Organocatalytic asymmetric reactions : aminooxylation, Michael and their tandem reactions

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**ORGANOCATALYTIC ASYMMETRIC REACTIONS:
AMINOXYLATION, MICHAEL & THEIR TANDEM
REACTIONS**

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ABSTRACT

Organocatalytic Asymmetric Reactions: Aminoxylation, Michael & Their Tandem Reactions

Chua Pei Juan

A highly enantioselective L-thiaproline-catalyzed α -aminoxylation of aldehydes in the presence of water and tetrabutylammonium bromide followed by in situ reduction to afford the respective α -aminoxy alcohols in good to high yields and excellent enantioselectivities was first developed.

Next, L-prolinol-catalyzed asymmetric Michael addition of cyclohexanone to nitroolefins in the presence of benzoic acid to afford Michael adducts with high diastereoselectivities and enantioselectivities was described.

The development of an organocatalytic tandem reaction involving aminoxylation of nitrosobenzene, in situ condensation and intramolecular nitron [3+2] cycloaddition with (*E*)-ethyl-3-(2-(formylmethyl)phenyl)acrylate and phenylhydroxylamine provided a single diastereomer of indane with four stereogenic centers with moderate yield and enantioselectivity.

The last reaction described the development of an organocatalytic tandem reaction involving Michael addition of bis(phenylsulfonyl)ethylene, in situ condensation and intramolecular nitron [3+2] cycloaddition with a variety of aldehydes and hydroxylamines to afford a single diastereomer of indanes with four stereogenic centers with excellent yields and enantioselectivities.

LIST OF PUBLICATIONS

1. Chua, P. J.; Tan, B.; Yang, L.; Zeng, X.; Zhu, D.; Zhong, G. Highly stereoselective synthesis of indanes with four stereogenic centers *via* sequential Michael and [3+2] cycloaddition reaction. *Chem Commun.* **2010**, 7611.
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APPENDIX

List of Symbols and Abbreviations

δ	NMR chemical shift/ppm
J	NMR coupling constant/Hz
λ	Wavelength/nm
Ac	Acetyl
Alk	Alkyl
Ar	Aryl
Boc	<i>tert</i> -Butyloxycarbonyl
Bn	Benzyl
Bu	Butyl
c	Concentration
Cat.	Catalyst
Cbz	Benzyloxy carbonyl
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DHQ	Dihydroquinine
DHQD	Dihydroquinidine
DMF	<i>N,N</i> -Dimethylformamide
DMSO	Dimethyl sulfoxide
dr	Diastereomeric ratio
E	Electrophile
EA	Ethyl acetate
ee	Enantiomeric excess

equiv.	Equivalent
Et	Ethyl
HPLC	High Performance Liquid Chromatography
<i>m</i>	<i>meta</i>
Me	Methyl
MS	Molecular seive
MTBE	Methyl- <i>tert</i> -butyl ether
NMR	Nuclear magnetic resonance
Nu	Nucleophile
<i>o</i>	<i>ortho</i>
<i>p</i>	<i>para</i>
Pg	Protecting group
Ph	Phenyl
PHAL	Phthalazine
PMP	<i>p</i> -methoxyphenyl
ppm	Parts per million
Pr	Propyl
R	Arbitrary substituent
r.t.	Room temperature
Solv.	Solvent
SOMO	Singly occupied molecular orbital
<i>t</i>	<i>tert</i>
TBBP	3, 3', 5, 5' Tetrabromobiphenol
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBS	Tributylsilyl

TEAB	Tetraethylammonium bromide
TES	Triethylsilyl
Tf	Trifluoromethanesulfonyl
TFA	2,2,2-Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
t_R	Retention time
TSA	p-Toluenesulfonic acid

CHAPTER 1

Introduction

1.1 Overview

Organocatalytic asymmetric reactions were once considered as inefficient and limited in scope, while metal catalysts were able to provide a versatile platform for many types of reactions. As such, metal catalyzed reactions attracted much more attention than organocatalytic asymmetric reactions. Although most of the reactions in asymmetric catalysis are still dominated by main group- and transition metals, organic catalysis is emerging to be a very valuable toolkit in organic chemistry. The large number of publications and references evidenced the rise in popularity of organocatalysis since 2000 and this may indicate that organocatalysis is filling up the gap that existed between metal and enzyme catalysis.

The history of organocatalytic asymmetric reactions has a rich past dating all the way back to the early 20th century. However, small organic molecules catalyzed reactions did not attract much attention. In 2000 when List reported L-proline-catalyzed aldol reaction¹ which opened an avenue for a number of related transformations such as enantioselective intermolecular cross-aldol reactions, Mannich, Michael and Diels-Alder-type transformations as well as the application of these transformations in domino reactions.

One of the reasons for this increased attention in organocatalysis lies in the advantages of organocatalysts. These catalysts are usually robust, non-toxic,

inexpensive and readily available. Though these organic catalysts are generally non-toxic, we should also bear in mind that little is currently known about the toxicity of many organic catalysts. Due to their inertness towards moisture and oxygen, stringent reactions conditions such as inert atmosphere, low temperatures and dry solvents are not required. Organocatalysis appeared to be a very attractive method to prepare compounds, such as pharmaceutical products, that do not tolerate metal contamination. Furthermore, because of the absence of transition metals, there is no risk of metal leakage and expensive recovery process during the waste treatment is also avoided. In addition, the high efficiency and selectivities attained in many organocatalytic transformations made the use of such organic catalysts very attractive for the formation of enantiomerically pure compounds.

1.2 Historical background

The historical roots of organocatalysis go back to the use of small naturally occurring compounds to understand and mimic catalytic activity and selectivity of enzymes.² The first organocatalytic asymmetric reaction was reported by Breiding in 1912 where the use of alkaloids such as quinine **1** and quinidine **2** accelerated the addition of hydrocyanide to benzaldehyde.³ Though the resulting hydrocyanohydrins were optically active and opposite in chirality, their optical yields were less than 10% (Scheme 1.1).

Scheme 1.1. Breiding's hydrocyanation of benzaldehyde with quinine or quinidine

A reinvestigation of the Breeding's work by Pracejus in 1960 brought to the discovery of a more efficient reaction that involved the addition of methanol to phenylmethylketene, using 1 mol % of alkaloid derivative **3**, to afford products with quite remarkable enantiomeric excess (ee) of 74% (Scheme 1.2).⁴

Scheme 1.2. Pracejus's ester synthesis from phenylmethylketene

Another key event in the history of organocatalytic reaction was the discovery of Hajos–Parrish–Eder–Sauer–Wiechert reaction in the early 1970s (Scheme 1.3).^{5,6} This efficient L-proline mediated asymmetric Robinson annulation allowed the access of unsaturated Wieland–Miescher ketone which is an important intermediate in steroid synthesis.

Scheme 1.3. Hajos–Parrish–Eder–Sauer–Wiechert reaction

Surprisingly, the catalytic potential of L-proline as catalyst was left largely unexplored until List reported L-proline mediated intermolecular aldol reaction of acetone and a variety of aldehydes to afford corresponding aldol products in excellent yields and enantioselectivities in 2000.¹ For example, addition of acetone to isobutyraldehyde gave the aldol product in 97% yield with 96% ee (Scheme 1.4).

Scheme 1.4. List's L-proline mediated intermolecular aldol reaction

In the same year, MacMillan reported a newly designed imidazolidinone catalyst **5** to catalyze Diels-Alder reaction of α,β -unsaturated aldehydes, affording adducts with up to 94% ee (Scheme 1.5).⁷

Scheme 1.5. MacMillan's Diels-Alder reaction

These two remarkable achievements sparked off tremendous interest among many research groups and triggered massive research on the design and discovery of new catalysts and new catalytic transformations based on small organic molecules. Besides proline and its derivatives, other novel catalysts such as chiral urea and thiourea catalysts, chiral phase transfer catalysts and chiral phosphoric acid, have also been developed in recent years. With deeper understanding and increased insights into iminium and enamine-based organocatalysis, aldol reaction, Mannich reactions, Michael additions, cycloadditions, nucleophilic substitutions and many other transformations can now be performed with high stereoselectivity.

1.3 Mechanisms

Before the discussion of various reactions by a variety of catalysts, the general mechanisms governing these reactions must be examined first. In contrast to the massive amount of publications on the design and discovery of new catalysts and new catalytic transformations, there are only a few very distinct activation methods for aminocatalysis. This further emphasized the versatility of these activation methods and the simplicity of organocatalysis. There are basically four distinct activation methods – α -functionalization of carbonyl compounds, β -functionalization of α,β -unsaturated carbonyl compounds, γ -functionalization of α,β -unsaturated carbonyl compounds as well as radical and photoredox chemistry in organocatalysis.⁸

1.3.1 α -Functionalization of carbonyl compounds

The insertion of electrophiles on the α -position of carbonyl compounds have indeed developed much from initial reports on aldol and Mannich reactions, as seen by the wealth of publications dedicated to it. Not only can carbon atoms be added to the α -position of carbonyl compounds, atoms such as nitrogen, oxygen, sulphur, fluorine, chlorine, bromine, iodine and selenium can also be added to provide α -functionalized carbonyl compounds.

The catalytic cycle (Scheme 1.6) begins with the condensation of the chiral secondary amine catalyst and the aldehyde to form an iminium ion. The iminium ion increases the acidity of the neighbouring α -protons and causes deprotonation which leads to a reactive nucleophilic enamine intermediate. This intermediate can then attack an electrophile (**E**) to reform the iminium ion, and hydrolysis of this α -functionalized iminium ion releases the product and the secondary amine catalyst,

which re-enters the catalytic cycle. This mechanism is also known as enamine catalysis.

Scheme 1.6. Catalytic cycle of enamine activation

The trajectory of the electrophile can be determined by the nature of the catalyst and two explanations have been proposed to account for the observed stereoinduction (Scheme 1.7): (1) H-bond interactions between catalyst having a H-bond donor, such as L-proline, and approaching electrophile having an electronegative heteroatom with an electron pair can determine the observed stereoinduction in aldol, Mannich, hydroxylation and amination reactions; (2) the steric hindrance provided by the catalyst having bulky substituents in the 2-position of the pyrrolidine catalyst, such as α,α -diarylprolinols, can direct the approach of the electrophile so as to account for the stereoinduction seen in aldol, Mannich, addition to electro-deficient olefins, amination, hydroxylation, fluorination, chlorination, bromination, iodination sulfenylation and selenation of aldehydes. These two directing effects will give rise to

different enantiomers of the product even though the two types of catalysts have the same absolute stereochemistry.

Scheme 1.7. H-bond and steric shielding of enamine intermediate

Due to the diversity of reagents used in α -functionalization of carbonyl compounds, this enamine mechanism does not hold for all. There are a few exceptions such as aminoxylation,⁹ direct addition of fluorine to enamine carbon atom and resolution of the α -fluorinated intermediate for α -fluorination reaction.¹⁰

1.3.2 β -Functionalization of α,β -unsaturated carbonyl compounds

Conjugate addition of nucleophiles to α,β -unsaturated carbonyl compounds is a mechanistic counterpart of α -functionalization. Similarly, the development of the range of nucleophiles for this type of reaction has evolved to incorporate hydrogen, carbon, nitrogen, oxygen, phosphorus and sulphur atoms.¹¹

Similar to enamine catalysis, the catalytic cycle (Scheme 1.8) also begins with the condensation of the chiral secondary amine catalyst and the α,β -unsaturated

aldehyde to form an iminium ion. However, this conjugated iminium ion, instead of the enamine in the α -functionalization of carbonyl compound, is the reactive species. The addition of nucleophile to the carbon atom of the iminium ion leads to the β -functionalized enamine which tautomerises to the corresponding iminium ion and hydrolysis of this β -functionalized iminium ion releases the product and the secondary amine catalyst re-enters the catalytic cycle. As the iminium ion is the reactive species, this mechanism is also known as iminium catalysis.

Scheme 1.8. Catalytic cycle of iminium activation

In contrast to enamine catalysis, the trajectory of the nucleophile in iminium catalysis can only be determined by the steric hindrance provided by the catalyst (Scheme 1.9). Due to the stability of the *s-trans* iminium ion and the steric repulsion offered by the catalyst, the incoming nucleophile will preferentially attack from the *Re*-face.

Scheme 1.9. Intermediates where the attack of nucleophile from *Re*-face is favored.

Furthermore, the nature of the nucleophile is very important due to the reversibility of the conjugate addition. Generally, the better the leaving group ability of the nucleophile, the more favored the 1,4 conjugate addition. Direct 1,2 addition can also occur in competition with 1,4 addition, especially in the presence of a hard incoming nucleophile due to a harder electrophilic atom at the 2-position.

1.3.3 γ -Functionalization of α,β -unsaturated carbonyl compounds

Jørgensen and co-workers discovered an unexpected intermediate – dienamine – during the mechanistic investigations of intermediates in the iminium catalysis.¹² The deprotonation in the γ -position of the iminium ion leads to the formation of electron-rich dienamine that can react with electrophiles to afford γ -functionalized product. The scope of electrophiles for γ -functionalization of α,β -unsaturated carbonyl compounds, which involves only carbon and nitrogen atoms, is not as diversified as that of the α -functionalization of carbonyl compounds.

This discovery opened up a new activation protocol and allowed electrophiles to add to what was traditionally considered as electrophilic enals. Mechanistic studies revealed that concerted [4+2] cycloaddition is responsible for high stereoselection and chemoselectivity for the γ -position (Scheme 1.10). After the cycloaddition step, hydrolysis of the hemiaminal will release the γ -functionalized *cis*- α,β -unsaturated

product, which equilibrates to the more stable *trans*-product, and the catalyst re-enters the catalytic cycle.

Scheme 1.10. [4+2] addition that leads to γ -functionalized α,β -unsaturated aldehyde

1.3.4 Radical and photoredox chemistry in organocatalysis

The mechanism for this last type of functionalization differs from those three discussed previously: Instead of involving electron pairs in the catalytic cycle, single unpaired electron was generated in the chiral intermediate and used in SOMO (Singly Occupied Molecular Orbital) catalysis, which was first introduced by MacMillan.¹³

The iminium ion that was formed between the condensation of the secondary amine catalyst and the aldehyde is in equilibrium with an enamine which can become

a carbocation radical in the presence of a mild oxidant (Scheme 1.11). This carbocation radical can then react with the SOMO-phile to generate a new radical intermediate, followed by a second oxidation to return the molecule to close-shell state and finally, hydrolysis to release the catalyst for re-entry into the catalytic cycle.

Scheme 1.11. Reaction of carbocation radical with two oxidations

Besides radical enamines, photochemically generated radical reagents can also react with the classic enamine intermediates to give a radical intermediate which is oxidized to an iminium ion and the photoredox co-catalyst is then regenerated (Scheme 1.12).

Scheme 1.12. Reaction of enamine with radical reagent

1.4 Catalyst

1.4.1 Proline and its derivatives

We can now start to look at how various catalysts are applied to chemical transformations to achieve good yields and selectivities. Since List reported on the use of L-proline **4** as catalyst for aldol¹ reaction and MacMillan described the use of imidazolidinone catalyst **5** for Diels-Alder⁷ reactions, the utility of L-proline for other

related reactions was quickly expanded. In the same year, riding on the success of the aldol reaction, List reported the successful use of L-proline for direct asymmetric three-component Mannich reaction to obtain adducts in moderate yields and with high enantioselectivities (Scheme 1.13).¹⁴

Scheme 1.13. List's L-proline-catalyzed three-component Mannich reaction

Jørgensen and List independently reported the use of L-proline **4** to catalyze α -amination reaction of aldehydes with azodicarboxylates followed by in situ reduction to afford alcohols with excellent yields and enantioselectivities (Scheme 1.14).^{15,16} List and co-workers also observed that the disappearance of the yellow colour of azodicarboxylate marked the endpoint of the reaction and the longer reaction time caused partial racemisation of the products. Blackmond suggested that autoinductive behaviour, where the reaction rate increases rather than decreases as substrate are being consumed, may be responsible for the relatively short reaction time of 3 hours.¹⁷

Jørgensen:

List:

Scheme 1.14. Jørgensen's and List's L-proline-catalyzed α -amination reaction

There is another instance where the endpoint of the reaction is marked by a disappearance of colour. In 2003, Zhong¹⁸, MacMillan¹⁹ and Hayashi²⁰ and co-workers independently reported a L-proline-catalyzed aminoxylation reaction involving aldehydes and nitrosobenzene followed by in situ reduction to obtain 1,2-diols precursors, where the secondary alcohol was protected by an O-amino group, in good yields with excellent enantioselectivities (Scheme 1.15). Instead of the disappearance of yellow color as observed in amination reaction, the consumption of nitrosobenzene is noted by the disappearance of green colour in the DMSO solvent. Another interesting aspect of this reaction lies in the very short reaction time of 10–20 minutes. Studies by Blackmond revealed that the unusual short reaction time is due to product-accelerated process.¹⁷ As the reaction proceeds, the higher reactivity of the product-catalyst intermediate will cause a greater amount of catalyst to enter a product-assisted cycle that is in parallel to the traditional catalytic cycle and result in an increase in the reaction rate.

Scheme 1.15. Zhong's L-proline-catalyzed aminoxylation

In the same year, Barbas reported a Mannich reaction using unmodified aldehydes and preformed imines with L-proline **4** as catalyst to afford *syn*-selective Mannich product in good yields, highly diastereoselectivities and enantioselectivities (Scheme 1.16).²¹

Scheme 1.16. Barbas's *syn*-Mannich reaction

In search for an effective organocatalyzed protocol to synthesize *anti*-Mannich product, Barbas designed an amino acid **6** that possesses steric hindrance to “force” the enamine to take on the less stable configuration so as to achieve *anti*-Mannich products in good yields, excellent diastereoselectivities and enantioselectivities (Scheme 1.17).²² This illustrates that the catalyst can be tuned to suit the requirements of reactions.

Scheme 1.17. Barbas's *anti*-Mannich reaction

Having discussed the use of L-proline for catalytic aldol and Mannich reactions, we shall now take a look at the Michael reaction. Pioneering efforts by List on the use of L-proline in Michael reaction²³ in 2001 did not give satisfactory results. Though the product yields were excellent (up to 95%), poor enantioselectivity was obtained (up to 23% ee). A major setback of L-proline is its poor solubility in non-polar solvents. This raised the awareness that designing and developing of new catalysts is an important task for improving the outcome of existing reactions or discovering new reactions. Much effort has been made to achieve good results for organocatalyzed reaction.

Many modifications have been done on “privileged” chiral structures such as prolines, cinchona alkaloids and binaphthol derivatives. Due to the large amount of catalysts reported, I will only focus on a few of them and briefly discuss some of their utilities in other reactions (Scheme 1.18).

Scheme 1.18. Some catalysts for organocatalytic Michael reaction

In 2001, Barbas demonstrated that (S)-2-(morpholinomethyl)pyrrolidine **7** could catalyze the Michael reaction between acetaldehyde and nitroolefins to provide adducts in high yields, diastereoselectively and enantioselectivities (up to 78% ee).²⁴ This was also the first instance where an aldehyde was used as a nucleophile in a reaction. Barbas later expanded the use of aldehyde as a nucleophile to aldol reaction where L-proline **4** was used to catalyze the direct asymmetric self-aldolization of acetaldehydes, giving the aldol adducts with up to 90% enantioselectivities albeit low yields.²⁵

To overcome the poor solubility of L-proline in non-polar solvent, Ley designed a new catalyst **8** by replacing the acidic unit of L-proline with a tetrazole unit.

Catalyst **8** was able to catalyze the Michael reaction in 1:1 mixture of ethanol and isopropanol at room temperature to give products with diastereoselectivities of up to >19:1 and enantioselectivities of up to 70%.²⁶ On a side note, catalyst **8** was also demonstrated to be able to catalyze the Mannich reaction²⁷ in non-polar solvents without any loss of enantioselectivity when compared to the L-proline-catalyzed counterpart. Furthermore, this catalyst was also shown to successfully catalyze aminooxylation^{28,29} to furnish products with excellent enantioselectivities.

Besides tetrazole unit, the acidic unit of L-proline can also be replaced by α,α -diphenylsilyl ether group. In 2005, Jørgensen reported α,α -diphenylprolinol silyl ether **9**-catalyzed conjugate addition of aldehydes to methylvinyl ketone to afford the Michael adducts in good yields and high enantioselectivities (up to 95% ee).³⁰ Incidentally, this catalyst is also a very good catalyst for stereoselective formation of C–F, C–S, C–C, C–N and C–Br bonds. Catalyst **9** made use of its steric hindrance at the 2-position of the pyrrolidine ring to direct the incoming nucleophile to achieve the high level of stereocontrol in α -functionalization.

Ni described the use of diphenylprolinol silyl ether salt **10** as efficient, water-soluble, and recyclable organocatalyst³¹ in asymmetric Michael addition of aldehydes to nitroolefins on pure water to provide adducts in excellent yields, diastereoselectivities (up to 98:2 *syn/anti*) and enantioselectivities (up to >99% ee). Furthermore, this catalyst was shown to be recycled for more than six times without significant loss of catalytic activity and stereochemical control.

In 2006, Barbas introduced a pyrrolidine based catalyst **11** that is attached to long chains of hydrophobic groups to catalyze reactions in water. After his successful attempt at aldol reaction,³² he reported a Michael reaction in brine, without the

presence of any organic solvents, using catalyst **11** to afford products with excellent reactivity, diastereoselectivity (up to 82:2 dr), and enantioselectivity (up to 97% ee).³³

Zhong reported a new catalyst **12** for the asymmetric Michael reaction of ketones and nitroolefins.³⁴ This catalyst has a phosphine oxide moiety attached to the pyrrolidine unit to act as a chiral induction group to interact favorably with the nitroolefin while retaining the catalytic site. Excellent diastereoselectivities (up to >99:1 dr) and enantioselectivities (up to >99% ee) have been achieved for the Michael reaction.

A chiral bifunctional catalyst consisting of an acidic sulfonamide and a basic pyrrolidine group (S)-pyrrolidine trifluoromethanesulfonamide **13** was employed by Wang to demonstrate its ability to catalyze Michael reactions of aldehydes and ketones with nitroolefins effectively to afford adducts with high levels of enantioselectivities (up to 99% ee) and diastereoselectivities (up to 50:1 d.r.).³⁵ Catalyst **13** was also shown to catalyze many reactions such as Mannich,³⁶ α -aminooxylation,³⁷ aldol,³⁸ α -selenenylation³⁹ and α -sulfenylation.⁴⁰

Tang also designed another bifunctional catalyst but this time, a thiourea group was added to the pyrrolidine group. Pyrrolidine-thiourea catalyst **14** was able to catalyze the Michael reaction of hexanone to nitroolefins in the presence of *n*-butyric acid to furnish adducts with high diastereoselectivities (up to 99:1 dr) and enantioselectivities (up to 98% ee).⁴¹

1.4.2 Other basic catalysts

All of the catalysts that we have seen so far revolve around secondary amines. Other than secondary amines, primary amines can also catalyze reactions. For example,

Lu demonstrated that L-threonine derived catalyst **15**-catalyzed a three component Mannich reaction involving *O*-benzyl hydroxyacetone, *p*-anisidine and aldehydes to afford *anti*-1,2-amino alcohols in good yields and enantioselectivities (up to 97% ee) (Scheme 1.19).⁴²

Scheme 1.19. Lu's Mannich reaction with L-threonine derived catalyst **15**

Lu later expanded his L-threonine derived catalyst to include a sulfonamide group forming a bifunctional catalyst **16**. Catalyst **16** could promote an asymmetric conjugate addition of α,α -disubstituted aldehydes to 1,1-bis(benzenesulfonyl)ethylene to afford adducts with quaternary stereogenic centers adjacent to an aldehyde group in high yields and with good enantioselectivities (Scheme 1.20).⁴³

Scheme 1.20. Lu's conjugate addition with L-threonine derived catalyst **16**

We shall now take a look at other classes of organocatalysts. Following pioneering works by Jacobsen,^{44a} Takemoto reported the successful use of bifunctional tertiary amine-thiourea catalyst **17** in the Michael addition of malonates to nitroolefins, achieving high yields and enantioselectivities (Scheme 1.21).^{44b} Takemoto made use of the basic site in the catalyst to form the enamine intermediate while the thiourea

moiety can form hydrogen bonds with the nitroolefin, thus bringing the reactants together in a stereoselective manner.

Scheme 1.21. Takemoto's Michael addition with amine-thiourea catalyst

Rawal also made use of alkaloids to provide the chiral environment for his new catalyst **18** which consists of an interesting core structure: the squaramides. Rawal, based on crystallographic and computational data, reasoned that the smaller distance between the two hydrogen responsible for hydrogen bonding in the squamide unit, when compared to the thiourea unit could provide a versatile core for the design of new catalysts. He reported the conjugate addition of 2,4-pentanedione to β -nitrostyrene in the presence of catalyst **17** to afford Michael product in up to 99% yield and 99% ee in 2008 (Scheme 1.22).⁴⁵

Scheme 1.22. Rawal's Michael reaction with squaramides derivatives

Guanidines have very high pK_a values as a free base and its ability to form hydrogen bonding in a specific pattern makes it an attractive organocatalyst. Tan demonstrated the use of chiral bicyclic guanidine **19** for Diels-Alder reaction between anthrones and various dienophiles to afford adducts in excellent yields, high regioselectivities and excellent enantioselectivities (up to 99% ee) (Scheme 1.23).⁴⁶ A range of substituents and substitution patterns could be tolerated by the catalyst. Furthermore, the same catalyst was also shown to catalyze Michael reaction between dithranol and various olefins effectively, furnishing adducts with high yields and enantioselectivities (up to 98% ee).⁴⁶

Scheme 1.23. Tan's bicyclic guanidine-catalyzed Diel-Alder and Michael reaction

Terada introduced an axially chiral guanidine base catalyst **20** where the chiral binaphthyl backbone provides the chiral environment and the guanidine caters for the strong basicity of the catalyst. Catalyst **20** was able to effectively catalyze the 1,4-addition reaction of 1,3-dicarbonyl compounds with conjugated nitroalkenes to give Michael adducts with up to 98% ee (Scheme 1.24).⁴⁷ Besides 1,3-dicarbonyl compounds, Terada has also used similar catalysts in many reactions such as the

addition of diphenyl phosphate to nitroalkenes,⁴⁸ amination of unsymmetrically substituted 1,3-dicarbonyl compounds⁴⁹ and vinylogous aldol reaction of furanone derivatives.⁵⁰

Scheme 1.24. Terada's Michael reaction with axially chiral guanidine base catalyst

Another type of interesting catalyst is the bispidine derivatives. After Feng successfully employed bispidine derivatives for aldol reaction⁵¹ of functionalized ketone, he extended the use of bispidine-based catalyst to Michael reaction.⁵² Cyclohexanone, acetone and other ketones were added to nitroolefins in the presence of catalyst **21** and 3,3',5,5'-tetrabromobiphenol (TBBP) as additive to afford Michael adducts in good yields, diastereoselectivities and excellent enantioselectivities (up to 99% ee) (Scheme 1.25).⁵²

Scheme 1.25. Feng's Michael reaction with bispidine-based catalyst

Brønsted acid catalysis is another interesting branch of organocatalysis that complements and enhances aminocatalysis. However, the detailed discussions of this

chiral acid catalysis as well as those on carbenes are beyond the scope of the introduction of this thesis and thus would not be examined further.

1.5 Organocatalytic domino reactions

Organocatalytic reactions also provide a flexible platform for multicomponents, tandem or domino-type multi-step reactions to construct structurally complex molecules from simple starting materials and with minimized production of wastes in a highly stereocontrolled manner.⁵³ Organocatalytic enantioselective domino processes, first reported by Barbas,⁵⁴ are particularly appealing not only because of their operational simplicity and environmental friendliness but also their ability to form multiple stereogenic centers and heavily functionalized products in a cascade manner. Organocatalytic enantioselective domino processes are gaining attention and there have been increasing number of reports on such processes published in recent years.

1.5.1 Proline and its derivatives

In 2005, List employed an imidazolidinone organocatalyst **22** in a highly efficient organocatalytic tandem conjugate reduction–Michael cyclization of enal enones with Hantzsch dihydropyridine. This afforded the cyclic keto aldehydes in high yields with high diastereo- and enantioselectivities (Scheme 1.26).⁵⁵ This reaction not only exhibits chemo- and regioselectivities, it also works well with aliphatic and aromatic substrates in the synthesis of five- and six-membered carbacyclic derivatives.

Scheme 1.26. List tandem conjugate reduction–Michael cyclization

One of the most commonly used catalyst for domino reactions is the α,α -diarylprolinol derivatives. For example, Jørgensen described the use of α,α -diarylprolinol silyl ether **23** to catalyzed an organocatalytic asymmetric multicomponent reaction involving a nucleophilic thiol addition to the β -carbon atom in the iminium ion intermediate, followed by an electrophilic amination of the α -carbon atom to the enamine intermediate (Scheme 1.27).⁵⁶ This reaction gave the amino-thiols in moderate to good yields and with high enantioselectivities.

Scheme 1.27. Jørgensen's thiol addition and amination reaction

A year later, Enders reported an asymmetric organocatalytic triple cascade reaction involving a three-component domino reaction *via* a Michael–Michael–aldol condensation sequence of linear aldehyde, nitroalkene and α,β -unsaturated aldehyde to afford polyfunctional cyclohexene derivatives with four stereogenic centres with high diastereoselectivities and excellent enantioselectivities (Scheme 1.28).⁵⁷

Scheme 1.28. Enders's three component triple cascade reaction

Wang described a highly enantioselective (*S*)-diphenylpyrrolinol triethylsilyl (TES) ether **24** promoted tandem oxa-Michael-aldol reaction of α,β -unsaturated aldehydes with salicylaldehydes to furnish synthetically and biologically useful chiral chromenes in high yields (up to 98%) with good to excellent levels of enantioselectivities (up to 99% ee) (Scheme 1.29).⁵⁸ Wang also used similar strategy to demonstrate the synthesis of chiral thiochromenes *via* an organocatalytic enantioselective tandem Michael-aldol reaction. This reaction, promoted by diarylpyrrolinol ether **23**, afforded synthetically useful chiral thiochromenes in high yields (72 to 97%) with good to high enantioselectivities (85 to 95% ee).⁵⁹ A broad range of α,β -unsaturated aldehydes and 2-mercaptobenzaldehydes can be tolerated in the process.

Scheme 1.29. Wang's Michael-aldol tandem reaction

Rueping described a diarylpyrrolinol ether **23**-catalyzed enantioselective addition-cyclization cascade of hydroxynaphthoquinone and α,β -unsaturated aldehydes to afford biologically interesting quinones.⁶⁰ This method can be applied to both aliphatic and aromatic α,β -unsaturated aldehydes to give 1,4-pyranonaphthoquinones in good yields and with excellent enantioselectivities (90-99%

ee) (Scheme 1.30). The 1,4-naphthoquinones obtained can further react to provide valuable 1,2-pyranonaphthoquinones and 1,4-naphthoquinonelactones without loss of enantiopurity.

Scheme 1.30. Rueping's enantioselective addition–cyclization cascade

Since the first reports of α -aminoxylation described in 2003 by Zhong¹⁸, MacMillan¹⁹ and Hayashi,²⁰ there have been numerous literatures on the application of this reaction either in the synthesis of biological active compounds⁶¹ or in the development of tandem reactions.⁶² For example, Ley demonstrated the use of α -aminoxylation followed by Wittig reaction in a one-pot manner to synthesize 1,2-oxazines with high enantioselectivities. Ley first started his investigation with aldehydes and nitrosobenzene as starting material and (S)-pyrrolidinyl-tetrazole **8** as

catalyst.²⁸ The reaction proceeded smoothly with a variety of aldehydes in good yields (39 to 82%) with excellent enantioselectivities (96 to 99%) (Scheme 1.31). The transformation involves an asymmetric organocatalytic α -aminoxylation with nitrosobenzene and the catalyst to afford an intermediate which undergoes conjugate addition to a vinylphosphonium salt. The resulting ylide then cyclizes to the dihydro-1,2-oxazine *via* an intramolecular Wittig process.

Scheme 1.31. Ley's α -aminoxylation–Wittig reaction with aldehydes

With the success of aldehydes, Ley extended his methodology to include ketones in the sequential one-pot synthesis of multi-substituted chiral 1,2-oxazines.⁶³ However, reaction conditions developed for aldehydes were disappointingly ineffective when applied to ketonic substrates. After some optimization, Ley and his co-workers were able to perform the domino reaction with only 5 mol % of catalyst **8** to furnish chiral 1,2-oxazines in moderate to good yields and excellent enantioselectivities (Scheme 1.32). Ley further demonstrated that the products can undergo facile N–O bond cleavage to provide *cis*-allylic alcohols, which are useful building blocks for synthetic chemistry.

Scheme 1.32. Ley's α -aminoxylation–Wittig reaction with ketones

L-proline **4** was used by Zhong in 2008 to demonstrate the first α -aminoxylation/aza Michael reaction for the synthesis of functionalized tetrahydro-1,2-oxazines from alkenals and nitrosobenzene (Scheme 1.33).⁶⁴ It was observed that conducting the reaction at -20 °C significantly suppressed the homo-dimerization of the nitrosobenzene and the reaction mixture was diluted to avoid making intractable byproducts. This reaction is well tolerated with a variety of alkenals and nitrosobenzenes. This domino reaction generates up to three stereogenic centers and forms only one out of eight possible stereoisomers. The origin of the high stereoselectivity was derived from the α -aminoxylation reaction, which is known to proceed with high enantioselectivity. This selectivity is maintained in the second step by going through a sterically favored transition state.

Scheme 1.33. Zhong's aminoxylation/aza Michael reaction

In 2010, Zhong reported a (*S*)-diphenylpyrrolinol trimethylsilyl ether **9**-catalyzed tandem Michael/nitrone formation/intramolecular [3+2] nitrone–olefin cycloaddition of rationally designed substrates with hydroxylamines to afford functionalized chiral tetrahydronaphthalene skeletons fused with an oxazolidine moiety in high diastereoselectivities and enantioselectivities (Scheme 1.34).⁶⁵ Water plays a double role in this reaction: (1) as an environmentally benign solvent and (2) increases the reactivity and selectivity of the reaction.

Scheme 1.34. Zhong's Michael/nitrone formation/[3+2] nitrone–olefin cycloaddition

1.5.2 Other basic catalysts

Besides L-proline and its derivatives, other bases can also act as catalysts for domino reactions. For example, Wang developed a highly stereoselective Michael–Michael cascade reaction that is catalyzed by a cinchona alkaloid thiourea **25** at a low catalyst loading (2 mol %) in a one-pot manner to afford enantioenriched thiochromanes with the creation of three new stereogenic centers with remarkably high efficiency (Scheme 1.35).⁶⁶ More significantly, a novel activation mode of the chiral amine–thiourea-catalyzed dynamic kinetic resolution (DKR) has been identified for this highly stereoselective cascade process.

Scheme 1.35. Wang's Michael–Michael cascade reaction

Chen reported an organocatalytic one-pot, three-component reaction of aldehydes, diethyl aminomalonate and nitroalkenes (Scheme 1.36).⁶⁷ In this case, monothiourea compound **26** was used to catalyze the [3+2] cycloaddition reaction to furnish highly functionalized pyrrolidine in good yields and enantioselectivity.

Scheme 1.36. Chen's one-pot three-component reaction

1.6 Conclusion

In conclusion, asymmetric organocatalytic reactions have emerged to be a powerful and efficient tool in organic chemistry. The search for new organocatalysts with a wide range of chemical and stereocontrol properties remains as one of the challenges in this developing field. The combination of the various modes of activations demonstrated the power of organocatalytic enantioselective domino reactions, mainly promoted by amines and Brønsted acids, in the synthesis of heterocyclic compounds. These cascade processes provided new and highly efficient approaches to complex chiral molecular architectures from simple achiral substances. The attractiveness of organocatalyzed processes is further emphasized by the very mild reaction conditions and simple operational procedures. Furthermore, the success of domino reactions in the synthesis of heterocyclic compounds affirmed that the use of cascade strategy to construct complex molecules is no longer limited to metal-catalysts or enzymes. There is huge potential for organocatalytic reactions to develop into an essential and indispensable tool in the chemist's toolkit and be applied for the efficient assembly of biologically interesting molecules, including natural products.

1.7 References

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CHAPTER 2

Highly Enantioselective L-Thiaproline-Catalyzed α -Aminoxylation of Aldehydes in the presence of Water

2.1 Abstract

Highly enantioselective L-thiaproline catalyzed α -aminoxylation of aldehydes in the presence of water and tetrabutylammonium bromide followed by in situ reduction to afford the respective α -aminoxy alcohols has been developed in good to high yields (74 to 88%) and excellent enantioselectivities (93 to >99%).

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2.2 Introduction

The presence of optically active hydroxy moieties such as 1,2-diols in many biologically active natural products motivated research into finding new routes to provide better stereocontrol for these synthetically useful synthons.¹ Asymmetric α -hydroxylation of enolates² and the Sharpless asymmetric dihydroxylation of olefins³ (Scheme 2.1) are some of the methods to synthesize these compounds.

Scheme 2.1. Sharpless asymmetric dihydroxylation of olefins

The year 2000 saw a renaissance of organocatalysis, and since then organocatalysis has emerged as an extremely useful tool for the preparation of enantiomerically pure compounds.⁴ Operational simplicity, availability and the non-toxicity of the organic catalysts compared to the corresponding transition metal species, as well as the high efficiencies and selectivities attained in many organocatalytic transformations made this methodology very attractive for the formation of enantiomerically pure compounds.

Nitrosobenzene, first prepared by Baeyer in the late 19th century,⁵ is widely recognised as a useful compound to introduce nitrogen and oxygen atoms into molecules. Due to the polarization of the nitrogen–oxygen bond, nitroso compounds are highly reactive and the formation of azodioxy dimers⁶ often causes difficulties in the development of selective reactions (Scheme 2.2).

Scheme 2.2. Equilibrium between monomer and dimers of nitroso compound

In 2003 Zhong,⁷ MacMillan⁸ and Hayashi⁹ and co-workers independently reported the direct L-proline-catalyzed α -aminoxylation of aldehydes with nitrosobenzene to afford the O-selective product (Scheme 2.3). It was suggested that the appropriate Brønsted acidity of the catalyst is important for the high enantioselectivity and the O-selectivity of the nitrosobenzene. The N-selectivity of nitrosobenzene to afford α -hydroxyamino ketones is usually accomplished by a variety of alkali metals or tin enolates.¹⁰

Scheme 2.3. L-Proline-catalyzed α -aminoxylation of aldehydes

The usefulness of this reaction was also demonstrated in the synthesis of several biologically active compounds (Scheme 2.4).¹¹

Scheme 2.4. Some biologically active compounds synthesized by α -aminoxylation

Though the scope of the above-mentioned reaction has been quickly extended to that of ketones (Scheme 2.5)¹² after the first report, there was little development in new organocatalysts¹³ or reaction protocols in the presence of water.¹⁴

Scheme 2.5. L-Proline-catalyzed α -aminoxylation of ketones

Conventional chemical synthesis usually focused on improving yield and selectivity, with little regard to a chemical's impact on the environment. Recently, increasing demand for innovative and imaginative synthetic methodologies to improve

efficiency and sustainability such as simplicity, atom economy, reduced chemical wastage and energy usage, safety, and environmental friendliness prompted much research in this area.¹⁵ To date, α -aminoxylation is usually carried out in organic solvents such as acetonitrile,^{10,16} chloroform,⁹ dichloromethane,¹⁷ dimethylformamide¹⁸ and dimethylsulfoxide.^{8,19} However, there have been no reports on α -aminoxylation in the presence of water.

Water, no doubt, is the most inexpensive and environmentally benign solvent. Since Breslow reported that the use of water instead of organic solvents could significantly increase the rate of the Diels–Alder reaction,²⁰ considerable attention has been directed towards the development of organic reactions in water. To date, all of the most useful organic reactions have at least a reaction protocol in the presence of water.²¹ Although Blackmond raised some doubts about the environmental friendliness and efficiency of water in organocatalysis,²² we cannot dismiss some of the advantages accompanying the use of water as a solvent: acceleration of reaction rates and enhancement of reaction selectivities; elimination of tedious protection–deprotection processes for certain acidic-hydrogen containing functional groups and the recycling of water-soluble catalysts after separation from water-insoluble organic products.

2.3 Results and discussion

To probe the feasibility of the α -aminoxylation of aldehydes in the presence of water using a phase-transfer catalyst, we first performed α -aminoxylation of propanal to nitrosobenzene in the presence of L-proline **4**, tetrabutylammonium bromide and water at 0 °C and then warmed to room temperature. To our disappointment, the yield obtained in this initial reaction was rather low, despite the high enantioselectivity achieved. This prompted us to screen more catalysts **8**, **30–33** (Table 2.1, entries 2–6).

Table 2.1. Catalyst Screening^a

Entry	Catalyst	Time	Yield ^b (%)	ee ^c (%)
1	4	1 h	64	96
2	30	6 h	39	43
3	8	20 min	62	96
4	31	30 min	14	23
5	32	30 min	65	82
6	33	1 h 40 min	75	93

^a Conditions: Nitrosobenzene **28a** (0.3 mmol), propanal **27a** (3 equiv.), catalyst (30 mol %), tetrabutylammonium bromide (2 equiv.) and water (0.10 mL) was added at 0 °C and then warmed to r.t. (22 °C) unless otherwise stated. ^b Isolated yields. ^c Determined by chiral phase HPLC.

Poor results obtained with catalyst **30** indicated that the piperidine ring in the catalyst is inferior to pyrrolidine ring. Catalyst **8** has been shown to be an efficient catalyst for α -aminoxylation.²³ However, like L-proline, this catalyst did not give high yield in the presence of water. Tryptophan **31** was employed by Lu to demonstrate its efficiency in catalyzing aldol reaction in water.²⁴ However, this water-compatible primary amine catalyst **31** did not work well with α -aminoxylation. Though the use of polymer supported catalyst, derived from catalyst **32**, gave good results for aldol reaction in water,^{14a} the use of catalyst **32** alone in water for α -aminoxylation did not give promising results. L-thiaproline **33** was used in aldol reaction by Barbas in 2001 but the results obtained were poor.²⁵ Surprisingly, L-thiaproline **33** is the only catalyst that gave a higher yield than **4**. Although **33** needed a longer reaction time and gave a slightly lower enantioselectivity than **4**, we believed that higher enantioselectivity could be achieved with the optimization of reaction conditions. This is the first instance where L-thiaproline **33** was used as a catalyst in α -aminoxylation. The use of **33** will potentially reduce hassle for stereoselective reactions as it is commercially available.

For optimisation of the reaction conditions, we first investigated the effects of catalyst loading on the reaction (Table 2.2, entries 1–3). Highest yield and enantioselectivity were obtained when 20 mol % of catalyst was used. Next, we excluded the addition of water from the reaction mixture. The results of the reaction did not improve under neat conditions (Table 2.2, entry 4). Screening of various organic solvents revealed that chloroform and dimethyl sulfoxide, preferred solvents for many α -aminoxylation reactions, were not the best solvents when **33** was employed as catalyst (Table 2.2, entries 5–6). Although acetonitrile gave comparable enantioselectivity, its lower yield and longer reaction time made water the preferred

Table 2.2. Optimisation of reaction condition^a

Entry	Solvent	Vol. of Solvent	Time	Yield ^b (%)	ee ^c (%)
1 ^d	H ₂ O	0.10 mL	2 h 10 min	78	93
2	H₂O	0.10 mL	2h	84	96
3 ^e	H ₂ O	0.10 mL	1 h 40 min	75	93
4	—	—	1 h 15 min	62	94
5	CHCl ₃	0.10 mL	1 h 50 min	60	92
6	DMSO	0.10 mL	2 h 15 min	68	90
7	CH ₃ CN	0.10 mL	3 h 50 min	73	97
8	H ₂ O	0.05 mL	2 h 20 min	56	93
9	H ₂ O	0.20 mL	2 h 10 min	67	96
10	H ₂ O	0.30 mL	1 h 45 min	58	93
11 ^f	H ₂ O	0.10 mL	1 h 55 min	62	94
12 ^g	H ₂ O	0.10 mL	1 h 45 min	62	95
13 ^h	H ₂ O	0.10 mL	2 h 15 min	52	90

Table 2.2. Optimisation of reaction condition^a (Continued)

Entry	Solvent	Vol. of Solvent	Time	Yield ^b (%)	ee ^c (%)
14 ⁱ	H ₂ O	0.10 mL	2 h 25 min	54	92
15 ^j	H ₂ O	0.10 mL	1 h 5 min	61	92
16 ^k	H ₂ O	0.10 mL	50 min	70	95

^a Conditions: Nitrosobenzene **28a** (0.3 mmol), propanal **27a** (3 equiv.), catalyst **33** (20 mol %), tetrabutylammonium bromide (2 equiv.) and water (0.10 mL) was added at 0 °C and stirred at r.t. (22 °C) unless otherwise stated. ^b Isolated yields. ^c Determined by chiral phase HPLC. ^d 10 mol % of **33**. ^e 30 mol % of **33**. ^f No Bu₄NBr added. ^g 1 equiv. Bu₄NBr added. ^h 1 equiv. propanal **27a** added. ⁱ 2 equiv. propanal **27a** added. ^j 0.2 equiv. PhCOOH added. ^k 0.2 equiv. *p*-NO₂-C₆H₄-COOH.

choice of solvent for this reaction (Table 2.2, entry 7). We discovered that 0.10 mL of water is the optimum amount of water added to the system to attain the highest yield and enantioselectivity (Table 2.2, entries 8–10). Both the yield and enantioselectivity dropped when the amount of phase transfer catalyst was reduced (Table 2.2, entries 11–12). A similar trend was also observed with decreasing amounts of propanal (Table

2.2, entries 13–14). The addition of benzoic acid and *p*-nitrobenzoic acid did not result in better yields or enantioselectivities (Table 2.2, entries 15–16).

With the optimal reaction conditions established, we probed the scope of the reaction for a variety of aldehydes. The results were summarized in Table 2.3. In the cases investigated, the α -aminoxy alcohols were obtained in good to high yields (74 to 88%) and excellent enantioselectivities (93 to >99%). The L-thiaproline-catalyzed α -aminooxylation reaction between nitrosobenzene and propanal was completed in 2 h with good yield (84%) and excellent enantioselectivity (96%) (Table 2.3, entry 1). Not only propanal, but linear chain aldehydes such as *n*-butanal, *n*-pentanal and *n*-hexanal react with nitrosobenzene, affording α -aminoxy alcohols in good yield with excellent enantioselectivities (Table 2.3, entries 2–4). Branched aldehydes such as 3-methylbutanal are also suitable substrates as it was successfully converted to the α -aminoxy alcohols in good yield with excellent enantioselectivity (Table 2.3, entry 5). Aldehydes containing an aromatic moiety such as phenylacetaldehyde and 3-phenylpropanal were successfully employed in this reaction (Table 2.3, entries 6 and 7). It is interesting to note that the reaction time for phenylacetylaldehyde was significantly reduced. This may be due to the activating effect of the benzene ring in the α -position of the phenylacetylaldehyde. The introduction of a terminal double bond on the aldehyde did not drastically affect the yield and enantioselectivity of the reaction (Table 2.3, entry 8). The reaction also proceeded smoothly with protecting groups such as benzyl ethers and *tert*-butoxycarbonyl carbamates to afford the α -aminoxy alcohols in good yield with excellent enantioselectivities (Table 2.3, entries 9–10).

Table 2.3. The generality of aldehydes for α -aminoxylation in the presence of water^a

Entry	R	Product	Time	Yield ^b (%)	ee ^c (%)
1	Me	29a	2 h	84	96
2	Et	29b	2 h 10 min	75	98
3	Pr	29c	2 h 20 min	79	97
4	Bu	29d	2 h 35 min	74	96
5	<i>i</i> -Pr	29e	2 h 10 min	76	97
6	Ph	29f	20 min	78	93
7	PhCH ₂	29g	2 h 30 min	77	> 99
8	CH ₂ =CHCH ₂	29h	1 h	88	96
9	BnOCH ₂ CH ₂	29i	2 h 20 min	86	97
10	BocNHCH ₂	29j	2 h 30 min	79	93

^a Conditions: Nitrosobenzene **28a** (0.3 mmol), respective aldehydes **27a–k** (3 equiv.), catalyst (20 mol %), tetrabutylammonium bromide (2 equiv.) and water (0.10 mL) was added at 0 °C and stirred at r.t. (22 °C) unless otherwise stated. ^b Isolated yields. ^c Determined by chiral phase HPLC.

The scope of nitroso compounds was briefly tested by replacing nitrosobenzene **28a** with nitrosotoluene **28b** (Scheme 2.6). When nitrosotoluene was treated with propanal under the optimised conditions, the corresponding α -aminoxy alcohols were obtained in 83% yield with 97% ee, which is consistent with the results of nitrosobenzene.

Scheme 2.6. The application of nitrosotoluene for α -aminoxylation

To understand the stereochemistry observed in α -aminoxylation, four types of transition states have been independently proposed (Figure 2.1): (1) carboxylic acid-activated proton transfer by Hayashi,⁹ (2) both proline amine- and carboxylic acid-activation proton transfer by Zhong,⁷ (3) enaminium-mediated ene-like zwitterions by MacMillan⁸ and (4) amine–nitroso complex by Yamamoto.^{13c}

Figure 2.1. Proposed transition states for α -aminoxylation

Computation studies by Houk revealed that (*E*)-anti proline enamine adopting the axial position of phenyl group in nitrosobenzene, which corresponds to Hayashi's proposed model, is the lowest energy transition structure.²⁶

Based on the above information, we hereby propose the following transition state to account for the stereochemistry observed for L-thiaproline catalyzed α -aminoxylation reaction between nitrosobenzene and aldehydes (Figure 2.2).

Figure 2.2. Proposed transition state for L-thiaproline catalyzed α -aminoxylation

2.4 Conclusion

In conclusion, catalyst screening and optimising reaction condition revealed that L-thiaproline can catalyze α -aminoxylation of a variety of aldehydes to nitrosobenzene in the presence of water and phase-transfer catalyst to afford the corresponding α -aminoxy alcohols in good to high yields (74 to 88%) and high enantioselectivities (83 to >99%). Besides nitrosobenzene, this reaction was also found to be compatible with nitrosotoluene. Based on previous literatures, a transition state model was also proposed. This reaction protocol may find potential use for industrial scale preparation due to its simple operation procedures, wide scope and excellent enantioselectivities.

2.5 References

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CHAPTER 3

L-Prolinol as a Highly Enantioselective Catalyst for Michael

Addition of Cyclohexanone to Nitroolefins

3.1 Abstract

The first L-prolinol catalyzed asymmetric Michael addition of cyclohexanone to nitroolefins in the presence of benzoic acid to afford Michael adducts with high diastereoselectivities (87:13 to >99:1) and enantioselectivities (82% to 96%) was described.

Chua, P. J.; Tan, B.; Zeng, X.; Zhong, G. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3915.

3.2 Introduction

Organocatalysis has emerged as an extremely useful tool for the preparation of enantiomerically pure compounds in the past few years.¹ Operational simplicity, availability and the non-toxicity of the organic catalysts compared to the corresponding transition-metal species, as well as its high efficiencies and selectivities attained in many organocatalytic transformations made this methodology very attractive for the formation of enantiomerically pure compounds. Organocatalysis has proven its worth in the synthesis of many natural products such as (+)-augustureine and (-)-brasoside (Figure 3.1).² Recently, Wang developed an efficient, organocatalytic, highly enantioselective, conjugate addition reaction which serves as the key step for a practical 3-step synthesis of chiral baclofen, a potent GABAs receptor agonist that is used for the treatment of spinal cord injury-induced spasm.³

Figure 3.1. Examples of natural products synthesized by organocatalysis

The Michael addition reaction is certainly one of the most general and versatile methods for formation of C–C bonds in organic synthesis.⁴ Among all the organocatalytic transformations reported to date, considerable attention has been directed towards the development of organocatalytic asymmetric addition of carbonyl compounds to electron deficient nitroolefins.^{5,6} This transformation has useful applications in organic synthesis due to the potential of forming up to 3 contiguous

stereocenters and the high synthetic versatility of the nitro group.⁷

Many chiral amines such as L-proline and its derivatives have proven to be versatile catalysts in many C–C and C–heteroatom bond-forming reactions *via* enamine or iminium intermediates.⁸ For example, in 2001, Barbas⁹, List¹⁰ and Enders¹¹ reported L-proline-catalyzed addition of acetone to *trans*- β -nitrostyrene (Scheme 3.1). However, these efforts did not give promising results as the enantioselectivities obtained were too poor.

Barbas:

List:

Enders:

Scheme 3.1. L-proline-catalyzed addition of acetone to *trans*- β -nitrostyrene

In the same year, Barbas also reported the use of L-proline in Michael reaction involving cyclopentanone and *trans*- β -nitrostyrene to afford the adduct with 52% ee.¹² However, when he used (*S*)-1-(2-pyrrolidinylmethyl)-pyrrolidine as a catalyst for the same reaction, the Michael adduct was obtained with a remarkable enantioselectivity of up to 78% (Scheme 3.2).^{12b}

Scheme 3.2. Michael addition of cyclopentanone to trans- β -nitrostyrene

In addition, Jørgensen¹³ and Alexakis¹⁴ described the use of chiral imidazoline, and 2,2'-bipyrrolidine derivatives respectively as catalysts for asymmetric Michael addition reaction (Scheme 3.3).

Jørgensen:

Alexakis:

Scheme 3.3. Imidazoline and 2,2'-bipyrrolidine derivatives catalyzed Michael reaction

Although these catalytic processes provide a unique methodology in asymmetric Michael addition reactions, development of effective catalysts is still very

much desired.¹⁵ Much attention has been paid to L-proline and its various derivatives but L-prolinol, first used in the Robinson annulations reaction¹⁶, was rarely reported as an effective and efficient organocatalyst for reactions mainly due to poor results, such as yield, diastereo-, and enantioselectivities (Scheme 3.4).¹⁷

Cheng:

Barbas:

Zhong:

Scheme 3.4. Poor results of L-prolinol catalyzed by Michael reaction

The activation of the donors and control of asymmetric induction most likely occur through the formation of enamine intermediates.¹⁸ Taking the proposed transition state of L-prolinol-type catalyst¹⁹ into consideration (Scheme 3.5), we envisioned that L-prolinol-catalyzed reaction of cyclohexanone to nitrostyrene will most probably proceed through similar hydrogen bonding in the transition state.

Proposed transition state:

Scheme 3.5: Wang's proposed transition state involving pyrrolidine-sulfonamide

Furthermore, the development of the simple and commercially available L-prolinol as a good organocatalyst will potentially reduce hassle for stereoselective reactions. It would be an added advantage if the reaction could be carried out under solvent-free conditions. In view of the above advantages, we would like to investigate the enantioselective organocatalytic Michael addition of cyclohexanone to nitroolefin using L-prolinol as catalyst under neat conditions, as well as the scope of the above-mentioned reaction.

3.3 Results and discussion

We first performed the Michael addition of cyclohexanone **36** to nitrostyrene **35a** in the presence of L-prolinol **38** under neat conditions at room temperature (Table 3.1, entry 1). It should be noted that due to the lack of proper equipments, all the reactions were not stirred. Despite the high diastereoselectivity (dr), low yield and enantioselectivity (ee) were obtained. This supported our initial idea and encouraged us to explore the reaction further. Thus, we tried to introduce an additive such as

Table 3.1. Optimization of reaction condition^a

Entry	36 (equiv.)	Cat. loading (mol %)	Time	Yield ^b (%)	dr ^c	ee ^d (%)
1 ^e	3	30	66 h	43	95:5	54
2	3	30	6.25 h	74	91:9	72
3 ^f	3	30	72h	43	85:15	68
4 ^g	3	30	66 h	87	92: 8	86
5	5	30	6.5 h	78	89:11	87
6	10	30	6.5 h	83	91:9	84
7	20	30	6.5 h	31	94:6	81
8 ^h	5	30	16 h	72	86:14	70
9 ⁱ	5	30	42 h	78	>99:1	86
10 ⁱ	3	20	3 days	77	96:4	92
11 ⁱ	5	20	3 days	77	>99:1	91
12ⁱ	10	20	3 days	92	98:2	95

Table 3.1. Optimization of reaction condition^a (Continued)

Entry	36 (equiv.)	Cat. loading (mol %)	Time	Yield ^b (%)	dr ^c	ee ^d (%)
13 ⁱ	5	10	<26 days	—	—	—

^a Conditions: Nitrostyrene **35a** (0.5 mmol), cyclohexanone **36**, L-prolinol **38** and benzoic acid (1 equiv. of catalyst) was added at 0–4 °C unless otherwise stated. ^b Isolated yields. ^c Determined by NMR. ^d Determined by chiral phase HPLC. ^e No benzoic acid added. ^f Trichloroacetic acid added. ^g 3-bromopropanoic acid added. ^h 60 mol % of benzoic acid. ⁱ Reaction at 0–4 °C.

benzoic acid to promote the reaction (Table 3.1, entry 2). Surprisingly, the reaction time was decreased drastically while the yield and ee increases significantly with only a slight drop in the dr. This encouraging finding prompted us to try more additives such as trichloroacetic acid and 3-bromopropanoic acid (Table 3.1, entries 3–4). Though these two additives gave better results than that of benzoic acid, they were not the additives of choice as the reaction times were much longer. Next, we investigated the effects of the amount of cyclohexanone on the yield, dr and ee of the reaction at room temperature (Table 3.1, entries 5–7). Increasing the amounts of cyclohexanone (up to 10 equivalences) is beneficial to both the dr and the ee. However, when cyclohexanone was used in large excess (20 equiv.), the yield of the product dropped

drastically (Table 3.1, entry 7). We also noticed that the yield, dr and ee decreased when the amount of benzoic acid was doubled (Table 3.1, entry 8).

We tried to improve the results further by carrying out the reaction at low temperature. There was a significant improvement in the diastereoselectivity when the reaction was carried out at 0–4 °C (Table 3.1, entry 9). Next, the catalyst loading was decreased to 20 mol % and the enantioselectivity increased without affecting the yield and dr (Table 3.1, entry 11). However, the reaction rate was significantly reduced when the catalyst loading was decreased further to 10 mol % (Table 3.1, entry 13). The impact of cyclohexanone loading on the yield, diastereo- and enantioselectivity of the reaction was also probed – this time at low temperatures (Table 3.1, entries 10–12). Highest yield and enantioselectivity was achieved when 10 equiv. of cyclohexanone was used. Although 3 equiv. of cyclohexanone gave very good dr, the ee values were lower. In view of the above findings and in consideration of the various factors, such as time, yield, dr and ee, the scope of the reaction was explored using the following reaction conditions: 10 equiv. of cyclohexanone added to 1 equiv. of nitroolefin in the presence of 20 mol % of L-prolinol and benzoic acid at 0–4 °C.

With the optimal reaction conditions established, we probed the scope of the reaction for a variety of nitroolefins and the results are summarized in Table 3.2. In the cases investigated, the Michael adducts were obtained in good to high yields (80 to 92%), with good to excellent diastereoselectivities (87:13 to 99:1) and enantioselectivities (82 to 96%). The Michael reaction between nitrostyrene and cyclohexanone was completed in 3 days and the Michael adduct was obtained in high yield (92%) with excellent diastereoselectivity (98:2) and enantioselectivity (95%) (Table 3.2, entry 1). The reaction times of *para*-substituted nitrostyrene are generally

Table 3.2. The generality of reaction of cyclohexanone and nitroolefin^a

Entry	R	37	Time (days)	Yield ^b (%)	dr ^c	ee ^d (%)
1	C ₆ H ₅	37a	3	92	98:2	95
2	4-Br-C ₆ H ₄	37b	3	87	98:2 ^d	93
3	2-Cl-C ₆ H ₄	37c	11	80	97:3 ^d	90
4	4-Cl-C ₆ H ₄	37d	4	83	93:7	92
5	2-Me-C ₆ H ₄	37e	11	82	95:5 ^d	92
6	3-Me-C ₆ H ₄	37f	17	85	94:6	89
7	4-Me-C ₆ H ₄	37g	7	83	91:9	92
8	2-OMe-C ₆ H ₄	37h	8	92	94:6	91
9	3-OMe-C ₆ H ₄	37i	8	83	> 99:1 ^d	84
10	4-OMe-C ₆ H ₄	37j	6	85	95:5	91
11	2-furanyl	37k	3	90	87:13	93
12	3-furanyl	37l	6	89	> 99:1 ^d	82
13	2-thienyl	37m	3	92	90:10	94

Table 3.2. The generality of reaction of cyclohexanone and nitroolefin^a (Continued)

Entry	R	37	Time (days)	Yield ^b (%)	dr ^c	ee ^d (%)
14	C ₆ H ₅ CH=CH	37n	12	82	97:3 ^d	96

^a Conditions: Nitrostyrene **35a-n** (0.5 mmol), cyclohexanone **36** (5 mmol), in the presence of 20 mol % of L-prolinol **38** and benzoic acid at 0–4 °C. ^b Isolated yields. ^c Determined by NMR unless otherwise stated. ^d Determined by chiral phase HPLC.

shorter than the *ortho*- or *meta*-substituted nitrostyrene, probably due to steric and electronic influences. Generally, the position and electronic properties (electron donating or electron withdrawing) of the substituents on the aromatic rings does not seem to affect the diastereo- and enantioselectivity of the addition reaction significantly (Table 3.2, entries 3–10). The *meta*-substituted compounds were observed to give a slightly lower enantioselectivity than the *ortho*- and *para*-substituents (Table 3.2, entry 6 and 9). The reaction also gave good results with heterocycles such as furanyl and thienyl compounds (Table 3.2, entries 11–13). On top of the diastereoselectivity and enantioselectivity of this reaction, product **37n** also showed that this reaction is regioselective as cyclohexanone was added selectively on the double bond closer to the nitro group (Table 3.2, entry 14).

We observed that the relative and absolute configurations of the product

generated from L-prolinol are the same as those catalyzed by pyrrolidine sulfonamide,¹⁹ thus affirming our initial hypothesis that L-prolinol-catalyzed reaction of cyclohexanone to nitrostyrene proceed through similar hydrogen bonding in the transition state. Hereby, we proposed a possible transition state for the L-prolinol-catalyzed Michael addition (Figure 3.2).

Figure 3.2. Proposed transition state

3.4 Conclusion

In conclusion, L-prolinol catalyzed asymmetric Michael additions of cyclohexanone to a variety of nitroolefins in the presence of benzoic acid to afford the respective adducts in good to high yields (82 to 92%) with high diastereoselectivities (87:13 to >99:1) and enantioselectivities (82% to 96%) was described. Besides the high diastereoselectivity and enantioselectivity, the regioselectivity of this reaction was also demonstrated by the selective addition cyclohexanone to the double bond that is closer to the nitro group. Based on previous literatures, a transition state model was proposed to account for the stereoselectivities observed in this reaction.

3.5 References

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CHAPTER 4

Stereocontrolled Synthesis of Indanes with Four Stereogenic Centers *via*

(1) Tandem Aminoxylation – [3+2] Cycloaddition Reaction

(2) Tandem Michael – [3+2] Cycloaddition Reaction

4.1 Abstract

4.1.1 Tandem aminoxylation – [3+2] cycloaddition reaction

An organocatalytic tandem reaction involving aminoxylation of nitrosobenzene, in situ condensation and intramolecular nitron [3+2] cycloaddition with (*E*)-ethyl-3-(2-(formylmethyl)phenyl)acrylate and phenylhydroxylamine affording a single diastereomer of indane with four stereogenic centers with moderate yield and enantioselectivity was discovered.

4.1.2 Tandem Michael – [3+2] cycloaddition reaction

An organocatalytic tandem reaction involving Michael addition of bis(phenylsulfonyl)ethylene, in situ condensation and intramolecular nitrone [3+2] cycloaddition with a variety of aldehydes and hydroxylamines to afford a single diastereomer of indanes with four stereogenic centers with excellent yields and enantioselectivities was developed. The advantages of this reaction protocol lie in the versatility of the multi-substituents on the indane core structure, simple operational procedures and excellent stereocontrol.

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4.2 Introduction

Indane ring structures are widely presented in a number of naturally occurring products such as Gnetuhainin E¹ and Mirabiloside C² and indane derivatives have attracted much attention due to the broad scope of their biological activities (Figure 4.1).³

Figure 4.1. Structures of Gnetuhainin E and Mirabiloside C

Although several approaches for the synthesis of this system have been explored, they usually require several steps and expensive reagents. Thus we were interested in developing a cascade reaction that allows the rapid establishment of these polycyclic indane skeletons in a single operation.

Organocatalytic tandem reactions have gained importance in recent years as they provide attractive methods to synthesize molecules with complex architecture without the need to isolate or purify intermediates. The attractiveness of tandem reactions prompted us to examine the feasibility of combining aminoxylation and [3+2] cycloaddition as well as Michael reaction and [3+2] cycloaddition for the synthesis of multi-substituted indanes.

We have come across α -aminoxylation in Chapter 2 of this thesis. Since Zhong,⁴ MacMillan⁵ and Hayashi⁶ and co-workers independently reported the direct L-proline-catalyzed α -aminoxylation of aldehydes with nitrosobenzene to afford the O-selective product, there has been a few reports on the use of aminoxylation in tandem reactions (Scheme 4.1).

Aminoxylation-allylation:

Aminoxylation/olefination:

Aminoxylation/N-O bond heterolysis:

Aminoxylation/aza-Michael:

Scheme 4.1. Tandem reactions involving aminoxylation

The first tandem reaction was disclosed by Zhong in 2004, involving α -aminoxylation and allylation reaction.⁷ Zhong also described a sequential asymmetric α -aminoxylation/Wadsworth–Emmons–Horner olefination reaction to obtain O-amino-substituted allylic alcohols.⁸ A year later, Barbas reported a tandem α -aminoxylation/N–O bond heterolysis reaction where excess nitrosobenzene reduced the aminoxylated product to its alcohol.⁹ In 2008, Zhong presented yet another tandem reaction that included α -aminoxylation/aza-Michael reaction in the synthesis of tetrahydro-1,2-oxazines.¹⁰

Another reaction that is of great interest is the Michael reaction. Direct Michael addition of carbonyl donors *via* enamine activation features an appealing route to obtain versatile functionalized adducts in an atom-economical manner. Much investigation has been done on nitroalkenes as Michael acceptors but the use of vinyl sulfones in Michael reactions was left largely unexplored until Alexakis reported the first organocatalyzed asymmetric Michael addition of aldehydes to vinyl sulfones in 2005 (Scheme 4.2).¹¹

Scheme 4.2. First organocatalyzed asymmetric addition of aldehydes to vinyl sulfones

Since then, there have been some reports on the use of vinyl sulfones as Michael acceptors for reactions with various aldehydes,¹² ketones¹³ and nitroalkanes (Scheme 4.3).¹⁴ However, to the best of our knowledge, there has been no reports on the application of vinyl sulfones in tandem reactions.

Aldehydes:

Ketones:

Nitroalkanes:

Scheme 4.3. Lu's reaction of aldehydes, ketones and nitroalkanes with vinyl sulfone

Besides Michael reaction, intramolecular nitron/alkene cycloadditions is also another useful methodology that have attracted much attention in the synthesis of interesting frameworks found in numerous biologically active compounds.¹⁵ Such reactions often provide products with high levels of regio- and stereocontrol. Our group has recently demonstrated the combination of these two useful reactions to furnish optically pure bicyclic isoxazolidines¹⁶ and tetrahydronaphthalenes (Scheme 4.4).¹⁷

Scheme 4.4. Synthesis of isioxazolidines and tetrahydronaphthalenes

With the success of L-thiaproline catalyzed aminooxylation of aldehydes in the presence of water, we reckon that we could combine α -aminooxylation with [3+2] cycloaddition in a one-pot fashion to synthesize indanes. Herein, we present a stereocontrolled synthesis of indanes with four stereogenic centers *via* a tandem reaction involving aminooxylation of nitrosobenzene and aldehyde, in situ condensation and intramolecular nitron [3+2] cycloaddition (Scheme 4.5).

Scheme 4.5. Proposed aminooxylation – [3+2] cycloaddition reaction

We also reasoned that if we change the Michael acceptor to vinyl sulfones, we can provide different yet optically pure dipolarophiles to direct the stereochemistry of the cycloaddition products so as to obtain indane skeleton with very high level of stereocontrol. We will also present a highly stereocontrolled synthesis of indanes with four stereogenic centers *via* a tandem reaction involving Michael addition of bis(phenylsulfonyl)ethylene, in situ condensation and intramolecular nitron [3+2] cycloaddition (Scheme 4.6). This reaction protocol may be useful in the synthesis of biologically interesting compounds due to the versatility of the multi-substituents on the tricyclic heterocycles, simple operating procedures and excellent stereocontrol.

Scheme 4.6. Proposed Michael – [3+2] cycloaddition reaction

4.3 Results and discussion

To access the viability of the tandem reactions, we first synthesized our rationally designed substrate **43a** through a series of simple transformations (Scheme 4.7). 2-bromoaldehyde was first protected with 2-methoxyvinyl group, followed by formylation of the halide group, Wittig reaction with the aldehyde group and finally deprotection of the 2-methoxyvinyl group to yield substrate **43a** in good yields.

Scheme 4.7. Synthesis of aldehyde 43a

4.3.1 Tandem α -aminoxylation – [3+2] cycloaddition reaction

To probe the feasibility of the tandem α -aminoxylation – [3+2] cycloaddition of aldehydes in the presence of water using a phase-transfer catalyst, we first performed α -aminoxylation of aldehyde 43a to nitrosobenzene 28 in the presence of L-proline 4, tetrabutylammonium bromide and water at 0 °C and then warmed to room temperature (22° C) until reaction changes from green to yellow. Upon the completion of reaction, hydroxylamine 44a (3 equiv.) was then added to the reaction mixture and stirred at room temperature for 3 h. However, this initial experiment gave disappointing results with only moderate yield and enantioselectivity (Table 4.1, entry 1). Next, we tried L-thiaproline 33 which is the catalyst used for the successful α -aminoxylation of aldehydes in the presence of water and tetrabutylammonium bromide as reported in Chapter 2. As expected, L-thiaproline 33 gave better yield (68%) and enantioselectivity (76%) than L-proline 4 (Table 4.1, entry 2). Catalyst 8 is also another potential catalyst that has demonstrated good selectivity in many aminoxy-

Table 4.1. Optimization of reaction conditions for tandem α -aminoxylation – [3+2] cycloaddition reaction with **43a**^a

Entry	Catalyst	Time (min)	Solvent	Yield ^b (%)	ee ^c (%)
1	4	70	H_2O	43	45
2	33	45	H_2O	68	76
3	8	15	H_2O	64	30
4	33	120	CH_3CN	71	55
5	33	120	CHCl_3	83	55
6	33	40	Brine	42	68
7 ^d	33	45	H_2O	52	69
8 ^e	33	45	H_2O	50	48
9 ^f	33	45	H_2O	61	69

Table 4.1. Optimization of reaction conditions for tandem α -aminoxylation – [3+2] cycloaddition reaction with **43a**^a (Continued)

Entry	Catalyst	Time (min)	Solvent	Yield ^b (%)	ee ^c (%)
10 ^g	33	45	H ₂ O	33	33

^a Conditions: Aldehyde **43a** (3 equiv.) was added to catalyst (20 mol %), nitrosobenzene **28** (0.1 mmol), tetrabutylammonium bromide (2 equiv.) and solvent (0.1 mL) at 0 °C for 10 min then r.t. (22 °C) until reaction completed. Upon completion of reaction, hydroxylamine **44a** (3 equiv.) was then added to the reaction mixture and stirred at r.t. for 3 h, unless otherwise stated. ^b Isolated yields. ^c Determined by chiral phase HPLC. ^d 2 equiv of **43a** and **44a** used. ^e 1.5 equiv of **43a** and **44a** used. ^f 0.2 mL of H₂O added. ^g 2nd step conducted at 40 °C.

lation reactions but its application in this tandem reaction gave poor results albeit short reaction time (Table 4.1, entry 3). A brief solvent screen with acetonitrile, chloroform and brine in the presence of catalyst **33** did not give any promising results (Table 4.1,

entries 4–6). Hence, we tried to vary the amounts of aldehyde **43a** as well as **44a** since the amounts of hydroxylamine **44a** is in the same equivalents as that of **43a**. We observed that both the yield and enantioselectivity decreases with decreasing equivalence of both **43a** and **44a** (Table 4.1, entries 7–8). Increasing the amount of water led to a decrease in both yield and enantioselectivity (Table 4.1, entry 9). Increasing the reaction temperature of the second step after the completion of the first step appeared to have detrimental effect on the results (Table 4.1, entry 10).

As we could not obtain excellent yields and enantioselectivities after all these optimizations, we decided not to investigate this reaction further and moved on to explore other reactions.

4.3.2 Tandem Michael – [3+2] cycloaddition reaction

Inspired by Alexakis's report on the first organocatalyzed asymmetric Michael addition of aldehydes to vinyl sulfones,¹¹ we decided to use vinyl sulfone instead of nitrosobenzene. Hence we proceeded to explore the feasibility of tandem reaction involving Michael addition of bis(phenylsulfonyl)ethylene. We started our investigation by conducting the Michael reaction with aldehyde **43a**, 1,1-bis(phenylsulfonyl)ethylene **46** and catalyst **4** in dichloromethane at –20 °C. Upon completion of reaction, hydroxylamine **44a** was then added to the reaction mixture and stirred at 22 °C for 3 h. To our delight, the desired product **47a** was isolated as a single diastereomer in 75% yield and 60% enantiomeric excess (ee) (Table 4.2, entry 1). Next, a brief catalyst screen with catalysts **33**, **9** and **48** were next carried out (Table 4.2, entries 2–4). Though catalyst **33**¹⁸ gave slightly higher ee, its yield was significantly lower than that of catalyst **9**. Thus, catalyst **9** was chosen for further optimization of the reaction conditions. Out of curiosity, we explored the effects of

Table 4.2. Optimization of reaction conditions^a

Entry	Solvent	Catalyst	Yield ^b (%)	ee ^c (%)
1	CH ₂ Cl ₂	4	75	60
2	CH ₂ Cl ₂	33	76	98
3	CH ₂ Cl ₂	9	92	94
4	CH ₂ Cl ₂	48	59	39
5 ^d	CH ₂ Cl ₂	9	96	95
6	CHCl ₃	9	81	76
7	THF	9	65	81
8	EA	9	65	85
9 ^e	Toluene	9	89	97
10 ^{e, f}	Toluene	9	98	98

Table 4.2. Optimization of reaction conditions^a (Continued)

Entry	Solvent	Catalyst	Yield ^b (%)	ee ^c (%)
11 ^{e, g}	Toluene	9	91	95
12 ^{e, f, h}	Toluene	9	82	76

^a Conditions: Aldehyde **43a** (1.5 equiv.) was added to catalyst (10 mol %), 1,1-bis(phenylsulfonyl)ethylene **46** (0.05 mmol) and solvent (0.1 mL) at -20 °C and upon completion of reaction, hydroxylamine **44a** (1.5 equiv.) was then added to the reaction mixture and stirred at 22 °C for 3 h, unless otherwise stated. ^b Isolated yields. ^c Determined by chiral phase HPLC. ^d 3 equiv of **43a** and **44a** used. ^e 0.3 mL of toluene. ^f 5 mol % catalyst loading. ^g 2 mol% catalyst loading. ^h Reaction conducted at 4 °C for the first step.

increasing the equivalents of aldehyde **43a** to 3 equivalents (Table 4.2, entry 5). As expected, there were slight improvements in both the yield and enantioselectivity but it seemed unjustifiable to use large excess of substrate for such minor improvements. A

brief solvent screening revealed that toluene was the best solvent as it gave the highest yield and enantioselectivity (Table 4.2, entries 6–9). Next, we investigated the effects of catalyst loading (Table 4.2, entries 10–11). Decreasing the catalyst loading to 5 mol % of catalyst **9** appeared to be the most suitable as further decrease of the catalyst loading led to a loss of enantioselectivity. We also looked into the influence of temperature on the reaction (Table 4.2, entry 12). Lower yield and enantioselectivity were observed for the reaction that was conducted at 4 °C for the first step. In view of the above optimizations, the most suitable reaction conditions for the tandem reaction was determined to be aldehyde **43a** (1.5 equiv.), catalyst **9** (5 mol %), 1,1-bis(phenylsulfonyl)ethylene **46** (0.05 mmol) and toluene (0.3 ml) at –20 °C, followed by addition of hydroxylamine **44a** (1.5 equiv.) at 22 °C for 3 hours upon completion of the first step.

With the optimized reaction conditions in hand, we explored the generality of the tandem Michael – [3+2] cycloaddition reaction. For all the substrates investigated, we only observed a single diastereomer for the tandem reactions and the products were obtained in excellent yields and ee with a variety of aldehydes **43a–d** and hydroxylamines **44a–g** (Table 4.3). First of all, we investigated the effects of using different hydroxylamines (Table 4.3, entries 1–10). Although the position and electronic properties of the substituents on the aromatic rings of hydroxylamines do not significantly affect the yield and enantioselectivity of the tandem reaction (Table 4.3, entries 2–9), we noticed that *ortho*- and *meta*-substituted phenylhydroxylamines required harsher reaction conditions for the cycloaddition reaction (Table 4.3, entries 4 and 8 vs entries 3 and 7), probably due to steric factors. Furthermore, *para*-chlorophenylhydroxylamine required a slightly longer time at room temperature for the reaction to complete (Table 4.3, entries 5–6). This may be due to the electron

Table 4.3. Generality of the tandem Michael – [3+2] cycloaddition reaction^a

Entry	R ¹	R ²	R ³	Pdt	Yield ^b (%)	ee ^c (%)
1	H	CO ₂ Et	Ph	47a	98	98
2	H	CO ₂ Et	4-BrC ₆ H ₄	47b	92	96
3	H	CO ₂ Et	3-ClC ₆ H ₄	47c	35	98
4 ^d	H	CO ₂ Et	3-ClC ₆ H ₄	47c	97	98
5	H	CO ₂ Et	4-ClC ₆ H ₄	47d	81	98
6 ^e	H	CO ₂ Et	4-ClC ₆ H ₄	47d	92	98
7	H	CO ₂ Et	2-CH ₃ C ₆ H ₄	47e	63	95
8 ^d	H	CO ₂ Et	2-CH ₃ C ₆ H ₄	47e	97	95
9	H	CO ₂ Et	4-CH ₃ C ₆ H ₄	47f	96	98
10	H	CO ₂ Et	CH ₂ Ph	47g	91	98

Table 4.3. Generality of the Michael – [3+2] cycloaddition reaction^a (Continued)

Entry	R ¹	R ²	R ³	Pdt	Yield ^b (%)	ee ^c (%)
11	H	CO ₂ Me	Ph	47h	90	98
12 ^{e, f}	3-OMe	CO ₂ Et	Ph	47i	98	92
13	3,4-OCH ₂ O	CO ₂ Et	Ph	47j	97	99

^a Conditions: Corresponding aldehyde **43a-d** (1.5 equiv.) was added to catalyst **9** (10 mol %), 1,1-bis(phenylsulfonyl)ethylene **46** (0.1 mmol) and toluene (0.6 mL) at -20 °C and upon completion of reaction, respective hydroxylamines **44a-g** (1.5 equiv.) was then added to the reaction mixture and stirred at 22 °C for 3 h, unless otherwise stated.

^b Isolated yields. ^c Determined by chiral phase HPLC. ^d Reaction conducted at 50 °C for the second step. ^e Reaction was conducted for 4 h for the second step. ^f Reaction was conducted for 48 h for the first step.

withdrawing nature of chlorine that interferes with the nitronium formation. Not only aryl hydroxylamines **44a-f** were able to give good results for the reaction, alkyl hydroxylamine **44g** was also able to afford comparable results (Table 4.3, entry 10).

The yields and enantioselectivities were not significantly affected by changing the ester group (Table 4.4, entry 11) or the substituents of aldehyde **43** (Table 4.3, entries 12–13).

With the success of employing the above reaction protocol for *ortho*-substituted phenylacetaldehydes, we decided to give linear aldehydes a try. The reaction proceeded smoothly in the presence of (*E*)-methyl-7-oxohept-2-enoate **43e** to afford the bicyclic compound **49** in 94% yield and 94% ee (Scheme 4.8). This demonstrated that the reaction protocol is not only restricted to *ortho*-substituted phenylacetaldehyde and is applicable to linear aldehydes of suitable chain length.

Scheme 4.8. Synthesis of bicyclic compound **49**

To determine the absolute configuration of the products, hydroxylamine **44d** was subjected to the tandem reaction involving **43a** and **46**. Based on X-ray structural analysis, the stereochemistry of product **47d** was assigned and this was in accordance with our prediction (Figure 4.2).

Figure 4.2. X-ray crystallographic determination of indane **47d**

To determine whether the enantioselectivity of this tandem reaction is dependent on the initial Michael reaction, we isolated the Michael product **50** with 97% ee (Scheme 4.9). This demonstrated that this stereocenter controls the formation of the other stereogenic centers.

Scheme 4.9. Isolated Michael product **50**.

In addition, we subjected indane **47a** to the cleavage of the N–O bond to afford α -hydroxy- γ -amino acid derivative **51** in almost quantitative yield and with insignificant loss of enantioselectivity (Scheme 4.10).

Scheme 4.10. Synthesis of α -hydroxy- γ -amino acid derivative **51**

Furthermore, we also treated indane **47j** with magnesium for desulfonation. To our surprise, in addition to successful desulfonylation, the cleavage of the N–O bond afforded α -hydroxy- γ -lactam derivative **52** in moderate yield with 94% ee (Scheme 4.11). A brief mechanistic proposal for the formation of α -hydroxy- γ -lactam derivative **52** is shown in Scheme 4.12. Both derivatives **51** and **52** may have potential applications in synthetic organic chemistry and the pharmaceutical industry.

Scheme 4.11. Synthesis of α -hydroxy- γ -lactam **52**

Scheme 4.12. Mechanistic proposal for the formation of **52**

Based on the well-established mechanism of the Michael reaction, we hereby propose the catalytic cycle and the reaction pathway for the tandem reaction (Scheme 4.13). Condensation between the aldehyde and catalyst gave the iminium ion which tautomerizes to its enamine form. Michael addition of 1,1-bis(phenylsulfonyl)ethylene to the enamine, followed by hydrolysis to remove the catalyst, nitron formation or in situ condensation and finally [3+2] cycloaddition afforded the final product in a hassle-free one-pot reaction.

4.4 Conclusion

In conclusion, we have developed an organocatalytic tandem reaction involving Michael addition of bis(phenylsulfonyl)ethylene, in situ condensation and intramolecular nitron [3+2] cycloaddition with a variety of aldehydes and hydroxylamines to afford a single diastereomer of indanes with four stereogenic centers with excellent yields (90 to 98%) and enantioselectivities (92 to 99% ee). Beside

Scheme 4.13. Proposed catalytic cycle and reaction pathway of the tandem reaction

the *ortho*-substituted phenylacetaldehydes, linear aldehyde (*E*)-methyl-7-oxohept-2-enoate was also able to afford the bicyclic compound in 94% yield and 94% ee. The structure of the product was determined by X-ray crystallography. We also demonstrated that stereocenter formed from the Michael addition controls the formation of the other stereogenic centers. Furthermore, cleavage of the N–O bond

afforded α -hydroxy- γ -amino acid derivative in almost quantitative yield and with insignificant loss of enantioselectivity. Desulfonylation as well as cleavage of the N–O bond with magnesium gave α -hydroxy- γ -lactam derivative in moderate yield with high enantioselectivity. We also proposed the catalytic cycle and reaction pathway of the tandem reaction. The advantages of this reaction protocol lie in the versatility of the multi-substituents on the indane core structure, simple operating procedures and excellent stereocontrol.

4.5 References

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CHAPTER 5

Supporting Information

5.1 General Information

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 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 were reported as δ in units of parts per million (ppm) downfield from SiMe_4 (δ 0.0) and relative to the signal of SiMe_4 (δ 0.0, 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 was indicated by nH. Coupling constants were reported as a J value in Hz. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were 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 77.23, triplet).

Enantioselectivities were determined by High Performance Liquid Chromatography (HPLC) analysis, employing a Daicel Chirapak AD-H (0.46cm x 25 cm), Chirapak AS-H (0.46cm x 25 cm), Chiralcel OD-H (0.46cm x 25 cm) or OJ-H (0.46cm x 25 cm) column.

Optical rotations were measured in CHCl_3 on a *Schmidt + Haensdch* polarimeter (Polartronic MH8) with a 1 cm cell (*c* given in g/100 mL). Absolute configuration of the products was determined by comparison with compounds previously published.

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

The enantiomers used to determine the ee values were synthesized with DL-proline as catalyst, unless otherwise stated.

All other reagents were available from commercial sources and used without further purification.

5.2 Highly Enantioselective L-Thiaproline Catalyzed α -Aminooxylation of Aldehydes in the presence of Water

5.2.1 Synthesis of starting materials

Aldehydes **27i** and **27j** were prepared according to literature procedures.^{1,2}

5.2.2 General experimental procedures for the α -aminooxylation of aldehydes to nitrosobenzene in the presence of water

Water (0.10 mL) and tetrabutylammonium bromide (193.4 mg, 0.6 mmol) was added to a 5 mL drum vial containing nitrosobenzene **28a** (32.1 mg, 0.3 mmol), corresponding aldehydes **27a–j** (0.9 mmol) and a magnetic stirring bar. After stirring for 5 min at 0 °C, L-thiaproline (8 mg, 0.06 mmol) was then added. The reaction was first stirred at this temperature for about 10 min and then at room temperature until the green solution turned yellow which indicated complete consumption of the nitrosobenzene. As the α -aminoxy aldehyde product is rather labile, isolation and characterization was performed after conversion to the corresponding α -aminoxy alcohol by treatment of the reaction mixture with NaBH₄. The excess NaBH₄ was quenched by the addition of water and then extracted with CH₂Cl₂ (3 x 30 ml). The combined organic extracts were dried with Na₂SO₄ and concentrated *in vacuo*. The crude oil was purified by flash column chromatography (Hexane/EA = 9/1~7/3) yielding pure α -aminoxy alcohols **29a–j**.

Relative and absolute configurations of the products were compared with the known ¹H NMR, chiral HPLC analysis, and optical rotation values. Most of the compounds in Table 2.3 are known in the literature.

5.2.3 Experimental data of compounds 29a–j and 34

(*R*)-2-(*N*-phenylaminoxy)propan-1-ol (29a)³

α -aminoxy alcohol **29a** was prepared according to the general procedure from propanal (0.07 mL, 0.9 mmol) to provide the title compound as a pale yellow liquid (42.3 mg, 84% yield) after flash column chromatography on silica gel (hexane/ EA = 9/1~7/3).

¹H NMR (400 MHz, CDCl₃): δ 7.29–7.25 (2H, m), 7.04–6.96 (3H, m), 4.16–4.08 (1H, m), 3.80–3.70 (2H, m), 2.56 (1H, brs), 1.25 (3H, d, J = 6.4 Hz).

¹³C NMR (100 MHz, CDCl₃): 148.7, 129.2, 122.6, 114.9, 80.2, 66.7, 15.6.

HPLC: Chiralpak AD–H (hexane/*i*-PrOH, 90/10, flow rate 1 mL/min, λ = 230 nm),

t_R (minor) = 10.6 min, t_R (major) = 12.1 min; 96% ee.

$[\alpha]_D^{25} = +2.9$ (c = 1.0, CHCl₃).

(*R*)-2-(*N*-phenylaminoxy)butan-1-ol (29b)³

α -aminoxy alcohol **29b** was prepared according to the general procedure from butanal (0.08 mL, 0.9 mmol) to provide the title compound as a pale yellow liquid (40.9 mg, 75% yield) after flash column chromatography on silica gel (hexane/EA = 9/1~7/3).

^1H NMR (400 MHz, CDCl_3): δ 7.29–7.25 (2H, m), 7.07–6.96 (2H, m), 3.91–3.74 (3H, m), 2.67 (1H, brs), 1.78–1.53 (2H, m), 1.01 (3H, t, $J = 7.5$ Hz).

^{13}C NMR (100 MHz, CDCl_3): 148.6, 129.2, 122.6, 115.0, 85.5, 65.1, 23.1, 10.3.

HPLC: Chiralpak AD–H (hexane/*i*-PrOH, 90/10, flow rate 1 mL/min, $\lambda = 230$ nm), t_R (minor) = 10.2 min, t_R (major) = 11.6 min; 98% ee.

$[\alpha]_D^{23} = +36.0$ ($c = 1.0$, CHCl_3).

(*R*)-2-(*N*-phenylaminoxy)pentan-1-ol (29c**)**³

α -aminoxy alcohol **29c** was prepared according to the general procedure from pentanal (0.10 mL, 0.9 mmol) to provide the title compound as a pale yellow liquid (46.0 mg, 79% yield) after flash column chromatography on silica gel (hexane/EA = 9/1~7/3).

^1H NMR (400 MHz, CDCl_3): δ 7.28–7.15 (3H, m), 6.98–6.94 (2H, m), 3.94–3.91 (1H, m), 3.85–3.82 (1H, m), 3.75–3.71 (1H, m), 2.93 (1H, brs), 1.67–1.61 (1H, m), 1.54–1.33 (3H, m), 0.97–0.89 (3H, m).

^{13}C NMR (100 MHz, CDCl_3): 148.6, 129.2, 122.5, 114.9, 83.9, 65.3, 32.2, 19.2, 14.4.

HPLC: Chiralpak AD–H (hexane/*i*-PrOH, 90/10, flow rate 1 mL/min, λ = 230 nm),

t_R (minor) = 10.0 min, t_R (major) = 11.4 min; 97% ee.

$[\alpha]_D^{23} = +28.6$ ($c = 1.0$, CHCl_3).

(*R*)-2-(*N*-phenylaminoxy)hexan-1-ol (29d**)⁴**

α -aminoxy alcohol **29d** was prepared according to the general procedure from hexanal (0.11 mL, 0.9 mmol) to provide the title compound as a pale yellow liquid (46.4 mg, 74% yield) after flash column chromatography on silica gel (hexane/EA = 9/1~7/3).

^1H NMR (400 MHz, CDCl_3): δ 7.29–7.26 (2H, m), 7.06–6.96 (3H, m), 3.98–3.92 (1H, m), 3.87–3.84 (1H, m), 3.79–3.72 (1H, m), 2.68 (1H, brs), 1.69–1.50 (1H, m), 1.47–1.30 (4H, m), 0.92 (3H, t, $J = 7.1$ Hz).

^{13}C NMR (100 MHz, CDCl_3): 148.6, 129.2, 122.7, 115.1, 84.2, 65.6, 29.8, 28.1, 22.2, 14.2.

HPLC: Chiralpak AD–H (hexane/*i*-PrOH, 90/10, flow rate 1 mL/min, λ = 230 nm),

t_R (minor) = 9.5 min, t_R (major) = 11.4 min; 96% ee.

$[\alpha]_D^{23} = +22.5$ ($c = 1.2$, CHCl_3).

(*R*)-3-methyl-2-(*N*-phenylaminoxy)butan-1-ol (29e)⁴

α -aminoxy alcohol **29e** was prepared according to the general procedure from 3-methylbutanal (0.10 mL, 0.9 mmol) to provide the title compound as a pale yellow liquid (44.8 mg, 76% yield) after flash column chromatography on silica gel (hexane/EA = 9/1~7/3).

¹H NMR (400 MHz, CDCl₃): δ 7.30–7.26 (2H, m), 7.03–6.99 (3H, m), 3.88–3.87 (2H, m), 3.76–3.74 (1H, m), 2.07–1.99 (1H, m), 1.05 (3H, d, J = 6.9 Hz), 1.01 (3H, d, J = 6.9 Hz).

¹³C NMR (100 MHz, CDCl₃): 148.5, 129.2, 122.7, 115.2, 88.8, 63.8, 28.9, 18.9, 18.8.

HPLC: Chiralpak AD–H (hexane/*i*-PrOH, 90/10, flow rate 1 mL/min, λ = 230 nm), t_R (minor) = 9.0 min, t_R (major) = 10.1 mins; 97% ee.

$[\alpha]_D^{22} = +33.4$ (c = 1.0, CHCl₃).

(*R*)-2-phenyl-2-(*N*-phenylaminoxy)ethanol (29f)³

α -aminoxy alcohol **29f** was prepared according to the general procedure from 2-phenylacetaldehyde (0.11 mL, 0.9 mmol) to provide the title compound as a pale

yellow liquid (53.5 mg, 78% yield) after flash column chromatography on silica gel (hexane/ether = 9/1~7/3).

^1H NMR (400 MHz, CDCl_3): δ 7.39–7.31 (5H, m), 7.28–7.20 (2H, m), 6.99–6.94 (3H, m), 5.00 (1H, dd, J = 3.5, 8.1 Hz), 3.99–3.92 (1H, m), 3.83–3.78 (1H, m), 2.58 (1H, brs).

^{13}C NMR (100 MHz, CDCl_3): 148.1, 137.9, 129.2, 128.9, 128.7, 127.2, 122.7, 115.2, 86.6, 66.6.

HPLC: Chiralpak OD–H (hexane/*i*-PrOH, 95/5, flow rate 1 mL/min, λ = 230 nm), t_R (major) = 25.8 mins, t_R (minor) = 30.2 min; 93% ee.

$[\alpha]_D^{24} = -85.5$ (c = 1.1, CHCl_3).

(*R*)-3-phenyl-2-(*N*-phenylaminoxy)propan-1-ol (29g)³

α -aminoxy alcohol **29g** was prepared according to the general procedure from 3-phenylpropanal (0.12 mL, 0.9 mmol) to provide the title compound as a pale yellow liquid (55.9 mg, 77% yield) after flash column chromatography on silica gel (hexane/ether = 9/1~7/3).

^1H NMR (400 MHz, CDCl_3): δ 7.32–7.18 (6H, m), 7.08 (1H, brs), 6.94 (1H, t, J = 7.3 Hz), 6.82 (2H, d, J = 8.0 Hz), 4.16–4.10 (1H, m), 3.85 (1H, d, J = 11.8 Hz), 3.04 (1H, dd, J = 6.8, 13.7 Hz), 2.84 (1H, dd, J = 7.0, 13.7 Hz), 2.62 (1H, brs).

^{13}C NMR (100 MHz, CDCl_3): 148.5, 138.0, 129.6, 129.1, 128.7, 126.6, 122.5, 114.8, 85.2, 64.3, 36.6.

HPLC: Chiralpak OD-H (hexane/*i*-PrOH, 91/9, flow rate 1 mL/min, λ = 230 nm), t_R (major) = 57.9 min, t_R (minor) = 62.4 min; >99% ee.

$[\alpha]_D^{22} = +55.2$ ($c = 1.3$, CHCl_3).

(*R*)-2-(*N*-phenylaminoxy)pent-4-en-1-ol (29h**)⁴**

α -aminoxy alcohol **29h** was prepared according to the general procedure from 4-pentenal (0.09 mL, 0.9 mmol) to provide the title compound as a pale yellow liquid (51.0 mg, 88% yield) after flash column chromatography on silica gel (hexane/EA = 9/1~7/3).

^1H NMR (400 MHz, CDCl_3): δ 7.29–7.26 (2H, m), 7.06–6.96 (3H, m), 5.93–5.82 (1H, m), 5.18–5.11 (2H, m), 4.05–4.00 (1H, m), 3.87–3.75 (2H, m), 2.54–2.32 (3H, m), 1.66 (1H, brs).

^{13}C NMR (100 MHz, CDCl_3): 148.5, 134.2, 129.2, 122.7, 118.0, 115.0, 83.5, 64.8, 34.8.

HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 90/10, flow rate 1 mL/min, λ = 230 nm), t_R (minor) = 10.5 min, t_R (major) = 12.5 min; 96% ee.

$[\alpha]_D^{23} = -22.9$ ($c = 1.0$, CHCl_3).

(R)-4-(benzyloxy)-2-(N-phenylaminoxy)butan-1-ol (29i) (New compound)

α -aminoxy alcohol **29i** was prepared according to the general procedure from 4-(benzyloxy)butanal (0.16 mL, 0.9 mmol) to provide the title compound as a pale yellow liquid (73.8 mg, 86% yield) after flash column chromatography on silica gel (hexane/EA = 9/1~7/3).

^1H NMR (400 MHz, CDCl_3): δ 7.34–7.23 (6H, m), 7.05 (1H, brs), 6.98–6.94 (3H, m), 4.54–4.52 (2H, m), 4.14–4.11 (1H, m), 3.93–3.87 (1H, m), 3.81–3.77 (1H, m), 3.66 (2H, t, J = 5.7 Hz), 2.81 (1H, t, J = 5.9 Hz), 2.06–1.89 (2H, m).

^{13}C NMR (100 MHz, CDCl_3): 148.5, 138.2, 129.2, 128.7, 128.0, 122.6, 116.3, 115.0, 81.7, 73.4, 66.9, 65.0, 30.5.

HPLC: Chiralpak AD–H (hexane/*i*-PrOH, 91/9, flow rate 1 mL/min, λ = 230 nm), t_R (minor) = 18.8 min, t_R (major) = 24.1 min; 97% ee.

$[\alpha]_D^{22}$ = + 15.5 (c = 1.1, CHCl_3).

HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{21}\text{NO}_3$, m/z 288.1600, found 288.1599.

(*R*)-tert-butyl 3-hydroxy-2-(*N*-phenylaminoxy)propylcarbamate (29j**) (New compound)**

α -aminoxy alcohol **29j** was prepared according to the general procedure from tert-butyl-3-oxopropylcarbamate (0.16 mL, 0.9 mmol) to provide the title compound as a pale yellow liquid (67.2 mg, 79% yield) after flash column chromatography on silica gel (hexane/EA = 9/1~7/3).

^1H NMR (400 MHz, CDCl_3): δ 7.32–7.24 (3H, m), 6.98–6.94 (2H, m), 5.02 (1H, brs), 3.94–3.92 (1H, m), 3.80 (2H, s), 3.50–3.36 (2H, m), 1.45 (9H, s).

^{13}C NMR (100 MHz, CDCl_3): 157.3, 148.5, 129.2, 122.6, 114.8, 82.6, 80.2, 61.5, 39.8, 28.5.

HPLC: Chiralpak OJ-H (hexane/*i*-PrOH, 95/5, flow rate 1 mL/min, $\lambda = 230$ nm), t_R (minor) = 24.8 min, t_R (major) = 26.6 min; 93% ee.

$[\alpha]_D^{22} = -8.2$ ($c = 1.3$, CHCl_3).

HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{23}\text{N}_2\text{O}_4$, m/z 282.1658, found 282.1659.

(*R*)-2-(*p*-toluidinoxy)propan-1-ol (34**) (New compound)**

α -aminoxy alcohol **34** was prepared according to the general procedure from propanal (0.07 mL, 0.9 mmol) and nitrosotoluene (36.3 mg, 0.3 mmol) to provide the title compound as a pale yellow liquid (45.0 mg, 83% yield) after flash column chromatography on silica gel (hexane/EA = 9/1~7/3).

^1H NMR (400 MHz, CDCl_3): δ 7.07 (2H, d, J = 8.1 Hz), 6.99 (1H, brs), 6.88 (2H, d, J = 8.3 Hz), 4.13–4.07 (1H, m), 3.78–3.68 (2H, m), 2.28 (3H, s), 1.22 (3H, d, J = 6.5 Hz).

^{13}C NMR (100 MHz, CDCl_3): 146.0, 132.2, 129.7, 115.5, 80.0, 66.8, 20.8, 15.6.

HPLC: Chiralpak AD–H (hexane/*i*-PrOH, 90/10, flow rate 1 mL/min, λ = 230 nm), t_{R} (minor) = 10.9 min, t_{R} (major) = 12.4 min; 97% ee.

$[\alpha]_{\text{D}}^{25} = +5.5$ (c = 1.5, CHCl_3).

HRMS (ESI) calcd for $\text{C}_{10}\text{H}_{16}\text{NO}_2$, m/z 182.1181, found 182.1181.

5.3 L-Prolinol as a highly enantioselective catalyst for Michael addition of cyclohexanone to nitroolefins

5.3.1 Synthesis of starting materials

Nitroolefins were prepared according to literature procedures.^{5,6} The enantiomers used to determine the ee values were synthesized with L-proline as catalyst. Although the L-proline catalyzed reaction gave very good diastereoselectivity, its enantioselectivity was very poor. As such, we used the product from L-proline catalyzed reaction as a reference to determine the ee values for our reaction.

5.3.2 General experimental procedures for the Michael addition of cyclohexanone to nitroolefins

Cyclohexanone **36** (5.0 mmol) was added to a 5 mL drum vial containing L-prolinol **38** (10 mol %) and a magnetic stirring bar. After stirring for 5 min at 0 °C, the corresponding nitroolefin **35a–n** (0.50 mmol) and benzoic acid (0.10 mmol) were added. The reaction was first stirred at this temperature for about 10 min and then placed at 4 °C without stirring until TLC analysis of aliquots indicated complete consumption of the nitroolefin. The crude reaction mixture was purified by flash column chromatography (hexane/EA = 9:1) yielding pure γ -nitroketones **37a–n**.

Relative and absolute configurations of the products were compared with the known ¹H NMR, chiral HPLC analysis, and optical rotation values. Most of the compounds in Table 3.2 are known in the literature.

5.3.3 Experimental data of compounds 37a–n

(*S*)-2-((*R*)-2-Nitro-1-phenylethyl)cyclohexanone (**37a**)⁷

γ -Nitroketone **37a** was prepared according to the general procedure from (*E*)-(2-nitrovinyl)benzene (75 mg, 0.5 mmol) to provide the title compound as a white solid (114 mg, 92% yield) after flash column chromatography on silica gel (hexane/EA = 9/1).

¹H NMR (400 MHz, CDCl₃): δ 7.34–7.24 (3H, m), 7.17 (2H, d, J = 7.2 Hz), 4.94 (1H, dd, J = 4.4, 12.4 Hz), 4.63 (1H, dd, J = 10.0, 12.0 Hz), 3.79–3.73 (1H, m), 2.76–2.67 (1H, m), 2.50–2.38 (2H, m), 2.10–2.06 (1H, m), 1.80–1.55 (4H, m), 1.26–1.22 (1H, m).

¹³C NMR (100 MHz, CDCl₃): 212.1, 137.9, 129.1, 128.3, 127.9, 79.1, 52.7, 44.1, 42.9, 33.5, 28.7, 25.2.

HPLC: Chiralpak AD–H (hexane/*i*-PrOH = 92:8, flow rate 1.0 mL/min, λ = 230 nm),

t_R (minor) = 10.5 min, t_R (major) = 13.1 min; 95% ee.

$[\alpha]_D^{25} = -28.4$ (c = 1.0, CHCl₃).

(*S*)-2-((*R*)-1-(4-Bromophenyl)-2-nitroethyl)cyclohexanone (37b)⁸

γ -Nitroketone **37b** was prepared according to the general procedure from (*E*)-1-bromo-4-(2-nitrovinyl)benzene (114 mg, 0.5 mmol) to provide the title compound as a white solid (144 mg, 88% yield) after flash column chromatography on silica gel (hexane/EA = 9/1).

¹H NMR (400 MHz, CDCl₃) δ 7.45 (2H, d, J = 8.4 Hz), 7.06 (2H, d, J = 8.4 Hz), 4.93 (1H, dd, J = 4.6, 12.6 Hz), 4.61 (1H, dd, J = 10.2, 12.6 Hz), 3.78–3.72 (1H, m), 2.68–2.61 (1H, m), 2.49–2.33 (2H, m), 2.11–2.08 (1H, m), 1.82–1.53 (4H, m), 1.28–1.22 (1H, m).

¹³C NMR (100 MHz, CDCl₃): δ 211.6, 137.0, 132.3, 130.1, 121.9, 78.7, 52.5, 43.6, 42.9, 33.3, 28.6, 25.3.

HPLC: Chiralpak AD–H (hexane/*i*-PrOH = 91:9, flow rate 1.0 mL/min, λ = 230 nm),

t_R (minor) = 11.5 min, t_R (major) = 18.4 min; 93% ee.

$[\alpha]_D^{25} = -23.5$ (c = 1.0, CHCl₃).

(*S*)-2-((*R*)-1-(2-Chlorophenyl)-2-nitroethyl)cyclohexanone (**37c**)⁹

γ -Nitroketone **37c** was prepared according to the general procedure from (*E*)-1-chloro-2-(2-nitrovinyl)benzene (92 mg, 0.5 mmol) to provide the title compound as a colourless liquid (114 mg, 81% yield) after flash column chromatography on silica gel (hexane/EA= 9/1).

¹H NMR (400 MHz, CDCl₃) δ 7.37 (1H, d, J = 7.6 Hz), 7.27–7.18 (3H, m), 4.92–4.88 (2H, m), 4.33–4.28 (1H, m), 2.91 (1H, m), 2.48–2.35 (2H, m), 2.12–2.08 (1H, m), 1.82–1.54 (4H, m), 1.38–1.26 (1H, m).

¹³C NMR (100 MHz, CDCl₃): δ 211.8, 135.6, 134.7, 130.4, 129.0, 127.5, 77.4, 51.8, 43.0, 41.0, 33.1, 28.6, 25.4.

HPLC: Chiralpak AS-H (hexane/*i*-PrOH = 85:15, flow rate 1.0 mL/min, λ = 230 nm), t_R (minor) = 9.9 min, t_R (major) = 13.0 min; 90% ee.

$[\alpha]_D^{25} = -44.3$ (c = 1.0, CHCl₃).

(*S*)-2-((*R*)-1-(4-Chlorophenyl)-2-nitroethyl)cyclohexanone (37d)⁹

γ -Nitroketone **37d** was prepared according to the general procedure from (*E*)-1-chloro-4-(2-nitrovinyl)benzene (92 mg, 0.5 mmol) to provide the title compound as a white solid (117 mg, 83% yield) after flash column chromatography on silica gel (hexane/EA = 9/1).

¹H NMR (400 MHz, CDCl₃) δ 7.29 (2H, d, *J* = 8.4 Hz), 7.12 (2H, d, *J* = 8.4 Hz), 4.94 (1H, dd, *J* = 4.4, 12.8 Hz), 4.60 (1H, dd, *J* = 10.4, 12.4 Hz), 3.79–3.73 (1H, m), 2.68–2.62 (1H, m), 2.48–2.36 (2H, m), 2.11–2.06 (1H, m), 1.81–1.55 (4H, m), 1.26–1.20 (1H, m).

¹³C NMR (100 MHz, CDCl₃): δ 211.7, 136.5, 133.7, 129.7, 129.2, 78.7, 52.5, 43.5, 42.9, 33.2, 28.6, 25.2.

HPLC: Chiralpak AD–H (hexane/*i*-PrOH = 91:9, flow rate 1.0 mL/min, λ = 230 nm), t_R (minor) = 12.2 min, t_R (major) = 18.2 min; 92% ee.

$[\alpha]_D^{25} = -22.4$ (c = 1.0, CHCl₃).

(S)- 2-((R)-1-(2-Methyl-phenyl)-2-nitro-ethyl)cyclohexanone (37e) (New compound)

γ -Nitroketone **37e** was prepared according to the general procedure from (*E*)-1-methyl-2-(2-nitrovinyl)benzene (82 mg, 0.5 mmol) to provide the title compound as a pale yellow liquid (108 mg, 83% yield) after flash column chromatography on silica gel (hexane/EA = 9/1).

^1H NMR (400 MHz, CDCl_3) δ 7.22–7.18 (1H, m), 7.08–7.06 (1H, m), 6.96–6.95 (2H, m), 4.92 (1H, dd, $J = 4.4, 12.4$ Hz), 4.62 (1H, dd, $J = 10.0, 12.4$ Hz), 3.74–3.67 (1H, m), 2.68–2.67 (1H, m), 2.49–2.35 (2H, m), 2.33 (3H, s), 2.09–2.06 (1H, m), 1.80–1.56 (4H, m), 1.26–1.22 (1H, m).

^{13}C NMR (100 MHz, CDCl_3): δ 212.2, 138.8, 137.9, 129.2, 129.0, 128.7, 125.2, 79.1, 52.7, 44.1, 42.9, 33.4, 28.7, 25.2, 21.6.

HPLC: Chiralpak AS-H (hexane/*i*-PrOH = 85:15, flow rate 1.0 mL/min, $\lambda = 230$ nm), t_R (minor) = 8.5 min, t_R (major) = 12.4 min; 92% ee.

$[\alpha]_D^{25} = -28.6$ ($c = 1.0$, CHCl_3).

HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{19}\text{O}_3\text{N}$, m/z 301.1049, found 301.1046.

(S)- 2-((R)-1-(3-Methyl-phenyl)-2-nitro-ethyl)cyclohexanone (37f)¹⁰

γ -Nitroketone **37f** was prepared according to the general procedure from (*E*)-1-methyl-3-(2-nitrovinyl)benzene (82 mg, 0.5 mmol) to provide the title compound as a white solid (111 mg, 85% yield) after flash column chromatography on silica gel (hexane/EA = 9/1).

¹H NMR (400 MHz, CDCl₃) δ 7.20–7.09 (4H, m), 5.00 (1H, dd, *J* = 4.4, 12.8 Hz), 4.61 (1H, dd, *J* = 10.2, 12.6 Hz), 4.15–4.10 (1H, m), 2.66–2.65 (1H, m), 2.49–2.38 (2H, m), 2.36 (3H, s), 2.11–2.07 (1H, m), 1.77–1.52 (4H, m), 1.25–1.21 (1H, m).

¹³C NMR (100 MHz, CDCl₃): δ 212.4, 137.6, 136.6, 131.1, 127.3, 126.9, 125.8, 78.9, 53.6, 43.1, 48.4, 33.0, 28.9, 25.5, 21.0.

HPLC: Chiralpak AS–H (hexane/*i*-PrOH = 85:15, flow rate 1.0 mL/min, λ = 230 nm), *t*_R (minor) = 8.5 min, *t*_R (major) = 11.8 min; 89% ee.

$[\alpha]_{\text{D}}^{25} = -32.3$ (*c* = 1.0, CHCl₃).

(S)- 2-((R)-1-(4-Methyl-phenyl)-2-nitro-ethyl)cyclohexanone (37g)¹⁰

γ -Nitroketone **37g** was prepared according to the general procedure from (*E*)-1-methyl-4-(2-nitrovinyl)benzene (82 mg, 0.5 mmol) to provide the title compound as a white solid (108 mg, 83% yield) after flash column chromatography on silica gel (hexane/EA = 9/1).

^1H NMR (400 MHz, CDCl_3) δ 7.12 (2H, d, J = 8.0 Hz), 7.04 (2H, d, J = 8.0 Hz), 4.91 (1H, dd, J = 4.6, 12.2 Hz), 4.60 (1H, dd, J = 10.0, 12.4 Hz), 3.75–3.69 (1H, m), 2.68–2.64 (1H, m), 2.46–2.37 (2H, m), 2.31 (3H, s), 2.09–2.04 (1H, m), 1.79–1.54 (4H, m), 1.24–1.21 (1H, m).

^{13}C NMR (100 MHz, CDCl_3): δ 212.3, 137.6, 134.7, 129.8, 128.2, 79.2, 52.8, 43.8, 42.9, 33.4, 28.7, 25.2, 21.2.

HPLC: Chiralpak AD–H (hexane/*i*-PrOH = 91:9, flow rate 1.0 mL/min, λ = 230 nm), t_{R} (minor) = 8.9 min, t_{R} (major) = 11.1 min; 92% ee.

$[\alpha]_{\text{D}}^{25} = -23.1$ (c = 1.0, CHCl_3).

(*S*)-2-((*R*)-1-(2-Methoxyphenyl)-2-nitroethyl)cyclohexanone (37h)⁷

γ -Nitroketone **37h** was prepared according to the general procedure from (*E*)-1-methoxy-2-(2-nitrovinyl)benzene (90 mg, 0.5 mmol) to provide the title compound as a white solid (128 mg, 92% yield) after flash column chromatography on silica gel (hexane/EA = 17/3).

^1H NMR (400 MHz, CDCl_3) δ 7.26–7.22 (1H, m), 7.09–7.07 (1H, m), 6.90–6.86 (2H, m), 4.84–4.82 (2H, m), 3.99–3.93 (1H, m), 3.83 (3H, s), 3.00–2.97 (1H, m), 2.48–2.38 (2H, m), 2.09–2.04 (1H, m), 1.78–1.56 (4H, m), 1.21–1.18 (1H, m).

^{13}C NMR (100 MHz, CDCl_3): δ 212.7, 157.7, 131.2, 129.1, 125.5, 121.0, 111.1, 77.6, 55.5, 50.7, 42.9, 41.5, 33.4, 28.7, 25.3.

HPLC: Chiralpak AS–H (hexane/*i*-PrOH = 85/15, flow rate 1.0 mL/min, λ = 230 nm), t_R (minor) = 12.0 min, t_R (major) = 13.6 min; 91% ee.

$[\alpha]_D^{25} = -41.2$ (c = 1.0, CHCl_3).

(*S*)-2-((*R*)-1-(3-Methoxyphenyl)-2-nitroethyl)cyclohexanone (37i)¹¹

γ -Nitroketone **37i** was prepared according to the general procedure from (*E*)-1-methoxy-3-(2-nitrovinyl)benzene (90 mg, 0.5 mmol) to provide the title compound as a white solid (115 mg, 83% yield) after flash column chromatography on silica gel (hexane/EA = 17/3).

^1H NMR (400 MHz, CDCl_3) δ 7.26–7.22 (1H, m), 6.81–6.70 (3H, m), 4.92 (1H, dd, J = 4.4, 12.4 Hz), 4.62 (1H, dd, J = 9.8, 12.6 Hz), 3.79 (3H, s), 3.76–3.70 (1H, m), 2.67–2.66 (1H, m), 2.49–2.38 (2H, m), 1.77–1.55 (4H, m), 1.27–1.23 (1H, m).

^{13}C NMR (100 MHz, CDCl_3): 212.1, 160.0, 139.6, 130.1, 120.5, 114.7, 112.8, 79.0, 55.4, 52.7, 44.1, 42.9, 33.4, 28.7, 25.2.

HPLC: Chiralpak AD-H (hexane/*i*-PrOH = 91:9, flow rate 1.0 mL/min, λ = 230 nm),

t_R (minor) = 12.7 min, t_R (major) = 13.9 min; 84% ee.

$[\alpha]_D^{25} = -31.2$ (c = 1.3, CH₂Cl₂).

(*S*)-2-((*R*)-1-(4-Methoxyphenyl)-2-nitroethyl)cyclohexanone (37j)¹¹

γ -Nitroketone **37j** was prepared according to the general procedure from (*E*)-1-methoxy-4-(2-nitrovinyl)benzene (90 mg, 0.5 mmol) to provide the title compound as a white solid (119 mg, 85% yield) after flash column chromatography on silica gel (hexane/EA = 17/3).

¹H NMR (400 MHz, CDCl₃) δ 7.08 (2H, d, J = 8.4 Hz), 6.85 (2H, d, J = 8.8 Hz), 4.91 (1H, dd, J = 4.6, 12.2 Hz), 4.61–4.56 (1H, m), 3.74 (3H, s), 3.73–3.68 (1H, m), 2.68–2.64 (1H, m), 2.49–2.34 (2H, m), 2.09–2.07 (1H, m), 1.80–1.52 (4H, m), 1.27–1.19 (1H, m).

¹³C NMR (100 MHz, CDCl₃): δ 212.3, 159.2, 129.7, 129.3, 114.5, 79.3, 55.4, 52.9, 43.4, 42.9, 33.3, 28.7, 25.2.

HPLC: Chiralpak AD-H (hexane/*i*-PrOH = 91:9, flow rate 1.0 mL/min, λ = 230 nm),

t_R (minor) = 11.8 min, t_R (major) = 14.6 min; 91% ee.

$[\alpha]_D^{25} = -35.4$ (c = 1.0, CHCl₃).

(*S*)-2-((*S*)-1-(Furan-2-yl)-2-nitroethyl) cyclohexanone (37k)¹¹

γ -Nitroketone **37k** was prepared according to the general procedure from (*E*)-2-(2-nitrovinyl)furan (70 mg, 0.5 mmol) to provide the title compound as a white solid (107 mg, 90% yield) after flash column chromatography on silica gel (hexane/EA = 9/1).

¹H NMR (400 MHz, CDCl₃): δ 7.35 (1H, m), 6.39–6.28 (1H, m), 6.18 (1H, m), 4.82–4.76 (1H, m), 4.70–4.64 (1H, m), 4.00–3.94 (1H, m), 2.79–2.72 (1H, m), 2.48–2.33 (2H, m), 2.17–2.09 (1H, m), 1.86–1.63 (4H, m), 1.33–1.25 (1H, m).

¹³C NMR (100 MHz, CDCl₃): 211.0, 151.1, 142.5, 110.5, 109.2, 76.8, 51.3, 42.7, 37.7, 32.6, 28.4, 25.3.

HPLC: Chiralpak AD–H (hexane/*i*-PrOH = 91:9, flow rate 1.0 mL/min, λ = 230 nm), t_R (major) = 10.6 min, t_R (minor) = 12.8 min; 93% ee.

$[\alpha]_D^{25} = -15.4$ ($c = 1.0$, CHCl₃).

(*S*)-2-((*S*)-1-(Furan-3-yl)-2-nitroethyl)cyclohexanone (37l) (New compound)

γ -Nitroketone **37l** was prepared according to the general procedure from (*E*)-3-(2-nitrovinyl)furan (70 mg, 0.5 mmol) to provide the title compound as a white solid (105 mg, 88% yield) after flash column chromatography on silica gel (hexane/EA = 9/1).

^1H NMR (400 MHz, CDCl_3): δ 7.38 (1H, s), 7.30 (1H, s), 6.26 (1H, s), 4.77 (1H, dd, J = 5.0, 12.2 Hz), 4.58 (1H, dd, J = 9.0, 12.2 Hz), 3.83–3.78 (1H, m), 2.64–2.58 (1H, m), 2.48–2.32 (2H, m), 2.11–1.84 (3H, m), 1.68–1.59 (2H, m), 1.37–1.27 (1H, m).

^{13}C NMR (100 MHz, CDCl_3): 211.5, 143.8, 141.0, 121.6, 109.3, 78.4, 52.1, 42.8, 34.8, 32.6, 28.3, 25.2.

HPLC: Chiralpak AD–H (hexane/*i*-PrOH = 91:9, flow rate 1.0 mL/min, λ = 230 nm),

t_R (minor) = 14.7 min, t_R (major) = 16.0 min; 82% ee.

$[\alpha]_D^{25} = -21.9$ (c = 1.0, CHCl_3).

HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{15}\text{O}_4\text{N}$, m/z 237.0996, found 237.0996.

(*S*)-2-((*S*)-2-(Nitro-1-(thiophen-2-yl)ethyl)cyclohexanone (**37m**)¹¹

γ -Nitroketone **37m** was prepared according to the general procedure from (*E*)-2-(2-nitrovinyl)thiophene (78 mg, 0.5 mmol) to provide the title compound as a white solid (117 mg, 92% yield) after flash column chromatography on silica gel (hexane/EA = 9/1).

^1H NMR (400 MHz, CDCl_3): δ 7.22–7.21 (1H, m), 6.94–6.86 (3H, m), 4.89 (1H, dd, J = 4.6, 12.6 Hz), 4.65 (1H, dd, J = 9.4, 12.6 Hz), 4.16–4.10 (1H, m), 2.71–2.66 (1H, m), 2.49–2.34 (1H, m), 2.12–2.07 (1H, m), 1.90–1.83 (2H, m), 1.69–1.63 (2H, m), 1.37–1.31 (1H, m).

^{13}C NMR (100 MHz, CDCl_3): 211.4, 140.7, 127.1, 126.8, 125.1, 79.4, 53.5, 42.8, 39.6, 32.9, 28.5, 25.2.

HPLC: Chiralpak AS-H (hexane/*i*-PrOH = 85/15, flow rate 1.0 mL/min, λ = 230 nm), t_{R} (minor) = 13.2 min, t_{R} (major) = 17.0 min; 94% ee.

$[\alpha]_{\text{D}}^{25} = -26.3$ (c = 1.0, CHCl_3).

(S)-2-((S,E)-1-Nitro-4-phenylbut-3-en-2-yl)cyclohexanone (**37n**)¹¹

γ -Nitroketone **37n** was prepared according to the general procedure from (1*E*,3*E*)-4-(nitrobuta-1,3-dienyl)benzene (79 mg, 0.5 mmol) to provide the title compound as a white solid (112 mg, 82% yield) after flash column chromatography on silica gel (hexane/EA = 9/1).

^1H NMR (400 MHz, CDCl_3): δ 7.35–7.24 (5H, m), 6.49 (1H, d, J = 16 Hz), 6.02 (1H, dd, J = 9.6, 16 Hz), 4.69–4.55 (2H, m), 2.58–2.52 (1H, m), 2.48–2.32 (2H, m), 2.20–2.09 (2H, m), 1.91 (1H, m), 1.71–1.65 (2H, m), 1.51–1.44 (1H, m).

^{13}C NMR (100 MHz, CDCl_3): 211.5, 136.5, 134.6, 128.8, 128.2, 126.7, 125.9, 78.3, 51.9, 42.9, 42.1, 32.8, 28.3, 25.3.

HPLC: Chiralpak AS-H (hexane/*i*-PrOH = 85:15, flow rate 1.0 mL/min, λ = 230 nm), t_{R} (minor) = 9.6 min, t_{R} (major) = 14.6 min; 96% ee.

$[\alpha]_{\text{D}}^{25} = -86.2$ ($c = 1.0$, CHCl_3).

5.4 Stereocontrolled synthesis of indanes with four stereogenic centers

5.4.1 Synthesis of starting materials

5.4.1.1 Typical procedures for the preparation of aldehydes 43a–d

(Adapted from Uchida, K.; Yokoshima, S.; Kan, T.; Fukuyama, T. *Org. Lett.* **2006**, *8*, 5311)

2.0 M sodium bis(trimethylsilyl)amide in tetrahydrofuran (6 mL, 12 mmol, 1.2 equiv.) was added dropwise to a stirred solution of (methoxymethyl)triphenylphosphonium chloride (3.77 g, 11 mmol, 1.1 equiv.) in 20 mL of anhydrous tetrahydrofuran at 0 °C under nitrogen atmosphere for 2 hours. A solution of the corresponding bromobenzaldehyde **39** (10 mmol) was then added dropwise to the reaction mixture. After stirring at 0 °C for 10 minutes, the reaction mixture was allowed to warm to room temperature (22 °C) and stirred for another 2 hours. The yellow solution was quenched with saturated aqueous ammonium chloride (5 mL) and the solvent was evaporated under reduced pressure. Diethyl ether was added to the residue and the mixture was filtered. The filtrate was washed with sodium bicarbonate, water and then finally with brine. The organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane:dichloromethane = 9:1) to give compound **40**. The product was the mixture of *E* and *Z* isomers.

(Adapted from Lin, M.-Y.; Das, A.; Liu, R.-S. *J. Am. Chem. Soc.* **2006**, *128*, 9340)

2.0 M *n*-butyllithium in cyclohexane (4 mL, 9.6 mmol, 1.2 equiv.) was added dropwise to a stirring solution compound **40** (8 mmol) in 20 mL anhydrous tetrahydrofuran at $-78\text{ }^{\circ}\text{C}$ under nitrogen atmosphere. After stirring at $-78\text{ }^{\circ}\text{C}$ for 2 hours, anhydrous N,N-dimethylformamide (0.92 mL, 12 mmol, 1.5 equiv.) was added to form a light yellow solution. After 30 min, 25 mL water was added to reaction mixture, extracted with diethyl ether and the combined organic layers were concentrated under reduced pressure. The crude product was eluted through a silica column (hexane/EA = 19/1) to afford compound **41**. The product was the mixture of *E* and *Z* isomers.

(Adapted from Tan, B.; Zhu, D.; Zhang, L.; Chua, P. J.; Zeng, X.; Zhong, G. *Chem. Eur. J.* **2010**, *16*, 3842)

Corresponding ylide **53** (1.1 equiv) was added portion wise to a stirring solution of compound **41** (6 mmol) in 10 mL of dichloromethane at $22\text{ }^{\circ}\text{C}$ and the reaction was stirred overnight. Diethyl ether was added to the residue and the mixture was filtered. The filtrate was washed with sodium bicarbonate, water and then finally with brine. The organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane/dichloromethane = 9/1) to give compound **42**. The product was the mixture of *E* and *Z* isomers.

(Adapted from Richter, F.; Bauer, M.; Perez, C.; Maichle-Mössner, C.; Maier, M. E. *J. Org. Chem.* **2002**, *67*, 2474)

70% perchloric acid in water (7 mL) was added dropwise to a stirring solution of compound **42** (5 mmol) in diethyl ether 10 mL at $0\text{ }^{\circ}\text{C}$. After 10 minutes, the cooling bath was removed and stirring continued until the reaction proceeds to

completion (reaction monitored by TLC). The mixture was diluted with water (10 mL) and extracted with ethyl acetate. The combined organic layers were washed with saturated sodium bicarbonate, brine, dried with sodium sulfate, filtered and concentrated *in vacuo* to afford compound **43**.

5.4.1.2 Experimental data of compounds **40a–42d** and **43a–e**

1-Bromo-2-(2-methoxyvinyl)benzene (**40a**)

Compound **40a** was prepared according to the general procedure from 2-bromobenzaldehyde **39a** (1.85 g, 10 mmol) to provide the title compound as a pale yellow liquid (1.97 g, 92% yield) after flash column chromatography. The product was the mixture of *E* and *Z* isomers (ratio 1:1.6)

^1H NMR (400 MHz, CDCl_3): δ 8.03 (1H, d, $J = 8$ Hz), 7.53 (2.6H, d, $J = 8$ Hz), 7.34 (1.6H, d, $J = 8$ Hz), 7.26–7.18 (2.6H, m), 7.02–6.96 (4.2H, m), 6.25 (1H, d, $J = 7.2$ Hz), 6.09 (1.6H, d, $J = 12.8$ Hz), 5.60 (1H, d, $J = 7.2$ Hz), 3.78, 3.73 (7.8H, s).

^{13}C NMR (100 MHz, CDCl_3): 150.7, 149.4, 136.5, 135.3, 133.1, 132.7, 130.5, 127.7, 127.3, 127.3, 127.3, 125.9, 123.2, 122.9, 104.6, 104.0, 61.1, 56.8.

2-(2-Methoxyvinyl)benzaldehyde (**41a**) (New Compound)

Compound **41a** was prepared according to the general procedure from 1-bromo-2-(2-methoxyvinyl)benzene **40a** (1.70 g, 8 mmol) to provide the title compound as a pale yellow liquid (1.26 g, 97% yield) after flash column chromatography. The product was the mixture of *E* and *Z* isomers (ratio 1:1).

¹H NMR (400 MHz, CDCl₃): δ 10.21 (2H, d, *J* = 15.6 Hz), 7.88 (1H, d, *J* = 7.6 Hz), 7.79 (2H, t, *J* = 7.6 Hz), 7.53–7.47 (2H, m), 7.42 (1H, d, *J* = 7.6 Hz), 7.34–7.29 (2H, m), 7.02 (1H, d, *J* = 12.8 Hz), 6.75 (1H, d, *J* = 12.8 Hz), 6.32 (1H, d, *J* = 7.2 Hz), 6.11 (1H, d, *J* = 7.2 Hz), 3.77, 3.76 (6H, s).

¹³C NMR (100 MHz, CDCl₃): 192.8, 152.3, 150.2, 138.9, 137.6, 133.7, 133.3, 132.5, 132.1, 131.9, 131.2, 130.2, 126.3, 126.1, 126.0, 101.2, 100.6, 60.7, 56.7.

HRMS (ESI) calcd for C₁₀H₁₁O₂, *m/z* 163.0759 [M+H], found 163.0751.

((2*E*)-Ethyl-3-(2-(2-methoxyvinyl)phenyl)acrylate (42a) (New Compound)

Compound **42a** was prepared according to the general procedure from 2-(2-methoxyvinyl)benzaldehyde **41a** (0.97 g, 6 mmol) and ylide **53a** (2.30 g, 1.1 equiv.) to provide the title compound as a pale yellow liquid (1.27 g, 91% yield) after flash column chromatography. The product was the mixture of *E* and *Z* isomers (ratio 1:1).

¹H NMR (400 MHz, CDCl₃): δ 8.01 (2H, dd, *J* = 15.8, 5.2 Hz), 7.83 (1H, d, *J* = 7.9 Hz), 7.50 (2H, d, *J* = 7.8 Hz), 7.32–7.26 (3H, m), 7.23–7.13 (2H, m), 6.82 (1H, d, *J* = 10.6 Hz), 6.33 (2H, dd, *J* = 15.9, 8.3 Hz), 6.22 (1H, d, *J* = 7.1 Hz), 6.04 (1H, d, *J* =

12.7 Hz), 5.46 (1H, d, $J = 7.1$ Hz), 4.26 (4H, dq, $J = 7.2, 2.3$ Hz), 3.71, 3.70 (6H, s), 1.33 (6H, t, $J = 7.2$ Hz).

^{13}C NMR (100 MHz, CDCl_3): 167.2, 167.1, 151.2, 149.0, 143.1, 142.8, 136.5, 135.2, 132.0, 132.0, 130.1, 130.0, 129.7, 127.1, 126.8, 126.7, 126.4, 119.5, 119.4, 102.2, 101.9, 60.7, 60.5, 60.5, 56.8, 14.4.

HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{17}\text{O}_3$, m/z 233.1178 $[\text{M}+\text{H}]$, found 233.1181.

(*E*)-Ethyl-3-(2-(formylmethyl)phenyl)acrylate (43a) (New compound)

Compound **43a** was prepared according to the general procedure from ((*2E*)-ethyl-3-(2-(2-methoxyvinyl)phenyl)acrylate **42a** (1.16 g, 5 mmol) to provide the title compound as a pale yellow liquid (1.06 g, 98% yield) after concentration *in vacuo*.

^1H NMR (400 MHz, CDCl_3): δ 9.75 (1H, s), 7.83 (1H, d, $J = 15.7$ Hz), 7.64 (1H, d, $J = 7.5$ Hz), 7.41–7.33 (2H, m), 7.22 (1H, d, $J = 7.3$ Hz), 6.39 (1H, d, $J = 15.7$ Hz), 4.27 (2H, q, $J = 7.1$ Hz), 3.89 (2H, s), 1.34 (3H, t, $J = 7.1$ Hz).

^{13}C NMR (100 MHz, CDCl_3): 198.3, 166.6, 141.1, 134.3, 131.7, 131.4, 130.4, 128.2, 127.1, 121.0, 60.7, 48.1, 14.3.

HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{13}\text{O}_3$, m/z 205.0865 $[\text{M}+\text{H}]$, found 205.0866.

1-Bromo-4-methoxy-2-(2-methoxyvinyl)benzene (40b)

Compound **40b** was prepared according to the general procedure from 2-bromo-5-methoxybenzaldehyde **39b** (2.31 g, 10 mmol) to provide the title compound as a pale yellow liquid (1.87 g, 77% yield) after flash column chromatography. The product was the mixture of *E* and *Z* isomers (ratio 1:1.3)

^1H NMR (400 MHz, CDCl_3): δ 7.65 (1H, d, $J = 2.6$ Hz), 7.38 (2.3H, d, $J = 8.8$ Hz), 6.96 (1.3H, d, $J = 12.9$ Hz), 6.85 (1.3H, d, $J = 2.2$ Hz), 6.57–6.56 (1.3H, m), 6.21 (1H, d, $J = 7.2$ Hz), 6.03 (1.3H, d, $J = 12.8$ Hz), 5.55 (1H, d, $J = 7.2$ Hz), 3.75–3.69 (13.8H, m).

^{13}C NMR (100 MHz, CDCl_3): 159.1, 158.7, 150.7, 149.6, 137.1, 135.8, 133.5, 132.9, 115.7, 113.8, 113.6, 113.2, 113.2, 111.1, 104.6, 103.9, 61.1, 56.7, 55.5, 55.5.

4-Methoxy-2-(2-methoxyvinyl)benzaldehyde (41b) (New Compound)

Compound **41b** was prepared according to the general procedure from 1-bromo-4-methoxy-2-(2-methoxyvinyl)benzene **40b** (1.70 g, 7 mmol) to provide the title compound as a pale yellow liquid (1.12 g, 77% yield) after flash column chromatography. The product was the mixture of *E* and *Z* isomers (ratio 1:1.5).

^1H NMR (400 MHz, CDCl_3): δ 10.06 (2.5H, d, J = 10.2 Hz), 7.73–7.70 (2.5H, m), 7.48 (1H, d, J = 2.4 Hz), 7.03 (1.5H, d, J = 12.8 Hz), 6.86–6.75 (5.5H, m), 6.31 (1H, d, J = 7.4 Hz), 6.22 (1H, d, J = 7.1 Hz), 3.86 (7.5H, s), 3.76 (7.5H, d, J = 11.9 Hz).

^{13}C NMR (100 MHz, CDCl_3): 191.5, 191.4, 163.8, 163.6, 152.3, 150.7, 141.4, 139.7, 135.4, 134.5, 126.1, 126.1, 115.2, 120.0, 111.9, 111.0, 101.4, 100.5, 61.0, 56.7, 55.5, 55.5.

HRMS (ESI) calcd for $\text{C}_{11}\text{H}_{13}\text{O}_2$, m/z 193.0865 $[\text{M}+\text{H}]$, found 193.0867.

(2*E*)-Ethyl-3-(4-methoxy-2-(2-methoxyvinyl)phenyl)acrylate (42b) (New Compound)

Compound **42b** was prepared according to the general procedure from 4-methoxy-2-(2-methoxyvinyl)benzaldehyde **41b** (1.04 g, 5 mmol) and ylide **53a** (1.91 g, 1.1 equiv.) to provide the title compound as a pale yellow liquid (0.76 g, 58% yield) after flash column chromatography. The product was the mixture of *E* and *Z* isomers (ratio 1:1.6).

^1H NMR (400 MHz, CDCl_3): δ 7.96 (2.6H, dd, J = 15.8, 9.2 Hz), 7.50 (2.6H, d, J = 15.7 Hz), 7.46–7.40 (1.6H, m), 6.85–6.77 (2H, m), 6.71 (2.6H, d, J = 8.6 Hz), 6.26 (1.6H, d, J = 5.6 Hz), 6.22 (2.6H, d, J = 6.5 Hz), 6.04 (1H, d, J = 12.6 Hz), 5.47 (1.6H, d, J = 7.2 Hz), 4.24 (4H, q, J = 7.0 Hz), 3.78 (7.8H, s), 3.70 (7.8H, d, J = 7.2 Hz), 1.31 (7.8H, t, J = 7.1 Hz).

^{13}C NMR (100 MHz, CDCl_3): 167.4, 167.3, 161.0, 160.7, 151.2, 148.6, 142.8, 142.1, 138.3, 136.8, 128.4, 124.7, 119.7, 112.5, 111.3, 110.9, 102.3, 102.1, 60.7, 60.2, 60.2, 60.0, 56.7, 55.2, 55.1, 14.0.

HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{19}\text{O}_4$, m/z 263.1283 $[\text{M}+\text{H}]$, found 263.1286.

(*E*)-Ethyl-3-(2-(formylmethyl)-4-methoxyphenyl)acrylate (43b) (New compound)

Compound **43b** was prepared according to the general procedure from (((*2E*)-ethyl-3-(4-methoxy-2-(2-methoxyvinyl)phenyl)acrylate **42b** (0.73 g, 2.8 mmol) to provide the title compound as a pale yellow liquid (0.43 g, 62% yield) after flash column chromatography (hexane/EA = 9/1)

^1H NMR (400 MHz, CDCl_3): δ 9.71 (1H, s), 7.76 (1H, d, J = 15.7 Hz), 7.60 (1H, d, J = 8.8 Hz), 6.86 (1H, dd, J = 8.7, 2.5 Hz), 6.72 (1H, d, J = 2.5 Hz), 6.28 (1H, d, J = 15.7 Hz), 4.24 (2H, q, J = 7.2 Hz), 3.85 (2H, s), 3.81, (3H, s), 1.32 (3H, t, J = 7.1 Hz).

^{13}C NMR (100 MHz, CDCl_3): 198.1, 166.9, 161.2, 140.5, 133.6, 128.6, 126.6, 118.3, 116.5, 113.9, 60.4, 55.4, 48.1, 14.3.

HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{17}\text{O}_4$, m/z 249.1127 $[\text{M}+\text{H}]$, found 249.1132.

5-Bromo-6-(2-methoxyvinyl)benzo[d][1,3]dioxole (40c)

Compound **40c** was prepared according to the general procedure from 6-bromobenzo[*d*][1,3]dioxole-5-carbaldehyde **39c** (2.29 g, 10 mmol) to provide the title compound as a pale yellow liquid (2.21 g, 86% yield) after flash column chromatography. The product was the mixture of *E* and *Z* isomers (ratio 1:3)

¹H NMR (400 MHz, CDCl₃): δ 7.61 (1H, s), 7.00, 6.99 (4H, s), 6.86 (3H, d, *J* = 12.8 Hz), 6.82 (3H, s), 6.15 (1H, d, *J* = 7.2 Hz), 6.02 (3H, d, *J* = 12.9 Hz), 5.94 (8H, s), 5.51 (1H, d, *J* = 7.2 Hz), 3.76, 3.70 (12H, s).

¹³C NMR (100 MHz, CDCl₃): 149.3, 147.8, 147.3, 146.7, 146.3, 145.9, 129.2, 128.4, 113.0, 112.9, 112.3, 112.0, 109.4, 104.8, 104.3, 103.6, 101.5, 101.4, 60.4, 56.2.

6-(2-Methoxyvinyl)benzo[*d*][1,3]dioxole-5-carbaldehyde (**41c**) (New Compound)

Compound **41c** was prepared according to the general procedure from 5-bromo-6-(2-methoxyvinyl)benzo[*d*][1,3]dioxole **40c** (2.05 g, 8 mmol) and 1.7 M *tert*-butyllithium in tetrahydrofuran (5.7 mL, 9.6 mmol, 1.2 equiv.) to provide the title compound as a pale yellow liquid (1.44 g, 87% yield) after concentration *in vacuo*. The crude product was used directly for the next step without purification.

HRMS (ESI) calcd for C₁₁H₁₁O₄, *m/z* 207.0657 [M+H], found 207.0652.

(*E*)-Ethyl-3-(6-(2-methoxyvinyl)benzo[*d*][1,3]dioxol-5-yl)acrylate (42c) (New Compound)

Compound **42c** was prepared according to the general procedure from 6-(2-methoxyvinyl)benzo[*d*][1,3]dioxole-5-carbaldehyde **41c** (1.24 g, 6 mmol) and ylide **53a** (2.30 g, 1.1 equiv.) to provide the title compound as a pale yellow liquid (0.66 g, 40% yield) after flash column chromatography. The product was the mixture of *E* and *Z* isomers (ratio 1:1.6).

¹H NMR (400 MHz, CDCl₃): δ 7.95 (2.6H, dd, *J* = 15.7, 8.0 Hz), 7.38, (1H, s), 7.01, (2.6H, s), 6.75 (1.6H, s), 6.72 (1H, s), 6.22–6.17 (3.2H, m), 6.03 (1.6H, d, *J* = 12.7 Hz), 5.97 (5.2H, s), 5.94 (1H, s), 5.45 (1H, d, *J* = 7.2 Hz), 4.25 (5.2H, q, *J* = 7.1 Hz), 3.75, 3.72 (7.8H, s), 1.33 (7.8H, t, *J* = 7.1 Hz).

¹³C NMR (100 MHz, CDCl₃): 167.5, 167.5, 150.8, 149.8, 149.3, 148.4, 146.8, 146.5, 142.4, 142.2, 132.3, 131.0, 126.0, 125.7, 117.2, 117.1, 109.7, 106.7, 106.0, 105.8, 102.2, 101.8, 101.6, 101.5, 60.8, 60.6, 60.5, 57.0, 14.5.

HRMS (ESI) calcd for C₁₅H₁₇O₅, *m/z* 277.1076 [M+H], found 277.1078.

(*E*)-Ethyl-3-(6-(2-oxoethyl)benzo[*d*][1,3]dioxol-5-yl)acrylate (43c) (New compound)

Compound **43c** was prepared according to the general procedure from (*E*)-ethyl-3-(6-(2-methoxyvinyl)benzo[*d*][1,3]dioxol-5-yl) acrylate **42c** (0.55 g, 2 mmol) to provide the title compound as a pale yellow liquid (0.47 g, 90% yield) after flash column chromatography (hexane/EA = 9/1)

¹H NMR (400 MHz, CDCl₃): δ 10.3 (1H, s), 8.42 (1H, d, *J* = 15.7 Hz), 7.35 (1H, s), 7.06 (1H, s), 6.31 (1H, d, *J* = 15.7 Hz), 6.11 (1H, s), 4.29 (2H, q, *J* = 7.2 Hz), 1.35 (3H, t, *J* = 7.1 Hz).

¹³C NMR (100 MHz, CDCl₃): 188.9, 166.4, 152.8, 149.8, 139.5, 134.1, 129.8, 122.6, 109.1, 107.0, 102.7, 61.0, 29.9, 14.5.

HRMS (ESI) calcd for C₁₄H₁₅O₅, *m/z* 263.0919 [M+H], found 263.0921.

((2*E*)-Ethyl-3-(2-(2-methoxyvinyl)phenyl)acrylate (42d) (New Compound)

Compound **42d** was prepared according to the general procedure from 2-(2-methoxyvinyl)benzaldehyde **41a** (0.97 g, 6 mmol) and ylide **53b** (2.20 g, 1.1 equiv.) to provide the title compound as a pale yellow liquid (1.18 g, 90% yield) after flash column chromatography. The product was the mixture of *E* and *Z* isomers (ratio 1:1.5).

¹H NMR (400 MHz, CDCl₃): δ 8.01 (2.5H, dd, *J* = 15.9, 4.8 Hz), 7.52 (1H, d, *J* = 7.8 Hz), 7.33 (2.5H, d, *J* = 7.7 Hz), 7.30 (4H, d, *J* = 4.2 Hz), 7.22–7.18 (2.5H, m), 6.83 (1.5H, d, *J* = 12.7 Hz), 6.34 (2.5H, dd, *J* = 15.9, 9.4 Hz), 6.25 (1H, d, *J* = 7.1 Hz), 6.04 (1.5H, d, *J* = 12.7 Hz), 5.47 (1H, d, *J* = 7.1 Hz), 3.81, 3.74 (12H, m).

^{13}C NMR (100 MHz, CDCl_3): 167.5, 167.4, 151.2, 149.0, 143.3, 143.0, 136.5, 135.3, 131.9, 131.9, 130.1, 129.9, 129.7, 127.1, 126.7, 126.7, 126.3, 119.0, 118.9, 102.1, 101.8, 60.6, 56.8, 51.7, 51.6.

HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{15}\text{O}_3$, m/z 219.1021 $[\text{M}+\text{H}]$, found 219.1017.

(*E*)-Methyl-3-(2-(formylmethyl)phenyl)acrylate (43d) (New compound)

Compound **43d** was prepared according to the general procedure from ((*2E*)-methyl-3-(2-(2-methoxyvinyl)phenyl)acrylate **42d** (1.10 g, 5 mmol) to provide the title compound as a pale yellow liquid (0.91 g, 95% yield) after concentration *in vacuo*.

^1H NMR (400 MHz, CDCl_3): δ 9.74 (1H, s), 7.83 (1H, d, $J = 15.7$ Hz), 7.63 (1H, d, $J = 7.4$ Hz), 7.41–7.33 (2H, m), 7.22 (1H, d, $J = 7.3$ Hz), 6.39 (1H, d, $J = 15.7$ Hz), 3.88 (2H, s), 3.81 (3H, s).

^{13}C NMR (100 MHz, CDCl_3): 198.4, 167.2, 141.5, 134.4, 131.8, 131.5, 130.6, 128.4, 127.3, 120.8, 52.0, 48.3.

HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{13}\text{O}_3$, m/z 205.0865 $[\text{M}+\text{H}]$, found 205.0868.

(*E*)-Methyl-6-formylhex-2-enoate (43e)

Compound **43e** was prepared according to the procedure¹² from 5,5-dimethoxypentanal (1.46 g, 10 mmol) to provide the title compound as a pale yellow liquid (1.29 g, 83% yield).

¹H NMR (400 MHz, CDCl₃): δ 9.78 (1H, s), 6.97–6.89 (1H, m), 5.85 (1H, d, *J* = 15.6 Hz), 3.73 (3H, s), 2.49 (2H, t, *J* = 7.2 Hz), 2.29–2.23 (2H, m), 1.85–1.78 (2H, m).

¹³C NMR (100 MHz, CDCl₃): 201.8, 167.1, 148.1, 122.1, 51.7, 43.2, 31.5, 20.5.

5.4.2 Stereocontrolled synthesis of indanes with four stereogenic centers *via* tandem aminoxylation – [3+2] cycloaddition reaction

5.4.2.1 General experimental procedures for the synthesis of indanes with four stereogenic centers *via* tandem aminoxylation – [3+2] cycloaddition reaction

Aldehyde **43a** (65.4 mg, 0.3 mmol, 3 equiv.) was added to a 5 mL drum vial containing a stirring mixture of L-thiaproline **33** (2.7 mg, 0.002 mmol, 20 mol %), nitrosobenzene **28** (10.7 mg, 0.1 mmol), tetrabutylammonium bromide (64.4 mg, 0.2 mmol, 2 equiv.) and water (0.1 mL, 1 M) at 0 °C for 10 min then at room temperature (22 °C) until the reaction turned yellow. Hydroxylamine **44a** (32.7 mg, 0.3 mmol, 3 equiv.) was then added to the reaction mixture and stirred at room temperature for 3 hours, unless otherwise stated. The reaction mixture was purified by flash column chromatography (hexane:EA = 19:1) yielding pure indanes **45**.

5.4.2.2 Experimental data of compound 45

Ethyl-1-phenyl-8-(phenylaminoxy)-3,3a,8,8a-tetrahydro-1*H*-indeno[2,1-*c*]isoxazole-3-carboxylate (**45**)

Indane **45** was prepared according to the general procedure from (*E*)-ethyl-3-(2-(formylmethyl)phenyl)acrylate **43a** (65.4 mg, 0.3 mmol, 3 equiv.) and *N*-phenylhydroxylamine **44a** (32.6 mg, 3 mmol, 3 equiv.) to provide the title compound as a yellow solid (28.3 mg, 68% yield) after flash column chromatography on silica gel.

¹H NMR (400 MHz, CDCl₃): δ 7.57 (1H, d, *J* = 7.5 Hz), 7.47–7.44 (2H, m), 7.38–7.34 (1H, m), 7.29–7.28 (2H, m), 7.26–7.20 (3H, m), 7.00–6.94 (5H, m), 5.53 (1H, s), 4.80–4.74 (2H, m), 4.61 (1H, d, *J* = 2.8 Hz), 4.15 (2H, q, *J* = 7.2 Hz), 1.20 (3H, t, *J* = 7.2 Hz).

¹³C NMR (100 MHz, CDCl₃): 170.3, 149.7, 148.4, 143.8, 140.2, 130.6, 129.2, 128.9, 128.7, 126.8, 124.7, 122.7, 122.3, 115.9, 115.1, 89.4, 82.3, 73.2, 61.9, 57.0, 14.1.

HPLC: Chiralpak AD–H (hexane/*i*-PrOH, 70/30, flow rate 1 mL/min, λ = 220 nm), *t*_R (major) = 15.8 min, *t*_R (minor) = 19.3 min; 76% ee.

5.4.3 Stereocontrolled synthesis of indanes with four stereogenic centers *via* tandem Michael – [3+2] cycloaddition reaction

5.4.3.1 General experimental procedure for the synthesis of indanes with four stereogenic centers *via* tandem Michael – [3+2] cycloaddition reaction

Corresponding aldehydes **43a–d** (0.15 mmol, 1.5 equiv.) was added to a 5 mL drum vial containing a stirring mixture of 2-[diphenyl[(trimethylsilyl)oxy]methyl]-(2*S*)-pyrrolidine **9** (1.6 mg, 0.005 mmol, 20 mol %), 1,1-bis(phenylsulfonyl)ethylene **46** (30.8 mg, 0.1 mmol) and toluene (0.6 mL, 0.17 M) at –20 °C. The reaction was stirred at this temperature for 24 hours (reaction monitored by TLC). Respective hydroxylamines **44a–g** (0.15 mmol, 1.5 equiv.) was then added to the reaction mixture and stirred at room temperature for 3 hours, unless otherwise stated. The reaction mixture was purified by flash column chromatography (hexane:EA = 85:15) yielding pure indanes **47a–j**.

5.4.3.2 Experimental data of compounds **47a–j** and **49**

(3*S*,3*aS*,8*S*,8*aR*)-Ethyl-8-(2,2-bis(phenylsulfonyl)ethyl)-1-phenyl-3,3*a*,8,8*a*-tetrahydro-1*H*-indeno[2,1-*c*]isoxazole-3-carboxylate (**47a**) (New compound)

Indane **47a** was prepared according to the general procedure from (*E*)-ethyl-3-(2-(formylmethyl)phenyl)acrylate **43a** (32.7 mg, 0.15 mmol, 1.5 equiv.) and *N*-

phenylhydroxylamine **44a** (16.3 mg, 0.15 mmol, 1.5 equiv.) to provide the title compound as a white solid (60.5 mg, 98% yield) after flash column chromatography on silica gel.

^1H NMR (400 MHz, CDCl_3): δ 7.79–7.11 (19H, m), 4.79–4.77 (1H, m), 4.51–4.48 (3H, m), 4.19–4.11 (2H, m), 4.68–3.66 (1H, m), 2.73–2.66 (1H, m), 2.57–2.50 (1H, m), 1.25 (3H, t, $J = 7.1$ Hz).

^{13}C NMR (100 MHz, CDCl_3): 170.3, 149.2, 142.9, 141.5, 138.3, 137.2, 134.9, 134.6, 130.1, 129.3, 129.3, 129.1, 128.7, 128.6, 125.1, 124.6, 124.4, 118.3, 83.4, 80.0, 76.5, 61.9, 56.0, 47.0, 31.1, 29.8, 14.2.

HPLC: Chiralpak AD–H (hexane/*i*-PrOH, 50/50, flow rate 1 mL/min, $\lambda = 220$ nm), t_R (major) = 13.0 min, t_R (minor) = 39.8 min; 98% ee.

$[\alpha]_D^{22} = -74.7$ ($c = 1.5$, CHCl_3).

HRMS (ESI) calcd for $\text{C}_{33}\text{H}_{32}\text{NO}_7\text{S}_2$, m/z 618.1620 $[\text{M}+\text{H}]$, found 618.1612.

(3*S*,3*aS*,8*S*,8*aR*)-Ethyl 8-(2,2-bis(phenylsulfonyl)ethyl)-1-(4-bromophenyl)-3,3*a*,8,8*a*-tetrahydro-1*H*-indeno[2,1-*c*]isoxazole-3-carboxylate (47b) (New compound)

Indane **47b** was prepared according to the general procedure from (*E*)-ethyl-3-(2-(formylmethyl)phenyl)acrylate **43a** (32.7 mg, 0.15 mmol, 1.5 equiv.) and *N*-(4-bromophenyl)hydroxylamine **44b** (28.2 mg, 0.15 mmol, 1.5 equiv.) to provide the title compound as a white solid (64.1 mg, 92% yield) after flash column chromatography on silica gel.

^1H NMR (400 MHz, CDCl_3): δ 7.82–7.21 (18H, m), 4.78–4.75 (1H, m), 4.51–4.43 (3H, m), 4.24–4.14 (2H, m), 3.74–3.70 (1H, m), 2.72–2.65 (1H, m), 2.58–2.51 (1H, m), 1.27 (3H, t, $J = 7.1$ Hz).

^{13}C NMR (100 MHz, CDCl_3): 170.2, 148.6, 142.7, 141.2, 138.2, 137.1, 135.0, 134.6, 132.1, 130.1, 129.4, 129.3, 129.0, 128.7, 125.1, 124.7, 119.4, 116.8, 83.4, 80.2, 68.2, 62.0, 56.0, 47.0, 29.7, 25.8, 14.3.

HPLC: Chiralpak AS–H (hexane/*i*-PrOH, 90/10, flow rate 1 mL/min, $\lambda = 220$ nm), t_R (minor) = 81.3 min, t_R (major) = 114.0 min; 96% ee.

$[\alpha]_D^{22} = -88.7$ ($c = 1.5$, CHCl_3).

HRMS (ESI) calcd for $\text{C}_{33}\text{H}_{31}\text{O}_7\text{S}_2\text{Br}$, m/z 696.0725 $[\text{M}+\text{H}]$, found 696.0716.

(3*S*,3*aS*,8*S*,8*aR*)-Ethyl-8-(2,2-bis(phenylsulfonyl)ethyl)-1-(3-chlorophenyl)-3,3*a*,8,8*a*-tetrahydro-1*H*-indeno[2,1-*c*]isoxazole-3-carboxylate (47c**) (New compound)**

Indane **47c** was prepared according to the general procedure from (*E*)-ethyl-3-(2-(formylmethyl)phenyl)acrylate **43a** (32.7 mg, 0.15 mmol, 1.5 equiv.) and *N*-(3-chlorophenyl)hydroxylamine **44c** (21.5 mg, 0.15 mmol, 1.5 equiv.) to provide the title compound as a white solid (63.2 mg, 97% yield) after flash column chromatography on silica gel.

¹H NMR (400 MHz, CDCl₃): δ 7.87–7.28 (13H, m), 7.24–7.03 (5H, m), 4.81 (1H, dd, *J* = 7.1, 3.2 Hz), 4.56–4.46 (3H, m), 4.21–4.12 (2H, m), 3.70–3.66 (1H, m), 2.71–2.66 (1H, m), 2.62–2.59 (1H, m), 1.28 (3H, t, *J* = 7.2 Hz).

¹³C NMR (100 MHz, CDCl₃): 170.2, 150.8, 142.6, 141.0, 138.2, 137.1, 135.1, 135.1, 135.0, 134.6, 130.3, 130.1, 129.4, 129.3, 129.0, 128.7, 125.0, 124.6, 123.5, 117.2, 114.6, 83.6, 80.2, 76.4, 62.1, 60.6, 55.6, 47.2, 29.8, 14.2.

HPLC: Chiralpak OD–H (hexane/*i*-PrOH, 90/10, flow rate 1 mL/min, λ = 220 nm), *t*_R (major) = 40.4 min, *t*_R (minor) = 47.2 min; 98% ee.

[α]_D²² = –102.8 (*c* = 1.5, CHCl₃).

HRMS (ESI) calcd for C₃₃H₃₁NO₇S₂Cl, *m/z* 652.1230 [M+H], found 652.1234.

(3*S*,3*aS*,8*S*,8*aR*)-Ethyl-8-(2,2-bis(phenylsulfonyl)ethyl)-1-(4-chlorophenyl)-3,3*a*,8,8*a*-tetrahydro-1*H*-indeno[2,1-*c*]isoxazole-3-carboxylate (47d**) (New compound)**

Indane **47d** was prepared according to the general procedure from (*E*)-ethyl-3-(2-(formylmethyl)phenyl)acrylate **43a** (32.7 mg, 0.15 mmol, 1.5 equiv.) and *N*-(4-chlorophenyl)hydroxylamine **44d** (21.5 mg, 0.15 mmol, 1.5 equiv.) to provide the title compound as a white solid (60.1 mg, 92% yield) after flash column chromatography on silica gel.

¹H NMR (400 MHz, CDCl₃): δ 7.81–7.21 (18H, m), 4.75 (1H, dd, *J* = 7.1, 2.9 Hz), 4.51–4.43 (3H, m), 4.22–4.11 (2H, m), 3.73–3.70 (1H, m), 2.72–2.65 (1H, m), 2.57–2.50 (1H, m), 1.28 (3H, t, *J* = 7.2 Hz).

¹³C NMR (100 MHz, CDCl₃): 170.2, 148.0, 142.7, 141.2, 138.2, 137.1, 135.0, 134.6, 130.1, 129.4, 129.3, 129.2, 129.0, 128.7, 125.1, 124.7, 119.3, 83.4, 80.2, 62.0, 60.6, 56.0, 47.0, 29.8, 21.2, 14.4, 14.3.

HPLC: Chiralpak AS–H (hexane/*i*-PrOH, 80/20, flow rate 1 mL/min, λ = 220 nm), *t*_R (minor) = 29.6 min, *t*_R (major) = 39.5 min; 98% ee.

[α]_D²² = –96.3 (*c* = 1.3, CHCl₃).

HRMS (ESI) calcd for C₃₃H₃₁NO₇S₂Cl, *m/z* 652.1230 [M+H], found 652.1237.

(3*S*,3*aS*,8*S*,8*aR*)-Ethyl-8-(2,2-bis(phenylsulfonyl)ethyl)-1-*o*-tolyl-3,3*a*,8,8*a*-tetrahydro-1*H*-indeno[2,1-*c*]isoxazole-3-carboxylate (47e**) (New compound)**

Indane **47e** was prepared according to the general procedure from (*E*)-ethyl-3-(2-(formylmethyl)phenyl)acrylate **43a** (32.7 mg, 0.15 mmol, 1.5 equiv.) and *N*-*o*-tolylhydroxylamine **44e** (18.5 mg, 0.15 mmol, 1.5 equiv.) to provide the title compound as a white solid (61.0 mg, 97% yield) after flash column chromatography on silica gel.

¹H NMR (400 MHz, CDCl₃): δ 7.67–7.29 (15H, m), 7.25–7.21 (3H, m), 4.62 (1H, dd, *J* = 7.4, 4.6 Hz), 4.50 (1H, dd, *J* = 7.2, 2.3 Hz), 4.40 (1H, d, *J* = 4.6 Hz), 4.34 (1H, dd, *J* = 7.4, 3.4 Hz), 4.13–4.09 (1H, m), 4.01–3.97 (1H, m), 3.39–3.36 (1H, m), 2.69–2.62 (1H, m), 2.39 (3H, s), 2.38–2.31 (1H, m), 1.17 (3H, t, *J* = 7.1 Hz).

¹³C NMR (100 MHz, CDCl₃): 170.6, 145.1, 143.3, 142.3, 138.3, 137.3, 136.9, 134.8, 134.6, 131.3, 129.8, 129.4, 129.2, 128.6, 128.5, 127.5, 126.8, 125.2, 124.6, 121.5, 83.1, 80.0, 74.5, 61.6, 57.6, 46.9, 30.0, 18.6, 14.2.

HPLC: Chiralpak AD–H (hexane/*i*-PrOH, 50/50, flow rate 1 mL/min, λ = 220 nm), *t*_R (major) = 8.6 min, *t*_R (minor) = 46.9 min; 95% ee.

[α]_D²² = –57.8 (*c* = 0.9, CHCl₃).

HRMS (ESI) calcd for C₃₄H₃₄NO₇S₂, *m/z* 632.1777 [M+H], found 632.1764.

(3*S*,3*aS*,8*S*,8*aR*)-Ethyl-8-(2,2-bis(phenylsulfonyl)ethyl)-1-*p*-tolyl-3,3*a*,8,8*a*-tetrahydro-1*H*-indeno[2,1-*c*]isoxazole-3-carboxylate (47f**) (New compound)**

Indane **47f** was prepared according to the general procedure from (*E*)-ethyl-3-(2-(formylmethyl)phenyl)acrylate **43a** (32.7 mg, 0.15 mmol, 1.5 equiv.) and *N*-*p*-tolylhydroxylamine **44f** (18.5 mg, 0.15 mmol, 1.5 equiv.) to provide the title compound as a white solid (60.8 mg, 96% yield) after flash column chromatography on silica gel.

^1H NMR (400 MHz, CDCl_3): δ 7.76–7.16 (18H, m), 4.15–4.68 (1H, m), 4.47–4.43 (2H, m), 4.37–4.35 (1H, m), 4.22–4.14 (2H, m), 3.66–3.61 (1H, m), 2.72–2.65 (1H, m), 2.51–2.43 (1H, m), 2.35 (1H, s), 1.27 (3H, t, $J = 7.1$ Hz).

^{13}C NMR (100 MHz, CDCl_3): 170.4, 146.5, 143.0, 141.7, 138.3, 137.2, 134.8, 134.7, 134.6, 130.1, 129.8, 129.3, 129.3, 129.2, 128.6, 128.6, 125.1, 124.7, 119.4, 83.2, 80.0, 76.9, 61.8, 56.3, 46.9, 29.8, 21.1, 14.3.

HPLC: Chiralpak AS–H (hexane/*i*-PrOH, 80/20, flow rate 1 mL/min, $\lambda = 220$ nm), t_R (minor) = 41.9 min, t_R (major) = 64.9 min; 98% ee.

$[\alpha]_D^{22} = -73.5$ ($c = 1.5$, CHCl_3).

HRMS (ESI) calcd for $\text{C}_{34}\text{H}_{34}\text{NO}_7\text{S}_2$, m/z 632.1777 $[\text{M}+\text{H}]$, found 632.1764.

(3*S*,3*aS*,8*S*,8*aR*)-Ethyl-1-benzyl-8-(2,2-bis(phenylsulfonyl)ethyl)-3,3*a*,8,8*a*-tetrahydro-1*H*-indeno[2,1-*c*]isoxazole-3-carboxylate (47g**) (New compound)**

Indane **47g** was prepared according to the general procedure from (*E*)-ethyl-3-(2-(formylmethyl)phenyl)acrylate **43a** (32.7 mg, 0.15 mmol, 1.5 equiv.) and *N*-benzylhydroxylamine **44g** (18.5 mg, 0.15 mmol, 1.5 equiv.) to provide the title compound as a white solid (57.7 mg, 91% yield) after flash column chromatography on silica gel.

¹H NMR (400 MHz, CDCl₃): δ 7.89 (4H, dd, *J* = 19.0, 7.9 Hz), 7.67 (2H, t, *J* = 7.4 Hz), 7.52–7.46 (4H, m), 7.35–7.30 (8H, m), 7.14–7.12 (1H, m), 5.27–5.25 (1H, m), 4.42–4.25 (4H, m), 4.17 (1H, d, *J* = 13.7 Hz), 4.02–3.99 (1H, m), 3.95 (1H, d, *J* = 13.8 Hz), 3.60–3.57 (1H, m), 2.78–2.71 (1H, m), 2.39–2.32 (1H, m), 1.34 (3H, t, *J* = 7.1 Hz).

¹³C NMR (100 MHz, CDCl₃): 171.9, 142.5, 141.4, 138.7, 137.1, 134.9, 134.5, 130.4, 129.4, 129.3, 129.2, 129.2, 128.7, 128.6, 128.4, 127.7, 125.1, 124.2, 83.6, 79.9, 79.4, 77.4, 62.2, 61.9, 56.3, 46.4, 29.7, 14.4.

HPLC: Chiralpak OD–H (hexane/*i*-PrOH, 70/30, flow rate 1 mL/min, λ = 220 nm),

*t*_R (minor) = 14.9 min, *t*_R (major) = 19.1 min; 98% ee.

[α]_D²² = –30.8 (*c* = 1.5, CHCl₃).

HRMS (ESI) calcd for C₃₄H₃₄NO₇S₂, *m/z* 632.1777 [M+H], found 632.1783.

(3*S*,3*aS*,8*S*,8*aR*)-Methyl-8-(2,2-bis(phenylsulfonyl)ethyl)-1-phenyl-3,3*a*,8,8*a*-tetrahydro-1*H*-indeno[2,1-*c*]isoxazole-3-carboxylate (47h**) (New compound)**

Indane **47h** was prepared according to the general procedure from (*E*)-methyl-3-(2-(formylmethyl)phenyl)acrylate **43d** (30.6 mg, 0.15 mmol, 1.5 equiv.) and *N*-phenylhydroxylamine **44a** (16.3 mg, 0.15 mmol, 1.5 equiv.) to provide the title compound as a white solid (54.2 mg, 90% yield) after flash column chromatography on silica gel.

¹H NMR (400 MHz, CDCl₃): δ 7.79–7.12 (19H, m), 4.74 (1H, dd, *J* = 7.3, 2.6 Hz), 4.50 (3H, s), 3.71 (3H, s), 3.66–3.63 (1H, m), 2.71–2.64 (1H, m), 2.55–2.48 (1H, m).

¹³C NMR (100 MHz, CDCl₃): 170.8, 148.9, 143.0, 141.5, 138.3, 137.2, 134.9, 134.6, 130.1, 129.4, 129.3, 129.3, 129.1, 128.7, 128.7, 125.1, 124.6, 124.6, 118.5, 83.3, 80.1, 76.4, 56.0, 52.7, 46.9, 30.0.

HPLC: Chiralpak AD–H (hexane/*i*-PrOH, 50/50, flow rate 1 mL/min, λ = 220 nm), *t*_R (major) = 14.9 min, *t*_R (minor) = 27.9 min; 98% ee.

[α]_D²² = –21.0 (*c* = 1.3, CHCl₃).

HRMS (ESI) calcd for C₃₂H₂₈NO₇S₂, *m/z* 602.1307 [M+H], found 602.1301.

(3*S*,3*aS*,8*S*,8*aR*)-Ethyl-8-(2,2-bis(phenylsulfonyl)ethyl)-6-methoxy-1-phenyl-3,3*a*,8,8*a*-tetrahydro-1*H*-indeno[2,1-*c*]isoxazole-3-carboxylate (47i) (New compound)

Indane **47i** was prepared according to the general procedure from (*E*)-ethyl-3-(2-(formylmethyl)-4-methoxyphenyl)acrylate **43b** (37.2 mg, 0.15 mmol, 1.5 equiv.) and *N*-phenylhydroxylamine **44a** (16.3 mg, 0.15 mmol, 1.5 equiv.) to provide the title compound as a white solid (63.4 mg, 98% yield) after flash column chromatography on silica gel.

¹H NMR (400 MHz, CDCl₃): δ 7.79–7.10 (16H, m), 6.83 (1H, dd, *J* = 8.3, 1.8 Hz), 6.72 (1H, s), 4.80–4.78 (1H, m), 4.51–4.39 (3H, m), 4.16–4.10 (2H, m), 3.80 (3H, s), 3.67–3.64 (1H, m), 2.73–2.66 (1H, m), 2.57–2.51 (1H, m), 1.24 (3H, t, *J* = 7.2 Hz).

¹³C NMR (100 MHz, CDCl₃): 170.4, 160.4, 149.2, 144.4, 138.3, 137.2, 134.9, 134.5, 133.4, 130.1, 129.3, 129.3, 129.2, 129.0, 125.8, 124.3, 118.2, 114.9, 109.6, 83.6, 80.0, 76.9, 61.8, 55.7, 55.3, 47.0, 29.7, 14.2.

HPLC: Chiralpak AD–H (hexane/*i*-PrOH, 50/50, flow rate 1 mL/min, λ = 220 nm), *t*_R (major) = 11.0 min, *t*_R (minor) = 22.8 min; 92% ee.

[α]_D²² = –33.4 (*c* = 1.0, CHCl₃).

HRMS (ESI) calcd for C₃₄H₃₄NO₈S₂, *m/z* 648.1726 [M+H], found 648.1721.

(3*S*,3*aS*,8*S*,8*aR*)-Ethyl-8-(2,2-bis(phenylsulfonyl)ethyl)- 5,6-dioxomethylenyl -1-phenyl-3,3*a*,8,8*a*-tetrahydro-1*H*-indeno[2,1-*c*]isoxazole-3-carboxylate (47j) (New compound)

Indane **47j** was prepared according to the general procedure from (*E*)-ethyl-3-(6-(2-oxoethyl)benzo[*d*][1,3]dioxol-5-yl)acrylate **43c** (39.3 mg, 0.15 mmol, 1.5 equiv.) and *N*-phenylhydroxylamine **44a** (16.3 mg, 0.15 mmol, 1.5 equiv.) to provide the title compound as a white solid (62.5 mg, 97% yield) after flash column chromatography on silica gel.

¹H NMR (400 MHz, CDCl₃): δ 7.79–7.29 (14H, m), 7.13 (1H, d, *J* = 7.0 Hz), 6.76 (1H, s), 6.63 (1H, s), 5.97 (2H, d, *J* = 8.8 Hz), 4.65 (1H, dd, *J* = 7.1, 2.7 Hz), 4.41–4.34 (3H, m), 4.19–4.11 (2H, m), 3.55–3.51 (1H, m), 2.61–2.54 (1H, m), 2.49–2.42 (1H, m), 1.25 (3H, t, *J* = 10.4 Hz).

¹³C NMR (100 MHz, CDCl₃): 170.2, 149.1, 148.4, 138.2, 137.2, 135.8, 134.9, 134.6, 134.2, 130.1, 129.4, 129.3, 129.2, 124.6, 118.5, 105.2, 105.0, 101.7, 83.3, 80.1, 76.8, 61.8, 56.0, 46.9, 30.2, 14.2.

HPLC: Chiralpak AD–H (hexane/*i*-PrOH, 50/50, flow rate 1 mL/min, λ = 220 nm), *t*_R (major) = 44.7 min, *t*_R (minor) = 51.8 min; 99% ee.

[α]_D²² = –57.2 (*c* = 1.1, CHCl₃).

HRMS (ESI) calcd for $C_{34}H_{32}NO_9S_2$, m/z 662.1519 [M+H], found 662.1515.

Methyl-6-(2,2-bis(phenylsulfonyl)ethyl)-hexahydro-1-phenyl-1*H*
cyclopenta[*c*]isoxazole-3-carboxylate (49) (New Compound)

Compound **49** was prepared according to the general procedure from (*E*)-methyl-6-formylhex-2-enoate **43e** (23.4 mg, 0.15 mmol, 1.5 equiv.) and *N*-phenylhydroxylamine **44a** (16.3 mg, 0.15 mmol, 1.5 equiv.) to provide the title compound as a white solid (52.2 mg, 94% yield) after flash column chromatography on silica gel.

1H NMR (400 MHz, $CDCl_3$): δ 7.76 (4H, dd, $J = 13.4, 7.8$ Hz), 7.63–7.58 (2H, m), 7.46 (2H, t, $J = 7.8$ Hz), 7.40 (2H, t $J = 7.8$ Hz), 7.30–7.26 (2H, m), 7.16 (2H, d, $J = 8$ Hz), 7.00 (1H, t $J = 7.3$ Hz), 4.90–4.88 (1H, m), 4.27 (1H, d, $J = 4.6$ Hz), 4.00–3.97 (1H, m), 3.57, (3H, s), 3.46–3.38 (1H, m), 2.40 (3H, s), 2.10–1.97 (2H, m), 1.76–1.68 (1H, m), 1.42–1.37 (1H, m).

^{13}C NMR (100 MHz, $CDCl_3$): 171.0, 149.6, 138.4, 137.4, 134.7, 134.5, 129.9, 129.3, 129.2, 129.2, 129.0, 123.1, 116.4, 84.0, 80.7, 75.6, 52.4, 49.9, 42.2, 30.9, 29.5, 28.3.

HPLC: Chiralpak AD–H (hexane/*i*-PrOH, 70/30, flow rate 1 mL/min, $\lambda = 220$ nm), t_R (minor) = 20.7 min, t_R (major) = 23.0 min; 94% ee.

$[\alpha]_D^{20} = -81.5$ ($c = 1.0$, $CHCl_3$).

HRMS (ESI) calcd for $C_{28}H_{30}NO_7S_2$, m/z 556.1464 [M+H], found 556.1459.

5.4.3.3 Experimental procedure and data for the synthesis of Michael adduct 50

(*E*)-ethyl 3-(2-((*S*)-1-formyl-3,3-bis(phenylsulfonyl)propyl)phenyl)acrylate (50)

(New compound)

Michael adduct **50** was prepared according to the general procedure from (*E*)-ethyl 3-(2-(formylmethyl)phenyl)acrylate **43a** (35.4 mg, 0.15 mmol, 1.5 equiv.), without the addition of hydroxylamines, to provide the title compound as a white solid (63.4 mg, 87% yield) after flash column chromatography (hexane/EA = 9/1~7/3) on silica gel.

¹H NMR (400 MHz, CDCl₃): δ 9.55 (1H, s), 8.12 (1H, d, *J* = 15.6 Hz), 7.96-7.94 (2H, m), 7.80-7.79 (2H, m), 7.73-7.64 (3H, m), 7.58 (2H, t, *J* = 7.6 Hz), 7.50 (2H, t, *J* = 7.6 Hz), 7.36 (1H, t, *J* = 7.2 Hz), 7.31-7.29 (1H, m), 6.85-6.84 (1H, m), 6.41 (1H, d, *J* = 15.6 Hz), 4.80-4.76 (1H, m), 4.46-4.43 (1H, m), 4.31-4.26 (2H, m), 2.94-2.86 (1H, m), 2.56-2.48 (1H, m), 1.33 (3H, t, *J* = 7.2 Hz).

¹³C NMR (100 MHz, CDCl₃): 198.0, 166.3, 140.7, 138.0, 137.3, 135.6, 135.0, 134.9, 133.8, 131.1, 130.2, 129.9, 129.8, 129.4, 129.4, 129.2, 128.3, 123.0, 80.2, 61.1, 52.3, 26.5, 14.5.

HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 70/30, flow rate 1 mL/min, λ = 220 nm), *t*_R (major) = 31.2 min, *t*_R (minor) = 37.6 min; 97% ee.

[α]_D²² = −51.9 (c = 1.4, CHCl₃).

HRMS (ESI) calcd for $C_{27}H_{27}O_7S_2$, m/z 527.1198 [M+H], found 527.1211.

5.4.3.4 Experimental procedure and data for the synthesis α -hydroxy- γ -amino acid derivative **51**

(*S*)-Ethyl-2-((1*S*,2*R*,3*S*)-3-(2,2-bis(phenylsulfonyl)ethyl)-2-(phenylamino)-2,3-dihydro-1*H*-inden-1-yl)-2-hydroxyacetate (**51**) (New compound)

10% Pd/C (30 mg) was added to a solution of indane **47a** (0.1 mmol) in methanol (5.0 mL) at room temperature under an atmosphere of hydrogen by means of a balloon. After stirring overnight, the mixture was filtered through Celite. Removal of the solvent from the filtrate under reduced pressure afforded the α -hydroxy- γ -amino acid derivative **51** as a white solid (60.5 mg, 98% yield).

1H NMR (400 MHz, $CDCl_3$): δ 7.91 (2H, d, J = 7.6 Hz), 7.68 (1H, t, J = 7.4 Hz), 7.55–7.49 (3H, m), 7.38 (2H, d, J = 7.6 Hz), 7.30–7.22 (7H, m), 7.04–7.03 (1H, m), 6.82 (1H, t, J = 7.2 Hz), 6.64 (2H, d, J = 7.8 Hz), 5.39 (1H, d, J = 9.1 Hz), 4.41 (1H, d, J = 9.5 Hz), 4.35 (1H, s), 4.19–4.10 (1H, m), 4.05 (1H, d, J = 7.8 Hz), 3.83–3.73 (2H, m), 3.19–3.11 (1H, m), 3.02 (1H, s), 2.77–2.72 (1H, m), 2.57–2.50 (1H, m), 0.98 (3H, t, J = 7.1 Hz).

^{13}C NMR (100 MHz, CDCl_3): 174.0, 146.1, 143.7, 140.9, 138.0, 137.2, 134.8, 134.1, 129.9, 129.7, 129.3, 129.1, 129.1, 128.4, 128.0, 124.9, 123.3, 118.3, 112.9, 79.1, 73.7, 62.3, 62.1, 49.2, 47.1, 30.0, 13.9.

HPLC: Chiralpak IA (hexane/*i*-PrOH, 90/10, flow rate 1 mL/min, $\lambda = 220$ nm), t_R (minor) = 74.4 min, t_R (major) = 96.0 min; 97% ee.

$[\alpha]_D^{21} = -42.0$ ($c = 1.6$, CHCl_3).

HRMS (ESI) calcd for $\text{C}_{33}\text{H}_{34}\text{NO}_7\text{S}_2$, m/z 620.1777 $[\text{M}+\text{H}]$, found 620.1768.

5.4.3.5 Experimental procedure and data for the synthesis α -hydroxy- γ -amino lactam **52**

(3*S*,3*aS*,8*S*,8*aR*)-8-ethyl-3-hydroxy-5,6-dioxomethylenyl-1-phenyl-3,3*a*,8,8*a*-tetrahydroindeno[2,1-*b*]pyrrol-2(1*H*)-one (**52**) (New compound)

To magnesium turnings (77.8 mg, 32 equiv.), activated by TMSCl (1 drop) and 1,2-dibromoethane (1 drop), was added dropwise a solution of indane **47j** (66.0 mg, 0.1 mmol) in anhydrous methanol (10 mL) with stirring. The mixture was heated to 50 °C to initiate hydrogen generation and then to reflux for 2 hours. After cooling down to room temperature, 2N HCl solution (10 mL) was then added and extracted with ether. The organic extracts were dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel

column chromatography (hexane/EA = 7/3) to afford the α -hydroxy- γ -lactam **52** as a pale yellow solid (15.9 mg, 47% yield).

^1H NMR (400 MHz, CDCl_3): δ 7.41-7.24 (5H, m), 7.10 (1H, s), 6.51 (1H, s), 5.93 (1H, s), 4.74 (1H, d, J = 8.6 Hz), 4.63 (1H, d, J = 5.3 Hz), 4.17 (1H, t, J = 6.9 Hz), 3.13 (1H, s), 2.95 (1H, t, J = 6.6 Hz), 1.60-1.51 (2H, m), 0.92 (3H, t, J = 7.3 Hz).

^{13}C NMR (100 MHz, CDCl_3): 172.7, 148.0, 147.3, 138.5, 137.1, 130.6, 129.3, 126.3, 123.4, 109.0, 105.2, 101.4, 72.0, 65.7, 49.6, 45.6, 27.9, 11.5.

HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 60/40, flow rate 1 mL/min, λ = 220 nm), t_R (minor) = 10.0 min, t_R (major) = 13.1 min; 94% ee.

$[\alpha]_D^{21} = -107.7$ (c = 1.0, CHCl_3).

HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{20}\text{NO}_4$, m/z 338.1892 $[\text{M}+\text{H}]$, found 338.1389.

5.5 References

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