Organocatalytic asymmetric mannich, formal [4+1] and [4+2] annulation reactions

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**ORGANOCATALYTIC ASYMMETRIC MANNICH, FORMAL
[4+1] AND [4+2] ANNULATION REACTIONS**

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Abstract

In this doctoral thesis, the research work that was carried out during the last four years will be divided into 5 chapters. Firstly, an introduction to the field of organocatalysis will be described in chapter 1. This will be followed by the first example of an organocatalytic asymmetric Mannich reaction of α -isothiocyanamide with tosyl imines. This methodology leads to the facile synthesis of protected α , β -diamino acid derivatives with excellent diastereo- and enantioselectivities. A simple quinine derivative was proven to be an efficient catalyst to promote this reaction, and only low catalyst loading (2.5 mmol%) was required. A wide substrate scope, involving aromatic and aliphatic aldehydes derived imines, was well tolerated.

Isoxazoline *N*-oxides are intriguing synthetic targets as they can be readily converted into highly functionalized γ -hydroxy- α -amino acids or γ -amino- α -hydroxy acids. In chapter 3, a novel methodology for the preparation of optically active *cis*-isoxazoline *N*-oxides developed *via* a formal [4+1] annulation reaction of α -Iodoaldehydes with 2-nitroacrylates, in the presence of (*S*)-diphenyl trimethylsilyl ether pyrrolidine will be discussed. Additionally, a concise synthesis of chiral densely functionalized α -amino lactone from the isoxazoline *N*-oxide product will be demonstrated.

In chapter 4, a new [4+2] annulation reaction of vinyl ketones with *N*-sulfonyl-1-aza-1, 3-dienes, using PPh_3 as catalyst, will be presented. Phenol additives were found to improve reaction rates and diastereoselectivities. This protocol established a practical process to the preparation of highly substituted

tetrahydropyridines, in good to excellent yields and diastereoselectivities, with broad substrates scope.

Lastly, in chapter 5, the asymmetric version of this [4+2] annulation reaction was realized by chiral phosphines derived from amino acids. Good yields, moderate to good diastereo- and enantioselectivities were obtained. In addition, benzensulfonamide was proven to be effective in improving enantioselectivity.

Appendix

Ac	Acetyl
Ar	Aryl
Bn	Benzyl
Boc	<i>t</i> -Butyloxycarbonyl
Bs	Benzensulfonyl
Bu	Butyl
Bz	Benzoyl
Cat.	Catalyst
DABCO	1, 4-Diazabicyclo[2.2.2]octane
DCM	Dichloromethane
dr	Diastereomeric ratio
DIPEA	<i>N</i> -Ethyl- <i>N,N</i> -diisopropylamine
DMAP	4-Dimethylaminopyridine
Ee	Enantiomeric excess
Eq.	Equivalent
HPLC	High performance liquid chromatography
IPA	<i>iso</i> -Propyl alcohol
<i>J</i>	NMR coupling constant/Hz
NMR	Nuclear magnetic resonance
NOE	Nuclear overhauser effect

PG	Protecting group
Ph	Phenyl
PTC	Phase transfer catalyst
rt	Room temperature
SOMO	Singly occupied molecular orbital
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMS	Trimethyl silyl
TBS	<i>tert</i> -Butyl dimethyl silyl
TBDPS	<i>tert</i> -Butyl diphenyl silyl
Ts	Tosyl

Introduction

1.1 Asymmetric Organocatalysis

Enzymes are highly efficient and enantioselective proteins that are widely used in industrial applications, of those known, approximately half of them do not contain any metal in their active site. The concept of asymmetric organocatalysis, which makes use of small organic molecules to catalyze reactions, stems from natural enzyme catalysis. Small organic molecules were first found to catalyze asymmetric reactions in 1912, when *Bredig* and *Fiske* observed the catalytic action of cinchona alkaloids in the asymmetric synthesis of cyanohydrins.¹ In the early of 1960s, *Pracejus* reported the cinchona alkaloid catalyzed asymmetric ester synthesis from alcohols and ketenes.²

Scheme 1.1 Cinchona alkaloid catalyzed asymmetric ester synthesis.

Subsequently, in the 1970s and 1980s, cinchona alkaloids were intensively investigated as chiral catalysts in Michael reactions,³ epoxidations⁴ and [2+2] cycloaddition.⁵

In the 1970s, the highly asymmetric intramolecular aldol reaction catalyzed by the simple amino acid *L*-proline, which was named as *Hajos-Parrish-Eder-Sauer-Wiechert* reaction due its founders, stimulated the interest of numerous chemists

towards organocatalysis.⁶

Scheme 1.2 The *Hajos-Parrish-Eder-Sauer-Wiechert* reaction.

Following that seminal report, *Fiaud* and co-workers reported the first example of an asymmetric alkylation reactions catalyzed by a chiral phase transfer catalyst (catalyst **3**), albeit with low asymmetric induction.⁷

Scheme 1.3 Chiral phase transfer catalyzed asymmetric alkylation.

The breakthrough of chiral phase transfer catalysis, was later on achieved by the Merck group in 1984.⁸ In the presence of quaternarized derivatives of cinchonine and

Scheme 1.4 Breakthrough of chiral phase transfer catalysis.

cinchonidine, highly enantioselective alkylations of indanone derivative were realized. Subsequently, O'Donnell and Maruoka respectively, made invaluable contributions to this field.⁹

The pioneering work of Zhang and co-workers introduced the use of chiral phosphines to catalyzed [3+2] cycloaddition between allenes and chalcones, and led to the development of nucleophilic phosphine in the following 10 years.¹⁰

Scheme 1.5 Chiral phosphine catalyzed [3+2] cycloaddition.

In 2000, the popularity of organocatalysis increase dramatically after List reported the first example of an asymmetric intermolecular aldol reaction of aldehydes, using simple natural amino acid, *L*-proline, as catalyst.¹¹ since then, based on the enamine platform, such as asymmetric Michael addition, Mannich reaction,¹² α -functionalization of carbonyl compounds, such as nitroso-aldol,¹³ amination,¹⁴ halogenations reactions¹⁵ and alkylations,¹⁶ as well as dienamine or trienamine motivated Diels-Alder reactions, have been developed.¹⁷

Scheme 1.6 *L*-proline catalyzed intermolecular aldol reaction

In the past decade, numerous catalysts that make use of the enamine mode of activation have been developed. Among them, the diarylpyrrolidine silyl ether, developed by Jørgenson and Hayashi, represents the most powerful catalyst for enamine catalysis.¹⁸

Scheme 1.7 Diarylpyrrolidine silyl ether catalyzed reactions

In 2000, MacMillan and co-workers developed the chiral imidazolidinone catalyzed Diels-Alder reaction, *via* a LUMO-lowering strategy by iminium formation. Subsequently, this concept was expanded to 1,3-dipolar cycloadditions, 1, 4-additions and domino reactions.¹⁹

Scheme 1.8 Chiral imidazolidinone catalyzed Diels-Alder cycloaddition.

Enamine catalysis and iminium catalysis, which were developed by List, Barbas and MacMillan, have proven to be useful in numerous methodologies. Interestingly, in

2007, MacMillan explored a novel activation mode called the singly occupied molecular orbital (SOMO), which involves the oxidation of a 4- π -electron enamine to a 3- π -electron radical cation. This concept has enabled a number of enantioselective α -functionalization of carbonyl compounds, such as allylations,²⁰ enolations,²¹ arylations,²² trifluomethylations,²³ vinylations²⁴ and polyenecyclizations.²⁵

Scheme 1.9 SOMO catalysis.

The milestone achievement of thiourea bifunctional catalysts was disclosed by Takemoto and co-workers in 2003, which paved the way for bifunctional catalysis.²⁶

Scheme 1.10 Milestone achievement of bifunctional catalysis.

Around the same time, Akiyama and Terada independently reported the use of BINOL derived phosphoric acids as chiral Brønsted acid, and hence developed a new class of organocatalysis. This class of catalyst is especially effective towards activating imines, and imine-like substrate.²⁷

Scheme 1.11 Chiral phosphoric acid catalyzed Mannich reaction.

1.2 Organocatalytic Asymmetric Synthesis of α , β -Diamino Acid

Derivatives

Optically active α , β -diamino acids and their ester or amide derivatives are intriguing synthetic targets that can be frequently found in a number of natural products and biologically active compounds. As a result, these unnatural amino acids have attracted extensive attention from organic chemists and biochemists throughout the years. Organocatalysis has emerged as a powerful tool for the synthesis of chiral amino acid derivatives since the year 2000, when List and co-workers pioneered the three component asymmetric Mannich reaction between ketones, *p*-anisidine and

different aldehydes, with the use of *L*-proline, as catalyst.²⁸

Scheme 1.12 First reported three component asymmetric Mannich reaction.

After that study, tremendous efforts have been devoted to this field, which has led to the development of many efficient methodologies for the synthesis of chiral amino acids, especially α , β -diamino acids.

1.2.1 Mannich Reactions

To date, the Mannich reaction of glycine ester Schiff base with imines considered to be the most successful strategy for the synthesis of α , β -diamino acids, due to the ease of access of the starting material from naturally occurring glycine, operational simplicity and easy deprotection.

Scheme 1.13 Mannich reaction of glycinate ester Schiff bases with imines

In 2004, Maruoka and co-workers reported the asymmetric synthesis of α , β -diamino acids from *tert*-butyl glycinate ester Schiff base and *N*-aryl α -imino ester using a chiral *N*-spiro quaternary ammonium bromide as the catalyst and aqueous NaOH as base. This methodology could deliver the product in 88% yield, with good diastereoselectivity and enantioselectivity (*syn/anti* = 82:18, 92% *ee*).²⁹

Scheme 1.14 Chiral PTC catalyzed Mannich reaction of glycinate ester Schiff bases with imines

A year later, Shibasaki and co-workers developed a more general method, in which *N*-Boc imine was chosen as the imine participant, thus avoiding the need to carry out a PMP deprotection, which is suffered by low yield and toxic reagent. In this reaction system, tartrate-derived two-center diammonium salt catalysts were proven to be effective for stereocontrol. In general, near quantitative chemical yields, excellent diastereoselectivities and good enantioselectivities could be obtained.³⁰

Scheme 1.15 Mannich reaction of glycinate ester Schiff bases with *N*-Boc imines

In 2008, Ooi *et al.* reported a new bifunctional chiral phase transfer catalyst based on a chiral quaternary tetraamino-phosphonium salt possessing a carboxylate counter anion. Racemic azalactones derived from amino acids could react with *N*-2,6-dimethylbenzenesulfonyl imines give protected α , β -diamino acids with an α -tetrasubstituted carbon stereocenter, in excellent yields (91-99%) and enantioselectivities (90-96% *ee*), and moderate to good *syn*-diastereoselectivities

(70:30 to 92:8).³¹

Scheme 1.16 Chiral PTC catalyzed Mannich reaction of azalactone with imines

The fluorenone imine of a glycine ester was demonstrated as an excellent substrate for the direct Mannich reaction with *N*-Boc imines, due to its higher reactivity compared to the corresponding benzophenone imine. This remarkable contribution was made by Kobayashi and co-workers in 2008.³² In the presence of 10 mol% of chiral guanidine **15**, aromatic, heteroaromatic and aliphatic *N*-Boc imines undergo direct Mannich reactions smoothly to afford optically active α , β -diamino acids in high yields, with excellent diastereoselectivities and enantioselectivities.

Scheme 1.17 Chiral guanidine catalyzed Mannich reaction

1.2.2 Aza-Henry Reactions

The Mannich reaction of nitro acetic acid esters with imines is also called the “aza-Henry reaction”, as it is considered to be an alternative approach to the synthesis

of α , β -diamino acids. In parallel to the amino acid ester Schiff base approach, this strategy has experienced alarming progress. Both *syn*- and *anti*- diastereoisomers can be obtained in a catalytic asymmetric manner *via* an organocatalytic platform.

Scheme 1.18 Synthesis of α , β -diamino acid *via* aza-Henry reaction

In 2007, Johnston and co-workers reported a straightforward synthesis of epimerizable non-natural α , β -diamino acids from nitro acetic acid esters, by using an unsymmetrical Bis(AMidine) triflate salt as an effective bifunctional catalyst. They demonstrated that highly *anti*-selective addition of unsubstituted nitroacetates to *N*-Boc aryl aldehyde was realized with 5 mol% catalyst loading. *In situ* reduction of the nitro group with NaBH_4 combined with CoCl_2 gave the corresponding *anti*-, β -diamino acid derivatives in high diastereo- (*syn:anti* = 17:83 to 8:92) and enantioselectivities (87-95% *ee*).³³

Scheme 1.19 Chiral Brønsted acid catalyzed aza-Henry reaction.

The same group later reported a diastereo- and enantioselective synthesis of

α -substituted *syn*- α , β -diamino acids, by using α -substituted *tert*-butyl nitro acetate as the nucleophile, in the presence of a modified catalyst. Simple introduction of a methyl group at α -position of the nitro acetic acid ester, led to diminished reaction conversion. Fortunately, this challenge was overcome *via* installment of a methoxy group on the catalyst. The reaction time was significantly shortened from several days to within 48 hours, and improved enantioselectivity was observed. Replacing the use of *tert*-butyl nitro acetate with the more sterically hindered 2, 6-diisopropylphenyl nitro acetate also saw an improvement of diastereoselectivity from 2:1 to 10:1.³⁴

Scheme 1.20 Chiral Brønsted acid catalyzed aza-Henry reaction.

More recently, Chen and co-workers developed a chiral 1,2-diphenylethylenediamine derived thiourea bifunctional catalyst catalyzed aza-Henry reaction between α -substituted methyl nitro acetates and *N*-Boc imines. Good to excellent diastereoselectivities (4:1-17:1), high enantioselectivities (91-96%) and moderate to good yields (38-86%) could be obtained under optimized reaction conditions.³⁵

Scheme 1.21 Chiral thiourea catalyst catalyzed aza-Henry reaction.

In 2008, the group of Rueping reported a direct chiral phosphoric acid catalyzed aza-Henry reaction between α -imino ester and nitro alkanes as a complementary route to α , β -diamino acid ester derivatives. The direct activation of nitro compound with a chiral Brønsted acid, was realized by an octahydro-BINOL derived phosphoric acid. This conceptually new activation model enabled reliable a synthetic approach to α , β -diamino acids on account of its good catalytic performance.³⁶

Scheme 1.22 Chiral Brønsted acid catalyzed aza-Henry reaction

In the same year 2008, Ooi and co-workers reported a chiral betaine, which relies on hydrogen bonding and ionic interaction between the nucleophile and catalyst to achieve greater stereocontrol. This newly developed chiral betaine catalyst was

proven to be effective towards promoting the aza-Henry reaction between nitro acetates and *N*-Boc imines, in almost quantitative chemical yields and excellent enantioselectivities, with only 1 mol% catalyst loading. This work not only explored a new method for the synthesis of α , β -diamino acid ester derivatives, but also paved the way for further development of this novel catalytic platform.³⁷

Scheme 1.23 Chiral betaine catalyzed aza-Henry reaction

1.3 Organocatalytic Asymmetric Michael Addition Initiated Cyclization Reactions

After List reported the application of the simple natural amino acid, *L*-proline, towards catalyzing intermolecular aldol reactions, chiral amines were demonstrated to be synthetic useful for asymmetric C-C bond formations. Subsequently, Barbas and co-workers reported a concise synthetic route to Wieland-Miescher ketones (WMK), which was believed to undergo *via* an iminium-enamine pathway, with *L*-proline as the catalyst.³⁸

Scheme 1.24 Proline-catalyzed asymmetric Robinson annulation

Chiral amines that trigger domino reactions have attracted attentions from worldwide, and this has led to the establishment of various methodologies for the construction of invaluable ring systems. Among the protocols documented, the more predominant examples are Michael addition triggered cascade processes, which are either initiated by iminium or enamine activation

1.3.1 Iminium initiated cascade

One of the most important cascades is that initiated by intermolecular Michael addition of a nucleophile to an iminium intermediate. The enamine intermediate formed is then trapped by an electrophile.

Scheme 1.25 Platform of iminium-enamine activation

In 2004, Jørgensen developed a straightforward route to the synthesis of optically active cyclohexanones with up to four stereocenters. This cascade began from iminium activation of α , β -unsaturated enone by the imidazolidine catalyst. After conjugate addition of the β -ketoester to the iminium intermediate, the desired cyclohexanone was obtained by an intramolecular aldol reaction.³⁹

Scheme 1.26 Asymmetric synthesis of cyclohexanone

The intramolecular tandem process involving an imine-enamine activation pathway, was discovered by List. This cascade reaction was initiated by an organocatalytic hydrogenation of the iminium intermediate by Hantzsch ester, followed by an intramolecular Michael addition to form five-membered or six-membered carbocycle in good chemical yields, enantiomeric excess and diastereomeric ratios.⁴⁰

Scheme 1.27 Reductive Michael addition

Another landmark iminium-enamine reaction cascade was explored for the synthesis of chiral thiochromenes in 2006. Wang and co-workers reported an organocatalytic enantioselective Michael-aldol reaction, promoted by a pyrrolidine silyl ether catalyst. This methodology served as an efficient method for the preparation of synthetically useful and optically active thiochromenes, in good to excellent enantioselectivities. A broad range of enals and 2-mercaptobenzaldehydes could participate in this cascade process.⁴¹

Scheme 1.28 Michael-aldol condensation cascade

Subsequently, synthesis of chiral benzopyrans and hydroquinolines were achieved based on the above strategy by the groups of Arvidsson and Wang, respectively.⁴²

Hexahydrofuro[3,4-c]furanes are biologically intriguing compounds, and they can be readily assembled in a single operation by the reaction of a dihydroxyacetone dimer with α , β -unsaturated aldehydes. In 2009, Vicario and co-workers reported an enantioselective organocatalytic domino oxa-Michael/aldol/Hemiacetalization process. Hexahydrofuro[3,4-c]furanes were synthesized in good diastereomeric ratios and enantiomeric excess, in the presence of a chiral pyrrolidine silyl ether as catalyst.⁴³

Scheme 1.29 oxa-Michael/aldol/Hemiacetalization cascade

Generally, the substrate scope of the iminium-enamine cascade was limited to enals. In 2010, Wang demonstrated that alkenals could also proceed in this process to produce 4*H*-chromenes in high enantioselectivities, with chiral amine catalysis.⁴⁴

Scheme 1.30 Iminium-Allenamine cascade

Iminium initiated reactions can be further expanded to other cascade designs. In 2005, MacMillan developed 2-carboxylic acid dihydroindole catalyzed cyclopropanation of α, β -unsaturated aldehydes, by employing a sulfur ylide as the nucleophile. The carboxylate group on the catalyst was believed to be crucial for the enantiocontrol due to electrostatic interaction between the carboxylate and sulfur ylide and thereby directing nucleophilic attack to the *Re* face of the activated olefins.⁴⁵

Scheme 1.31 Organocatalytic asymmetric cyclopropanation

Cyclopropanes are biologically relevant building blocks frequently occurring in numerous natural products and pharmaceuticals. The synthesis of such kind of 3-membered ring systems has attracted intensive attention in recent years. In 2006, the group of Córdova and Wang, independently developed a catalytic asymmetric cyclopropanation reaction, by using bromomanonates and enals. Good to excellent chemical yields, high diastereo- and enantioselectivities could be obtained.⁴⁶

Scheme 1.32 Organocatalytic asymmetric cyclization

This Michael/alkylation strategy could also be expanded to cyclopentane synthesis. Enders and co-workers realized a straightforward route to cyclic γ -amino acid (*E*)-5-iodo-1-nitropent-1-ene and aldehydes.⁴⁷

Scheme 1.33 Organocatalytic asymmetric cyclization

1.3.2 Enamine initiated cascade

The enamine-iminium cascade represents another important example of merging these two activation models in one operation. A large number of carbon-, or heterocycles were efficiently synthesized with high levels of stereocontrol, by chiral amine catalysis. Typically, the reaction is initiated by enamine formation, which is subsequently followed by nucleophilic addition.

The use of this strategy goes back to 2003, when the group of Ohsawa disclosed a cascade reaction between 9-toxyl-3,4-dihydro- β -carboline and 3-buten-2-one, catalyzed by *L*-proline. A straightforward construction of 3, 4, 6, 7, 12,

12b-Hexahydro-1*H*-indolo[2,3-*a*]quinolizin-2-one was realized in a single step. The formation of this molecular complex was believed to take place through an enamine initiated Mannich reaction, which was followed by an iminium promoted intramolecular Michael addition. The target compound was obtained in 76% yield with 92% *ee*, albeit with a long reaction time of 7 days.⁴⁸

Scheme 1.34 Enamine-Iminium cascade

L-proline catalyzed aminooxylation of aldehydes was discovered by Zhong, MacMillan and Haiyashi in 2003, independently.⁴⁹ This reaction is initiated by enamine followed by nucleophilic addition to nitroso compounds. In 2004, Yamamoto *et al.* combined an α -aminooxylation and aza-Michael addition in one operation, by using cyclic enones, thereby establishing an elegant reaction cascade. A *L*-proline

Scheme 1.35 α -aminooxylation and aza-Michael addition cascade

based tetrazole catalyst was proved to be effective in generating aza oxa

bicycloketones in moderate to good yields and excellent enantiomeric excess.⁵⁰

Córdova and co-workers reported a similar cascade sequence in 2005. The first one-pot three components direct catalytic enantioselective aza-Diels-Alder reaction was realized, by employing aqueous formaldehyde, *para*-anisidine and cyclic enones, with *L*-proline as the catalyst. Under the optimized reaction conditions, this protocol could efficiently construct protected azabicyclic amino acids with excellent *exo*- and enantioselectivities.⁵¹

Scheme 1.36 *L*-proline catalyzed aza-Diels-Alder reaction

A landmark domino reaction was documented by Enders and co-workers in 2006. Enolizable aldehydes, α , β -unsaturated aldehydes and nitroolefins, were directly assembled through an enamine-iminium-enamine triple activation pathway. Optically pure *tetra*-substituted cyclohexene carbaldehydes could be synthesized in one simple operation with high chemo-, diastereo- and enantioselectivities.⁵²

Scheme 1.37 Enamine-iminium-enamine triple cascade

In 2007, Haiyashi and co-workers reported a highly diastereo- and enantioselective tandem Michael/Henry reaction, which was catalyzed by a readily available diphenylprolinol silyl ether. This tandem methodology established a practical synthetic route to nitro-cyclohexane derivatives containing four stereogenic centers, with up to 99% *ee*.⁵³

Scheme 1.38 Tandem Michael/Henry reaction.

Most of the cascade reactions were catalyzed by chiral secondary amines, and the substrates were limited to enals. In 2009, Melchiorre and his colleagues demonstrated that chiral primary amine catalysis could achieve stereochemically and structurally complex compounds through enamine-iminium cascade catalysis with the use of

acyclic enones were employed. Various multisubstituted cyclohexanes were prepared through this catalytic platform, with high stereocontrol (3:1->19:1 dr, 88-99% *ee*).⁵⁴

Scheme 1.39 Primary amine catalyzed double Michael addition

In the last three years, our group independently developed several domino reactions catalyzed by cinchona alkaloid derived primary amine catalyst **26**. Nitro

85-94% yield, up to 99:1 dr, up to >99% *ee*

Scheme 1.40 Primary amine catalyzed Michael/Henry cascade

81-92% yield, 95:5->99:1 dr, 94-97% *ee*

Scheme 1.41 Primary amine catalyzed Michael/Michael cascade

substituted five-membered and six-membered carbocycles have been constructed by Michael/Henry, or Michael/Michael cascades in an asymmetric manner.⁵⁵

1.4 Phosphine catalyzed cyclization reactions

Trivalent phosphines are typical Lewis base that, have proven to be effective in a number of nucleophilic addition initiated tandem processes. Among them, the Rauhut-Currier reaction, [3+2] cycloaddition of allenes with electron deficient alkenes or imines, and [4+2] annulations of 2-methylene-but-3-enoate with imines or electron deficient alkenes represent the most synthetically useful examples for ring formation.

1.4.1 Rauhut-Currier Reaction

The Rauhut-Currier reaction was discovered half a century ago,⁵⁶ in which electron-deficient alkenes, acrylonitrile and ethyl acrylate underwent dimerization in the presence of a phosphine catalyst. This reaction was triggered by the nucleophilic addition of the phosphine catalyst to an alkene, thereby generating zwitterionic

Scheme 1.42 Phosphine catalyzed Rauhut-Currier reaction

intermediate, which subsequently undergoes a Michael addition with another electron-deficient alkene.

The Rauhut-Currier reaction did not attract enough attention until in recent years. In 1999, Erguden and Moore exploited an intramolecular tandem reaction for the concise synthesis of the Waihoensene ring system, in 92% yield. This study is considered to be the first example of an intramolecular Rauhut-Currier reaction.⁵⁷

Scheme 1.43 Intramolecular Rauhut-Currier reaction

Later on, the group of Roush and Krische independently developed an intramolecular Rauhut-Currier reaction in detail, by using tethering coupling partners with different electrophilicity. Both groups demonstrated that trialkylphosphine was an efficient catalyst to promote cycloisomerization of symmetrical and unsymmetrical bis(enones), to generate five- and six-membered ring systems with high efficiency.⁵⁸

Scheme 1.44 Intramolecular Rauhut-Currier reaction

The asymmetric version of the Rauhut-Currier reaction was realized in 2007 by the group of Miller. They found that thio anion generated from cysteine, by treatment

of *t*-BuOK, could promote the intramolecular Rauhut-Currier reaction in an asymmetric manner, though only 32% *ee* was induced. Intriguingly, H₂O was found to be effective in improving enantioselectivity. When 20 equivalents of H₂O were added, the enantioselectivity significantly increased to 81% *ee*. After further optimization of reaction conditions, up to 95% *ee* could be obtained. The catalyst loading could be lowered to 20 mol% catalyst to generate the desired product in 75% yield with 92% *ee*.⁵⁹

Scheme 1.45 Enantioselective Rauhut-Currier reaction

1.4.2 [3+2] cycloaddition

The [3+2] annulation reaction has emerged as a powerful tool for the construction of five-membered carbocycles or heterocycles. A typical reaction involves phosphine catalyzed cycloaddition of allenes with electron deficient alkenes or alkynes. This

reaction has been extensively investigated in both an asymmetric and non-asymmetric manner since Lu and co-workers developed the [3+2] cycloaddition of 2,3-butadienoates or 2-butyneates with electron-deficient olefins, such as diethyl fumarate and diethyl maleate.⁶⁰

Scheme 1.46 Phosphine catalyzed [3+2] cycloaddition

In 1996, Vedejs first documented their achievement in chiral phosphine catalyzed enantioselective acylations.⁶¹ A year later, Zhang pioneered the asymmetric version of [3+2] cycloadditions of allenes with electron-deficient olefins, by using novel chiral 2,5-dialkyl-7-phenyl-7-phosphabicyclo[2.2.1]heptanes as catalysts.⁶²

Scheme 1.47 Chiral phosphine catalyzed [3+2] cycloaddition

After Zhang's seminal work in 1997, intensive attention has been attracted to the field of developing new chiral phosphine catalysts for [3+2] cycloadditions or other

related reactions. However, chemists worldwide did not achieve significant progress until recent years. In 2007, Miller and co-workers developed a simple natural amino acid, *D*-serine, derived chiral phosphine catalyst, which could efficiently catalyzed [3+2] additions of allenic ester with enones, thereby leading to the construction of spirocycles in high yields and good to excellent enantioselectivities.⁶³

Scheme 1.48 *D*-Serine derived phosphine catalyzed [3+2] cycloaddition

Subsequently, the group of Marinetti developed a novel 2-phospha[3]ferrocenophanes with planar chirality, and showed its efficiency as an enantioselective nucleophilic organocatalyt in [3+2] cycloadditions. This catalyst was stable to air, could be easily handled, and thus possessed its high practical utility.⁶⁴

Scheme 1.49 Chiral phosphine with planar chirality catalyzed [3+2] cycloaddition

The breakthrough of asymmetric [3+2] cycloaddition of allenes with imines was achieved by Jacobson and co-workers in 2008.⁶⁵ They successfully merged nucleophilic catalysis with hydrogen-bonding catalysis together, by synthesizing a phosphinothiourea catalyst from a cyclohexanyl backbone. They observed that

protection groups of imines had a significant influence on the enantioinduction, and the diphenylphosphinoyl imine was proved to be the best choice in terms of enantioselectivity. After a systematic investigation of catalysts, up to 98% *ee* could be obtained with the Alanine derived catalyst. In addition, the use of 0.2 equivalents of H₂O was found to accelerate this process, which is consistent with the findings by Yu and co-workers.⁶⁶

Scheme 1.50 Phosphinothiourea catalysis of imine-allene [3+2] cycloaddition

The interest of chiral amino acids or amino alcohols derived phosphine attracted continuous effort, and led to some remarkable works in the last two years. In 2010, Zhao and his colleagues discovered that *L*-isoleucine derived phosphines could efficiently promote [3+2] cycloadditions between allenates and dual activated olefins, with high yields and good to excellent diastereo- and enantioselectivities. The

Scheme 1.51 [3+2] cycloaddition of allenates and dual activated olefins

proposed transition state was based on Miller's work, in which hydrogen-bonding

leads to the formation of a six-membered ring configuration.⁶⁷ Dipeptide derived phosphines were found to be an alternative method for such transformations that are similar to those mentioned above. Earlier this year, Lu demonstrated that chiral phosphines based on dipeptide backbones could offer a new solution for phosphine triggered reactions. *D*-Thr-*L*-*tert*-Leu based phosphine catalyzed α -substituted acrylates participated in [3+2] cycloadditions with allenates efficiently to afford functionalized cyclopentenes containing quaternary stereocenters in excellent yields, and regio-, and enantioselectivities.⁶⁸

Scheme 1.52 Dipeptide derived phosphine catalyzed [3+2] cycloaddition of allenates and substituted acrylates

1.4.3 [4+2] annulations

The original [3+2] cycloaddition of allenes relied on exclusive α -addition of a zwitterionic intermediate to an imine or electron-deficient olefins by phosphine catalysts. In 2003, Kwon and her colleagues introduced methyl group at the 2-position of allenate, thereby suppressing α -addition, and leading to a novel 1,4-dipole synthon, which resulted in the development of a [4+2] annulations reaction for the construction of six-membered heterocycles and carbocycles. This protocol showed that

Scheme 1.53 [4+2] annulations of 2-methylene allenoate with imines

it possessed high potential for the preparation of multifunctionalized tetrahydropyridines. With tosyl imines, the corresponding products could be obtained quantitatively in excellent diastereoselectivities.⁶⁹

Later on, the same group further extended this concept to the synthesis of cyclohexenes derivatives and it was found that the reaction regioselectivity could be readily adjusted by changing the nucleophilicity of the catalyst.⁷⁰

Scheme 1.54 Synthesis of cyclohexenes by [4+2] annulations of 2-methylene allenoate with activated alkenes

The asymmetric version of [4+2] annulations of 2-methylene allenoate with imines was disclosed by Fu and co-workers in 2005. Intensive screening of chiral phosphines indicated that binaphthyl-based C_2 -symmetric phosphines delivered the best enantioselectivity.⁷¹

Scheme 1.55 Asymmetric [4+2] cycloaddition of 2-methylene allenoates with imines

In 2010, Tong and co-workers developed an elegant [4+2] annulation reaction of terminal alkynes with aza-dienes and oxo-dienes. Highly functionalized 2*H*-dihydropyridines and dihydropyrans were efficiently constructed, in the presence of PPh_3 as the catalyst. It was proposed that the reaction took place *via* a stepwise manner.⁷²

Scheme 1.56 [4+2] Annulations of terminal alkynes and hetero-dienes

1.5 Reference

1. G. Bredig, P. S. Fiske, *Eiochem. Z.* **1912**, 7, 46.
2. a) H. Pracejus, *Justus Liebigs Ann. Chem.*, **1960**, 23, 634; b) H. Pracejus, H. Matje, *J. Prakt. Chem.* **1964**, 195, 296; c) H. Pracejus, G. Kohl, *Justus Liebigs Ann. Chem.* **1969**, 1, 722.
3. H. Wynberg, R. Helder, *Tetrahedron Lett.* **1975**, 4057.
4. R. Helder, J. C. Hummelen, R. W. P. M. Laane, J. S. Wiering, H. Wynberg, *Tetrahedron Lett.* **1976**, 1831.
5. H. Wynberg, E. G. J. Staring, *J. Chem. Soc. Chem. Commun.* **1984**, 1181.
6. a) Z. G. Hajos, D. R. J. Parrish, *J. Org. Chem.*, **1974**, 39, 1615; b) U. Eder, G. Sauer and R. Wiechert, *Angew. Chem., Int. Ed.* **1971**, 10, 496.
7. J.-C. Fiaud, *Tetrahedron Lett.* **1975**, 3495.
8. U. Dolling, P. Davis, E. J. J. Grabowski, *J. Am. Chem. Soc.* **1984**, 106, 446.
9. a) M. J. O'Donnell, *Acc. Chem. Res.* **2004**, 37, 506; b) T. Ooi, K. Maruoka, *Acc. Chem. Res.* **2004**, 37, 526.
10. G. Zhu, Z. Chen, Q. Jiang, D. Xiao, P. Cao, X. Zhang, *J. Am. Chem. Soc.* **1997**, 119, 3836.
11. B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, 122, 2395.
12. B. List, *J. Am. Chem. Soc.* **2000**, 122, 9336.
13. a) G. Zhong, *Angew. Chem. Int. Ed.* **2003**, 42, 4247; b) S. P. Brown, M. P. Brochu, C. J. Sinz, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2003**, 125, 10808; c) Y. Hayashi, J. Yamaguchi, K. Hibino, M. Shoji, *Tetrahedron Lett.* **2003**, 44, 8293.

14. B. List, *J. Am. Chem. Soc.* **2002**, *124*, 5656.
15. M. P. Brochu, S. P. Brown, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2004**, *126*, 4108.
16. N. Vignola, B. List, *J. Am. Chem. Soc.* **2004**, *126*, 450.
17. a) J. Li, T. Kang, S. Zhou, R. Li, L. Wu, Y. Chen. *Angew. Chem. Int. Ed.* **2010**, *49*, 6418; b) Z. Jia, H. Jiang, J. Li, B. Gschwend, Q. Li, X. Yin, J. Grouleff, Y. Chen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2011**, *133*, 5053.
18. a) M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2005**, *44*, 794; b) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem. Int. Ed.* **2005**, *44*, 4212.
19. a) K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243; b) W. S. J. Jen, J. J. M. Wiener, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 9874.
20. T. D. Beeson, A. Mastracchio, J. Hong, K. Ashton, D. W. C. MacMillan, *Science* **2007**, *316*, 582.
21. H. Jang, J. Hong, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2007**, *129*, 7004.
22. A. E. Allen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2011**, *133*, 4260.
23. D. A. Nagib, M. E. Scott, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 10875.
24. H. Kim, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2008**, *130*, 398.
25. S. Rendler, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2010**, *132*, 5027.
26. T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672.

27. a) T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem. Int. Ed.* **2004**, 43, 1566; b) D. Uraguchi, M. Terada, *J. Am. Chem. Soc.* **2004**, 126, 5356.
28. B. List, *J. Am. Chem. Soc.* **2000**, 122, 9336.
29. Ooi T, Kameda M, Fujii J, Maruoka K. *Org Lett.* **2004**, 6, 2397.
30. a) Okada A, Shibuguchi T, Ohshima T, Masu H, Yamaguchi K, Shibasaki M. *Angew. Chem. Int. Ed.*, **2005**, 44, 4564; b) Shibuguchi T, Mihara H, Kuramochi A, Kuramochi A, Ohshima T, Shibasaki M. *Chem. Asian J.* **2007**, 2, 794.
31. D. Uraguchi, Y. Ueki and T. Ooi, *J. Am. Chem. Soc.* **2008**, 130, 14088.
32. S. Kobayashi, R. Yazaki, K. Seki and Y. Yamashita, *Angew. Chem. Int. Ed.* **2008**, 47, 5613.
33. A. Singh, R. A. Yoder, B. Shen and J. N. Johnston, *J. Am. Chem. Soc.* **2007**, 129, 3466.
34. A. Singh and J. N. Johnston, *J. Am. Chem. Soc.* **2008**, 130, 5866
35. B. Han, Q. Liu, R. Li, X. Tian, X. Xiong, J. Deng, Y. Chen, *Chem. Eur. J.* **2008**, 14, 8094
36. M. Rueping and A. P. Antonchick, *Org. Lett.*, **2008**, 10, 1731.
37. D. Uraguchi, K. Koshimoto and T. Ooi, *J. Am. Chem. Soc.*, **2008**, 130, 10878.
38. T. Bui, C. F. Barbas III, *Tetrahedron Lett.* **2000**, 41, 6951.
39. N. Halland, P. S. Aburel, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2004**, 43, 1272.
40. J. W. Yang, M. T. H. Fonseca, B. List, *J. Am. Chem. Soc.* **2005**, 127, 15036
41. W. Wang, H. Li, J. Wang, L. Zu, *J. Am. Chem. Soc.* **2006**, 128, 10354.
42. a) T. Govender, L. Hojabri, F. M. Moghaddam, P. I. Arvidsson, *Tetrahedron:*

- Asymmetry* 17 **2006**, 1763; b) H. Li, J. Wang, H. Xie, L. Zu, W. Jiang, E. N. Duesler, W. Wang, *Org. Lett.* **2007**, 9, 965.
43. E. Reyes, G. Talavera, J. L. Vicario, D. Badía, L. Carrillo, *Angew. Chem. Int. Ed.* **2009**, 48, 5701.
44. X. Zhang, S. Zhang, W. Wang, *Angew. Chem. Int. Ed.* **2010**, 49, 1481.
45. R. K. Kunz, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, 125, 3240.
46. a) R. Rios, H. Sundén, J. Vesely, G. Zhao, P. Dziedzic, A. Córdova, *Adv. Synth. Catal.* **2007**, 349, 1028; b) H. Xie, L. Zu, H. Li, J. Wang, W. Wang, *J. Am. Chem. Soc.* **2007**, 129, 10886.
47. D. Enders, C. Wang, J. W. Bats, *Angew. Chem. Int. Ed.* **2008**, 47, 7539.
48. T. Itoh, M. Yokoya, K. Miyauchi, K. Magata, A. Ohsawa, *Org. Lett.* **2003**, 5, 4301.
49. a) G. Zhong, *Angew. Chem. Int. Ed.* **2003**, 42, 4247; b) S. P. Brown, M. P. Brochu, C. J. Sinz, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2003**, 125, 10808; c) Y. Hayashi, J. Yamaguchi, K. Hibino, M. Shoji, *Tetrahedron Lett.* **2003**, 44, 8293.
50. Y. Yamamoto, N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* **2004**, 126, 5962.
51. H. Sundén, I. Ibrahim, L. Eriksen, A. Córdova, *Angew. Chem. Int. Ed.* **2005**, 44, 4877.
52. D. Enders, M. R. M. Hüttl, C. Grondal, G. Raabe, *Nature* **2006**, 441, 861.
53. Y. Hayashi, T. Okano, S. Aratake, D. Hazelard, *Angew. Chem. Int. Ed.* **2007**, 46, 4922.
54. L. Wu, G. Bencivenni, M. Mancinelli, A. Mazzanti, G. Bartoli, P. Melchiorre,

Angew. Chem. Int. Ed. **2009**, *48*, 7196.

55. a) B. Tan, P. J. Chua, Y. Li, G. Zhong, *Org. Lett.* **2008**, *10*, 2437; b) B. Tan, Z. Shi, P. J. Chua, G. Zhong, *Org. Lett.* **2008**, *10*, 3425.

56. M. M. Rauhut, H. Currier, American Cyanamid Co., 1963, U.S. Patent 307499

57. J. K. Erguden, H. W. Moore, *Org. Lett.* **1999**, *1*, 375.

58. a) S. A. Frank, D. J. Mergott, W. R. Roush, *J. Am. Chem. Soc.* **2002**, *124*, 2404; b) L.-C. Wang, A. L. Luis, K. Agapiou, H. Jang, M. Krische, *J. Am. Chem. Soc.* **2002**, *124*, 2402.

59. C. E. Aroyan, S. J. Miller, *J. Am. Chem. Soc.* **2007**, *129*, 256.

60. C. Zhang, X. Lu, *J. Org. Chem.* **1995**, *60*, 2906.

61. E. Vedejs, O. Daugulis, S. T. Diver, *J. Org. Chem.* **1996**, *61*, 430.

62. G. Zhu, Z. Chen, Q. Jiang, D. Xiao, P. Cao, X. Zhang, *J. Am. Chem. Soc.* **1997**, *119*, 3836.

63. B. J. Cowen, S. J. Miller, *J. Am. Chem. Soc.* **2007**, *129*, 10988.

64. A. Voituriez, A. Panossian, N. Fleury-Brégeot, P. Retailleau, A. Marinetti, *J. Am. Chem. Soc.* **2008**, *130*, 14030.

65. Y. Fang, E. N. Jacobsen, *J. Am. Chem. Soc.* **2008**, *130*, 5660.

66. Y. Xia, Y. Liang, Y. Chen, M. Wang, L. Jiao, F. Huang, S. Liu, Y. Li, Z.-X. Yu, *J. Am. Chem. Soc.* **2007**, *129*, 3470.

67. H. Xiao, Z. Chai, C. Zheng, Y. Yang, W. Liu, J. Zhang, G. Zhao, *Angew. Chem. Int. Ed.* **2010**, *49*, 4467.

68. X. Han, Y. Wang, F. Zhong, Y. Lu, *J. Am. Chem. Soc.* **2011**, *133*, 1726.

69. X. Zhu, J. Lan, O. Kwon, *J. Am. Chem. Soc.* **2003**, *125*, 4717.
70. Y. S. Tran, O. Kwon, *J. Am. Chem. Soc.* **2007**, *129*, 12632.
71. R. P. Wurz, G. Fu, *J. Am. Chem. Soc.* **2005**, *127*, 12234.
72. a) H. Liu, L. Zhang, L. Wang, X. Tong, *Chem. Commun.* **2010**, 312; b) Q. Zhang, T. Fang, X. Tong, *Tetrahedron* **2010**, *66*, 8095.

Organocatalytic Asymmetric Synthesis of Protected α , β -Diamino Acids *via* Mannich Reaction of Tosyl Imines with α -Isothiocynato Imide

2.1 Introduction

Amino acids, such as α -amino acids,¹ β -amino acids² and β -hydroxy- α -amino acids,³ are frequently found in many biological active peptides and natural products. It has attracted intensive investigation from numerous research groups. However, α , β -diamino acids,⁴ which are also versatile intermediates in academic and industrial fields, as well as some other types of amino acids, were less studied, especially for its asymmetric syntheses.

In 2007, Willis and co-workers developed a direct asymmetric Mannich reaction of Tosyl imines with α -isothiocynato imide, by using Mg/DBFox complex (scheme 2.1). This protocol afforded a facile route for the synthesis chiral α , β -amino acid derivatives. Although some of the methodologies realized the asymmetric versions by employing chiral ligand/metal complexes, the development of a more efficient,

Scheme 2.1 Metal catalyzed Mannich reaction of Tosyl imines with α -isothiocynato imide

economical and operationally simple strategy that, avoided toxic metal and expensive chiral ligands, remains a challenge.⁵

Herein, we report a catalytic asymmetric synthetic protocol for the synthesis of protected α , β -diamino acids, by the Mannich reaction of Ts-protected imines and α -isothiocynato imides with a cheap and readily available quinine derivative as the catalyst under mild reaction conditions.⁶

2.2 Results and discussion

PMP and Boc-protected phenyl imines were first examined for this transformation, in the presence of 10 mol% of catalyst **4f**, which was previously demonstrated as an effective bifunctional catalyst.⁷ However, no reaction was observed to occur, which is presumably due to the lower electrophilicity of the imines. To our delight, when the more reactive Ts-protected phenyl imine **2c** was employed, the reaction proceeded smoothly to give the desired product with 92% yield. Although no enantioselectivity was achieved (Table 2.1, entry 5), this promising result prompted us to design and synthesize three new bifunctional catalysts **4l**, **4m** and **4n**. Unfortunately, they could not promote this transformation. Further catalysts screening showed that *Cinchona* alkaloid derivatives catalyzed this reaction to give low levels of asymmetric induction (entries 1, 3 and 6-9), while simple (*R*)-BINOL derived phosphoric acid **4k** could not induce any reaction. When the more acidic catalyst **4c** (compared to **4b**) was examined, the enantioselectivity was significantly increased to 85% *ee* (entry 2, 95:5 *dr*, and 92% yield).⁸ Decreasing reaction temperature to 0-4°C led to the diminished diastereo- and enantioselectivity (entry 10, 70% *ee* and 89:11 *dr*). Protection of the

Scheme 2.1 Catalysts screened

9-hydroxy group on catalyst **4c** with a benzoyl group dramatically improved the catalytic efficiency, thus achieving excellent stereoselective control (entry 4, >99% *ee*, and 95:5 dr).⁹

The effect of catalyst loading, solvent and reactant concentration for this transformation was further investigated (Table 2.2). Catalyst **4e** proved to be the best catalyst and it afforded **3a** with excellent yield (98%), enantio-(98%) and good diastereoselectivity (90:10 dr), even with a low catalyst loading (1.0 mol% in entry 5). In addition, various nonpolar solvents were well tolerated, with *m*-xylene giving the best result in the presence of 2.5mol% catalyst **4e**, at room temperature (entry 10, in 99% yield, > 99% *ee* and 95:5 dr).

Table 2.1 Catalyst screening^a

1a or **1b** + **2a-c** $\xrightarrow{\text{Cat. 4}}$ Product

a Pg = PMP, **b** Pg = Boc, **c** Pg = Ts

Entry	1	2	4	t (h)	yield (%) ^b	dr ^c	ee (%) ^d
1	1b	2a	4f	24	n.r.	n.d.	n.d.
2	1b	2b	4f	24	n.r.	n.d.	n.d.
3	1b	2c	4f	5	92	n.d.	0.
4 ^e	1b	2c	-	48	n.r.	n.d.	n.d.
5	1a	2c	4e	48	n.r.	n.d.	n.d.
6	1b	2c	4b	5	73	95:5	43
7	1b	2c	4c	5	92	95:5	85
8	1b	2c	4d	24	81	91:9	40
9	1b	2c	4g	6	95	67:33	-24
10	1b	2c	4h	6	91	95:5	-48
11	1b	2c	4i	24	50	95:5	-40
12	1b	2c	4j	24	78	87:13	-50
13	1b	2c	4k	48	n.r.	n.d.	n.d.
14	1b	2c	4l	48	n.r.	n.d.	n.d.

Table 2.1 (*continued*)

15	1b	2c	4m	48	n.r.	n.d.	n.d.
16	1b	2c	4n	48	<10%	n.d.	n.d.
17 ^f	1b	2c	4c	10	88	89:11	70
18	1b	2c	4e	4	99	95:5	>99

^a Reaction was performed at rt (23 °C) on a 0.1mmol scale in toluene (0.1 M) using 1.2 equiv. **2** and 10 mol% **4**. Reaction conditions see Experimental Section. ^b Isolated yield of both diastereomers. ^c Determined by crude ¹H NMR. ^d Determined by chiral HPLC chiral AD-H column or AS-H column of the major isomer. ^e Without catalyst. ^f Reaction was performed at 0-4 °C. n.r. = no reaction, n.d. = not determined

Table 2.2 Reaction conditions optimization.

Entry	mol% (4e)	solvent	M (1)	t (h)	yield (%) ^b	<i>Dr</i> ^c	<i>ee</i> (%) ^d
1	10.0	toluene	0.1	4	99	95:5	>99
2	7.5	toluene	0.1	4	91	93:7	>99
3	5.0	toluene	0.1	4	97	95:5	>99
4	2.5	toluene	0.1	5	94	95:5	>99
5	1.0	toluene	0.1	13	98	90:10	98
6	2.5	toluene	0.1	5	94	95:5	>99

Table 2.2 (*continued*)

7	2.5	benzene	0.1	10	74	95:5	98
8	2.5	CHCl ₃	0.1	24	60	92:8	99
9	2.5	MTBE	0.1	8	96	95:5	96
10	2.5	<i>m</i> -xylene	0.1	5	99	96:4	>99
11	2.5	<i>m</i> -xylene	0.2	2	99	95:5	>99
12	2.5	<i>m</i> -xylene	0.05	8	99	96:4	>99

^a Reaction was performed at rt (23°C) on a 0.1 mmol scale in toluene (0.1 M) using 1.2 equiv. **2c** and **4e**. Reaction conditions see Experimental Section. ^b Isolated yield. ^c Determined by ¹H NMR of crude reaction mixtures. ^d Determined by chiral HPLC using chiral AD-H column or AS-H column of the major isomer.

With the optimal reaction conditions in hand, the scope of Ts-protected imines was explored as shown in Table 2.3. Aromatic, heteroaromatic and aliphatic Ts-protected imines were good substrates for this reaction, affording the desired adducts in high yields and stereoselectivities. 3 or 4-substituted and non-substituted phenyl Ts-protected imines were excellent substrates for this reaction, furnishing the desired products in $\geq 90\%$ yields, $\geq 95\%$ *ee* and $\geq 93:7$ *dr* (entries 1-6). In the case of 2-substituted Ts-protected imines, higher catalyst loadings and longer reaction times were needed, probably due to steric hindrance. Correspondingly, lower diastereoselectivities and slightly diminished enantioselectivities, especially for 2-methyl phenyl Ts-protected imine (entry 8, 91% *ee*), were observed. It is worthwhile to note that, even with highly unstable aliphatic Ts-protected imine

substrates, the Mannich reaction could still proceed smoothly with excellent yield, acceptable diastereoselectivity and good enantioselectivity, in the presence of 10mol% **4e** and 20mg 4Å molecular sieves (entry 13, 90% yield, 86% *ee*, and 83:17 *dr*).

Table 2.3 Substrate scope^a.

Entry	R	t (h)	3	Yield (%) ^b	<i>dr</i> ^c	<i>ee</i> (%) ^d
1	Ph	5	3a	90	96:4	>99
2	4-MeC ₆ H ₄	4	3b	99	97:3	>99
3	4-ClC ₆ H ₄	3	3c	97	96:4	>99
4	4-BrC ₆ H ₄	5	3d	92	97:3	>99
5	3-MeC ₆ H ₄	4	3e	98	97:3	>99
6	3-ClC ₆ H ₄	2	3f	99	93:7	95
7 ^e	3-furyl	6	3g	96	89:11	98
8 ^f	2-MeC ₆ H ₄	72	3h	80	91:9	91
9 ^e	2-FC ₆ H ₄	10	3i	91	67:33	97
10	2-thienyl	6	3j	99	93:7	99
11 ^e	2-naphthyl	5	3k	90	95:5	97
12 ^e	cinnamyl	30	3l	97	80:20	98
13 ^g	n-butyl	48	3m	90	83:17	86

^a Standard conditions see Experimental Section. ^b Isolated yield. ^c Determined by ^1H NMR of reaction mixtures. ^d Determined by chiral HPLC. ^e 5 mol% **4e** was used. ^f 10 mol% **4e** was used. ^g 10 mol% **4e** and 20mg 4 Å MS were employed.

The absolute configuration of **3f** was determined to be (4*S*, 5*R*) by X-ray crystallography (Figure 2.1).

Figure 2.1 Absolute configuration of **3f** determined by X-ray diffraction crystallography

Based on the experimental results, a rational transition state was proposed as below to account for observed consistent high *anti*-diastereoselectivities. In the

Scheme 2.2 Transition state for *anti*-diastereoselectivity

presence of bifunctional organocatalyst **4e**, *trans*-enolate was formed predominantly; it then participated in six-membered chair transition state, in which the **R** group of tosyl imine was believed to adopt pseudoequatorial direction, thus provided high level *anti*-diastereocontrol (eq. a, Scheme 2.2). In transition state **b**, strong 1, 3-diaxial steric repulsion would make it disfavorable.

The excellent enantioselectivities of this methodology should be stemmed from efficient face differentiation. As depicted in Scheme 2.3, *Si* face attack was favored, whilst the *Re* face attack was disfavored due to the steric repulsion of **R** group and oxazolidinone ring.

Scheme 2.3 Transition state account for enantioselectivity

2.3 Conclusion

In summary, we have developed a highly efficient organocatalytic asymmetric protocol for the preparation of enantiomerically pure protected α , β -diamino acids, through the Mannich reaction between different Ts-protected imines and α -isothiocynato imide **1b**, catalyzed by readily available and environmentally friendly quinine derived catalyst **4e** under mild conditions.

2.4 Experimental section

Analytical thin layer chromatography (TLC) was performed using Merck 60 F254 precoated silica gel plate (0.2 mm thickness). Subsequent to elution, plates were visualized using UV radiation (254 nm) on Spectroline Model ENF-24061/F 254 nm. Further visualization was possible by staining with basic solution of potassium permanganate or acidic solution of ceric molybdate.

Flash column chromatography was performed using Merck silica gel 60 with freshly distilled solvents. Columns were typically packed as slurry and equilibrated with the appropriate solvent system prior to use. Proton nuclear magnetic resonance spectra (^1H NMR) were recorded on Bruker AMX 400 spectrophotometer (CDCl_3 as solvent). Chemical shifts for ^1H NMR spectra are reported as δ in units of parts per million (ppm) downfield from SiMe_4 (δ 0.0) and relative to the signal of chloroform-d (δ 7.2600, singlet). Multiplicities were given as: s (singlet), d (doublet), t (triplet), dd (doublets of doublet) or m (multiplets). The number of protons (n) for a given resonance is indicated by n H. Coupling constants are reported as a J value in Hz. Carbon nuclear magnetic resonance spectra (^{13}C NMR) are reported as δ in units of parts per million (ppm) downfield from SiMe_4 (δ 0.0) and relative to the signal of chloroform-d (δ 77.03, triplet).

Enantioselectivities were determined by High Performance Liquid Chromatography (HPLC) analysis (Shimadzu, LC-20AD) employing a Chiralpak AD-H or AS-H. Optical rotations were measured in CHCl_3 on a Schmidt + Haensdch polarimeter (Polartronic MH8) with a 10 cm cell (c given in g/100 mL).

High resolution mass spectrometry (HRMS) was recorded on Finnigan MAT 95 $\times$ P spectrometer.

2.4.1 Typical Procedure for the catalytic synthesis of α , β -diamino acid ethyl ester derivatives

To a stirred solution of catalyst **4e** (2.5 mol%) and Ts-protected imines **2** (0.12 mmol) in 1.0 mL *m*-xylene, was added α -isothiocynato imide **1b** (0.1 mmol). The reaction mixture was kept stirring at room temperature (23 °C) for the time given in Table 3. After the reaction was completed, solvent was removed under reduced pressure, and then dried THF was added and cooled to 0-4°C. A THF solution of magnesium bromide ethanolate (2 mL, 3.0 eq), prepared from methyl magnesium bromide (0.1 mL, 3 M in DCM) and ethanol (0.1 mL) in 2 mL THF at 0 °C, was slowly added. After 3 min, reaction was quenched by saturated aqueous NH_4Cl . Then, the crude product was purified by silica gel chromatography with the eluent (hexane/acetone from 8:1 to 2:1) to give the corresponding protected α , β -diamino acid ethyl ester derivatives.

2.4.2 Products characters

(4*S*, 5*R*)-ethyl 5-phenyl-2-thioxo-1-tosylimidazolidine-4-carboxylate

$[\alpha]_{\text{D}}^{22} +18.9$ (c 2.7, CHCl_3 , > 99% *ee*); ^1H NMR (400 MHz, CDCl_3) δ 7.51 (d, J = 8.4 Hz, 2H), 7.35-7.38 (m, 5H), 7.11 (d, J = 8.0 Hz, 2H), 5.94 (d, J = 2.4 Hz, 1H), 4.25-4.34 (m, 2H), 4.18 (d, J = 1.6 Hz, 1H), 2.37 (s, 3H), 1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 179.6, 168.4, 144.9, 138.7, 134.8, 129.4, 129.2,

128.8, 126.6, 67.5, 63.2, 62.9, 21.7, 14.1; HRMS (ESI) Calcd for $C_{19}H_{20}N_2O_4S_2$ $[M+H]^+$ 405.0943, found 405.0939; HPLC (Hexane: *i*-PrOH, 85:15, 220nm, 1.0mL/min, Chiralpak AD-H column): t_R = 21.2 min (major), t_R = 25.0 min (minor).

(4*S*, 5*R*)-ethyl 2-thioxo-5-p-tolyl-1-tosylimidazolidine-4-carboxylate

$[\alpha]_D^{22} +33.6$ (*c* 2.8, $CHCl_3$, > 99% *ee*); 1H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 7.11-7.17 (m, 5H), 5.90 (d, J = 2.4 Hz, 1H), 4.25-4.33 (m, 2H), 4.15 (d, J = 2.0 Hz, 1H), 2.37 (s, 3H), 2.38 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.6, 168.4, 144.9, 139.2, 135.8, 134.9, 129.8, 129.4, 128.8, 126.6, 67.4, 63.3, 62.9, 21.7, 21.2, 14.1; HRMS (ESI) Calcd for $C_{20}H_{22}N_2O_4S_2$ $[M+H]^+$ 419.1099, found 419.1100; HPLC (Hexane: *i*-PrOH, 85:15, 220nm, 1.0mL/min, Chiralpak AD-H column): t_R = 17.3 min (major), t_R = 22.4min (minor).

(4*S*, 5*R*)-ethyl 5-(4-chlorophenyl)-2-thioxo-1-tosylimidazolidine-4-carboxylate

$[\alpha]_D^{22} +24.0$ (*c* 3.4, $CHCl_3$, > 99% *ee*); 1H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 8.0 Hz, 2H), 7.28-7.35 (m, 4H), 7.23 (s, 1H), 7.17 (d, J = 8.0 Hz, 2H), 5.91 (d, J = 2.4 Hz, 1H), 4.24-4.34 (m, 2H), 4.13 (d, J = 2.4 Hz, 1H), 2.39 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.5, 168.1, 145.2, 137.3,

135.2, 134.7, 129.4, 128.9, 128.0, 126.6, 66.8, 63.0, 21.7, 14.1; HRMS (ESI) Calcd for $C_{19}H_{19}ClN_2O_4S_2$ $[M+H]^+$ 439.0553, found 439.0543; HPLC (Hexane: *i*-PrOH, 85:15, 220nm, 1.0mL/min, Chiralpak AD-H column): t_R = 15.9 min (major), t_R = 28.0min (minor).

(4*S*, 5*R*)-ethyl 5-(4-bromophenyl)-2-thioxo-1-tosylimidazolidine-4-carboxylate

$[\alpha]_D^{22} +32.3$ (*c* 3.4, $CHCl_3$, > 99% *ee*); 1H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 8.1 Hz, 2H), 7.49 (d, J = 8.2 Hz, 2H), 7.16-7.27 (m, 4H), 5.89 (s, 1H), 4.27-4.30 (m, 2H), 4.13 (s, 1H), 2.39 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.5, 168.1, 145.3, 137.8, 134.7, 132.4, 129.3, 128.9, 128.3, 123.3, 66.9, 63.1, 62.9, 21.7, 14.1; HRMS (ESI) Calcd for $C_{19}H_{19}ClN_2O_4S_2$ $[M+H]^+$ 485.0027, found 485.0007; HPLC (Hexane: *i*-PrOH, 85:15, 230nm, 1.0mL/min, Chiralpak AD-H column): t_R = 16.1 min (major), t_R = 28.5min (minor).

(4*S*, 5*R*)-ethyl 2-thioxo-5-m-tolyl-1-tosylimidazolidine-4-carboxylate

$[\alpha]_D^{22} -3.4$ (*c* 1.2, $CHCl_3$, > 99% *ee*); 1H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 8.4 Hz, 2H), 7.23-7.27 (m, 1H), 7.18 (d, J = 7.2 Hz, 1H), 7.12 (d, J = 8.0 Hz, 3H), 7.07 (s, 1H), 7.03 (s, 1H), 5.90 (d, J = 2.4 Hz, 1H), 4.25-4.34 (m, 2H), 4.14 (d, J = 2.8 Hz, 1H), 2.37 (s, 3H), 2.29 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.7, 168.3, 144.9, 139.1, 138.5, 134.8, 129.9, 128.7, 127.0, 123.7, 67.6, 63.2, 62.9, 21.6, 21.4, 14.1; HRMS (ESI) Calcd for $C_{20}H_{22}N_2O_4S_2$ $[M+H]^+$

419.1099, found 419.1096; HPLC (Hexane: *i*-PrOH, 85:15, 220nm, 1.0mL/min, Chiralpak AD-H column): t_R = 16.0 min (major), t_R = 18.9min (minor).

(4*S*, 5*R*)-ethyl 5-(3-chlorophenyl)-2-thioxo-1-tosylimidazolidine-4-carboxylate

$[\alpha]_D^{22}$ -21.2 (*c* 0.7, CHCl₃, 95% *ee*); ¹H NMR (400 MHz, CDCl₃) δ 7.59 (d, *J* = 8.1 Hz, 2H), 7.29 -7.37 (m, 2H), 7.18-7.26 (m, 1H), 7.16 (d, *J* = 8.1Hz, 2H), 5.90 (d, *J* = 2.7 Hz, 1H), 4.25-4.33 (m, 2H), 4.12 (d, *J* = 2.8 Hz, 1H), 2.39 (s, 3H), 1.32 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 179.5, 168.0, 145.3, 140.5, 135.2, 134.6, 130.6, 129.4, 129.3, 128.9, 126.6, 124.8, 66.9, 63.1, 62.9, 21.7, 14.1; HRMS (ESI) Calcd for C₁₉H₁₉N₂O₄S₂ [M+H]⁺ 439.0555, found 439.0549; HPLC (Hexane: *i*-PrOH, 85:15, 220nm, 1.0mL/min, Chiralpak AD-H column): t_R = 16.0 min (major), t_R = 21.1min (minor).

(4*S*, 5*R*)-ethyl 5-(furan-3-yl)-2-thioxo-1-tosylimidazolidine-4-carboxylate

$[\alpha]_D^{22}$ 27.1 (*c* 2.9, CHCl₃, 98% *ee*); ¹H NMR (400 MHz, CDCl₃) δ 7.65 (d, *J* = 8.0 Hz, 2H), 7.38 (s, 1H), 7.18 (d, *J* = 8.1Hz, 1H), 7.11 (s, 1H), 6.32 (s, 1H), 5.98 (s, 1H), 4.26-4.31 (m, 2H), 4.16 (s, 1H), 2.38 (s, 3H), 1.31 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 179.3, 168.2, 145.0, 144.3, 141.4, 134.8, 129.4, 128.9, 123.3, 108.1, 62.9, 62.2, 59.8, 21.7, 14.1; HRMS (ESI) Calcd for C₁₇H₁₈N₂O₅S₂ [M+H]⁺ 395.0735, found 395.0730; HPLC (Hexane: *i*-PrOH, 85:15, 220nm, 1.0mL/min, Chiralpak AD-H column): t_R = 20.9 min (major), t_R = 26.8min

(minor).

(4*S*, 5*R*)-ethyl 2-thioxo-5-*o*-tolyl-1-tosylimidazolidine-4-carboxylate

$[\alpha]_D^{22}$ -3.4 (*c* 1.6, CHCl_3 , 91% *ee*); ^1H NMR (400 MHz, CDCl_3) δ 7.54 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 1.2 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 7.07 (d, *J* = 1.6 Hz, 1H), 7.03 (s, 1H), 6.23 (d, *J* = 2.8 Hz, 1H), 4.25-4.35 (m, 2H), 4.07 (d, *J* = 2.8 Hz, 1H), 2.52 (s, 3H), 2.38 (s, 3H), 1.33 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 179.8, 168.4, 145.0, 136.83, 135.3, 134.8, 129.6, 128.9, 126.9, 64.0, 63.1, 62.9, 21.7, 14.1; HRMS (ESI) Calcd for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_4\text{S}_2$ $[\text{M}+\text{H}]^+$ 419.1099, found 419.1098; HPLC (Hexane: *i*-PrOH, 85:15, 220nm, 1.0mL/min, Chiralpak AS-H column): t_R = 41.6 min (major), t_R = 51.7min (minor).

(4*S*, 5*R*)-ethyl 5-(2-fluorophenyl)-2-thioxo-1-tosylimidazolidine-4-carboxylate

$[\alpha]_D^{22}$ -6.6 (*c* 0.8, CHCl_3 , 91% *ee*); ^1H NMR (400 MHz, CDCl_3) δ 7.67 (d, *J* = 8.0 Hz, 2H), 7.36-7.43 (m, 2H), 7.19 (d, *J* = 8.8 Hz, 3H), 7.08-7.16 (m, 1H), 6.88 (s, 1H), 6.25 (d, *J* = 2.8 Hz, 1H), 4.23-4.34 (m, 2H), 4.17 (d, *J* = 2.8 Hz, 1H), 2.39 (s, 3H), 1.31 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 179.5, 168.0, 145.2, 134.8, 131.0, 129.3, 129.0, 128.6, 124.9, 116.2, 116.0, 62.9, 62.4, 62.2, 21.7, 14.0; HRMS (ESI) Calcd for $\text{C}_{19}\text{H}_{19}\text{N}_2\text{O}_4\text{S}_2$ $[\text{M}+\text{H}]^+$ 423.0849, found 423.0859; HPLC (Hexane: *i*-PrOH, 85:15, 220nm, 1.0mL/min, Chiralpak AS-H column): t_R = 20.9 min (major), t_R = 31.4 min (minor).

(4*S*,5*S*)-ethyl 5-(thiophen-2-yl)-2-thioxo-1-tosylimidazolidine-4-carboxylate

$[\alpha]_{\text{D}}^{22}$ 32.0 (c 1.5, CHCl_3 , 99% *ee*); ^1H NMR (400 MHz, CDCl_3) δ 7.51 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 5.0 Hz, 1H), 7.25 (d, J = 4.4 Hz, 1H), 7.13 (d, J = 8.0 Hz, 2H), 7.02 (s, 1H), 6.99-7.02 (m, 1H), 6.28 (d, J = 1.4 Hz, 1H), 4.27-4.34 (m, 3H), 2.37 (s, 3H), 1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 178.9, 167.8, 144.9, 140.5, 134.7, 129.3, 128.8, 128.2, 126.9, 126.8, 63.3, 63.1, 63.0, 21.7, 14.1; HRMS (ESI) Calcd for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_4\text{S}_3$ $[\text{M}+\text{H}]^+$ 411.0507, found 411.0505; HPLC (Hexane: *i*-PrOH, 85:15, 230nm, 1.0mL/min, Chiralpak AD-H column): t_{R} = 23.8 min (major), t_{R} = 27.5 min (minor).

(4*S*, 5*R*)-ethyl 5-(naphthalen-2-yl)-2-thioxo-1-tosylimidazolidine-4-carboxylate

$[\alpha]_{\text{D}}^{22}$ 53.4 (c 2.8, CHCl_3 , 97% *ee*); ^1H NMR (400 MHz, CDCl_3) δ 7.79-7.84 (m, 4H), 7.49-7.55 (m, 4H), 7.32-7.37 (m, 2H), 6.98 (d, J = 8.1 Hz, 2H), 6.11 (d, J = 2.6 Hz, 1H), 4.29-4.33 (m, 2H), 4.23 (d, J = 2.6 Hz, 1H), 2.41 (s, 3H), 1.34 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 178.9, 167.8, 144.9, 140.5, 134.7, 129.3, 128.8, 128.2, 126.9, 126.8, 63.3, 63.1, 63.0, 21.7, 14.1; HRMS (ESI) Calcd for $\text{C}_{23}\text{H}_{22}\text{N}_2\text{O}_4\text{S}_2$ $[\text{M}+\text{H}]^+$ 455.1099, found 455.1102; HPLC (Hexane: *i*-PrOH, 85:15, 230nm, 1.0mL/min, Chiralpak AD-H column): t_{R} = 25.2 min (major), t_{R} = 30.9 min (minor).

(4S, 5R, E)-ethyl 5-styryl-2-thioxo-1-tosylimidazolidine-4-carboxylate

$[\alpha]_D^{22}$ 13.7 (*c* 3.5, CHCl_3 , 98% *ee*); ^1H NMR (400 MHz, CDCl_3) δ 7.92 (d, J = 8.4 Hz, 2H), 7.49-7.55(m, 4H), 7.32-7.39 (m, 5H), 7.18 (d, J = 8.4 Hz, 2H), 7.12 (s, 1H), 6.88 (d, J = 15.6Hz, 1H), 6.14-6.22 (m, 1H), 5.59-5.62 (m, 1H), 4.24-4.32 (m, 2H), 4.07 (d, J = 2.0 Hz, 1H), 2.37 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 179.3, 168.3, 145.1, 135.6, 135.2, 129.7, 128.9, 128.8, 126.9, 123.9, 66.9, 62.9, 61.1, 21.7, 14.1; HRMS (ESI) Calcd for $\text{C}_{21}\text{H}_{21}\text{N}_2\text{O}_4\text{S}_2$ $[\text{M}+\text{H}]^+$ 431.1099, found 431.1090; HPLC (Hexane: *i*-PrOH, 85:15, 230nm, 1.0mL/min, Chiralpak AD-H column): t_R = 21.4 min (major), t_R = 27.2 min (minor).

(4S, 5R)-ethyl 5-butyl-2-thioxo-1-tosylimidazolidine-4-carboxylate

$[\alpha]_D^{22}$ -22.2 (*c* 1.4, CHCl_3 , 86% *ee*); ^1H NMR (400 MHz, CDCl_3) δ 7.90 (d, J = 7.9 Hz, 2H), 7.49-7.55(d, J = 8.0 Hz, 2H), 6.83 (s, 1H), 4.12-4.22 (m, 2H), 3.98 (s, 1H), 2.42 (s, 3H), 1.95-2.08 (m, 2H), 1.38-1.41 (m, 2H), 1.24-1.28 (m, 2H), 0.94 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 179.6, 168.9, 145.1, 135.2, 129.1, 65.7, 62.6, 59.6, 34.9, 26.0, 22.2, 21.7, 14.0, 13.9; HRMS (ESI) Calcd for $\text{C}_{17}\text{H}_{24}\text{N}_2\text{O}_4\text{S}_2$ $[\text{M}+\text{H}]^+$ 385.1256, found 385.1261; HPLC (Hexane: *i*-PrOH, 85:15, 230nm, 1.0mL/min, Chiralpak AD-H column): t_R = 13.2 min (major), t_R = 18.4 min (minor).

2.5 Reference

1. a) C. Najera, J. M. Sansano, *Chem. Rev.* **2007**, *107*, 4584; b) M. J. O'Donnell, *Acc. Chem. Res.* **2004**, *37*, 506.
2. a) C. Cassani, L. Bernardi, F. Fini, A. Ricci, *Angew. Chem. Int. Ed.* **2009**, *48*, 5694; b) S. S. V. Ramasastry, H. Zhang, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2007**, *129*, 288; c) S. Saito, T. Tsubogo, S. Kobayashi, *Chem. Commun.* **2007**, 1236; d) J. W. Yang, M. Stadler, B. List, *Angew. Chem. Int. Ed.* **2007**, *46*, 609; e) Y. Hayashi, W. Tsuboi, I. Ashimine, T. Urushima, M. Shoji, K. Sakai, *Angew. Chem. Int. Ed.* **2003**, *42*, 3677; f) B. Shen, J. N. Johnston, *Org. Lett.*, **2008**, *10*, 4397; g) A. G. Wenzel, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 12964.
3. a) D. A. Evans, A. E. Weber, *J. Am. Chem. Soc.* **1986**, *108*, 6757; b) M. C. Willis, G. A. Cutting, V. J.-D. Piccio, M. J. Durbin, M. P. John, *Angew. Chem. Int. Ed.* **2005**, *44*, 154; c) L. Li, E. G. Klauber, D. Seidel, *J. Am. Chem. Soc.* **2008**, *130*, 12248.
4. a) For a review of α , β -diamino acids, see: A. Viso, R. F. de la Pradilla, A. Garca, and A. Flores, *Chem. Rev.* **2005**, *105*, 3167; b) for a review of vicinal diamines, see : D. Lucet, T. L. Gall and C. Mioskowski, *Angew. Chem. Int. Ed.* **1998**, *37*, 2580.
5. For selected examples involving asymmetric synthesis of α , β -diamino acids, see: a) A. Singh, J. N. Johnston, *J. Am. Chem. Soc.* **2008**, *130*, 5866; b) J. Wang, T. Shi, G. Deng, H. Jiang, H. Liu, *J. Org. Chem.* **2008**, *73*, 8563; c) J. Herná'ndez-Toribio, R. G. Arrayás, J. C. Carretero, *J. Am. Chem. Soc.* **2008**, *130*, 16150; d) G. A. Cutting, N. E.

Stainforth, M. P. John, G. Kociok-Khn, M. C. Willis, *J. Am. Chem. Soc.* **2007**, *129*, 10632; e) Z. Chen, H. Morimoto, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2008**, *130*, 2170; f) A. Singh, R. A. Yoder, B. Shen, J. N. Johnston, *J. Am. Chem. Soc.* **2007**, *129*, 3466; g) A. Okada, T. Shibuguchi, T. Ohshima, H. Masu, K. Yamaguchi, M. Shibasaki, *Angew. Chem. Int. Ed.* **2005**, *44*, 4564; h) T. Ooi, M. Kameda, J. Fujii, K. Maruoka, *Org. Lett.* **2004**, *6*, 2397; i) L. Bernardi, A. S. Gothelf, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem.* **2003**, *68*, 2583.

6. An excellent work on the Mannich reactions of Bs-protected imines with α -isothiocynato imide was reported by Seidel and co-workers, where the quinidine derivatives were employed as catalysts, see: L. Li, M. Ganesh and D. Seidel, *J. Am. Chem. Soc.* **2009**, *131*, 11648.

7. a) B. Tan, P. J. Chua, Y. Li, G. Zhong, *Org. Lett.* **2008**, *10*, 2437; b) B. Tan, Z. Shi, P. J. Chua, G. Zhong, *Org. Lett.* **2008**, *10*, 3425.

8. For the pioneering work, see: H. Li, Y. Wang, L. Tang and L. Deng, *J. Am. Chem. Soc.* **2004**, *126*, 9906.

9. For the seminal work, see: H. Li, B. Wang and L. Deng, *J. Am. Chem. Soc.* **2006**, *128*, 732.

10. a) For the preparation of aromatic Ts-protected imines, please see: R. Fan, D. Pu, F. Wen, Y. Ye, and X. Wang, *J. Org. Chem.* **2008**, *73*, 3623; b) For the preparation of aliphatic Ts-protected imines, please see: F. Chemla, V. Hebbe, J. F. Normant, *Synthesis* **2000**, *1*, 75.

Catalytic Asymmetric Formal [4+1] Annulation Leading to Optically Active *cis*-Isoxazoline *N*-Oxides

3.1 Introduction

Isoxazoline *N*-oxides are intriguing synthetic targets as they can be readily converted into highly functionalized γ -hydroxy- α -amino acids or γ -amino- α -hydroxy acids.¹ Despite the fact that several synthetic methodologies have been developed,² only sporadic examples achieved asymmetric versions by using stoichiometric amounts of chiral reactants.³ As such, the catalytic asymmetric approach to optically active isoxazoline *N*-oxides is still viewed as a formidable synthetic challenge.⁴

Stereoselective construction of ring systems is still considerably important in organic synthesis. In the past few decades, the [4 + 1] annulation has proved to be a powerful strategy in the construction of dihydrofurans, cyclopentenones, cyclopentenones, and pyrrolidines.⁵ However, the catalytic asymmetric version of [4 + 1] annulations are rarely documented, due to the difficulty in controlling the relative and absolute stereochemistry.^{6,7}

Scheme 3.1 Regio- and chemoselectivities of enamine cyclization.

Inspired by organocatalytic enamine chemistry⁸ and our previous study of the fluoroaldol reaction,⁹ we decided to address these challenges. It was hypothesized that the catalytic asymmetric synthesis of isoxazoline *N*-oxides could be achieved through a [4 + 1] annulation between 2-nitroacrylates¹⁰ and chiral enamines via elegant control of regio- and chemoselectivity (Scheme 3.1, eq 1). In this way, the formation of cyclopropane adducts, which are formed *via* the [2 + 1] pathway, can be avoided (eq 2). Herein, we report our preliminary results of this strategy, which gives rise to the formation of *cis*-isoxazoline *N*-oxides. To our knowledge, this is the first example in which *cis*-adducts are achieved.

3.2 Results and discussion

Initial studies were focused on investigating suitable enamine precursors (Table 3.1). Readily available α -halogenated hexanals were examined with methyl 2-nitro-3-phenylacrylate (*E/Z*) 2:1), in the presence of catalyst **4a**, which was previously reported to possess high efficiency in enamine chemistry (entries 1-4).¹¹ The feasibility of our designed catalytic system was first tested with α -chlorohexanal. To our delight, the [4 + 1] annulation product was observed, without any formation of cyclopropane, albeit with unsatisfactory chemical yield and stereoselectivity (entry 1). When α -bromohexanal and α -iodohexanal were employed, the yields were significantly increased to 90% and 79%, respectively, and accompanied by excellent enantioselectivities (99% and 96% *ee*'s), with the latter showing promising diastereocontrol and highest reactivity (entries 3 and 4). Replacing the solvent TBME with toluene led to better diastereoselectivity (entry 5). In addition, β -elimination

would occur occasionally, hence requiring the use of a slight excess of base as additive.

Table 3.1 Catalyst screening^a

4a R = OTMS, Ar = Ph
4b R = OTMS, Ar = 3,5-CF₃-Ph
4c R = OTMS, Ar = 4-MePh
4d R = OMe, Ar = Ph
4e R = N₃, Ar = Ph
4g R = NHAc, Ar = Ph

4h

4f

4i

1 **2** **cis-3c** **trans-3c**

entry	4	Lg	solvent	additive	<i>t</i> (h)	yield (%) ^b	<i>cis/trans</i> ^c	<i>ee</i> (%) ^d
1	4a	Cl	TBME	DIPEA	48	50	1:1.4	70
2	4b	Cl	TBME	DIPEA	96	18	n.d.	0
3	4a	Br	TBME	DIPEA	24	90	1.3:1	99
4	4a	I	TBME	DIPEA	5	79	1.8:1	96
5	4a	I	toluene	DIPEA	5	77	4.5:1	96
6	4c	I	toluene	DIPEA	5	78	2.2:1	95
7	4d	I	toluene	DIPEA	3	60	6:1	95
8	4e	I	toluene	DIPEA	7	83	9:1	98

Table 3.1 (continued)

9	4f	I	toluene	DIPEA	24	20	3:1	n.d.
10	4g	I	toluene	DIPEA	24	n.d.	n.d.	n.d.
11	4h	I	toluene	DIPEA	24	n.d.	n.d.	n.d.
12	4i	I	toluene	DIPEA	24	n.d.	n.d.	n.d.

^a Unless otherwise noted, reactions were performed at rt on a 0.1 mmol scale, in 0.5 mL toluene, with a molar ratio of α -halohexanal/2-nitroacrylate/DIPEA/**4** = 4:1:1.1:0.2.

^b The sum of both isomers. ^c Analysis of crude ¹H NMR. ^d Determined by HPLC for *cis*-isomer. n.r.= no reaction, n.d.= no determination.

Further catalyst screening with α -iodohexanal revealed that catalyst **4e** showed the best catalytic performance (entry 8), while catalyst **4f**, **4g**, **4h**, **4i** showed low catalytic efficiency. The superior diastereocontrol achieved by **4e** might have resulted from the predominant formation of the *Z*-enamine and electrostatic interaction between the azido moiety and nitro group in 2-nitroacrylate.

Additives were proven to play an important role in this catalytic process, as shown in Table 3.2. When triethyl amine was used, the diastereo- and stereoselectivity were further improved, with slightly higher chemical yield (entry 2). 2, 6-Lutidine could efficiently promote the reaction, albeit with lower dr and *ee* (entry 3). Other basic additives examined, such as pyridine and DABCO, provided diminished chemical yields, while NaOAc could not promote reaction at all (entries 4, 5, 6). In addition, decreasing the amount of TEA to 1.0 equivalent resulted in a lower yield and longer reaction time (entry 7).

Table 3.2 Survey of additive^a

entry	additive	<i>t</i> (h)	yield (%) ^b	<i>cis/trans</i> ^c	<i>ee</i> (%) ^d
1	DIPEA	7	83	9:1	98
2	TEA	8	89	11:1	>99
3	2,6-lutidine	48	85	7:1	96
4	NaOAc	48	n.r.	n.d.	n.d.
5	Pyridine	48	47	8:1	96
6	DABCO	48	20	11:1	97
7 ^e	TEA	10	80	11:1	>99

^a Unless otherwise noted, reactions were performed at rt on a 0.1 mmol scale, in 0.5 mL toluene, with a molar ratio of α -iodohexanal/2-nitroacrylate/additive/**4e** = 4:1:1.1:0.2. ^b The sum of both isomers. ^c Analysis of crude ¹H NMR. ^d Determined by HPLC for *cis*-isomer. ^e 1.0 equivalent TEA was employed. n.r.= no reaction, n.d.= no determination

The reaction concentration significantly influenced the chemical yield, as shown in Table 3.3. Lower concentration led to a higher yield of the desired product, while maintaining excellent diastereo- and enantiomericselectivity, although slightly longer reaction time was required (entry 2).

Table 3.3 Concentration effect^a

entry	Mol/L (2a)	<i>t</i> (h)	yield (%) ^b	<i>cis/trans</i> ^c	<i>ee</i> (%) ^d
1	0.5	8	89	11:1	>99
2	0.1	14	94	11:1	>99

^a Unless otherwise noted, reactions were performed at rt on a 0.1 mmol scale, in toluene, with a molar ratio of α -iodohexanal/2-nitroacrylate/TEA/4e = 4:1:1.1:0.2. ^b The sum of both isomers. ^c Analysis of crude ¹H NMR. ^d Determined by HPLC for *cis*-isomer

Table 3.4 Solvent effect^a

entry	solvent	<i>t</i> (h)	yield (%) ^b	<i>cis/trans</i> ^c	<i>ee</i> (%) ^d
1	toluene	14	94	11:1	>99
2	benzene	14	82	11:1	>99
3	<i>m</i> -xylene	21	72	13:1	98
4	TBME	14	61	9:1	99

^a Unless otherwise noted, reactions were performed at rt on a 0.1 mmol scale, at 0.1

mol/L concentration, with a molar ratio of α -iodohexanal/2-nitroacrylate/TEA/**4e** = 4:1:1.1:0.2. ^b The sum of both isomers. ^c Analysis of crude ¹H NMR. ^d Determined by HPLC for *cis*-isomer

Solvents effect was then examined, as shown in Table 3.4. Toluene, benzene and *m*-xylene were proven to be good reaction media, to afford the desired product in good to excellent yield, diastero- and enantioselectivity (entries 1, 2, 3). When *tert*-butyl methyl ether (TBME) was used as solvent, acceptable yield was obtained, with excellent stereoinduction (entry 4).

Table 3.5 Catalyst loading and temperature effect^a

entry	mol % of 4e	T (°C)	<i>t</i> (h)	yield (%) ^b	<i>cis/trans</i> ^c	<i>ee</i> (%) ^d
1	20	23	14	94	11:1	>99
2	10	23	23	69	9:1	99
3	20	0	48	n.r.	n.d.	n.d.
4	20	30	24	92	7:1	95
5	10	30	24	62	10:1	95

^a Unless otherwise noted, reactions were performed at rt on a 0.1 mmol scale, at 0.1 M concentration in toluene, with a molar ratio of α -iodohexanal/2-nitroacrylate/TEA/**4e** =

4:1:1.1:0.2. ^b The sum of both isomers. ^c Analysis of crude ¹H NMR. ^d Determined by HPLC for *cis*-isomer. n.r.= no reaction, n.d.= no determination.

It was found that the catalyst loading could be decreased to 10 mol %, to achieve acceptable chemical yield, as well as slightly lower diastereoselectivity, while maintaining enantioselectivity (Table 3.5, entry 5). Reaction temperature could influence on the reaction progress. When the reaction was performed at 0 °C, no reaction was observed (entry 3). Increasing reaction temperature from 23 to 30 °C, resulted in loss of *dr* and *ee* (entry 4).

Table 3.6 Scope of α -Iodoaldehydes^a

entry	1 (R)	yield (%) ^b	<i>dr</i> ^c	<i>ee</i> (%) ^d
1	1a (ethyl)	3a 64	10:1	95
2	1b (propyl)	3b 68	11:1	94
3	1c (butyl)	3c 94	11:1	>99
4	1d (heptyl)	3d 84	9:1	92
5	1e (benzyloxymethyl)	3e 75	18:1	99
6	1f (benzyl)	3f 70	8:1	99

^a Unless otherwise noted, reactions were performed at rt on a 0.2 mmol scale, in 2.0 mL toluene, with a molar ratio of α -iodohexanal/**2a**/TEA/**4e** = 4:1:1.1:0.2. ^b The

sum of both diastereoisomers. ^c *dr* = *cis/trans*, determined by ¹H NMR. ^d Determined by chiral HPLC for *cis*-isomer.

The scope of α -iodoaldehydes was next explored (Table 3.6). Under the optimized reaction conditions, α -iodoaldehydes with linear alkyl substituents proceeded in the [4 + 1] annulation smoothly to afford optically active isoxazoline *N*-oxides **3** in good yields (64-94%), with excellent enantioselectivities (92 to >99% ee's) and good diastereoselectivities (9:1-11:1 *dr*, entries 1-4). Furthermore, arylsubstituted α -iodoaldehydes proved to be good donors, affording desired products in good yields and remarkable stereocontrol (entries 5 and 6).

To further evaluate the versatility of this reaction, a variety of 2-nitroacrylates were used (Table 3). Aromatic and heteroaromatic substrates were observed to be suitable acceptors in this [4 + 1] annulation process. Systematic tuning of electron-withdrawing and electron-donating substituents at *ortho*-, *meta*- and *para*-positions of the aromatic ring gave rise to densely functionalized isoxazoline *N*-oxides in good yields, and with high stereoselectivities (entries 2-8). Notably, electron rich substrates delivered higher yields compared to electronpoor substrates, thus demonstrating that the electronic nature of the aromatic substrates had drastic effects. However, longer reaction times were needed (entries 2 and 3). Interestingly, for all cases, comparable results were obtained, regardless of the double bond geometry of the 2-nitroacrylate substrates. This may be due to isomerization of the 2-nitroacrylate during the course of the reaction,¹² which was proved by the detection

Table 3.7 Scope of 2-Nitroacrylates^a

entry	2 (R, <i>E/Z</i>)	yield of 3 (%) ^b	<i>dr</i> ^c	<i>ee</i> (%) ^d
1	2g (Ph, 1:1)	3g 87	9:1	91
2	2h (<i>o</i> -MePh, 1.2:1)	3h 81	11:1	97
3	2i (<i>o</i> -ClPh, 1.5:1)	3i 64	11:1	96
4	2j (<i>m</i> -MePh, 1.8:1)	3j 80	11:1	92
5	2k (<i>m</i> -ClPh, <i>Z</i>)	3k 63	>20:1	96
6	2l (<i>p</i> -BrPh, <i>Z</i>)	3l 78	14:1	94
7	2m (<i>p</i> -MePh, 2:1)	3m 81	10:1	92
8	2n (<i>p</i> -MeOPh, 4:1)	3n 73	13:1	91
9	2o (1-naphthyl, 1.5:1)	3o 62	12:1	94
10 ^e	2p (2-naphthyl, 1.7:1)	3p 74	11:1	87(>99) ^f
11 ^g	2q (3-furanyl, 2:1)	3q 67	>20:1	85
12	2r (2-furanyl, 1:1)	3r 61	11:1	84

^a Unless otherwise noted, reactions were performed at rt, on a 0.2 mmol scale, in 2.0 mL toluene, with a molar ratio of **1b**/**2** / TEA/**4e** = 4:1:1.1:0.2, for 9-24 h. ^b The sum of both diastereoisomers. ^c *dr* = *cis/trans*, determined by ¹H NMR. ^d Determined by chiral HPLC for *cis*-isomer. ^e Methyl ester **2p** was used. ^f After a simple recrystallization. ^g α -iodohexanal was employed.

of benzaldehyde in the reaction system, and subsequently resulted in relatively low

yields of isoxazoline *N*-oxides for some cases. The absolute configuration of the major diastereomer *cis*-**3l** was determined to be (4*S*, 5*R*) by X-ray crystallography (Figure 3.1).

Figure 3.1 Absolute configuration of *cis*-**3l** determined by X-ray diffraction crystallography

Having established the catalytic asymmetric formal [4 + 1] annulation methodology of 2-nitroacrylates and α -iodoaldehydes, the synthetic utilities of these previously undocumented *cis*-isoxazoline *N*-oxides were further explored. Apart from the typical transformation of the chiral isoxazoline core into numerous valuable synthons, such as α -amino acids,¹ γ -hydroxy- α -amino acids, and amino alcohols,² a concise approach to a densely functionalized chiral γ -lactone **6**, an important building block in the synthesis of natural products and biologically active compounds,¹³ was realized (Scheme 2). Optically pure *cis*-isoxazoline *N*-oxide **3c** was readily converted to intermediate **5** by simple reduction and protection. A deoxygenation was then carried out to provide isoxazoline **6** in quantitative yield. This was followed by treatment of **6** with nickel borohydride which was formed in situ, to give highly substituted 2-amino- γ -lactone **7** as a single diastereoisomer in good yield, albeit with slight loss of optical purity.

Scheme 3.2 Transformation of *cis*-isoxazoline *N*-oxide into densely functionalized γ -lactone. TBS = *tert*-butyldimethylsilyl, Boc = *tert*-butoxycarbonyl

Scheme 3.3 Proposed mechanism

It is proposed that the tandem sequence^{14,15} is initiated by condensation of α -iodoaldehyde **1** and catalyst **4e**, to generate enamine **8**, which then undergoes a

Michael addition with 2-nitroacrylate **2** (Scheme 3). The oxyanion of intermediate **9** then proceeds *via* an intramolecular S_N2-type O-alkylation to complete the catalytic cycle.¹⁶

3.3 Conclusion

In conclusion, we have presented the first catalytic asymmetric [4 + 1] annulation of 2-nitroacrylates and α -iodoaldehydes for the highly stereoselective synthesis of valuable *cis*-isoxazoline *N*-oxides with readily available substrates with novel use of the catalyst **4e**. Racemic α -iodoaldehydes, which were rarely employed as nucleophiles, proved to be suitable donors for this enamine cyclization process. Moreover, a concise synthetic approach to the biologically and medicinally relevant building block, chiral α -amino- γ -lactone, has been developed. This catalytic platform has opened up a new entry to the construction of five-membered ring systems. Additional investigations of the mechanism and other synthetic utilities of this protocol, such as extension to three-membered ring formation as well as total synthesis of natural products, are currently underway.

3.4 Experimental Section

Analytical thin layer chromatography (TLC) was performed using Merck 60 F254 precoated silica gel plate (0.2 mm thickness). Subsequent to elution, plates were visualized using UV radiation (254 nm) on Spectroline Model ENF-24061/F 254 nm. Further visualization was possible by staining with basic solution of potassium permanganate or acidic solution of ceric molybdate.

Flash column chromatography was performed using Merck silica gel 60 with

freshly distilled solvents. Columns were typically packed as slurry and equilibrated with the appropriate solvent system prior to use. Proton nuclear magnetic resonance spectra (^1H -NMR) were recorded on Bruker AMX 400 spectrophotometer (CDCl_3 as solvent). Chemical shifts for ^1H NMR spectra are reported as δ in units of parts per million (ppm) downfield from SiMe_4 (δ 0.0) and relative to the signal of chloroform-d (δ 7.26, singlet). Multiplicities were given as: s (singlet), d (doublet), t (triplet), dd (doublets of doublet) or m (multiplets). The number of protons (n) for a given resonance is indicated by nH. Coupling constants are reported as a J value in Hz. Carbon nuclear magnetic resonance spectra (^{13}C -NMR) are reported as δ in units of parts per million (ppm) downfield from SiMe_4 (δ 0.0) and relative to the signal of chloroform-d (δ 77.0, triplet).

Enantioselectivities were determined by High Performance Liquid Chromatography (HPLC) analysis (Shimadzu, LC-20AD) employing a chiralcel OD-H or chiralpak AD-H. Optical rotations were measured in CHCl_3 on a Schmidt + Haensch polarimeter (Polartronic MH8) with a 10 cm cell (c given in g/100 mL).

High resolution mass spectrometry (HRMS) was recorded on Finnigan MAT 95 $\times$ P spectrometer.

α -Iodoaldehyde¹⁷ and 2-nitroacrylate¹⁸ substrates were prepared according to the procedure of literatures, catalyst **4a**,¹⁹ **4b**,¹⁹ **4c**,¹⁹ **4d**²⁰ and **4f**²¹ were synthesized following documented methods. Catalyst **4e**,²² **4g**,²² **4h**²³ and **4i**²¹ were prepared with modified method of literatures.

General procedure of catalytic [4+1] annulation reaction

α -iodoaldehyde (0.8 mmol, 4.0 equivalent), (*S*)-2-(azidodiphenylmethyl)pyrrolidine (**4e**, 0.04 mmol, 0.2 equivalent) were dissolved in 2.0 mL toluene at room temperature (23 °C), then 2-nitroacrylate derivatives (0.2 mmol) and triethyl amine (0.22 mmol) were added successively. The reaction progress was monitored by TLC analysis. Upon consumption of 2-nitroacrylate derivatives, the crude reaction mixture was applied to silica gel and the desired products were obtained by flash chromatography (hexane/ethyl acetate, 10:1 to 2:1).

Racemic adducts were synthesized using 2-(diphenyl(trimethylsilyloxy)methyl)pyrrolidine as catalyst.

(*S*)-2-(Azidodiphenylmethyl)pyrrolidine (4e**)**

Catalyst **4e** was synthesized using modified method of literature.²² (*S*)-Diphenyl (pyrrolidin-2-yl)methanol (0.81 g, 3.2 mmol) was dissolved in 20 mL TFA, then cooled with ice bath. NaN₃ (1.25 g, 19.2 mmol) was portionwise added, then stirred at room temperature for 24 h. Reaction was quenched with saturated aqueous Na₂CO₃ solution, extracted with dichloromethane, dried over Na₂SO₄, concentrated under vacuo, then the residue was applied to column chromatography, gave 0.73 g solid product (Mp: 70-71 °C), with 82% yield.

^1H NMR (400 MHz, CDCl_3): δ 1.61-1.75 (m, 5H), 2.98 (t, J = 8 Hz, 2H), 4.35 (t, J = 8 Hz, 1H), 7.22-7.49 (m, 8H), 7.52 (d, J = 7.5 Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 26.1, 28.0, 47.3, 65.3, 75.2, 127.0, 127.2, 127.5, 128.0, 128.2, 128.5, 142.3, 142.7.

(4*S*,5*R*)-3-(Methoxycarbonyl)-5-formyl-4-phenyl-5-ethyl-4,5-dihydroisoxazole 2-oxide (3a)

According to general procedure: 16 h, at room temperature, the product was obtained from flash chromatography (hexane/EtOAc = 10:1 to 2:1), as white solid 36 mg (Mp: 126-128 °C), 64% yield, 10:1 dr, 95% *ee*. HPLC analysis: Chiralcel OD-H (hexane/*i*-PrOH = 90/10, 1.0 mL/min), t_R (major) 11.66 min, t_R (minor) 16.57 min. $[\alpha]_D^{22}$ = +119.2° (c = 3.17, CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 1.03 (t, J = 7.4 Hz, 3H), 2.07-2.17 (m, 2H), 3.72 (s, 3H), 4.55 (s, 1H), 7.14-7.16 (m, J = 6.8 Hz, 2H), 7.32-7.38 (m, 3H), 9.13 (s, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 7.2, 28.9, 52.8, 57.0, 88.6, 110.4, 127.9, 129.1, 129.6, 133.1, 158.7, 196.7. HRMS (ESI) Calcd for $\text{C}_{14}\text{H}_{16}\text{NO}_5$ ($[\text{M}+\text{H}]^+$) 278.1028, found 278.1032.

(4*S*,5*R*)-3-(Methoxycarbonyl)-5-formyl-4-phenyl-5-propyl-4,5-dihydroisoxazole 2-oxide (3b)

According to general procedure: 16 h, at room temperature, the product was obtained from flash chromatography (hexane/EtOAc = 10:1 to 2:1), as white solid 39 mg (Mp: 149-152 °C), 68% yield, 11:1 dr, 94% *ee*. HPLC analysis: Chiralcel OD-H (hexane/*i*-PrOH = 90/10, 1.0 mL/min), t_R (major) 9.35 min, t_R (minor) 18.61 min. $[\alpha]_D^{22} = +92.3^\circ$ ($c = 1.65$, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 0.97 (t, $J = 7.3$ Hz, 3H), 1.30-1.39 (m, 1H), 1.53-1.59 (m, 1H), 2.01-2.10 (m, 2H), 3.73 (s, 3H), 4.54 (s, 1H), 7.14-7.15 (m, $J = 6.9$ Hz, 2H), 7.32-7.36 (m, 3H), 9.13 (s, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 14.2, 16.3, 38.1, 52.8, 57.4, 88.4, 110.4, 127.9, 129.2, 129.6, 133.3, 158.1, 196.8. HRMS (ESI) Calcd for C₁₅H₁₈NO₅ ($[M+H]^+$) 292.1185, found 292.1179.

(4*S*,5*R*)-3-(Methoxycarbonyl)-5-formyl-4-phenyl-5-butyl-4,5-dihydroisoxazole 2-oxide (3c)

According to general procedure: 14 h, at room temperature, the product was obtained from flash chromatography (hexane/EtOAc = 10:1 to 2:1), as white solid 57 mg (Mp: 145-147 °C), 94% yield, 11:1 dr, >99% *ee*. HPLC analysis: Chiralcel OD-H (hexane/*i*-PrOH = 90/10, 1.0 mL/min), t_R (major) 8.48 min, t_R (minor)

17.81 min. $[\alpha]_{\text{D}}^{22} = +108.3^\circ$ ($c = 1.70$, CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 0.91 (t, $J = 7.2$ Hz, 3H), 1.33-1.38 (m, 3H), 1.45-1.54 (m, 1H), 2.02-2.12 (m, 2H), 3.73 (s, 3H), 4.55 (s, 1H), 7.14-7.15 (m, $J = 6.6$ Hz, 2H), 7.34-7.36 (m, 3H), 9.13 (s, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 13.7, 22.8, 24.8, 35.8, 52.8, 57.3, 88.5, 110.4, 127.9, 129.2, 129.6, 133.3, 158.7, 196.8. HRMS (ESI) Calcd for $\text{C}_{16}\text{H}_{20}\text{NO}_5$ ($[\text{M}+\text{H}]^+$) 306.1341, found 306.1343.

(4*S*,5*R*)-3-(Methoxycarbonyl)-5-formyl-4-phenyl-5-heptyl-4,5-dihydroisoxazole 2-oxide (3d)

According to general procedure: 16 h, at room temperature, the product was obtained from flash chromatography (hexane/EtOAc = 10:1 to 2:1), as white solid 58 mg (Mp: 82-85 °C), 84% yield, 9:1 dr, 92% *ee*. HPLC analysis: Chiralcel OD-H (hexane/*i*-PrOH = 90/10, 1.0 mL/min), t_{R} (major) 8.96 min, t_{R} (minor) 23.50 min. $[\alpha]_{\text{D}}^{22} = +94.9^\circ$ ($c = 4.00$, CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 0.87 (t, $J = 7.0$ Hz, 3H), 1.26-1.29 (m, 9H), 1.51-1.54 (m, 1H), 2.02-2.11 (m, 2H), 3.72 (s, 3H), 4.55 (s, 1H), 7.13-7.15 (m, $J = 6.6$ Hz, 2H), 7.31-7.35 (m, 3H), 9.12 (s, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 14.1, 22.6, 22.8, 28.9, 29.6, 31.6, 36.0, 52.8, 57.3, 88.5, 110.4, 127.9, 129.2, 129.6, 133.1, 158.7, 196.8. HRMS (ESI) Calcd for $\text{C}_{19}\text{H}_{26}\text{NO}_5$ ($[\text{M}+\text{H}]^+$)

348.1811, found 348.1811.

(4*S*,5*S*)-5-(Benzyloxymethyl)-5-formyl-3-(Methoxycarbonyl)-4-phenyl-4,5-dihydroisoxazole 2-oxide (3e)

According to general procedure: 14 h, at room temperature, the product was obtained from flash chromatography (hexane/EtOAc = 10:1 to 2:1), as sticky oil 55 mg, 75% yield, 18:1 dr, 99% *ee*. HPLC analysis: Chiralcel OD-H (hexane/*i*-PrOH = 90/10, 1.0 mL/min), t_R (major) 22.48 min, t_R (minor) 29.62 min, $[\alpha]_D^{22} = +44.6^\circ$ ($c = 2.60$, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 3.72 (s, 3H), 3.82-3.94 (dd, $J = 8, 36$ Hz, 2H), 4.65-4.66 (m, $J = 4$ Hz, 2H), 7.13-7.15 (m, $J = 8.0$ Hz, 2H), 7.32-7.38 (m, 8H), 9.14 (s, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 52.8, 53.9, 70.6, 74.1, 86.7, 110.1, 127.8, 128.0, 128.2, 128.6, 129.2, 129.7, 132.9, 136.9, 158.6, 195.1. HRMS (ESI) Calcd for C₂₀H₂₀NO₆ ($[M+H]^+$) 370.1291, found 370.1299.

(4*S*,5*R*)-5-Benzyl-4-phenyl)-5-formyl-3-(methoxycarbonyl)-4,5-dihydroisoxazole 2-oxide (3f)

According to general procedure: 24 h, at room temperature, the product was obtained from flash chromatography (hexane/EtOAc = 4:1 to 2:1), as

sticky oil 47 mg, 70% yield, 8:1 dr, 99% *ee*. HPLC analysis: Chiralcel OD-H (hexane/*i*-PrOH = 95/05, 1.0 mL/min), t_R (major) 25.77 min, t_R (minor) 43.81 min. $[\alpha]_D^{21} = +60.8^\circ$ ($c = 1.40$, CHCl₃). ¹H NMR (400 MHz, ¹H CDCl₃): δ 3.28 (s, 2H), 3.63 (s, 3H), 4.63 (s, 1H), 7.15-7.16 (d, $J = 2.7$ Hz, 2H), 7.31-7.35 (m, 8H), 9.14 (s, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 40.9, 52.7, 56.3, 87.6, 110.0, 127.8, 128.0, 128.7, 129.2, 129.2, 129.7, 130.3, 132.5, 132.9, 158.2, 196.6. HRMS (ESI) Calcd for C₁₉H₁₈NO₅ ($[M+H]^+$) 340.1185, found 340.1179.

(4*S*,5*R*)-3-(Ethoxycarbonyl)-5-formyl-4-phenyl-5-propyl-4,5-dihydroisoxazole

2-oxide (3g)

According to general procedure: 16 h, at room temperature, the product was obtained from flash chromatography (hexane/EtOAc = 10:1 to 2:1), as white solid 38 mg (Mp: 113-114 °C), 87% yield, 9:1 dr, 91% *ee*. HPLC analysis: Chiralcel OD-H (hexane/*i*-PrOH = 90/10, 1.0 mL/min), t_R (major) 8.44 min, t_R (minor) 19.44 min. $[\alpha]_D^{22} = +90.1^\circ$ ($c = 3.80$, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 0.97 (t, $J = 7.2$ Hz, 3H), 1.11 (t, $J = 7.2$ Hz, 3H), 1.31-1.39 (m, 1H), 1.52-1.61 (m, 1H), 1.99-2.14 (m, 2H), 4.12-4.22 (m, 2H), 4.54 (s, 1H), 7.14 (t, $J = 6.4$ Hz, 2H), 7.31-7.37 (m, 3H), 9.16 (s, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 13.9, 14.2, 16.3, 38.1, 57.6, 62.0, 88.3, 110.4, 127.9, 129.1, 133.3, 158.1, 196.9. HRMS (ESI) Calcd for C₁₆H₂₀NO₅ ($[M+H]^+$) 306.1341, found 306.1344.

(4*S*,5*R*)-3-(Ethoxycarbonyl)-5-formyl-5-propyl-4-*o*-tolyl-4,5-dihydroisoxazole

2-oxide (3h)

According to general procedure: 24 h, at room temperature, the product was obtained from flash chromatography (hexane/EtOAc = 10:1 to 2:1), as white solid 52 mg (Mp: 75-77 °C), 81% yield, 11:1 dr, 97% *ee*. HPLC analysis: Chiralcel OD-H (hexane/*i*-PrOH = 90/10, 1.0 mL/min), t_R (major) 6.37 min, t_R (minor) 22.00 min. $[\alpha]_D^{22} = +59.9^\circ$ ($c = 4.50$, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 0.97 (t, $J = 7.2$ Hz, 3H), 1.12 (t, $J = 7.2$ Hz, 3H), 1.29-1.38 (m, 1H), 1.53-1.62 (m, 1H), 2.00-2.236 (m, 2H), 2.32 (s, 3H), 4.13-4.21 (m, 2H), 4.77 (s, 1H), 7.10-7.13 (q, $J = 1.6$ Hz, 1H), 7.19 (d, $J = 5.2$ Hz, 3H), 9.11 (s, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 13.9, 14.2, 16.4, 38.5, 52.9, 62.0, 88.2, 110.8, 126.6, 127.0, 128.9, 131.5, 131.8, 158.0, 197.3. HRMS (ESI) Calcd for C₁₇H₂₂NO₅ ([M+H]⁺) 320.1498, found 320.1494.

(4*S*,5*R*)-4-(2-Chlorophenyl)-3-(ethoxycarbonyl)-5-formyl-5-propyl-4,5-dihydrois**oxazole 2-oxide (3i)**

According to general procedure: 16 h, at room temperature, the product was obtained from flash chromatography (hexane/EtOAc = 10:1 to 2:1), as white solid 43 mg (Mp: 78-79 °C), 64% yield, >20:1 dr, 96% *ee*. HPLC analysis: Chiralcel OD-H (hexane/*i*-PrOH = 90/10, 1.0 mL/min), t_R (major) 8.78 min, t_R (minor)

30.14 min. $[\alpha]_{\text{D}}^{22} = +46.1^\circ$ ($c = 3.507$, CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 0.99 (t, $J = 7.2$ Hz, 3H), 1.12 (t, $J = 7.3$ Hz, 3H), 1.33-1.41 (m, 1H), 1.55-1.62 (m, 1H), 2.07-2.24 (m, 2H), 4.13-4.22 (m, 2H), 5.24 (s, 1H), 7.16-7.18 (m, 1H), 7.27 (t, $J = 3.0$ Hz, 2H), 7.41-7.44 (m, 1H), 9.13 (d, $J = 0.5$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 13.8, 14.2, 16.3, 38.0, 52.8, 62.1, 88.0, 109.8, 127.8, 128.4, 130.3, 130.6, 131.5, 133.8, 157.9, 195.5. HRMS (ESI) Calcd for $\text{C}_{16}\text{H}_{19}\text{NO}_5\text{Cl}$ ($[\text{M}+\text{H}]^+$) 340.0952, found 340.0956.

(4*S*,5*R*)-3-(Ethoxycarbonyl)-5-formyl-5-propyl-4-*m*-tolyl-4,5-dihydroisoxazole

2-oxide (3j)

According to general procedure: 16 h, at room temperature, the product was obtained from flash chromatography (hexane/EtOAc = 10:1 to 2:1), as white solid 51 mg (Mp: 111-113 °C), 80% yield, 11:1 dr, 92% *ee*. HPLC analysis: Chiralcel OD-H (hexane/*i*-PrOH = 90/10, 1.0 mL/min), t_{R} (major) 6.39 min, t_{R} (minor) 15.20 min. $[\alpha]_{\text{D}}^{22} = +66.9^\circ$ ($c = 4.80$, CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 0.97 (t, $J = 7.2$ Hz, 3H), 1.14 (t, $J = 7.2$ Hz, 3H), 1.33-1.35 (m, 1H), 1.54-1.58 (m, 1H), 1.98-2.13 (m, 2H), 2.32 (s, 3H), 4.13-4.23 (m, 2H), 4.49 (s, 1H), 6.94 (s, 2H), 7.11 (d, $J = 7.6$ Hz, 1H), 7.23 (t, $J = 8.0$ Hz, 1H), 9.15 (s, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 13.9, 14.2, 16.3, 21.4, 38.1, 57.5, 62.0, 88.2, 110.5, 125.0, 128.4, 129.4, 129.9, 133.2, 139.5, 158.2, 196.9. HRMS (ESI) Calcd for $\text{C}_{17}\text{H}_{22}\text{NO}_5$ ($[\text{M}+\text{H}]^+$)

320.1498, found 320.1496.

(4*S*,5*R*)-4-(3-Chlorophenyl)-3-(ethoxycarbonyl)-5-formyl-5-propyl-4,5-dihydroisoxazole 2-oxide (3k)

According to general procedure: 9 h, at room temperature, the product was obtained from flash chromatography (hexane/EtOAc = 10:1 to 2:1), as white solid 43 mg (Mp: 106-108 °C), 63% yield, >20:1 dr, > 96% *ee*. HPLC analysis: Chiralcel OD-H (hexane/*i*-PrOH = 90/10, 1.0 mL/min), t_R (major) 8.30 min, t_R (minor) 21.12 min. $[\alpha]_D^{22} = +40.7^\circ$ ($c = 1.70$, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 0.97 (t, $J = 7.3$ Hz, 3H), 1.15 (t, $J = 7.1$ Hz, 3H), 1.33-1.36 (m, 1H), 1.54-1.60 (m, 1H), 1.98-2.12 (m, 2H), 4.14-4.24 (m, 2H), 4.50 (s, 1H), 7.03 (d, $J = 3.4$ Hz, 1H), 7.15 (s, 1H), 7.29 (d, $J = 4.8$ Hz, 2H), 9.22 (s, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 13.9, 14.2, 16.3, 38.3, 57.1, 62.2, 88.2, 110.0, 126.0, 128.1, 129.4, 130.8, 135.5, 135.6, 157.9, 196.8. HRMS (ESI) Calcd for C₁₆H₁₉NO₅Cl ([M+H]⁺) 340.0952, found 340.0956.

(4*S*,5*R*)-4-(4-Bromophenyl)-3-(ethoxycarbonyl)-5-formyl-5-propyl-4,5-dihydroisoxazole 2-oxide (3l)

According to general procedure: 16 h, at room temperature, the product was obtained from flash chromatography (hexane/EtOAc = 10:1 to 2:1), as white solid 60 mg (Mp: 99-101 °C), 78% yield, 14:1 dr, 94% *ee*. HPLC analysis: Chiralcel OD-H (hexane/*i*-PrOH = 90/10, 1.0 mL/min), t_R (major) 8.58 min, t_R (minor) 26.68 min. $[\alpha]_D^{24} = +44.4^\circ$ ($c = 2.40$, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 0.96 (t, $J = 7.2$ Hz, 3H), 1.14 (t, $J = 7.2$ Hz, 3H), 1.25-1.36 (m, 1H), 1.52-1.59 (m, 1H), 1.97-2.13 (m, 2H), 4.14-4.22 (m, 2H), 4.50 (s, 1H), 7.03 (d, $J = 8.4$ Hz, 2H), 7.48 (t, $J = 8.4$ Hz, 2H), 9.18 (s, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 13.9, 14.2, 16.3, 38.2, 57.0, 62.2, 88.2, 110.1, 123.3, 129.5, 132.5, 132.7, 158.0, 196.9. HRMS (ESI) Calcd for C₁₆H₁₉NO₅Br ([M+H]⁺) 384.0447, found 384.0446.

(4*S*,5*R*)-3-(Ethoxycarbonyl)-5-formyl-5-propyl-4-*p*-tolyl-4,5-dihydroisoxazole

2-oxide (3m)

According to general procedure: 16 h, at room temperature, the product was obtained from flash chromatography (hexane/EtOAc = 10:1 to 2:1), as white solid 52 mg (Mp: 93-96 °C), 81% yield, 10:1 dr, 92% *ee*. HPLC analysis: Chiralcel OD-H (hexane/*i*-PrOH = 90/10, 1.0 mL/min), t_R (major) 6.73 min, t_R (minor) 15.74 min. $[\alpha]_D^{22} = +69.8^\circ$ ($c = 4.20$, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 0.96 (t, J

= 7.2 Hz, 3H), 1.13 (t, J = 7.2 Hz, 3H), 1.33-1.39 (m, 1H), 1.53-1.63 (m, 1H), 1.98-2.15 (m, 2H), 2.34 (s, 3H), 4.16-4.24 (m, 2H), 4.53 (s, 1H), 7.03-7.05 (q, J = 7.6 Hz, 2H), 7.17 (d, J = 7.6 Hz, 2H), 9.17 (s, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 13.9, 14.2, 16.3, 38.0, 57.2, 62.0, 88.3, 110.5, 127.7, 130.1, 130.2, 139.0, 158.2, 197.1. HRMS (ESI) Calcd for $\text{C}_{17}\text{H}_{22}\text{NO}_5$ ($[\text{M}+\text{H}]^+$) 320.1498, found 320.1495.

(4*S*,5*R*)-3-(Ethoxycarbonyl)-5-formyl-4-(4-methoxyphenyl)-5-propyl-4,5-dihydroisoxazole 2-oxide (3n)

According to general procedure: 24 h, at room temperature, the product was obtained from flash chromatography (hexane/EtOAc = 10:1 to 2:1), as white solid 49 mg (Mp: 88-89 °C), 73% yield, 13:1 dr, 91% *ee*. HPLC analysis: Chiralcel OD-H (hexane/*i*-PrOH = 90/10, 1.0 mL/min), t_R (major) 11.31 min, t_R (minor) 27.46 min. $[\alpha]_D^{22}$ = +69.1° (c = 4.50, CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 0.96 (t, J = 7.2 Hz, 3H), 1.13 (t, J = 7.2 Hz, 3H), 1.30-1.36 (m, 1H), 1.51-1.58 (m, 1H), 1.95-2.12 (m, 2H), 3.78 (s, 3H), 4.13-4.22 (m, 2H), 4.49 (s, 1H), 6.85 (d, J = 8.8 Hz, 2H), 7.05 (d, J = 8.8 Hz, 2H), 9.15 (d, J = 0.4 Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 13.9, 14.2, 16.3, 38.0, 55.3, 56.8, 62.0, 88.3, 110.5, 114.9, 125.0, 129.1, 158.2, 160.0, 197.1. HRMS (ESI) Calcd for $\text{C}_{17}\text{H}_{22}\text{NO}_6$ ($[\text{M}+\text{H}]^+$) 336.1447, found 336.1443.

(4*S*,5*R*)-3-(Ethoxycarbonyl)-5-formyl-4-(naphthalen-1-yl)-5-propyl-4,5-dihydroisoxazole 2-oxide (3o)

According to general procedure: 16 h, at room temperature, the product was obtained from flash chromatography (hexane/EtOAc = 10:1 to 2:1), as white solid 44 mg (Mp: 114-115 °C), 62% yield, 12:1 dr, 94% *ee*. HPLC analysis: Chiralcel OD-H (hexane/*i*-PrOH = 90/10, 1.0 mL/min), t_R (major) 10.47 min, t_R (minor) 31.92 min. $[\alpha]_D^{22} = +5.7^\circ$ ($c = 3.20$, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 0.97-1.04 (m, 6H), 1.36-1.43 (m, 1H), 1.60-1.68 (m, 1H), 2.17-2.33 (m, 2H), 4.08-4.14 (m, 2H), 5.43 (s, 1H), 7.37 (d, $J = 7.2$ Hz, 1H), 7.45 (t, $J = 7.2$ Hz, 1H), 7.56 (t, $J = 7.6$ Hz, 1H), 7.64 (t, $J = 8.0$ Hz, 1H), 7.83-7.92 (m, 3H), 8.98 (s, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 13.8, 14.2, 16.4, 38.0, 51.8, 62.0, 88.0, 110.5, 122.3, 125.30, 125.33, 126.5, 127.3, 129.3, 129.9, 130.9, 134.2, 158.1, 195.5. HRMS (ESI) Calcd for C₂₀H₂₂NO₅ ($[M+H]^+$) 356.1498, found 356.1496.

(4*S*, 5*R*)-5-Formyl-3-(methoxycarbonyl)-4-(naphthalen-2-yl)-5-propyl-4,5-dihydroisoxazole 2-oxide (3p)

According to general procedure: 12 h, at room temperature, the product was obtained from flash chromatography (hexane/EtOAc = 8:1 to 2:1), as white solid 50 mg (Mp: 164-165 °C), 74% yield, 11:1 dr, 87% *ee*. After

recrystallization, > 99% *ee*. HPLC analysis: Chiralcel OD-H (hexane/*i*-PrOH = 90/10, 1.0 mL/min), t_R (major) 11.68 min, t_R (minor) 33.67 min. $[\alpha]_D^{23} = +126.7^\circ$ ($c = 2.00$, CHCl₃). ¹H NMR (400 MHz, ¹H CDCl₃): δ 0.99 (t, $J = 7.4$ Hz, 3H), 1.34-1.40 (m, 1H), 1.55-1.63 (m, 1H), 2.07-2.16 (m, 2H), 3.71 (s, 3H), 4.71 (s, 1H), 7.23 (d, $J = 8.4$ Hz, 1H), 7.52 (t, $J = 4.5$ Hz, 2H), 7.64 (s, 1H), 7.81-7.86 (m, 3H), 9.15 (s, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 14.2, 16.3, 38.2, 52.9, 57.5, 88.6, 110.4, 125.0, 126.9, 127.0, 127.3, 127.8, 128.0, 129.8, 130.5, 133.3, 133.4, 158.7, 196.7. HRMS (ESI) Calcd for C₁₉H₂₀NO₅ ([M+H]⁺) 342.1341, found 342.1344.

(4*S*,5*R*)-3-(Ethoxycarbonyl)-5-formyl-4-(furan-3-yl)-5-butyl-4,5-dihydroisoxazole 2-oxide (3q)

According to general procedure: 16 h, at room temperature, the product was obtained from flash chromatography (hexane/EtOAc = 10:1 to 6:1), as white solid 41 mg (Mp: 68-69 °C), 67% yield, >20:1 dr, 85% *ee*. HPLC analysis: Chiralcel OD-H (hexane/*i*-PrOH = 90/10, 1.0 mL/min), t_R (major) 8.38 min, t_R (minor) 18.39 min. $[\alpha]_D^{22} = +30.8^\circ$ ($c = 1.70$, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 0.91 (t, $J = 7.2$ Hz, 3H), 1.27 (t, $J = 7.2$ Hz, 3H), 1.30-1.41 (m, 3H), 1.47-1.51 (m, 1H), 1.98-2.08 (m, 2H), 4.22-4.26 (m, 2H), 4.53 (s, 1H), 6.25 (s, 1H), 7.37 (s, 1H), 7.41 (s, 1H), 9.34 (s, 1H). ¹³C NMR (400 MHz, CDCl₃): δ 13.7, 14.0, 22.8, 24.8, 35.0, 48.1, 62.1, 87.9, 109.4, 109.5, 117.9, 140.9, 144.7, 158.0, 196.8, HRMS (ESI) Calcd for C₁₅H₂₀NO₆ ([M+H]⁺) 310.1291, found 310.1288.

(4*S*,5*R*)-3-(Ethoxycarbonyl)-5-formyl-4-(furan-2-yl)-5-propyl-4,5-dihydroisoxazole 2-oxide (3r)

According to general procedure: 16 h, at room temperature, the product was obtained from flash chromatography (hexane/EtOAc = 8:1 to 2:1), as white solid 36 mg (Mp: 103-105 °C), 61% yield, 11:1 dr, 84% *ee*. HPLC analysis: Chiralcel OD-H (hexane/*i*-PrOH = 90/10, 1.0 mL/min), t_R (major) 9.18 min, t_R (minor) 15.85 min. $[\alpha]_D^{22} = +12.5^\circ$ ($c = 2.50$, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 0.96 (t, $J = 7.6$ Hz, 3H), 1.19 (t, $J = 6.8$ Hz, 3H), 1.35-1.40 (m, 1H), 1.48-1.59 (m, 1H), 1.92-2.11 (m, 2H), 4.17-4.29 (m, 2H), 4.70 (s, 1H), 6.28 (d, $J = 3.2$ Hz, 1H), 6.33-6.35 (dd, $J_1 = 3.2$ Hz, $J_2 = 22.0$ Hz, 1H), 7.36 (d, $J = 1.2$ Hz, 1H), 9.35 (s, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 14.0, 14.2, 16.2, 37.4, 50.7, 62.1, 87.6, 107.7, 110.1, 111.2, 143.5, 145.9, 157.9, 196.2, HRMS (ESI) Calcd for C₁₄H₁₈NO₆ ($[M+H]^+$) 296.1134, found 296.1135.

Transformation of *cis*-isoxazoline *N*-oxides into densely functionalized2-amino- γ -lactone

**(4*S*,5*R*)-5-Butyl-5-((tert-butyldimethylsilyloxy)methyl)-3-(methoxycarbonyl)-4-p
henyl-4,5-dihydroisoxazole 2-oxide (5)**

To the solution of **3c** (100 mg, 0.33 mmol) in MeOH/DCM 2 mL(1:3) under $-10\text{ }^\circ\text{C}$, was added NaBH_4 (25 mg, 0.66 mmol) portionwise. Reaction completed in 10 minutes, then quenched with 5 mL saturated aqueous ammonium chloride. After separation, and dry on anhydrous magnesium sulfate, the solvent was removed under reduced pressure. Obtained residue and imidazole (45 mg, 0.66 mmol) dissolved in 1.0 mL anhydrous DMF, then TBDMSCl (99 mg, 0.66 mmol) was added in one portion. Reaction finished in 5h, with TLC monitor. Subsequent chromatography purification on silicon gel gave colorless oil in 77% yield for two steps.

^1H NMR (400 MHz, CDCl_3): δ -0.29 (s, 3H), -0.16 (s, 3H), 0.78 (s, 9H), 0.93 (t, *J*

= 7.2 Hz, 3H), 1.33-1.52 (m, 4H), 1.94-1.96 (m, 2H), 3.23 (d, J = 10.5 Hz, 1H), 3.35 (d, J = 10.5 Hz, 1H), 3.68 (s, 3H), 4.40 (s, 1H), 7.14-7.17 (m, 2H), 7.30-7.32 (m, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ -6.1, -6.0, 14.0, 18.0, 22.9, 24.9, 25.7, 35.5, 52.5, 55.9, 61.3, 86.7, 113.0, 128.2, 128.7, 135.1, 159.4.

(4*S*,5*R*)-Methyl-5-butyl-5-((*tert*-butyldimethylsilyloxy)methyl)-4-phenyl-4,5-dihydroisoxazole-3-carboxylate (6)

A solution of **5** (82 mg, 0.2 mmol) in 1.0 mL $\text{P}(\text{OMe})_3$ was stirred at 100 °C for 16 h, with N_2 protection, hereafter diluted with Et_2O (5 mL), then 5 mL 1M HCl was added at -10 °C. After separation, dried over magnesium sulfate, solution was concentrated in *vacuo*, then applied to silicon gel to give colorless oil in quantitative yield.

^1H NMR (400 MHz, CDCl_3): δ -0.33 (s, 3H), -0.17 (s, 3H), 0.77 (s, 9H), 0.93 (t, J = 7.2 Hz, 3H), 1.25-1.48 (m, 4H), 1.80-1.83 (m, 2H), 3.25 (d, J = 10.5 Hz, 1H), 3.46 (d, J = 10.5 Hz, 1H), 3.76 (s, 3H), 4.30 (s, 1H), 7.03 (d, J = 6.6 Hz, 2H), 7.26-7.32 (m, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ -6.1, -6.0, 14.0, 18.0, 23.0, 25.1, 25.7, 36.0, 52.6, 58.9, 61.6, 94.7, 127.9, 128.6, 128.8, 133.8, 154.0, 160.8.

***tert*-Butyl (3*R*, 4*S*, 5*R*)-5-butyl-5-((*tert*-butyldimethylsilyloxy)methyl)-2-oxo-4-phenyl tetrahydrofuran-3-ylcarbamate (7)**

$\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ (0.33 mmol, 3 equiv), Boc_2O (0.33 mmol, 3 equiv) and **6** (0.11 mmol, 1 equiv) were suspended in a 3:1 mixture of MeOH/THF (0.8 mL) at -30 °C. After 10 min of stirring, NaBH_4 (1.1 mmol, 10 equiv) was added portionwise. The stirring was maintained at -30 °C for 24h. After the reaction was completed, it was quenched with

conc. NH_4OH (2 mL), extracted with dichloromethane, dried over magnesium sulfate and concentrated in *vacuo*. Silicon gel chromatography purification gave 31 mg colorless oil in 60% yield, 96% *ee*. HPLC analysis: Chiralcel IA-H (hexane/*i*-PrOH = 98/2, 1.0 mL/min), t_R (major) 6.87 min, t_R (minor) 8.36 min. $[\alpha]^{21}_D = +52.8^\circ$ ($c = 2.30$, CHCl_3).

^1H NMR (400 MHz, CDCl_3): δ -0.25 (s, 3H), -0.11 (s, 3H), 0.80 (s, 9H), 0.92 (t, $J = 7.2$ Hz, 3H), 1.29 (s, 9H), 1.35-1.41 (m, 4H), 1.87-1.92 (m, 2H), 3.33 (d, $J = 12.0$ Hz, 1H), 3.56 (d, $J = 12.0$ Hz, 1H), 3.72 (d, $J = 12.0$ Hz, 1H), 4.89 (d, $J = 8.0$ Hz, 1H), 5.05 (t, $J = 8.0$ Hz, 1H), 7.07 (d, $J = 8.0$ Hz, 2H), 7.26-7.31 (m, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ -6.1, 14.0, 18.1, 23.0, 25.6, 25.7, 25.7, 28.1, 35.2, 52.5, 53.3, 62.7, 80.2, 88.8, 127.8, 128.6, 129.6, 133.9, 155.1, 174.9. HRMS (ESI) Calcd for $\text{C}_{26}\text{H}_{43}\text{NO}_5\text{SiNa}$ ($[\text{M}+\text{Na}]^+$) 500.2808, found 500.2805.

3.5 References

1. For references of synthetic utilities of isoxazoline *N*-oxides, see: a) A. R. Minter, A. A. Fuller, A. K. Mapp, *J. Am. Chem. Soc.* **2003**, *125*, 6846; b) A. A. Fuller, B. Chen, A. R. Minter, A. K. Mapp, *J. Am. Chem. Soc.* **2005**, *127*, 5376; c) V. Jäger, W. Schwab, *Tetrahedron Lett.* **1978**, *19*, 3129; d) V. Jäger, W. Schwab, *Tetrahedron Lett.* **1978**, *19*, 3133; e) E. P. Schreiner, H. Gstach, *Synlett* **1996**, 1131; f) S. P. Ashburn, R. M. Coater, *J. Org. Chem.* **1984**, *49*, 3127; g) J. R. Manning, H. M. L. Davies, *J. Am. Chem. Soc.* **2008**, *130*, 8602; h) F. Damkaci, P. DeShong, *J. Am. Chem. Soc.* **2003**, *125*, 4408; i) R. Annunziata, M. Cinquini, F. Cozzi, L. Raimondi, *Tetrahedron* **1986**, *42*, 2129; j) P. Righi, E. Marotta, A. Landuzzi, G. Rosini, *J. Am. Chem. Soc.* **1996**, *118*, 9446.
2. For selected synthetic approaches to racemic isoxazoline *N*-oxides, see: a) R. A. Kunetsky, A. D. Dilman, S. L. Ioffe, A. M. Struchkova, Y. Strelenko, V. A. Tartakovsky, *Org. Lett.* **2003**, *5*, 4907; b) M. Clagett, A. Gooch, P. Graham, N. Holy, B. Mains, J. Strunk, *J. Org. Chem.* **1976**, *41*, 4033; c) R. A. Kunetsky, A. D. Dilman, M. I. Struchkova, P. A. Belyakov, V. A. Tartakovsky, S. L. Ioffe, *Synthesis* **2006**, *13*, 2265; d) B. B. Snider, Q. Che, *Tetrahedron* **2002**, *58*, 7821; e) P. M. Khan, R. Wu, K. S. Bisht, *Tetrahedron* **2007**, *63*, 1116; f) J. M. Mélot, F. Texier-Boullet, A. Foucaud, *Synthesis* **1988**, 558; g) S. Zen, M. Koyama, *Bull. Chem. Soc. Jpn.* **1971**, *44*, 2882.
3. For references of asymmetric synthesis of isoxazoline *N*-oxides using chiral reactants, see: (a) C.-Y. Zhu, X.-M. Deng, X.-L. Sun, J.-C. Zheng, Y. Tang, *Chem.*

Commun. **2008**, 738; b) C.-Y. Zhu, X.-L. Sun, X.-M. Deng, J.-C. Zheng, Y. Tang, *Tetrahedron* **2008**, 64, 5583.

4. H. Jiang, P. Elsner, K. L. Jensen, A. Falcicchio, V. Marcos, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2009**, 48, 6844.

(5) For references of racemic [4+1] annulation reactions, see: (a) A. Padwa, B. H. Norman, *Tetrahedron Lett.* **1988**, 29, 3041; b) A. M. Dalton, Y. Zhang, C. P. Davie, R. L. Danheiser, *Org. Lett.* **2002**, 4, 2465; c) J. L. Loebach, D. M. Bennett, R. L. Danheiser, *J. Am. Chem. Soc.* **1998**, 120, 9690; d) N. Chatani, M. Oshita, M. Tobisu, Y. Ishii, S. Murai, *J. Am. Chem. Soc.* **2003**, 125, 7812. (e) J. H. Rigby, Z. Wang, *Org. Lett.* **2002**, 4, 4289; f) J. H. Rigby, Z. Wang, *Org. Lett.* **2003**, 5, 263; g) M. Oshita, K. Yamshita, M. Tobisu, N. Chatani, *J. Am. Chem. Soc.* **2005**, 127, 761; h) M. W. Giese, W. H. Moser, *Org. Lett.* **2008**, 10, 4215; i) R. L. Danheiser, K. Bronson, S. Okano, *J. Am. Chem. Soc.* **1985**, 107, 4579; j) L. Lu, F. Li, J. An, J. Zhang, X. An, Q. Hua, W.-J. Xiao, *Angew. Chem. Int. Ed.* **2009**, 48, 9542.

6. For reference of asymmetric [4+1] annulation reactions using chiral reactants, see: a) J.-C. Zheng, C.-Y. Zhu, X.-L. Sun, Y. Tang, L.-X. Dai, *J. Org. Chem.* **2008**, 73, 6909; b) L.-Q. Lu, J.-J. Zhang, F. Li, Y. Cheng, J. An, J.-R. Chen, W.-J. Xiao, *Angew. Chem. Int. Ed.* **2010**, 49, 4495.

7. For reference of catalytic asymmetric [4+1] annulation reactions, see: S. Son, G. C. Fu, *J. Am. Chem. Soc.* **2007**, 129, 1046.

8. For reviews of enamine chemistry, see: a) B. List, *Acc. Chem. Res.* **2004**, 37, 548. b) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, 107, 5471.

9. G. Zhong, J. Fan, C. F. Barbas III, *Tetrahedron Lett.* **2004**, *45*, 5681.
10. For general review of nitro group, see: N. Ono, *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001.
11. For selected references of chiral pyrrolidine derivatives catalyzed reactions, see: a) J. Franzén, M. Marigo, D. Fielenbach, T. C. Wabnitz, A. Kjrsgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 18296; b) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem. Int. Ed.* **2005**, *44*, 4212; c) H. Xie, L. Zu, H. Li, J. Wang, W. Wang, *J. Am. Chem. Soc.* **2007**, *129*, 10886; d) D. Enders, M. R. M. Hüttl, C. Grondal, G. Raabe, *Nature* **2006**, *441*, 861; e) K. Shibatomi, H. Yamamoto, *Angew. Chem. Int. Ed.* **2008**, *47*, 5796; f) D. Zhu, M. Lu, L. Dai, G. Zhong, *Angew. Chem. Int. Ed.* **2009**, *48*, 60892; g) B. Tan, X. Zeng, Y. Lu, P. J. Chua, Zhong, G. *Org. Lett.* **2009**, *11*, 1927.
12. For selected reference of similar double bond geometric isomerization, see: J. Wang, F. Yu, X. Zhang, D. Ma, *Org. Lett.* **2008**, *10*, 2561.
13. For selected references of biologically active natural products containing 2-amino- γ -lactones as core, see: a) V. Matic, K. Kosowska, B. Bozdogan, L. M. Kelly, K. Smith, L. M. Ednie, G. Lin, K. L. Credito, C. L. Clark, P. McGhee, G. A. Pankuch, M. R. Jacobs, P. C. Appelbaum, *Antimicrob. Agents Chemother.* **2004**, *48*, 4103; b) K. Kosowska, K. Credito, G. A. Pankuch, D. Hoellman, G. Lin, C. Clark, B. Dewasse, P. McGhee, M. R. Jacobs, P. C. Appelbaum, *Antimicrob. Agents Chemother.* **2004**, *48*, 4113; c) G. Bringmann, T. A. M. Gulder, G. Schmitt, S. Lang, R. Stöhr, J. Wiese, K. Nagel, J. F. Imhoff, *Mar. Drugs*, **2007**, *5*, 23.

14. For reviews of tandem reactions, see: a) K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem. Int. Ed.* **2006**, *45*, 7134; b) H. Guo, J. Ma, *Angew. Chem. Int. Ed.* **2006**, *45*, 354; c) D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem. Int. Ed.* **2007**, *45*, 1570; d) D. Enders, A. Narine, *J. Org. Chem.* **2008**, *73*, 7857; e) X.-L. Sun, Y. Tang, *Acc. Chem. Res.* **2008**, *41*, 937.
15. For selected references of tandem reactions, see: a) Y. Huang, A. M. Walji, C. H. Larsen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 15051; b) B. Tan, Z. Shi, P. Chua, Y. Li, G. Zhong, *Angew. Chem. Int. Ed.* **2009**, *48*, 758; c) M. Lu, D. Zhu, Y. Lu, Y. Hou, B. Tan, Zhong, G. *Angew. Chem. Int. Ed.* **2008**, *47*, 10187; d) C. Zhang, C. K. De, R. Mal, D. Seidel, *J. Am. Chem. Soc.* **2007**, *130*, 416; e) D. Zhu, M. Lu, P. J. Chua, B. Tan, F. Wang, X. Yang, G. Zhong, *Org. Lett.* **2008**, *10*, 4585; f) J. Wang, F. Yu, X. Zhang, D. Ma, *Org. Lett.* **2008**, *10*, 5425; g) C. Cao, Y. Zhou, J. Zhou, X. Sun, Y. Tang, Y. Li, G. Li, J. Sun, *Chem. Eur. J.* **2009**, *15*, 11384; h) S. Belot, K. A. Vogt, C. Besnard, N. Krause, A. Alexakis, *Angew. Chem. Int. Ed.* **2009**, *48*, 8923.
16. For selected references involving intramolecular nucleophilic substitution, see: a) M. Marigo, S. Bertelsen, A. Landa, K. A. Jørgensen, *J. Am. Chem. Soc.* **2006**, *128*, 5475; b) D. Enders, C. Wang, J. W. Bats, *Angew. Chem. Int. Ed.* **2008**, *47*, 7539; c) N. Vignola, B. List, *J. Am. Chem. Soc.* **2004**, *126*, 450.
17. a) M. Kanao, Y. Watanabe, Y. Kimura, *J. Med. Chem.* **1989**, *32*, 1326; b) J. J. Riehl, A. Fougerousse, *Tetrahedron Lett.* **1968**, *42*, 4415.
18. R. Fornicola, E. Oblinger, J. Montgomery, *J. Org. Chem.* **1998**, *63*, 3528.
19. Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem. Int. Ed.* **2005**, *44*,

4212.

20. Y. Chi, S. H. Gellman, *Org. Lett.* **2005**, 7, 4253.

21. C. Cao, M. Ye, X. Sun, Y. Tang, *Org. Lett.* **2006**, 8, 2901.

22. O. J. Luis, J. Eusebio, *Tetrahedron* **2008**, 64, 9992.

23. J. V. B. Kanth, M. Periasamy, *Tetrahedron* **1993**, 49, 5127.

PPh₃-Catalyzed Formal [4+2] Annulation of Vinyl Ketones with *N*-Sulfonyl-1-Aza-1,3-Dienes

4.1 Introduction

Tetrahydropyridines are intriguing synthetic targets as they can be readily converted into highly functionalized pyridines or piperidines derivatives, which frequently occur in natural products and biologically active compounds.¹ However, existing synthetic methodologies used to synthesis such highly valuable heterocycles mainly rely on Lewis acid catalyzed aza-Diels-Alder reactions,² that have drawbacks such as harsh reaction conditions, and relatively narrow substrates scope. Thus the development of efficient, environmentally benign, and practical strategies for the construction of tetrahydropyridines is of great importance.

1) [4+2] annulation of 2-methylene-but-3-enoate and imines (Kwon's methodology)

2) [4+2] annulation of vinyl ketones and *N*-sulfonyl-1-aza-1,3-dienes (this work)

Scheme 4.1 Phosphine-Catalyzed [4 + 2] Annulations

In 2003, Kwon and co-workers developed an elegant protocol for the synthesis of highly functionalized tetrahydropyridines, *via* a phosphine

catalyzed [4+2] annulation reaction of 2-methyl-2,3-butadienoate with aldimines (Scheme 1, Eq. 1).³⁻⁵ However, the reactions had to be carried out under inert atmosphere, which limited its potential for large-scale chemical production. The same group later reported a phosphine promoted [3+3] annulation of aziridines with allenates.⁶ A major limitation was that a stoichiometric amount of PPh₃ was required. In order to demonstrate the versatility of organocatalysis,⁷ we decided to address these formidable challenges. Herein, we report a novel [4+2] annulation reaction of readily available vinyl ketones with *N*-sulfonyl-1-aza-1,3-dienes, which leads to access of valuable tetrahydropyridine derivatives (Scheme 1, Eq. 2).^{8,9} To the best of our knowledge, this is the first example of a [4+2] annulation between vinyl ketones and *N*-sulfonyl-1-aza-1,3-dienes.¹⁰

4.2 Results and Discussion

Initially, we tested the reaction of (*E*)-1,3-diphenyl-*N*-(tosyl) prop-2-en-1-imine **2a** with commercially available methyl vinyl ketone (MVK) **1a** in the presence of PPh₃ (20 mol %), and dichloromethane as solvent. To our delight, the starting materials were consumed completely at room temperature within 24h, and the desired product was isolated with good yield and diastereoselectivity (Table 4.1, entry 1). The effects of various sulfonyl protecting groups were subsequently investigated. It was found that all these reactions proceeded smoothly, with benzensulfonyl (Bs) protected 1, 3-azadiene

affording the [4+2] adduct **3a** with the highest yield and diastereoselectivity (entries 2-4).

Table 4.1 Protection group effect^a

	1a	2		3
Entry	2	t (h)	dr ^b	yield (%) ^c
1	2a Ts	24	10:1	74
2	2b Bs	24	10:1	87
3	2c Cs	10	6:1	67
4	2d Ns	10	8:1	69

^a Unless otherwise noted, the reactions were performed on a 0.1 mmol scale, in 0.2 mL DCM, at room temperature. ^b dr = *trans/cis*, determined by ¹H NMR. ^c Isolated yield of *trans* isomer.

Subsequent catalyst screening indicated that PPh₃ was the best choice, in terms of its catalytic performance, low cost, and operational simplicity. Other catalysts examined, such as DABCO and DMAP, gave unsatisfactory results (Table 4.2, entries 2, 5), while BINAP and POME₃ were ineffective catalysts (entries 1, 4). The more nucleophilic phosphine, PBU₃, afforded the product with excellent diastereoselectivity, albeit with disappointing yield (entry 3).

Table 4.2 Catalysts survey^a

Entry	4	t (h)	Dr ^b	yield (%) ^c
1	4a BINAP	48	nd	nr
2	4b DABCO	48	5:1	10
3	4c PBu ₃	24	>20:1	20
4	4d P(OMe) ₃	48	nd	nr
5	4e DMAP	48	4:1	40
6	4f PPh ₃	24	10:1	87

^a Unless otherwise noted, the reactions were performed on a 0.1 mmol scale, in 0.2 mL DCM, at room temperature. ^b dr = *trans/cis*, determined by ¹H NMR. ^c Isolated yield of *trans* isomer.

Solvent screening revealed that solvent effects significantly influenced the reaction outcome. Dichloromethane proved to be a superior with respect to yield and diastereoselectivity (Table 4.3, entry 1), whereas ethereal solvents, such as THF, showed a deleterious effect on reactivity (entry 6). Interestingly, an improvement in diastereoselectivity was observed, when chloroform was used (entry 3). Seeing that the main difference between dichloromethane and chloroform is the acidity, we hypothesized that solvents with suitable acidity or hydrogen-bonding ability would provide higher levels of stereocontrol. Thus, a

Table 4.3 Solvent screening^a

<div style="display: flex; align-items: center; justify-content: center; gap: 20px;"> <div style="text-align: center;"> <p>1a</p> </div> <div>+</div> <div style="text-align: center;"> <p>2b</p> </div> <div style="text-align: center;"> $\xrightarrow[\text{DCM, rt}]{20\text{mol\% PPh}_3}$ </div> <div style="text-align: center;"> <p>3a</p> </div> </div>				
Entry	Solvent	t (h)	dr ^b	yield (%) ^c
1	DCM	24	10:1	87
2	Toluene/DCM 2:1	24	10:1	67
3	CHCl ₃	10	12:1	80
4	MeCN/DCM 2:1	9	8:1	77
5	DCM/MeOH 1:1	24	>20:1	26
6	THF	24	nd	nr
7	DCM/MeOH 9:1	23	24:1	64
8	DCM/IPA 9:1	23	8:1	71
9	CHCl ₃ /MeOH 9:1	23	21:1	72
10	CHCl ₃ /IPA 9:1	23	9:1	74
11	DCM/H ₂ O 9:1	23	12:1	60
12	CHCl ₃ /EtOH 9:1	18	11:1	74
13	DCM/EtOH 9:1	16	10:1	79
14	DCM/MeOH 39:1	6	10:1	71
15	DCM/MeOH 19:1	22	13:1	81
16	DCM/MeOH 9:1	22	18:1	81

^a Unless otherwise noted, the reactions were performed on a 0.1 mmol scale, at room temperature. ^b dr = *trans/cis*, determined by ¹H NMR. ^c Isolated yield of

trans isomer.

mixture of dichloromethane and methanol (9:1) was examined for this transformation. As predicted, the product was obtained with excellent diastereoselectivity and good yield.

Table 4.4 Investigation of additives^a

<div style="display: flex; justify-content: space-around; margin-top: 10px;"> 1a 2b 3a </div>				
Entry	additive	t (h)	dr ^b	yield (%) ^c
1	LiCl	20	6:1	66
2	LiBr	20	3:1	69
3	LiClO ₄ ·3H ₂ O	20	3:1	20
4	Benzoic acid	22	12:1	78
5	Phenol	22	17:1	88
6	4-NO ₂ phenol	17	15:1	57
7	4-MeOphenol	8	16:1	91
8	4-Clphenol	16	16:1	78
9	2,2'-Biphenol	17	18:1	68
10	<i>R</i> -BINOL	17	11:1	85
11	3,5-Dimethoxyphenol	12	18:1	73

^a Unless otherwise noted, the reactions were performed on a 0.1 mmol scale, in 0.2 mL DCM, at room temperature. ^b dr = *trans/cis*, determined by ¹H NMR. ^c Isolated yield of *trans* isomer.

Encouraged by these results, we envisioned that methanol may act as a hydrogen bond donor, which stabilizes the enolate intermediate that is formed by nucleophilic addition of PPh₃ to MVK, thereby driving the reaction forward and accelerating the reaction (Figure 4.2). A series of Lewis and Brønsted acids was then tested (Table 4.4).¹¹ Among all the additives examined, 4-methoxyphenol afforded the product with the best yield and diastereoselectivity (entry 7), and in a significantly shorter time. Brønsted acids with lower pK_a, such as benzoic acid, 4-nitrophenol and 4-chlorophenol resulted in diminished yields (entries 4, 6 and 8). On the other hand, Brønsted acids with higher pK_a, like 3,5-dimethoxyphenol, delivered the product with better diastereoselectivity, but at the expense of chemical yield (entry 10). Lewis acids were found to give no improvement in yields and diastereoselectivities (entries 1-3).

Notably, when 30 mol% of 4-methoxyphenol was used, the reaction rate was further accelerated, and afforded almost exclusive *trans* diastereoselectivity and quantitative yield (Table 4.5). A control reaction, in which no PPh₃ was added, was carried out, and it was found that the reaction did not proceed when only 4-methoxyphenol was present (entry 4). This ruled out the possibility of a Diels-Alder reaction occurring between MVK and N-sulfonyl-1-aza-1,3-diene

2a catalyzed by the phenol additive.¹²

Table 4. 5 Effect of additive loading^a

Entry	X (mol%)	t (h)	dr ^b	yield (%) ^c
1	10	10	17:1	90
2	20	8	16:1	91
3	30	6	26:1	95
4 ^d	30	48	nd	nr

^a Unless otherwise noted, the reactions were performed on a 0.1 mmol scale, in 0.2 mL DCM, at room temperature. ^b dr = *trans/cis*, determined by ¹H NMR. ^c Isolated yield of *trans* isomer. ^d Without PPh₃. nd = no detection, nr = no reaction.

When the catalyst loading was reduced to 10 mol%, the excellent diastereoselectivity was maintained, but a lower yield and longer reaction time was observed (Table 4.6, entries 1, 2). Reaction concentration had significant influence on the reaction rate. Higher reaction concentration resulted in shorter reaction time at the expense of relatively lower chemical yield (entry 4). The use of 2 equivalents of MVK could still deliver the desired product satisfactorily, although there was a slight drop in yield (entry 6).

Table 4.6 Effect of catalyst loading, reaction concentration of **1a**^a

Entry	Y (mol%)	M of 2b	t (h)	dr ^b	yield (%) ^c
1	10	0.5	24	19:1	78
2	15	0.5	21	19:1	88
3	20	0.5	6	26:1	95
4	20	1.0	4	23:1	89
5	20	0.25	24	20:1	90
6 ^d	20	0.5	12	21:1	91

^a Unless otherwise noted, the reactions were performed on a 0.1 mmol scale, with 3 equiv. MVK, in 0.2 mL DCM, at room temperature. ^b dr = *trans/cis*, determined by ¹H NMR. ^c Isolated yield of *trans* isomer. ^d 2 equiv. MVK was used.

With the optimized reaction conditions established, the generality of this reaction was then explored (table 3). This protocol possessed high tolerance to various substituents. *Ortho*-substituted substrates, which usually lead to lower yields or unsatisfactory stereocontrol, due to steric hindrance, underwent this process to give products with complete diastereoselectivities and excellent yields were obtained (entries 2, 3). In addition, *meta*-, and *para*-substituted

phenyl-*N*-sulfonyl-1-aza-1,3-dienes also gave the corresponding products with good yields and diastereoselectivities. Regardless of the electronic nature of the

Table 4.7 Generality of [4+2] Annulation of Vinyl Ketones with *N*-sulfonyl-1-aza-1,3-dienes^a

Entry	2 (R ² , R ³)	3 (dr ^b , yield % ^c)
1	2a (Ph, Ph)	3a (>20:1, 95)
2	2b (2-FC ₆ H ₄ , Ph)	3b (>20:1, 90)
3	2c (2-Cl-5-NO ₂ C ₆ H ₄ , Ph)	3c (>20:1, 96)
4	2d (3-BrC ₆ H ₄ , Ph)	3d (19:1, 95)
5	2e (3-MeOC ₆ H ₄ , Ph)	3e (13:1, 83)
6	2f (3-MeC ₆ H ₄ , Ph)	3f (18:1, 81)
7	2g (4-NO ₂ C ₆ H ₄ , Ph)	3g (>20:1, 94)
8	2h (4-BrC ₆ H ₅ , Ph)	3h (17:1, 75)
9	2i (4-MeC ₆ H ₄ , Ph)	3i (13:1, 72)
10	2j (4-ClC ₆ H ₄ , Ph)	3j (10:1, 89)
11	2k (4-FC ₆ H ₄ , Ph)	3k (>20:1, 83)
12	2l (4-MeOC ₆ H ₄ , Ph)	3l (18:1, 83)
13	2m (2-Naphthyl, Ph)	3m (>20:1, 80)

Table 4.7 (continued)

14	2n (2,3-Dihydrobenzofuran-5-yl, Ph)	3n (18:1, 87)
15	2o (2-Furyl, Ph)	3o (19:1, 91)
16	2p (2-Thiophenyl, Ph)	3p (7:1, 87)
17	2q (Styryl, Ph)	3q (>20:1, 75)
18	2r (4-IC ₆ H ₄ , Ph)	3r (>20:1, 92)
19	2s (Styryl, Ph)	3s (20:1, 93)

^a Unless otherwise specified, the reactions were performed using 0.1 mmol of **2** and 0.3 mmol of **1a** in 0.2 mL DCM at room temperature, in the presence of 0.02 mmol PPh₃ and 0.03 mmol 4-methoxyphenol. ^b dr = *trans/cis*, determined by crude ¹H NMR. ^c Isolated yield of *trans* isomer.

phenyl rings, good to excellent chemical yields and dr values were obtained (entries 4-12). 2-naphthyl and 2, 3-dihydrobenzofuran-5-yl substituted aza-1,3-dienes were also well tolerated (entries 13, 14). This protocol could be further extended to heteroaryl *N*-sulfonyl-1-aza-1,3-dienes, although the substrate bearing a 2-thiophenyl substituent gave lower diastereoselectivity (entries 15, 16). Moreover, styryl and 4-iodophenyl substituted *N*-sulfonyl-1-aza-1,3-dienes, which can undergo ozonolysis and coupling reactions, to give synthetically useful products, could also be tolerated (entries 17-19).

It is also noteworthy that the scope of vinyl ketones was not strictly limited to MVK (Table 4.8). Ethyl vinyl ketone **1b** could also successfully undergo the

[4+2] annulations to generate the desired product **3t**, in 86% yield and with excellent diastereocontrol. Under the standard reaction conditions, vinyl ketones **1c**, **1d**, **1e**, **1f** only delivered moderate yields (50-70%), due to significant homo-coupling. Fortunately, this side reaction can be easily suppressed by the slow addition of a solution of **1c-f** to **2a**, *via* syringe pump, and the [4+2] annulations adducts could be obtained with good yields and excellent diastereoselectivities (entries 2-6).

Table 4.8 Scope of vinyl ketones^a

<p>1b-g 2a 3t-y</p> <p>1b R¹ = Et, 1c R¹ = cyclohexyl, 1d R¹ = phenyl, 1e R¹ = 2-furyl, 1f R¹ = 2-thiophenyl, 1g R¹ = <i>p</i>-tolyl</p>		
Entry	1	3 (dr ^b , yield % ^c)
1	1b	3t (>20:1, 86)
2 ^d	1c	3u (10:1, 85)
3 ^d	1d	3v (>20:1, 92)
4 ^d	1e	3w (>20:1, 90)
5 ^d	1f	3x (>20:1, 89)
6 ^d	1g	3y (>20:1, 94)

^a Unless otherwise specified, reactions were performed using 0.1 mmol of **2a** and 0.3 mmol of **1** in 0.2 mL DCM at room temperature, in the presence of 0.02

mmol PPh_3 and 0.03 mmol 4-methoxyphenol. ^b dr = *trans/cis*, determined by crude ^1H NMR. ^c Isolated yield of *trans* isomer. ^d 0.3 mmol **1c-g** in 0.2 mL DCM was added to 0.1 mL DCM solution of 0.1 mmol **2a** and 0.03 mmol 4-methoxyphenol, in 6 hours *via* syringe pump.

To demonstrate the ease and feasibility of scaling up this reaction, this reaction was carried out using 5 mmol of **2a**. The pure crystalline product **3a** (1.92g, 92% yield and >20:1 dr) was obtained after recrystallization from hexane and acetone, hence proving the potential of this strategy for scaling up (Scheme 4.2).

Scheme 4.2 Large Scale Annulation Reaction

X-ray crystallographic analysis of **3a** further confirmed the structure of the product which was previously established by NMR spectroscopy (Figure 4.1).

Figure 4.1 X-ray structure of **3a**

Hydrobenzo[*h*]quinoline is a core substructure which is frequently found in many biologically active natural products, such as *Sanguinarine*, *Chelerythrine*, *Tetrahydroberberine*,¹³ and *Corynoline*.¹⁴ To highlight the synthetic utility of this methodology, this molecular complex was efficiently assembled in a single step *via* the reaction of *N*-sulfonyl-1-aza-1,3-dienes **2t** and methyl vinyl ketone.

Scheme 4.3 Synthesis of *N*-containing tricyclic compounds.

Alternatively, hydro-1H-indeno[1,2-*b*]pyridine derivatives, which are potent antispermatogenic agents,¹⁵ were also synthesized *via* this protocol, with excellent diastereoselectivity, and 84% yield (Scheme 4.3).

The synthetic utility of this methodology was further demonstrated (Scheme 4.4). Deprotection of the benzensulfonyl group was readily carried out under mild reaction conditions to give imine product **4**, which leads to the synthesis of highly substituted pyridine **5**,¹⁶ by oxidation with 2, 3-dichloro-5, 6-dicyanobenzo-quinone (DDQ), in 88% yield. Furthermore, simple reduction of

imine intermediate **4** with sodium cyanoborohydride directly afforded piperidine adduct **6** in almost quantitative yield and good diastereoselectivity.¹⁷ Lastly, racemic piperidine adduct **6** could be resolved with a chiral acid, such as tartaric acid, to give the optically active product.

Scheme 4.4 Synthesis of Pyridine and Piperidine from Tetrahydro-pyridine

Adduct **3a**. a) TFA/thioanisole, *p*-TSA.H₂O, rt, 5h, 88% yield, b) DDQ, DCM, rt, 2h, 70% yield, c) NaBH₃CN, rt, 0.5h, 95% yield, 4:1 dr.

In order to better understand this novel [4+2] annulation reaction, preliminary mechanistic investigations were carried out (Scheme 4.5). Surprisingly, when deuterium labeled **1g'** (>99% D) was used, 40% of the deuterium was incorporated at the 3-position of **4y'** (eq. a). This interesting phenomenon suggests that carbanion at the 3-position might be generated during the course of reaction. This hypothesis was further proved by experiment **b**. Deuterium labelled *N*-sulfonyl-1-aza-1,3-diene **2a'** (>99% D) was subjected to the standard reaction conditions, and as predicted, similar incorporation of

deuterium at the 3-position was observed (eq. b). The erosion of deuterium content probably resulted from the presence of adventitious H₂O and additives. To elucidate our speculation, a reaction between **1g** and **2a** was conducted in the presence of 10 equiv. D₂O under standard conditions. The reaction proceeded smoothly to deliver the product with similar chemical outcomes, in which 69% deuterium incorporation occurred at the 3-position of **3y''**, accompanied with 44% deuterium incorporation at the 5-position (eq. c).

Scheme 4.5 Mechanistic Investigation

Based on the above observations, a rational mechanism was proposed (Figure 4.2). The reaction is initiated by the addition of PPh₃ to the vinyl ketone,

to generate enolate intermediate **7**, which subsequently undergoes a 1,4-addition to *N*-sulfonyl-1-aza-1,3-diene **2a**, to form key intermediate **8**.¹⁸ An equilibrium of enamine **8** and carbanion **9** then affords enolate **10** after an intramolecular proton transfer. This is followed by the formation of imine intermediate **11** and regeneration of the catalyst. Subsequent imine-enamine isomerisation affords intermediate **12**, which is believed to undergo an intramolecular Micheal addition (IMMA) with the assistance of the phenol additive, to finally deliver the desired product **3**.

Figure 4.2 Proposed Catalytic Cycle of [4+2] Annulation Between Vinyl Ketones and *N*-Sulfonyl-1-aza-1, 3-Dienes

4.3 Conclusion

In summary, a novel [4 + 2] annulation reaction between vinyl ketones and *N*-sulfonyl-1-aza-1,3-dienes was developed. This reaction furnishes highly functionalized tetrahydropyridines in good to excellent yields (up to 96%) and excellent diastereoselectivities (up to >20:1) with the utilization of the cheap, easily accessible and environmentally friendly catalyst, PPh₃. This protocol has potential for industrial application due to its simple operation, wide substrate scope and economic significance. Additional investigation on the mechanism and an asymmetric version of this reaction is currently underway in our laboratory.

4.4 Experimental Section

Analytical thin layer chromatography (TLC) was performed using Merck 60 F254 precoated silica gel plate (0.2 mm thickness). Subsequent to elution, plates were visualized using UV radiation (254 nm) on Spectroline Model ENF-24061/F 254 nm. Further visualization was possible by staining with basic solution of potassium permanganate or acidic solution of ceric molybdate. Flash column chromatography was performed using Merck silica gel 60 with freshly distilled solvents. Columns were typically packed as slurry and equilibrated with the appropriate solvent system prior to use. Proton nuclear magnetic resonance spectra (¹H-NMR) were recorded on Bruker AMX 400 spectrophotometer (CDCl₃ as solvent). Chemical shifts for ¹H NMR spectra are reported as δ in units of parts per million (ppm) downfield from SiMe₄ (δ 0.0) and relative to the signal of chloroform-d (δ 7.26, singlet). Multiplicities were

given as: s (singlet), d (doublet), t (triplet), dd (doublets of doublet) or m (multiplets). The number of protons (n) for a given resonance is indicated by nH. Coupling constants are reported as a *J* value in Hz. Carbon nuclear magnetic resonance spectra (¹³C-NMR) are reported as δ in units of parts per million (ppm) downfield from SiMe₄ (δ 0.0) and relative to the signal of chloroform-d (δ 77.0, triplet). High resolution mass spectrometry (HRMS) was recorded on Finnigan MAT 95 × P spectrometer

Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification.

Preparation of vinyl ketones

General Procedure for the Synthesis of Vinyl Ketones (1c-f)

R¹ = cyclohexyl, phenyl, 2-Furyl, 2-Thiophenyl

Typical Procedure for the Preparation of Vinyl Alcohols

To a stirred solution of aldehyde (4.0 mmol) in THF (10 mL) was slowly added vinylmagnesium bromide solution (1.0 M in THF, 8 mL, 2 equiv) at 0 °C under nitrogen. The solution was stirred at 0 °C for 15 min and then at room temperature for 3 h. The resulting solution was quenched with saturated NaHCO₃ aqueous solution (5 mL). The mixture was extracted with DCM (3 × 10 mL). The combined organic layers were successively washed with brine, dried over MgSO₄, and concentrated under vacuum. Purification by flash column chromatography on silica gel in ethyl acetate and hexane gave vinyl

alcohols as pale yellow viscous liquids quantitatively.

1-cyclohexylprop-2-en-1-ol

^1H NMR (400MHz, CDCl_3): δ 5.80-5.88 (m, 1H), 5.10-5.20 (m, 2H), 3.82 (brs, 1H), 0.97-1.87 (m, 12H).

1-phenylprop-2-en-1-ol

^1H NMR (500MHz, CDCl_3): δ 7.31-7.40 (m, 5H), 6.05-6.11 (m, 1H), 5.39 (d, $J = 1.3$ Hz, 1H), 5.22-5.36 (m, 2H), 2.24 (brs, 1H).

1-(furan-2-yl)prop-2-en-1-ol

^1H NMR (400MHz, CDCl_3): δ 7.39 (s, 1H), 6.34 (s, 1H), 6.25 (d, $J = 3.1$ Hz, 1H), 6.08-6.16 (m, 1H), 5.42 (d, $J = 17.2$ Hz, 1H), 5.22 (d, $J = 5.3$ Hz, 2H), 2.17 (brs, 1H).

1-(thiophen-2-yl)prop-2-en-1-ol

^1H NMR (400MHz, CDCl_3): δ 7.27 (t, $J = 4.7$ Hz, 1H), 6.98 (t, $J = 4.2$ Hz, 1H), 6.09-6.17 (m, 1H), 5.41 (d, $J = 17.0$ Hz, 2H), 5.23 (d, $J = 10.2$ Hz, 1H), 2.25 (brs, 1H).

Typical procedure for the preparation of vinyl ketones¹⁹

IBX (1.26 g, 4.5 mmol, 1.5 equiv) was added portionwise to a solution of vinyl alcohol (3.0 mmol) in DMSO (3 mL) at room temperature. The reaction

mixture was stirred for 1.5 h, then water (1.8 mL) and DCM (1.8 mL) were added. After filtration through a pad of Celite, the aqueous phase was extracted with DCM (3 × 6 mL). The organic phases were combined and washed with water (2 × 3 mL), dried over MgSO₄, and concentrated under vacuum. Purification by column chromatography on silica gel in ethyl acetate and hexane afforded the enones **1** as pale yellow oils.

1- cyclohexylprop-2-en-1-one (1c)

Yield: 75%; ¹H NMR (400MHz, CDCl₃): δ 6.38-6.45 (m, 1H), 6.24 (dd, *J* = 17.5, 1.3 Hz, 1H), 5.73 (dd, *J* = 10.5, 1.3 Hz, 1H), 2.60 (m, 1H), 1.18-1.83 (m, 10H); ¹³C NMR (100MHz, CDCl₃): δ 203.5, 135.0, 127.7, 48.2, 28.5, 25.9, 25.7.

1- phenylprop-2-en-1-one (1d)

Yield: 80%; ¹H NMR (500MHz, CDCl₃): δ 7.94-7.96 (m, 2H), 7.56-7.59 (m, 3H), 7.46-7.49 (m, 1H), 6.43 (dd, *J* = 17.1, 1.7 Hz, 1H), 5.93 (dd, *J* = 10.6, 1.7 Hz, 1H); ¹³C NMR (125MHz, CDCl₃): δ 191.1, 137.3, 133.0, 132.4, 130.2, 128.7, 128.6, 128.5.

1-(furan-2-yl)prop-2-en-1-one (1e)

Yield: 72%; ¹H NMR (400MHz, CDCl₃): δ 7.62-7.63 (m, 1H), 7.25-7.26 (m, 1H), 7.02-7.08 (m, 1H), 6.50-6.56 (m, 2H), 5.86 (dd, *J* = 10.5,

1.6 Hz, 1H); ^{13}C NMR (100MHz, CDCl_3): δ 178.1, 153.0, 146.9, 131.3, 129.5, 118.3, 112.5.

1-(thiophen-2-yl)prop-2-en-1-one (1f)

Yield: 74%; ^1H NMR (400MHz, CDCl_3): δ 7.66-7.78 (m, 2H), 7.04-7.16 (m, 2H), 6.49 (dd, J = 17.0, 1.6 Hz, 1H), 5.86 (dd, J = 10.4, 1.6 Hz, 1H); ^{13}C NMR (100MHz, CDCl_3): δ 182.5, 144.6, 134.3, 132.4, 131.9, 129.5, 128.3.

1-*p*-tolylprop-2-en-1-one (1g) was prepared according literature²⁰:

1-*p*-tolylprop-2-en-1-one (1g)

Yield: 60%; ^1H NMR (400MHz, CDCl_3): δ 7.86 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 7.17 (dd, J = 17.2, 10.8 Hz, 1H), 6.90 (dd, J = 17.2, 1.6 Hz, 1H), 5.89 (dd, J = 10.8, 1.6 Hz, 1H); ^{13}C NMR (100MHz, CDCl_3): δ 190.6, 143.9, 132.4, 129.7, 129.3, 128.9

General Procedure for the Synthesis of *N*-Benzenesulfonyl-1-Aza-1,3-Dienes (2a-u)²¹

Chalcone and its derivatives were purchased from Sigma-Aldrich, or synthesized according to previous reported protocols.²²

To a solution of benzenesulfonamide (471 mg, 3.0 mmol) and chalcone or its derivative (3 mmol) in DCM (15 mL), cooled to 0 °C, were successively added Et_3N (0.75 mL, 9.0 mmol) and TiCl_4 (0.36 mL, 3.0 mmol) under nitrogen.

The reaction mixture was heated at reflux overnight. The solution was cooled to room temperature, quenched with water (100 mL), and extracted with DCM (3 × 30 mL). The combined organic phase was dried over MgSO₄ and concentrated. The residue was purified by flash chromatography on silica gel in DCM and hexane to afford the substrate **2**.

(E)-1,3-diphenyl-N-(benzenesulfonyl)prop-2-en-1-imine (2a)

2a

Yield: 78%; ¹H NMR (400MHz, CDCl₃): δ 8.04-8.06 (m, 3H), 7.42-7.65 (m, 13H), 7.08 (d, *J* = 16.1 Hz, 1H).

(E)-3-(2-fluorophenyl)-1-phenyl-N-(benzenesulfonyl)prop-2-en-1-imine (2b)

2b

Yield: 74%; ¹H NMR (500MHz, CDCl₃): δ 7.68-8.05 (m, 4H), 7.52-7.61 (m, 4H), 7.39-7.47 (m, 3H), 7.21-7.26 (m, 4H), 7.08-7.12 (m, 1H).

(E)-3-(2-chloro-5-nitrophenyl)-1-phenyl-N-(benzenesulfonyl)prop-2-en-1-imine (2c)

2c

Yield: 68%; ¹H NMR (500MHz, CDCl₃): δ 8.63 (m, 1H), 8.19-8.21 (m, 4H), 7.40-8.06 (m, 10 H).

(E)-3-(3-bromophenyl)-1-phenyl-N-(benzenesulfonyl)prop-2-en-1-imine

(2d)

2d

Yield: 80%; ^1H NMR (300MHz, CDCl_3): δ

8.03-8.06 (d, $J = 7.5$ Hz, 3H), 7.29-7.68 (m, 12H), 6.98 (d, $J = 16.1$ Hz, 1H).

(E)-3-(3-methoxyphenyl)-1-phenyl-N-(benzenesulfonyl)prop-2-en-1-imine

(2e)

2e

Yield: 78%; ^1H NMR (400MHz, CDCl_3): δ

8.06-8.08 (d, $J = 6.4$ Hz, 3H), 6.99-7.67 (m, 13H), 3.87 (s, 3H).

(E)-3-(m-tolyl)-1-phenyl-N-(benzenesulfonyl)prop-2-en-1-imine (2f)

2f

Yield: 77%; ^1H NMR (400MHz, CDCl_3): δ 9.05 (m,

3H), 7.06-8.08 (m, 13H), 2.41 (s, 3H).

(E)-3-(4-nitrophenyl)-1-phenyl-N-(benzenesulfonyl)prop-2-en-1-imine (2g)

2g

Yield: 78%; ^1H NMR (400MHz, CDCl_3): δ

8.27 (d, $J = 8.6$ Hz, 2H), 8.05 (d, $J = 6.3$ Hz, 3H), 7.46-7.74 (m, 10H), 7.09 (d, J

= 16.3 Hz, 1H).

(E)-3-(4-bromophenyl)-1-phenyl-N-(benzenesulfonyl)prop-2-en-1-imine

(2h)

2h

Yield: 81%; ^1H NMR (400MHz, CDCl_3): δ 8.04

(d, J = 7.0 Hz, 3H), 7.40-7.65 (m, 12H), 7.01 (d, J = 16.1 Hz, 1H).

(E)-3-(p-tolyl)-1-phenyl-N-(benzenesulfonyl)prop-2-en-1-imine (2i)

2i

Yield: 68%; ^1H NMR (400MHz, CDCl_3): δ 9.02

(m, 3H), 7.46-8.05 (m, 10H), 7.21-7.23 (m, 2H), 7.07 (d, J = 16.0 Hz, 1H), 2.40

(s, 3H).

(E)-3-(4-chlorophenyl)-1-phenyl-N-(benzenesulfonyl)prop-2-en-1-imine (2j)

2j

Yield: 82%; ^1H NMR (400MHz, CDCl_3): δ 8.04

(d, J = 6.9 Hz, 3H), 7.38-7.64 (m, 12H), 7.03 (d, J = 16.1 Hz, 1H).

(E)-3-(4-fluorophenyl)-1-phenyl-N-(benzenesulfonyl)prop-2-en-1-imine (2k)

2k

Yield: 81%; ^1H NMR (400MHz, CDCl_3): δ 8.05

(d, $J = 6.7$ Hz, 3H), 7.43-7.64 (m, 10H), 7.03-7.13 (m, 3H).

(E)-3-(4-methoxyphenyl)-1-phenyl-N-(benzenesulfonyl)prop-2-en-1-imine

(2l)

2l

Yield: 72%; ^1H NMR (400MHz, CDCl_3): δ

8.04 (d, $J = 4.0$ Hz, 3H), 7.42-7.97 (m, 10H), 7.06 (d, $J = 16.0$ Hz, 1H), 6.93 (d,

$J = 8.0$ Hz, 2H), 3.86 (s, 3H).

(E)-3-(naphthalen-2-yl)-1-phenyl-N-(benzenesulfonyl)prop-2-en-1-imine

(2m)

2m

Yield: 61%; ^1H NMR (400MHz, CDCl_3): δ

7.24-8.09 (m, 19H).

(E)-3-(2,3-dihydrobenzofuran-5-yl)-1-phenyl-N-(benzenesulfonyl)prop-2-en-1-imine (2n)

2n

Yield: 74%; ^1H NMR (500MHz, CDCl_3): δ 8.05

(d, $J = 6.3$ Hz, 3H), 7.28-7.61 (m, 10H), 7.06 (d, $J = 15.8$ Hz, 1H), 6.79 (d, $J =$

8.3 Hz, 1H), 4.66 (t, $J = 8.7$ Hz, 2H), 3.26 (d, $J = 8.7$ Hz, 2H).

(E)-3-(furan-2-yl)-1-phenyl-N-(benzenesulfonyl)prop-2-en-1-imine (2o)

Yield: 74%; ^1H NMR (500MHz, CDCl_3): δ 8.11-8.19

(m, 3H), 7.42-8.05 (m, 9H), 6.85 (d, $J = 15.7$ Hz, 1H), 6.69 (d, $J = 3.1$ Hz, 1H), 6.51-6.52 (m, 1H).

(E)-3-(thiophen-2-yl)-1-phenyl-N-(benzenesulfonyl)prop-2-en-1-imine (2p)

Yield: 79%; ^1H NMR (400MHz, CDCl_3): δ 8.04 (d, J

$= 4.0$ Hz, 3H), 7.28-7.62 (m, 10H), 7.19 (d, $J = 16.0$ Hz, 1H), 7.09 (t, $J = 4.0$ Hz, 1H).

(2E,4E)-1,5-diphenyl-N-(benzenesulfonyl)penta-2,4-dien-1-imine (2q)

Yield: 70%; ^1H NMR (500MHz, CDCl_3): δ

8.04 (m, 2H), 7.34-7.60 (m, 14H), 7.05-7.14 (m, 1H), 6.86-6.95 (m, 2H).

(E)-1-(4-iodophenyl)-3-phenyl-N-(benzenesulfonyl)prop-2-en-1-imine (2r)

Yield: 84%; ^1H NMR (400MHz, CDCl_3): δ 8.03

(d, $J = 6.9$ Hz, 3H), 7.80 (d, $J = 8.3$ Hz, 2H), 7.37-7.59 (m, 10H), 7.05 (d, $J =$

16.1 Hz, 1H).

(2*E*,4*E*)-1,5-diphenyl-*N*-(benzenesulfonyl)penta-2,4-dien-1-imine (2s)

2s

Yield: 68%; ¹H NMR (500MHz, CDCl₃): δ 8.06 (d, *J* = 7.1 Hz, 2H), 7.63-7.61 (m, 10H), 7.42-7.43 (m, 7H).

((*E*)-2-benzylidene-3,4-dihydronaphthalen-1(2H)-ylidene)benzenesulfonamide (2t)

de (2t)

2t

Yield: 50%; ¹H NMR (400MHz, CDCl₃): δ 8.19 (d, *J* = 7.2 Hz, 1H), 8.10 (d, *J* = 8.0 Hz, 2H), 7.89 (s, 1H), 7.52-7.59 (m, 3H), 7.43-7.48 (m, 5H), 7.34-7.38 (m, 1H), 7.27-7.31 (m, 1H), 7.20 (d, *J* = 7.6 Hz, 1H), 2.99 (s, 4H).

((*E*)-2-benzylidene-2,3-dihydroinden-1-ylidene)benzenesulfonamide (2u)

2u

Yield: 60%; ¹H NMR (400MHz, CDCl₃): δ 8.89 (d, *J* = 7.8 Hz, 1H), 8.15 (d, *J* = 6.6 Hz, 2H), 7.86 (s, 1H), 7.37-7.66 (m, 11H), 4.08 (s, 2H).

General procedure for the [4 + 2] Annulations

Small scale: To a stirred solution of imine **2** (0.1 mmol), PPh₃ (5.24 mg,

0.02 mmol, 0.2 equiv) and 4-Methoxyphenol (3.72mg, 0.03 mmol, 0.3 equiv) in DCM (0.2 mL) vinyl ketone **1** (0.3 mmol, 3 equiv) was added. After completion of the reaction (monitored by TLC), the solvent was evaporated under reduced pressure. Purification by flash column chromatography on silica gel in acetone and hexane gave the annulation product **3** as crystalline solid.

Larger scale: To a stirred solution of **2a** (1.73 g, 5 mmol), PPh₃ (0.262 g, 1 mmol, 0.2 equiv) and 4-methoxyphenol (0.186 g, 1.5 mmol, 0.3 equiv) in DCM (10 mL), **1a** (0.84 mL, 10 mmol, 2 equiv) was added. After completion of the reaction (monitored by TLC), the solvent was evaporated under reduced pressure. Recrystallization from hexane/acetone afforded **3a** as white crystalline solid (1.92 g, 92%).

Product characteristic data

1-(*trans*-4,6-diphenyl-1-(phenylsulfonyl)-1,2,3,4-tetrahydropyridin-3-yl)ethanone (**3a**)

3a

Yield: 95%; White crystalline solid. m.p. = 182-184 °C; ¹H NMR (400MHz, CDCl₃): δ 7.72 (d, *J* = 7.2 Hz, 2H), 7.62 (t, *J* = 7.6 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 2H), 7.34-7.36 (m, 2H), 7.21-7.28 (m, 6H), 6.89 - 6.91 (m, 2H), 5.50 (d, *J* = 3.6 Hz, 1H), 4.47 (dd, *J* = 13.8, 3.0 Hz, 1H), 3.84 (dd, *J* = 10.8, 3.2 Hz, 1H), 3.37 (dd, *J* = 13.6, 11.6 Hz, 1H), 2.76 (dt, *J* = 10.8, 3.2 Hz, 1H), 1.91 (s, 3H); ¹³C NMR (100MHz, CDCl₃) δ 208.1, 141.5, 139.4, 138.8, 137.9, 133.1, 129.1, 128.8, 128.3, 127.7, 127.5, 127.2, 122.7, 52.2, 49.1, 43.4,

31.0; HRMS (ESI): calcd. for $[M+H]^+$ ($C_{25}H_{24}NO_3S$) requires 418.1477, found 418.1476.

1-(*trans*-4-(2-fluorophenyl)-6-phenyl-1-(phenylsulfonyl)-1,2,3,4-tetrahydropyridin-3-yl)ethanone (3b)

3b

Yield: 90%; White crystalline solid. m.p. = 140-142 °C; 1H NMR (400MHz, $CDCl_3$): δ 7.69 (d, J = 8.0 Hz, 2H), 7.61 (t, J = 8.0 Hz, 1H), 7.50 (t, J = 8.0 Hz, 2H), 7.18-7.33 (m, 6H), 6.97-7.05 (m, 2H), 6.83-6.85 (m, 1H), 5.42 (d, J = 3.6 Hz, 1H), 4.46 (dd, J = 16.0, 4.0 Hz, 1H), 4.16 (dd, J = 8.0, 4.0 Hz, 1H), 3.46 (dd, J = 16.0, 12.0 Hz, 1H), 2.89 (dt, J = 12.0, 4.0 Hz, 1H), 1.96 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 207.6, 161.8, 159.3, 139.5, 139.2, 137.8, 133.1, 129.2, 129.2, 128.9, 128.9, 128.3, 128.1, 127.9, 127.8, 127.5, 124.6, 124.5, 121.2, 115.9, 115.7, 50.8, 49.0, 36.5, 30.4; HRMS (ESI): calcd. for $[M+H]^+$ ($C_{25}H_{23}NO_3SF$) requires 436.1383, found 436.1382.

1-(*trans*-4-(2-chloro-5-nitrophenyl)-6-phenyl-1-(phenylsulfonyl)-1,2,3,4-tetrahydropyridin-3-yl)ethanone (3c)

3c

Yield: 96%; Brown crystalline solid. m.p. = 135-137 °C; ^1H

NMR (400MHz, CDCl_3): δ 8.01-8.04 (m, 1H), 7.52-7.75 (m, 7H), 7.26-7.34 (m, 5H), 5.30 (d, J = 3.1 Hz, 1H), 4.48-4.52 (m, 2H), 3.55 (dd, J = 14.1, 10.9 Hz, 1H), 2.89 (m, 1H), 2.03 (s, 3H); ^{13}C NMR (100MHz, CDCl_3) δ 206.0, 146.9, 141.1, 140.7, 140.3, 138.7, 137.5, 133.8, 131.1, 129.5, 128.6, 127.9, 127.6, 127.6, 123.5, 123.3, 118.7, 49.7, 48.6, 39.4, 30.1; HRMS (ESI): calcd. for $[\text{M}+\text{H}]^+$ ($\text{C}_{25}\text{H}_{22}\text{N}_2\text{O}_5\text{SCl}$) requires 497.0938, found 497.0937.

**1-(*trans*-4-(3-bromophenyl)-6-phenyl-1-(phenylsulfonyl)-1,2,3,4-tetrahydro
pyridin-3-yl)ethanone (3d)**

3d

Yield: 95%; White crystalline solid. m.p. = 137-139 °C; ^1H

NMR (400MHz, CDCl_3): δ 7.77 (d, J = 7.4 Hz, 1H), 7.58-7.69 (m, 4H), 7.28-7.41 (m, 7H), 7.09-7.13 (m, 1H), 6.90-6.97 (m, 1H), 5.46 (d, J = 3.2 Hz, 1H), 4.53 (dd, J = 14.0, 3.1 Hz, 1H), 3.88 (dd, J = 10.5, 3.2 Hz, 1H), 3.36 (dd, J = 13.9, 11.8 Hz, 1H), 2.59 (dt, J = 11.3, 3.0 Hz, 1H), 1.98 (s, 3H); ^{13}C NMR (100MHz, CDCl_3) δ 207.2, 143.8, 139.4, 138.9, 137.8, 133.6, 130.5, 130.3,

130.2, 129.4, 128.5, 127.9, 127.8, 127.5, 126.9, 122.8, 121.7, 51.7, 49.1, 42.6, 30.8; HRMS (ESI): calcd. for $[M+H]^+$ ($C_{25}H_{23}NO_3SBr$) requires 496.0582, found 496.0585.

1-(*trans*-4-(3-methoxyphenyl)-6-phenyl-1-(phenylsulfonyl)-1,2,3,4-tetrahydropyridin-3-yl)ethanone (3e)

3e

Yield: 83%; Light yellow crystalline solid. m.p. = 103-107 °C; 1H NMR (400MHz, $CDCl_3$): δ 7.70 (d, J = 8.0 Hz, 2H), 7.60 (t, J = 8.0 Hz, 1H), 7.50 (t, J = 6.0 Hz, 2H), 7.32-7.34 (m, 2H), 7.21-7.27 (m, 3H), 7.14 (t, J = 8.0 Hz, 1H), 6.75 (dd, J = 2.0 8.4 Hz, 1H), 6.58 (s, 1H), 6.49 (d, J = 7.6 Hz, 1H), 5.50 (d, J = 4.0 Hz, 1H), 4.46 (dd, J = 16.0, 4.0 Hz, 1H), 3.79-3.84 (m, 4H), 3.36 (dd, J = 16.0, 12.0 Hz, 1H), 2.77 (dt, J = 12.0, 4.0 Hz, 1H), 1.94 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 208.1, 159.9, 143.1, 139.4, 138.9, 137.9, 133.2, 129.7, 129.1, 128.2, 127.8, 127.8, 127.5, 122.4, 119.9, 113.8, 112.3, 55.3, 52.1, 49.1, 43.5, 31.1; HRMS (ESI): calcd. for $[M+H]^+$ ($C_{26}H_{26}NO_4S$) requires 448.1583, found 448.1587.

1-(*trans*-6-phenyl-1-(phenylsulfonyl)-4-m-tolyl-1,2,3,4-tetrahydropyridin-3-yl)ethanone (3f)

Yield: 81%; White crystalline solid. m.p. = 135-138 °C; ^1H NMR (400MHz, CDCl_3): δ 7.74 (d, J = 8.0 Hz, 2H), 7.62-7.65 (m, 1H), 7.54 (t, J = 8.0 Hz, 2H), 7.01-7.38 (m, 7H), 6.67-6.70 (m, 2H), 5.48 (d, J = 4.0 Hz, 1H), 4.48 (dd, J = 16.0, 4.0 Hz, 1H), 3.79 (dd, J = 12.0, 4.0 Hz, 1H), 3.38 (dd, J = 16.0, 12.0 Hz, 1H), 2.72 (dt, J = 12.0, 4.0 Hz, 1H), 2.30 (s, 3H), 1.91 (s, 3H); ^{13}C NMR (100MHz, CDCl_3) δ 208.2, 141.3, 139.3, 138.6, 138.4, 138.0, 133.2, 129.2, 128.6, 128.3, 128.0, 127.9, 127.8, 127.5, 124.8, 122.9, 51.8, 49.1, 43.5, 31.1, 21.5; HRMS (ESI): calcd. for $[\text{M}+\text{H}]^+$ ($\text{C}_{26}\text{H}_{26}\text{NO}_3\text{S}$) requires 432.1633, found 432.1634.

1-(*trans*-4-(4-nitrophenyl)-6-phenyl-1-(phenylsulfonyl)-1,2,3,4-tetrahydropyridin-3-yl)ethanone (3g)

Yield: 94%; Brown crystalline solid. m.p. = 142-145 °C; ^1H NMR (400MHz, CDCl_3): δ 8.11 (d, J = 8.0 Hz, 2H), 7.65-7.73 (m, 3H), 7.54 (t, J = 8.0 Hz, 2H), 7.24-7.34 (m, 5H), 7.15 (d, J = 8.0 Hz, 2H), 5.48 (d, J = 4.0 Hz,

1H), 4.63 (dd, $J = 12.0, 4.0$ Hz, 1H), 4.12 (dd, $J = 8.0, 4.0$ Hz, 1H), 3.35 (dd, $J = 12.0, 10.0$ Hz, 1H), 2.86 (dt, $J = 12.0, 4.0$ Hz, 1H), 2.08 (s, 3H); ^{13}C NMR (100MHz, CDCl_3) δ 206.3, 149.5, 147.1, 140.1, 139.4, 137.2, 133.3, 129.2, 128.9, 128.7, 128.0, 127.8, 127.6, 124.0, 120.6, 52.7, 49.1, 42.2, 30.5; HRMS (ESI): calcd. for $[\text{M}+\text{H}]^+$ ($\text{C}_{25}\text{H}_{23}\text{N}_2\text{O}_5\text{S}$) requires 463.1328, found 463.1324.

1-(trans-4-(4-bromophenyl)-6-phenyl-1-(phenylsulfonyl)-1,2,3,4-tetrahydropyridin-3-yl)ethanone (3h)

Yield: 75%; White crystalline solid. m.p. = 161-165 °C; ^1H NMR (400MHz, CDCl_3): δ 7.70 (d, $J = 8.0$ Hz, 2H), 7.63 (t, $J = 8.0$ Hz, 1H), 7.51 (t, $J = 8.0$ Hz, 2H), 7.23-7.35 (m, 7H), 6.78 (d, $J = 8.0$ Hz, 2H), 5.44 (d, $J = 4.0$ Hz, 1H), 4.52 (dd, $J = 16.0, 4.0$ Hz, 1H), 3.86 (dd, $J = 12.0, 4.0$ Hz, 1H), 3.33 (dd, $J = 16.0, 12.0$ Hz, 1H), 2.73 (dt, $J = 12.0, 4.0$ Hz, 1H), 1.98 (s, 3H); ^{13}C NMR (100MHz, CDCl_3) δ 207.3, 140.6, 139.4, 139.3, 137.6, 133.2, 131.9, 129.5, 129.2, 128.4, 127.9, 127.8, 127.5, 121.9, 121.1, 52.3, 49.1, 42.4, 30.8; HRMS (ESI): calcd. for $[\text{M}+\text{H}]^+$ ($\text{C}_{25}\text{H}_{23}\text{NO}_3\text{SBr}$) requires 496.0582, found 496.0582.

1-(trans-6-phenyl-1-(phenylsulfonyl)-4-p-tolyl-1,2,3,4-tetrahydropyridin-3-yl)ethanone (3i)

Yield: 72%; White crystalline solid. m.p. = 119-122 °C; ^1H NMR (400MHz, CDCl_3): δ 7.73 (d, J = 8.0 Hz, 2H), 7.62 (d, J = 7.8 Hz, 1H), 7.53 (t, J = 8.0 Hz, 2H), 7.34-7.37 (m, 2H), 7.25-7.28 (m, 3H), 7.03 (d, J = 8.0 Hz, 2H), 6.77 (d, J = 8.0 Hz, 2H), 5.48 (d, J = 4.0 Hz, 1H), 4.47 (dd, J = 12.0, 4.0 Hz, 1H), 3.79 (dd, J = 10.0, 4.0 Hz, 1H), 3.37 (dd, J = 16.0, 12.0 Hz, 1H), 2.73 (dt, J = 10.7, 2.3 Hz, 1H), 2.31 (s, 3H), 1.91 (s, 3H); ^{13}C NMR (100MHz, CDCl_3) δ 208.2, 139.4, 138.6, 138.3, 138.0, 136.9, 133.1, 129.4, 129.1, 128.2, 127.9, 127.8, 127.6, 127.5, 123.0, 52.1, 49.1, 43.1, 31.0, 21.1; HRMS (ESI): calcd. for $[\text{M}+\text{H}]^+$ ($\text{C}_{26}\text{H}_{26}\text{NO}_3\text{S}$) requires 432.1633, found 432.1633.

1-(*trans*-4-(4-chlorophenyl)-6-phenyl-1-(phenylsulfonyl)-1,2,3,4-tetrahydropyridin-3-yl)ethanone (3j)

Yield: 89%; White crystalline solid. m.p. = 167-169 °C; ^1H NMR (400MHz, CDCl_3): δ 7.72 (d, J = 1.6 Hz, 2H), 7.63-7.65 (m, 1H), 7.53 (t, J = 7.2 Hz, 2H), 7.28-7.36 (m, 5H), 7.20-7.23 (m, 2H), 6.86-6.88 (m, 2H), 5.47

(d, $J = 4.0$ Hz, 1H), 4.53 (dd, $J = 16.0, 4.0$ Hz, 1H), 3.90 (dd, $J = 12.0, 4.0$ Hz, 1H), 3.36 (dd, $J = 16.0, 12.0$ Hz, 1H), 2.77 (dt, $J = 11.0, 2.3$ Hz, 1H), 2.00 (s, 3H); ^{13}C NMR (100MHz, CDCl_3) δ 207.4, 140.1, 139.3, 139.3, 137.6, 133.2, 133.0, 129.1, 128.9, 128.4, 127.9, 127.8, 127.5, 122.0, 123.0, 52.4, 49.1, 42.4, 30.8; HRMS (ESI): calcd. for $[\text{M}+\text{H}]^+$ ($\text{C}_{25}\text{H}_{23}\text{NO}_3\text{SCl}$) requires 452.1087, found 452.1091.

1-(*trans*-4-(4-fluorophenyl)-6-phenyl-1-(phenylsulfonyl)-1,2,3,4-tetrahydropyridin-3-yl)ethanone (3k)

Yield: 83%; White crystalline solid. m.p. = 146-149 °C; ^1H NMR (400MHz, CDCl_3): δ 7.70-7.72 (m, 2H), 7.60-7.62 (m, 1H), 7.49-7.53 (m, 2H), 7.24-7.34 (m, 5H), 6.89-6.94 (m, 4H), 5.46 (d, $J = 4.0$ Hz, 1H), 4.50 (dd, $J = 12.0, 4.0$ Hz, 1H), 3.88 (dd, $J = 9.0, 2.0$ Hz, 1H), 3.35 (dd, $J = 16.0, 12.0$ Hz, 1H), 2.75 (dt, $J = 11.0, 3.0$ Hz, 1H), 1.96 (s, 3H); ^{13}C NMR (100MHz, CDCl_3) δ 207.7, 139.4, 139.1, 137.7, 137.3, 137.2, 133.2, 129.3, 129.2, 129.1, 128.4, 127.9, 127.8, 127.5, 122.4, 115.7, 115.5, 52.6, 49.2, 42.4, 30.9; HRMS (ESI): calcd. for $[\text{M}+\text{H}]^+$ ($\text{C}_{25}\text{H}_{23}\text{NO}_3\text{SF}$) requires 436.1383, found 436.1379.

1-(*trans*-4-(4-methoxyphenyl)-6-phenyl-1-(phenylsulfonyl)-1,2,3,4-tetrahydropyridin-3-yl)ethanone (3l)

Yield: 83%; Light yellow crystalline solid. m.p. = 141-145 °C; ^1H NMR (400MHz, CDCl_3): δ 7.60-7.64 (m, 3H), 7.50-7.54 (m, 2H), 7.25-7.34 (m, 5H), 6.74-6.82 (m, 4H), 5.47 (d, $J = 3.2$ Hz, 1H), 4.46 (dd, $J = 14.0, 3.2$ Hz, 1H), 3.76-3.80 (m, 4H), 3.36 (dd, $J = 14.0, 12.0$ Hz, 1H), 2.75 (dt, $J = 11.4, 2.8$ Hz, 1H), 1.91 (s, 3H); ^{13}C NMR (100MHz, CDCl_3) δ 208.3, 158.7, 139.3, 138.6, 138.0, 133.4, 133.1, 129.1, 128.7, 128.2, 127.8, 127.5, 123.1, 114.1, 55.2, 52.2, 49.2, 42.7, 31.1; HRMS (ESI): calcd. for $[\text{M}+\text{H}]^+$ ($\text{C}_{26}\text{H}_{26}\text{NO}_4\text{S}$) requires 448.1583, found 448.1581.

1-(*trans*-4-(naphthalen-2-yl)-6-phenyl-1-(phenylsulfonyl)-1,2,3,4-tetrahydropyridin-3-yl)ethanone (3m)

Yield: 80%; Yellow crystalline solid. m.p. = 163-167 °C; ^1H NMR (400MHz, CDCl_3): δ 7.67-7.84 (m, 6H), 7.59 (t, $J = 8.0$ Hz, 2H), 7.48-7.51 (m, 2H), 7.40-7.43 (m, 3H), 7.29-7.32 (m, 3H), 6.96-6.99 (m, 1H), 5.58 (d, $J = 3.2$ Hz, 1H), 4.55 (dd, $J = 14.0, 3.2$ Hz, 1H), 4.05 (dd, $J = 10.6,$

3.4 Hz, 1H), 3.45 (dd, $J = 14.0, 11.6$ Hz, 1H), 2.85-2.91 (m, 1H), 1.92 (s, 3H); ^{13}C NMR (100MHz, CDCl_3) δ 208.0, 139.3, 139.0, 138.8, 137.9, 133.4, 133.3, 132.6, 129.2, 128.6, 128.3, 127.9, 127.7, 127.6, 127.5, 126.6, 126.3, 125.9, 125.5, 122.6, 51.9, 49.1, 43.6, 31.1; HRMS (ESI): calcd. for $[\text{M}+\text{H}]^+$ ($\text{C}_{29}\text{H}_{26}\text{NO}_3\text{S}$) requires 468.1633, found 468.1632.

1-(*trans*-4-(2,3-dihydrobenzofuran-5-yl)-6-phenyl-1-(phenylsulfonyl)-1,2,3,4-tetrahydropyridin-3-yl)ethanone (3n)

3n

Yield: 87%; Pale yellow crystalline solid. m.p. = 104-109 °C;

^1H NMR (400MHz, CDCl_3): δ 7.72 (d, $J = 8.0$ Hz, 2H), 7.60-7.62 (m, 1H), 7.50-7.53 (m, 2H), 7.25-7.36 (m, 6H), 6.61-6.72 (m, 2H), 5.48 (d, $J = 4.0$ Hz, 1H), 4.55 (t, $J = 8.0$ Hz, 2 H), 4.46 (dd, $J = 14.0, 2.0$ Hz, 1H), 3.77 (dd, $J = 12.0, 4.0$ Hz, 1H), 3.36 (dd, $J = 16.0, 12.0$ Hz, 1H), 3.13-3.17 (m, 2H), 2.75 (dt, $J = 10.7, 2.7$ Hz, 1H), 1.94 (s, 3H); ^{13}C NMR (100MHz, CDCl_3) δ 208.3, 159.3, 139.4, 138.5, 137.9, 133.3, 133.1, 129.1, 128.2, 127.9, 127.8, 127.5, 127.4, 124.2, 123.4, 109.3, 71.3, 52.4, 49.2, 43.0, 31.1, 29.7; HRMS (ESI): calcd. for $[\text{M}+\text{H}]^+$ ($\text{C}_{27}\text{H}_{26}\text{NO}_4\text{S}$) requires 460.1583, found 460.1588.

1-(*trans*-4-(furan-2-yl)-6-phenyl-1-(phenylsulfonyl)-1,2,3,4-tetrahydropyridin-3-yl)ethanone (3o)

3o

Yield: 91%; Reddish brown crystalline solid. m.p. = 111-114 °C; ^1H NMR (400MHz, CDCl_3): δ 7.69 (d, J = 7.2 Hz, 2H), 7.57-7.61 (m, 1H), 7.46-7.50 (m, 2H), 7.37-7.39 (m, 2H), 7.22-7.31 (m, 4H), 6.23-6.24 (m, 1H), 5.86 (d, J = 4.0 Hz, 1H), 5.54 (d, J = 3.2 Hz, 1H), 4.38 (dd, J = 16.0, 4.0 Hz, 1H), 3.33 (dd, J = 16.0, 10.0 Hz, 1H), 2.67 (dt, J = 10.0, 2.7 Hz, 1H), 2.06 (s, 3H); ^{13}C NMR (100MHz, CDCl_3) δ 207.3, 153.9, 141.7, 139.5, 139.0, 138.0, 130.1, 129.1, 128.4, 127.9, 127.7, 127.4, 118.8, 110.2, 105.7, 48.6, 48.5, 36.3, 30.2; HRMS (ESI): calcd. for $[\text{M}+\text{H}]^+$ ($\text{C}_{23}\text{H}_{22}\text{NO}_4\text{S}$) requires 408.1270, found 408.1277.

1-(*trans*-6-phenyl-1-(phenylsulfonyl)-4-(thiophen-2-yl)-1,2,3,4-tetrahydropyridin-3-yl)ethanone (3p)

3p

Yield: 87%; Light brown crystalline solid. m.p. = 138-141 °C; ^1H NMR (400MHz, CDCl_3): δ 7.71-7.73 (m, 2H), 7.50-7.63 (m, 3H), 7.26-7.40 (m, 5H), 7.12 (d, J = 4.0 Hz, 1H), 6.85-6.87 (m, 1H), 6.66 (d, J = 4.0 Hz, 1H), 5.55 (d, J = 3.2 Hz, 1H), 4.43 (dd, J = 16.0, 4.0 Hz, 1H), 4.21

(dd, $J = 10.0, 3.0$ Hz, 1H), 3.34 (dd, $J = 16.0, 12.0$ Hz, 1H), 2.67 (dt, $J = 12.0, 2.7$ Hz, 1H), 2.00 (s, 3H); ^{13}C NMR (100MHz, CDCl_3) δ 207.4, 144.6, 138.9, 138.8, 137.9, 133.3, 129.3, 128.4, 127.9, 127.7, 127.6, 126.8, 125.1, 124.2, 121.5, 52.1, 48.9, 38.0, 30.7; HRMS (ESI): calcd. for $[\text{M}+\text{H}]^+$ ($\text{C}_{23}\text{H}_{22}\text{NO}_3\text{S}_2$) requires 424.1041, found 424.1053.

1-(*trans*-6-phenyl-1-(phenylsulfonyl)-4-((*E*)-styryl)-1,2,3,4-tetrahydropyridin-3-yl)ethanone (3q)

3q

Yield: 75%; White crystalline solid. m.p. = 129-132 °C; ^1H NMR (400MHz, CDCl_3): δ 7.73-7.75 (m, 2H), 7.54-7.65 (m, 3H), 7.28-7.43 (m, 10H), 6.36 (d, $J = 16.0$ Hz, 1H), 5.58 (dd, $J = 16.0, 12.0$ Hz, 1H), 5.50 (d, $J = 4.0$ Hz, 1H), 4.44 (dd, $J = 12.0, 4.0$ Hz, 1H), 3.44 (dt, $J = 10.0, 3.0$ Hz, 1H), 3.29 (dd, $J = 16.0, 12.0$ Hz, 1H), 2.67 (dt, $J = 12.0, 4.0$ Hz, 1H), 2.17 (s, 3H); ^{13}C NMR (100MHz, CDCl_3) δ 207.4, 139.2, 139.1, 138.1, 136.6, 133.2, 132.1, 129.2, 129.1, 128.6, 128.3, 127.9, 127.8, 127.7, 127.3, 126.2, 121.4, 50.2, 48.5, 40.2, 30.7; HRMS (ESI): calcd. for $[\text{M}+\text{H}]^+$ ($\text{C}_{27}\text{H}_{26}\text{NO}_3\text{S}$) requires 444.1633, found 444.1630.

1-(*trans*-6-(4-iodophenyl)-4-phenyl-1-(phenylsulfonyl)-1,2,3,4-tetrahydropyridin-3-yl)ethanone (3r)

3r

Yield: 92%; White crystalline solid. m.p. =

100-105 °C; ^1H NMR (400MHz, CDCl_3): δ 7.52-7.73 (m, 7H), 7.60-7.62 (m, 1H), 7.10-7.22 (m, 3H), 7.08-7.10 (m, 2H), 6.86-6.88 (m, 2H), 5.50 (d, J = 4.0 Hz, 1H), 4.45 (dd, J = 12.0, 4.0 Hz, 1H), 3.82 (dd, J = 12.0, 4.0 Hz, 1H), 3.35 (dd, J = 16.0, 12.0 Hz, 1H), 2.75 (dt, J = 12.0, 3.0 Hz, 1H), 1.90 (s, 3H); ^{13}C NMR (100MHz, CDCl_3) δ 207.8, 141.1, 139.1, 138.0, 137.5, 137.0, 133.3, 129.3, 129.2, 128.8, 127.8, 127.7, 127.3, 123.2, 94.1, 51.9, 49.0, 43.5, 31.0; HRMS (ESI): calcd. for $[\text{M}+\text{H}]^+$ ($\text{C}_{25}\text{H}_{23}\text{NO}_3\text{SI}$) requires 544.0433, found 544.0439.

1-(*trans*-4-phenyl-1-(phenylsulfonyl)-6-((*E*)-styryl)-1,2,3,4-tetrahydropyridin-3-yl)ethanone (3s)

3s

Yield: 93%; White crystalline solid. m.p. = 140-145 °C;

^1H NMR (400MHz, CDCl_3): δ 7.90-7.92 (m, 2H), 7.58-7.70 (m, 3H), 7.17-7.42 (m, 8H), 6.90 (d, J = 16.0 Hz, 1H), 6.69-6.73 (m, 3H), 5.62 (d, J = 4.0 Hz, 1H), 4.38 (dd, J = 16.0, 4.0 Hz, 1H), 3.77-3.80 (m, 1H), 3.26-3.32 (m, 1H), 2.42-2.48 (m, 1H), 1.85 (s, 3H); ^{13}C NMR (100MHz, CDCl_3) δ 207.6, 141.4,

139.3, 136.8, 136.6, 133.2, 129.6, 129.4, 128.7, 128.7, 128.0, 127.8, 127.6, 127.2, 126.8, 126.4, 118.8, 51.8, 48.4, 43.3, 30.8; HRMS (ESI): calcd. for $[M+H]^+$ ($C_{27}H_{26}NO_3S$) requires 444.1633, found 444.1630.

1-(*trans*-4,6-diphenyl-1-(phenylsulfonyl)-1,2,3,4-tetrahydropyridin-3-yl)propan-1-one (3t)

3t

Yield: 86%; White crystalline solid. m.p. = 169-171 °C; 1H NMR (400MHz, $CDCl_3$): δ 7.71-7.73 (m, 2H), 7.50-7.62 (m, 3H), 7.20-7.38 (m, 8H), 6.85-6.88 (m, 1H), 5.52 (d, J = 4.0 Hz, 1H), 4.42 (dd, J = 15.0, 3.0 Hz, 1H), 3.85 (dd, J = 11.0, 3.0 Hz, 1H), 3.40 (dd, J = 16.0, 12.0 Hz, 1H), 2.69-2.75 (m, 1H), 2.31-2.38 (m, 1H), 1.84-1.91 (m, 1H), 1.85 (t, J = 8 Hz, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 210.9, 141.5, 139.4, 138.9, 138.0, 133.1, 129.1, 128.7, 128.3, 127.9, 127.8, 127.6, 127.5, 127.2, 122.7, 51.3, 49.4, 43.8, 37.3, 7.1; HRMS (ESI): calcd. for $[M+H]^+$ ($C_{26}H_{26}NO_3S$) requires 432.1633, found 432.1638.

cyclohexyl(*trans*-4,6-diphenyl-1-(phenylsulfonyl)-1,2,3,4-tetrahydropyridin-3-yl)methanone (3u)

3u

Yield: 85%; White crystalline solid. m.p. =

189-191 °C; ^1H NMR (400MHz, CDCl_3): δ 7.73-7.75 (m, 2H), 7.37-7.63 (m, 3H), 7.18-7.29 (m, 8H), 6.82-6.85 (m, 1H), 5.56 (d, $J = 4.0$ Hz, 1H), 4.38 (dd, $J = 12.0, 4.0$ Hz, 1H), 3.90 (dd, $J = 12.0, 4.0$ Hz, 1H), 3.33 (dd, $J = 16.0, 12.0$ Hz, 1H), 2.80-2.83 (m, 1H), 1.06-2.01 (m, 11H); ^{13}C NMR (100MHz, CDCl_3) δ 213.0, 141.5, 139.4, 138.9, 138.1, 133.1, 129.1, 128.6, 128.2, 127.9, 127.8, 127.7, 127.5, 127.2, 122.9, 51.4, 50.1, 49.8, 43.7, 27.3, 27.1, 25.6, 25.5, 25.3; HRMS (ESI): calcd. for $[\text{M}+\text{H}]^+$ ($\text{C}_{30}\text{H}_{32}\text{NO}_3\text{S}$) requires 486.2103, found 486.2098.

(*trans*-4,6-diphenyl-1-(phenylsulfonyl)-1,2,3,4-tetrahydropyridin-3-yl)(phenyl)methanone (3v)

Yield: 90%; White crystalline solid. m.p. = 131-133 °C;

^1H NMR (400MHz, CDCl_3): δ 7.01-7.61 (m, 20H), 5.68 (d, $J = 4.0$ Hz, 1H), 4.50 (dd, $J = 12.0, 4.0$ Hz, 1H), 4.23 (dd, $J = 10.0, 4.0$ Hz, 1H), 3.82 (dt, $J = 11.7, 3.0$ Hz, 1H), 3.48 (dd, $J = 16.0, 12.0$ Hz, 1H); ^{13}C NMR (100MHz, CDCl_3) δ 200.0, 141.6, 139.7, 138.9, 138.0, 136.2, 133.5, 133.0, 129.1, 128.7, 128.6, 128.5, 128.2, 127.9, 127.5, 127.1, 123.0, 50.3, 47.8, 43.7; HRMS (ESI): calcd. for $[\text{M}+\text{H}]^+$ ($\text{C}_{30}\text{H}_{26}\text{NO}_3\text{S}$) requires 480.1633, found 480.1627.

(*trans*-4,6-diphenyl-1-(phenylsulfonyl)-1,2,3,4-tetrahydropyridin-3-yl)(furan-2-yl)methanone (3w)

3w

Yield: 90%; White crystalline solid. m.p. = 189-193 °C;

^1H NMR (400MHz, CDCl_3): δ 6.91-7.76 (m, 17H), 6.45-6.46 (m, 1H), 5.62 (d, J = 3.6 Hz, 1H), 4.58-4.61 (m, 1H), 4.16-4.19 (m, 1H), 3.50-3.54 (m, 2H); ^{13}C NMR (100MHz, CDCl_3) δ 187.4, 152.0, 147.3, 141.4, 139.6, 138.9, 137.9, 133.1, 129.0, 128.6, 128.3, 128.0, 127.9, 127.5, 127.1, 123.0, 119.2, 112.5, 50.3, 48.2, 42.8; HRMS (ESI): calcd. for $[\text{M}+\text{H}]^+$ ($\text{C}_{28}\text{H}_{24}\text{NO}_4\text{S}$) requires 470.1426, found 470.1428.

(*trans*-4,6-diphenyl-1-(phenylsulfonyl)-1,2,3,4-tetrahydropyridin-3-yl)(thiophen-2-yl)methanone (**3x**)

3x

Yield: 89%; White crystalline solid. m.p. = 158-161 °C;

^1H NMR (400MHz, CDCl_3): δ 7.00-7.70 (m, 18H), 5.65 (d, J = 4.0 Hz, 1H), 4.50 (dd, J = 12.0, 4.0 Hz, 1H), 4.18 (dd, J = 8.0, 4.0 Hz, 1H), 3.65-3.71 (m, 1H), 3.54 (dd, J = 14.0, 11.0 Hz, 1H); ^{13}C NMR (100MHz, CDCl_3) δ 192.3, 144.0, 141.7, 140.0, 139.1, 137.9, 135.2, 133.3, 133.2, 129.2, 128.9, 128.6, 128.4, 128.1, 128.1, 128.0, 127.7, 127.3, 123.0, 50.8, 49.7, 43.7; HRMS (ESI): calcd. for $[\text{M}+\text{H}]^+$ ($\text{C}_{28}\text{H}_{24}\text{NO}_3\text{S}_2$) requires 486.1198, found 486.1198.

(*trans*-4,6-diphenyl-1-(phenylsulfonyl)-1,2,3,4-tetrahydropyridin-3-yl)(p-tol

yl)ethanone (3y)

3y

Yield: 94%; White crystalline solid. m.p. = 75-77 °C;

^1H NMR (400MHz, CDCl_3): δ 7.71 (d, J = 8.0 Hz, 2H), 7.58-7.62 (m, 3H), 7.49 (d, J = 7.6 Hz, 2H), 7.36-7.38 (m, 2H), 7.26-7.29 (m, 3H), 7.15-7.18 (m, 5H), 7.02 (t, J = 6.4 Hz, 2H), 5.66 (d, J = 3.2 Hz, 1H), 4.50 (dd, J = 14.0, 2.8 Hz, 1H), 4.24 (dd, J = 10.4, 3.2 Hz, 1H), 3.75-3.81 (m, 1H), 3.51 (dd, J = 14.0, 11.6 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (100MHz, CDCl_3) δ 199.4, 144.5, 139.8, 138.9, 138.0, 133.8, 129.3, 129.0, 128.7, 128.6, 128.2, 127.9, 127.8, 127.5, 127.0, 123.2, 50.4, 47.6, 43.6, 21.7; HRMS (ESI): calcd. for $[\text{M}+\text{Na}]^+$ ($\text{C}_{31}\text{H}_{27}\text{NO}_3\text{SNa}$) requires 516.1609, found 516.1600.

1-(*trans*-4-phenyl-1-(phenylsulfonyl)-1,2,3,4,5,6-hexahydrobenzo[*h*]quinolin

-3-yl)ethanone (m)

m

Yield: 60%; White crystalline solid. m.p. = 169-170 °C;

^1H NMR (400MHz, CDCl_3): δ 7.89 (d, J = 7.6 Hz, 2H), 7.68 (t, J = 7.6 Hz, 1H), 7.57 (t, J = 7.6 Hz, 2H), 7.44-7.46 (m, 1H), 7.08-7.20 (m, 6H), 6.80 (t, J = 3.6 Hz, 2H), 4.41 (dd, J = 13.2, 3.2 Hz, 1H), 3.74 (d, J = 9.2, 1H), 3.15-3.27 (m, 2H), 2.49-2.63 (m, 2H), 2.06 (m, 1H), 1.92 (s, 3H), 1.90 (m, 1H); ^{13}C NMR

(100MHz, CDCl₃) δ 207.7, 142.9, 139.2, 135.4, 133.9, 133.2, 132.2, 129.3, 128.8, 128.4, 128.0, 127.3, 127.0, 126.8, 125.6, 125.2, 115.6, 114.7, 53.5, 49.0, 46.8, 30.9, 27.8, 26.9; HRMS (ESI): calcd. for [M+Na]⁺ (C₂₇H₂₅NO₃SNa) requires 466.1453, found 466.1456.

1-(*trans*-4-phenyl-1-(phenylsulfonyl)-2,3,4,5-tetrahydro-1H-indeno[1,2-*b*]pyridin-3-yl)ethanone (n)

n

Yield 84%; White crystalline solid. m.p. = 219-222 °C;

¹H NMR (400MHz, CDCl₃): δ 8.01 (d, *J* = 7.6 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 2H), 7.67 (t, *J* = 7.6 Hz, 1H), 7.58 (t, *J* = 8.0 Hz, 2H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.27 (t, *J* = 4.4 Hz, 1H), 7.10-7.22 (m, 4H), 6.63 (d, *J* = 7.2 Hz, 2H), 4.32 (dd, *J* = 14.4, 3.2 Hz, 1H), 3.33 (dd, *J* = 14.0, 3.6 Hz, 1H), 3.03 (s, 3H), 2.66-2.72 (m, 1H), 1.84 (s, 3H); ¹³C NMR (100MHz, CDCl₃) δ 207.6, 141.6, 141.2, 140.4, 138.5, 136.9, 136.4, 133.4, 129.5, 128.7, 128.2, 127.8, 127.3, 126.5, 125.3, 123.5, 122.6, 51.8, 49.7, 44.6, 37.3, 31.1; HRMS (ESI): calcd. for [M+Na]⁺ (C₂₆H₂₃NO₃SNa) requires 452.1296, found 452.1294.

1-(*trans*-4,6-diphenyl-2,3,4,5-tetrahydropyridin-3-yl)ethanone (4)

4

Yield 88%; Light yellow solid. m.p. = 89-91 °C; ¹H NMR (400MHz, CDCl₃): δ 7.78 (d, *J* = 6.0 Hz, 2H), 7.32-7.41 (m, 5H), 7.22-7.27

(m, 3H), 4.24 (dd, $J = 17.8, 3.7$ Hz, 1H), 3.85-3.92 (m, 1H), 3.24-3.30 (m, 1H), 3.07-3.16 (m, 1H), 2.68-2.16 (m, 1H), 1.95 (s, 3H); ^{13}C NMR (100MHz, CDCl_3) δ 210.2, 165.3, 142.8, 138.9, 130.1, 128.9, 128.4, 127.3, 127.2, 126.1, 52.5, 52.4, 40.7, 44.1, 34.8, 30.8; HRMS (ESI): calcd. for $[\text{M}+\text{H}]^+$ ($\text{C}_{19}\text{H}_{20}\text{NO}$) requires 278.1545, found 278.1555.

1-(4,6-diphenylpyridin-3-yl)ethanone (5)

5

Yield 70%; colorless oil; ^1H NMR (400MHz, CDCl_3): δ 8.87 (d, $J = 6.0$ Hz, 2H), 8.07 (d, $J = 6.8$ Hz, 2H), 7.74 (s, 1H), 7.48-7.52 (m, 5H), 7.40-7.43 (m, 2H), 2.11 (s, 3H); ^{13}C NMR (100MHz, CDCl_3) δ 202.0, 159.3, 149.3, 149.2, 138.6, 138.3, 133.8, 129.8, 129.2, 129.0, 128.9, 128.4, 127.3, 121.2, 30.5; HRMS (ESI): calcd. for $[\text{M}+\text{H}]^+$ ($\text{C}_{19}\text{H}_{16}\text{NO}$) requires 274.1232, found 274.1230.

1-(*trans*-4,6-diphenylpiperidin-3-yl)ethanol (6)

6

Yield 95%; colorless oil; ^1H NMR (400MHz, CDCl_3): δ 7.38 (d, $J = 8.0$ Hz, 2H), 7.19-7.32 (m, 8H), 3.77 (d, $J = 12.0$ Hz, 1H), 3.64-3.66 (m, 1H), 3.53 (dd, $J = 12.0, 4.0$ Hz, 1H), 2.81 (t, $J = 9.0$ Hz, 1H), 2.56-2.63 (m, 1H), 2.15-2.21 (m, 1H), 1.92-1.98 (m, 3H), 1.80 (q, $J = 12.0$ Hz, 1H), 1.14 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (100MHz, CDCl_3) δ 144.3, 144.2, 128.8, 128.4, 127.4,

127.3, 126.6, 67.7, 62.4, 48.0, 47.0, 46.9, 44.1, 17.6; HRMS (ESI): calcd. for

$[M+H]^+$ ($C_{19}H_{24}NO$) requires 282.1858, found 282.1870.

Preliminary Mechanistic Investigation

Synthesis of deuterium labelled 1-*p*-tolylprop-2-en-1-one (**1g'**)

^1H NMR (400MHz, CDCl_3): δ 7.85 (d, $J = 16.1$ Hz, 2H), 7.27 (d, $J = 6.5$ Hz, 2H), 6.42 (q, $J = 1.7$ Hz, 1H), 5.89 (d, $J = 1.1$ Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (100MHz, CDCl_3): δ 190.5, 143.9, 134.8, 132.2, 132.1, 131.9, 129.6, 129.3, 128.8, 21.7. HRMS (ESI): calcd. for $[\text{M}+\text{H}]^+$ ($\text{C}_{10}\text{H}_{10}\text{DO}$) requires 148.0873, found 148.0878.

Synthesis of deuterium labelled (*E*)-1, 3-diphenylallylidene) benzenesulfonamide (>99% D) (2a'**)**

2a'

^1H NMR (400MHz, CDCl_3): δ 8.06 (d, $J = 7.2\text{ Hz}$, 2H), 7.42-7.67 (m, 13H), 7.09 (s, 1H); HRMS (ESI): calcd. for $[\text{M}+\text{H}]^+$ ($\text{C}_{21}\text{H}_{17}\text{DNO}_2\text{S}$) requires 349.1121, found 349.1123.

Deuterium Labelled Experiments:

To a 0.1 mL dichloromethane solution of 0.1mmol *N*-sulfonyl-1-aza-1,3-diene **2a**, 0.2 mL dichloromethane solution of 0.3 mmol vinyl ketone **1g'** was added in dropwise via syringe pump over 6h, then reaction mixture was concentrated under reduced pressure. Subsequent column chromatography with eluent of hexane and EA (15:1 to 10:1), afforded white solid product.

4.5 References

1. a) J. P. Michael, *Nat. Prod. Rep.* **2004**, *21*, 625; b) D. O'Hagan, *Nat. Prod. Rep.* **2000**, *17*, 435; c) W. Maison, *Pipecolic acid derivatives: In Highlights in Bioorganic Chemistry*, Wiley-VCH, New York, **2004**, 18; d) M. Rubiralta, E. Giralt, A. Diez, *Piperidine: Structure, Preparation, Reactivity, and Synthetic Applications of Piperidine and Its Derivatives*, Elsevier, New York, **1991**.
2. a) D. L. Boger, A. M. Kasper, *J. Am. Chem. Soc.* **1989**, *111*, 1517; b) R. C. Clark, S. S. Pfeiffer, D. L. Boger, *J. Am. Chem. Soc.* **2006**, *128*, 2587; c) J. Esquivias, R. G. Arrayás, J. C. Carretero, *J. Am. Chem. Soc.* **2007**, *129*, 1480; d) P. D. Bailey, P. D. Smith, F. Pederson, W. Clegg, G. M. Rosair, S. J. Teat, *Tetrahedron Letts.* **2002**, *43*, 1067.
3. a) X. F. Zhu, J. Lan, O. Kwon, *J. Am. Chem. Soc.* **2003**, *125*, 4716; b) R. P. Wurz, G. C. Fu, *J. Am. Chem. Soc.* **2005**, *127*, 12234-12235; c) Y. S. Tran, O. Kwon, *J. Am. Chem. Soc.* **2007**, *129*, 12632.
4. For selected reviews of phosphine catalysis, see: a) J. L. Methot, W. R. Roush, *Adv. Synth. Catal.* **2004**, *346*, 1035; b) L.-W. Ye, J. Zhou, Y. Tang, *Chem. Soc. Rev.* **2008**, *37*, 1140; c) X. Lu, C. Zhang, Z. Xu, *Acc. Chem. Res.* **2001**, *34*, 535. d) B. J. Cowen, S. J. Miller, *Chem. Soc. Rev.* **2009**, *38*, 3102.
5. For recent phosphine catalyzed cycloadditions involving allenes, see: a) G. Zhu, Z. Chen, Q. Jiang, D. Xiao, P. Cao, X. Zhang, *J. Am. Chem. Soc.* **1997**, *119*, 3836; c) B. J. Cowen, S. J. Miller, *J. Am. Chem. Soc.* **2007**, *129*, 10989; d) Y. Fang, E. N. Jacobsen, *J. Am. Chem. Soc.* **2008**, *130*, 5660; e) H. Xiao, Z.

Chai, C. Zheng, Y. Yang, W. Liu, J. Zhang, G. Zhao, *Angew. Chem. Int. Ed.* **2010**, *49*, 4467; f) X. Han, Y. Wang, F. Zhong, Y. Lu, *J. Am. Chem. Soc.* **2011**, *133*, 1726; g) X. Zhang, S. Cao, Y. Wei, M. Shi, *Org. Lett.* **2011**, *13*, 1142; h) X. Chen, M. Wen, S. Ye, Z. Wang, *Org. Lett.* **2011**, *13*, 1138; i) R. Zhou, C. Wang, H. Song, Z. He, *Org. Lett.* **2010**, *12*, 976; j) J. Li, Y. Liu, C. Li, X. Jia, *Chem. Eur. J.* **2011**, *17*, 7409; k) X. Zhu, C. E. Henry, J. Wang, T. Dudding, O. Kwon, *Org. Lett.* **2005**, *7*, 1387.

6. H. Guo, Q. Xu, O. Kwon, *J. Am. Chem. Soc.* **2009**, *131*, 6318

7. a) Z. Shi, P. Yu, P. J. Chua, G. Zhong, *Adv. Synth. Catal.* **2009**, *351*, 2797;

b) Z. Shi, B. Tan, W. W. Y. Leong, X. Zeng, M. Lu, G. Zhong, *Org. Lett.* **2010**, *12*, 5402.

8. For the references of annulation reactions involving vinyl ketones, see: a)

S. Takizawa, N. Inoue, S. Hirata, H. Sasai, *Angew. Chem.* **2010**, *122*, 9919;

Angew. Chem. Int. Ed. **2010**, *49*, 9725; b) S. Takizawa, N. Inoue, H. Sasai, *Tetrahedron Lett.* **2011**, *52*, 377; c) L. Cai, B. Zhang, G. Wu, H. Song, Z. He, *Chem. Commun.* **2011**, *47*, 1045

9. For selected examples using *N*-sulfonyl-1-aza-1, 3-dienes, see: a) B. Han,

J.-L. Li, C. Ma, S.-J. Zhang, Y.-C. Chen, *Angew. Chem.* **2008**, *120*, 10119;

Angew. Chem. Int. Ed. **2008**, *47*, 9971; b) B. Han, Z. He, J.-L. Li, R. Li, K. Jiang, T. Liu, Y.-C. Chen, *Angew. Chem. Int. Ed.* **2009**, *48*, 5474; c) J. Tian, R. Zhou, H. Sun, H. Song, Z. He, *J. Org. Chem.* **2011**, *76*, 2374.

10. For other phosphine catalyzed annulations reactions, see: a) Q. Zhang, L.

Yang, X. Tong, *J. Am. Chem. Soc.* **2010**, *132*, 2550; b) H. Liu, Q. Zhang, L. Wang, X. Tong, *Chem. Commun.* **2010**, *46*, 312; c) Q. Zhang, T. Fang, X. Tong, *Tetrahedron*, **2010**, *66*, 8095; d) C. Jung, J. Wang, M. Krische, *J. Am. Chem. Soc.* **2004**, *126*, 4118; e) J. E. Wilson, J. Sun, G. C. Fu, *Angew. Chem.* **2010**, *122*, 165; *Angew. Chem. Int. Ed.* **2010**, *49*, 161.

11. For references of the effect of Brønsted acids in Morita-Balis-Hillman reaction, see: a) M. Shi, Y. Liu, *Org. Biomol. Chem.* **2006**, *4*, 1468; b) J. Cai, Z. Zhou, G. Zhao, Tang, C. *Org. Lett.* **2002**, *4*, 4723; c) N. Abermil, G. Masson, J. Zhu, *J. Am. Chem. Soc.* **2008**, *130*, 12596; d) T. Yukawa, B. Seelig, Y. Xu, H. Morimoto, S. Matsunaga, A. Berkessel, M. Shibasaki, *J. Am. Chem. Soc.* **2010**, *132*, 11988

12. For reference of phenol catalyzed Diel-Alder reaction, see: L. Liu, J. Han, G. Yue, C. Li, Z. Yang, *J. Am. Chem. Soc.* **2010**, *132*, 13608

13. A. Vogt, A. Tamewitz, J. Skoko, R. P. Sikorski, K. A. Giuliano, J. S. Lazo, *J. Bio. Chem.* **2005**, *280*, 19078.

14. a) D. K. Kim, *Arch. Pharm. Res.* **2002**, *25*, 817; b) M. Kamigauchi, Y. Noda, J. Nishijo, K. Iwasaki, K. Tobetto, Y. In, K. Tomoo, T. Ishida, *Bioorg. Med. Chem.* **2005**, *13*, 1867.

15. a) R. Kunstmann, U. Lerch, H. Gerhards, M. Leven, U. Schacht, *J. Med. Chem.* **1984**, *27*, 432; b) C. E. Cook, M. C. Wani, J. M. Jump, Y. Lee, P. A. Fail, S. A. Anderson, Y. Gu, V. Petrow, *J. Med. Chem.* **1994**, *38*, 753.

16. For recent literatures of synthesis of pyridine, see: a) Y. Wang, S. Chiba, J.

Am. Chem. Soc., **2009**, *131*, 12570; b) D. A. Colby, R. G. Berman, J. A. Ellman, *J. Am. Chem. Soc.*, **2008**, *130*, 3645; c) J. R. Manning, H. M. L. Davies, *J. Am. Chem. Soc.* **2008**, *130*, 8602; d) C. Wang, X. Li, F. Wu, B. Wan, *Angew. Chem. Int. Ed.* **2011**, *50*, early view.

17. For selected references of synthesis of piperidines, see: a) S. J. Hedley, W. J. Moran, A. H. G. P. Prenzel, D. A. Price, J. P. A. Harrity, *Synlett* **2001**, *10*, 1596; b) L. Zu, H. Xie, H. Li, J. Wang, X. Yu, W. Wang, *Chem. Eur. J.* **2008**, *14*, 6333; c) Y. Hayashi, H. Gotoh, R. Masui, H. Ishikawa, *Angew. Chem.* **2008**, *120*, 4076; *Angew. Chem. Int. Ed.* **2008**, *47*, 4012; d) J. Franzén, A. Fisher, *Angew. Chem.* **2009**, *121*, 806; *Angew. Chem. Int. Ed.* **2009**, *48*, 787; e) Y. Chen, C. Zhong, J. L. Petersen, N. G. Akhmedov, X. Shi, *Org. Lett.* **2009**, *11*, 2333.

18. For references of intermolecular Michael addition initiated by nucleophilic catalyst, see: a) X. Sun, S. Sengupta, J. L. Petersen, H. Wang, J. P. Lewis, X. Shi, *Org. Lett.* **2007**, *9*, 4495; b) C. Zhong, Y. Chen, J. L. Petersen, N. G. Akhmedov, X. Shi, *Angew. Chem.* **2009**, *121*, 1305; *Angew. Chem. Int. Ed.* **2009**, *48*, 1279

19. D. Cuperly, J. Petriguet, C. Crévisy, R. Grée, *Chem. Eur. J.* **2006**, *12*, 3261.

20. X. An, J. Chen, C. Li, F. Zhang, Y. Zou, Y. G. W. Xiao, *Chem. Asian J.* **2010**, *5*, 2258.

21. J. Esquivias, R. G. Arraya's, J. C. Carretero, *J. Org. Chem.* **2005**, *70*, 7451.

22. A. T. Nielsen, W. J. Houlihan., *Org. React.* **1968**, *16*, 1.

Chiral Phosphine Catalyzed [4+2] Annulation of Vinyl Ketones with *N*-Sulfonyl-1-Aza-1, 3-Dienes

5.1 Introduction

N-containing heterocycles are important building blocks in natural products and biologically active compounds. One example is chiral piperidines which can be frequently found in numerous pharmaceuticals. Typically, the synthesis of such valuable six-membered heterocycles mainly involves an inverse-demand Diels-Alder reaction of *N*-sulfonyl-1-aza-1,3-dienes with electron-rich olefins, which was originally developed by Boger and co-workers.¹ The asymmetric variant of this reaction was realized by using optically active enol ethers as the dienophiles. Unfortunately, this methodology is limited in synthetic utility because only *N*-sulfonyl-1-aza-1, 3-butadiene can be employed.²

Scheme 5.1 Diels-Alder reaction of optically active enol ether with *N*-sulfonyl-1-aza-1,3-butadiene

Later in 2007, Carretero made a significant contribution to this field, by developing a catalytic asymmetric Diels-Alder reaction of *N*-sulfonyl-1-aza-1, 3-dienes with vinyl ether by using Ni^{II}/DBFOX-Ph complex as catalyst. The high enantioselectivities achieved in this reaction were not only attributed to the efficient

catalyst but also due to the installation of a *N*-(8-quinolinesulfonyl) group at the iminic nitrogen.³

Scheme 5.2 Ni^{II} /DBFOX-Ph complex catalyzed Diels-Alder reaction of vinyl ether with *N*-sulfonyl-1-aza-1,3-dienes

In recent years, asymmetric organocatalysis has appeared as a powerful tool in organic synthesis in recent years. Fu and Bode independently demonstrated methodologies for the construction of chiral piperidine derivatives by using chiral phosphines and *N*-heterocyclic carbenes, respectively.⁴

Scheme 5.3 Chiral phosphine catalyzed [4+2] annulations of allenes with imines

In 2006, the later reported the use of chiral *N*-heterocyclic carbenes to catalyze Diels-Alder reactions of enals with α , β -unsaturated imines. They successfully realized a facile route to the asymmetric synthesis of hydropyridinones, which can be readily converted to piperidine derivatives.⁵

Scheme 5.4 Chiral *N*-heterocyclic carbenes catalyzed Diels-Alder reaction.

Although several protocols for the enantioselective synthesis of piperidine derivatives have been documented, their synthetic utilities are limited by either a narrow reaction scope, the need for expensive chiral auxiliaries, or harsh reaction conditions. Thus the development of new methodologies is highly desirable.

Our previous work established a new [4+2] annulation reaction of vinyl ketones with *N*-sulfonyl-1-aza-1,3-dienes, by using PPh_3 as catalyst. This methodology has opened up a fast entry to the construction of tetrahydropyridines with broad substrate scope under mild reaction conditions. Our attention was subsequently switched to explore this reaction in an asymmetric manner.

Scheme 5.5 Phosphine catalyzed [4+2] annulations of vinyl ketones and *N*-sulfonyl-1-aza-1,3-dienes

5.2 Results and discussion

Our efforts to develop an asymmetric [4+2] annulation of vinyl ketones and *N*-sulfonyl-1-aza-1,3-dienes focused on chiral phosphines, which were previously

proven to be efficient nucleophilic catalysts. Recent, the development of new chiral phosphines based on natural amino acids has attracted extensive attentions. Consequently, their remarkable catalytic performance has been demonstrated in a number of transformations. Considering the easy accessibility, low cost and good asymmetric induction provided by natural amino acids, preliminary studies were carried out using the chiral phosphine derived from *L*-leucine (scheme 5.6).

Scheme 5.6 Asymmetric [4+2] annulation catalyzed by L-leucine based phosphine

To our delight, in the presence of 20 mol% catalyst **4a**, the model reaction of methyl vinyl ketone (MVK) with benzenesulfonyl (Bs) protected 1,3-azadiene delivered the desired product in 64% yield, with modest diastereo- and enantioselectivity (55% *ee*, 5:1 dr). Various *N*-sulfonyl-1-aza-1,3-dienes were then tested to elucidate the effect of protection group on stereoselective induction, as summarized in Table 5.1. More electron withdrawing 4-chlorobenzenesulfonyl protected 1,3-azadiene **2b** provided similar results to **2a**, while *N*-toluenesulfonyl-1-aza-1,3-diene **2c** gave slightly higher diastereo- and enantioselectivity. *N*-(8-quinolyl)-1-aza-1,3-diene **2d**, which offered another coordinating site for metal catalysis in Carretero's aza-Diels-Alder reaction system,³ did not provide any improvement (65% yield, 5:1 dr and 59% *ee*). *tert*-Butylsulfonyl protected substrate

2e could not participate in this process at all. The diphenylphosphinoyl (DPP) protection group on the iminic nitrogen, which was proved be beneficial in Jacobson's [3+2] cycloaddition of allenes and imines,⁶ as well as in Shibasaki's aza-Morita-Balys-Hillman reaction,⁷ was not a good substrate in our reaction. This was determined by the fact that, no reaction was observed with substrate **2f**, presumably because it was not adequately electron deficient. A similar observation was made with substrate **2g** with the use of a chiral auxiliary, which was synthesized from (*R*)-2-methylpropane-2-sulfinamide.

Table 5.1 Effect of protection groups^a

1a	2	3	4a
<hr/>

2a	2b	2c	2d
64% yield, 5:1 dr, 55% ee	60% yield, 4:1 dr, 56% ee	66% yield, 6:1 dr, 63% ee	65% yield, 5:1 dr, 59% ee

2e	2f	2g	
no reaction	no reaction	no reaction	

^a Unless otherwise noted, the reaction was performed on a 0.05 mmol scale in dichloromethane at room temperature, in the presence of 20 mol% catalyst.

Table 5.2 Catalytic performance of commercially available catalysts^a

1a	2c		3	
4	t (h)	yield (%) ^b	dr ^c	ee (%) ^d
III	48	91	13:1	-43
IV	3	90	8:1	20

^a Unless otherwise noted, the reaction was performed on a 0.05 mmol scale in dichloromethane at room temperature, in the presence of 20 mol% catalyst. ^b isolated yield. ^c Determined by crude ¹H NMR. ^d Determined by chiral AD-H column.

Subsequently, *N*-toluenesulfonyl (Ts)-1-aza-1, 3-diene **2c** was chosen as the substrate for catalyst screening. Two commercially available chiral phosphines, were then examined in this reaction. (*R*)-2'-(diphenylphosphino)-1,1'-binaphthyl-2-ol **III** is an efficient bifunctional catalyst for Morita-Baylis-Hillman reaction developed by Shi Min and co-workers in 2005. When **III** was employed, excellent chemical yield and

Table 5.3 Screening of chiral backbone^a

1a	2c		3	
4	t (h)	yield (%) ^b	dr ^c	ee (%) ^d
 4a	6	66	6:1	63
 4b	6	82	8:1	0
 4c	6	90	2:1	58
 4d	6	68	4:1	60
 4e	6	92	12:1	3
 4f	6	73	14:1	47

^a Unless otherwise noted, the reaction was performed on a 0.05 mmol scale in dichloromethane at room temperature, in the presence of 20 mol% catalyst. ^b Isolated yield. ^c Determined by crude ¹H NMR. ^d Determined by chiral IA-H column.

diastereoselectivity could be obtained, albeit with only 41% *ee*. The reaction required 48 hours to go to completion, due to lower nucleophilicity of such an aryl substituted phosphine. With the use of more nucleophilic (*R, R*)-DIPAMP IV, the reaction could be completed in several hours with 90% chemical yield, albeit with disappointing enantiocontrol (8:1 dr, 20% *ee*).

Since *L*-leucine based catalyst **4a** gave promising enantioselectivity, our attention was then switched to synthesize various chiral phosphines by using natural amino acids or chiral α -hydroxy acid as the backbone. As summarized in Table 5.3, the *L*-leucine based catalyst **4a** gave superior asymmetric induction. Notably, TBS protected catalyst **4e** delivered the product in an almost racemic manner, while catalyst **4f** bearing a free hydroxyl group afforded the corresponding product in 47% *ee*. These results indicate that hydrogen bonding between the catalyst and substrate, is crucial to achieving high levels asymmetric induction. The better *ee* achieved by catalysts **4a**, **4c**, and **4d** further suggest that the NH group in these catalyst may play a similar role by acting as the hydrogen bonding donor. Inspired by these findings, efforts were devoted to develop a catalyst with suitable hydrogen bonding ability based on *L*-leucine.

Systematic modification of *L*-leucine was then conducted, as summarized in Table 5.4. Catalyst **4g**, which possesses a free amino group gave low *ee*, although

excellent dr and good yield were obtained. Acetyl, benzoyl, 4-fluorobenzoyl, 4-methoxybenzoyl and 2-naphthyl protected amino phosphines afforded comparable *ee* with **4a**. Our attempt to increase the acidity of amide group by introduction of a strong electron-withdrawing group resulted in diminished enantioselectivity, as seen from the lackluster result obtained with catalyst **4l**. Installation of another hydrogen bonding donor, such as catalyst **4n** and **4o**, which possess a phenol and hydroxyl group respectively, did not show any improvement. The use of catalyst **4o** even led to a diminished reaction rate and almost no asymmetric induction. This result prompted us to hypothesize that the use of a catalyst with opposite chirality at the second chiral center might have a positive effect on hydrogen bonding. As expected, when catalyst **4p** was employed, 54% *ee* was observed, with 6:1 dr and 74% yield. The NH amide

Table 5.4 Catalyst screening based on *L*-leucine^a

4	t (h)	yield (%) ^b	dr ^c	<i>ee</i> (%) ^d
4g	24	76	15:1	35
4h	6	80	4:1	56
4i	6	85	5:1	61

Table 5.4 (continued)

<p>4j</p>	6	82	5:1	59
<p>4k</p>	6	81	5:1	58
<p>4l</p>	24	70	2:1	37
<p>4m</p>	6	84	5:1	54
<p>4n</p>	24	70	4:1	40

Table 5.4 (continued)

<p>4o</p>	24	32	4:1	-3
<p>4p</p>	24	74	6:1	54
<p>4q</p>	6	93	14:1	8
<p>4r</p>	6	74	6:1	68
<p>4r</p>	8	79	4:1	71 ^e

^a Unless otherwise noted, the reaction was performed on a 0.05 mmol scale in dichloromethane at room temperature, in the presence of 20 mol% catalyst. ^b Isolated yield. ^c Determined by crude ¹H NMR. ^d Determined by chiral IA-H column. ^e

N-(4-methoxybenzenesulfonyl)-1-aza-1,3-diene **2h** was used instead of *N*-toluene sulfonyl-1-aza-1,3-diene.

group in the catalyst was proved to be crucial. When Schiff Base **4q** was used as the catalyst, only 8% ee was delivered, though the yield and diastereoselectivity were excellent. Use of catalyst **4r**, which has a bulky amide group, showed promising enantioselectivity (68% ee), which was further improved to 71% by using *N*-(4-methoxybenzenesulfonyl)-1-aza-1,3-diene instead of *N*-toluenesulfonyl-1-aza-1,3-diene.

Encouraged by these good results, we moved on to investigate other chiral backbones, that could be easily modified. *L*-threonine was chosen due to the presence of a hydroxyl group at its β -position. Extensive investigation was then carried out to develop a more efficient catalyst (Table 5.5). It was found that *tert*-butyl dimethyl silyl protected catalyst **4s** furnished the desired product in good yield and diastereoselectivity, albeit with slightly lower ee (87% yield, 7:1 dr, 65% ee). Catalyst **4t**, which contains pivaloyl amide group, showed similar enantioselectivity with **4r**, while an improvement of diastereoselectivity (7:1) was observed. Introduction of a more bulky *tert*-butyl diphenyl silyl protection group (catalyst **4w**) further increased enantioselectivity to 72%, while other derivatives, such as tosylamide **4x** and thiourea **4y**, did not give any improvement. A new bifunctional chiral phosphine catalyst **4z** based on *R*-camphor was also synthesized and tested in this reaction; however, disappointing results were obtained.

Table 5.5 Catalyst screening^a

4	t (h)	yield (%) ^b	dr ^c	ee (%) ^d
4s	6	87	7:1	65
4t	6	87	7:1	71
4u	6	76	4:1	62
4v	6	80	9:1	25
4w	6	85	7:1	72
4x	6	50	5:1	46

Table 5.5 (continued)

<p style="text-align: center;">4y</p>	9	60	3:1	28
<p style="text-align: center;">4z</p>	24	63	6:1	5
<p style="text-align: center;">4w</p>	11	86	10:1	72 ^e

^a Unless otherwise noted, the reaction was performed on a 0.05 mmol scale in dichloromethane at room temperature, in the presence of 20 mol% catalyst. ^b Isolated yield. ^c Determined by crude ¹H NMR. ^d Determined by chiral IA-H column.

In our previously developed PPh₃ catalyzed [4+2] annulation reaction, we observed that Brønsted acid additives accelerated the reaction rate, and improved diastereoselectivity. Using catalyst **4w** as the choice of catalyst, screening of various additives was carried out. Surprisingly, the use of 4-methoxyphenol, which was shown to be effective additive in our non-asymmetric [4+2] annulation system, decreased reaction rate, and a diminished yield and *ee* were afforded. (*R*)-H₈-BINOL, as well as other phenol additives like *p*-tert-butylcatechol and hydroquinone, resulted in a sluggish reaction. Furthermore, the employment of a thiourea derived from (1*R*,

Table 5.6 Additive screening^a

additive	t (h)	yield (%) ^b	dr ^c	ee (%) ^d
	24	50	>10:1	71
	24	50	>10:1	72
	24	trace	nd	nd
	24	trace	nd	nd
	24	<20%	nd	nd
 Ar = 3,5-CF ₃ C ₆ H ₃	24	55	7:1	73
	24	70	10:1	73

Table 5.6 (continued)

24	68	10:1	73
24	63	10:1	73
24	64	8:1	72
21	67	10:1	74 ^e

^a Unless otherwise noted, the reaction was performed on a 0.025 mmol scale in dichloromethane at room temperature, in the presence of 10 mol% catalyst. ^b Isolated yield. ^c Determined by crude ¹H NMR. ^d Determined by chiral IA-H column. ^e 10 mol% benzenesulfonamide was used. nd = no detection

2*R*-cyclohexane-1, 2-diamine slightly improved the enantioselectivity, but required a longer reaction time of 24 hours. Interestingly, when the simple benzenesulfonamide was used, the corresponding product was obtained with 73% *ee* and 70% yield. Further investigation of other sulfonamides delivered similar results. When 10 mol% benzenesulfonamide was employed, the enantioselectivity was further elevated to 74%.

The reason for the decreased reaction rate arising from the additives is still ambiguous. However, it is proposed that as the Lewis basicity of chiral phosphines **4w** is much higher than that of PPh₃, may directly form hydrogen bond with additives, and thus results in a lower nucleophilicity (Scheme 5.7). In contrast, when PPh₃ is

used, the additive would prefer to form hydrogen bonding with the enolate intermediate, thereby increasing the reaction rate.

Scheme 5.7 Hydrogen bonding between chiral phosphine with Brønsted acid

Subsequent solvent screening indicated that chloroform was the best choice, in terms of chemical yield, diastereo- and enantioselectivity. Other solvents examined, such as ethyl acetate (EA) and toluene gave sluggish reactions, while acetone afforded

Table 5.7 Solvent and concentration effects^a

Entry	solvent	t (h)	yield (%) ^b	dr ^c	ee (%) ^d
1	CHCl ₃	24	86	10:1	74
2	EA	24	30	nd	nd
3	toluene	24	20	nd	nd
4	acetone	24	80	6:1	73
5 ^e	CHCl ₃	24	70	10:1	76
6 ^f	CHCl ₃	7	86	10:1	76

^a Unless otherwise noted, the reaction was performed on a 0.025 mmol scale in dichloromethane at room temperature, in the presence of 10 mol% catalyst. ^b Isolated yield. ^c Determined by crude ¹H NMR. ^d Determined by chiral IA-H column. ^e 0.2 M concentration. ^f 0.5M concentration. nd = no detection

comparable results. The reactant concentration significantly influenced the reaction outcome, higher concentration delivering better enantioselectivity.

With the optimized conditions in hand, the generality of this reaction was explored, as summarized in Table 5.8. In general, aryl substituted α , β -unsaturated imines could provide the desired products in good yields, diastereo- and enantioselectivities, regardless of whether the substituents are electron-donating or electron-withdrawing. Reactions involving a heteroaromatic aza-diene also proceeded smoothly to generate the product with good yield, dr and *ee* (entry 11), whereas electron rich aza-diene demonstrated relatively lower reactivity (entry 10). When a highly electrophilic aza-diene, which was derived from ethyl 4-oxo-4-phenylbut-2-enoate, was used, the reaction was completed within 1 hour, albeit with unsatisfactory results (entry 12). Ethyl vinyl ketone was well tolerated in this process, affording the product in 86% yield, 5:1 dr and 68% *ee* (entry 13), while 4-iodophenyl substituted aza-diene gave rise to the product with good yield, diastereo- and enantioselectivity (entry 14).

The absolute configuration of [4+2] annulation adducts was established by X-ray analysis, the two continuous chiral centers were determined to be 3*R*, 4*S* (Scheme 5.8).

Table 5.8 Substrate scope of [4+2] annulation reaction^a

entry	R ² , R ³	t (h)	Yield (%) ^b	dr ^c	ee (%) ^d
1	Ph, Ph	7	86	10:1	76
2	2-FPh, Ph	24	80	10:1	73
3	2-Cl-5-NO ₂ Ph, Ph	24	86	3:1	62
4	3-ClPh, Ph	12	88	9:1	80
5	3-BrPh, Ph	12	92	5:1	76
6	3-MePh, Ph	24	78	10:1	73
7	4-FPh, Ph	12	87	8:1	81
8	4-ClPh, Ph	12	70	10:1	84
9	2-Naphthyl, Ph	9	80	7:1	82
10	2-Benzofuran, Ph	24	60	6:1	61
11	2-thiophenyl, Ph	24	80	8:1	78
12	Ethyl carboxylate	1	60	6:1	25
13 ^e	4-ClPh, Ph	12	86	5:1	68
14	Ph, 4-IPh	12	71	10:1	74

^a Unless otherwise noted, the reaction was performed on a 0.05 mmol scale in chloroform at room temperature, in the presence of 10 mol% **4y** and 10 mol% benzensulfonamide, at 0.5 M concentration. ^b Isolated yield. ^c Determined by crude ¹H NMR. ^d Determined by chiral IA-H column. ^e Ethyl vinyl ketone was used instead

of methyl vinyl ketone.

Scheme 5.8 X-ray diffraction crystallography

Based on observed stereo- outcomes, a rational transition state was proposed to account for the stereochemistry of this methodology. As shown in Scheme 5.9, the NH group of pivalyl amide formed hydrogen bonding with 1, 3-azadiene, whilst the enolate generated by nucleophilic addition of phosphine, attacked from less hindered *Re* face. The moderate to good enantioselectivities were believed due to the flexibility of the hydrogen bonding, and this suggestion would give us positive information to improve the face differentiation in future, by introducing more rigid transition state.

Scheme 5.9 Proposed transition state of [4+2] annulation reaction

5.3 Conclusion

The first example of a catalytic asymmetric [4+2] annulation of vinyl ketones with *N*-sulfonyl-1-aza-1, 3-dienes was developed. After a systematic investigation of catalysts, the *L*-threonine based chiral phosphine **4w** proved to be the best choice. Furthermore, it was determined that use of a benzenesulfonamide additive is beneficial for enantioinduction, although its exact role is not clear yet. This protocol has opened up a fast entry to the synthesis of chiral multifunctionalized tetrahydropyridines, which are valuable synthetic intermediates in natural products and pharmaceuticals. This reaction system has the potential to be applied towards the construction of more complicated molecules, such as tricyclic *N*-containing compounds, in a one pot operation.

5.4 Experimental section

Catalyst **4a**, **4b**, **4c**, **4d** were prepared following below route⁸

(S)-methyl 2-(tert-butoxycarbonylamino)-3-(diphenylphosphino)propanoate 4b

According to general procedure: colorless oil obtained from flash chromatography (hexane/EtOAc = 50:1-30:1) under nitrogen protection, characteristic data are identical with literature report.⁹

(S)-tert-butyl 1-(diphenylphosphino)-3-methylbutan-2-ylcarbamate 4c

According to general procedure: colorless oil obtained from flash chromatography (hexane/EtOAc = 40:1-30:1) under nitrogen protection, characteristic data are identical with literature report.¹⁰

(S)-tert-butyl 1-(diphenylphosphino)-3-phenylpropan-2-ylcarbamate 4d

According to general procedure: white solid obtained from flash chromatography (hexane/EtOAc = 30:1) under nitrogen protection, characteristic data are identical with literature report.¹¹

Catalyst 4e and 4f was prepared following below route:

(S)-2-(tert-butyldimethylsilyloxy)-2-phenylethyl)diphenylphosphine 4e

According to general procedure: 70% yield, colorless oil obtained from flash chromatography (hexane/EtOAc = 30:1) under nitrogen protection, characteristic data are identical with literature report.¹²

(S)-2-(diphenylphosphino)-1-phenylethanol 4f

According to general procedure: 85% yield colorless oil obtained from flash chromatography (hexane/EtOAc = 10:1) under nitrogen protection, characteristic data are identical with literature report.¹³

(S)-1-(diphenylphosphino)-4-methylpentan-2-amine 4g

To 2 mL dichloromethane solution of **4a** (2 mmol) was added 1.0 mL TFA at 0 °C, then warmed to room temperature for 1 hour. Reaction was quenched with saturated NaHCO₃ solution, dried over MgSO₄ gave pure colorless oil product in quantitative yield. Characteristic data is identical with literature report.¹⁴

(S)-N-(1-(diphenylphosphino)-4-methylpentan-2-yl)acetamide 4h

 White solid, $[\alpha]_{\text{D}}^{22} = -34.9^\circ$ ($c = 0.2$, CHCl_3); ^1H NMR (400 MHz, CDCl_3): δ 0.84 (d, $J = 6.3$ Hz, 3H), 0.87 (d, $J = 6.4$ Hz, 3H), 1.44-1.51 (m, 2H), 1.55-1.61 (m, 1H), 1.75 (s, 3H), 2.28-2.43 (m, 2H), 4.19-4.28 (m, 1H), 5.23 (d, $J = 8.4$ Hz, 1H), 7.28-7.38 (m, 6H), 7.42-7.53 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3): 22.2, 22.8, 23.3, 25.0, 34.9, 35.0 (d, $J = 14.4$ Hz), 45.2 (d, $J = 9.2$ Hz), 46.1 (d, $J = 14.0$ Hz), 53.4, 128.5 (d, $J = 1.9$ Hz), 128.6 (d, $J = 1.4$ Hz), 128.7, 132.8 (d, $J = 9.3$ Hz), 133.0 (d, $J = 9.1$ Hz), 138.4 (d, $J = 11.6$ Hz), 169.3; ^{31}P -NMR (160 MHz, CDCl_3) δ -25.0; HRMS (ESI) Calcd for $\text{C}_{20}\text{H}_{27}\text{NOP}$ ($[\text{M}+\text{H}]^+$) 328.1830, found 328.1824.

(S)-N-(1-(diphenylphosphino)-4-methylpentan-2-yl)benzamide 4i

 White solid, $[\alpha]_{\text{D}}^{22} = -0.6^\circ$ ($c = 0.1$, CHCl_3), ^1H NMR (400 MHz, CDCl_3): δ 0.89 (d, $J = 6.1$ Hz, 3H), 0.91 (d, $J = 6.2$ Hz, 3H), 1.62-1.68 (m, 3H), 2.49 (t, $J = 5.6$ Hz, 1H), 4.45-4.50 (m, 2H), 5.98 (d, $J = 8.5$ Hz, 1H), 7.29-7.39 (m, 8H), 7.44-7.56 (m, 7H). ^{13}C NMR (100 MHz, CDCl_3): 22.3, 22.8, 25.2, 35.1 (d, $J = 15.5$ Hz), 45.4 (d, $J = 9.5$ Hz), 46.6 (d, $J = 14.0$ Hz), 126.8, 128.5 (d, $J = 16.6$ Hz), 128.7 (d, $J = 4.2$ Hz), 128.8 (d, $J = 7.0$ Hz), 131.2, 132.8 (d, $J = 8.8$ Hz), 133.0 (d, $J = 8.8$ Hz), 134.7, 138.7, 166.6; ^{31}P -NMR (160 MHz, CDCl_3) δ -25.1; HRMS (ESI) Calcd for $\text{C}_{25}\text{H}_{28}\text{NOPNa}$ ($[\text{M}+\text{Na}]^+$) 412.1806, found 412.1809.

(S)-N-(1-(diphenylphosphino)-4-methylpentan-2-yl)-4-fluorobenzamide 4j

White solid, $[\alpha]_{\text{D}}^{22} = +13.9^\circ$ ($c = 0.2$, CHCl_3), ^1H NMR (400 MHz, CDCl_3): δ 0.89 (d, $J = 6.1$ Hz, 3H), 0.92 (d, $J = 6.2$ Hz, 3H), 1.63-1.65 (m, 3H), 2.41-2.49 (m, 2H), 4.43-4.50 (m, 1H), 5.90 (d, $J = 8.5$ Hz, 1H), 7.00-7.06 (m, 2H), 7.29-7.38 (m, 6H), 7.43-7.52 (m, 6H). ^{13}C NMR (100 MHz, CDCl_3): 22.4, 22.8, 25.1, 34.9 (d, $J = 14.5$ Hz), 45.4 (d, $J = 9.3$ Hz), 46.8 (d, $J = 13.9$ Hz), 115.4 (d, $J = 22.0$ Hz), 128.6 (d, $J = 3.2$ Hz), 128.8 (d, $J = 4.2$ Hz), 129.1 (d, $J = 8.7$ Hz), 130.8 (d, $J = 8.7$ Hz), 132.8 (d, $J = 4.2$ Hz), 132.9 (d, $J = 15.0$ Hz), 138.3 (d, $J = 11.4$ Hz), 138.7 (d, $J = 12.4$ Hz), 166.3, 165.5, 165.8; ^{31}P -NMR (160 MHz, CDCl_3) δ -25.2; HRMS (ESI) Calcd for $\text{C}_{25}\text{H}_{28}\text{NOPF}$ ($[\text{M}+\text{Na}]^+$) 408.1893, found 408.1901.

(S)-N-(1-(diphenylphosphino)-4-methylpentan-2-yl)-4-methoxybenzamide 4k

White solid, $[\alpha]_{\text{D}}^{22} = +11.5^\circ$ ($c = 0.1$, CHCl_3), ^1H NMR (400 MHz, CDCl_3): δ 0.89 (d, $J = 6.1$ Hz, 3H), 0.91 (d, $J = 6.2$ Hz, 3H), 1.61-1.66 (m, 3H), 2.47 (d, $J = 6.3$ Hz, 2H), 3.85 (s, 3H), 4.44-4.48 (m, 1H), 5.98 (d, $J = 8.5$ Hz, 1H), 6.85 (d, $J = 8.7$ Hz, 2H), 7.31-7.38 (m, 6H), 7.42-7.46 (m, 2H), 7.50-7.55 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3): 22.4, 22.8, 25.1, 35.1 (d, $J = 14.6$ Hz), 45.4 (d, $J = 9.3$ Hz), 46.5 (d, $J = 13.8$ Hz), 55.4, 113.5, 130.0, 128.6 (d, $J = 6.7$ Hz), 128.7 (d, $J = 10.2$ Hz),

132.8 (d, $J = 11.0$ Hz), 133.0 (d, $J = 11.4$ Hz), 138.4 (d, $J = 11.5$ Hz), 138.8 (d, $J = 12.2$ Hz), 162.0, 166.1; ^{31}P -NMR (160 MHz, CDCl_3) δ -25.1; HRMS (ESI) Calcd for $\text{C}_{26}\text{H}_{31}\text{NO}_2\text{P}$ ($[\text{M}+\text{H}]^+$) 420.2092, found 420.2089

(S)-N-(1-(diphenylphosphino)-4-methylpentan-2-yl)-3,5-dinitrobenzamide 4l

White solid, $[\alpha]_{\text{D}}^{22} = +57.3^\circ$ ($c = 0.1$, CHCl_3), ^1H NMR (400 MHz, CDCl_3): δ 0.94 (d, $J = 4.8$ Hz, 3H), 0.91 (d, $J = 6.2$ Hz, 3H), 1.67-1.75 (m, 3H), 2.40-2.46 (m, 1H), 2.60-2.65 (m, 1H), 4.6 (s, 1H), 6.11 (d, $J = 4.5$ Hz, 1H), 7.22-7.33 (m, 6H), 7.43-7.49 (m, 4H), 8.64 (d, $J = 2.0$ Hz, 2H), 9.10 (t, $J = 1.7$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3): 22.3, 22.7, 34.5 (d, $J = 15.2$ Hz), 45.4 (d, $J = 9.0$ Hz), 47.8 (d, $J = 13.8$ Hz), 120.8, 126.9, 128.7 (d, $J = 7.2$ Hz), 128.9, 132.6 (d, $J = 19.4$ Hz), 138.0 (d, $J = 19.5$ Hz), 138.2, 148.4, 161.8; ^{31}P -NMR (160 MHz, CDCl_3) δ -25.1; HRMS (ESI) Calcd for $\text{C}_{25}\text{H}_{27}\text{N}_3\text{O}_5\text{P}$ ($[\text{M}+\text{H}]^+$) 480.1688, found 480.1688.

(S)-N-(1-(diphenylphosphino)-4-methylpentan-2-yl)-2-naphthamide 4m

White solid, $[\alpha]_{\text{D}}^{22} = +18.8^\circ$ ($c = 0.1$, CHCl_3), ^1H NMR (400 MHz, CDCl_3): δ 0.92 (d, $J = 6.1$ Hz, 3H), 0.95 (d, $J = 6.2$ Hz, 3H), 1.68-1.74 (m, 3H), 2.49-2.60 (m, 2H), 4.52-4.60 (m, 1H), 6.12 (d, $J = 4.6$ Hz, 1H), 7.28-7.38 (m, 6H), 7.47-7.51 (m, 6H), 7.52 (d, $J = 2.4$ Hz, 1H), 7.53-7.66 (m, 3H), 8.10 (s, 1H). ^{13}C NMR (100 MHz, CDCl_3): 22.4, 22.8, 25.2, 35.1 (d, $J = 14.6$ Hz), 45.5 (d, $J = 9.4$ Hz),

46.8 (d, $J = 13.8$ Hz), 126.6 (d, $J = 7.5$ Hz), 127.1, 127.5, 127.7, 128.2, 128.6, 128.7, 128.8 (d, $J = 4.7$ Hz), 128.9, 131.9, 132.5, 132.8, 133.0 (d, $J = 6.6$ Hz), 134.6, 138.4, 138.6, 166.7; ^{31}P -NMR (160 MHz, CDCl_3) δ -25.1; HRMS (ESI) Calcd for $\text{C}_{29}\text{H}_{31}\text{NOP}$ ($[\text{M}+\text{H}]^+$) 440.2143, found 440.2145.

(S)-3,5-dibromo-N-(1-(diphenylphosphino)-4-methylpentan-2-yl)-2-hydroxybenzamide 4n

yellow oil, $[\alpha]_{\text{D}}^{22} = +36.2^\circ$ ($c = 0.1$, CHCl_3), ^1H NMR (400 MHz, CDCl_3): δ 0.89 (d, $J = 5.0$ Hz, 3H), 0.91 (d, $J = 5.8$ Hz, 3H), 1.58-1.63 (m, 4H), 2.36-2.40 (m, 1H), 2.51-2.55 (m, 1H), 4.51 (s, 1H), 5.79 (d, $J = 4.6$ Hz, 1H), 6.78 (d, $J = 2.2$ Hz, 1H), 7.28-7.31 (m, 6H), 7.40-7.47 (m, 4H), 7.71 (d, $J = 2.2$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3): 22.3, 22.7, 25.1, 34.5 (d, $J = 15.1$ Hz), 45.4 (d, $J = 8.9$ Hz), 47.1, 109.6, 113.2, 126.8, 128.7 (d, $J = 2.8$ Hz), 128.8 (d, $J = 2.8$ Hz), 129.0, 132.7 (d, $J = 4.3$ Hz), 132.9 (d, $J = 4.4$ Hz), 139.1, 157.4, 167.4; ^{31}P -NMR (160 MHz, CDCl_3) δ -25.0; HRMS (ESI) Calcd for $\text{C}_{25}\text{H}_{27}\text{Br}_2\text{NO}_2\text{P}$ ($[\text{M}+\text{H}]^+$) 564.0129, found 564.0134.

(S)-N-((S)-1-(diphenylphosphino)-4-methylpentan-2-yl)-2-hydroxy-2-phenylacetamide 4o

White solid, $[\alpha]_{\text{D}}^{22} = +7.6^\circ$ ($c = 0.1$, CHCl_3), ^1H NMR (400 MHz, CDCl_3): δ 0.75 (t, $J = 3.2$ Hz, 3H), 0.81 (t, $J = 3.2$ Hz, 3H), 1.43-1.53 (m, 3H), 2.29 (d,

$J = 6.4$ Hz, 2H), 3.26 (d, $J = 3.2$ Hz, 1H), 4.09-4.19 (m, 1H), 4.85 (d, $J = 3.6$ Hz, 1H), 6.26 (d, $J = 8.8$ Hz, 1H), 7.29-7.39 (m, 13H), 7.44-7.49 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3): 22.0, 22.8, 25.0, 34.2 (d, $J = 15.8$ Hz), 45.0 (d, $J = 8.9$ Hz), 46.1 (d, $J = 14.9$ Hz), 126.7, 128.5 (d, $J = 7.2$ Hz), 128.7 (d, $J = 3.0$ Hz), 128.8, 132.7, 132.9 (d, $J = 3.2$ Hz), 133.0, 138.2, 138.7, 139.3, 171.3; ^{31}P -NMR (160 MHz, CDCl_3) δ -24.8; HRMS (ESI) Calcd for $\text{C}_{26}\text{H}_{30}\text{NO}_2\text{PNa}$ ($[\text{M}+\text{Na}]^+$) 442.1912, found 442.1904.

(S)-N-(1-(diphenylphosphino)-4-methylpentan-2-yl)pivalamide 4r

White solid, $[\alpha]_{\text{D}}^{22} = -38.9^\circ$ ($c = 0.1$, CHCl_3), ^1H NMR (400 MHz, CDCl_3): δ 0.82 (d, $J = 2.0$ Hz, 3H), 0.87 (d, $J = 6.0$ Hz, 3H), 1.08 (s, 9H), 1.25 (d, $J = 12.0$ Hz, 1H), 1.43-1.55 (m, 2H), 2.30-2.37 (m, 2H), 4.20 (d, $J = 6.0$ Hz, 1H), 5.53 (d, $J = 11.6$ Hz, 1H), 7.30-7.51 (m, 10H). ^{13}C NMR (100 MHz, CDCl_3): 22.3, 22.8, 25.1, 27.5, 35.0 (d, $J = 4.5$ Hz), 38.6, 45.2 (d, $J = 9.2$ Hz), 45.9 (d, $J = 14.1$ Hz), 128.6 (d, $J = 5.7$ Hz), 128.6, 128.7 (d, $J = 5.6$ Hz), 132.8 (d, $J = 3.5$ Hz), 133.0 (d, $J = 3.5$ Hz), 138.3, 138.4, 138.8, 138.9, 177.5; ^{31}P -NMR (160 MHz, CDCl_3) δ -25.3; HRMS (ESI) Calcd for $\text{C}_{26}\text{H}_{32}\text{NONaP}$ ($[\text{M}+\text{Na}]^+$) 392.2119, found 392.2114.

N-((2S,3R)-3-(tert-butyldimethylsilyloxy)-1-(diphenylphosphino)butan-2-yl)pivalamide 4t

$[\alpha]_{\text{D}}^{22} = -22.9^\circ$ ($c = 0.2$, CHCl_3), ^1H NMR (400 MHz, CDCl_3): δ 0.12 (d, $J = 7.4$ Hz, 6H), 0.91 (d, $J = 2.7$ Hz, 9H), 1.06 (d, $J = 6.2$ Hz, 3H), 1.16 (s, 9H),

2.04-2.20 (m, 1H), 2.43-2.49 (m, 1H), 3.82-3.89 (m, 1H), 4.30 (q, $J = 1.5$ Hz, 1H), 6.13 (d, $J = 8.5$ Hz, 1H), 7.27-7.29 (m, 3H), 7.33-7.41 (m, 5H), 7.67 (q, $J = 7.2$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3): -4.5, -4.2, 17.9, 21.2, 25.9, 27.6, 31.9, 38.8, 52.1 (d, $J = 16.0$ Hz), 68.8 (d, $J = 10.6$ Hz), 128.4 (d, $J = 7.0$ Hz), 128.6 (d, $J = 12.5$ Hz), 128.7 (d, $J = 4.5$ Hz), 132.7 (d, $J = 3.4$ Hz), 132.9 (d, $J = 3.3$ Hz), 177.8; ^{31}P -NMR (160 MHz, CDCl_3) δ -24.5; HRMS (ESI) Calcd for $\text{C}_{27}\text{H}_{42}\text{NO}_2\text{NaSiP}$ ($[\text{M}+\text{Na}]^+$) 494.2620, found 494.2628.

tert-butyl (2*S*,3*R*)-3-(tert-butyldiphenylsilyloxy)-1-(diphenylphosphino)butan-2-ylcarbamate 4u

$[\alpha]_{\text{D}}^{22} = +22.8^\circ$ ($c = 0.6$, CHCl_3), ^1H NMR (400 MHz, CDCl_3): δ 0.96 (d, $J = 6.0$ Hz, 3H), 1.05 (s, 9H), 1.45 (s, 9H), 2.20-2.34 (m, 2H), 3.62 (s, 1H), 4.06 (d, $J = 5.2$ Hz, 1H), 4.76 (d, $J = 9.6$ Hz, 1H), 7.24-7.42 (m, 16H), 7.66 (d, $J = 6.4$ Hz, 4H). ^{13}C NMR (100 MHz, CDCl_3): 14.1, 19.4, 20.4, 27.2, 28.5, 29.7, 32.9 (d, $J = 13.7$ Hz), 53.7, 71.6, 79.0, 127.7 (d, $J = 18.7$ Hz), 128.4 (d, $J = 5.2$ Hz), 128.6 (d, $J = 7.7$ Hz), 129.8 (d, $J = 12.2$ Hz), 132.6, 132.9 (d, $J = 14.1$ Hz), 133.1, 136.0, 155.5. ^{31}P -NMR (160 MHz, CDCl_3) δ -23.0; HRMS (ESI) $\text{C}_{37}\text{H}_{46}\text{NO}_3\text{NaSiP}$ ($[\text{M}+\text{Na}]^+$) 634.2882, found 634.2905.

***N*-((2*S*,3*R*)-3-(tert-butyldiphenylsilyloxy)-1-(diphenylphosphino)butan-2-yl)pivalamide 4w**

White solid, $[\alpha]_D^{22} = +14.1^\circ$ ($c = 0.1$, CHCl_3), ^1H NMR (400 MHz, CDCl_3): δ 0.93 (d, $J = 6.4$ Hz, 3H), 1.09 (d, $J = 2.7$ Hz, 9H), 1.20 (s, 9H), 2.13 (dd, $J = 13.6, 7.2$ Hz, 1H), 2.47 (dd, $J = 14.0, 8.0$ Hz, 1H), 3.90-3.94 (m, 1H), 4.27 (dd, $J = 12.4, 7.6$ Hz, 1H), 6.19 (d, $J = 8.8$ Hz, 1H), 7.25-7.49 (m, 16H), 7.66-7.71 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3): 19.5, 21.2, 27.2, 27.7, 32.8 (d, $J = 14.4$ Hz), 38.9, 52.2 (d, $J = 6.1$ Hz), 71.2 (d, $J = 10.2$ Hz), 79.0, 127.8 (d, $J = 10.7$ Hz), 128.4 (d, $J = 3.4$ Hz), 128.6 (d, $J = 6.6$ Hz), 129.9 (d, $J = 13.3$ Hz), 132.9 (d, $J = 19.0$ Hz), 133.3, 136.0 (d, $J = 5.3$ Hz), 137.9 (d, $J = 1.9$ Hz), 139.3 (d, $J = 3.8$ Hz), 178.5. ^{31}P -NMR (160 MHz, CDCl_3) δ -23.8; HRMS (ESI) Calcd for $\text{C}_{37}\text{H}_{46}\text{NO}_2\text{NaSiP}$ ($[\text{M}+\text{Na}]^+$) 618.2933, found 618.2935.

(2R,3S)-3-(diphenylphosphino)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol 4z

White solid, $[\alpha]_D^{22} = +15.4^\circ$ ($c = 0.1$, CHCl_3), ^1H NMR (400 MHz, CDCl_3): δ 0.8 (s, 3H), 0.97 (s, 3H), 1.06-1.10 (m, 1H), 1.14-1.20 (m, 1H), 1.48 (s, 3H), 1.55-1.60 (m, 2H), 1.77 (d, $J = 4.0$ Hz, 1H), 2.74 (t, $J = 8.0$ Hz, 1H), 3.95 (t, $J = 8.0$ Hz, 1H), 7.28-7.33 (m, 6H), 7.45-7.49 (m, 2H), 7.53-7.58 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3): 11.8, 21.9, 22.2, 22.4, 30.7 (d, $J = 5.2$ Hz), 33.7, 47.3, 48.8 (d, $J = 8.7$ Hz), 50.5, 51.0, 51.2, 82.0 (d, $J = 3.6$ Hz), 128.1, 128.3 (d, $J = 5.5$ Hz), 128.4 (d, $J = 4.1$ Hz), 128.7, 129.9 (d, $J = 13.3$ Hz), 132.4 (d, $J = 18.1$ Hz), 134.2 (d, $J = 11.1$ Hz),

139.5 (d, $J = 15.3$ Hz), 140.8, 141.0. ^{31}P -NMR (160 MHz, CDCl_3) δ -14.4; HRMS (ESI) Calcd for $\text{C}_{22}\text{H}_{28}\text{OP}$ ($[\text{M}+\text{H}]^+$) 339.1878, found 339.1878.

Products characteristic data

According to general procedure: the product was obtained from flash chromatography (hexane/EtOAc = 10:1 to 6:1), 76% *ee*. HPLC analysis: Chiralpak IA-H (hexane/*i*-PrOH = 95/5, 1.0 mL/min), t_R (major) 23.8 min, t_R (minor) 30.3 min. $[\alpha]_D^{22} = -24.6^\circ$ ($c = 0.9$, CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 1.94 (t, s, 3H), 2.84 (td, $J = 11.3, 2.9$ Hz, 1H), 3.34 (dd, $J = 13.8$ Hz, 11.8 Hz, 1H), 3.86 (dd, $J = 9.2$ Hz, 3.2 Hz, 1H), 3.85 (s, 3H), 3.86 (dd, $J = 10.4$ Hz, 3.2 Hz, 1H), 4.46 (dd, $J = 14.0$ Hz, 3.1 Hz, 1H), 5.50 (d, $J = 3.3$ Hz, 1H), 6.91-6.93 (m, 2H), 6.96 (d, $J = 8.9$ Hz, 2H), 7.21-7.27 (m, 6H), 7.35-7.37 (m, 2H), 7.64 (d, $J = 8.9$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 31.0, 43.4, 49.1, 52.2, 55.8, 114.2, 122.6, 127.2, 127.5, 127.8, 128.2, 128.7, 131.0, 138.1, 139.0, 141.7, 163.4, 208.1. HRMS (ESI) Calcd for $\text{C}_{26}\text{H}_{25}\text{NO}_4\text{SNa}$ ($[\text{M}+\text{Na}]^+$) 470.1402, found 470.1404.

According to general procedure: the product was obtained from

flash chromatography (hexane/EtOAc = 10:1 to 6:1), 73% *ee*. HPLC analysis: Chiralpak IA-H (hexane/*i*-PrOH = 95/5, 1.0 mL/min), t_R (major) 29.4 min, t_R (minor) 33.9 min. $[\alpha]_D^{22} = +2.5^\circ$ ($c = 1.8$, CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 1.98 (s, 3H), 2.94 (td, $J = 11.3, 2.4$ Hz, 1H), 3.43 (dd, $J = 14.0$ Hz, 2.4 Hz, 1H), 3.89 (s, 3H), 4.16 (dd, $J = 10.4$ Hz, 3.2 Hz, 1H), 4.43 (dd, 14.0 3.2 Hz, 1H), 5.41 (d, $J = 3.2$ Hz, 1H), 6.87 (t, $J = 2.0$ Hz, 1H), 6.94-6.98 (m, 2H), 7.00-7.03 (m, 3H), 7.24-7.26 (m, 3H), 7.31-7.33 (m, 2H), 7.62 (d, $J = 8.8$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 30.4, 36.4, 48.9, 50.8, 55.7, 114.2, 115.7, 115.9, 121.1, 124.5, 127.8, 128.2, 128.8, 129.3, 130.0, 131.1, 137.9, 139.3, 163.3, 207.6. HRMS (ESI) Calcd for $\text{C}_{26}\text{H}_{24}\text{FNO}_4\text{SNa}$ ($[\text{M}+\text{Na}]^+$) 488.1308, found 488.1311.

According to general procedure: the product was obtained from flash chromatography (hexane/EtOAc = 10:1 to 4:1), 62% *ee*. HPLC analysis: Chiralpak IA-H (hexane/*i*-PrOH = 95/5, 1.0 mL/min), t_R (minor) 41.2 min, t_R (major) 52.3 min. $[\alpha]_D^{22} = +2.5^\circ$ ($c = 1.6$, CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 2.04 (s, 3H), 2.78 (td, $J = 11.3, 2.4$ Hz, 1H), 3.53 (dd, $J = 14.0, 10.8$ Hz, 1H), 3.91 (s, 3H), 4.50 (m, 2H), 5.29 (d, $J = 3.2$ Hz, 1H), 7.03 (t, $J = 8.8$ Hz, 2H), 7.25-7.35 (m, 5H), 7.53 (d, $J = 8.8$ Hz, 1H), 7.66 (d, $J = 8.8$ Hz, 2H), 7.75 (d, $J = 2.4$ Hz, 1H), 8.02 (dd, $J = 8.8, 2.4$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 30.1, 39.4, 48.5, 55.0, 55.8, 114.6, 118.6, 123.2, 123.6, 124.5, 127.6, 128.5, 129.9, 130.3, 131.1, 137.7, 141.1, 147.0, 163.7,

206.1. HRMS (ESI) Calcd for $C_{26}H_{23}N_2O_6SNa$ ($[M+H]^+$) 549.0863, found 549.0856.

According to general procedure: the product was obtained from flash chromatography (hexane/EtOAc = 10:1 to 6:1), 80% *ee*. HPLC analysis: Chiralpak IA-H (hexane/*i*-PrOH = 95/5, 1.0 mL/min), t_R (major) 23.7 min, t_R (minor) 28.4 min. $[\alpha]_D^{22} = -4.4^\circ$ ($c = 1.9$, $CHCl_3$). 1H NMR (400 MHz, $CDCl_3$): δ 1.98 (s, 3H), 2.68 (td, $J = 11.2, 3.2$ Hz, 1H), 3.30 (dd, $J = 14.0, 12.0$ Hz, 1H), 3.87 (d, $J = 3.6$ Hz, 1H), 3.89 (s, 3H), 4.49 (dd, $J = 10.0, 3.2$ Hz, 1H), 5.44 (d, $J = 3.2$ Hz, 1H), 6.83 (s, 1H), 6.87 (d, $J = 4.8$ Hz, 1H), 7.10 (d, $J = 6.8$ Hz, 2H), 7.13-7.20 (m, 2H), 7.29 (t, $J = 3.6$ Hz, 3H), 7.38-7.40 (m, 2H), 7.66 (d, $J = 8.8$ Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.8, 42.6, 49.0, 51.8, 55.7, 114.4, 121.6, 126.5, 127.4, 127.9, 128.4, 130.0, 130.6, 134.5, 138.0, 139.6, 143.8, 163.5, 207.2. HRMS (ESI) Calcd for $C_{26}H_{24}ClNO_4SNa$ ($[M+Na]^+$) 504.1012, found 504.1012.

According to general procedure: the product was obtained from flash chromatography (hexane/EtOAc = 10:1 to 6:1), 76% *ee*. HPLC analysis: Chiralpak IA-H (hexane/*i*-PrOH = 95/5, 1.0 mL/min), t_R (major) 25.1 min, t_R (minor)

30.5 min. $[\alpha]_D^{22} = +2.3^\circ$ ($c = 2.0$, CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 1.98 (s, 3H), 2.65 (td, $J = 11.6, 3.2$ Hz, 1H), 3.30 (dd, $J = 14.0, 12.0$ Hz, 1H), 3.86 (t, $J = 3.2$ Hz, 1H), 3.90 (s, 3H), 4.48 (dd, $J = 6.0, 3.2$ Hz, 1H), 5.44 (d, $J = 3.2$ Hz, 1H), 6.91 (d, $J = 7.6$ Hz, 1H), 6.99-7.03 (m, 3H), 7.09 (t, $J = 8.0$ Hz, 1H), 7.28-7.30 (m, 3H), 7.34 (dd, $J = 6.8, 0.4$ Hz, 1H), 7.37-7.64 (m, 2H), 7.66 (d, $J = 4.8$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 30.8, 42.6, 49.0, 51.8, 55.8, 114.4, 121.6, 127.0, 127.4, 127.9, 128.4, 130.0, 130.2, 130.3, 130.4, 130.6, 138.0, 139.6, 144.1, 163.5, 207.2. HRMS (ESI) Calcd for $\text{C}_{26}\text{H}_{24}\text{BrNO}_4\text{SNa}$ ($[\text{M}+\text{Na}]^+$) 550.0490, found 550.0997.

According to general procedure: the product was obtained from flash chromatography (hexane/EtOAc = 10:1 to 8:1), 73% *ee*. HPLC analysis: Chiralpak IA-H (hexane/*i*-PrOH = 95/5, 1.0 mL/min), t_R (major) 20.7 min, t_R (minor) 25.6 min. $[\alpha]_D^{22} = -12.8^\circ$ ($c = 1.0$, CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 1.93 (s, 3H), 2.29 (s, 3H), 2.78 (td, $J = 11.3, 3.0$ Hz, 1H), 3.34 (dd, $J = 14.0, 11.8$ Hz, 1H), 3.80 (dd, $J = 10.6, 3.2$ Hz, 1H), 3.88 (s, 3H), 4.45 (dd, $J = 14.0, 3.1$ Hz, 1H), 5.48 (d, $J = 3.2$ Hz, 1H), 6.69 (d, $J = 7.2$ Hz, 1H), 6.72 (s, 1H), 6.97 (d, $J = 8.8$ Hz, 2H), 7.02 (d, $J = 7.6$ Hz, 1H), 7.11 (t, $J = 7.5$ Hz, 1H), 7.27-7.28 (m, 3H), 7.36-7.38 (m, 2H), 7.65 (d, $J = 8.8$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 21.4, 31.0, 43.5, 49.1, 51.8, 55.7, 114.3, 122.8, 124.9, 127.4, 127.8, 127.9, 128.2, 128.3, 128.6, 130.0, 131.0, 138.2, 138.8, 163.4, 208.2. HRMS (ESI) Calcd for $\text{C}_{27}\text{H}_{27}\text{NO}_4\text{SNa}$ ($[\text{M}+\text{Na}]^+$)

484.1559, found 484.1557.

According to general procedure: the product was obtained from flash chromatography (hexane/EtOAc = 10:1 to 6:1), 81% *ee*. HPLC analysis: Chiralpak IA-H (hexane/*i*-PrOH = 95/5, 1.0 mL/min), t_R (major) 26.0 min, t_R (minor) 37.7 min. $[\alpha]_D^{22} = -27.8^\circ$ ($c = 1.8$, CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 1.99 (s, 3H), 2.83 (td, $J = 11.2, 3.0$ Hz, 1H), 3.31 (dd, $J = 14.4, 12.0$ Hz, 1H), 3.87-3.90 (m, 4H), 4.48 (dd, $J = 14, 3.2$ Hz, 1H), 5.46 (d, $J = 3.2$ Hz, 1H), 6.90 (d, $J = 7.2$ Hz, 3H), 6.95 (d, $J = 8.8$ Hz, 2H), 7.26 (t, $J = 4.8$ Hz, 3H), 7.32-7.34 (m, 2H), 7.61 (d, $J = 8.8$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 30.9, 42.3, 49.1, 52.6, 55.8, 114.2, 115.4, 115.6, 122.3, 127.5, 127.8, 128.3, 129.3, 129.4, 130.0, 131.0, 137.5, 139.2, 163.4, 207.7. HRMS (ESI) Calcd for $\text{C}_{26}\text{H}_{24}\text{FNO}_4\text{S}$ ($[\text{M}+\text{Na}]^+$) 488.1308, found 488.10311.

According to general procedure: the product was obtained from flash chromatography (hexane/EtOAc = 10:1 to 6:1), 84% *ee*. HPLC analysis: Chiralpak IA-H (hexane/*i*-PrOH = 95/5, 1.0 mL/min), t_R (major) 15.4 min, t_R (minor)

19.9 min. $[\alpha]_{\text{D}}^{22} = -26.9^\circ$ ($c = 1.4$, CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 2.02 (s, 3H), 2.84 (td, $J = 11.6, 3.2$ Hz, 1H), 3.31 (dd, $J = 14.0, 12.0$ Hz, 1H), 3.89-3.92 (m, 4H), 4.48 (dd, $J = 14, 3.2$ Hz, 1H), 5.46 (d, $J = 3.6$ Hz, 1H), 6.90 (dd, $J = 6.8, 2.0$ Hz, 2H), 6.97 (dd, $J = 6.8, 2.0$ Hz, 2H), 7.21 (dd, $J = 6.0, 2.0$ Hz, 2H), 7.27-7.30 (m, 3H), 7.34-7.36 (m, 2H), 7.63 (dd, $J = 6.8, 2.0$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 30.8, 42.3, 49.1, 52.4, 55.8, 114.2, 122.0, 127.5, 122.3, 127.9, 128.3, 128.8, 129.2, 130.0, 132.9, 137.8, 140.3, 163.4, 207.5. HRMS (ESI) Calcd for $\text{C}_{26}\text{H}_{24}\text{ClNO}_4\text{SNa}$ ($[\text{M}+\text{Na}]^+$) 504.1012, found 504.1015.

According to general procedure: the product was obtained from flash chromatography (hexane/EtOAc = 10:1 to 6:1), 82% *ee*. HPLC analysis: Chiralpak IA-H (hexane/*i*-PrOH = 95/5, 1.0 mL/min), t_{R} (major) 28.6 min, t_{R} (minor) 37.5 min. $[\alpha]_{\text{D}}^{22} = +5.1^\circ$ ($c = 1.7$, CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 1.87 (s, 3H), 2.88 (td, $J = 11.2, 2.8$ Hz, 1H), 3.31 (dd, $J = 13.2, 12.0$ Hz, 1H), 3.82 (s, 3H), 4.46 (dd, $J = 14.0, 2.8$ Hz, 1H), 5.50 (d, $J = 3.2$ Hz, 1H), 6.95 (dd, $J = 10.0, 2.0$ Hz, 3H), 7.20-7.23 (m, 3H), 7.33-7.35 (m, 3H), 7.38-7.44 (m, 2H), 7.62-7.67 (m, 4H), 7.69 (d, $J = 2.0$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 31.0, 43.5, 49.2, 51.9, 55.7, 114.3, 122.6, 125.7, 125.9, 126.2, 126.6, 127.5, 127.6, 127.7, 127.8, 128.3, 128.5, 130.1, 131.0, 132.6, 133.4, 138.1, 139.0, 139.2, 163.4, 208.0. HRMS (ESI) Calcd for

$C_{30}H_{27}NO_4SNa$ ($[M+Na]^+$) 520.1559, found 520.1552.

According to general procedure: the product was obtained from flash chromatography (hexane/EtOAc = 12:1 to 6:1), 61% *ee*. HPLC analysis: Chiralpak IA-H (hexane/*i*-PrOH = 95/5, 1.0 mL/min), t_R (major) 32.5 min, t_R (minor) 42.2 min. $[\alpha]_D^{22} = -4.4^\circ$ ($c = 1.3$, $CHCl_3$). 1H NMR (400 MHz, $CDCl_3$): δ 1.96 (s, 3H), 2.81 (td, $J = 11.2, 2.8$ Hz, 1H), 3.12-3.17 (m, 2H), 3.32 (dd, $J = 13.6, 12.0$ Hz, 1H), 3.78 (dd, $J = 10.4, 2.8$ Hz, 1H), 3.89 (s, 3H), 4.44 (dd, $J = 14.0, 3.2$ Hz, 1H), 4.55 (t, $J = 8.8$ Hz, 2H), 5.47 (d, $J = 2.8$ Hz, 1H), 6.61 (s, 2H), 6.75 (s, 1H), 6.96 (d, $J = 8.8$ Hz, 2H), 7.27 (d, $J = 1.6$ Hz, 3H), 7.35 (t, $J = 3.6$ Hz, 2H), 7.64 (d, $J = 8.8$ Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.7, 31.0, 42.9, 49.2, 52.4, 55.7, 109.2, 114.2, 123.4, 124.3, 127.4, 127.8, 128.1, 130.1, 131.0, 133.5, 138.1, 138.6, 159.2, 163.3, 208.3. HRMS (ESI) Calcd for $C_{28}H_{27}NO_5SNa$ ($[M+Na]^+$) 512.1508, found 512.1512.

According to general procedure: the product was obtained from flash chromatography (hexane/EtOAc = 12:1 to 6:1), 78% *ee*. HPLC analysis: Chiralpak IA-H (hexane/*i*-PrOH = 95/5, 1.0 mL/min), t_R (major) 29.5 min, t_R (minor)

37.8 min. $[\alpha]^{22}_{\text{D}} = -20.1^\circ$ ($c = 1.7$, CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 2.03 (s, 3H), 2.67 (td, $J = 10.8$, 2.8 Hz, 1H), 3.30 (dd, $J = 14.0$, 12.0 Hz, 1H), 3.86 (s, 3H), 4.22 (dd, $J = 10.4$, 3.2 Hz, 1H), 4.42 (dd, $J = 10.4$, 2.8 Hz, 1H), 5.55 (d, $J = 2.8$ Hz, 1H), 6.68 (d, $J = 2.8$ Hz, 1H), 6.87 (dd, $J = 5.2$, 3.6 Hz, 1H), 6.95 (d, $J = 4.8$ Hz, 2H), 7.12 (d, $J = 5.2$ Hz, 1H), 7.29 (d, $J = 2.0$ Hz, 3H), 7.39 (dd, $J = 7.6$, 2.0 Hz, 2H), 7.63 (d, $J = 8.8$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 30.7, 37.8, 48.9, 52.1, 55.8, 114.4, 121.4, 124.1, 125.0, 126.8, 127.5, 127.9, 128.3, 129.9, 130.5, 138.1, 144.8, 163.4, 207.4. HRMS (ESI) Calcd for $\text{C}_{24}\text{H}_{23}\text{NO}_4\text{S}_2\text{Na}$ ($[\text{M}+\text{Na}]^+$) 476.0966, found 476.0964.

According to general procedure: the product was obtained from flash chromatography (hexane/EtOAc = 12:1 to 6:1), 25% *ee*. HPLC analysis: Chiralpak IA-H (hexane/*i*-PrOH = 95/5, 1.0 mL/min), t_{R} (major) 15.9 min, t_{R} (minor) 18.5 min. $[\alpha]^{22}_{\text{D}} = -6.8^\circ$ ($c = 0.9$, CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 1.23 (t, $J = 7.2$ Hz, 3H), 2.27 (s, 3H), 2.91 (td, $J = 11.6$, 3.2 Hz, 1H), 3.13 (dd, $J = 13.6$, 12.0 Hz, 1H), 3.75 (dd, $J = 10.4$, 3.6 Hz, 1H), 3.87 (s, 3H), 4.09 (q, $J = 7.2$ Hz, 2H), 4.38 (dd, $J = 14.0$, 3.6 Hz, 1H), 5.65 (d, $J = 4.0$ Hz, 1H), 6.93 (dd, $J = 11.6$, 2.8 Hz, 1H), 7.27-7.30(m, 4H), 7.32-7.36 (m, 2H), 7.56 (dd, $J = 12.0$, 7.2 Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 14.1, 29.6, 42.0, 45.8, 47.9, 55.7, 61.4, 114.2, 115.1, 127.4, 127.9, 128.4, 129.7, 130.6, 137.9, 140.1, 163.4, 170.4, 206.7. HRMS (ESI) Calcd for $\text{C}_{23}\text{H}_{25}\text{NO}_6\text{SNa}$ ($[\text{M}+\text{Na}]^+$) 466.1300, found 466.1306.

According to general procedure: the product was obtained from flash chromatography (hexane/EtOAc = 10:1 to 6:1), 68% *ee*. HPLC analysis: Chiralpak IA-H (hexane/*i*-PrOH = 95/5, 1.0 mL/min), t_R (major) 36.7 min, t_R (minor) 49.8 min. $[\alpha]_D^{22} = -17.9^\circ$ ($c = 1.6$, CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 0.89 (t, $J = 7.2\text{ Hz}$, 3H), 1.93-2.05 (m, 1H), 2.39-2.47 (m, 1H), 2.80 (td, $J = 11.1, 3.0\text{ Hz}$, 1H), 3.31 (dd, $J = 14.0, 12.0\text{ Hz}$, 1H), 3.87-3.91 (m, 4H), 4.43 (dd, $J = 14, 3.2\text{ Hz}$, 1H), 5.45 (d, $J = 3.2\text{ Hz}$, 1H), 6.84 (d, $J = 8.4\text{ Hz}$, 2H), 6.95 (d, $J = 8.8\text{ Hz}$, 2H), 7.18 (d, $J = 8.4\text{ Hz}$, 2H), 7.25-7.28 (m, 3H), 7.61 (d, $J = 8.8, 2.0\text{ Hz}$, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 7.2, 37.1, 42.7, 49.4, 51.4, 55.8, 114.2, 122.0, 127.5, 127.9, 127.9, 128.3, 128.8, 129.1, 130.0, 131.0, 132.9, 137.9, 139.5, 140.3, 163.4, 210.5. HRMS (ESI) Calcd for $\text{C}_{27}\text{H}_{26}\text{ClNO}_4\text{SNa}$ ($[\text{M}+\text{Na}]^+$) 518.1169, found 518.1171.

According to general procedure: the product was obtained from flash chromatography (hexane/EtOAc = 10:1 to 6:1), 74% *ee*. HPLC analysis: Chiralpak IA-H (hexane/*i*-PrOH = 95/5, 1.0 mL/min), t_R (major) 30.4 min, t_R (minor) 50.9 min. $[\alpha]_D^{22} = -22.5^\circ$ ($c = 1.6$, CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ

1.94 (s, 3H), 2.84 (td, $J = 11.2, 3.2$ Hz, 1H), 3.31 (dd, $J = 14.0, 12.0$ Hz, 1H), 3.84 (dd, $J = 10.4, 3.2$ Hz, 1H), 3.91 (s, 3H), 4.45 (dd, $J = 14, 3.2$ Hz, 1H), 5.49 (d, $J = 3.2$ Hz, 1H), 6.92 (q, $J = 3.6$ Hz, 2H), 6.96 (d, $J = 8.8$ Hz, 2H), 7.07 (d, $J = 8.4$ Hz, 2H), 7.22-7.23 (m, 3H), 7.56 (d, $J = 8.4$ Hz, 2H), 7.61 (d, $J = 8.4$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 31.0, 43.4, 49.0, 52.1, 55.8, 114.3, 123.2, 127.3, 127.8, 128.8, 129.2, 130.0, 136.9, 137.6, 138.1, 141.3, 163.5, 207.9. HRMS (ESI) Calcd for $\text{C}_{26}\text{H}_{24}\text{INO}_4\text{SNa}$ ($[\text{M}+\text{Na}]^+$) 596.0369, found 596.0364.

5.5 References

1. a) D. L. Boger, A. M. Kasper, *J. Am. Chem. Soc.* **1989**, *111*, 1517; b) D. L. Boger, T. Curran, *J. Org. Chem.* **1990**, *55*, 5439.
2. R. C. Clark, S. S. Pfeiffer, D. L. Boger, *J. Am. Chem. Soc.* **2006**, *128*, 2587.
3. J. Esquivias, R. G. Arrayás, J. C. Carretero, *J. Am. Chem. Soc.* **2007**, *129*, 1480.
4. R. P. Wurz, G. C. Fu, *J. Am. Chem. Soc.* **2005**, *127*, 12235.
5. M. He, J. R. Struble, J. W. Bode, *J. Am. Chem. Soc.* **2006**, *128*, 8418.
6. Y. Fang, E. N. Jacobsen, *J. Am. Chem. Soc.* **2008**, *130*, 5660.
7. T. Yukawa, B. Seelig, Y. Xu, H. Morimoto, S. Matsunaga, A. Berkessel, M. Shibasaki, *J. Am. Chem. Soc.* **2010**, *132*, 11988.
8. H. Xiao, Z. Chai, C. Zheng, Y. Yang, W. Liu, J. Zhang, G. Zhao, *Angew. Chem. Int. Ed.* **2010**, *49*, 4467.
9. B. J. Cowen, S. J. Miller, *J. Am. Chem. Soc.* **2007**, *129*, 10988.
10. F. Zhong, Y. Wang, X. Han, K. Huang, Y. Lu, *Org. Lett.* **2011**, *13*, 1310.
11. H. Xiao, Z. Chai, C. Zheng, Y. Yang, W. Liu, J. Zhang, G. Zhao, *Angew. Chem. Int. Ed.* **2010**, *49*, 4467.
12. M. Hayashi, Y. Matsuura, Y. Nishimura, T. Yamasaki, Y. Imai, Y. Watanabe, *J. Org. Chem.* **2007**, *72*, 7798.
13. C. Jens, R. Ulrich, *Tetrahedron: Asymmetry* **1999**, *10*, 1207.
14. I. Masato, O. Akihito, K. Chiba, S. Akira, I. Takao, *Organometallics* **2009**, *28*, 390.