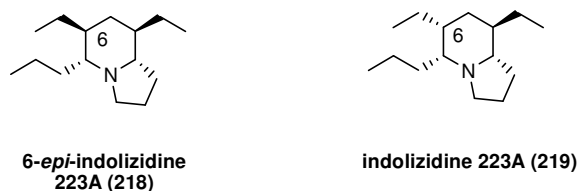
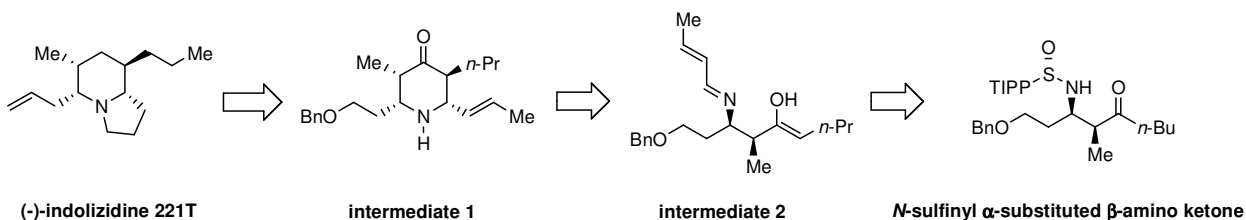


Figure 3.3

After that, it was found that the C6 configuration established in the proposed structure **218** was incorrect. In 2002, Toyooka et al. finished the first synthesis of indolizidine **223A** via series of Michael additions and revised its structure to **219**.²²¹ For further structure elucidation and biological testing, a straightforward and flexible synthetic access toward large scale of optically pure material 5,6,8-*tri*-substituted indolizidine **223A** (**219**) and its derivatives is highly desirable.

Another example of 5,6,8-*tri*-substituted indolizidine is **221T** and is a member of a large family of indolizidines and about 70 alkaloids have been assigned to this class. As for indolizidine **223A**, the key step in the synthesis of the 5,6,8-*tri*-substituted indolizidine (-)-**221T** is the stereocontrolled construction of the core piperidine ring.²²² In this regard, the acid-catalyzed intramolecular Mannich cyclization of *N*-sulfinyl *syn*- α -methyl β -amino ketones provides a powerful method for the asymmetric synthesis of multi-substituted stereodefined piperidones (Scheme 3.1). The reaction of Grignard reagents with sulfinimine-derived enantiopure *N*-sulfinyl β -amino Weinreb amides readily affords the requisite *N*-sulfinyl *syn*- α -methyl β -amino ketones.²²³



Scheme 3.1

Correspondingly, utilization of this method to prepare *N*-sulfinyl *anti*- α -methyl β -amino ketones would lead to the formation of the *anti*-C5, C6 diastereomer of the

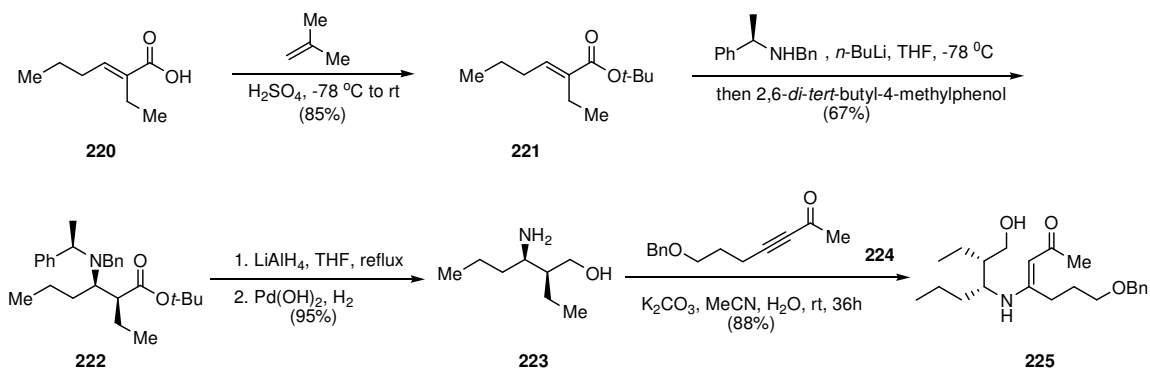
indolizidine **221T**. Although little is known about the biological activities of indolizidine **221T** and its derivatives, the synthesis of *anti*- α -methyl β -amino ketones will provide more details on the intramolecular Mannich cyclization reaction and valuable structural information will be obtained from the newly prepared target molecule.

3.2. Background of syntheses of (-)-indolizidine **223A** and its 6-epimer

To date, different strategies toward 5,6,8-trisubstituted indolizidine **223A** have been developed; total syntheses of alkaloid **223A** (**219**)^{221,224-227} and total syntheses of 6-*epi*-**223A** (**218**) have been reported.^{226,228,229} The critical problem in the various syntheses of highly substituted indolizidine **223A** (**219**) involves the assembly of the piperidine core with the correct stereochemistry.

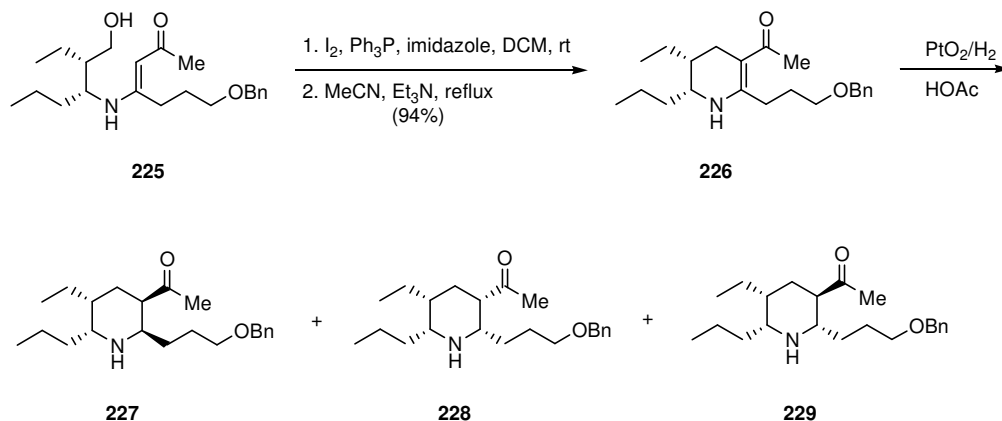
3.2.1. Ma's asymmetric synthesis of (-)-indolizidine **223A**

Ma's synthesis of the originally proposed structure of (-)-indolizidine **223A** began with the esterification of 2-ethyl-2-hexenoic acid (**220**) with 2-methylpropene and provided α,β -unsaturated ester **221** in 85% yield (Scheme 3.2).²²⁴ Michael addition of lithium *N*-benzyl (*R*)- α -methylbenzylamine to *t*-butyl ester **221** gave the resultant anion, which reacted with a sterically hindered proton source to produce *syn-di*-substituted ester **222** in 67% yield and over 98% d.e.. Next, reduction of ester **222** followed by catalytic hydrogenation gave the γ -amino alcohol **223** in 95% yield in 2 steps. The obtained 1,3-amino alcohol **223** reacted with the alkynyl methyl ketone **224** in the presence of K_2CO_3 affording the β -amino methyl ketone **225** in 88% yield.



Scheme 3.2

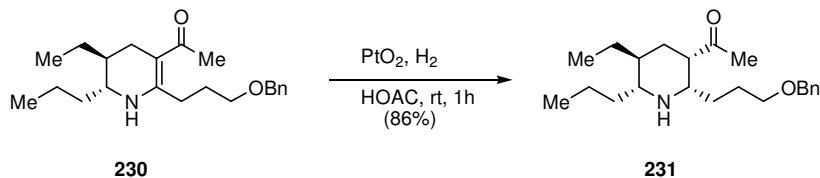
Iodization of alcohol **225** and subsequent Baylis-Hillman cyclization afforded the *tetra*-substituted cyclic enamine **226** in 94% yield in 2 steps (Scheme 3.3). Catalytic hydrogenation of the enamine **223** with platinum oxide afforded a mixture of three diastereoisomers of *tetra*-substituted piperidine **227**, **228**, and **229** in 34%, 33% and 22% yield, respectively.



Scheme 3.3

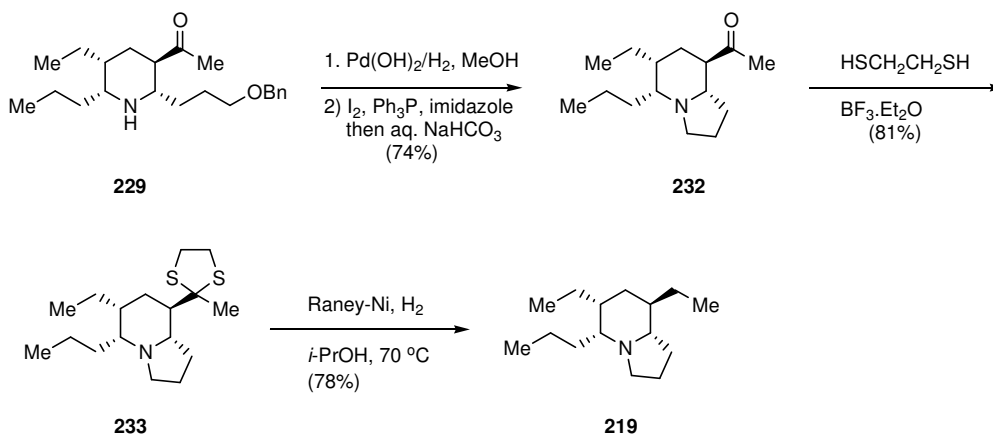
In a parallel experiment, *tetra*-substituted cyclic enamine **230** produced the *tetra*-substituted piperidine **231** as a single isomer in 86% yield (Scheme 3.4). It was found that hydrogenation of the cyclic enamine **226** and **230** led to a different stereo-induction.

These results were rationalized in terms of different stereoelectronic control of the formed half chair conformation within the transition state.²³⁰



Scheme 3.4

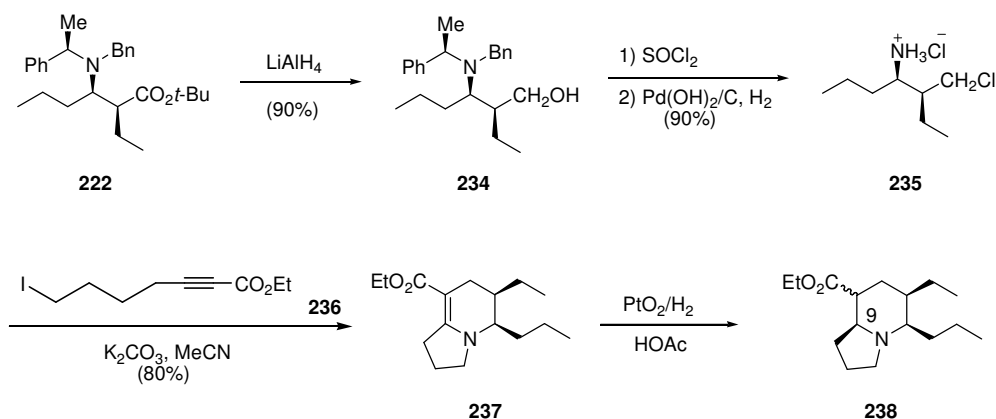
Conversion of *tetra*-substituted piperidine **229** into the alkaloid **223A (219)** was initiated by removal of the benzoyl group (Scheme 3.5). Next, intramolecular cyclization in the presence of I₂, triphenylphosphine and imidazole gave the bicyclic ketone **232** in 74% yield over 2 steps. Treating methyl ketone **232** with 1,2-ethanedithiol activated by trifluoroborane etherate afforded the 1,3-dithiolane **233** in 81% yield. Finally, Raney-Ni desulfurization of 1,3-dithiolane **233** produced the desire *tetra*-substituted indolizidine **223A (219)** in 78% yield.



Scheme 3.5

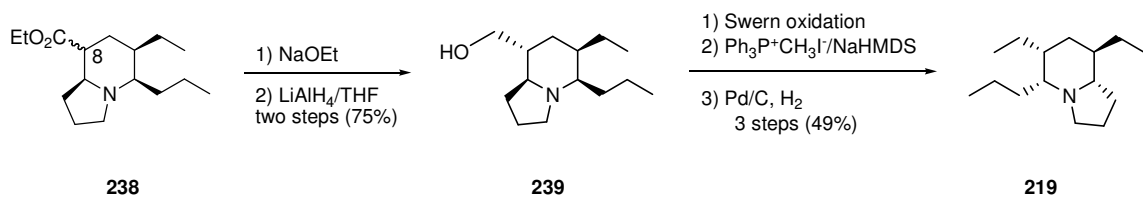
3.2.2. Ma's revised asymmetric synthesis of (-)-indolizidine **223A**

A revised asymmetric synthesis of alkaloid **223A (219)** was designed by Ma and co-workers starting from the common chiral intermediate *syn*- α -ethyl β -amino ester **222** (Scheme 3.6).²²⁵ Reduction of *t*-butyl ester **222** afforded δ -amino alcohol **234** in 90% yield; halogenation and subsequent catalytic hydrogenation converted the 1,3-amino alcohol into δ -chloro amine HCl **235** in 90% yield in two steps. The bicyclic enamine **237** was assembled in 80% yield from iodide alkynyl ester **236** and δ -amino alcohol HCl salt **235** via the S_N2 substitution-Michael addition-Baylis Hillman one-pot process.^{231,232} Catalytic hydrogenation of the bicyclic enamine **237** formed a racemic mixture of 5,6,8-*tri*-substituted indolizidine **238** in a quantitative yield with the requisite stereocenter built at C9.



Scheme 3.6

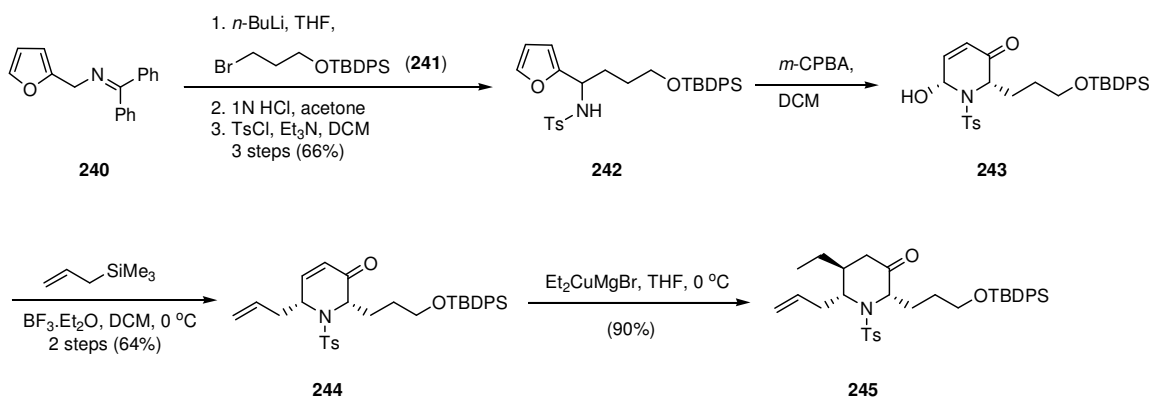
Epimerization at C8 in indolizidine **238** using sodium ethoxide gave exclusively the *anti*-C8, C9-substituted indolizidine (Scheme 3.7). Reduction of *anti*-C8, C9 indolizidine gave the *tetra*-substituted indolizidine **239** in 2 steps and 75% yield. Swern oxidation of bicycle-**239**, Wittig methylenation and catalytic hydrogenation gave the alkaloid **223A (219)** a 49% yield over 3 steps.



Scheme 3.7

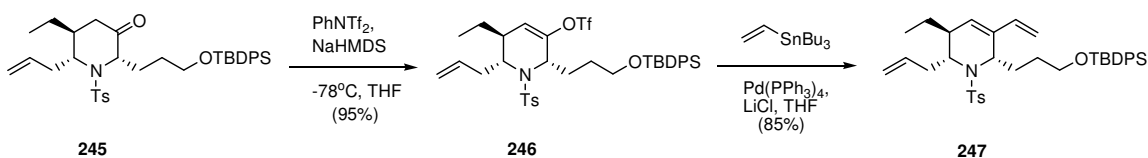
3.2.3. Padwa's synthesis of 6-*epi*-Indolizidine (\pm)-223A

It is known that products of *aza*-Achmatowicz reactions incorporate functionality that is easily modified to construct complex nitrogen heterocycles.²³³ Padwa's synthetic route started with imine **240** derived from benzophenone (Scheme 3.8).²²⁸ Treatment of diphenyl imine **240** with *n*-BuLi followed by addition of bromo-siloxypopane **241** afforded the furyl aliphatic amine. The formed amine reacted with tosyl chloride to produce the sulfonamide **242** in 66% yield from **240**. Under standard *aza*-Achmatowicz oxidative condition, treatment of furyl sulfonamide **242** with *m*-CPBA yielded the *cis*-2,6-dihydropyridinone **243** as a single diastereomer. Reacting pyridinone **243** with allyl silane produced the dihydropyridinone **244** in 64% yield.²³⁴ Michael addition of Et₂CuMgBr with dihydropyridinone **244** resulted in the formation of *tri*-substituted pyridinone **245** as a single diastereomer in 90% yield.²³⁵



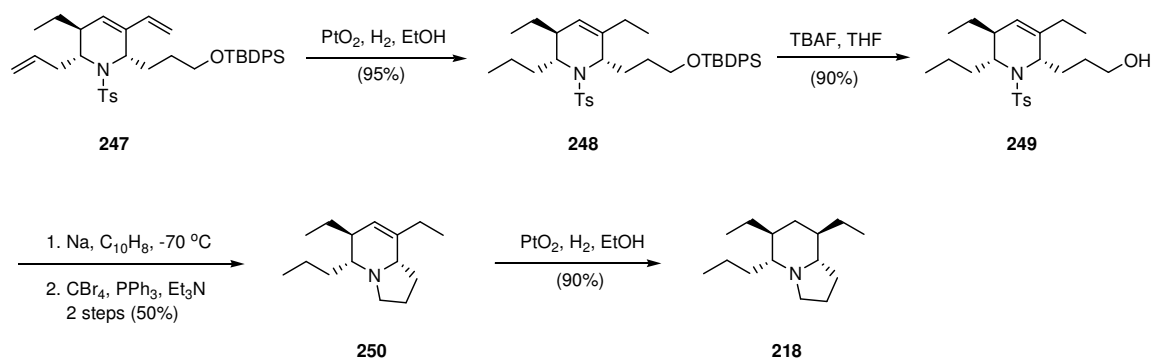
Scheme 3.8

Treatment of pyridinone **245** with NaHMDS and *N*-phenyltrifluoromethane sulfonamide afforded triflate **246** in 95% yield (Scheme 3.9). Installation of the vinyl group at C2 using standard Stille coupling conditions afforded the *tetra*-substituted tetrahydropyridine **247** in 85% yield.



Scheme 3.9

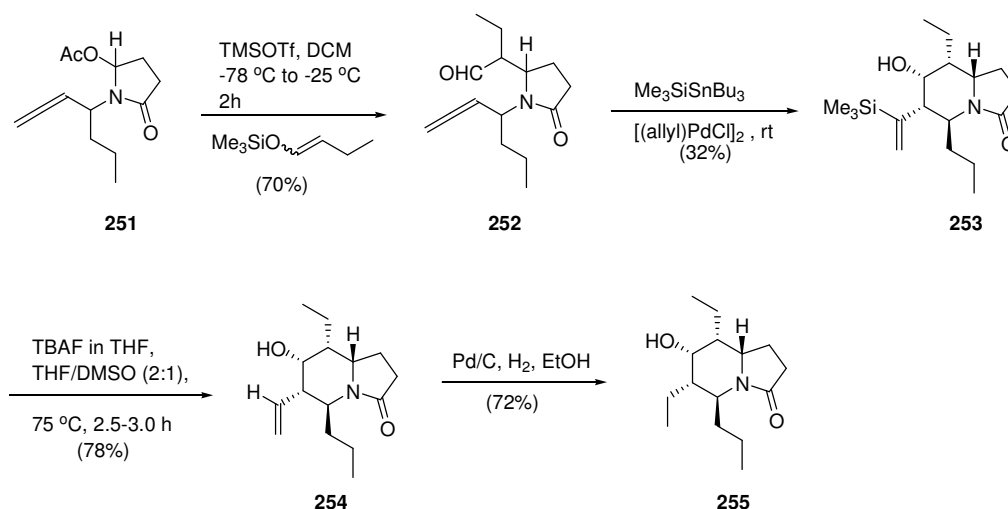
Hydrogenation of **247** gave the product 1,2,3,6-*tetra*-hydropyridine **248** in 95% yield, and removal of the silyl gave the amino alcohol **249** (Scheme 3.10). Deprotection of the tosyl group and subsequent cyclization using a standard bromination condition resulted in a 50% yield of *tri*-substituted indolizidine **250** over 2 steps. Reduction of intermediate **253** proceeded without difficulty which gave the racemic *epi*-indolizidine (±)-**223A** (**218**) in 98% yield.



Scheme 3.10

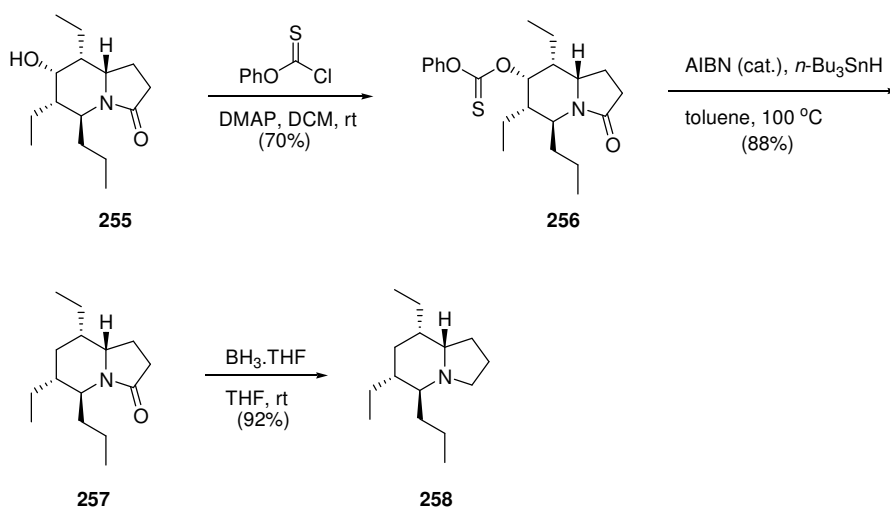
3.2.4. RajanBabu's synthesis of 6-*epi*-indolizidine (\pm)-**223A**

RajanBabu's synthesis of racemic alkaloid **223A** began with the Lewis acid activated addition of an enolsilane to the iminium ion derived from acetoxy lactam **251**, which gave the racemic lactam **252** in 70% yield (Scheme 3.11).²²⁹ Treatment of lactam **252** with *n*-Bu₃SnSiMe₃ in the presence of catalytic amount of [(allyl)PdCl]₂ afforded a mixture of diastereomers via the silylstannylation-cyclization.^{236, 237} The desired *tetra*-substituted 3-indolizinone **253** was separated by chromatography with a yield of 32%. Desilylation with TBAF and subsequent catalytic hydrogenation converted the silyl olefin **253** into the saturated indolizinone **255** in 56% yield in two steps.



Scheme 3.11

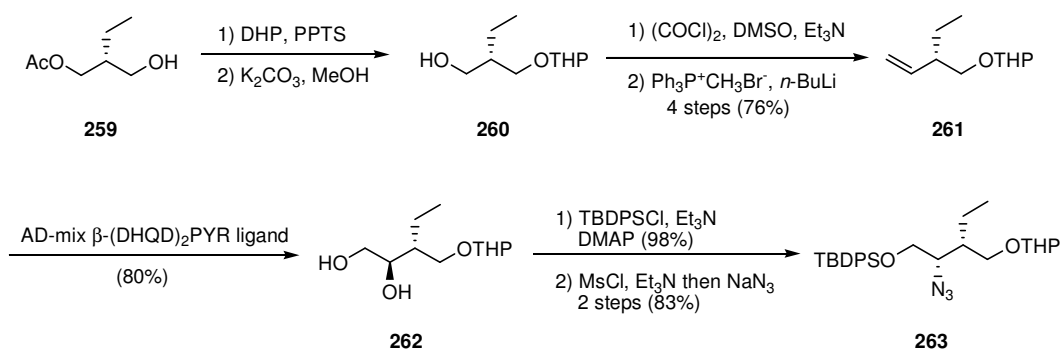
Reaction of 7-hydroxyl-3-indolizinone **255** with phenyl chlorothionoformate under Robins reaction conditions afforded a 70% yield of phenyl thionocarbonate **256** (Scheme 3.12). Reduction using *tri-n*-butyltin hydride and AIBN produced the *tri*-substituted bicyclic lactam **257** in 88% yield. Treatment of indolizinone **257** with borane gave *tri*-substituted indolizidine **258** in 92% yield without any detection of the epimerization.



Scheme 3.12

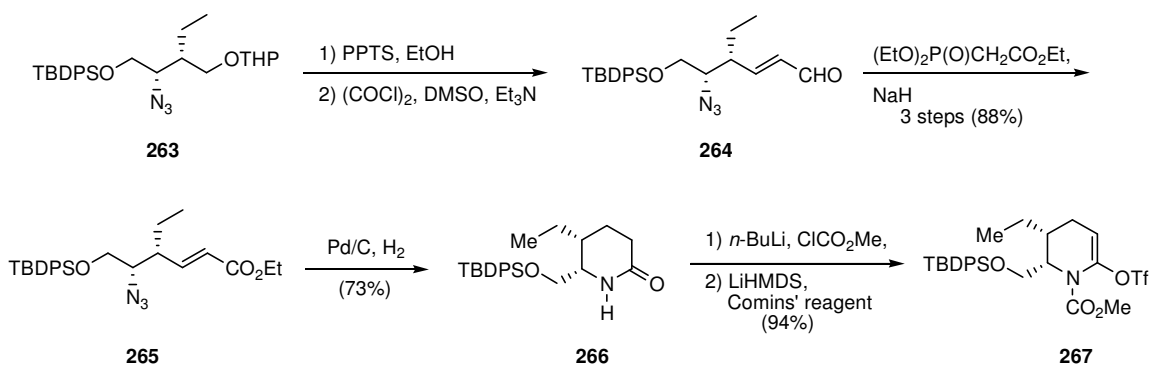
3.2.5. Toyooka's synthesis of indolizidine (-)-223A epimer

Toyooka et al. achieved the synthesis of indolizidine (-)-223A (**219**) and the original proposed structure 6-*epi*-alkaloid **223A** (**218**).²²¹ Their synthesis started with (*R*)-1,3-propanediol-2-ethyl-monoacetate (**259**), protection of the primary alcohol with dihydropyran and deprotection of the acetate which gave primary alcohol **260** (Scheme 3.13).²³⁸ Swern oxidation and Wittig methylenation gave the terminal alkene **261** in 76% yield over 4 steps. A (DHQD)₂-PYR ligand-induced AD reaction of alkene **261** gave the enantiopure pentandiol **262** in 80% yield. Regioselective protection of pentandiol **262** gave a 98% yield of the intermediate secondary alcohol, which was transformed into azide **263** in 83% yield via the mesylate. Here the absolute configuration of the azide-substituted carbon was inverted.



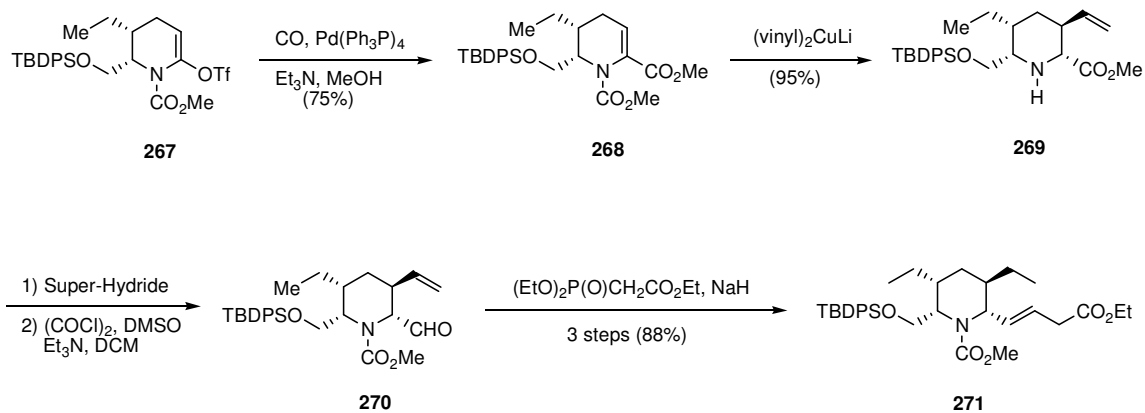
Scheme 3.13

Removal of the protecting group and Swern oxidation following a HWE reaction provided the unsaturated ester **265** in 88% yield (Scheme 3.14). Hydrogenation of the obtained δ-azide ester **265** led to the formation of lactam **266** in 73% yield. Treatment of **266** with *n*-BuLi and ClCO₂Me afforded the corresponding methyl carbamate, which was converted to enoltriflate **267** using Commins' triflating agent in 94% yield over 2 steps.



Scheme 3.14

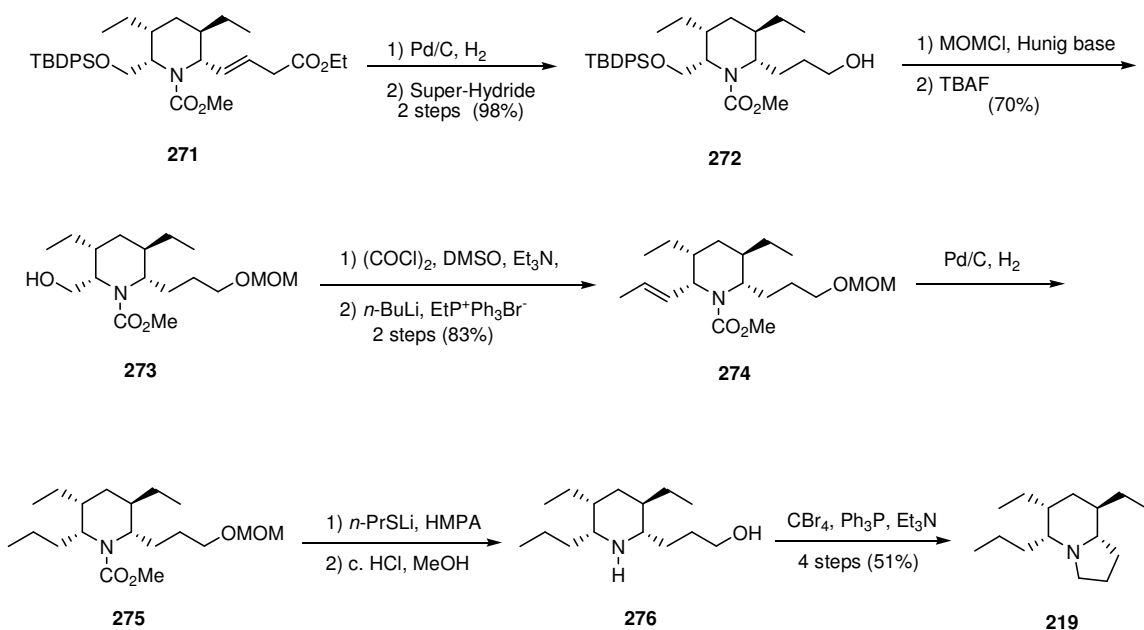
A palladium-catalyzed CO insertion reaction gave enamino ester **268** in 75% yield (Scheme 3.15). Michael addition of the enamine **268** gave the 3,5-*trans*-adduct **269** as a single isomer in 95% yield. Reduction of **269** with super hydride followed by Swern oxidation produced the aldehyde **270** smoothly. The crude aldehyde **270** was subject to HWE reaction without further purification, affording unsaturated ethyl ester **271** in 88% yield over 3 steps.



Scheme 3.15

Catalytic hydrogenation of *tetra*-substituted piperidine **271** and metal hydride reduction produced the primary alcohol piperidine **272** in 98% yield (Scheme 3.16).

Protection of the primary alcohol and subsequent desilylation with TBAF afforded the MOM methyl ester **273** in 70% yield. Piperidine **274** was prepared from the primary alcohol **273** with a yield of 83% via Swern oxidation and a HWE reaction. Catalytic hydrogenation, decarboxylation and MOM deprotection produced the *tetra*-aliphatic piperidine **276**. Finally bromination of the alcohol **276** led to an *in situ* intramolecular cyclization, which gave the indolizidine **223A (219)** in 51% yield via 4 steps from piperidine **274**.

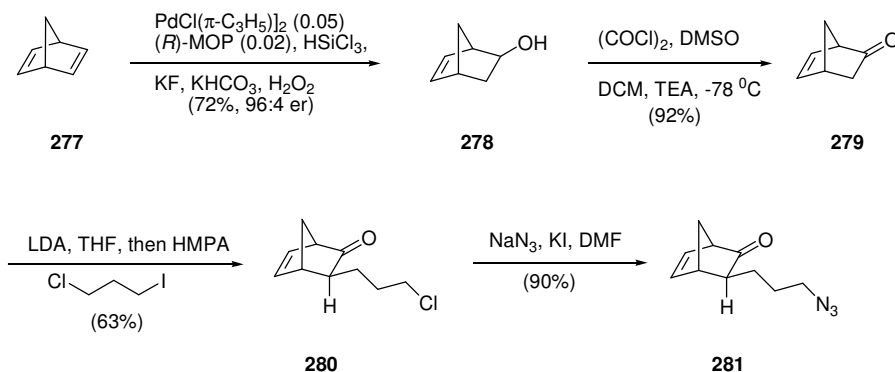


Scheme 3.16

3.2.6. Aube's asymmetric synthesis of alkaloids (-)-223A and 6-*epi*-223A

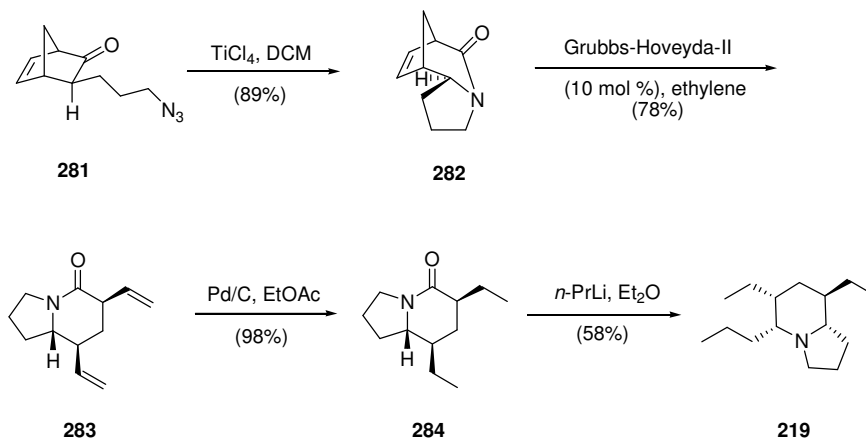
Aube's synthesis began with norbornadiene **277** in a one-step enantioselective hydrosilylation/oxidation reaction to afford known alcohol **278** in 72% yield and 96:4 e.r. (Scheme 3.17).²²⁶ Swern oxidation gave the norbornenone **279** in 92% yield, and α -alkylation of norbornenone **280** with 1-chloro-3-iodopropane, followed by substitution

with sodium azide gave the *exo*-substituted norbornenone **281** with an overall yield of 57% for the 2 steps.



Scheme 3.17

Intramolecular Schmidt reaction of azide **281** in the presence of TiCl_4 resulted in the formation of lactam **282** as a single isomer in 89% yield. The ring-opening metathesis of lactam **282** via the Grubbs-Hoveyda-II catalyst resulted in a 78% yield of the indolizinone diene **283**. Subsequent catalytic hydrogenation of diene **283** gave the 6,8-*cis*-disubstituted indolizinone **284** in 98% yield.



Scheme 3.18

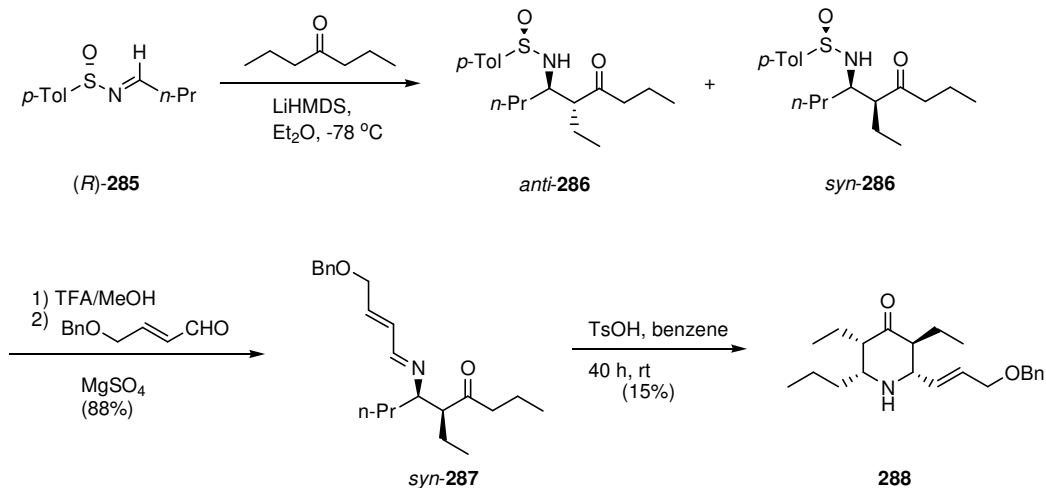
Propylation of the lactam **284** followed by dehydration is proposed to form an iminium ion, which might suffer from A^{1,2} strain between the 6-ethyl and *n*-propyl group.²³⁹ Among the conditions screened for the *n*-propylation,²⁴⁰ the best result was obtained via the addition of *n*-propyllithium, then allowed reaction to equilibrate for 12 h, gave the indolizidine **223A (219)** in 58% yield.

3.3. Asymmetric synthesis of (-)-223A via intramolecular Mannich protocol from *syn*- α -substituted β -amino ketone.

Sulfinimine-derived *N*-sulfinyl β -amino ketones provided an efficient and highly stereoselective way to prepare diverse 2,3,4,6-*tetra*-substituted piperidines via an intramolecular Mannich protocol. Related studies using this methodology included the asymmetric synthesis of indolizidine **209B**,²⁴¹ **223A**²²⁷ and **221T**²²².

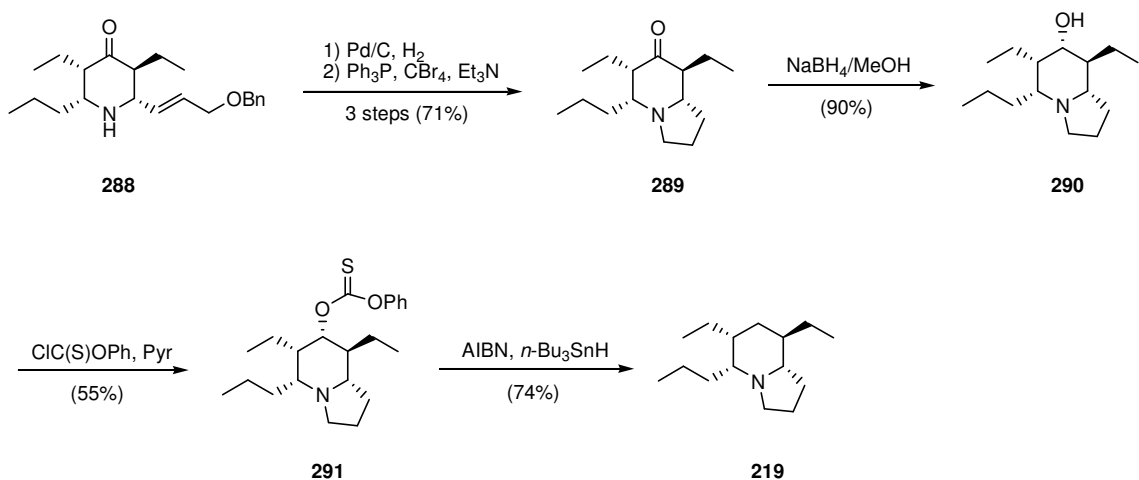
3.3.1. Davis and Yang's synthesis of alkaloid (-)-223A from *p*-toluenesulfinimines.

Davis and Yang reported the synthesis of alkaloid (-)-**223A (219)** using the intramolecular Mannich protocol from enantiopure *syn*- α -methyl β -amino ketone **286**, which was readily prepared from sulfinimine (*R*)-**285** as outlined in Scheme 3.19.²²⁷ The *N*-sulfinyl *syn*- α -substituted β -amino ketone (-)-**286** was deprotected and followed by treatment with (*E*)-4-benzyloxybut-2-enal to give the crude *syn*-imine **287** in ca. 88% yield. However, the intramolecular Mannich cyclization, resulted in only a 15% yield of the desired 2,3,5,6-*tetra*-substituted piperidin-4-one (+)-**288**.



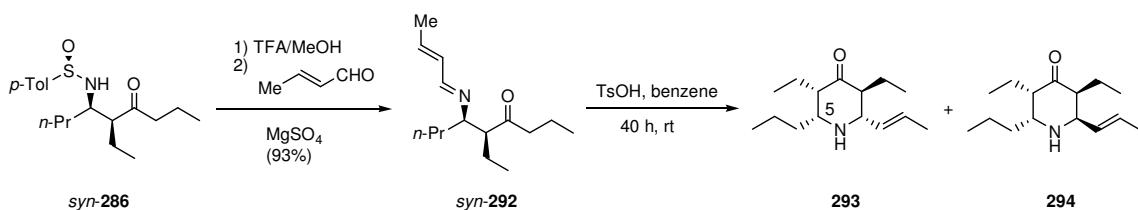
Scheme 3.19

Precursor (+)-**288** was hydrogenated and the intermediate alcohol was subjected to cyclization with $\text{CBr}_4/\text{Ph}_3\text{P}/\text{Et}_3\text{N}$, affording the indolizidine (+)-**289** in 71% yield in 3 steps (Scheme 3.20). Reduction of (+)-**289** gave alcohol (+)-**290** as a single isomer. Treatment of indolizidine alcohol (+)-**290** with phenylthionochloroformate and pyridine in DCM afforded the phenylthionocarbonate (-)-**291** in 55% yield; *tri-n*-butyltin hydride and AIBN furnished indolizidine (-)-**223A** (**219**) in 74% yield.



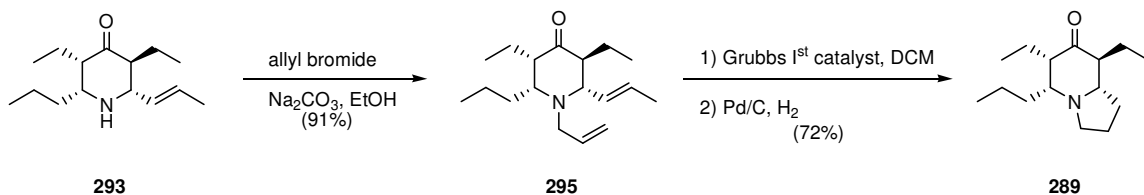
Scheme 3.20

In an effort to circumvent the poor yields in the intramolecular Mannich cyclization, a ring-closing metathesis strategy was explored to install the bicyclic indolizidine structure. The deprotected *syn*- β -amino ketone was treated with crotonaldehyde to give the crude *syn*-imine **292** in 93% yield. Subsequent treatment with TsOH resulted in two diastereomeric piperidines (2*S*, 3*S*, 5*S*, 6*R*)-(+)-**293** and (2*R*, 3*S*, 5*S*, 6*R*)-(+)-**294** in 58% and 18% isolated yields, respectively (Scheme 3.21). Importantly, no epimerization was noted at C-5 during the acid-catalyzed Mannich cyclization.



Scheme 3.21

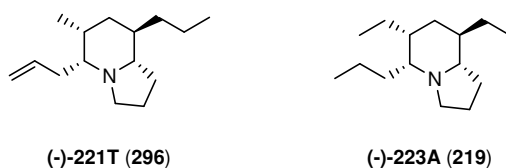
With the requisite *tetra*-substituted piperidinone (+)-**293** in hand, heating piperidinone **293** with allyl bromide/ Na_2CO_3 in EtOH afforded product diene (+)-**295** in 91% yield (Scheme 3.23). Ring-closing metathesis using 5 mol % of the Grubbs first generation catalyst, followed by catalytic hydrogenation, gave the common synthetic intermediate *tetra*-substituted indolizidinone (+)-**289** in 72% yield in two steps.



Scheme 3.23

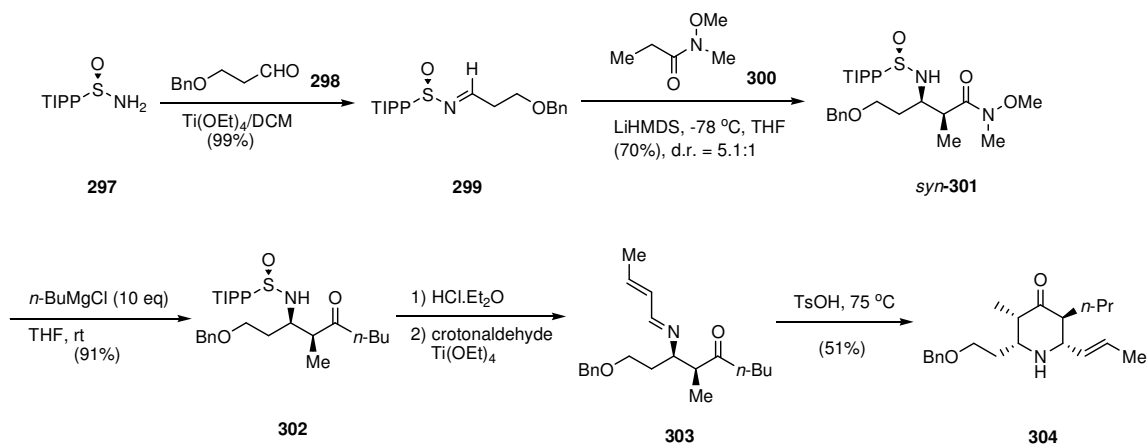
3.3.2. Davis and Song's synthesis of (5*R*, 6*R*, 8*R*, 9*S*)-(-)-5,9 *Z*-indolizidine 221T using *p*-toluenesulfinimines derived *N*-sulfinyl β -amino ketones.

Davis and Song disclosed an acid-catalyzed intramolecular Mannich cyclization of *N*-sulfinyl β -amino ketone as the method for the synthesis of *tri*-substituted stereodefined piperidones (-)-**221T** (**296**).²²²



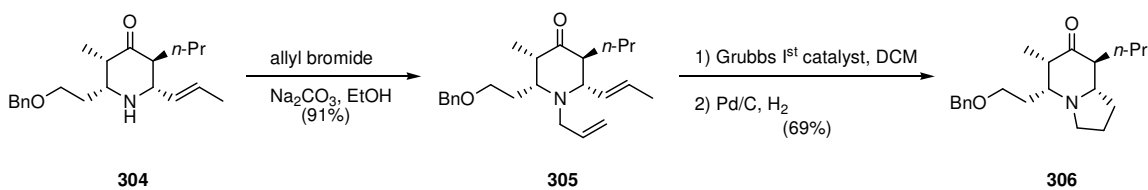
Scheme 3.24

Conversion of (-)-*syn*-**302** to piperidone (-)-**304** involved removal of sulfinyl auxiliary, condensation with crotonaldehyde, and the acid catalyzed intramolecular Mannich cyclization. Under optimized conditions developed by Davis and Yang, the crude imine *syn*-**303** was heated in toluene with 2 equivalent of anhydrous *p*-toluenesulfonic acid at 75 °C for 8 h to give piperidone (2*R*, 3*S*, 5*S*, 6*S*)-(-)-**304** in 51% yield for three step sequence. Use of toluenesulfonic acid hydrate, longer or shorter reaction times, and lower temperatures all resulted in poor yields (30-40%) of the piperidone. The structure of piperidone (-)-**304** was based on the NOE studies, and it was also observed that the intramolecular Mannich reaction of β -amino ketones generally gave piperidones which have C-2 and C-6 substituents in a *cis* relationship.



Scheme 3.25

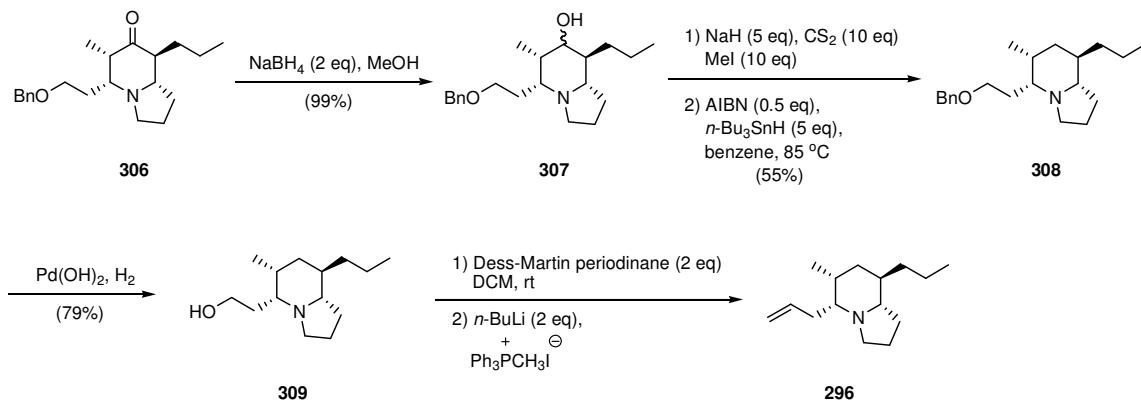
After that, following Yang's procedure for preparation of alkaloid **223A** (**219**), heating the *tetra*-substituted piperidinone (-)-**304** with allyl bromide/Na₂CO₃ in EtOH gave the product piperidinone diene (+)-**305** in 91% yield. On heating diene **305** at 40 °C with Grubbs 1st-generation catalyst in CH₂Cl₂ gave the cyclized product, which was then hydrogenated to form the bicyclic indolizinone **306** with 69% yield in 2 steps (Scheme 3.26).



Scheme 3.26

Reduction of (-)-indolizinone **306** with NaBH₄ gave a mixture of isomeric alcohols **307** in quantitative yield. The Barton-McCombie radical deoxygenation reaction yielded indolizidine (5*R*, 6*R*, 8*R*, 9*S*)-(-)-**308** in 55% yield for two steps (Scheme 3.27). Deprotection of the benzyloxy group gave alcohol (5*R*, 6*R*, 8*R*, 8*S*)-(-)-**309** in 79% yield. Swern oxidation of the primary alcohol (-)-**309** led to the formation of the

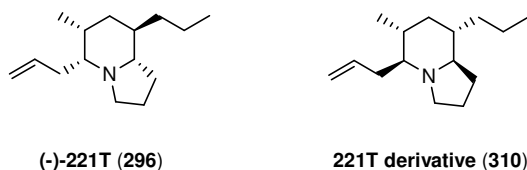
corresponding aldehyde, which was carried onto the next step directly in crude form. The Wittig reagent reacting with the aldehyde produced the terminal alkene, which completed the first total synthesis of (5*R*, 6*R*, 8*R*, 9*S*)-(-)-5,9 *Z*-indolizidine **221T** (**296**).



Scheme 3.27

3.4. Asymmetric synthesis of (5*R*, 6*R*, 8*R*, 9*S*)-(-)-5,9 *Z*-indolizidine **221T** using *p*-toluenesulfinimines derived *N*-sulfinyl β -amino ketones (Present study).

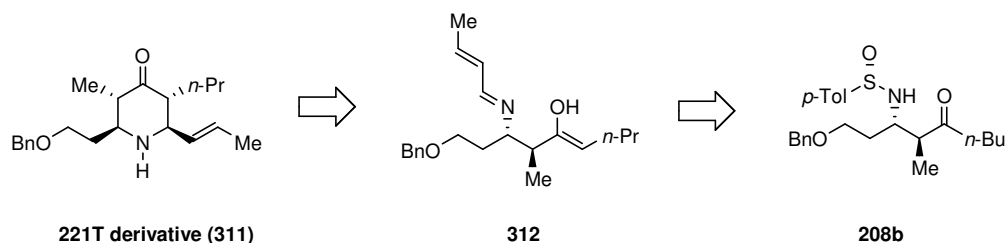
The bicyclic indolizidine ring systems have been the targets of efforts due to their significant biological activities. Importantly, the scarcity of 5,6,8-*tri*-substituted indolizidine and its derivatives as well as the uncertainty of the newly formed stereocenters at the *anti*-C5, and C6 positions inspired its synthesis (Scheme 3.28).



Scheme 3.28

3.4.1. Proposed retro-synthetic analysis

Similar to indolizidine alkaloid **223A** the critical problem in the total synthesis of indolizidine **221T** (**310**) is setting the stereocenters in the piperidine ring. It is reported that *syn*- α -methyl *N*-sulfinyl β -amino ketone was converted into the *syn*-C5, C6-*tetra*-substituted indolizidine **221T** (**296**) via a key step of intramolecular Mannich cyclization. Therefore, it is proposed that the synthesis of *anti*-C5, C6-*tetra*-substituted indolizidine **221T** derivative (**310**) could be obtained from the corresponding *anti*- α -methyl *N*-sulfinyl β -amino ketone **208b** via the important intermediate **311** (Scheme 3.29).

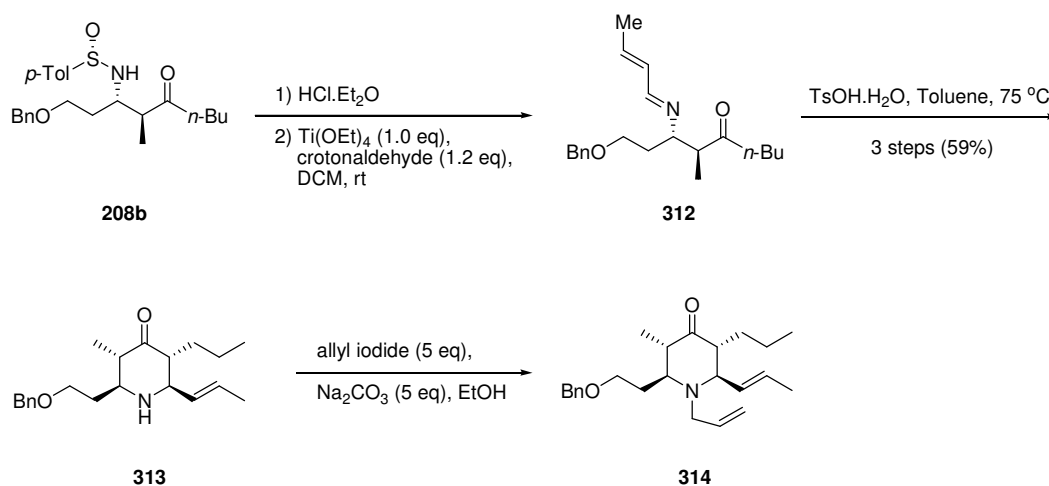


Scheme 3.29

As illustrated in Scheme 3.29, the *anti*- α -methyl *N*-sulfinyl β -amino ketone **208b** is a known compound that was prepared, in the course of this thesis, from the *p*-toluenesulfinimine derived *anti*- α -methyl β -amino Weinreb amide.²⁴² After removal of the *N*-sulfinyl group and condensation with crotonaldehyde, diene **312** could be cyclized to give the *tetra*-substituted piperidinone **311**. The α,β -stereocenter in the *anti*- β -amino enol **312** would have directing effects on the assembly of the enol generated *in situ* formed iminium ion. After construction of the stereodivergent 2,3,5,6-*tetra*-substituted piperidinone **311**, a strategy similar to that reported earlier could transform piperidinone **311** into the target molecule indolizidine **310**.

3.4.2. Synthetic route to *anti*-C5, C6 derivative of indolizidine **221T**

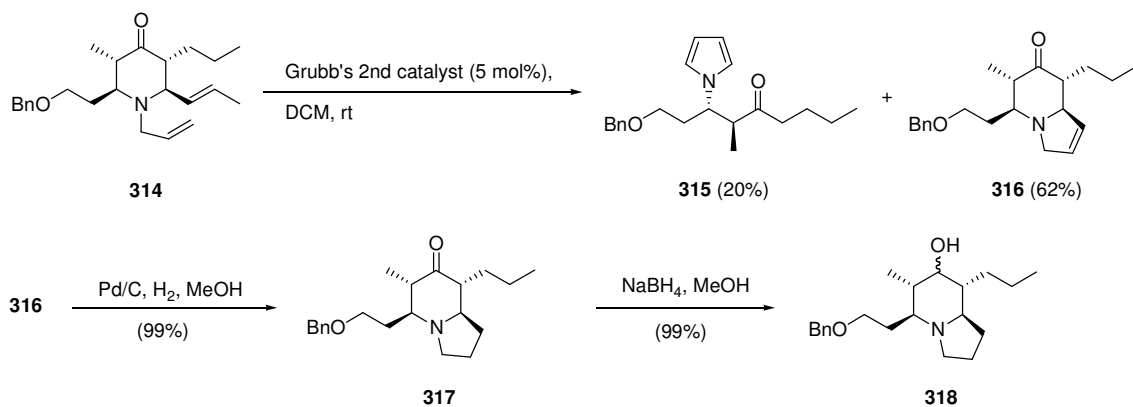
The synthesis of *anti*-C5, C6 derivative of indolizidine **221T** started from the *anti*- α -methyl β -amino ketone **208b** (Scheme 3.30). Removal of the *N*-sulfinyl group and condensation with crotonaldehyde by using Ti(OEt)₄ afforded the *anti*- α -methyl β -amino ketone **312** (Scheme 3.30). Heating the obtained hetero-diene ketone **312** with *p*-toluenesulfonic acid monohydrate led to the formation of *tetra*-substituted piperidinone **313** in 59% yield over 3 steps from β -amino ketone **208b**. The configuration of the two newly formed stereocenters of the *tetra*-substituted piperidinone **313** was established by NOE NMR experiments. Next, allylation of piperidinone **313** via heating with allyl iodide and Na₂CO₃ in EtOH gave diene **314** in 75% yield.



Scheme 3.30

Ring-closing metathesis of diene **314** using 5 mol % of the Grubbs “first generation” catalyst in CH₂Cl₂ at rt for 8 hours gave indolizinone **316** in 62% yield, and a 20% yield of β -pyrrole ketone **315** obtained as a blue oil (Scheme 3.31). Variation of solvents, reaction times and temperatures, to optimize the reaction conditions, were unsuccessful in elimination the formation of β -pyrrole ketone **315**. The formation of the

β -pyrrole ketone **315** is consistent with the earlier results observed in the synthesis of indolizidine **221T** (**296**).^{222,243} Following catalytic hydrogenation and NaBH₄ reduction, a mixture of diastereomeric *tetra*-substituted indolizidines **318** was produced in quantitative yield (Scheme 3.31).

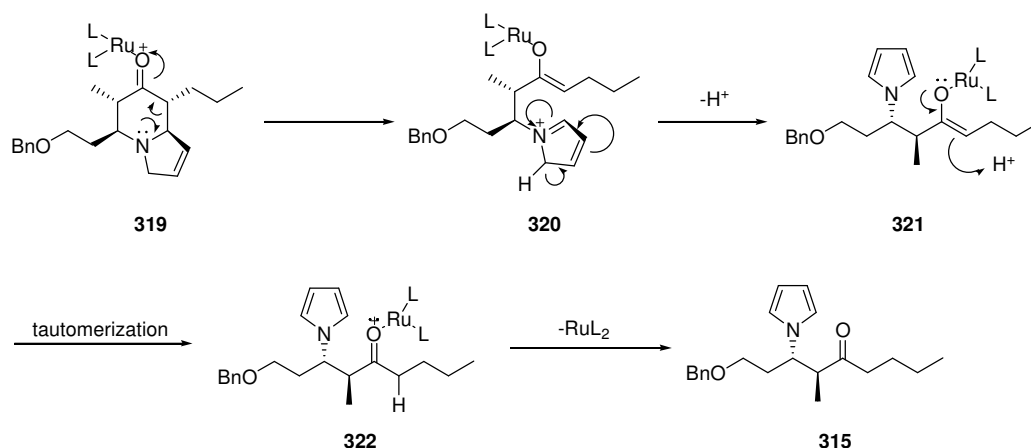


Scheme 3.31

3.4.3. Discussion

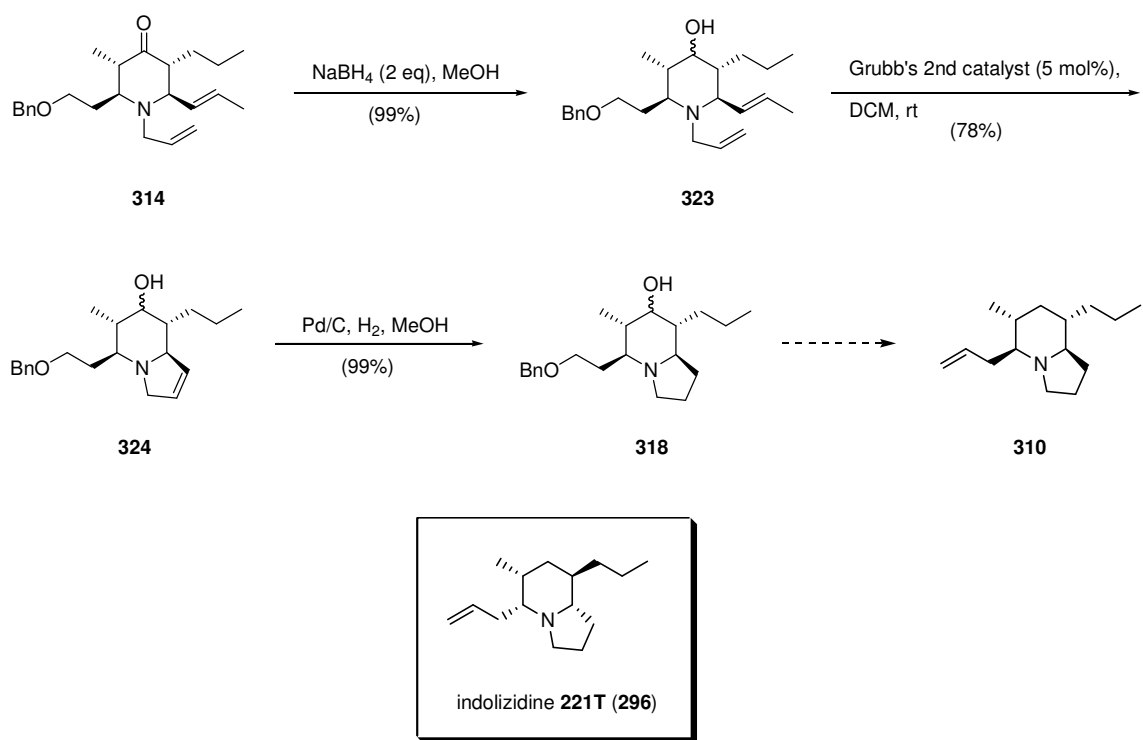
In the formation of *tetra*-substituted indolizidone **316**, *anti*- β -pyrrole ketone **315** was a side product (Scheme 3.32). A possible reason for its formation could be chelation between the ruthenium cation and carbonyl group oxygen atom accelerates the *retro*-Mannich process which leads to iminium cation **320** followed by aromatization to give β -pyrrole enol **321**. Subsequent protonation and tautomerization affords the *anti*- α -methyl β -pyrrole ketone **315**.

Proposed mechanism:



Scheme 3.32

Considering the high affinity of the carbonyl group, it was envisioned that reduction of the ketone **314** into the alcohol would avoid the strong bonding between the metal cation and the oxygen atom.²⁴⁴ Starting from *tetra*-substituted piperidinone **314**, reduction with $NaBH_4$ in MeOH gave a mixture of diastereomeric hydroxyl piperidines **323** in quantitative yield (Scheme 3.33). Importantly, ring-closing metathesis using the same conditions reported earlier afforded a mixture of diastereomeric bicyclic alcohol **324** in 78% yield without forming any of the pyrrole by-product. It is important to point out that the exchanged step-sequence not only increased the efficiency of the synthetic route, but strongly supported the mechanism proposed for the formation of side product. After that, catalytic hydrogenation of the formed bicyclic indolizidine **324** led to the formation of the common intermediate saturated indolizidine **318** in 99% yield (Scheme 3.33).



Scheme 3.33

Synthesis is at the stage for the formation of indolizidine isomer **221T** (**310**) following procedures reported earlier by Davis and co-workers in the preparation of alkaloid **221T** (**296**).²²²

**CHAPTER 4 ASYMMETRIC SYNTHESIS OF (R)-(-)-COCAINE C-1 METHYL
C-2 PHOSPHONATE ANALOG FROM N-SULFINYL β -AMINO ESTER
KETALS**

4.1. Introduction

(R)-(-)-Cocaine (**336**) belongs to the family of tropane alkaloids which are isolated from the leaves of *Erythroxylon coca* (Figure 4.1).²⁴⁵ Its profound behavioral and neuronal reinforcing properties are commonly believed to be associated with the inhibition of dopamine reuptake,²⁴⁶ and nowadays its abuse has become a major social and health problem. Untill now, there is no effective medication for the treatment of cocaine addition. As a result, major efforts are being expended in the search for cocaine antagonists²⁴⁷ and development of antibodies and vaccines.²⁴⁸ For these purposes, a number of cocaine-related tropane analogues have been synthesized,^{249,250} leading to high affinity and selective cocaine receptor ligands, which provided valuable information about the structure-activity relationship.

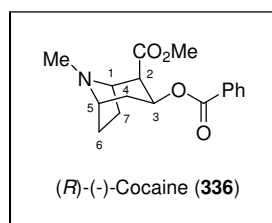


Figure 4.1

The pharmacodynamic study of cocaine revealed that complex relationships were involved among cocaine and neurotransmitters.²⁵¹ The studied effect of cocaine on the central nervous system is the blockade of the dopamine transporter protein. Dopamine

transmitter was released during neural signaling which is normally recycled via the transporter. Cocaine binds tightly at the dopamine transporter forming a complex that blocks the transporter's function. The dopamine transporter can no longer perform its reuptake function, which leads to the accumulation of dopamine in the synaptic cleft. The enhanced postsynaptic effect caused by prolonged exposure to cocaine will lead to homeostatic dysregulation of normal dopaminergic signaling. The decreased dopaminergic signaling may contribute to the mood disorders and sensitize the brain circuit to the reinforcing effects of cocaine, of which sensitization results in the intractable nature of addiction and relapse.

It is known that dopamine transporter (DAT) plays an important role in the regulation of dopaminergic transmission and cocaine was a competitive inhibitor of dopamine uptake. Schematic representation of putative interactions of cocaine with its receptor at the DAT are illustrated (Figure 4.2).²⁵² Results demonstrated that cocaine and dopamine have common binding domains on the DAT, if cocaine and dopamine have distinct binding sites on the DAT, it is therefore possible to develop a small molecule cocaine antagonist which would specifically inhibit cocaine recognition by the DAT while permitting the transporter to maintain all or most of its functions. Such a selective compound would then have clinical utility since it could block the physiological effects of cocaine and also leave normal dopamine transmission within the brain intact.

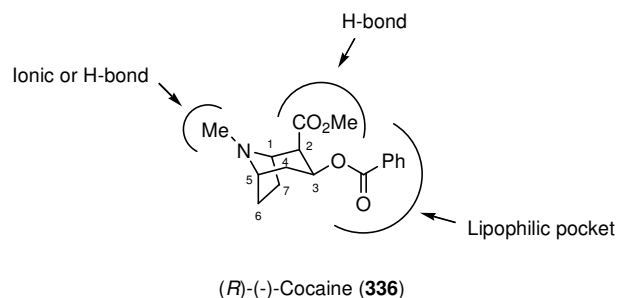


Figure 4.2

Furthermore, structure-based cocaine analog chemical modifications would be a powerful strategy to improve the efficiency of the target molecule filtration.^{253,254}

Cocaine contains an 8-azabicyclo-[3.2.1] octane frame-work and is one of the eight possible stereoisomers of methyl 3-benzoyloxy-8-methyl-8-azabicyclo-[3.2.1] octane-2-carboxylate (Figure 4.3). In addition to the construction of this azabicyclo ring system, the major hurdle the synthesis must control the stereochemistry, both of enantiomeric integrity and of the thermodynamically unstable axial carboxylate function.

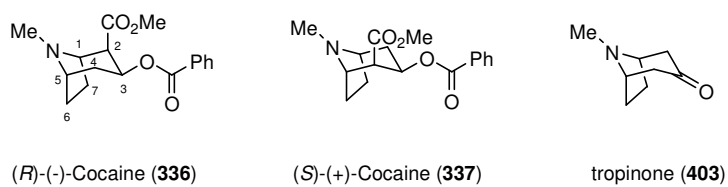


Figure 4.3

A common approach to nonracemic cocaine analogues was the direct derivatization of natural cocaine derivatives (Figure 4.3).²⁵⁵⁻²⁵⁷ Synthesis in the tropane family was initiated by Willstatter starting from cycloheptanone over a century ago.^{258,259} Soon thereafter, Robinson devised an elegant approach involving the condensation of succinaldehyde, methylamine and the calcium salt of 1,3-acetonedicarboxylic acid to synthesize tropinone.²⁶⁰ From then on, several cycloaddition methods were employed,

such as cyclization between rhodium (II)-stabilized vinylcarbenoids with pyrroles,²⁶¹ [3+4] cycloaddition of iron oxyallyl cations to pyrrole,²⁶² [3+2] nitrene cycloaddition,²⁶³ nitroso cycloaddition,²⁶⁴ and pyridinium betaine-based dipolar cycloaddition.²⁶⁵

To date, there are a few asymmetric syntheses of cocaine and only four total syntheses that do not need enantiomerically pure starting materials. Rapoport prepared (*R*)-(-)-cocaine (**336**) from L-glutamic acid using an intramolecular nucleophilic substitution to form the tropane ring.²⁶⁶ The relative stereochemistry at C-2 and C-3 in (-)-**336** was established via a [3 + 2] cycloaddition of an *in situ* generated nitrile *N*-oxide to a nonracemic tropene. Pearson synthesized (*S*)-(+)-cocaine (**337**) using 2-azaallyllithium [3 + 2] cycloaddition to prepare a *meso*-pyrrolidine dialdehyde which was subjected to an asymmetric proline-catalyzed intramolecular enol-*exo*-aldol reaction.²⁶⁷

Technically, Tufariello and co-workers introduced the most efficient method to control the stereochemistry at C-2, C-3 in the synthesis of (\pm)-cocaine.²⁶³ Heating of the intermediate nitrene resulted in an intramolecular cyclization to give the tricyclic isoxazolidine, which was readily transformed into (\pm)-cocaine. Importantly, Davis and Theddu developed an innovative preparative method of (*S*)-(+)-cocaine (**337**) starting from enantiopure α,β -unsaturated pyrrolidine nitrenes.²⁶⁸ Lewis acid catalyzed the intramolecular [3 + 2] dipolar cycloaddition with high stereoselectivity, the formed key intermediate isoxazoline was transformed to C-1 cocaine analog in 3 steps.

Built on this developed method, series of enantiopure C-1 cocaine analogs have been prepared from corresponding *p*-toluenesulfinimines.²⁶⁹ However, reports on the synthesis of C-2 substituted cocaine or tropane skeleton are relatively few and still suffer

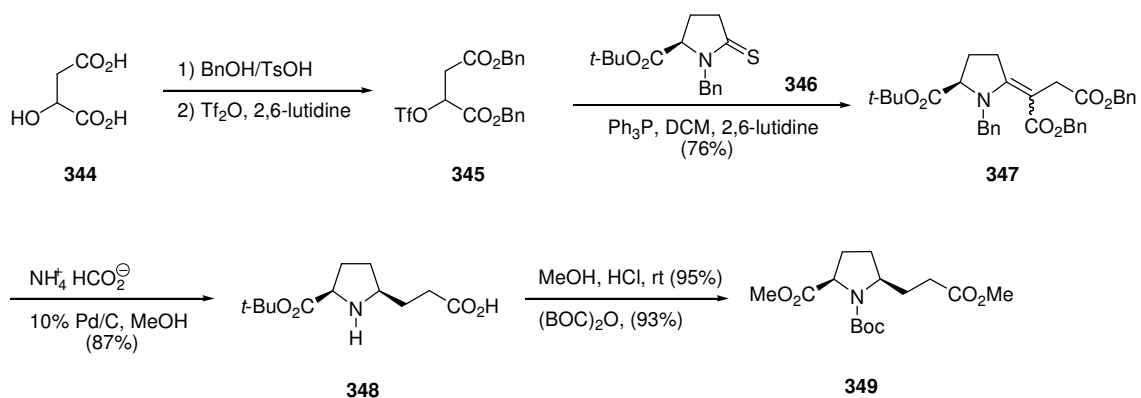
from low yield and poor stereoselectivity. It was thought that C-2 branched cocaine analog would have varied bioactivities and potent therapeutical use. Therefore, a design for the building structure of C-2 substituted cocaine analogs would be much meaningful.

4.2. Synthetic background of (-)-cocaine and its analogs

As mentioned earlier in this chapter, only a few total syntheses of enantiopure cocaine were reported. All of these synthetic methods started from commercially available chemicals, and each of these routes employed imaginative and modern synthetic procedures but nonetheless required long synthetic steps to prepare this seemingly simple natural alkaloid. Cha et al. reported an asymmetric synthesis of (*S*)-(+)-cocaine (**337**) via enantioselective deprotonation of tropinone.²⁷⁰

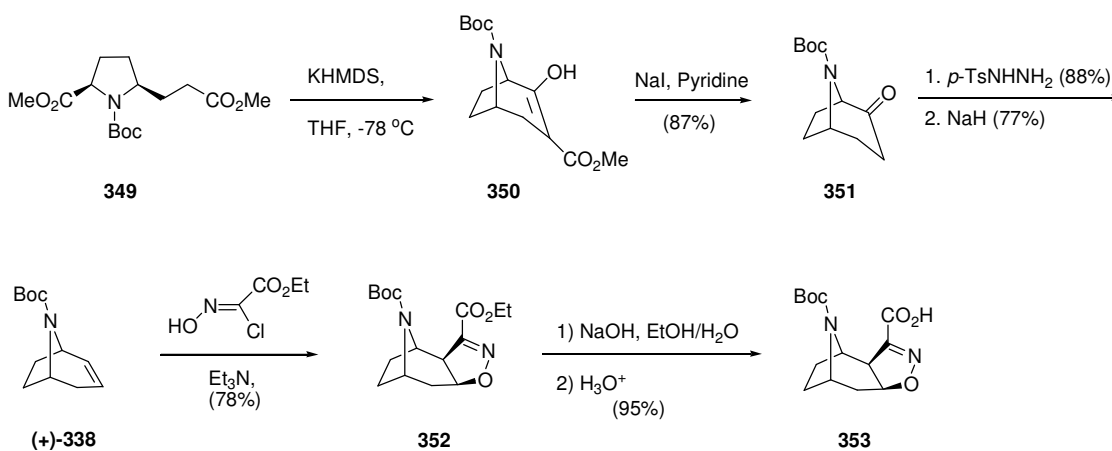
4.2.1. Rapoport's synthesis of (-)-cocaine and (+)-cocaine

Rapoport's synthesis, started from racemic malic acid (**344**), dibenzyl esterification and subsequent treatment with Tf₂O and 2,6-lutidine, gave the dibenzyl triflate **345** in 95% yield (Scheme 4.1). Thiolactam **346** derived from D-glutamic acid, reacted with dibenzyl triflate **345** followed by sulfide contraction to afford the vinyl carbamate **347** in 76% yield as a 5.5:1 ratio of isomers. Treatment of olefin **347** with ammonium formate in the presence of catalytic 10% Pd/C in MeOH gave the decarboxylated pyrrolidine **348** in 87% yield. Esterification of the γ -amino acid **348** with MeOH/HCl led to the formation of dimethyl ester in 95% yield, which subsequently reacted with the Boc anhydride to give the Boc protected dimethyl ester **349** in 93% yield.



Scheme 4.1

Treatment of diester **349** with KHMDS at -78°C resulted in a Dieckmann condensation to give the β -keto ester in 90% yield, which exists predominantly as the enol ester **350** (Scheme 4.2). Decarboxylation was achieved by treatment with NaI in pyridine at reflux to give the ketone **351** in 90% yield. The *N*-Boc ketone **351** was converted to the tosylhydrazone in 88% yield, from which olefin (1*R*, 5*S*)-(+)-tropene **338** was obtained by reaction with NaH in 70% yield.



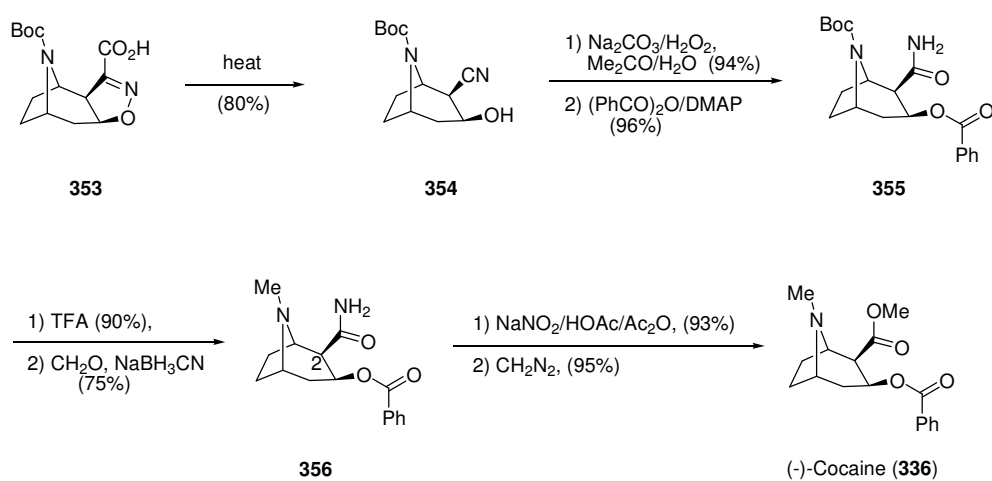
Scheme 4.2

The [3 + 2] dipolar cycloaddition of (1*R*, 5*S*)-*N*-Boc nortropene (**338**) with ethoxycarbonylformonitrile oxide was investigated resulting in **352** in 78% yield.

Treatment of dihydro-isoxazole **352** with NaOH in EtOH/H₂O, followed by careful acidification, gave the carboxylic acid **353** in 95% yield (Scheme 4.2).

Thermal decarboxylation and fragmentation of the isoxazoline **353** was achieved by heating at 105-110 °C, affording the β-hydroxy nitrile **354** in 80% yield (Scheme 4.3).

The β-hydroxy nitrile **354** was hydrolyzed by treatment with H₂O₂ in the presence of Na₂CO₃ in acetone/H₂O. Corresponding β-hydroxy amide was obtained in 94% yield without any epimerization detected at C-2 position, and subsequent reaction with benzoyl anhydride/DMAP resulted in the formation of benzoate **355** in 96% yield.



Scheme 4.3

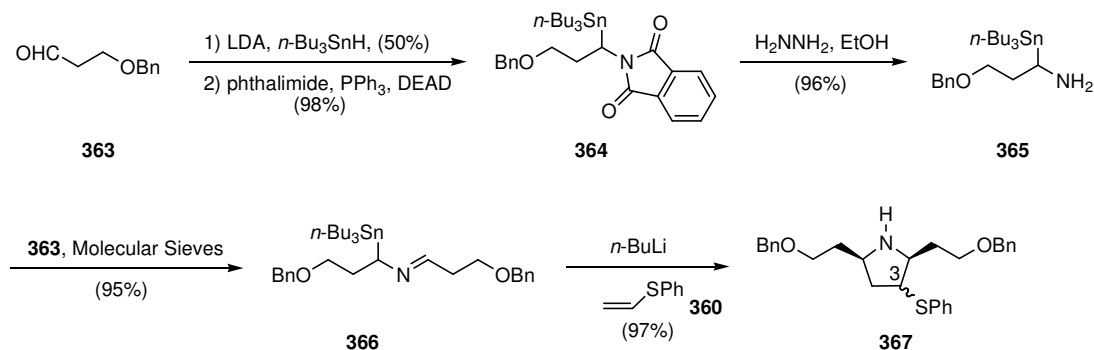
Removal of the Boc group with TFA gave the deprotected tropane in a yield of 90%, and reductive methylation at the bridgehead nitrogen in the tropane led to the formation of tertiary amine **356** in 75% yield. Nitrosation with NaNO₂/HOAc/Ac₂O proved to be an efficient way to convert the amide **356** to its carboxylic acid in 93% yield with the stereochemistry at C-2 unaffected. Reacting the C-2 carboxylic acid with the

diazomethane completed the methyl ester formation and furnished the target molecule (-)-cocaine (**336**) in 95% yield.

4.2.2. Pearson's synthesis of (+)-cocaine

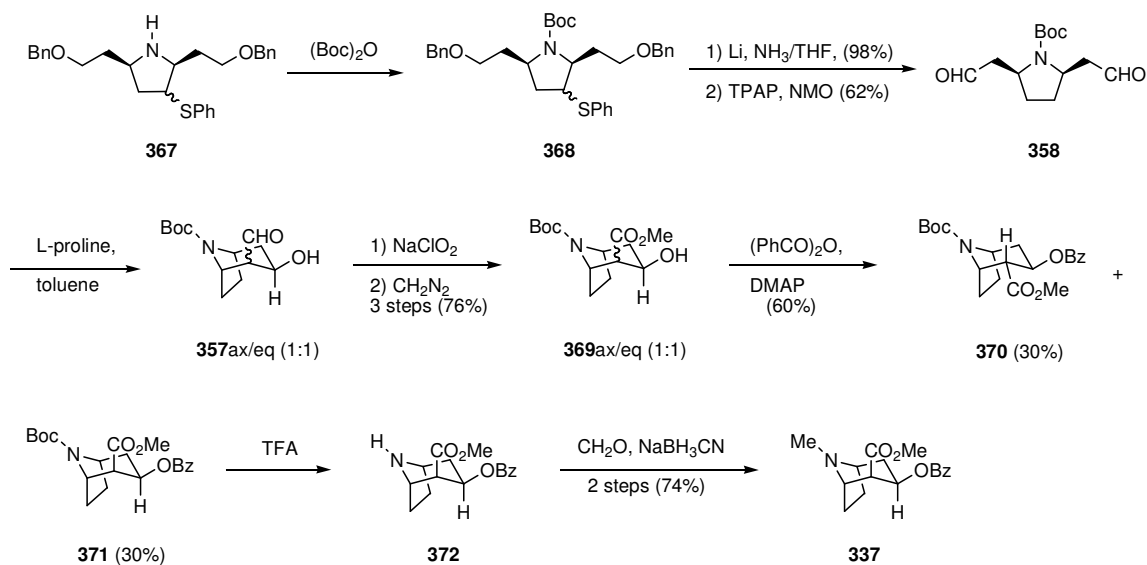
The 3-benzyloxypropionaldehyde (**363**), prepared from commercially available 3-benzyloxy-1-propanol, was treated with tributylstannyl lithium to give an intermediate α -benzyloxy stannane in 50% yield (Scheme 4.4). Mitsunobu reaction of the intermediate with phthalimide provided the α -stannyl phthalimide **364** in 98% yield. It was observed that the overall yield improved when the α -hydroxy stannane was purified, although the tin addition/Mitsunobu reaction was generally carried out without purification.

Hydrazinolysis of phthalimide **364** gave the deprotected the α -amino stannane **365** in 96% yield. Condensation of 3-benzyloxypropionaldehyde **363** with α -amino stannane **365** gave 2-azaallylstannane **366** in 95% yield. Gratifyingly, treatment of imine **366** with *n*-butyllithium and phenyl vinyl sulfide led to a [3 + 2] cycloaddition and *cis*-pyrrolidine **367** was formed in 97% yield as a 1:1 mixture of C3-isomers.



Scheme 4.4

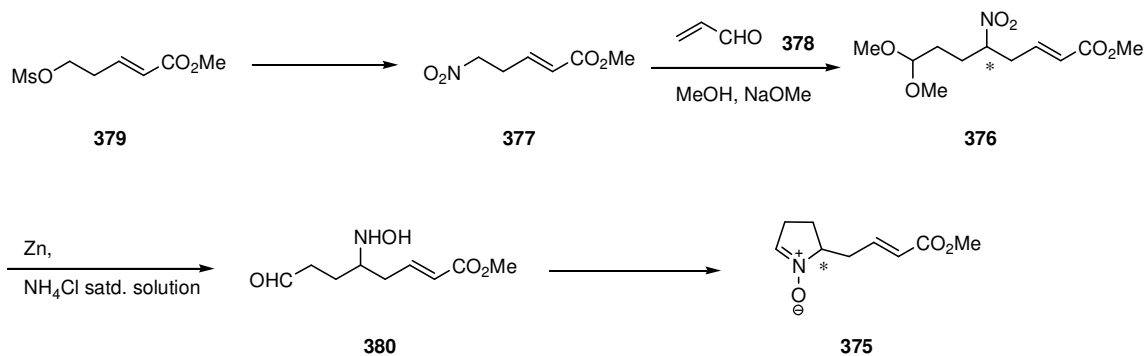
Subsequent protection of the *tri*-substituted pyrrolidine **367** and metal reduction removal of benzyl and phenylthio group led to an excellent yield of the *meso*-diol, which was oxidized to the Boc *cis*-dialdehyde **358** in 62% yield (Scheme 4.5). Oxidation to dialdehyde **358** proved to be less straightforward and many attempted oxidation methods failed to give good results. However, oxidation with TPAP/NMO of the diol led to the formation of the dialdehyde **358**. With the key *meso*-dialdehyde **358** in hand, the proline catalyzed aldol reaction was attempted. Due to the instability of the 1:1 mixture of crude aldol products, **357** ax/eq were immediately converted to the methyl esters via oxidation to the acid followed by esterification to provide α -hydroxy esters **369** ax/eq in 76% overall yield from dialdehyde **358**. Separation of the α -hydroxy esters diastereomers **369** ax/eq was not feasible. However, benzylation of these mixtures with benzoic anhydride and DMAP provided a 60% yield of Boc-protected tropane **371/370**, which were separated by HPLC. Removal of the Boc carbamate from the desired tropane **371** with trifluoroacetic acid followed by reductive amination provided (+)-cocaine **373** in 74% yield over two steps with 86% e.e..



Scheme 4.5

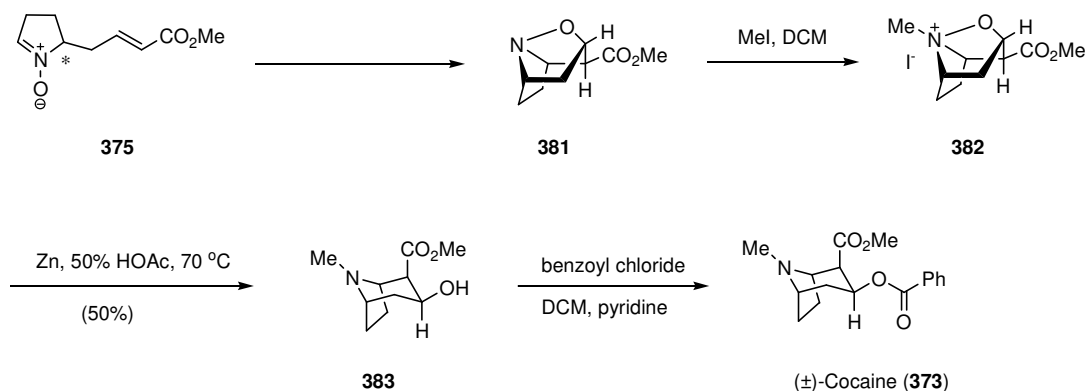
4.2.3. Tufariello's synthesis of (\pm) cocaine

Tufariello's racemic cocaine synthesis began with nitro ester **377**, prepared from mesylate olefin **379** (Scheme 4.6). Michael addition of **377** to acrolein **378** followed by *in situ* protection of aldehyde provided dimethyl acetal **376** in 94% yield. The conversion of **376** into the hydroxylamine aldehyde **381** was realized by reaction with zinc, aqueous NH_4Cl and acidification. Next aldehyde **381** was capable of a spontaneous cyclization, however, only a slight yield of desired racemic nitron **375** was obtained.



Scheme 4.6

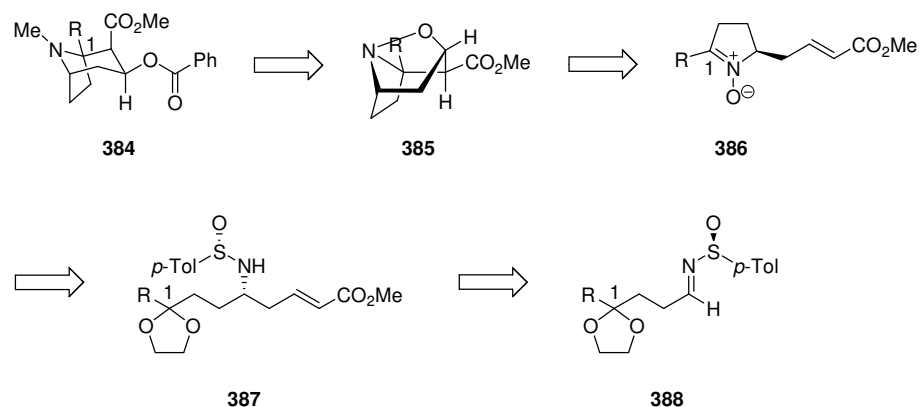
After numerous attempts at cyclization the yields of cycloadduct **381** were only in the range of 4 to 11% (Scheme 4.7). Methylation of *tri*-cyclic product **381** with methyl iodide afforded methiodide **382**, which was then treated with activated zinc in acetic acid to cleave the nitrogen-oxygen bond affording the amino alcohol **383** in 50% yield. Following benzylation of alcohol **383** afforded the racemic-cocaine (**373**) in good yield.



Scheme 4.7

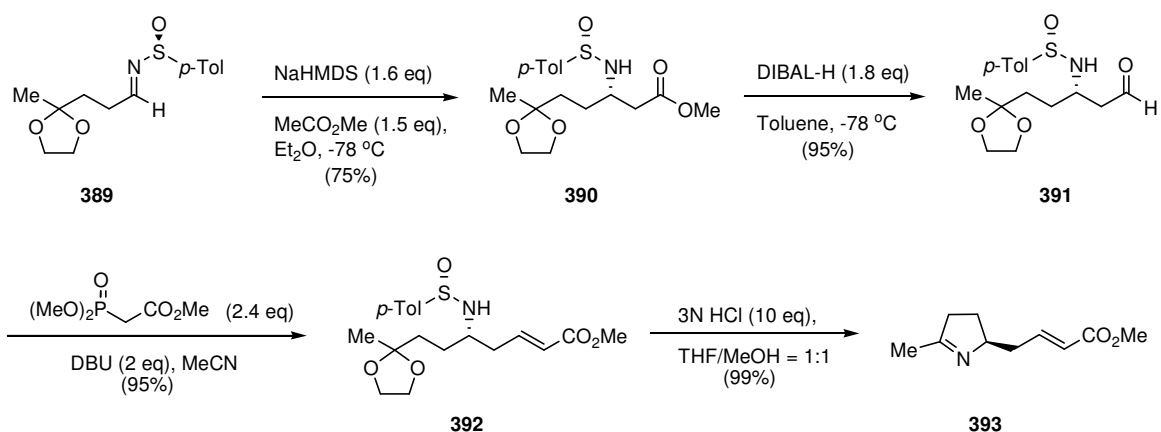
4.2.4. Davis synthesis of (*S*)-(+)-cocaine and (*R*)-(-)-cocaine C-1 analogs

Davis and Theddu disclosed a method for the asymmetric synthesis of (*S*)-cocaine (**337**) and (*R*)-cocaine analogs which have a C-1 bridgehead substituent.²⁶⁸ The synthetic strategy to prepare (*R*)-cocaine C-1 analogs could be derived from its precursor *tri*-cyclic isoxazolidine **385** (Scheme 4.8). The key step in the formation of isoxazolidine **385** was realized by Tufariello using a [3 + 2] nitron cyclo-addition reaction. Importantly, the utilization of the non-racemic nitron **386** would lead to the production of chiral intermediate **385** and desired enantiopure (*R*)-cocaine C-1 analog **384**. It is envisioned that non-racemic nitron **386** could be prepared from *N*-sulfinyl β -amino ester ketal **387**, which was prepared from *p*-toluenesulfinimine **388**.



Scheme 4.8

The synthesis of (*R*)-cocaine C-1 methyl derivative begins with sulfinimine (*S*)-(+)-**389** (Scheme 4.9). On treatment with an excess of the sodium enolate of methyl acetate, (+)-**389** afforded the corresponding *N*-sulfinyl β-amino ester ketal (*S_S*,*3S*)-(+)-**390** as a single diastereoisomer. Reduction of methyl ester (+)-**390** with DIBAL-H in toluene gave aldehyde (*S_S*,*3S*)-(+)-**391** in 75% yield without epimerization at the C-N stereocenter.

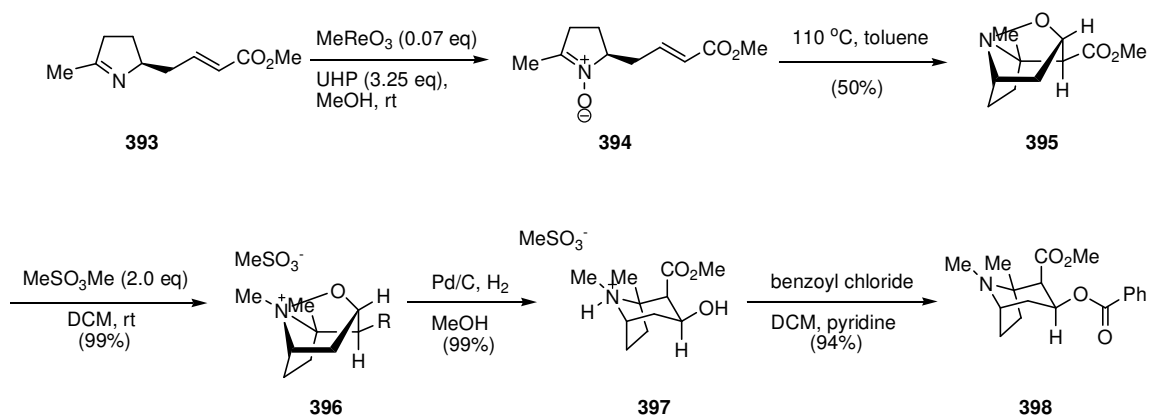


Scheme 4.9

Submission of aldehyde (+)-**391** to the Roush-Masamune modified HWE olefination,²⁷¹ gave α,β-unsaturated *N*-sulfinyl amino ketal (*S_S*,*5S*)-(+)-**392** as an

inseparable 9:1 *E:Z* mixture of isomers (Scheme 4.9). Hydrolysis of α,β -unsaturated *N*-sulfinyl amino ketal (*S_s,5S*)-(+)-**392** with 3 N HCl gave the corresponding dehydropyrrolidines (*S*)-(+)-**393** in quantitative yield.

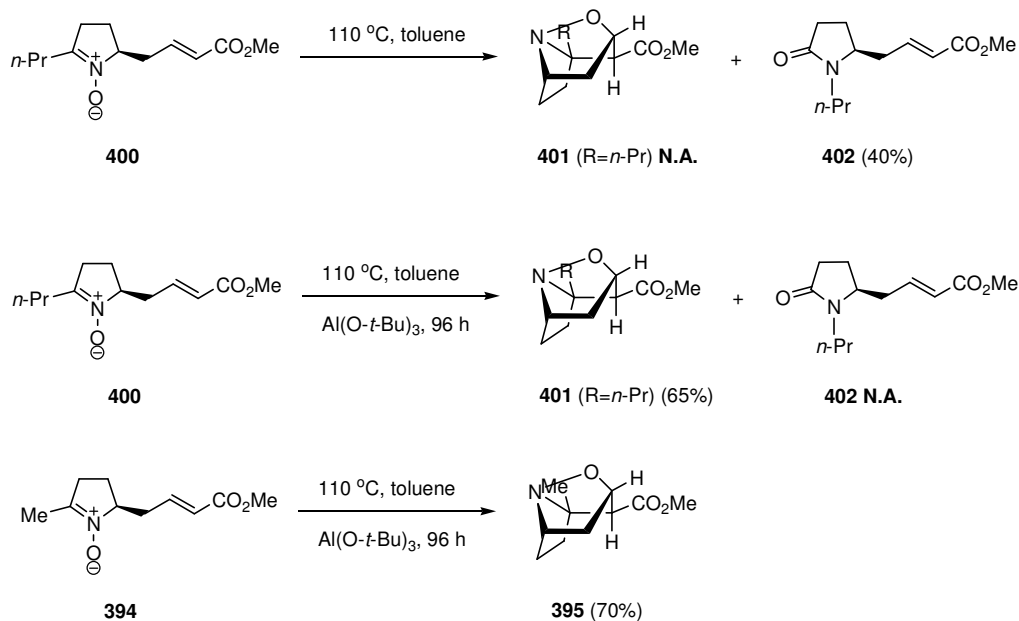
Treatment of dehydropyrrolidines (+)-**393** with urea hydrogen peroxide catalyzed by methyltrioxorhenium led to the formation of corresponding nitrone **394** in quantitative yield (Scheme 4.10).²⁷² Refluxing nitrone **394** in toluene for 48 h afforded tricyclic isoxazolidine (1*S*,2*R*,3*R*,6*S*)-(-)-**395** in 50% yield. With methylmethanesulfonate in benzene (-)-**395** afforded methanesulfonate salts (-)-**396** in 98% yield. Catalytic hydrogenation cleaved the N-O bond and afforded (-)-**397** in 99% yield, which was then transformed into the C-1 methyl cocaine analog (-)-**398** with benzoyl chloride and pyridine in 94% yield. Following the established synthetic route, (*R*)-cocaine C-1 having Et, *n*-Pr, *n*-C₅H₁₁ and Ph at C-1 were prepared in high optical purity.



Scheme 4.10

It is worthy of notice that in the process of preparing the C-1 *n*-propyl tricyclic isoxazolidine **401**, *n*-propyl nitrone **400** did not give the tricyclic isoxazolidine **401** under the conventional heating conditions but amide **402** was formed in 40% yield as a single

isomer via an oxaziridine intermediate (Scheme 4.11). Here the *n*-propyl group in nitrone **400** may sterically inhibit the cycloaddition reaction.

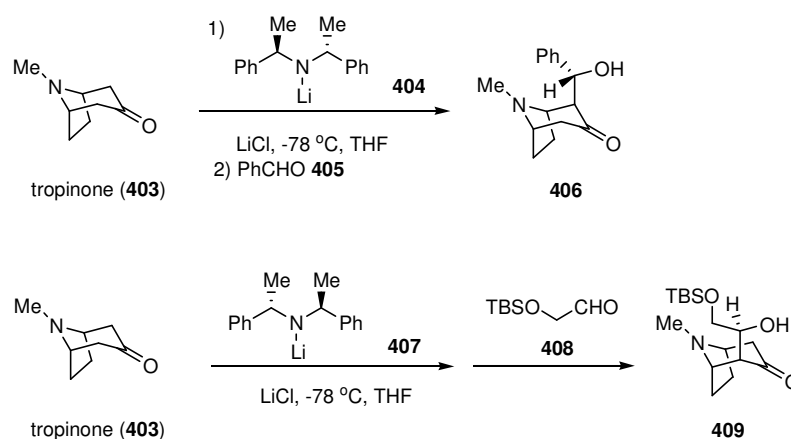


Scheme 4.11

Lewis acids catalyzed 1,3-dipolar cycloadditions have been extensively investigated,²⁷³ it was believed that both nitrone and α,β -unsaturated carbonyl functionality could be activated due to the Lewis acid coordination to their oxygen atoms. Moreover, it was thought that a bulky Lewis acid would preferentially activate the α,β -unsaturated ester via oxygen bonding while maintaining the reactivity of nitrone, accelerating the reaction rate. After various Lewis acids were screened, it was observed that after reacting *n*-propyl nitrone **400** with aluminum *t*-butoxide, isoxazolidine **401** was obtained with a 65% yield. Submission of the methyl nitrone **394** to heating with aluminum *t*-butoxide, the yield of (-)-**395** improved from 50% to 70%.

4.2.5. Miscellaneous method in the synthesis of (*S*)-cocaine and (*R*)-cocaine

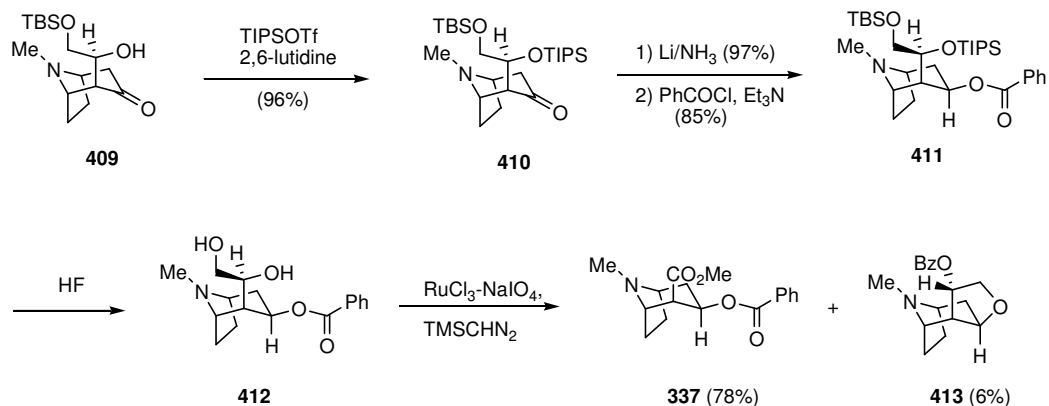
Cha et al. reported a preparation of (*S*)-(+)-cocaine (**337**) via desymmetrization of the tropinone (**403**), using a chiral base and an aldol reaction to install the carbomethoxy group at C-2 in the required axial position (Scheme 4.12).²⁷⁰ Treatment of tropinone with lithium (*R,R*)-bis(1-phenylethyl)amide (**404**) in the presence of lithium chloride, followed by benzaldehyde **405**, afforded the *exo-anti* adduct **406** as a single diastereomer. Similarly, enantioselective deprotonation of tropinone (**403**) by the action of lithium (*S,S*)-bis(1-phenylethyl)amide (**407**) in the presence of lithium chloride, followed by *in situ* trapping with the known aldehyde **408**, afforded the aldol product **409** as a single diastereomer as well in 72% yield.



Scheme 4.12

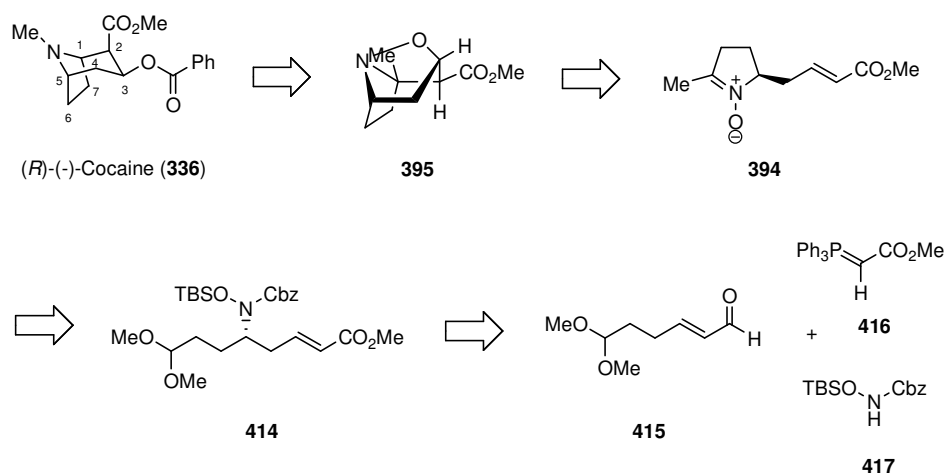
Beginning with C2-substituted tropinone **409**, silylation of the alcohol gave the disilyl tropinone **410** in 96% yield (Scheme 4.13). Stereoselective lithium ammonia reduction and subsequent benzylation gave the *di*-substituted tropane **411** in 82% overall yield for the 2 steps. Oxidation of diol **412** with RuO₄ gave the carboxylic acid in the thermodynamically unfavorable axial position. Methylation of the acid furnished (*S*)-

(+)-cocaine (**337**) in 78% yield, together with 6% yield of the side product *multi*-substituted furan **413**.



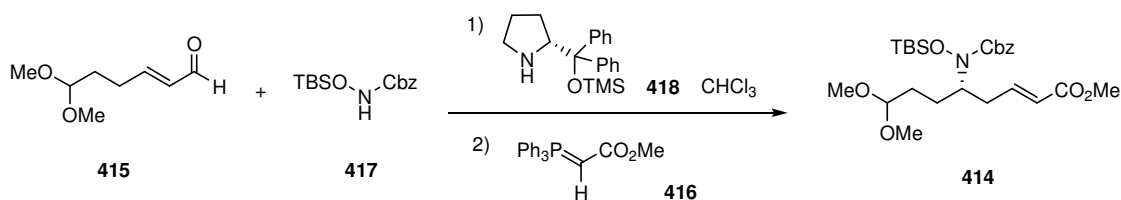
Scheme 4.13

Cordova and co-workers reported the asymmetric synthesis of (*R*)-(-)-cocaine (**336**), (*S*)-(+)-cocaine (**337**) and their derivatives via the utilization of Tufariello-Davis intramolecular [1, 3]-dipolar cycloaddition (Scheme 4.14).²⁷⁴ Importantly, the dipolar cycloaddition precursor α,β -unsaturated δ -amino ester **414** was assembled via an organocatalyzed one-pot three-component reaction.



Scheme 4.14

The synthesis involves a one-pot enantioselective three-component catalytic *aza*-Michael/Wittig tandem reaction between acetal-functionalized enal **415**, hydroxylamines **417** and alkyl 2-(triphenylphosphoranylidene)acetates **416** using chiral amine **418** as the catalyst. Reaction conditions were screened and the optimum results are summarized in Table 4.1. After highly enantioselective α,β -unsaturated δ -amino ester **414** was prepared, construction of (-)-cocaine was same as the Davis synthesis of cocaine analogs outlined above (Scheme 4.15).



Scheme 4.15

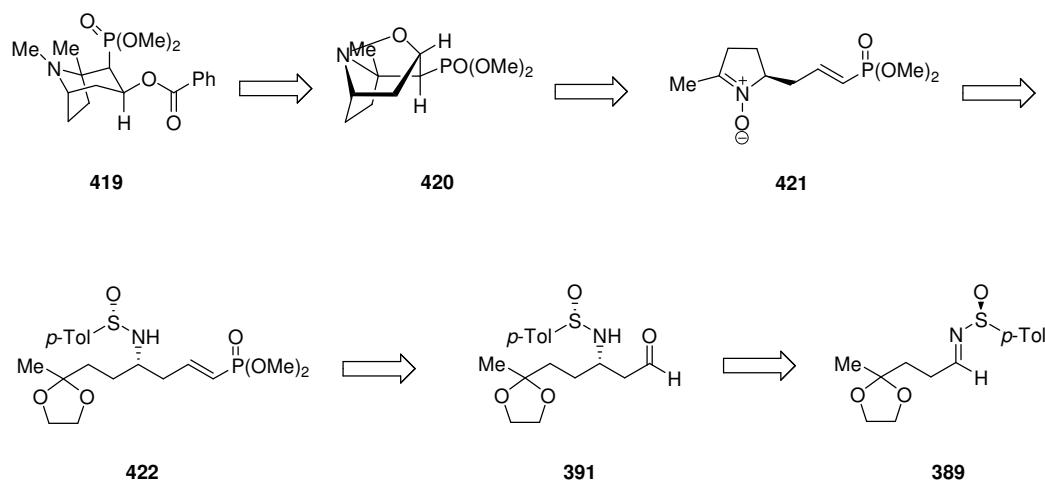
Table 4.1 Screening of conditions for the one-pot three-component reaction between amine **417**, enal **415** and catalyst **418**.

Entry	Temp. (°C)	Time (h)	Yield (%)	e.e. (%)
1	25	40	40	90
2	25	24	67	90
3	4	40	68	92
4	-20	135	48	96
5	4	96	41	92
6	4	40	69	92
7	4	17	68	96
8	4	17	70	96

^a Enal **415** (0.25 mmol), amine **417** (2 mmol) and catalyst **418** (20 mol %) were stirred in CHCl₃ (0.5 mL). ^b Isolated yield of pure compound. ^c Determined by chiral-phase HPLC analysis. ^d 1 mL CHCl₃ and 0.5 mmol **417**. ^e 10 mol % of **418**. ^f 1 mmol of **415**.

4.3. Proposed synthetic strategy for the asymmetric synthesis of C-1 methyl C-2 phosphonate cocaine analogs.

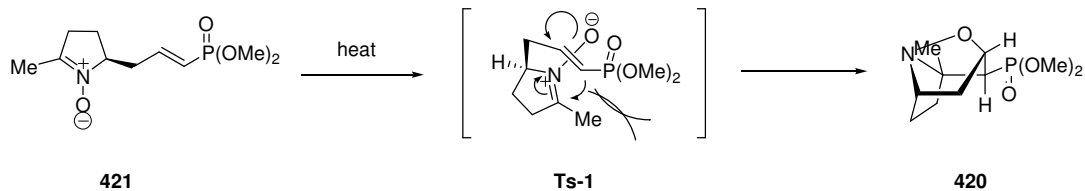
The retrosynthetic strategy for the asymmetric synthesis of C-2 phosphonate substituted cocaine analogs **419** is built on the results described by Davis and co-workers. Cocaine phosphonate analog **419** would be prepared from the tricyclic isoxazolidine **420** via ring-opening hydrogenation (Scheme 4.16). The isoxazolidine **420** would be assembled from dehydropyrrolidine nitron **421** via the [3 + 2] nitron cycloaddition reaction and prepared from a *p*-toluenesulfinimine derived *N*-sulfinyl β -amino aldehyde **391**.



Scheme 4.16

The dimethyl phosphonate group is bulkier than the methyl carboxylate group with A values of 2.6 and 1.27, respectively (Scheme 4.17). It is believed that in the process of the forming the *tri*-cyclic isoxazolidine **420**, the *di*-substituted dehydropyrrolidine nitron forms a specific transition state and the carbon-carbon double bond comes close to the nitron for the [3 + 2] intramolecular cycloaddition. The

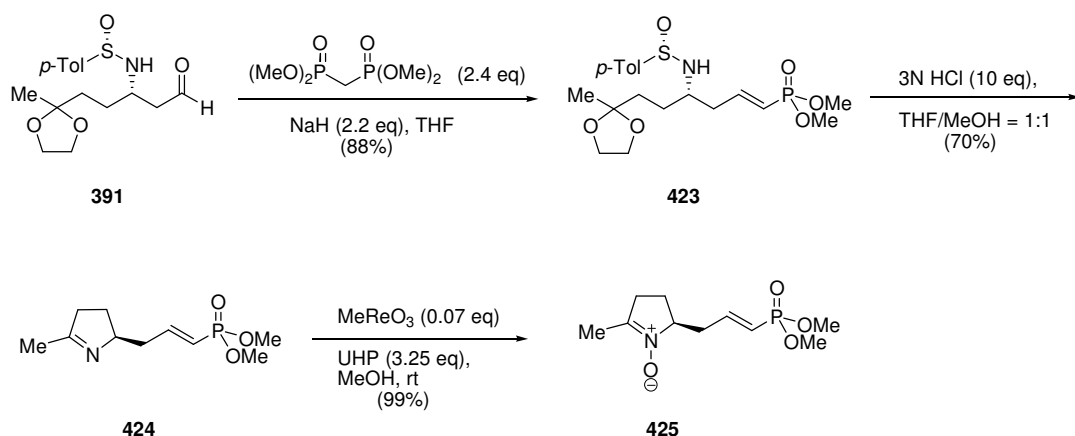
phosphonate steric repulsion between the C-2 substituent and the C-1 methyl group may destabilize the requisite transition state resulting in no reaction or a slower reaction rate.



Scheme 4.17

4.4. Present study

The synthesis of C-2 phosphonate cocaine analog begins with aldehyde **391** prepared earlier in 76% yield (Scheme 4.18). Aldehyde **391** was subjected to the HWE reaction with *tetra*-methyl methylene diphosphonate to give the (*E*)- δ -amino dimethylphosphonate **423** in 88% yield as a single isomer. Hydrolysis of α,β -unsaturated *N*-sulfinyl amino ketal **423** with 3 N HCl gave the corresponding dehydropyrrolidines **424** in 70% yield.

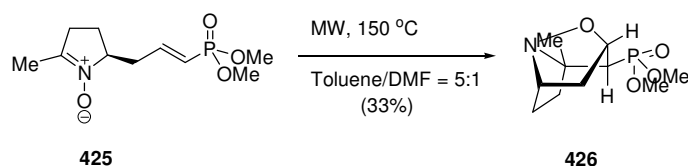


Scheme 4.18

Oxidation of the dehydropyrrolidine **424** afforded the pyrrolidine nitron **425** in 99% yield (Scheme 4.19). In contrast to other pyrrolidine nitrones reported earlier, it was possible to separate the pure dimethylphosphonate pyrrolidine nitron **425** via chromatography. In the key step of building the tricyclic structure of isoxazolidine **426**, initial reaction was refluxed in toluene for 96 h. Product 2-*exo*-phosphonate isoxazolidine **426** was obtained in 30% yield along with undefined dark sticky materials. Microwave irradiation of the purified nitron **425** in mixed solvent gave the 2-phosphonate tricyclic isoxazolidine **426** in 33% yield. The reason why the crude nitron gave a lower yield of isoxazolidine **426** could be that the Rhenium cation of MeReO₃ binds to the nitron oxygen atom, which decreased its nucleophilicity to carbon-carbon double bond. To improve the conversion rate and reduce the amount of side products, the reaction was heated in microwave reactor, and the results are listed below in Table 4.2.

In the first experiment, the solution of dimethylphosphonate nitron **425** in acetonitrile was heated by microwave irradiation at 150 °C for 5 h (Table 4.2, entry 1). Unexpectedly, a low conversion rate **425:426** = 1:0.16 was observed. It was reported that when [3 + 2] cyclization of nitron and vinyl dimethylphosphonate occurred in acetonitrile, usually moderate yields around 50% were observed. The low yield of the tricyclic product **426** could be caused by the bulky dimethylphosphonate which might inhibit the [3 + 2] cycloaddition due to the steric repulsion. Using a binary solvent mixture of toluene and ethanol (5:1) increased the conversion rate a little bit, whereas raising the amount of ethanol led to a drop of the isoxazolidine **426** production (Table 4.2, entry 2 and 3).

To maintain the high polarity of a mixed binary solvent without bringing proton into solvent, DMF was used as the co-solvent with toluene as an alternative to ethanol. It is important to note that heating the dimethylphosphonate nitrene **425** at 150 °C for 5 h resulted in an increase of the conversion rate and isoxazolidine **426** was isolated in 33% yield (Table 4.2, entry 4). Longer reaction times did not lead to an increase of the yield, but more decomposition (Table 4.2, entry 5). Davis and Theddu disclosed that the addition of Al(O-*t*Bu)₃ in the [3 + 2] intramolecular cyclo-addition increased the yield of the product isoxazolidine while inhibiting the formation of side product amide. Among the variations of solvents, temperature and time, it was found that C-2 phosphonate isoxazolidine **426** could be produced, affording a 33% yield of **426** at 150 °C for 5 h (Table 4.2, entries 6-9).



Scheme 4.19

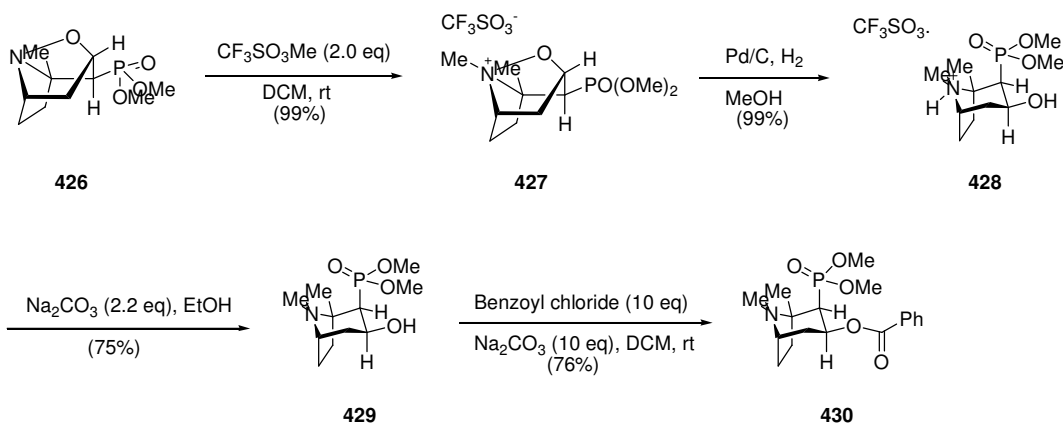
Table 4.2 Screened condition of Microwave irradiation for the [3 + 2] nitrene cycloaddition of **425**.

Entry	Additive	Temp. (°C)	Time (h)	Solvent	Ratio (425:426)	Yield (%)
1	--	150	5	CH ₃ CN	1:0.16	--
2	--	150	5	Toluene:EtOH (5:1)	1:0.22	--
3	--	150	5	Toluene:EtOH (2:1)	1:0.18	--
4	--	150	5	Toluene:DMF (5:1)	1:0.61	33
5	--	150	10	Toluene:DMF (5:1)	1:0.19	--
6	Al(O- <i>t</i> Bu) ₃ (0.5)	150	5	Toluene	1:0.45	--

Table 4.2, continued

7	Al(O- <i>t</i> Bu) ₃ (0.5)	150	5	Toluene:DMF (5:1)	1:0.78	35
8	Al(O- <i>t</i> Bu) ₃ (0.5)	190	5	Toluene:DMF (5:1)	1:0.66	31
9	Al(O- <i>t</i> Bu) ₃ (0.5)	150	10	Toluene:DMF (5:1)	1:0.18	--

Methylation with methyl triflate and catalytic hydrogenation ring-opening formed the methyl triflate salt **428** in quantitative yield (Scheme 4.20). Neutralization of the trifluoromethanesulfonic acid salt **428** with sodium carbonate gave the *tri*-substituted tropane **429** in 75% yield. Benzoylation of the equatorial hydroxyl group with benzoyl chloride and sodium carbonate produced the target molecule 1-methyl 2-phosphonate cocaine **430** in 76% yield. This is the first example of a cocaine analog to have a phosphonate group at the C-3 position.

**Scheme 4.20**

4.5. Discussions

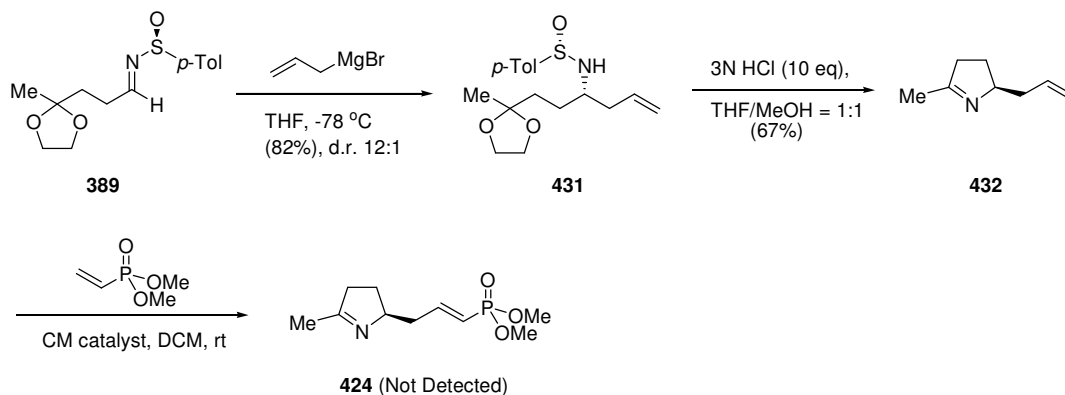
In the process of making intermediates **423** and **424**, it was found that the established route needed several additional steps to prepare them. Furthermore,

tetramethyl diphosphonate methylene required all expensive starting material tetrachloride diphosphonate methylene. All of these drawbacks reduced the efficiency of the synthesis of C-2 phosphonate cocaine analog.

In efforts to shorten the synthesis while maintaining the high stereoselectivities of the intermediates, the synthetic route was modified as discussed below. To get the desired dehydropyrrolidine phosphonate **424**, *N*-sulfinyl allyl amine **431**, derived from *p*-toluenesulfinimine **389**, was cyclized into allyl dehydropyrrolidine **432** using 3 N HCl in THF/MeOH in 67% yield (Scheme 4.21). With intermediate **432** in hand, the next step was to couple the terminal allyl compound with the vinyl dimethylphosphonate to build the (*E*)-dimethylphosphonate **424** using cross metathesis²⁷⁵.

Using the standard condition for olefin metathesis, allyl dehydropyrrolidine **432** was mixed with vinyl dimethylphosphonate in the presence of catalytic amount of Grubbs 1st generation catalyst. After stirring for 8 h at rt, none of the desired (*E*)-dimethylphosphonate **424** was detected by ¹H NMR (Table 4.3, entry 1). Using Grubbs 2nd generation catalyst and refluxing the mixture for 8 h did not give any improvement on the production of **424**, either (Table 4.3, entry 2-3). Since temperature did not provide any modification to the reaction, a four fold excess of Grubbs' 2nd generation catalyst as entry 1 was used, but still no (*E*)-dimethylphosphonate **424** was formed. Both heating the reaction at 100 °C in the presence of Grubbs' 1st generation catalyst and reacting the mixture with Hoveyda-Grubbs' catalyst failed to give any of the metathesis product (Table 4.3, entry 4-5). It is known that a complex interplay of steric and electronic factors determine the ability of olefins to participate in selective cross metathesis reactions. Hence, the possible reason for the lack of cross coupling metathesis between

431 and vinyl dimethylphosphonate could be that the nitrogen atom binds to the metal atom and or the bulky phosphonate group sterically hinders the reaction.



Scheme 4.21

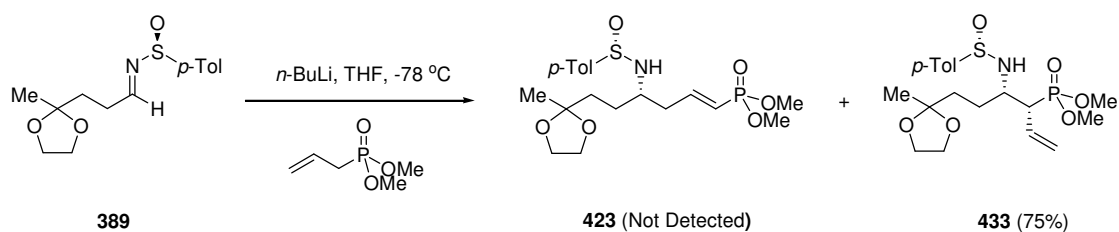
Table 4.3 Screened condition of cross metathesis between allyl dehydropyrrolidine and vinyl phosphonate.

Entry	Catalyst (eq.)	Solvent	Temperature (°C)	Yield (%)
1	Grubbs' 1 st (0.05)	DCM	25	N/A
2	Grubbs' 2 nd (0.05)	DCM	25	N/A
2	Grubbs' 2 nd (0.05)	DCM	40	N/A
3	Grubbs' 2 nd (0.20)	DCM	40	N/A
4	Grubbs' 2 nd (0.20)	toluene	100	N/A
5	Hoveyda-Grubbs catalyst (0.20)	DCM	40	N/A

Since olefin cross metathesis resulted in no formation of the dimethylphosphonate dehydropyrrolidine **424**, it is planned that addition of the lithium allylphosphonate anion to *p*-toluenesulfinimine **389** would form the desired the α,β -unsaturated δ -amino

phosphonate **423** in good yield and (*Z*)/(*E*) selectivity. Then the phosphonate **423** could cyclize to dehydropyrrolidine **424** without difficulty (Scheme 4.22).

Unexpectedly, *syn*- α -vinyl- β -amino phosphonate **433** was formed exclusively as a single isomer in 75% yield, and none of the (*E*)- α,β -unsaturated δ -amino phosphonate **423** was detected. The addition of LiCl or ZnCl₂, and changing reaction temperature and solvents did not give any improvement on the yield of product **423**. The relative configuration was temporarily assigned as *syn*- based on the ¹H NMR study of the α -substituted β -amino phosphonate derivative.



Scheme 4.22

CHAPTER 5 EXPERIMENTAL SECTION

General Methods

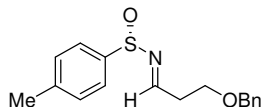
Reagents and solvents were purchased from Sigma-Aldrich Company or Acros Organics and used without additional purification unless otherwise noted. Glassware was oven-dried at 120 °C and cooled to ambient temperature in desiccators prior to use. Reactions involving sensitive substances and/or requiring anhydrous reaction conditions were performed under argon atmosphere. Reagent grade tetrahydrofuran, diethyl ether, toluene and methylene chloride were purified by filtration on a Glass Contour Solvent Dispensing System. Column chromatography was performed on silica gel, Merck grade 60 (230-400 mesh). Analytical and preparative thin-layer chromatography was performed on pre-coated silica gel plates (250 and 1000 microns) purchased from Analtech Inc. TLC plates were visualized with UV, in an iodine chamber, or with ninhydrin unless noted.

Melting points were recorded on a Me1-Temp apparatus. Optical rotations were measured on a Perkin-Elmer 341 polarimeter. Infrared spectra were recorded on a Perkin-Elmer 1600 FTIR spectrometer using NaCl plates for liquid and KBr disc for solids. ^1H and ^{13}C NMR spectra were obtained in CDCl_3 or CD_3OD solution and were referenced to TMS (0.00 ppm), CHCl_3 (7.25 ppm for ^1H NMR and 77.36 for ^{13}C NMR), or methanol (3.35 ppm for ^1H NMR and 49.86 ppm for ^{13}C NMR) using GE Omega 500 MHz, Bruker 400 MHz or Varian 300 MHz NMR spectrometer. ^{31}P NMR spectra were obtained in CDCl_3 solution and referenced externally to 85% H_3PO_4 . High resolution

mass spectra were collected at the Department of Chemistry, Drexel University, Philadelphia, PA.

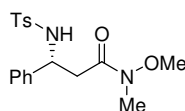
CHAPTER 2:

Weinreb amide ($S_S,3R$)-(+)-*N*-(*p*-toluenesulfinyl)-3-amino-*N*-methoxy-*N*-methyl-3-phenylpropionamide, *N*-sulfinyl β -amino esters, (S_S,R)-(+)-methyl 3-(4-ethylphenylsulfinamido)-3-phenylpropanoate and (S_S,R)-(+)-methyl 3-(4-methylphenylsulfinamido)-3-pent-4-enonate were prepared as previously described.

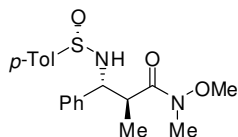


(*S*)-(+)-*N*-(3-(Benzyloxy)propylidene)-*p*-toluenesulfinamide. In a flame dried, 50-mL round bottom flask equipped with a magnetic stirring bar, rubber septum, and argon inlet were placed (*S*)-(+)-*p*-toluenesulfinamide (0.500 g, 3.23 mmol), 3-(benzyloxy)-1-propanal (0.636 g, 3.88 mmol) (This aldehyde is commercially available) and DCM (10 mL). To the solution was added $\text{Ti}(\text{OEt})_4$ (3.56 mL, 16.15 mmol). The reaction mixture was stirred for 8 h at rt at which time the solution was poured into a 50-mL ice/water mixture and stirred vigorously. The reaction mixture was filtered through Celite, and the Celite was washed with DCM (2×5 mL). The organic phase was washed with sat. aqueous NaHCO_3 (10 mL), brine (10 mL), dried (MgSO_4) and concentrated. Chromatography (EtOAc/hexanes 1:1) gave a 0.597 g (61%) of a clear oil: $[\alpha]_D^{25} +268$ (c 1.7, CHCl_3); IR (thin film) 2865, 2365, 2335, 1624, 1094 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 2.40

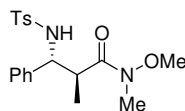
(s, 3H), 2.80 (m, 2H), 3.78 (m, 2H), 4.50 (s, 2H), 7.32 (m, 7H), 7.55 (m, 2H), 8.30 (t, $J = 4.8$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 21.7, 36.7, 66.4, 73.5, 125.0, 125.7, 128.0, 128.2, 128.8, 128.82, 130.0, 130.2, 165.5. HRMS cacl'd for $\text{C}_{17}\text{H}_{20}\text{NO}_2\text{S}$ (M+H) 302.1215, found 302.1215.



(R)-(+)-N-Methoxy-N-methyl-3-phenyl-3-(tosylamino)propanamide (179). To a 25-mL round bottom flask was placed *m*-CPBA (77% of 0.183 g, 0.820 mmol). A solution of (+)-**1a** (0.142 g, 0.410 mmol) in dry CHCl_3 (6 mL) was added and the reaction mixture stirred at rt for 8 h. At this time satd. aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (2 mL) was added, the organic phase was washed with satd. aqueous NaHCO_3 (5 mL), dried (MgSO_4) and concentrated. Chromatography (EtOAc/hexane 50:50) gave 0.128 g (86%) of a white solid mp 105-6 °C; $[\alpha]_D^{25} +58.3$ (c 2.46, CHCl_3), IR (KBr) 1641, 1462, 1327 cm^{-1} ; ^1H NMR (CDCl_3) δ 2.36 (s, 3H), 2.77 (dd, $J = 5.6$ Hz, $J = 16.0$ Hz, 1H), 2.97 (dd, $J = 5.6$ Hz, $J = 16.0$ Hz, 1H), 3.02 (s, 3H), 3.43 (s, 3H), 4.71 (q, $J = 6.0$ Hz, $J = 13.2$ Hz, 1H), 6.40 (d, $J = 6.8$ Hz, 1H), 7.17 (m, 7H), 7.59 (m, 2H); ^{13}C NMR (CDCl_3) δ 21.8, 32.1, 38.4, 55.0, 61.6, 127.0, 127.5, 127.8, 128.7, 129.7, 138.0, 140.5, 143.3, 171.5; HRMS cacl'd for $\text{C}_{18}\text{H}_{23}\text{N}_2\text{O}_4\text{S}$ (M+H) 363.1379. Found 363.1376.



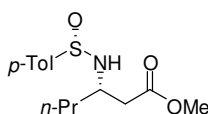
(*S_s,2*S*,3*R)-(+)-*N*-methoxy-*N*, 2-dimethyl-3-(4-methylphenyl-sulfinamido)-3-phenylpropanamide (180). Typical Procedure.** In a Schlenk tube equipped with a magnetic stirring bar, rubber septum and argon inlet was placed *N,O*-dimethyl hydroxylamine hydrochloride (0.187 g, 1.88 mmol, Aldrich) in THF (3 mL). The formed suspension was cooled to -78 °C, *n*-BuLi (3.71 mmol, 1.48 mL of 2.5 M in hexane) was added dropwise. The reaction mixture was slowly warmed to rt and the solution was stirred for 1 h. At this time the solution was cooled to -78 °C and a solution of (+)-**6a** (0.104 g, 0.314 mmol) in THF (2 mL) was added dropwise. The reaction mixture was stirred for 4 h, and quenched by addition of satd. aqueous NH₄Cl (3 mL). The solution was warmed to rt and diluted with H₂O (3 mL). The aqueous phase was extracted with EtOAc (2 × 5 mL), and combined organic phases were washed with satd. aqueous NH₄Cl (5 mL), brine (5 mL), dried (MgSO₄) and concentrated. Chromatography (EtOAc:*n*-hexane, 50:50) gave 0.085 g (75%) of a clear oil: $[\alpha]_D^{25} +133.6$ (*c* 1.73, CHCl₃); IR (thin film) 2404, 1640, 1518, 1428, 1217 cm⁻¹; ¹H NMR (CDCl₃) δ 1.19 (d, *J* = 6.8 Hz, 3H), 2.4 (s, 3H), 3.03 (s, 3H), 3.27 (s, 3H), 4.49 (t, 1H), 5.97 (d, *J* = 6.8 Hz, 1H), 7.25 (m, 3H), 7.33 (m, 4H), 7.57 (m, 2H); ¹³C NMR (CDCl₃) δ 16.5, 21.7, 32.2, 41.6, 61.6, 62.0, 125.6, 126.1, 127.6, 127.9, 128.5, 128.8, 129.0, 129.8, 130.0, 141.4, 142.2, 142.7, 175.9. HRMS calcd for C₁₉H₂₅N₂O₃S (M + H) 361.1586. Found 361.1588.



(2*S*,3*R*)-(+)-*N*-Methoxy-*N*,2-dimethyl-3-phenyl-3-(tosylamino)propanamide

(182). In a Schlenk tube equipped with a magnetic stirring bar and rubber septum was placed LiCl (0.029 g, 0.691 mmol). The tube was flame-dried under vacuum, and filled with argon. This procedure was repeated three times. The Schlenk tube was cooled to rt and diisopropylamine (0.036 mL, 0.259 mmol) and THF (1 mL) were added, and the solution was cooled to 0 °C. At this time *n*-BuLi (0.207 mmol, 0.12 mL of 1.73 M in hexane) was added dropwise, the solution was stirred for 15 min, cooled to -78 °C. In a separate 25-mL round bottom flask equipped with a magnetic stir bar and argon inlet was placed Weinreb amide (+)-**1b** (0.025 g, 0.0691 mmol) in THF (1 mL), and the solution was cooled to -78 °C. At this time the preformed LDA solution was added dropwise and the reaction mixture was stirred at -78 °C for 1 h. MeI (0.180 mmol, 0.09 mL of a 2 M solution in *tert*-butyl methyl ether) was added dropwise at this time. The reaction mixture was stirred at this temperature for 1 h, warmed to -50 °C (dry ice/MeCN), stirred for 1 h and quenched at this temperature by addition of sat. aqueous NH₄Cl (2 mL). The solution was diluted with H₂O (2 mL). THF was evaporated, and the residue was extracted with EtOAc (2 × 5 mL). The combined organic phases were washed with brine (5 mL), dried (MgSO₄), and concentrated. Chromatography (hexanes/EtOAc, 1:1) gave 0.0096 g (37%) a clear oil: $[\alpha]_D^{25} +71.0$ (*c* 0.3, CHCl₃); IR (thin film) 1639, 1452, 1329 cm⁻¹; ¹H NMR (CDCl₃) δ 1.23 (d, *J* = 6.8 Hz, 3H), 2.31 (s, 3H), 2.99 (s, 3H), 3.10 (s, 3H), 3.28 (m, 1H), 4.56 (dd, *J* = 4.4 Hz, *J* = 8.4 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 1H), 7.05 (m,

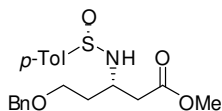
60.7, 126.8, 127.2, 127.6, 128.6, 129.5, 138.3, 139.8, 143.1, 215.4. HRMS calcd for C₂₁H₂₈NO₃S (M+H) 374.1790. Found 374.1785.



(S_S,3S)-(+)-Methyl 3-(4-methylphenylsulfinamido)hexanoate (187).

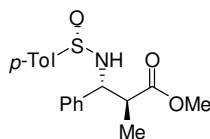
Typical procedure. In a Schlenk tube equipped with a magnetic stirring bar, rubber septum and argon inlet was added NaHMDS solution (0.54 mmol, 0.54 mL of 1 M NaHMDS in THF) by syringe and ether (5 mL) at rt. The solution was cooled to -78 °C. A solution of methyl acetate (0.04 mL, 0.503 mmol) in ether (2 mL) was added dropwise at the reaction mixture was stirred for 1 h. At this time (*S*)-(+)-*N*-butylidene-*p*-toluenesulfinamide (0.070 g, 0.335 mmol) in ether (2 mL) was added dropwise. The reaction mixture was stirred at -78 °C for 40 min, and quenched with satd. aqueous NH₄Cl solution (2 mL). Water (2 mL) was added, the aqueous phase was extracted with EtOAc (3 × 5 mL), the combined organic phases were washed with satd. aqueous NH₄Cl solution (2 mL), brine (2 mL), dried (MgSO₄), and concentrated. Chromatography (hexanes/EtOAc, 67:33) gave 0.071 g (75%) of a clear oil: [α]_D²⁵ +118 (*c* 1.0, CHCl₃); IR (thin film) 1738, 1178, 1092, 1061, 811 cm⁻¹; ¹H NMR (CDCl₃) δ 0.89 (t, *J* = 7.2 Hz, 3H), 1.51 (m, 4 overlapping H), 2.36 (s, 3H), 2.55 (dq, *J* = 5.6 Hz, *J* = 12 Hz, *J* = 16 Hz, 2H), 3.61 (s, 3H), 3.62 (m, 1H), 4.56 (d, *J* = 8.8 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.53 (m,

2H); ^{13}C NMR (CDCl_3) δ 14.1, 19.6, 21.7, 38.3, 40.8, 52.0, 52.7, 125.9, 129.8, 141.6, 142.7, 172.4. HRMS calcd for $\text{C}_{14}\text{H}_{22}\text{NO}_3\text{S}$ ($\text{M} + \text{H}$) 284.1320. Found 284.1319.



($S_S,3S$)-(+)-Methyl 3-(4-methylphenylsulfinamido)-5-benzyloxypentanoate

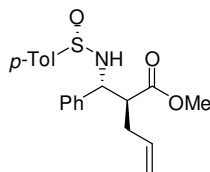
(188). Prepared from (S)-(+)- N -(3-benzyloxy)propylidene)- p -toluenesulfinamide in 67% yield. Chromatography (hexanes/EtOAc, 67:33) gave 0.125 g (67%) of a clear oil: $[\alpha]_D^{25} +64$ (c 0.8, CHCl_3); IR (CHCl_3) 2360, 2340, 1734, 1459, 1094 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.94 (m, 2H), 2.40 (s, 3H), 2.62 (dq, $J = 5.6$ Hz, $J = 16$ Hz, $J = 42$ Hz, 2H), 3.62 (s, 3H), 3.63 (m, 2H), 3.90 (m, 1H), 4.51 (q, $J = 11.6$ Hz, $J = 18.4$ Hz, 2H), 4.86 (d, $J = 9.2$ Hz, 1H), 7.26 (m, 3H), 7.32 (m, 4H), 7.50 (m, 2H); ^{13}C NMR (CDCl_3) δ 21.1, 35.1, 39.9, 49.6, 51.3, 66.5, 72.8, 125.3, 125.6, 127.1, 127.3, 127.4, 127.5, 127.9, 128.1, 129.2, 137.9, 140.9, 141.9, 171.7. HRMS calcd for $\text{C}_{20}\text{H}_{26}\text{NO}_4\text{S}$ ($\text{M} + \text{H}$) 376.1583. Found 376.1580.



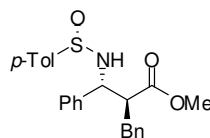
($S_S,2S,3R$)-(+)-Methyl-2-Methyl-3-(4-methylphenylsulfinamido)-3-

phenylpropanoate (185). Typical Procedure for the α -Alkylation of N -Sulfinyl β -

amino esters. In a Schlenk tube equipped with a magnetic stirring bar and rubber septum was placed LiCl (0.033 g, 0.789 mmol), the tube was flame-dried under vacuum, and filled with Argon. This procedure was repeated three times at which time the Schlenk tube was cooled to ambient temperature. To the Schlenk tube was added diisopropylamine (0.042 mL, 0.296 mmol), THF (1 mL) and the solution was cooled to 0 °C. At this time *n*-BuLi (0.237 mmol, 0.14 mL of 1.73 M in hexane) was added dropwise, and stirred for 15 min. The solution was cooled to -78 °C. To the preformed LDA solution was added dropwise β -amino ester (+)-**6a** (0.025 g, 0.0789 mmol) in THF (1 mL) and the reaction mixture was stirred at -78 °C for 1 h. At this time MeI (0.205 mmol, 0.1 mL of a 2 M solution in *tert*-butyl methyl ether) was then added dropwise. The solution was stirred at this temperature for 1 h and warmed to -50 °C (dry ice MeCN) and stirred for 1 h. Reaction mixture was quenched with at -78 °C by addition of satd. aqueous NH₄Cl (2 mL), and then warmed to rt and diluted with H₂O (2 mL). The THF was evaporated, the residue was extracted with EtOAc (2 \times 5 mL), and the combined organic phases were washed with brine (5 mL), dried (MgSO₄), and concentrated. Chromatography (hexanes/EtOAc, 2:1) gave 0.020 g (80%) of a clear oil as a mixture of inseparable *anti/syn* (88:12) isomers: $[\alpha]_D^{25} +64.7$ (*c* 0.7, CHCl₃); IR (CHCl₃) 1423, 1263, 1218 cm⁻¹; ¹H NMR (CDCl₃) major isomer: δ 1.06 (d, *J* = 7.2 Hz, 3H), 2.41 (s, 3H), 2.85 (m, 1H), 3.63 (s, 3H), 4.54 (dd, *J* = 5.2 Hz, *J* = 7.6 Hz, 1H), 5.09 (d, *J* = 5.6 Hz, 1H), 7.34 (m, 7H), 7.54 (d, *J* = 8.0 Hz, 2H); major isomer: ¹³C NMR (CDCl₃) δ 15.5, 21.7, 46.7, 52.4, 61.2, 125.7, 125.8, 126.1, 127.6, 128.1, 128.4, 129.0, 129.9, 130.0, 140.2, 141.7, 142.7, 175.3. HRMS calcd for C₁₈H₂₂NO₃S (M + H) 332.1320. Found 332.1317.

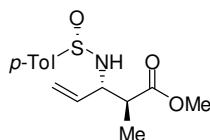


(*S*_S,2*S*,3*R*)-(+)-Methyl 2-(2-propenyl)-3-(4-methylphenylsulfinamido)-3-phenylpropanoate (190b). Chromatography (hexanes/EtOAc, 2:1) gave 64% of a clear oil. Mixture of inseparable *anti/syn* (92:8) isomers: $[\alpha]_D^{25} +102$ (*c* 1.7, CHCl₃); IR (thin film) 2365, 2340, 1734, 1059 cm⁻¹; major isomer: ¹H NMR (CDCl₃) δ 2.19 (m, 1H), 2.32 (m, 1H), 2.41 (s, 3H), 2.85 (m, 1H), 3.58 (s, 3H), 4.60 (t, *J* = 6.8 Hz, 1H), 5.03 (m, 2H), 5.17 (d, *J* = 6.4 Hz, 1H), 5.64 (m, 1H), 7.30 (m, 5H), 7.37 (m, 2H), 7.53 (m, 2H); major isomer: ¹³C NMR (CDCl₃) δ 21.7, 34.5, 52.2, 52.5, 59.9, 118.1, 125.7, 125.9, 127.7, 128.1, 128.4, 128.9, 129.1, 129.9, 130.0, 134.5, 140.7, 141.7, 142.5, 174.2. HRMS calcd for C₂₀H₂₄NO₃S (M + H) 358.1477. Found 358.1474.

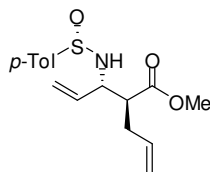


(*S*_S,2*S*,3*R*)-(+)-Methyl 2-Benzyl-3-(4-methylphenylsulfinamido)-3-phenylpropanoate (190c). Chromatography (hexanes/EtOAc, 2:1) gave 72% of a clear oil. Mixture of inseparable *anti/syn* (96:4) isomers: $[\alpha]_D^{25} +50.1$ (*c* 1.2, CHCl₃); IR (thin film) 2365, 2340, 1734, 1459, 1059 cm⁻¹; major isomer: ¹H NMR (CDCl₃) δ 2.42 (s, 3H), 2.77 (dd, *J* = 6 Hz, *J* = 13.6 Hz, 1H), 2.92 (m, 1H), 3.06 (m, 1H), 3.45 (s, 3H), 4.63 (t, *J* = 6.8

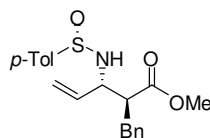
Hz, 1H), 5.33 (d, $J = 6.8$ Hz, 1H), 7.12 (m, 2H), 7.18 (m, 1H), 7.25 (m, 2H), 7.31 (m, 5H), 7.38 (m, 2H), 7.55 (m, 2H); major isomer: ^{13}C NMR (CDCl_3) δ 21.7, 36.5, 52.1, 54.9, 60.1, 125.7, 125.9, 126.8, 126.9, 127.5, 128.1, 128.3, 128.5, 128.8, 129.10, 129.15, 129.9, 130.2, 138.7, 141.1, 141.7, 142.5, 174.2. HRMS calcd for $\text{C}_{24}\text{H}_{26}\text{NO}_3\text{S}$ ($\text{M} + \text{H}$) 408.1633. Found 408.1624.



($S_s,2S,3R$)-(+)-Methyl 2-methyl-3-(4-methylphenylsulfinamido)-3-pent-4-enonate (190d). Chromatography (hexanes/EtOAc, 2:1) gave 88% of a clear oil. Mixture of inseparable *anti/syn* isomers: (89:11): $[\alpha]_D^{25} +92.3$ (c 1.15, CHCl_3); 2365, IR (thin film) 2340, 1734, 1459, 1059 cm^{-1} ; major isomer: ^1H NMR (CDCl_3) δ 1.11 (d, $J = 7.2$ Hz, 3H), 2.40 (s, 3H), 2.63 (m, 1H), 3.65 (s, 3H), 3.97 (dd, $J = 1.2$ Hz, $J = 6.8$ Hz, 1H), 4.76 (d, $J = 7.2$ Hz, 1H), 5.28 (m, 2H), 5.84 (m, 1H), 7.29 (m, 2H), 7.58 (m, 2H); major isomer: ^{13}C NMR (CDCl_3) δ 14.4, 21.7, 44.6, 52.2, 59.1, 118.4, 125.96, 126.02, 129.8, 136.0, 137.4, 141.7, 142.2, 175.0. HRMS calcd for $\text{C}_{14}\text{H}_{20}\text{NO}_3\text{S}$ ($\text{M} + \text{H}$) 282.1164. Found 282.1163.

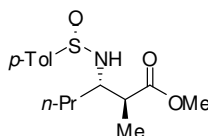


(*S_S,2*S*,3*R)-(+)-Methyl 2-(2-propenyl)-3-(4-methylphenylsulfinamido)-3-pent-4-enonate (190e).** Chromatography (hexanes/EtOAc, 2:1) gave 76% of a clear oil. Mixture of inseparable *anti/syn* (91:9) isomers: $[\alpha]_D^{25} +51.4$ (*c* 0.8, CHCl₃); IR (thin film) 2365, 2340, 1734, 1459, 1169, 1059 cm⁻¹; major isomer: ¹H NMR (CDCl₃) δ 2.19 (m, 1H), 2.36 (m, 1H), 2.41 (s, 3H), 2.62 (dt, *J* = 5.6 Hz, *J* = 8.8 Hz, 1H), 3.63 (s, 3H), 3.98 (m, 1H), 4.90 (d, *J* = 7.6 Hz, 1H), 5.03 (m, 2H), 5.27 (m, 2H), 5.63 (m, 1H), 5.88 (dq, *J* = 7.2 Hz, *J* = 10.4 Hz, *J* = 17.2 Hz, 1H), 7.29 (m, 2H), 7.57 (m, 2H); major isomer: ¹³C NMR (CDCl₃) δ 21.7, 33.9, 50.2, 52.1, 58.0, 117.7, 117.8, 118.0, 126.0, 129.9, 134.9, 137.7, 137.9, 141.7, 142.1, 174.1. HRMS calcd for C₁₆H₂₂NO₃S (M + H) 308.1320. Found 308.1316.



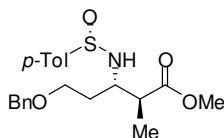
(*S_S,2*S*,3*R)-(+)-Methyl 2-benzyl-3-(4-methylphenylsulfinamido)-3-pent-4-enonate (190f).** Chromatography (hexanes/EtOAc, 2:1) gave 78% of a clear oil. Mixture of inseparable *anti/syn* (95:5) isomers: $[\alpha]_D^{25} +40.7$ (*c* 1.25, CHCl₃); IR (thin film) 2360, 2340, 1734, 1459, 1059 cm⁻¹; major isomer: ¹H NMR (CDCl₃) δ 2.42 (s, 3H),

2.85 (m, 2H), 2.95 (m, 1H), 3.53 (s, 3H), 4.03 (m, 1H), 4.97 (d, $J = 8.0$ Hz, 1H), 5.29 (m, 2H), 5.91 (m, 2H), 7.14 (m, 2H), 7.20 (m, 1H), 7.28 (m, 4H), 7.60 (m, 2H); major isomer: ^{13}C NMR (CDCl_3) δ 21.7, 35.7, 52.0, 52.4, 58.2, 117.8, 117.9, 126.1, 126.9, 128.9, 129.0, 129.2, 129.4, 129.9, 135.6, 138.1, 138.9, 141.8, 142.1, 174.1; HRMS calcd for $\text{C}_{20}\text{H}_{24}\text{NO}_3\text{S}$ ($\text{M} + \text{H}$) 358.1477. Found 358.1475.



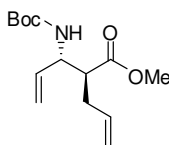
($S_S,2S,3S$)-(+)-Methyl 2-methyl-3-(4-methylphenylsulfonamido)hexanoate

(190g). Chromatography (hexanes/EtOAc, 50:50) gave 89% of a clear oil: $[\alpha]_D^{25} +108$ (c 0.97, CHCl_3); IR (thin film) 3205, 2962, 1728, 1199, 1055 cm^{-1} ; ^1H NMR (CDCl_3) δ 0.92 (t, $J = 7.2$ Hz, 3H), 1.14 (d, $J = 7.2$ Hz, 3H), 1.45 (m, 3H), 1.58 (m, 1H), 2.40 (s, 3H), 2.67 (m, 1H), 3.43 (m, 1H), 3.66 (s, 3H), 4.63 (d, $J = 9.6$ Hz, 1H), 7.29 (d, $J = 8.0$ Hz, 2H), 7.59 (m, 2H); ^{13}C NMR (CDCl_3) δ 14.2, 14.3, 19.8, 21.7, 37.4, 43.6, 52.1, 57.8, 126.0, 129.8, 141.6, 142.8, 175.7. HRMS calcd for $\text{C}_{15}\text{H}_{24}\text{NO}_3\text{S}$ ($\text{M} + \text{H}$) 298.1477. Found 298.1474.



(*S,S,2S,3S*)-(+)-Methyl 2-methyl-3-(4-methylphenylsulfonamido)-5-

benzyloxypentanoate (190h). Chromatography (hexanes/EtOAc 1:1) gave a 70% of a clear oil: $[\alpha]_D^{25} +67.0$ (*c* 0.8, CHCl₃); IR (thin film) 1734, 1454, 1204, 1089 cm⁻¹; ¹H NMR (CDCl₃) δ 1.14 (d, *J* = 7.6 Hz, 3H), 1.86 (q, *J* = 5.6 Hz, *J* = 6.8 Hz, 2H), 2.64 (m, 1H), 3.58 (m, 1H), 3.62 (s, 3H), 3.65 (m, 1H), 4.50 (s, 2H), 4.87 (d, *J* = 9.2 Hz, 1H), 7.26 (m, 3H), 7.32 (m, 4H), 7.52 (m, 2H); ¹³C NMR (CDCl₃) δ 14.6, 21.7, 35.1, 43.6, 52.1, 55.1, 67.3, 73.4, 125.8, 126.0, 128.0, 128.1, 128.8, 129.8, 138.6, 141.5, 142.5, 175.7. HRMS cacl'd for C₂₁H₂₈NO₄S (M + H) 390.1739. Found 390.1735.

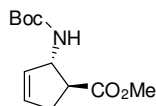


(*2S,3R*)-(-)-Methyl 2-(2-propenyl)-3-(*tert*-butoxycarbonylamino)-pent-4-

enonate (193). In a single-neck, oven-dried, 25-mL round bottom flask equipped with a magnetic stirring bar and rubber septum was placed (+)-**10b** (0.064 g, 0.208 mmol) in MeOH (4 mL). HCl/Et₂O solution (1.04 mL of 1 M hydrogen chloride in ether, 1.04 mmol) was added via syringe at rt. The reaction mixture was stirred for 2 h, and then concentrated. The residue was dissolved with DCM (10 mL), and the solution was neutralized to pH 8 by dropwise addition of sat'd aqueous NaHCO₃. The aqueous phase was extracted with DCM (5 mL), the combined organic phases were washed with brine, dried (MgSO₄), and concentrated. To the residue was added DCM (2 mL), (Boc)₂O

solution (1 mmol, 1 mL of 1 M (Boc)₂O in THF), and the reaction mixture was stirred for 8 h at rt. At this time sat. aqueous NaHCO₃ (4 mL) was added. The solution was diluted with H₂O (2 mL) and mixture was extracted with EtOAc (2 × 5 mL). The combined organic phases were washed with brine (5 mL), dried (MgSO₄) and concentrated.

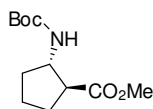
Chromatography (hexanes/EtOAc, 80:20) gave 0.048 g (86%) of a clear oil: $[\alpha]_D^{25} -45.9$ (*c* 1.7, CHCl₃); IR (thin film) 2980, 1721, 1506, 1170 cm⁻¹; ¹H NMR (CDCl₃) δ 1.43 (s, 9H), 2.33 (m, 1H), 2.40 (m, 1H), 2.68 (m, 1H), 3.64 (s, 3H), 4.36 (m, 1H), 5.11 (m, 4H), 5.43 (d, *J* = 8.8 Hz, 1H), 5.74 (m, 2H); ¹³C NMR (CDCl₃) δ 27.7, 28.7, 34.2, 49.2, 52.9, 53.3, 115.8, 118.0, 134.8, 137.1, 155.8, 174.7. HRMS calcd for C₁₄H₂₃NNaO₄ (M + Na) 292.1525. Found 292.1522.



(1*S*,2*R*)-(+)-Methyl 2-(*tert*-butoxycarbonylamino)-cyclopentenecarboxylate

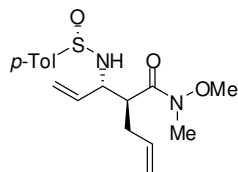
(194). In a Schlenk tube equipped with a magnetic stirring bar, rubber septum and argon inlet was placed Grubbs 2nd generation catalyst (0.012 g, 0.0138 mmol). The brown solid was dried under vacuum for 5 min and then the tube was filled with argon. After the above procedure was repeated 3 times, a solution of (-)-**14** (0.074 g, 0.275 mmol) in DCM (3 mL) was added at rt and reaction mixture stirred overnight. The solution was concentrated and chromatographed (hexanes/EtOAc, 80:20) to give 0.038 g (58%) of a clear oil: $[\alpha]_D^{25} +98.5$ (*c* 0.65, CHCl₃); IR (thin film) 2978, 1699, 1508, 1169 cm⁻¹; ¹H

NMR (CDCl₃) δ 1.44 (s, 9H), 2.60 (m, 1H), 2.74 (m, 1H), 2.83 (m, 1H), 3.72 (s, 3H), 4.63 (brs, 1H), 4.96 (brs, 1H), 5.62 (d, $J = 2.8$ Hz, 1H), 5.83 (m, 1H); ¹³C NMR (CDCl₃) δ 28.7, 30.0, 35.7, 51.0, 52.4, 61.1, 130.9, 132.4, 155.4, 175.3. HRMS calcd for C₁₂H₁₉NNaO₄ (M + Na) 264.1212. Found 264.1208.

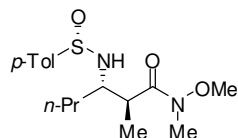


(1S,2S)-(+)-Methyl 2-(*tert*-butoxycarbonylamino)cyclopentanecarboxylate

(195). In a 25-mL round-bottom flask equipped with a magnetic stirring bar and rubber septum was placed (+)-**14** (0.021 g, 0.0871 mmol) and 10% Pd/C (0.004 g, 20% w/w). The flask was connected to the vacuum, and then filled with hydrogen. After this procedure was repeated 3 times, MeOH (2 mL) was added via syringe, and the dark suspension was stirred at rt for 4 h. At this time the solution was filtered through a short pad of Celite. The Celite was washed with MeOH (2 \times 2 mL), and the combined solutions were concentrated to give 0.019 g (90%) of a white solid: mp 66-67 °C; $[\alpha]_D^{25} +39.3$ (c 0.9, CHCl₃); IR (thin film) 2971, 1717, 1522, 1172 cm⁻¹; ¹H NMR (CDCl₃) δ 1.43 (s, 9H), 1.47 (m, 1H), 1.65 (m, 1H), 1.72 (m, 2H), 1.87 (m, 1H), 1.98 (m, 1H), 2.11 (m, 1H), 2.57 (dd, $J = 8.0$ Hz, $J = 16.0$ Hz, 1H), 3.68 (s, 3H), 4.10 (m, 1H), 4.58 (brs, 1H); ¹³C NMR (CDCl₃) δ 23.1, 28.5, 28.7, 30.0, 33.2, 51.2, 52.2, 56.4, 155.6, 175.6; HRMS calcd for C₁₂H₂₁NNaO₄ (M + Na) 266.1368. Found 266.1367.

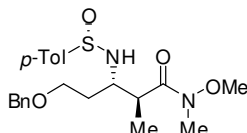


(*S*_S,2*S*,3*R*)-(+)-*N*-methoxy-*N*-methyl-2-(2-propenyl)-3-(4-methylphenylsulfonamido)-pent-4-ene-amide (202). Chromatography (EtOAc:*n*-hexane, 33:67) gave (81%) of a clear oil: $[\alpha]_D^{25} +94.3$ (*c* 1.15, CHCl₃); IR (thin film) 3260, 2935, 1644, 1389 cm⁻¹; ¹H NMR (CDCl₃) δ 2.27 (m, 1H), 2.39 (s, 3H), 2.41 (m, 1H), 3.09 (s, 3H), 3.62 (s, 3H), 3.92 (m, 1H), 4.98 (m, 1H), 5.07 (dd, *J* = 1.6 Hz, *J* = 17.2 Hz, 1H), 5.22 (m, 2H), 5.55 (d, *J* = 8 Hz, 1H), 5.64 (m, 1H), 5.90 (m, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.58 (m, 2H); ¹³C NMR (CDCl₃) δ 21.7, 32.3, 34.3, 44.9, 58.5, 61.9, 116.9, 117.7, 125.8, 126.2, 129.8, 135.4, 139.1, 141.4, 142.2, 174.9. HRMS calcd for C₁₇H₂₄N₂O₃S (M+H) 337.1586. Found 337.1584.

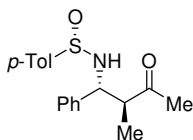


(*S*_S,2*S*,3*S*)-(+)-*N*-methoxy-*N*, 2-dimethyl-3-(4-methylphenylsulfonamido)-3-hexanamide (203). Chromatography (hexanes/EtOAc, 50:50) gave 87% of a clear oil: $[\alpha]_D^{25} +103$ (*c* 0.5, CHCl₃); IR (thin film) 1657, 1560 cm⁻¹; ¹H NMR (CDCl₃) δ 0.92 (t, *J* = 6.8 Hz, 3H), 1.19 (d, *J* = 6.8 Hz, 3H), 1.39 (m, 1H), 1.50 (m, 2H), 1.59 (m, 1H), 2.39 (s, 3H), 3.15 (m, 4 overlapping H), 3.35 (m, 1H), 3.68 (s, 3H), 5.41 (d, *J* = 9.2 Hz, 1H), 7.27

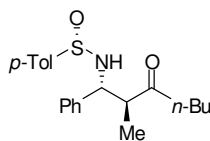
(d, $J = 9.2$ Hz, 2H), 7.60 (m, 2H); ^{13}C NMR (CDCl_3) δ 13.3, 14.2, 20.0, 21.7, 32.3, 38.2, 38.4, 59.0, 62.0, 126.1, 129.7, 141.3, 143.2, 176.9. HRMS calcd for $\text{C}_{16}\text{H}_{27}\text{N}_2\text{O}_3\text{S}$ (M + H) 327.1742. Found 327.1742.



(*S,S,2S,3S*)-(+)-*N*-Methoxy-*N*, 2-dimethyl-3-(4-methylphenylsulfinamido)-5-benzyloxypentanamide (204). Chromatography (hexanes/EtOAc 1:1) gave 83% of a clear oil: $[\alpha]_{\text{D}}^{25} +66$ (c 0.5, CHCl_3); IR (thin film) 1654, 1459, 1089, 1064 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.17 (d, $J = 14$ Hz, 1H), 1.89 (m, 2H), 2.40 (s, 1H), 3.13 (s, 3H), 3.61 (m, 1H), 3.62 (s, 3H), 3.69 (s, 1H), 4.53 (dd, $J = 5.6$ Hz, $J = 12$ Hz, 2H), 5.61 (d, $J = 8.8$ Hz, 1H), 7.25 (d, $J = 8$ Hz, 2H), 7.29 (m, 1H), 7.34 (m, 4H), 7.55 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (CDCl_3) δ 17.6, 23.6, 34.1, 38.0, 40.5, 57.9, 63.8, 69.2, 75.1, 75.3, 127.7, 127.9, 129.9, 130.0, 130.1, 130.4, 130.6, 131.6, 140.5, 143.1, 144.9, 178.7; HRMS calcd for $\text{C}_{22}\text{H}_{31}\text{N}_2\text{O}_4\text{S}$ (M + H) 419.2005. Found 419.2004.

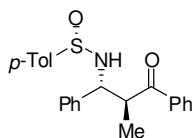


(*S_S,2*S*,3*R)-(+)-*N*-(4-*p*-Toluenesulfinyl)-4-amino-3-methyl-4-phenylbutan-2-one (180).** **Typical procedure.** In a Schlenk tube equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed a solution of compound (+)-**2a** (0.014 g, 0.0389 mmol) in THF (2 mL) at rt. The solution was cooled to 0 °C. MeMgBr (0.389 mmol, 0.13 mL of 3.0 M in THF) was added dropwise. The reaction mixture was stirred at 0 °C for 10 min, and warmed to rt. After 1 h the solution was cooled to -78 °C, and quenched by dropwise addition of satd. aqueous NH₄Cl (1 mL). The mixture was warmed to rt, diluted with H₂O (1 mL), and the aqueous phase was extracted with EtOAc (3 × 3 mL). The combined organic phases were washed with brine (5 mL), dried (MgSO₄), and concentrated. Chromatography (EtOAc:*n*-hexane, 50:50) gave 0.011 g (90%) of a clear oil: [α]_D²⁵ +125.9 (*c* 2.73, CHCl₃); IR (thin film) 2404, 1525, 1428, 1217 cm⁻¹; ¹H NMR (CDCl₃) δ 0.95 (d, *J* = 7.2 Hz, 3H), 1.98 (s, 3H), 2.34 (s, 3H), 2.90 (m, 1H), 4.46 (dd, *J* = 5.2 Hz, *J* = 7.6 Hz, 1H), 4.98 (d, *J* = 5.6 Hz), 7.26 (m, 3H), 7.35 (m, 4H), 7.45 (m, 2H); ¹³C NMR (CDCl₃) δ 15.3, 21.7, 29.8, 53.4, 60.9, 125.8, 128.2, 128.4, 129.0, 129.1, 129.9, 130.0, 140.0, 141.7, 142.5, 212.2. HRMS calcd for C₁₈H₂₂NO₂S (M + H) 316.1371. Found 316.1365.

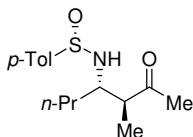


(*S_S,2*S*,3*R)-(+)-2-methyl-3-(4-methylphenylsulfonamido)-1-butyl-3-phenylpropan-1-one (206b).** Chromatography (EtOAc:*n*-hexane, 50:50) gave (0.011 g)

38% of a clear oil: $[\alpha]_D^{25} +109$ (c 0.5, CHCl_3); IR (thin film) 3190, 2958, 2931, 2872, 1709, 1452 cm^{-1} ; ^1H NMR (CDCl_3) δ 0.8 (t, $J = 7.2$ Hz, 3H), 1.06 (d, $J = 7.2$ Hz, 3H), 1.15 (m, 2H), 1.38 (m, 2H), 2.12 (dt, $J_1 = 7.2$ Hz, $J_2 = 17.2$ Hz, 1H), 2.27 (dt, $J_1 = 7.2$ Hz, $J_2 = 17.2$ Hz, 1H), 2.41 (s, 3H), 2.98 (m, 1H), 4.53 (t, $J = 6.4$ Hz, 1H), 5.19 (d, $J = 5.6$ Hz, 1H), 7.29 (m, 3H), 7.36 (m, 4H), 7.54 (m, 2H); ^{13}C NMR (CDCl_3) δ 14.1, 15.7, 21.7, 22.5, 25.6, 42.8, 52.4, 61.3, 125.8, 127.9, 128.2, 129.0, 129.9, 140.9, 141.6, 142.7, 214.7. HRMS calcd for $\text{C}_{21}\text{H}_{28}\text{NO}_2\text{S}$ (M+H) 358.1841. Found 358.1840.

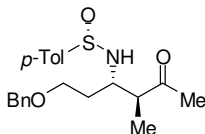


(S_S,2S,3R)-(+)-2-Methyl-3-(4-methylphenylsulfonamido)- 1,3-diphenylpropan-1-one (206c). Chromatography (EtOAc:*n*-hexane, 50:50) gave a 61% of a clear oil: $[\alpha]_D^{25} +35.7$ (c 0.95, CHCl_3); IR (thin film) 3195, 3060, 2924, 1680, 1452 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.14 (s, 3H), 2.39 (s, 3H), 3.92 (m, 1H), 4.78 (m, 1H), 5.17 (d, $J = 5.2$ Hz, 1H), 7.28 (m, 4H), 7.38 (m, 6H), 7.53 (m, 2H), 7.81 (m, 2H); ^{13}C NMR (CDCl_3) δ 16.8, 21.7, 47.4, 61.5, 125.9, 128.3, 128.7, 129.0, 129.1, 129.8, 133.7, 136.6, 140.4, 141.6, 142.7, 203.4. HRMS calcd for $\text{C}_{23}\text{H}_{24}\text{NO}_2\text{S}$ (M + H) 378.1528. Found 378.1524.



(S_S,3S,4S)-(+)-N-(4-*p*-Toluenesulfinyl)-4-amino-3-methyl-4-heptan-2-one

(207a). Chromatography (EtOAc:*n*-hexane, 50:50) gave a 33% of a clear oil: $[\alpha]_D^{25} +126.5$ (*c* 0.2, CHCl₃); IR (thin film) 3219, 2959, 2922, 1705, 1454 cm⁻¹; ¹H NMR (CDCl₃) δ 0.92 (t, *J* = 7.2 Hz, 3H), 1.10 (d, *J* = 7.2 Hz, 3H), 1.42 (m, 4H), 2.09 (s, 3H), 2.41 (s, 3H), 2.75 (m, 1H), 3.47 (m, 1H), 4.61 (d, *J* = 9.2 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.59 (m, 2H); ¹³C NMR (CDCl₃) δ 13.3, 14.2, 19.9, 21.7, 29.9, 36.7, 50.9, 57.4, 125.9, 129.9, 141.6, 142.7, 212.0; HRMS calcd for C₁₅H₂₄NO₂S (M⁺) 282.1528. Found 282.1529.

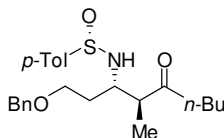


N-[(S_s,3S,4S)-(+)-1-(Benzyloxy)-4-methyl-5-oxohexan-3-yl]-4-

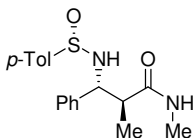
methylbenzenesulfinamide (208a) Chromatography (EtOAc:*n*-hexane, 50:50) gave 45% of a clear oil: $[\alpha]_D^{25} +64.8$ (*c* 0.5, CHCl₃); IR (thin film) 3232, 2922, 2868, 1709, 1452 cm⁻¹; ¹H NMR (CDCl₃) δ 1.01 (d, *J* = 7.2 Hz, 3H), 1.76 (m, 2H), 1.97 (s, 3H), 2.34 (s, 3H), 2.66 (m, 1H), 3.50 (m, 1H), 3.57 (m, 2H), 4.43 (m, 2H), 4.89 (d, *J* = 9.2 Hz, 1H), 7.19 (m, 3H), 7.25 (m, 4H), 7.45 (m, 2H); ¹³C NMR (CDCl₃) δ 13.6, 21.7, 29.8, 34.7,

50.6, 54.8, 67.5, 73.4, 126.1, 128.1, 128.2, 128.8, 129.8, 138.6, 141.6, 142.4, 212.2.

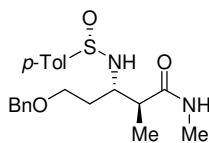
HRMS calcd for C₂₁H₂₈NO₃S (M+H) 374.1790. Found 374.1786.



***N*-[(*Ss,3S,4S*)-(+)-1-(Benzyloxy)-4-methyl-5-oxononan-3-yl]-4-methylbenzenesulfonamide (22b).** Chromatography (EtOAc:*n*-hexane, 50:50) gave 40% of a clear oil: $[\alpha]_D^{25} +68.5$ (*c* 1.25, CHCl₃); IR (thin film) 3365, 2919, 2852, 1708, 1449, 1049 cm⁻¹; ¹H NMR (CDCl₃) δ 0.86 (t, *J* = 7.2 Hz, 3H), 1.07 (d, *J* = 7.2 Hz, 3H), 1.22 (m, 2H), 1.43 (m, 2H), 1.81 (m, 2H), 2.31 (m, 2H), 2.41 (s, 3H), 2.71 (m, 1H), 3.57 (m, 1H), 3.64 (m, 2H), 4.5 (s, 2H), 5.07 (d, *J* = 8.8 Hz, 1H), 7.26 (m, 3 overlapping H), 7.33 (m, 4H), 7.53 (d, *J* = 8.0 Hz, 2H); ¹³C NMR (CDCl₃) δ 14.0, 14.2, 21.7, 22.6, 25.9, 34.9, 42.4, 49.6, 54.9, 67.5, 73.4, 125.8, 126.1, 128.0, 128.1, 128.2, 128.6, 128.7, 129.8, 138.6, 141.5, 141.6, 142.5, 214.7; HRMS calcd for C₂₄H₃₄NO₃S (M + H) 416.2259, found 416.2259.

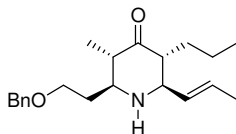


(*S_S,2*S*,3*R)-(+)-3-amino-*N*,2-dimethyl-3-(4-methylphenylsulfinamido)-3-phenylpropanamide (23a).** Chromatography (EtOAc:*n*-hexane, 50:50) gave 24 % of a clear oil; $[\alpha]_D^{25} +153.4$ (*c* 0.5, CHCl₃), IR: 3293, 2920, 1651, 1556 cm⁻¹; ¹H NMR (CDCl₃) δ 1.18 (d, *J* = 7.2 Hz, 3H), 2.40 (s, 3H), 2.51 (m, 1H), 2.63 (d, *J* = 5.2 Hz, 3H), 4.46 (t, *J* = 5.6 Hz, 1H), 5.29 (brs, 1H), 5.82 (d, *J* = 5.6 Hz, 1H), 7.32 (m, 7H), 7.56 (m, 2H); ¹³C NMR (CDCl₃) δ 16.7, 21.7, 26.5, 47.9, 61.8, 125.9, 127.5, 127.7, 128.1, 128.9, 129.8, 141.5, 141.8, 142.7, 174.9. HRMS calcd for C₁₈H₂₂N₂O₂S (M+H) 330.1402. Found 330.1408.



(*S_S,2*S*,3*S)-(+)-*N*,2-dimethyl-3-(4-methylphenylsulfinamido)-5-benzyloxypentanamide (23b).** Chromatography (EtOAc:*n*-hexane, 50:50) gave 30% of a clear oil; $[\alpha]_D^{25} +47.7$ (*c* 0.3, CHCl₃), IR: 3296, 2918, 2850, 1666, 1454 cm⁻¹; ¹H NMR (CDCl₃) δ 1.14 (d, *J* = 6.8 Hz, 3H), 1.95 (m, 1H), 2.09 (m, 1H), 2.40 (s, 3H), 2.49 (m, 1H), 3.23 (s, 3H), 3.40 (m, 1H), 3.62 (m, 2H), 4.51 (m, 2H), 5.29 (d, *J* = 8.8 Hz, 1H), 6.46 (brs, 1H), 7.31 (m, 7H), 7.55 (m, 2H); ¹³C NMR (CDCl₃) δ 15.9, 21.7, 30.1, 36.3, 44.0, 56.7, 68.2, 71.5, 73.7, 126.2, 128.3, 128.8, 128.9, 129.8, 138.2, 141.5, 142.2, 175.9; HRMS calcd for C₂₁H₂₈N₂O₃S (M+) 388.1821. Found 388.1821.

CHAPTER 3:



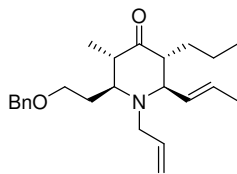
(2*S*, 3*S*, 5*R*, 6*R*, *E*)-(+)-2-(2-(Benzyloxy)ethyl)-3-methyl-6-(prop-1-enyl)-5-propylpiperidin-4-one (313)

In a flame dried round bottom flask equipped with a magnetic stirring bar, rubber septum and argon inlet was placed (+)-**22b** (0.297 g, 0.716 mmol) in dry MeOH (15 mL). The solution was cooled to 0 °C. HCl solution (7.16 mL, 7.16 mmol, 1.0 M solution in Et₂O) was added via syringe, and the reaction mixture was stirred for 30 min at 0 °C. After that, the reaction mixture was warmed up to rt, and a sticky oil residue was obtained after concentration. Satd. aqueous NaHCO₃ was added to the reaction residue and the mixture pH was adjusted 9. The aqueous phase was extracted with DCM (10 mL × 2), and then combined organic phases were washed with brine (10 mL), dried over MgSO₄ and concentrated. The crude amine (0.192 g) was used in the next step without further purification.

In a dried round bottom flask equipped with a magnetic stirring bar, rubber septum and argon inlet was placed crude amine (0.192 g) in DCM (10 mL) at 0 °C. Then crotonaldehyde (0.57 mL, 6.93 mmol) and Ti(OEt)₄ (0.835 g, 3.47 mmol) were added via syringe. Reaction mixture was stirred at rt for 3 h, after which the mixture was diluted with water (50 mL) at 0 °C and stirred vigorously. The formed solid liquid mixture was

filtered through a short pad of Celite, and DCM (10 mL \times 2) was used to rinse the Celite. Combined organic phases were washed with satd. aqueous NaHCO₃ and brine. The separated organic phase was then dried over MgSO₄ and concentrated to give the crude imine which was carried onto the next step without further purification.

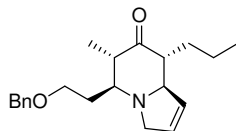
In a dry round bottom flask equipped with a magnetic stirring bar, rubber septum and Argon inlet was placed TsOH.H₂O (0.239 g, 1.26 mmol) and a solution of crude imine (0.208 g, 0.632 mmol) in dry toluene (20 mL). The reaction mixture was heated at 75 °C for 8 h and then cooled to rt. Satd. aqueous NaHCO₃ was then added to the reaction mixture, and the aqueous layer pH value was adjusted to 9. Two phases were separated and the aqueous layer was then extracted with DCM (15 mL \times 2). The combined organic phases were washed with brine, dried and concentrated to give a crude product as a sticky oil. Chromatography (EtOAc:*n*-hexane, 33:67) gave (0.121 g) 58% of a clear oil; $[\alpha]_D^{25} +4.3$ (*c* 1.2, CHCl₃), IR: 2365, 2345, 1545, 670 cm⁻¹; ¹H NMR (CDCl₃) δ 0.85 (t, *J* = 7.2 Hz, 3H), 0.98 (d, *J* = 6.4 Hz, 3H), 1.17 (m, 3H), 1.37 (m, 1H), 1.63 (m, 1H), 1.69 (dd, *J* = 1.6 Hz, *J* = 6.4 Hz, 3H), 1.77 (m, 1H), 1.96 (m, 1H), 2.18 (t, *J* = 9.2 Hz, 1H), 2.29 (m, 1H), 2.62 (m, 1H), 3.60 (m, 1H), 3.66 (m, 1H), 4.49 (d, *J* = 2 Hz, 3H), 5.43 (m, 1H), 5.56 (m, 1H), 7.30 (m, 5H); ¹³C NMR (CDCl₃) δ 10.5, 14.8, 18.1, 21.4, 27.3, 27.8, 34.1, 50.3, 51.0, 56.0, 62.8, 65.5, 68.9, 73.4, 127.9, 128.0, 128.7, 132.8, 133.0, 138.5, 211.5; HRMS calcd for C₂₁H₃₂NO₂ (M+H) 330.2433. Found 330.2429.



(2*S*, 3*S*, 5*R*, 6*R*, *E*)-(-)-1-Allyl-2-(2-(benzyloxy)ethyl)-3-methyl-6-(prop-1-enyl)-5-propylpiperidin-4-one (314)

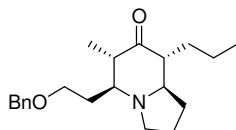
In a 50-mL flame dried round bottom flask equipped with a magnetic stirring bar, rubber septum and an argon inlet was placed piperidone (+)-**313** (0.076 g, 0.231 mmol) in absolute EtOH (10 mL). Anhydrous Na₂CO₃ (0.368 g, 3.47 mmol) and allyl iodide (0.21 mL, 2.31 mmol) were added at rt, and then the suspension mixture was heated at 75 °C for 24 h. Concentration of the reaction mixture gave a solid liquid mixture residue.

DCM (20 mL) was added into the residue. The obtained solution was filtered through a short pad of Celite and formed clear solution was concentrated to give a pale yellow sticky oil. Chromatography (EtOAc:*n*-hexane, 33:67) gave (0.058 g) 68% of a clear oil; $[\alpha]_D^{25} -17.3$ (*c* 1.65, CHCl₃), IR: 1716, 1455 cm⁻¹; ¹H NMR (CDCl₃) δ 0.84 (t, *J* = 6.4 Hz, 3H), 1.04 (d, *J* = 6.4 Hz, 3H), 1.13 (m, 2H), 1.19 (m, 1H), 1.63 (m, 1H), 1.73 (d, *J* = 6.8 Hz, 3H), 1.94 (m, 1H), 2.26 (t, *J* = 9.6 Hz, 1H), 2.49 (m, 1H), 2.59 (m, 1H), 2.97 (t, *J* = 9.6 Hz, 1H), 3.30 (m, 1H), 3.49 (m, 1H), 3.65 (t, *J* = 7.2 Hz, 2H), 4.52 (s, 2H), 5.11 (m, 2H), 5.31 (m, 1H), 5.51 (m, 1H), 5.78 (m, 1H), 7.33 (m, 5H); ¹³C NMR (CDCl₃) δ 12.6, 14.7, 18.0, 21.3, 28.7, 31.0, 48.2, 51.7, 53.6, 64.2, 66.7, 69.9, 73.5, 118.0, 127.9, 128.7, 129.1, 132.9, 133.8, 138.8, 212.1. HRMS calcd for C₂₄H₃₆NO₂ (M+H) 370.2746. Found 370.2747.



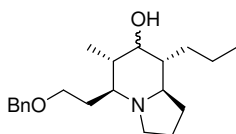
(5*S*, 6*S*, 8*R*, 9*R*)-(+)-5-(2-(Benzyloxy)ethyl)-6-methyl-8-propyl-5,6,8,8a-tetrahydroindolizin-7(3H)-one (316)

In a 50 mL dried round bottom flask equipped with a magnetic stirring bar, reflux condenser, rubber septum and argon inlet was placed piperidone (-)-**314** (0.012 g, 0.0325 mmol) in dry DCM (10 mL). Grubbs 1st generation catalyst (0.001 g, 5 mol %) was added to the reaction at rt. The solution changed from clear to blue when mixture was stirred. The reaction mixture stirred at rt for 8 h, and then solution was concentrated to give the crude product as a dark oil. Chromatography (EtOAc:*n*-hexane, 1:10) gave (0.007 g) 62% of a clear oil; $[\alpha]_D^{25} +20.2$ (*c* 0.7, CHCl₃), IR: 2958, 2767, 1702 cm⁻¹; ¹H NMR (CDCl₃) δ 0.89 (t, *J* = 7.6 Hz, 3H), 1.03 (d, *J* = 6.4 Hz, 3H), 1.19 (m, 2H), 1.42 (m, 2H), 1.90 (m, 2H), 2.01 (m, 1H), 2.22 (t, *J* = 8.4 Hz, 1H), 2.47 (m, 1H), 2.70 (m, 1H), 3.36 (m, 2H), 3.66 (m, 4H), 4.50 (s, 2H), 5.98 (m, 1H), 6.08 (m, 1H), 7.30 (m, 5H); ¹³C NMR (CDCl₃) δ 9.1, 12.9, 19.7, 26.4, 28.2, 30.2, 45.3, 50.8, 53.3, 61.6, 65.8, 71.0, 71.6, 71.7, 106.5, 117.8, 126.0, 126.4, 126.9, 130.7, 210.1. HRMS calcd for C₂₁H₃₀NO₂ (M+H) 328.2277. Found 328.2278.



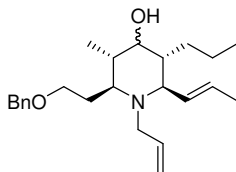
(5*S*, 6*S*, 8*R*, 9*R*)-(+)-5-(2-(Benzyloxy)ethyl)-6-methyl-8-propylhexahydroindolizin-7(1*H*)-one (317)

To a 50 mL dried round bottom flask equipped with a magnetic stirring, rubber septum and H₂ balloon was placed indolizidinone **316** (0.012 g, 0.037 mmol) and Pd/C (0.001 g, 10% w./w.). Flask was dried under vacuum and then filled with H₂ gas, and same process was repeated 3 times. To the H₂ filled flask, anhydrous MeOH (10 mL) was added via the syringe. Reaction mixture stirred 24 h, and the obtained solution was filtered through a short pad of Celite. The filtrate was concentrated to give the crude product as a clear sticky oil. Chromatography (EtOAc:*n*-hexane, 20:80) gave (0.012 g) 99% of a clear oil; $[\alpha]_D^{25} +19.2$ (*c* 0.5, CHCl₃), IR: 2958, 2870, 1713, 1454 cm⁻¹; ¹H NMR (CDCl₃) δ 0.88 (t, *J* = 7.6 Hz, 3H), 1.03 (d, *J* = 6.4 Hz, 3H), 1.20 (m, 2H), 1.40 (m, 1H), 1.72 (m, 2H), 1.84 (m, 1H), 1.98 (m, 3H), 2.08 (m, 3H), 2.28 (t, *J* = 9.6 Hz, 1H), 2.47 (m, 1H), 3.20 (dt, *J* = 2.4 Hz, *J* = 8.8 Hz, 1H), 3.67 (t, *J* = 6.8 Hz, *J* = 7.6 Hz, 2H), 4.52 (s, 2H), 7.28 (m, 2H), 7.34 (m, 4H); ¹³C NMR (CDCl₃) δ 10.9, 14.8, 21.4, 21.6, 28.5, 30.1, 30.5, 31.6, 47.4, 51.0, 55.5, 66.3, 66.5, 69.8, 73.4, 127.8, 127.9, 128.7, 138.9, 212.1. HRMS calcd for C₂₁H₃₂NO₂ (M+H) 330.2433. Found 330.2418.



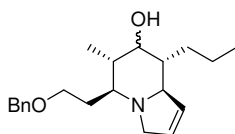
(5*S*, 6*S*, 8*R*, 9*R*)-5-(2-(Benzyloxy)ethyl)-6-methyl-8-propyloctahydroindolizin-7-ol (318)

In a 50 mL dried round bottom flask equipped with a magnetic stirring bar, rubber septum and an argon inlet was placed indolizinone-(+)-**317** (0.005 g, 0.015 mmol) in anhydrous MeOH (10 mL). Reaction mixture was cooled to 0 °C and then NaBH₄ (0.002 g, 0.061 mmol) was added. After addition, the reaction was maintained at the same temperature for 2 h. Then satd. aqueous NH₄Cl was added. The obtained solution was extracted with Et₂O (10 mL × 2), and then combined organic phases were dried and concentrated to give a mixture of diastereomeric alcohols. IR: 3031, 2957, 2870, 2786 cm⁻¹; ¹H NMR (CDCl₃) δ 0.90 (t, *J* = 7.6 Hz, *J* = 6.8 Hz, 3H), 1.05 (d, *J* = 6.8 Hz, 3H), 1.46 (m, 5H), 1.72 (m, 7H), 1.99 (m, 5H), 3.57 (m, 1H), 3.65 (m, 1H), 3.78 (m, 1H), 4.51 (m, 2H), 7.32 (m, 5H); ¹³C NMR (CDCl₃) δ 14.5, 14.8, 15.2, 19.8, 21.2, 23.0, 30.0, 31.9, 32.3, 39.7, 42.7, 65.0, 67.2, 73.4, 127.9, 128.0, 128.7. HRMS calcd for C₂₁H₃₄NO₂ (M+H) 332.2590. Found 332.2587.



(2*S*, 3*S*, 5*R*, 6*R*, *E*)-1-Allyl-2-(2-(benzyloxy)ethyl)-3-methyl-6-(prop-1-enyl)-5-propylpiperidin-4-ol (324)

In a 50 mL dried round bottom flask equipped with a magnetic stirring bar, rubber septum and an argon inlet was placed indolizinone **314** (0.022 g, 0.060 mmol) in anhydrous MeOH (10 mL). Reaction mixture was cooled to 0 °C and then NaBH₄ (0.009 g, 0.238 mmol) was added. After addition, the reaction was maintained at the same temperature for 2 h. Then satd. aqueous NH₄Cl was added. The obtained solution was extracted with Et₂O (10 mL × 2), and then combined organic phases were dried and concentrated to give (0.022 g) 99% of a mixture of diastereomeric alcohols **324**. IR: 3025, 2958, 2767 cm⁻¹; ¹H NMR (CDCl₃) δ 0.86 (t, *J* = 6.8 Hz, 3H), 1.05 (d, *J* = 6.8 Hz, 3H), 1.18 (m, 1H), 1.38 (m, 2H), 1.70 (m, 3H), 3.33 (m, 1H), 3.48 (m, 1H), 3.58 (m, 2H), 3.65 (brs, 1H), 4.51 (m, 2H), 5.14 (m, 3H), 5.15 (m, 3H), 5.51 (m, 1H), 5.85 (m, 1H), 7.28 (m, 1H), 7.33 (m, 4H); HRMS calcd for C₂₄H₃₈NO₂ (M+H) 372.2903. Found 372.2908.

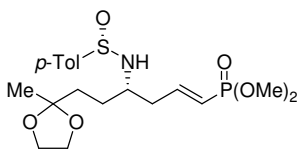


(5*S*, 6*S*, 8*R*, 9*R*)-(+)-5-(2-(Benzyloxy)ethyl)-6-methyl-8-propyl-5,6,8,8a-tetrahydroindolizin-7(3H)-ol (325)

In a 50 mL dried round bottom flask equipped with a magnetic stirring bar, reflux condenser, rubber septum and argon inlet was placed piperidone **324** (0.022 g, 0.059 mmol) in dry DCM (10 mL). Grubbs 1st generation catalyst (0.002 g, 5 mol %) was

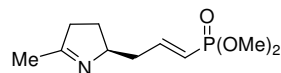
added into the reaction at rt. Reaction mixture stirred at rt for 8 h, and then the solution was concentrated to give the crude product as a dark oil. Chromatography (EtOAc:*n*-hexane, 33:67) gave (0.016 g) 78% of a clear oil; $[\alpha]_D^{25} +58.4$ (*c* 0.5, CHCl₃), IR: 2929, 2870, 1453 cm⁻¹; ¹H NMR (CDCl₃) δ 0.92 (t, *J* = 6.8 Hz, 3H), 1.02 (d, *J* = 6.8 Hz, 3H), 1.26 (m, 7H), 1.43 (m, 5H), 1.85 (m, 2H), 1.92 (m, 2H), 2.75 (m, 1H), 2.94 (m, 1H), 3.18 (m, 1H), 3.62 (m, 3H), 4.51 (m, 2H), 5.91 (m, 1H), 6.03 (m, 1H), 7.29 (m, 1H), 7.33 (m, 4H); ¹³C NMR (CDCl₃) δ 14.7, 15.1, 20.1, 20.8, 26.5, 26.7, 27.2, 27.3, 30.1, 30.4, 30.7, 35.4, 38.7, 44.5, 54.0, 56.7, 66.6, 67.8, 72.4, 73.4, 79.2, 127.9, 127.93, 128.7, 128.8, 132.8. HRMS calcd for C₂₁H₃₁NO₂ (M+H) 329.2355. Found 329.2355.

CHAPTER 4:



(*Ss*, *4S*, *1E*)-(+)-*N*-(*p*-toluenesulfinyl)-1-(dimethoxyphosphinyl)-4-amino-6-(2-methyl-1,3-dioxolan-2-yl)hex-1-ene (**423**). In a flame-dried 25-mL Schlenk tube equipped with a magnetic stir bar, rubber septum and argon inlet was placed a solution of tetramethyl methylenephosphonate (0.23 g, 0.992 mmol) in THF (5 mL) at rt. The reaction mixture was cooled to 0 °C with an ice-bath, and NaHMDS (0.992 mmol, 0.99 mL of 1.0 M in THF) was added drop by dropwise after 15 min. The reaction mixture was maintained at 0 °C for 20 min, and a solution of *N*-sulfinyl β -amino aldehyde **391** (0.077 g, 0.248 mmol) in THF (5 mL) was added at a constant rate during 5 min. The solution was stirred at 0 °C for 15 min, warmed to rt, and stirred for 2 h. The clear

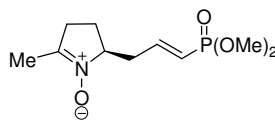
solution was cooled to 0 °C, and after 15 min a satd. aqueous of NH₄Cl (4 mL) solution was added dropwise. The reaction was warmed to rt and EtOAc (5 mL) and H₂O (4 mL) were added. The phases were separated and the aqueous phase was extracted with EtOAc (2 × 5 mL). Combined organic phases were washed with brine (5 mL), dried (MgSO₄) and concentrated. Chromatography (DCM/MeOH, 10:1) gave 0.091 g (88%) of a clear oil as a (*E*)-single isomer: $[\alpha]_D^{25} +47.2$ (*c* 0.75, CHCl₃); IR (thin film) 3203, 2953, 1631, 1442 cm⁻¹; ¹H NMR (CDCl₃) δ 1.30 (s, 3H), 1.58 (m, 1H), 1.72 (m, 2H), 1.83 (m, 1H), 2.39 (m, 2 H overlapping), 2.40 (s, 3H), 3.68 (d, *J* = 2.8 Hz, 3H), 3.71 (d, *J* = 3.2 Hz, 3H), 3.92 (m, 4H), 4.11 (d, *J* = 7.6 Hz, 1H), 5.66 (dd, *J* = 17.2 Hz, *J* = 20.8 Hz, 1H), 6.67 (m, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.56 (d, *J* = 8.4 Hz, 2H); ¹³C NMR (CDCl₃) δ 21.7, 24.3, 30.1, 35.4, 41.4, 41.6, 52.70, 52.71, 53.6, 64.99, 65.05, 110.1, 118.8, 120.6, 125.9, 129.9, 141.8, 142.4, 149.9. ³¹P NMR (CDCl₃) δ 11.2 ; HRMS calcd for C₁₉H₃₁NO₆PS (M+H) 432.1610, found 432.1611.



(4*S*, 1*E*)-(+)- 1-(dimethoxyphosphinyl)-3-(3,4-dihydro-5-methyl-2*H*-pyrrol-2-yl)-prop-1-ene (424). To a 25-mL round bottom flask equipped with a magnetic stir bar, rubber septum and argon inlet was added δ-amino dimethyl phosphonate **423** (0.033 g, 0.0793 mmol), MeOH (2 mL) and THF (2 mL) at rt. At this time HCl (0.793 mmol,

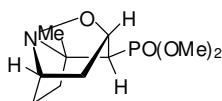
0.26 mL of 3.0 M HCl in water) was added dropwise. The reaction mixture was stirred at rt for 8 h, and concentrated. The residue was washed with hexane (3 × 3 mL) and then mixed with DCM (10 mL). At this time satd aqueous NaHCO₃ solution was added dropwise until the pH was adjusted to 9. The phases were separated, the organic phase was washed with satd aqueous NaHCO₃ (5 mL), the DCM layer was dried (MgSO₄), filtered and concentrated to give 0.012 g (64%) of a clear oil as a (*E*)-single isomer:

$[\alpha]_D^{25} +6.8$ (*c* 1.7, CHCl₃); IR (thin film) 1722, 1630 cm⁻¹; ¹H NMR (CDCl₃) δ 1.48 (m, 1H), 2.01 (d, *J* = 1.6 Hz, 3H), 2.06 (m, 1H), 2.36 (m, 1H), 2.49 (m, 1H), 2.69 (m, 1H), 3.69 (d, *J* = 2.8 Hz, 3H), 3.72 (d, *J* = 2.8 Hz, 3H), 4.07 (m, 1H), 5.70 (qt, *J* = 1.6 Hz, *J* = 17.2 Hz, *J* = 21.2 Hz, 1H), 6.79 (m, 1H); ¹³C NMR (CDCl₃) δ 20.0, 28.7, 39.4, 41.5, 52.6, 71.4, 117.1, 118.9, 151.9, 175.4; ³¹P NMR (CDCl₃) δ 11.7; HRMS calcd for C₁₀H₁₉NO₃P (M+H) 232.1103, found 232.1098.



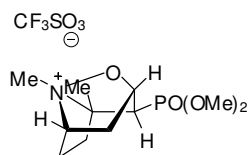
(4*S*, 1*E*)-(+)- 1-(dimethoxyphosphinyl)-3-(3,4-dihydro-5-methyl-2*H*-pyrrol-2-yl)-prop-1-ene-*N*-oxide (425). In a flame-dried 50-mL bottom flask equipped with a magnetic stir bar, rubber septum and argon inlet was placed dehydropyrrolidine dimethylphosphonate **2** (0.103 g, 0.446 mmol), urea hydrogen peroxide (0.136 g, 1.45 mmol) and methyltrioxorhenium (0.008 g, 0.031 mmol). Anhydrous MeOH (10 mL) was

added via syringe, and the solution was stirred at rt for 8 h, then concentrated. To the residue was added DCM (10 mL); the solution was filtered and the filtrate was concentrated to afford a yellow sticky oil. Flash chromatography (MeOH) gave 0.11 g (99%) of colorless oil as a (*E*)-single isomer; $[\alpha]_D^{25}$ -20.5 (*c* 1.9, CHCl₃); IR (thin film) 3056, 2360, 1716, 1265 cm⁻¹; ¹H NMR (CDCl₃) δ 1.81 (m, 1H), 2.04 (d, *J* = 1.6 Hz, 3H), 2.27 (m, 1H), 2.64 (m, 3H), 3.02 (m, 1H), 3.69 (d, *J* = 3.6 Hz, 3H), 3.72 (d, *J* = 3.6 Hz, 3H), 4.14 (m, 1H), 5.79 (qt, *J* = 1.6 Hz, *J* = 17.2 Hz, *J* = 20.4 Hz, 1H), 6.70 (m, 1H); ¹³C NMR (CDCl₃) δ 13.2, 22.5, 31.4, 37.2, 37.4, 52.7, 71.0, 119.3, 121.2, 148.6; HRMS calcd for C₁₀H₁₉NO₄P (M+H) 248.1052, found 248.1050.



(1*S*, 2*R*, 3*R*, 6*S*)-(-)-Methyl-3-methyl-7-aza-8-oxatricyclo[4,2,1,0]-nonane-2-dimethylphosphonate (426). In a 10 mL microwave tube were placed dimethylphosphonate nitron **3** (0.055 g, 0.223 mmol), toluene (5 mL) and DMF (1 mL). The reaction mixture was irradiated at 150 °C for 5 h at 300W power. The solution was cooled down to rt and concentrated to give a pale yellow oil. Chromatography (MeOH/DCM, 1:10) gave 0.018 g (33%) of a clear oil as the only *exo*-isomer. $[\alpha]_D^{25}$ -1.14 (*c* 0.7, CHCl₃); IR (thin film) 3056, 2360, 1265, 1036 cm⁻¹; ¹H NMR (CDCl₃) δ 1.36 (dd, *J* = 1.6 Hz, *J* = 2.0 Hz, 1H), 1.53 (s, 3H), 1.79 (m, 2H), 1.90 (s, 3H), 2.16 (m, 3

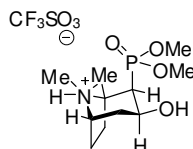
H overlapping), 3.63 (t, $J = 9.6$ Hz, 1H), 3.76 (d, $J = 3.2$ Hz, 3H), 3.79 (d, $J = 3.2$ Hz, 3H), 4.92 (dd, $J = 4.8$ Hz, $J = 8.8$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 22.8, 25.6, 33.9, 44.0, 44.1, 51.8, 52.7, 54.1, 61.9, 73.8, 80.3; ^{31}P NMR (CDCl_3) δ 20.1; HRMS calcd for $\text{C}_{10}\text{H}_{19}\text{NO}_4\text{P}$ (M+H) 248.1052, found 248.1045.



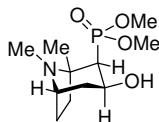
Trifluoromethylsulfonate salt of Methyl (1S, 2R, 3R, 6S)-(-)-3,7-dimethyl-7-aza-8-oxatricyclo[4,2,1,0]-nonane-2-dimethylphosphonate (427). In a 25-mL round bottom flask equipped with a magnetic stir bar, rubber septum and argon inlet were placed isoxazolidine **4** (0.015 g, 0.061 mmol) and dry DCM (3 mL). Methyl trifluoromethanesulfonate (0.030 g, 0.121 mmol) was added at rt and the reaction mixture stirred for 8 h. At this time the reaction was concentrated to give 0.025 g (99%) of a clear sticky oil. $[\alpha]_{\text{D}}^{25}$ -5.0 (c 1.2, MeOH); IR (thin film) 3506, 1256, 1033 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.79 (s, 3H), 2.31 (m, 3 H overlapping), 2.60 (m, 2H), 2.88 (m, 1H), 3.27 (s, 1H), 3.39 (s, 3H), 3.84 (d, $J = 2.0$ Hz, 3H), 3.87 (d, $J = 2.4$ Hz, 3H), 4.40 (m, 1H), 5.44 (dd, $J = 4.4$ Hz, $J = 9.6$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 19.5, 25.9, 35.0, 41.9, 44.1,

52.1, 53.6, 54.7, 78.6, 83.0, 88.0; ^{31}P NMR (CDCl_3) δ 14.7; HRMS calcd for

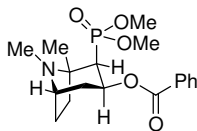
$\text{C}_{11}\text{H}_{21}\text{NO}_4\text{P}$ (M^+) 262.1208, found 262.1206.



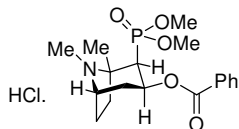
Trifluoromethylsulfonate salt of methyl (1*R*, 2*R*, 3*S*, 5*S*)-(-)-3-(hydroxy)-1,8-dimethyl-8-azabicyclo[3.2.1]octane-dimethylphosphonate (428). In a 25-mL round bottom flask equipped with a magnetic stir bar, rubber septum and hydrogen balloon was placed dimethylphosphonate triflate salt **427** (0.025 g, 0.061 mmol) in MeOH (4 mL). Palladium black (0.010 g, 5 w/w %) was added, and the reaction mixture was stirred under H_2 at 1 atm for 8 h at rt. The solution was filtered through a short pad of Celite, and the filtrate was concentrated to give 0.025 g (99%) of a clear sticky oil. $[\alpha]_{\text{D}}^{25}$ -2.25 (*c* 1.2, MeOH); IR (thin film) 2960, 1728, 1265 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.52 (s, 3H), 1.68 (m, 1H), 1.86 (m, 2H), 2.04 (m, 1H), 2.20 (m, 1H), 2.41 (m, 2H), 2.57 (dm, $J = 11.6$ Hz, 1H), 3.48 (m, 1H), 3.79 (d, $J = 11.2$ Hz, 3H), 3.77 (d, $J = 11.2$ Hz, 3H), 4.21 (dm, $J = 34.4$ Hz, 1H), 4.87 (s, 3H); ^{13}C NMR (CDCl_3) δ 24.1, 28.2, 37.2, 40.2, 53.3, 66.2, 120.6; ^{31}P NMR (CDCl_3) δ 21.2; HRMS calcd for $\text{C}_{11}\text{H}_{23}\text{NO}_4\text{P}$ (M^+) 264.1365, found 264.1362.



Methyl (1R, 2R, 3S, 5S)-(-)-3-(hydroxy)-1,8-dimethyl-8-azabicyclo[3.2.1]octane-dimethylphosphonate (429). In a 25-mL round bottom flask equipped with a magnetic stir bar, rubber septum and argon inlet was placed Na_2CO_3 (0.030 g, 0.286 mmol) in EtOH (3 mL) at rt. A solution of phosphonate triflate salt **428** (0.056 g, 0.136 mmol) in EtOH (2 mL) was added dropwise. After addition, the reaction mixture stirred at rt for 10 min, then filtered through a short pad Celite to give a clear solution. The solution was concentrated to give a sticky oil which was dissolved in DCM (10 mL). The solution was filtered again through Celite to afford a clear solution which was concentrated to give 0.028 g (78%) of a colorless oil; $[\alpha]_D^{25} +16.4$ (*c* 1.3, MeOH); IR (thin film) 3392, 2953, 1453, 1223 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.36 (s, 3H), 1.50 (m, 1H), 3.34 (m, 2H), 1.85 (dd, $J = 2.4$ Hz, $J = 8.4$ Hz), 2.03 (m, 1H), 2.17 (s, 3H), 2.45 (dd, $J = 6.0$ Hz, $J = 15.6$ Hz), 3.22 (p, $J = 3.6$ Hz, $J = 6.8$ Hz), 3.66 (d, $J = 10.8$ Hz), 3.72 (m, 1H), 3.84 (d, $J = 14.8$ Hz), 3.97 (dm, 1H), 4.89 (br, 1H); ^{13}C NMR (CDCl_3) δ 23.0, 27.3, 35.7, 35.8, 37.0, 41.4, 50.8, 53.6, 63.8, 65.2, 66.1; ^{31}P NMR (CDCl_3) δ 24.2; HRMS calcd for $\text{C}_{11}\text{H}_{22}\text{NO}_4\text{P}$ (M+H) 264.1365, found 264.1362.



Methyl (1R, 2R, 3S, 5S)-(-)-3-(benzyloxy)-1,8-dimethyl-8-azabicyclo[3.2.1]octane-2-dimethylphosphonate (430). In a 25-mL round bottom flask equipped with a magnetic stir bar, rubber septum and argon inlet were placed dimethylphosphonate amino alcohol **429** (0.028 g, 0.106 mmol), benzoyl chloride (0.149 g, 1.06 mmol), and dry DCM (5 mL) at rt. The reaction mixture was stirred at rt, and Na₂CO₃ (0.169 g, 1.59 mmol) was added and the solution was stirred for 8 h. To the reaction mixture was added MeOH (5 mL). The solution was stirred for 10 min, then the mixture was filtered through a short pad of Celite and concentrated. The residue was dissolved in DCM (10 mL), filtered and concentrated to give a colorless oil. Chromatography (MeOH/DCM, 1:10) gave 0.032 g (82%) of a clear oil. $[\alpha]_D^{25} -9.17$ (c 1.45, CHCl₃); IR (thin film) 2953, 1719, 1281, 1033 cm⁻¹; ¹H NMR (CDCl₃) δ 1.62 (s, 3H), 1.74 (m, 2H), 1.98 (m, 1H), 2.14 (m, 1H), 2.25 (s, 3H), 2.41 (td, $J = 2.0$ Hz, $J = 11.2$ Hz, 1H), 2.72 (dd, $J = 6.8$ Hz, $J = 15.2$ Hz, 1H), 3.35 (d, $J = 10.8$ Hz, 3H), 3.72 (d, $J = 10.8$ Hz, 1H), 3.78 (d, $J = 10.8$ Hz, 3H), 5.39 (dp, $J = 6.0$ Hz, $J = 12.4$ Hz, $J = 33.6$ Hz, 1H), 7.42 (m, 2H), 7.53 (m, 1H), 8.04 (m, 2H); ¹³C NMR (CDCl₃) δ 24.1, 27.8, 35.2, 36.6, 36.9, 49.9, 50.7, 51.0, 52.7, 64.1, 65.3, 68.8, 128.2, 129.7, 130.6, 132.7, 166.2; ³¹P NMR (CDCl₃) δ 21.2; HRMS calcd for C₁₈H₂₇NO₅P (M+H) 368.1627, found 368.1628.



Hydrochloric acid salt of methyl (1R, 2R, 3S, 5S)-(-)-3-(benzoyloxy)-1,8-dimethyl-8-azabicyclo[3.2.1]octane-2-dimethylphosphonate (431). In a 25-mL round bottom flask equipped with a magnetic stir bar, rubber septum and argon inlet were placed C-2 phosphonate cocaine analog **430** (0.015 g, 0.041 mol) and 6 mL ether. The mixture was cooled to 0 °C, and then a solution of 1 M HCl solution (0.160 mL, 0.164 mmol, 1 M HCl solution in Et₂O) was added into reaction dropwise. After addition, the reaction mixture maintained at 0 °C for 5 min. A white precipitate was formed at the bottom of the flask, and the upper clear solution was removed by using a long needle syringe. The obtained residue solids were washed with dry ether (5 mL × 2), and then dried under vacuum. Finally, HCl salt of C-2 phosphonate cocaine **431** (0.014 g) 82% was obtained as a white solid. Melting points are not available due to the highly hydroscopic nature of this phosphonate HCl salt. $[\alpha]_D^{25} -21.8$ (*c* 0.5, MeOH); IR (thin film) 3353, 2932, 1718, 1280 cm⁻¹; ¹H NMR (CDCl₃) δ 1.56 (s, 3H), 2.04 (m, 2H), 2.21 (m, 1H), 2.35 (m, 3H), 2.69 (s, 3H), 3.27 (dd, *J* = 6.4 Hz, *J* = 20.0 Hz, 1H), 3.52 (d, *J* = 11.2 Hz, 3H), 3.57 (d, *J* = 11.2 Hz, 3H), 3.90 (s, 1H), 5.38 (dp, *J* = 5.2 Hz, *J* = 11.2 Hz, *J* = 40.0 Hz, 1H), 7.32 (m, 2H), 7.46 (m, 1H), 7.88 (d, *J* = 7.2 Hz, 2H); ¹³C NMR (CDCl₃) δ 18.5, 21.4, 23.3, 24.8, 34.1, 35.1, 36.3, 44.0, 51.7, 52.1, 59.1, 66.18, 66.23,

126.9, 128.4, 129.5, 133.5, 166.0; ^{31}P NMR (CDCl_3) δ 13.5; HRMS calcd for

$\text{C}_{18}\text{H}_{27}\text{ClNO}_5\text{P}$ (M) 403.1315, found 403.1318.

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