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The Development and Application of Organocatalytic Asymmetric Michael Reactions and Domino Reactions

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School of Physical and Mathematical Sciences

A thesis submitted to the Nanyang Technological
University in fulfillment of the requirement for the
degree of Doctor of Philosophy

2010

“When heaven is about to confer a great responsibility on any man, it will test his resolution, exhaust his frame, make him suffer starvation, subject him to extreme poverty and frustrate his efforts, so as to stimulate his mind, harden his nature, and improve wherever he is incompetent.”----- 《The Mencius》

故天将降大任于斯人也，必先苦其心志，劳其筋骨，饿其体肤，空乏其身，行拂乱其所为；所以动心忍性，曾益其所不能。-----

《孟子·告子下》

献给锐意进取之人。。。。。。

Preface (Abstract)

The work embodied in this thesis was carried out from 2006 to 2009 at the Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, under the supervision of Professor Guofu Zhong.

The entire PhD work was devoted to the Organocatalytic Michael reactions and its domino reactions which is a fairly wide branch in the very young yet fast expanding field of organocatalysis.

The thesis consists of 8 chapters and is organized into 4 main parts. A brief introduction presents the current concept of asymmetric catalysis. After which, asymmetric organocatalysis (Chapter 1) is presented along with the main activations exploited during the course of my work. For a smoother and more relaxed reading, the references are given at the end and the numbering is reset at every chapter.

- Part I deals with secondary aminocatalysis: a novel rationally designed catalyst for Michael reaction of cyclic ketones to nitroolefins (Chapter 2) is followed by a domino Michael/intramolecular [3+2] nitron-olefin cycloaddition reaction (Chapter 3).
- Part II shifts the focus to the thiourea cinchona alkaloids catalyzed Michael reactions and domino Michael/Henry reaction. (Chapter 4 and 5). Each chapter demonstrates the various substrates used to emphasize the broad utility of the respective reactions. Each of these individual reactions is presented separately, with the aim to give a quick snapshot on the advancement.

- A journey around the simpler and more practical organocatalysts (Chap 5) brings the reader to the quinine-amine catalyzed Michael reaction, domino Michael/Henry and double Michael reactions which are presented in Part III. (Chapter 6 and 7)
- Part IV will describe the synthesis of a more useful structure-pyrrole via an unusual domino process to give synthetically useful multisubstituted pyrroles employing oxime as *N*-selective nucleophile (Chapter 8).

Acknowledgements

"Thunder is good, thunder is impressive," wrote Mark Twain "But it is the lightning that does the work." Many a time, it is someone's thunder which holds the credit and the attention, but another's lightning which is the main factor in one's success. The research presented here was possible thanks to a lot of people whom I shared many invaluable memories with.

First of all, I would like to acknowledge Professor Zhong for giving me the opportunity to be his first Ph. D. student in NTU and introducing me to the fascinating and challenging field of organocatalysis. I am deeply thankful to him for his continuous guidance and encouragement, and most importantly, our countless fruitful discussions, which have improved my ability to think critically. The autonomy that Prof. Zhong gave me greatly helped me reach my full potential as I had the space to explore new ideas and consequently, obtain good results.

I would also like to express my special thanks to Professor Teck Peng Loh (our former Head of CBC) for giving me the golden opportunity to be Professor Zhong's student.

I am grateful to all of my lab mates (Xiaofei Zeng, Pei Peijuan Chua, Fei Wang, Limin Yang, Min Lu, Di Zhu, Zugui Shi, Yuxuan Hou, Lu Dai, Wendy Wen Yi Leong) for providing a wonderful work atmosphere, constant help and support, especially to Xiaofei Zeng, Pei Juan Chua for their fruitful discussions and fascinating ideas during our successful collaborative works, as well as their help in improving my spoken and written English. I am thankful to my undergraduate students (Xuan Zhang,

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It gives me immense pleasure to thank all my friends, especially Jian Xiao, for many motivating discussions and interesting conversations on politics and society.

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Last, but not least, I would like to thank the person who was always there for me without any complains, anger or doubts, but unconditionally gave me her endless support, tolerance and encouragements through this long journey – my wife Fangna Cao. Saying a mere ‘thank you’ would be an insult to all her efforts. I am glad that she was willing to be always there for me. I am utterly grateful.

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Publications

1. Organocatalytic Asymmetric Tandem Michael-Henry Reactions: A Highly Stereoselective Synthesis of Multifunctionalized Cyclohexanes with Two Quaternary Stereocenters

Tan, B.; Chua, P. J.; Li, Y.; Zhong, G. *Org. Lett.* **2008**, *10*, 2437-2440.

2. Control of Four Stereocenters in an Organocatalytic Domino Double Michael Reaction: Efficient Synthesis of Multisubstituted Cyclopentanes

Tan, B.; Shi, Z.; Chua, P. J.; Zhong, G. *Org. Lett.* **2008**, *10*, 3425-3428.

3. A Highly Diastereo- and Enantioselective Synthesis of Multisubstituted Cyclopentanes with Four Chiral Carbons by the Organocatalytic Domino Michael-Henry Reaction

Tan, B.; Chua, P. J.; Zeng, X.; Lu, M.; Zhong, G. *Org. Lett.* **2008**, *10*, 3489-3492.

4. Unusual Domino Michael/Aldol Condensation Reactions Employing Oximes as N-Selective Nucleophiles: Synthesis of N-Hydroxypyrroles

Tan, B.; Shi, Z.; Chua, P. J.; Li, Y.; Zhong, G. *Angew. Chem. Int. Ed.* **2009**, *48*, 758-761.

5. Recyclable organocatalysis: highly enantioselective Michael addition of 1,3-diaryl-1,3-propanedione to nitroolefins (Cover Article)

Tan, B.; Zhang, X.; Chua, P. J.; Zhong, G. *Chem. Commun.* **2009**, 779-781.

6. Rational Design of Organocatalyst: Highly Stereoselective Michael Addition of Cyclic Ketones to Nitroolefins

Tan, B.; Zeng, X.; Lu, Y.; Chua, P. J.; Zhong, G. *Org. Lett.* **2009**, *11*, 1927-1930.

7. Rational Design of Domino Michael-Henry Reaction: Direct Construction of Bicyclo[3.2.1]octane Skeletons with Four Stereogenic Centers

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8. Water not just as a Green Solvent: One-pot Synthesis of α -Hydroxy- γ - Amino Acids Via a Domino Michael/Intramolecular [3+2] Cycloaddition Reaction

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9. A Highly Stereoselective Organocatalytic Tandem Aminoxylation/Aza-Michael Reaction for the Synthesis of Tetrahydro-1,2-Oxazines

Zhu, D.; Lu, M.; Chua, P. J.; Tan, B.; Wang, F.; Yang, X.; Zhong, G. **Org. Lett.** **2008**, *10*, 4585-4586.

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11. An Unexpected N-Heterocyclic Carbene-Catalyzed Annulation of Enals and Nitroso Compounds

Yang, L.; Tan, B.; Wang, F.; Zhong, G. **J. Org. Chem.** **2009**, *74*, 1744.

12. Highly Enantioselective L-Thiaproline Catalyzed α -Aminoxylation of Aldehydes in Aqueous Media

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13. Chiral Brønsted Acid-Catalyzed Enantioselective α -Hydroxylation of β -Dicarbonyl Compounds

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Chapter 1

INTRODUCTION

Organocatalysis

Infancy

Mature

Our endeavor

Adolescent

Organocatalysis

“Organocatalysis is catalytic reactions mediated by small organic molecule in absence of metals or metal ions.”

Carlos F. Barbas, III

“Organocatalysis is the catalysis of a reaction with an organic small molecule. By accepted convention, organic small molecule means a molecule without a metal, and not a macromolecule like protein, nucleic acid, or polymer.”

K. N. Houk

“Organocatalysis is the acceleration of a chemical transformation through addition of a sub-stoichiometric amount of an organic compound which does not contain a metal atom”

Peter I. Dalko and Lionel Moisan

These expressions are quite correct. In organic chemistry, the term “Organocatalysis” can be interpreted as the chemical processes in which the small organic molecules are active and catalyze organic reactions.

Organocatalysis--Introduction

Although first reported in the 1970s by Hajos and Wiechert groups, a highly catalytic enantioselective intramolecular aldol reaction using the simple amino acid *L*-proline (**I**) as an organocatalyst¹ remained a little more than a laboratory curiosity for almost thirty years. (Scheme 1.1)

Scheme 1.1 The Hajos-Parrish-Eder-Sauer-Wiechert reaction.

In 2000, List and coworkers expanded this reaction into intermolecular aldol reaction, which will be elaborated in the next section.² The real breakthrough in the area of organocatalysis was achieved with the discovery of this promising reaction. Since then, an explosive expansion in the area of organocatalysis was witnessed. Organocatalysts are generally air and moisture stable, non-toxic and easily available, making them viable catalysts in reactions involving water, often with beneficial consequences.³

Organocatalysis is not only impressive due to its synthetic usefulness, but also embodies the ability to gain a major role in a short time: barely 8 years! (Figure 1.1)

Figure 1.1 Number of articles published on organocatalysis (From SciFinder statistics)

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In fact, as illustrated by the statistics, it is obvious that organocatalysis has grown quite dramatically in recent years. However, the field should certainly not be considered as “mature”, and maybe not even “adolescent” as several areas are still completely unexplored. Thus, we can expect new concepts to arise within the more established ones in the future. Although some organocatalytic reactions have found uses in the pharmaceutical and chemical industries, organocatalytic reactions are generally not extensively used in the industry.

There are four major classes of organocatalysts: Lewis acids, Lewis bases, Brønsted acids and Brønsted bases. However, with the fascinating development of organocatalysis, these categories are not very clear-cut for many newly developed reactions. Thus, based on my own comprehension of organocatalysis, I will divide organocatalysis into two different types in the introduction of this thesis:

.....Single Component Activation Organocatalysis (SCAO) and

.....Dual Components Activation Organocatalysis (DCAO)

Therefore, I will focus my introduction on three aspects: **SCAO**, **DCAO** and **organocatalytic domino reactions** in accordance with my recent research.

1.1 Single Component Activation Organocatalysis (SCAO)

The formation of chiral center(s) is dependent on the steric hindrance of the substituents near the catalytic center when the catalyst interacts with only one substrate, this is called SCAO.

There are main three types of SCAO:

1.1.1 Base catalysis (The catalytic center acting as a Lewis base or Brønsted base)

In some reactions, a catalyst reacts with one of the substrates to form an iminium or enamine intermediate, in which the decrease in LUMO energy or the increase in HOMO energy will promote the reaction smoothly and control the stereochemistry selectively. In 2000, MacMillan and coworkers described the iminium ion activation of α,β -unsaturated aldehydes using a novel catalyst (**II**). Thus, the first asymmetric

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secondary amine catalyzed Diels-Alder reaction was discovered.^{4a} This type of catalyst could also be used as enamine activation of enantioselective α -chlorination of aldehydes.^{4b} (Scheme 1.2)

Scheme 1.2 Diels-Alder reaction and α -chlorination of aldehydes catalyzed by imidazolidinone.

After MacMillan's imidazolidinone catalyst was developed and used for iminium ion and enamine activation, a new type of organocatalyst based on diarylprolinol emerged as a prospective powerful iminium ion and enamine activation organocatalyst with the stereochemistry of the final product influenced by steric hindrance of the substituent beside the nitrogen atom of the pyrrolidine ring (Scheme 1.3).

Scheme 1.3 General model of enantioselectivity in the diarylprolinol ether catalyzed reactions via enamine and iminium activation.

This new class of organocatalysts was used as a new enamine activation in

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organocatalytic α -sulfonylation reaction and Michael addition reaction of aldehydes by Jørgensen's^{5a} and Hayashi's group (Scheme 1.4).^{5b}

Scheme 1.4 Diarylprolinol ethers catalyzed Michael addition and α -sulfonylation of aldehydes.

The epoxidation^{6a} and β -hydroxylation^{6b} of unsaturated aldehydes described by Jørgensen involving diarylprolinol silyl ether **IV** as efficient iminium ion activation organocatalyst. (Scheme 1.5) The epoxidation occurred via an iminium ion intermediate and steric hindrance of the diarylmethyl group pushes hydrogen peroxide to attack from the less hindrance direction. Using easily available oximes as Michael donors, the corresponding chiral carbonyl β -oxime ethers were afforded with good results compared to the previous reports when using organocatalyst **IV** as an iminium ion activation catalyst after activating α,β -unsaturated aldehydes.

Scheme 1.5 Epoxidation and β -hydroxylation catalyzed by **IV**.

Building on the established capacity of enamines and iminium ions to rapidly

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interconvert via a redox process (enamine has four π -electrons and iminium has two π -electrons), MacMillan and co-workers introduced a SOMO (Singly Occupied Molecular Orbital) catalysis which is a very important complementarity to enamine and iminium activation and this model utilized the cationic radical intermediate through oxidation of the enamine intermediate to form the transient three π -electron radical-cation species that can function as a generic platform of induction and reactivity. The first example of enantioselective α -allylation aldehyde involving SOMO activation was reported in *Science*.^{7a} (Scheme 1.6) Following the pioneering work, many other transformations have been reported by using SOMO activation.⁷ (Scheme 1.7)

Scheme 1.6 Enantioselective α -allylation aldehyde by SOMO activation.

Scheme 1.7 The SOMO activated α -functionalization of aldehydes.

Quite recently, a direct asymmetric benzoyloxylolation of aldehydes with benzoyl peroxide was found to be catalyzed by a newly designed catalyst **VI**.⁸ (Scheme 1.8) This method which also involves SOMO activation, provides a new approach for the preparation of optical 1,2-diol which were very useful chiral building blocks in natural

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product synthesis.

Scheme 1.8 Direct asymmetric benzoyloxylation of aldehydes catalyzed by **VI**.

1.1.2 Ion Pair catalysis (The key intermediate is formed as an ion pair)

Phase transfer catalysts are very useful catalysts for highly enantioselective reactions due to its three distinctive characteristics of the pairing cation (Q^+): good organic solubility, large ionic radius and readily structural modification. The steric hindrance of Q^+ can interact with the anionic substrate by ion pair interaction. Recent efforts have led to remarkable breakthroughs,⁹ which has made it possible to carry out numerous reactions under ambient conditions using phase-transfer catalysis (PTC).

Figure 1.2 Tetraalkylonium salts (phase-transfer catalysts) as single component mode catalyst.

Cinchona alkaloid derivatives were developed to be general useful phase-transfer catalysts for various chemical transformations under phase-transfer catalyzed conditions, even though there are immense challenges in rationally designing and modifying catalysts to achieve adequate selectivity and reactivity. A recent published example by Dixon and coworkers showcased the use of PTC **VII** to develop the first highly enantioselective aziridine alkylation reaction (Scheme 1.9)¹⁰ and this further documented the application. Maruoka and coworkers synthesized a chiral

Chapter 1 Introduction

spiroammonium salt **VIII**, as a novel C2-symmetric phase-transfer catalyst through changing the backbone of catalytic center. In order to demonstrate the activity and efficiency of the newly designed catalyst, the standard compared reaction α -alkylation reaction was applied for testing under mild phase-transfer conditions.¹¹

Scheme 1.9 Enantioselective alkylation reactions under phase transfer catalysis.

Although the use of ammonium salts has been successfully applied, the design and synthesis of new classes of PTCs have been a long withstanding challenge. Following the success of chiral spiroammonium salts of type **VIII**, Maruoka's group later successfully developed a chiral phosphine containing salt **IX** to catalyze the conjugated addition of 3-aryloxindoles and methyl vinyl ketone with remarkably high stereoselectivity.¹² (Scheme 1.10)

Scheme 1.10 Chiral phosphonium catalyzed Michael addition of 3-aryloxindoles.

Inspired by the Maruoka's strategy of replacing the nitrogen center with phosphine,

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Ooi and coworkers used tetraamino instead of tetraalkyl, and designed a chiral tetraaminophosphonium salt **X** with a spirocyclic core. The newly designed phosphonium salt was applied to catalyze the asymmetric direct nitro aldol reaction with good yields and highly enantioselectivity.^{13a} When they further changed the backbone of the tetraaminophosphonium salt, arylaminophosphonium salt **XI** as fresh cationic catalysts was first developed to conduct the Michael addition reaction of arylamines to nitroolefins with amazing and exciting results.^{13b} (Scheme 1.11) These studies demonstrated that changing functional group and catalytic center at the chiral phase-transfer catalysts should be promising ways to discover new reactions.

Scheme 1.11 Chiral aminophosphonium salts catalyzed Henry reaction and Michael reaction.

1.1.3 Acid catalysis (The catalytic center acting as a Lewis acid or Brønsted acid)

From the above mentioned, base and salt could be used in **SCAO** as efficient catalysts for many types of reactions. However, there are no report regarding the use of acids until List and coworkers discovered a powerful new chiral disulfonimide catalyst **XII** that was designed for the enantioselective Mukaiyama aldol reaction in 2009.¹⁴ (Scheme 1.12) The astonishing good results illustrated the highly potential of this type of catalysts to discover many new reactions in the near future.

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Scheme 1.12 Mukaiyama aldol reaction catalyzed by disulfonimide.

1.2 Dual Components Activation Organocatalysis (DCAO)

The formation of chiral center(s) is dependent on the interactions produced when the catalyst interacts with two substrates on different catalytic centers, this is called DCAO.

Coordination of the two substrates would result in a stronger stereo-discrimination, thereby giving rise to a highly enantioselective process. Analogous to assembling a specific instrument, our two hands must abide by the inherent model to catch the components (Figure 1.3).

Figure 1.3 General concepts of dual model activation organocatalysis.

1.2.1 Lewis base and Brønsted acid catalysis

Based on the dual activation model, the first catalyst that must be mentioned is a very simple amino acid *L*-proline (**I**). In 2000, List, Barbas and Lerner discovered that a

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catalytic amount of *L*-proline promoted the enantioselective intermolecular aldol reaction of a ketone and aldehyde (Scheme 1.13).² In this process, pyrrolidine nitrogen acted as a Lewis base center for interacting with ketone and the acid group acted as Brønsted acid center to catch the aldehyde. Today, we can say this discovery awakened the sleeping dragon (organocatalysis) and many chemists ride on the initial burst of energy, hoping to uncover some interesting and amazing aspects of this powerful and potential field.

Scheme 1.13 Proline catalyzed intermolecular aldol reactions.

Followed by this pioneer work, the first direction is to develop many other pyrrolidine derivatives for several types of reactions.¹⁵ (Figure 1.4) The use of pyrrolidine sulfonamide organocatalyst **XIII** to promote highly efficient, enantioselective Michael addition reactions of aldehydes and ketones to nitroolefins was discovered by Wang and coworkers.^{16a} In 2006, Tang and coworkers developed a pyrrolidine thiourea organocatalyst (**XIV**) for the transformation of cyclohexanone and nitroolefins with excellent diastereo- and enantioselectivity.^{16b} (Scheme 1.14) This catalyst exhibits a high catalytic activity due to pyrrolidine acting as a very efficient unit to activate the ketone or aldehyde and the thiourea part recognising the nitro group by multiple hydrogen bonds. This is the first report of combining with two efficient catalytic centers to catalyze the Michael addition reactions.

Figure 1.4 Some pyrrolidine derivated catalysts.

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Scheme 1.14 Pyrrolidine thiourea catalyzed the Michael reactions.

After the successful examples of changing the Brønsted acid unit as shown in Scheme 1.14, a new family of phosphinthiourea catalysts **XV** was developed for the highly enantioselective synthesis of 2-aryl-2,5-hydropyrroles via a [3+2] cycloaddition of an electron-deficient allene with aryl and heteroaryl diphenylphosphinoylimines by changing the Lewis base center from nitrogen to phosphine.¹⁷ (Scheme 1.15) The displayed high reactivity and enantioselectivity was due to the dual activation of both nucleophile and electrophile by the bifunctional catalyst.

Scheme 1.15 Phosphinthiourea catalyzed [3+2] cycloaddition.

Recently, by changing the connecting backbone of the two catalytic centers as compared to Jacobsen's catalyst, Shi established an efficient bifunctional chiral phosphine catalyst (**XVI**). (Scheme 1.16) The efficiency was shown in the reaction of Morita–Baylis–Hillman (MBH) acetates with 2-trimethyl-silyloxy furan which provide an easy access to optically active γ -butenolides under mild conditions.¹⁸

Scheme 1.16 Chiral phosphine amide catalyzed allylic substitution reactions.

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1.2.2 Brønsted base and Brønsted acid catalysis

The above mentioned catalysts have a common character: the Lewis base center needs to react with one substrate by covalent bond for the purpose of activating the substrate. This brings us to question: What about non-covalent bond catalytic center? This may also act as an efficient organocatalyst to some other types of reactions. In 2003, Takemoto and coworkers developed a tertiary amine and thiourea-based bifunctional organocatalyst **XVII** for the enantioselective Michael addition of malonates to nitroolefins (Scheme 1.17).¹⁹ This type of catalyst is an elegant combination of the Brønsted acidic thiourea and a Brønsted basic tertiary amine. The two functionalities combining in a single chiral environment is the main reason to explain the highly efficient and high enantioselectivities results of the Michael addition.

Scheme 1.17 Asymmetric Michael addition of malonate to nitroolefins involving a bifunctional thiourea catalyst.

Following the report of Takemoto, a number of thiourea-tertiary amine bifunctional organocatalysts for a wide array of asymmetric transformations with good results in most cases were reported by changing the connecting backbone.²⁰ Among all these bifunctional catalyst, the cinchona alkaloids with thiourea moiety (Figure 1.6) which were independently developed by the groups of Soós, Connon, and Dixon were most attractive due to the relatively simple synthesis and the versatile usefulness for many asymmetric successfully transformations²¹ (Scheme 1.18) such as the addition of malonates to nitroalkenes,^{20d} addition of nitromethane^{20a} and malonates to chalcones,^{21a} Friedel-Crafts reaction of indoles with imines,^{21b} conjugate addition of vinyl sulfones,^{21c} and Mannich reaction of malonates.^{21d} Hiemstra and co-workers²² further developed the utility of the cinchona alkaloid backbone by replacing the phenolic functional group with a thiourea to yield 6'-thiourea-substituted cinchona alkaloid derivative (**XVIIIe**), which serves as an

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effective enantioselective catalyst for addition of nitromethane to carbonyl compounds (the Henry or nitroaldol reaction).

Fi

Figure 1.6 Bifunctional cinchona alkaloids with thiourea moiety.

Scheme 1.18 The reaction scope catalyzed by thiourea derivatives of cinchona alkaloids.

Based on the above mentioned, thioureas represented a dominant platform for hydrogen bond promoted asymmetric **DCAO** catalysts. A large number of reactions have been successfully promoted by chiral thiourea catalysts. Considering that the thiourea unit only catches substrates through multiple hydrogen bonds, thus other units also can activate the substrates if they can provide hydrogen bond. This was proven by the following example which reported the use of squaramides (**XIX**) as a highly

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effective new scaffold for the development of chiral hydrogen bond donor **DCAO** catalysts. (Scheme 1.19) The results presented below showed the squaramide unit to be an effective scaffold on which chiral H-bond donor catalysts was built on. The modular nature of the catalyst provides a general method of designing new organocatalysts by tuning the pKa of the hydrogens.

Scheme 1.19 Michael reaction catalyzed by a squaramide derivative catalyst.

By changing the pKa of the hydrogen, Deng and coworkers demonstrated that a new type of readily accessible bifunctional chiral catalyst (**XX**) (Figure 1.7) based on the quinine and quinidine via demethylation reaction was born (Scheme 1.20) and these catalysts have been shown to catalyze highly enantioselective Michael reaction,^{24a} amination of α -substituted α -cyanoacetates,^{24b} Henry reaction,^{24c} Friedel-Crafts reaction,^{24d} and Diels-Alder reaction.^{24e} Tan and coworkers also made use of the advantage of tuning the pKa of the hydrogen on organocatalyst to develop an efficient and atom economical reaction, which proceeded through a conjugate addition and protonation sequences to catalyze the Michael addition of phthalimidoacrylates to thiols with high enantioselectivities using chiral bicyclic guanidine **XXI**.²⁵ In this catalyst the hydrogen bond was provided by a common amine, which is complementary to the thiourea catalyst. This type of useful catalysts can also be applied to other types of reactions, such as the Michael reaction, the Mannich reaction.²⁶

Figure 1.7 Deng's catalysts for asymmetric reactions.

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Scheme 1.20 Chiral bicyclic guanidine catalyzed the tandem conjugate addition-enantioselective protonation reaction.

1.2.3 Brønsted acid catalysis

In 2003, Rawal and co-workers reported a highly enantioselective hetero-Diels-Alder (HDA) reaction catalyzed by a TADDOL derivative **XXII** (Scheme 1.21).²⁷ This simple chiral alcohol used hydrogen bonding to catalyze an important family of cycloaddition reactions of a diene with various aldehydes with highly stereocontrolled results. These results indicated that the Brønsted acid has broad potential for **DCAO** in asymmetric synthesis.

Scheme 1.21 Asymmetric hetero-Diels-Alder reaction catalyzed by diol.

Diol is well-known as a very weak Brønsted acid catalyst, and its ability for limited interaction with the substrates indicated that this type of catalysts can only catalyze certain reactions. Thus, a stronger Brønsted acid emerged to match the demand of fast development in the field of organocatalysis. Phosphoric acids **XXIII** (Scheme 1.22) for the activation of imines was established by Terada and Akiyama independently in 2004.²⁸ These relatively strong chiral Brønsted acid catalysts containing a particularly successful backbone were used in many other transformations. Later on, Nakashima and Yamamoto²⁹ designed more acidic N-triflyl phosphoramides catalysts and greatly widened the substrate scope.

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Scheme 1.22 The chiral phosphoric catalysts of Terada and Alkiyama.

We have seen how weak Brønsted acid diol and strong Brønsted acid phosphoric acid can promote reactions smoothly, one question remains: what about the carboxylic acid? Carboxylic acid's acidity is in between diol and phosphoric acid, so I think that such catalyst may be suitable for some types of reactions. In 2007, Hashimoto and Maruoka proved the truth of this assumption. They established a novel chiral dicarboxylic acid (**XXIV**) catalyzed asymmetric Mannich reactions of diazo compounds to imines.³⁰ (Scheme 1.23)

Scheme 1.23 Asymmetric Mannich reaction catalyzed by dicarboxylic acid.

1.3 Organocatalytic Domino Reactions

Organocatalytic domino reactions are highly efficient to construct complicated molecules in a biomimetic way which are frequently used in natural product synthesis. The advantages include avoidance of further purification of the intermediates, shorter reaction steps, greener reaction conditions, and construction of multiple stereogenic centers with high stereochemistry. Due to these advantages, organocatalytic domino reactions is a thriving field in organic chemistry.³¹

Organocatalytic domino reactions are growing more and more consideration and there have been a large number of publications on such reactions reported in recent years.^{31b} The following introduction aspires to account the progress on organocatalytic

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domino reactions according to our two main categories of catalysis.

1.3.1 SCAO catalyzed domino reactions

The iminium-enamine approach is widely used in discovering innovative asymmetric organocatalytic domino reactions. All reactions applying this idea make use of enal or enone systems and one nucleophile and one electrophile. The enal/enone is activated towards nucleophilic Michael addition using a secondary or primary amine to form an iminium-ion species. Subsequently, the enamine intermediate reacts with an electrophile to give products with at least two new stereocenters (Scheme 1.24).

Scheme 1.24 Domino iminium – enamine activation catalyzed reaction

Nu = nucleophiles, E = electrophiles.

Pioneering work of this strategy was firstly discovered by Barbas in 2000, as demonstrating the first designed organocatalytic iminium-enamine domino asymmetric Robinson annulations reaction.^{32a} Five years later, Jorgensen and co-workers^{32b} developed the organocatalytic asymmetric conjugate thiol addition/amination reaction where two stereoselective steps are made intermolecular due to the use of the iminium-enamine activation strategy using secondary amine **III** as the organocatalyst (Scheme 1.25).

Scheme 1.25 Organocatalytic domino sulfa-Michael addition/amination.

Another milestone was achieved in organocatalysis when Enders and coworkers disclosed a three-component domino reaction to synthesize multisubstituted cyclohexene derivatives. The key step was a Michael/Michael/aldol condensation

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sequence which led to the formation of three C-C bonds in one pot with only one catalyst. (Scheme 1.26)³³

Scheme 1.26 Secondary amine catalyzed domino Michael/Michael/aldol reaction.

In 2006, Wang reported an organocatalytic enantioselective domino Michael-aldol reaction, promoted by diarylprolinol ether (**III**) to prepare synthetically useful chiral thiochromenes with high yields and good to high enantioselectivities.³⁴ (Scheme 1.27) A broad range of α,β -unsaturated aldehydes and 2-mercaptobenzaldehydes can be tolerated. In this process only two substrates were used, unlike previous examples by Jorgensen and Enders. In this case, one of the substrate first acted as a nucleophile for the first step and then it became an electrophile for the next step. Such approach usually provides a very useful strategy to construct ring system.

Scheme 1.27 Tandem Michael/aldol reaction.

Just like the same catalytic model as secondary amine catalyzed domino reaction, the primary amine **XXV** also can perform iminium-enamine activation. (Scheme 1.28) This was displayed in a chiral primary amine catalyzed double Michael addition

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reaction which provides a new avenue for the achievement of stereochemical and structural complexity.³⁵

Scheme 1.28 Primary amine catalyzed double Michael reaction.

1.3.2 DCAO catalyzed domino reactions

The **SCAO** catalyzed domino reactions in above examples displayed that the catalyst is essential to each steps; on the contrary, the **DCAO** catalyzed domino reaction, in which the catalyst usually only plays a significant role in the first step. This made the design of new reactions and new catalysts more difficult. However, with the rapid development in organocatalysis, such problems seem less daunting and many of these problems are often met with timely solution, and thus, many publications have been producing in the recent years.

Our group discovered a new domino aminooxylation-Michael addition reaction for the creation of multi-substituted tetrahydro-1,2-oxazines by using L-proline and a rational designed substrate.³⁶ (Scheme 1.29)

Scheme 1.29 Domino aminoxylation-Michael reaction.

Wang disclosed a highly stereoselective one-pot double Michael reaction catalyzed by a cinchona alkaloid thiourea **XVIIIa** to afford highly enantioselective thiochromanes containing three chiral centers in very high efficiency.³⁷ (Scheme 1.30) Furthermore, the determination of a new activation mode of the chiral tertiary amine

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thiourea catalyzed dynamic kinetic resolution (DKR) for this domino reaction has been carried out.

Scheme 1.30 Domino double Michael reaction.

Gong described the use of cinchona alkaloid derivatives **XXVI** in the [3+2] cycloaddition of isocynoesters with nitroolefins to afford products with high stereoselectivities.³⁸ (Scheme 1.31) This reaction serves as an easy way to obtain polysubstituted enantiopure heterocyclic compounds.

Scheme 1.31 Domino cycloaddition reactions.

In 2007, Terada and coworkers developed an efficient and highly diastereo and enantioselective domino aza-ene type reaction/cyclization using a chiral monoposphoric acid catalyst and a one pot entry to piperidine derivatives.³⁹ (scheme 1.32) The domino transformations can be widely applied by simple enecarbamates and a broad range of aldimines to produce complex molecules.

Scheme 1.32 One-pot entry to piperidine derivatives via domino aza-ene type reaction/cyclization.

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Quite recently, Zhu and coworkers successfully developed the first catalytic enantioselective three-component Povarov reaction.⁴⁰ (Scheme 1.33) A wide variety of aromatic and aliphatic aldehydes as well as anilines with different electronic properties were tolerated. This approach combines the advantages of both MCRs and organocatalysis, leading to a highly efficient synthesis of enantiomerically pure tetrahydroquinolines.

Scheme 1.33 Brønsted acid catalyzed one pot Povarov reaction.

Our group also developed several domino reactions which will be reported in the upcoming chapters.

1.4 Summary

After this brief introduction on organocatalysis, it should be obvious to the reader that both single component activation and dual components activation catalysis offer a unique platform for the development of new reactions and methodologies. SCMO forms a chiral pocket around the intermediate and brings it into contact with the electrophile and nucleophile. These can be easily derivatised to fine-tune their characteristics in order to produce better steric hindrance and modulate the activation of the reagents which may result in less screening. On the other hand, DCAO gives easy access to the complex molecules. Their model of action and mechanism is harder to understand than single component activation organocatalysis. Therefore we must screen a lot of possible catalysts and the outcomes of such screening can be less predictable. Furthermore, different activations models allow us to design domino reactions which are at the forefront of current research. The attractiveness of organocatalytic domino reaction is further emphasized by the very mild reaction conditions and simple operational procedures.

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1.5 Reference

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Chapter 2

RATIONAL DESIGN OF SECONDARY AMINE ORGANOCATALYST

Rational Design of Organocatalyst: Highly Stereoselective Michael Addition of Cyclic Ketones to Nitroolefins

2.1 Background

As we all known, only by careful consideration and modification of the catalyst structure, a good stereocontrolled product can be obtained during the course of a new bond formation. When the catalyst structure changed a little, the action of the catalyst can often lead to huge and unexpected differences, especially related to the stereoselectivity.¹

Most of the attempted that aimed to attain asymmetric versions of this reaction through the use of chiral organocatalysts not only gave moderate enantioselectivity, but also required low temperature, additive and a large excess of organic solvents.^{2,3} Since the millennium, the use of numerous pyrrolidine-type organocatalysts have been widely adopted.^{4,5,6} (Figure 1) These cyclic secondary amines are considered synthetically practical scaffolds. Below are the general strategies used by researchers previously to control the selectivity of catalysts.

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Figure 1. Reported pyrrolidine-type organocatalysts.

So far, the discovery of robust organocatalysts and more practical approaches in Michael conjugate additions to achieve higher enantio- and diastereoselectivity is still a major challenge. As such, we have developed and designed a set of new catalysts to overcome the challenge. Thus, our design of catalyst **II** comprises of this “privileged” pyrrolidine covalently bonded to a phosphate moiety.⁷(Scheme 1) In order to test the feasibility of the above-mentioned catalysts, nitroolefins were chosen as Michael acceptors due to their polar nitro group. The strong polar P=O may interact favorably with the nitro group via dipole interactions mediated by water to allow greater control in enantio- and diastereoselectivity. (Figure 2)

Scheme 1. Synthesis of newly designed catalysts.

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Figure 2. The structures and action of designed catalysts.

2.2 DFT calculations

Based on these hypotheses, DFT calculations were carried out. Two transition state geometries are reported to demonstrate the fact that hydrogen bonds formed with water molecule are one of the important factors to control the stereochemistry (Figure 3). **TS1** is a transition state from *syn*-enamine as **TS2** is a transition state from *anti*-enamine. In **TS1**, the forming C-C bond length between enamine and nitrostyrene is 1.9901 Å, and the C=C bond of the nitrostyrene is elongated to 1.4205 Å; and hydrogen bond distance mediated by water is reasonable. In gas phase, the energy of **TS1** is 4.36 kCal/mol lower than that of **TS2** due to the fact that the bulky phosphine group has less steric interaction with the six-member ring in the *syn*-enamine.

Figure 3. The DFT calculated transition state **TS1** (left) and **TS2** (right).

2.3 Results and discussion

Orienting experiments were conducted with nitrostyrene as a Michael acceptor and cyclohexanone.⁸ Initially, the conjugated addition reaction was examined in several solvents at room temperature with catalyst **II**. Only moderate yield of the desired adduct was observed in polar solvents (Table 1, entries 4-6), whereas moderate to excellent yields with excellent enantioselectivities of the product were observed in non-polar solvents such as benzene and hexane (Table 1, entries 2-3). Although the addition of catalyst loading of up to 30 mol% could dramatically increase the reaction rate (entry 10) without affecting the yield, the diastereoselectivity and enantioselectivity dropped from 99% to 96%. When the reaction was tested under solvent free condition, we could achieve almost quantitative yield with over 99% enantiomeric excess (ee) and over 99:1 diastereomeric ratio (dr).

This initial finding strengthened our suggestion that the polar bond P=O of the new catalyst is an important role for the addition reaction to proceed. To further investigate

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the effects of dipole interaction, we have tested chiral catalysts **I** (without any polar bond) and **III** (bearing P=S bond). Although moderate yield and dr was obtained when non-polar bond catalyst **I** was used (Table 1, entry 9), there was almost no ee detected in the product. When the catalyst **III** containing a weaker polar bond (P=S) was utilized, the yield was excellent but the dr and ee are somewhat slightly decreased (Table 1, entry 8). These results further demonstrated that the P=O bond in catalyst **II** is indispensable in achieving excellent diastereoselectivity and enantioselectivity.

Table 1. Effect of Solvents and Catalysts on the Reaction between Cyclohexanone and *trans*-Nitrostyrene^a

1a + 2a $\xrightarrow[\text{solvent, rt.}]{15 \text{ mol\% catalyst}}$ 3a

entry	catalyst	solvent	t (h)	yield (%) ^b	dr ^c	ee (%) ^d
1	II	CH ₂ Cl ₂	24	67	99/1	99
2	II	benzene	24	86	>99/1	>99
3	II	hexane	24	98	>99/1	>99
4	II	DMSO	24	41	97/3	90
5	II	MeOH	24	62	97/3	94
6	II	THF	24	61	98/2	98
7	II	neat	16	99	>99/1	>99
8	I	neat	16	77	95/5	17
9	III	neat	16	99	97/3	91

^a Unless otherwise noted, all reactions were conducted using nitroolefin **2a** (0.3 mmol, 1 eq) and cyclohexanone (1.5 mmol, 5 eq) with 15 mol% catalyst loading at room temperature. ^b Isolated yield. ^c Determined by ¹H NMR of the crude mixture or HPLC. ^d Determined by chiral HPLC analysis (chiralpak AS-H, hexane/2-propanol = 85/15, 1 mL/min). ^e 30 mol% catalyst **II**.

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Table 2. The Michael Addition of Cyclohexanone with Nitroolefins Catalyzed by **II** under Neat Condition at Room Temperature^a

entry	reactant (R)	product	time (h)	yield (%) ^b	dr ^c	ee (%) ^d
1	C ₆ H ₅		16	99	>99/1	>99
2	2-OCH ₃ -C ₆ H ₄		24	96	>99/1	97
3	3,4-methylene dioxo-C ₆ H ₃		18	92	>99/1	>99
4	3-CH ₃ -C ₆ H ₄		24	98	>99/1	98
5	2-CH ₃ -C ₆ H ₄		26	95	>99/1	98
6	2-Furanyl		14	97	>99/1	>99
7	3-Furanyl		13	98	99/1	98
8	4-Br-C ₆ H ₄		13	97	>99/1	99
9	4-Cl-C ₆ H ₄		17	96	98/2	98
10	2-Cl-C ₆ H ₄		24	93	99/1	99

^a Unless otherwise noted, all reactions were conducted using nitroolefin (0.3 mmol, 1 eq) and cyclohexanone (1.5 mmol, 5 eq) in the presence of 15 mol% of catalyst **II** under neat condition at room temperature. ^b Isolated yield. ^c Determined by ¹H NMR of the crude mixture or HPLC. ^d Determined by chiral HPLC analysis.

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With the optimized conditions have been constructed, a variety of nitroolefins with different structures were explored. From the results displayed in Table 2, we can see that different nitroolefins reacted efficiently with cyclohexanone and obtained excellent yield, diastereoselectivities and enantioselectivities (entries 1-10). In general, aryl compounds containing electron-withdrawing and electron-donating substituents influenced the result slightly, especially in dr (up to >99/1) and ee (up to >99%). Excellent enantioselectivities achieved for the heteroaryl-substrate (Table 2, entries 5-7) have also indicated that they are good Michael acceptors to cyclohexanone. Furthermore, other cyclic ketones (**1b**, **1c**) also reacts smoothly with nitroolefin and maintain excellent stereoselectivities. (Scheme 3)

Based on the experimental results described above, the stereochemical outcome may be accounted for by a synclinal transition state assembly. We propose that the pyrrolidine ring would first react with a carbonyl compound to form an enamine. Subsequently, the P=O via a strong H-bond mediated by water, will orientate the nitro group so that the enamine will attack the nitroolefin from the *Re*-face to give highly enantio- and diastereoselective product. This explanation was consistent with the observed experimental results. We believe that electronic influence of the polarity of the reactants has a significant role in the determination of enantio- and diastereoselectivity of products. The absolute configuration of **3h** was determined by X-ray crystallography (Figure 4).

Scheme 3. Different Ketones Reacted With *trans*-Nitrostyrene.

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Figure 4. X-ray crystal structure of **3h**.

Performing such reactions on water could potentially give rise to ideal reactions from the green chemistry's perspective. Our first attempt on water,⁹ although the stereoselectivity doesn't change too much, low conversion and yield were also observed using catalyst **II**. When brine was used as a solvent, excellent yield and a high level of diastereo- and enantioselectivities were provided. In these electrolyte rich aqueous solutions, the anion intermediate is readily complexed by metal cations, which may attribute to the result (Scheme 4).

Scheme 4. Michael Reaction in Aqueous Medium.

2.4 Conclusion

We have developed a remarkably active organocatalyst that facilitates the excellent stereoselective (98:2->99:1 dr, 92->99% ee) Michael addition of cyclohexanone to nitroolefins, hence producing various types of optically active nitroalkane derivatives of synthetic and biological importance.¹⁰ The new catalyst containing a pyrrolidine unit and a phosphate moiety is proved to be very important in controlling the practical operational procedure that involves the mixing of reactants with catalyst at room

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temperature increases the attractiveness of this reaction. We hope that more efficient and practical catalysts could be designed based on the nature of the reaction and may this strategy be the leader for a range of enantiomeric reactions that involves rationally designed catalysts?

2.5 Experimental section

General experimental conditions

Thin layer chromatography (TLC)

Merck 60 F254 precoated silica gel plate (0.2 mm thickness).

The spots were visualized in UV-light ($\lambda = 254$ nm)

Stained with iodine, basic solution of potassium permanganate or acidic solution of ceric molybdate, followed by heating on a hot plate.

Analytical high performance liquid chromatography (HPLC)

Shimadzu LC-20AD

Materials: *Daicel* Chiralpak AD-H column (0.46 cm $\times$ 25 cm), Chiralpak AS-H (0.46 cm $\times$ 25 cm), Chiralcel OD-H (0.46 cm $\times$ 25 cm), *Daicel* Chiralcel OJ column (0.46 cm $\times$ 25 cm)

Nuclear magnetic resonance spectroscopy (NMR)

Proton nuclear magnetic resonance spectra (^1H NMR) were recorded on Bruker AMX 300, 400, 500 NMR spectrometers. Chemical shifts for ^1H NMR spectra are reported as δ in units of parts per million (ppm) downfield from SiMe_4 (δ 0.0) and relative to the signal of chloroform-d (δ 7.26, singlet). Multiplicities were given as: s (singlet), d (doublet), t (triplet), dd (doublets of doublet) or m (multiplets). The number of protons (n) for a given resonance is indicated by nH. Coupling constants are reported as a J value in Hz. Carbon nuclear magnetic resonance spectra (^{13}C NMR) are reported as δ in units of parts per million (ppm) downfield from SiMe_4 (δ 0.0) and relative to the signal of chloroform-d (δ 77.0, triplet).

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High resolution mass spectrometry (HRMS)

Finnigan MAT 95XP spectrometer (GC) and

Waters Micromass Q-ToF Premier Mass spectrometer (LC).

X-Ray structure analysis (X-RAY)

Bruker X8 APEX X-ray diffractionmeter

Specific rotation ($[\alpha]$)*Schmidt + Haensdch* polarimeter (Polartronic MH8)1 cm cell (c given in g/100 mL).**2.5.1 Synthesis of new catalysts:** **(S)-2-(Diphenylphosphinomethyl) pyrrolidine (I)**

(S)-N-(*tert*-Butoxycarbonyl)-2-(diphenylphosphinomethyl) pyrrolidine (0.74 g, 2 mmol), as dissolved in trifluoroacetic acid (2 mL) and CH_2Cl_2 (6 mL) at room temperature and the solution was stirred for 12 h. The trifluoroacetic acid was then removed in vacuo to afford (S)-2-(diphenylphosphinomethyl) pyrrolidinium trifluoroacetate. The salt was first dissolved in CH_2Cl_2 and extracted with water (20 mL $\times$ 2). 10% Aqueous ammonia was then added to the aqueous layer. The mixture was stirred for 10 min and then extracted with CH_2Cl_2 (20 mL $\times$ 3). The organic layer was washed with brine, dried over anhydrous Na_2SO_4 , and concentrated under reduce pressure to afford (S)-2 (diphenylphosphinomethyl) pyrrolidine (0.45 g, 86%).

^1H NMR (400 MHz, CDCl_3): δ 7.46-7.31 (m, 10H), 6.47 (br, 1H), 3.20-3.11 (m, 2H), 3.01-2.96 (m, 1H), 2.56 (dd, $J = 6.4, 13.6$ Hz, 1H), 2.33 (dd, $J = 8.0, 13.2$ Hz, 1H), 2.18-2.02 (m, 1H), 1.93-1.90 (m, 1H), 1.81-1.78 (m, 4 H), 1.61-1.56 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 137.7, 132.7, 128.9, 128.6, 57.2, 45.5, 33.8, 32.3, 24.6. ^{31}P { ^1H } NMR (CDCl_3 , 161.9 MHz): δ -21.2; HRMS (EI) calcd for $\text{C}_{17}\text{H}_{20}\text{NP}$, m/z

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269.1328, found 269.1323; $[\alpha]_D^{25} = -36.2$ ($c = 1.2$, CH_2Cl_2).

(S)-2-((Diphenylphosphoryl) methyl) pyrrolidine (II)

(S)-N-(*tert*-Butoxycarbonyl)-2-(diphenylphosphinomethyl) pyrrolidine (1.1 g, 3 mmol) was dissolved in CH_2Cl_2 (6 mL) and 30% hydrogen peroxide (3 mL) was then added. After being stirred for 30 minutes, the solution was extracted with CH_2Cl_2 (20 mL $\times$ 2) and the organic layer was concentrated under reduce pressure to obtain the crude product. Trifluoroacetic acid (3 mL) and CH_2Cl_2 (9 mL) were then added to the crude product at room temperature and the solution was stirred for 12 h. The trifluoroacetic acid was then removed in vacuo to afford (S)-2-((diphenylphosphoryl) methyl) pyrrolidinium trifluoroacetate. The salt was first dissolved in CH_2Cl_2 and extracted with water (20 mL $\times$ 2) and 10% aqueous ammonia was then added to the aqueous layer. The mixture was stirred for 10 min and then extracted with CH_2Cl_2 (20 mL $\times$ 3). The organic layer was washed with brine, dried over anhydrous Na_2SO_4 , and concentrated under reduce pressure to afford (S)-2-((diphenylphosphoryl) methyl) pyrrolidine (0.69 g, 92%).

^1H NMR (400 MHz, CDCl_3): δ 7.73-7.69 (m, 4H), 7.43-7.41 (m, 6H), 3.36-3.31 (m, 1H), 2.94-2.90 (m, 1H), 2.77-2.73 (m, 2H), 2.54-2.49 (m, 1H), 2.46-2.42 (m, 1H), 1.86-1.84 (m, 1H), 1.71-1.61 (m, 2H), 1.39-1.36 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 137.7 (m), 132.7 (m), 130.6 (m), 128.6 (m), 53.2 (m), 45.7, 36.2 (m), 33.0 (m), 24.3; ^{31}P $\{^1\text{H}\}$ NMR (CDCl_3 , 161.9 MHz): δ 30.4; HRMS (EI) calcd for $\text{C}_{17}\text{H}_{20}\text{ONP}$, m/z 285.1277, found 285.1271; $[\alpha]_D^{25} = 8.8$ ($c = 1.0$, CH_2Cl_2).

(S)-2-((Diphenylphosphorothioyl) methyl) pyrrolidine (III)

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(*S*)-*N*-(*tert*-Butoxycarbonyl)-2-(diphenylphosphinomethyl) pyrrolidine (0.74 g, 2 mmol) was dissolved in CH_2Cl_2 (6 mL), followed by the addition of sulfur (1.0 g). After being stirred for 30 minutes, the mixture was filtered and concentrated under reduced pressure to afford crude product. Trifluoroacetic acid (3 mL) and CH_2Cl_2 (9 mL) was then added to the crude product at room temperature and the solution was stirred for 12 h. The trifluoroacetic acid was then removed in vacuo to afford (*S*)-2-((diphenylphosphorothioyl) methyl) pyrrolidinium trifluoroacetate. The salt was first dissolved in CH_2Cl_2 and extracted with water (20 mL $\times$ 2). 10% Aqueous ammonia was then added to the aqueous layer. The mixture was stirred for 10 min and then extracted with CH_2Cl_2 (20 mL $\times$ 3). The organic layer was washed with brine, dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure to afford (*S*)-2-((diphenylphosphorothioyl) methyl) pyrrolidine (0.49 g, 91%): $[\alpha]_{\text{D}}^{25} = -35.2$ ($c = 1.0$, CH_2Cl_2).

^1H NMR (400 MHz, CDCl_3): δ 7.88-7.85 (m, 4H), 7.50-7.46 (m, 6H), 3.52-3.46 (m, 1H), 2.99-2.93 (m, 1H), 2.83-2.67 (m, 3H), 2.18 (br, 1H), 1.78-1.62 (m, 3H), 1.39-1.28 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 133.7 (m), 131.5 (m), 131.2 (m), 128.6 (m), 53.6 (m), 45.7, 38.4 (m), 32.8 (m), 24.1; HRMS (EI) calcd for $\text{C}_{17}\text{H}_{20}\text{NPS}$, m/z 301.1049, found 301.1043; $[\alpha]_{\text{D}}^{25} = 19.0$ ($c = 1.0$, CH_2Cl_2).

2.5.2 General experimental procedure for the Michael addition of cyclohexanone to nitroolefins:

Procedure A (in solvent free): To a solution of cyclohexanone (0.10 mL, 1.0 mmol, 5 eq) and nitroolefin (0.3 mmol, 1eq) was added catalyst **II** ($\text{P}=\text{O}$) (0.15 eq). The resulting mixture was stirred at room temperature (22 $^\circ\text{C}$). After the reaction was complete (monitored by TLC), the mixtures were well purified by flash chromatography (Hexane:EtOAc = 8:1) to give the product.

Procedure B (in solvent): To a solution of nitrostyrene (0.3 mmol, 1eq) and cyclohexanone (1.5 mmol, 5 eq) in solvent (0.2mL) was added catalyst **I** or **II** or **III**, (0.15 eq). The resulting mixture was stirred at room temperature (22 $^\circ\text{C}$). After the reaction was complete (monitored by TLC), the mixture was concentrated under

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reduced pressure, the resulting residue was then purified by flash chromatography (Hexane/EtOAc = 8/1) to give the product as white solid.

Relative and absolute configurations of the products were determined by X-ray analysis and comparison with the known ^1H NMR, chiral HPLC analysis, and optical rotation values. The compounds in **Table 2** are known in the literature.

(S)-2-((R)-2-Nitro-1-phenylethyl)cyclohexanone (3a)

Prepared according to the general procedure A from (*E*)-(2-nitrovinyl) benzene (45 mg, 0.3 mmol) to provide the title compound as a white solid (73 mg, 99% yield) after silica gel chromatography (EtOAc:Hexane = 1:8). ^1H NMR (400 MHz, CDCl_3): δ 7.34-7.23 (m, 3H), 7.19 (d, J = 7.1 Hz, 2H), 4.96 (dd, J = 4.5, 12.8 Hz, 1H), 4.67 (dd, J = 10, 12.4 Hz, 1H), 3.79 (dt, J = 4.5, 10.0 Hz, 1H), 2.75-2.68 (m, 1H), 2.52-2.49 (m, 1H), 2.48-2.37 (m, 1H), 2.13-2.07 (m, 1H), 1.79-1.57 (m, 4H), 1.28-1.24 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3): 210.0, 137.8, 129.0, 128.2, 127.8, 79.0, 52.5, 44.0, 42.8, 33.3, 28.6, 25.1. HPLC: Chiralpak AS-H (hexane/*i*-PrOH, 85/15, flow rate 1 mL/min, λ = 230 nm), t_R (minor) = 11.4 min, t_R (major) = 16.4 min; >99% ee. $[\alpha]_D^{25}$ = - 21.4 (c = 1.1, CH_2Cl_2).

(S)-2-((R)-1-(2-Methoxyphenyl)-2-nitroethyl)cyclohexanone (3b)

Prepared according to the general procedure A from (*E*)-1-methoxy-2-(2-nitrovinyl) benzene (54 mg, 0.3 mmol) to provide the title compound as a white solid (80 mg, 96% yield) after silica gel chromatography (EtOAc:Hexane = 1:7). ^1H NMR (400 MHz, CDCl_3): δ 7.28-7.23 (m, 1H), 7.10-7.08 (m, 1H), 6.91-6.86 (m, 2H), 4.86-4.83 (m, 2H), 3.97 (dt, J = 5.2, 10.0 Hz, 1H), 3.85 (s, 3H), 3.02-2.96 (m, 1H), 2.52-2.36 (m, 2H), 2.10-2.06 (m, 1H), 1.81-1.55 (m, 4 H), 1.27-1.21 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 212.6, 157.6, 131.1, 129.0, 125.4, 120.9, 111.0, 77.3, 55.4, 50.6, 42.8, 41.4, 33.3, 28.6, 25.2. HPLC: Chiralpak AS-H (hexane/*i*-PrOH, 85/15, flow rate 1 mL/min, λ = 230 nm), t_R (minor) = 9.8 min, t_R (major) = 10.9 min; 97% ee. $[\alpha]_D^{25}$ = - 16.6 (c = 1.3, CH_2Cl_2).

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(S)-2-((R)-1-(Benzo[d][1,3]dioxol-5-yl)-2-nitroethyl)cyclohexanone (3c)

Prepared according to the general procedure A from (*E*)-5-(2-nitrovinyl) benzo[d][1,3] dioxole benzene (58 mg, 0.3 mmol) to provide the title compound as a white solid (80 mg, 92% yield) after silica gel chromatography (EtOAc:Hexane = 1:6). ^1H NMR (400 MHz, CDCl_3) δ 6.76 (d, J = 7.6 Hz, 1H), 6.67-6.63 (m, 2H), 5.97 (s, 2H), 4.90 (dd, J = 4.4, 12.4 Hz, 1H), 4.57 (dd, J = 10.4, 12.4 Hz, 1H), 3.68 (dt, J = 4.4, 10.0 Hz, 1H), 2.65-2.56 (m, 1H), 2.52-2.33 (m, 2H), 2.15-2.05 (m, 1H), 1.83-1.59 (m, 4H), 1.31-1.18 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 212.0, 148.1, 147.1, 131.3, 121.7, 108.6, 108.1, 79.1, 52.7, 43.8, 42.8, 33.2, 28.6, 25.1. HPLC: Chiralpak AS-H (hexane/*i*-PrOH, 85/15, flow rate 1 mL/min, λ = 230 nm), t_R (minor) = 30.8 min, t_R (major) = 37.3 min; 99% ee. $[\alpha]_D^{25}$ = - 12.3 (c = 1.0, CH_2Cl_2).

(S)- 2-((R)-1-(3-Methyl-phenyl)-2-nitro-ethyl)cyclohexanone (3d)

Prepared according to the general procedure A from (*E*)-1-methyl-3-(2-nitrovinyl)benzene (49 mg, 0.3 mmol) to provide the title compound as a white solid (77 mg, 98% yield) after silica gel chromatography (EtOAc:Hexane = 1:8). ^1H NMR (400 MHz, CDCl_3) δ 7.24-7.20 (m, 1H), 7.08 (d, J = 2.0 Hz, 1H), 6.98-6.95 (m, 2H), 4.95 (dd, J = 4.4, 12.4 Hz, 1H), 4.57 (dd, J = 10.4, 12.4 Hz, 1H), 3.68 (dt, J = 4.4, 10.0 Hz, 1H), 2.69-2.56 (m, 1H), 2.48-2.32 (m, 2H), 2.34 (s, 3H), 2.11-2.08 (m, 1H), 1.81-1.57 (m, 4H), 1.27-1.23 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 212.1, 138.6, 137.7, 129.0, 128.8, 128.5, 125.0, 78.9, 52.6, 43.9, 42.8, 33.3, 28.6, 21.5. HPLC: Chiralpak AS-H (hexane/*i*-PrOH, 85/15, flow rate 1 mL/min, λ = 230 nm), t_R (minor) = 8.5 min, t_R (major) = 12.4 min; 98% ee. $[\alpha]_D^{25}$ = - 14.2 (c = 1.1, CH_2Cl_2).

(S)- 2-((R)-1-(2-Methyl-phenyl)-2-nitro-ethyl)cyclohexanone (3e)

Prepared according to the general procedure A from

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(*E*)-1-methyl-2-(2-nitrovinyl)benzene (49 mg, 0.3 mmol) to provide the title compound as a white solid (74 mg, 95% yield) after silica gel chromatography (EtOAc:Hexane = 1:8). ^1H NMR (400 MHz, CDCl_3) δ 7.21-7.11 (m, 4H), 4.95 (dd, J = 4.4, 12.8 Hz, 1H), 4.63 (dd, J = 10.4, 12.4 Hz, 1H), 3.68 (dt, J = 4.0, 10.0 Hz, 1H), 2.67-2.56 (m, 1H), 2.50-2.36 (m, 2H), 2.37 (s, 3H), 2.12-2.09 (m, 1H), 1.77-1.53 (m, 4H), 1.26-1.23 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 212.3, 137.4, 136.5, 131.0, 127.3, 126.7, 125.7, 78.8, 53.4, 42.9, 38.3, 32.9, 28.8, 25.4, 20.0. HPLC: Chiralpak AS-H (hexane/*i*-PrOH, 85/15, flow rate 1 mL/min, λ = 230 nm), t_{R} (minor) = 9.2 min, t_{R} (major) = 12.9 min; 98% ee. $[\alpha]_{\text{D}}^{25}$ = - 21.1 (c = 1.2, CH_2Cl_2). HRMS (EI) calcd for $\text{C}_{15}\text{H}_{19}\text{O}_3\text{N}$, m/z 301.1049, found 301.1043.

(*S*)-2-((*S*)-1-(Furan-2-yl)-2-nitroethyl)cyclohexanone (3f)

Prepared according to the general procedure A from (*E*)-2-(2-nitrovinyl)furan (42 mg, 0.3 mmol) to provide the title compound as a white solid (69 mg, 97% yield) after silica gel chromatography (EtOAc:Hexane = 1:8). ^1H NMR (400 MHz, CDCl_3): δ 7.36 (m, 1H), 6.30-6.28 (m, 1H), 6.19 (m, 1H), 4.82 (dd, J = 4.8, 12.4 Hz, 1H), 4.68 (dd, J = 9.2, 12.4 Hz, 1H), 4.00 (dt, J = 4.8, 9.2 Hz, 1H), 2.80-2.72 (m, 1H), 2.48-2.47 (m, 1H), 2.40-2.33 (m, 1H), 2.18-2.09 (m, 1H), 1.89-1.60 (m, 4H), 1.35-1.26 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3): 211.0, 150.9, 142.3, 110.3, 109.0, 77.1, 51.1, 42.6, 37.6, 32.5, 28.2, 25.1. HPLC: Chiralpak AS-H (hexane/*i*-PrOH, 85/15, flow rate 1 mL/min, λ = 230 nm), t_{R} (minor) = 11.6 min, t_{R} (major) = 13.1 min; > 99% ee. $[\alpha]_{\text{D}}^{25}$ = - 8.7 (c = 1.5, CH_2Cl_2).

(*S*)-2-((*S*)-1-(Furan-3-yl)-2-nitroethyl)cyclohexanone (3g)

Prepared according to the general procedure A from (*E*)-3-(2-nitrovinyl)furan (42 mg, 0.3 mmol) to provide the title compound as a white solid (70 mg, 98% yield) after silica gel chromatography (EtOAc:Hexane = 1:8). ^1H NMR (400 MHz, CDCl_3): δ 7.38 (s, 1H), 7.31 (s, 1H), 6.28 (s, 1H), 4.78 (dd, J = 4.8, 12.4 Hz, 1H), 4.68 (dd, J = 10.0, 12.4 Hz, 1H), 4.00 (dt, J = 4.8, 8.8 Hz, 1H), 2.65-2.58 (m, 1H),

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2.45-2.32 (m, 2H), 2.15-2.07 (m, 1H), 1.98-1.86 (m, 1H), 1.78-1.68 (m, 1H), 1.69-1.58 (m, 2H), 1.37-1.26 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3): 211.3, 143.6, 140.8, 121.4, 109.1, 78.3, 51.9, 42.6, 34.6, 32.4, 28.2, 25.0. HPLC: Chiralpak AS-H (hexane/*i*-PrOH, 85/15, flow rate 1 mL/min, $\lambda = 210$ nm), t_{R} (minor) = 17.8 min, t_{R} (major) = 18.9 min; 98% ee. $[\alpha]_{\text{D}}^{25} = -15.2$ ($c = 1.5$, CH_2Cl_2). HRMS (EI) calcd for $\text{C}_{12}\text{H}_{15}\text{O}_4\text{N}$, m/z 237.0996, found 237.0996.

(*S*)-2-((*R*)-1-(4-Bromophenyl)-2-nitroethyl)cyclohexanone (3h)

Prepared according to the general procedure A from (*E*)-1-bromo-4-(2-nitrovinyl)benzene (68 mg, 0.3 mmol) to provide the title compound as a white solid (95 mg, 97% yield) after silica gel chromatography (EtOAc:Hexane = 1:8). ^1H NMR (400 MHz, CDCl_3) δ 7.46 (d, $J = 8.4$ Hz, 2H), 7.06 (d, $J = 8.4$ Hz, 2H), 4.94 (dd, $J = 5.2, 12.4$ Hz, 1H), 4.61 (dd, $J = 9.6, 12.4$ Hz, 1H), 3.75 (dt, $J = 4.4, 10.0$ Hz, 1H), 2.69-2.60 (m, 1H), 2.51-2.32 (m, 2H), 2.15-2.05 (m, 1H), 1.83-1.57 (m, 4H), 1.26-1.22 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 211.5, 136.8, 132.1, 129.9, 121.7, 78.5, 52.3, 43.4, 42.8, 33.2, 28.4, 25.1. HPLC: Chiralpak AS-H (hexane/*i*-PrOH, 85/15, flow rate 1 mL/min, $\lambda = 220$ nm), t_{R} (minor) = 12.3 min, t_{R} (major) = 20.2 min; > 99% ee. $[\alpha]_{\text{D}}^{25} = -14.7$ ($c = 1.0$, CH_2Cl_2).

(*S*)-2-((*R*)-1-(4-Chlorophenyl)-2-nitroethyl)cyclohexanone (3i)

Prepared according to the general procedure A from (*E*)-1-chloro-4-(2-nitrovinyl)benzene (55 mg, 0.3 mmol) to provide the title compound as a white solid (81 mg, 96% yield) after silica gel chromatography (EtOAc:Hexane = 1:8). ^1H NMR (400 MHz, CDCl_3) δ 7.31 (d, $J = 8.4$ Hz, 2H), 7.13 (d, $J = 8.4$ Hz, 2H), 4.96 (dd, $J = 4.8, 12.8$ Hz, 1H), 4.62 (dd, $J = 10.0, 12.8$ Hz, 1H), 3.78 (dt, $J = 4.4, 10.0$ Hz, 1H), 2.69-2.60 (m, 1H), 2.51-2.34 (m, 2H), 2.15-2.05 (m, 1H), 1.83-1.52 (m, 4H), 1.28-1.23 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 211.6, 136.3, 133.7, 129.6, 129.2, 78.6, 52.4, 43.4, 42.8, 33.2, 28.5, 25.1. HPLC: Chiralpak AS-H (hexane/*i*-PrOH, 85/15, flow rate 1 mL/min, $\lambda = 210$ nm), t_{R} (minor) = 12.3 min, t_{R}

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(major) = 19.9 min; 98% ee. $[\alpha]_D^{25} = -8.0$ ($c = 1.5$, CH_2Cl_2).

(S)-2-((R)-1-(2-Chlorophenyl)-2-nitroethyl)cyclohexanone (3j)

Prepared according to the general procedure A from (*E*)-1-chloro-2-(2-nitrovinyl)benzene (55 mg, 0.3 mmol) to provide the title compound as a white solid (78 mg, 94% yield) after silica gel chromatography (EtOAc:Hexane = 1:8). ^1H

NMR (400 MHz, CDCl_3) δ 7.38 (d, $J = 7.2$ Hz, 1 H), 7.24-7.21 (m, 3H), 4.92-4.88 (m, 2H), 4.32-4.30 (m, 1H), 2.95-2.88 (m, 1H), 2.47-2.32 (m, 2H), 2.12-2.09 (m, 1H), 1.83-1.65 (m, 4H), 1.38-1.25 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 211.7, 135.5, 134.6, 130.4, 128.9, 77.3, 51.7, 42.8, 41.0, 33.0, 28.5, 25.3. HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 90/10, flow rate 1 mL/min, $\lambda = 254$ nm), t_R (minor) = 8.6 min, t_R (major) = 12.9 min; 99% ee. $[\alpha]_D^{25} = -64.4$ ($c = 1.0$, CH_2Cl_2).

(S)-Tetrahydro-3-((R)-2-nitro-1-phenylethyl)thiopyran-4-one (3k)

To a solution of nitrostyrene (0.2 mmol, 1eq) and tetrahydrothiopyran-4-one **2b** (0.1 mL, 5 eq) in toluene (0.2mL) was added catalyst **II**, (0.03 mmol). The resulting mixture was stirred at room temperature (22 °C). After the reaction was

complete (monitored by TLC), the resulting residue was then purified by flash chromatography (EtOAc:Hexane = 1:8) to give the product as white solid (87% yield).

^1H NMR (400 MHz, CDCl_3) δ 7.40-7.32 (m, 3H), 7.22 (d, $J = 7.6$ Hz, 2 H), 4.76 (dd, $J = 4.4, 12.4$ Hz, 1H), 4.63 (dd, $J = 10.0, 12.8$ Hz, 1H), 4.01 (dt, $J = 4.4, 10.0$ Hz, 1H), 3.11-2.99 (m, 3H), 2.92-2.82 (m, 2H), 2.66-2.62 (m, 1H), 2.48 (dd, $J = 9.2, 13.6$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 209.5, 136.5, 129.3, 128.3, 128.2, 78.6, 55.0, 44.6, 53.5, 35.1, 31.6. HPLC: Chiralpak AS-H (hexane/*i*-PrOH, 80/20, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (minor) = 17.2 min, t_R (major) = 26.6 min; 93% ee. $[\alpha]_D^{25} = -29.13$ ($c = 1.4$, CH_2Cl_2). HRMS (ESI) calcd for $[\text{M}+\text{H}]$ $\text{C}_{13}\text{H}_{16}\text{O}_3\text{NS}$, m/z 266.0851, found 266.0851.

(S)-7-((R)-2-Nitro-1-phenylethyl)-1,4-dioxaspiro[4.5]decan-8-one (3l)

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To a solution of nitrostyrene (0.2 mmol, 1eq) and 1,4-dioxaspiro[4.5]decan-8-one **2c** (0.1 mL, 5 eq) in toluene (0.2 mL) was added catalyst **II**, (0.03 mmol). The resulting mixture was stirred at room temperature (22 °C). After the reaction was complete (monitored by TLC), the resulting residue was then purified by flash chromatography (EtOAc:Hexane = 1:6) to give the product as white solid (88% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.36-7.28 (m, 3H), 7.18 (d, *J* = 7.6 Hz, 2 H), 4.96 (dd, *J* = 4.8, 12.4 Hz, 1H), 4.63 (dd, *J* = 10.0, 12.4 Hz, 1H), 4.01-3.83 (m, 5H), 3.12-3.05 (m, 1H), 2.76-2.68 (m, 1H), 2.51-2.45 (m, 1H), 2.09-1.93 (m, 2H), 1.72-1.69 (m, 1H), 1.57-1.54 (m, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 201.3, 137.2, 128.9, 128.1, 127.8, 106.9, 78.3, 64.7, 64.5, 48.1, 43.3, 39.2, 38.5, 35.0. HPLC: Chiralpak AS-H (hexane/*i*-PrOH, 80/20, flow rate 1 mL/min, λ = 210 nm), *t*_R (minor) = 15.4 min, *t*_R (major) = 24.5 min; 92% ee. [α]_D²⁵ = - 5.33 (*c* = 1.4, CH₂Cl₂). HRMS (ESI) calcd for [M+H] C₁₆H₂₀O₅N, *m/z* 306.1341, found 306.1335.

General experimental procedure for the Michael addition of cyclohexanone to nitroolefins on water or brine:

To a solution of nitrostyrene **2a** (0.2 mmol, 1eq) and **1a** (60 mg, 3 eq) in water or brine (0.2mL) was added catalyst **II**, (0.03 mmol). The resulting mixture was stirred at room temperature (22 °C). After 24 hours, the resulting residue was then purified by flash chromatography (Hexane/EtOAc = 8/1) to give the product as white solid. **(In water the reaction does not complete, only get 27% yield)**

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Chapter 3

DOMINO MICHAEL/INTRAMOLECULAR [3+2] CYCLOADDITION REACTIONS

Water More than Just a Green Solvent: A Stereoselective One-Pot Access to All Chiral Tetrahydronaphthalenes in Aqueous Media

3.1 Background

The constantly growing interest of tetrahydronaphthalene derivatives in the synthesis of natural products¹ and other important molecules which are applicable as pharmaceuticals² and chiral building blocks, has brought about the development of numerous synthetic approaches to synthesize them. (Figure 1) Organocatalytic³ domino reactions,⁴ whereby complex molecules are obtained without isolation and purification of intermediates, are very important in organic chemistry. The intramolecular 1,3-dipolar cycloaddition of nitrones to alkenes⁵ is a powerful method of offering high levels of regio- and stereocontrol to access bicyclic isoxazolidines, which are important precursors of alkaloids, amino acids, β -lactams, and amino sugars. Therefore, the optically pure dipole or dipolarophile can potentially direct the stereochemistry of cycloaddition products.

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Figure 1. Some natural products and pharmaceuticals containing multisubstituted tetrahydronaphthalene.

The asymmetric organocatalytic Michael addition of aldehydes to nitrostyrene⁶ and its related domino reactions⁷ have proved to be a very efficient approach to obtain enantiopure molecules containing functional groups. Although there are numerous publications on organocatalytic Michael reactions, there are barely any examples that make use of the domino reaction involving intramolecular nitron [3+2] cycloaddition as a strategy.⁸ Herein, we developed an asymmetric organocatalytic one-pot synthesis of multisubstituted tetrahydronaphthalene isoxazolidines, which can be further transformed into specific α -hydroxy- γ -amino acids (Figure 2), via a tandem Michael/intramolecular [3+2] nitron-olefin cycloaddition reaction.

Figure 2. Retrosynthetic analysis of α -hydroxy- γ -amino acid.

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3.2 Results and discussion

Rationally designed substrate **1a** was synthesized by several simple transformations (for details, see the Supporting Information) for the Michael reaction directed [3+2] cycloaddition. Initially, we conducted the Michael addition under the reported conditions.^{7d} Upon the completion of the Michael reaction, the adduct was first isolated by flash chromatography before [3+2] nitron-olefin cycloaddition reaction was carried out. The desired product **3a** was produced with good diastereoselectivity and enantioselectivity (Table 1, entry 1). However, the purification of the intermediate **4** prompted us to explore the reaction conditions required to carry out the reaction in one-pot. When the reaction was conducted in a one-pot fashion, it proceeded smoothly despite the poor diastereoselectivity (Table 1, entry 2). Changing the organic solvents and catalysts (Figure 2, **II**, **III** and **IV**) did not show any improved results (Table 1, entries 3-6).

Figure 2. Organocatalysts tested in the tandem reaction.

Inspired by the recent reports of Barbas⁹ and Ma^{6f} that brine and water were good media for organocatalytic Michael reactions of aldehydes and nitroolefins, we thought that maybe water can interact with the dipole and direct the configuration of the [3+2] cycloaddition reaction.¹⁰ If the in situ formation of a 1,3-dipole (nitron) followed by an intramolecular cycloaddition can be done in water, it will represent a powerful and greener concept in organic synthesis,¹¹ as the most of the reactions used to form nitrones are dehydration reactions of substituted hydroxylamine and carbonyl compounds using anhydrous conditions, dehydrating agents or surfactant catalysts.¹² We were pleased to find that the intermediate **4** and N-hydroxyphenylamine worked well in water to afford compound **3a** in good yield and excellent stereoselectivity

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Table 1. Screening of reaction conditions for the synthesis of chiral tetrahydronaphthalenes using the organocatalytic tandem reaction.^a

entry	Cat	solvent	additive	yield (%) ^b	dr ^c	ee (%) ^d
1 ^e	I	DCM	AcOH	77	95:5	>99
2	I	DCM	AcOH	71	68:32	>99
3	I	Hexane	none	35	72:28	>99
4	II	DCM	AcOH	<5	nd	nd
5	III	DCM	AcOH	56	81:19	97
6	IV	DCM	AcOH	<5	nd	nd
7 ^e	I	H ₂ O	AcOH	67	92:8	>99
8	I	H ₂ O	AcOH	56	92:8	>99
9	III	H ₂ O	AcOH	45	94:6	97
10	I	H ₂ O	PhCO ₂ H	67	92:8	>99
11 ^f	I	H ₂ O	PhCO ₂ H	72	95:5	>99
12 ^g	I	H ₂ O	PhCO ₂ H	73	98:2	>99

^a Reaction conditions: Unless specified, valeraldehyde (**2a**, 0.6 mmol, 3.0 equiv) was added to a suspension of catalyst (10 mol%), additive (20 mol%) and nitroolefin acrylate (**1a**, 0.2 mmol, 1.0 equiv) in solvent (1.0 mL). After the nitroolefin **1a** consumed, N-hydroxyphenylamine (0.8 mmol, 4.0 equiv) was added. ^b Isolated yields. ^c Determined by H-NMR and chiral HPLC. ^d Determined by HPLC analysis. ^e Isolated intermediate **4**. ^f 5 mol% catalyst was used. ^g 2 mol% catalyst was used.

(Table 1, entry 7). When the tandem reaction was examined in one-pot, the diastereoselectivity remained the same as with the isolated intermediate **4** (Table 1, entries 8-12). Finally, the optimized conditions were established by changing the catalyst loading and additive (Table 1, entry 12).

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Table 2. Scope of the organocatalytic tandem Michael/nitrone formation/intramolecular [3+2] cycloaddition^a

entry	OR ¹ , R	t (h) ^b	yield (%) ^c	dr ^d	ee (%) ^e
1	OEt, <i>n</i> -Pr	5 (3)	73	98:2	>99
2	OEt, Me	3 (3)	77	95:5	>99
3	OEt, Et	4 (3)	83	98:2	>99
4	OEt, <i>i</i> -Pr	10 (12)	48	99:1	>99
5	OEt, $\text{CH}_3(\text{CH}_2)_5$	6 (5)	71	99:1	>99
6	OEt, Bn	5 (3)	72	98:2	>99
7	OEt, $\text{BnO}(\text{CH}_2)_2$	6 (10)	51	97:3	>99
8	OBn, <i>n</i> -Pr	6 (4)	63	97:3	>99
9	OBn, Bn	6 (4)	73	98:2	>99
10	OBn, $\text{BnO}(\text{CH}_2)_2$	10 (10)	52	96:4	>99

^a Reaction conditions: See the Supporting Information. ^b Time in parenthesis indicates the reaction time of the cycloaddition step. ^c Isolated yields. ^d Determined by $^1\text{H-NMR}$ and chiral HPLC. ^e Determined by HPLC analysis.

The catalyst **I** promoted the tandem Michael/nitrone formation/intramolecular [3+2] nitrone–olefin cycloaddition reaction between a variety of aldehydes **2** and nitroolefin acrylate **1** under the optimized conditions was investigated. As revealed in Table 2, the new methodology provided a facile and general approach to a range of multisubstituted, highly functionalized tetrahydronaphthalene oxazolidines with the generation of five new stereogenic centers with excellent enantiomeric excesses (>99% ee) and high diastereoselectivities (94:6 to 99:1 dr) in moderate to good yields. It is noteworthy that steric hindrance played an important role to influence the yield of

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the tandem process (Table 2, entry 4). Significant variation of hydroxyphenylamines in their phenyl electronic feature (4-Me, Cl, Br) could be tolerated for the tandem processes (Scheme 1). Moreover, the process was applicable for less reactive aliphatic hydroxylamine (BnNHOH) with high efficiency (Scheme 1).

To determine the absolute configuration of the products, substrate **1c** was explored for the tandem reaction (Scheme 1). The X-ray structural analysis (Figure 3)¹³ assigned the stereochemistry of product **3o**, which is in accordance with our prediction. Furthermore, the isoxazolidine **3a** was transformed into α -hydroxy- γ -amino acid derivative **5** with almost quantitative yield which may have potential applications in the synthetic organic chemistry and pharmaceutical industry (Scheme 2).

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Scheme 1. Tandem reactions with different hydroxyamines.

Figure 3. X-ray crystallographic determination of **3o**. Scheme 2. Synthesis of α -hydroxy- γ -amino acid derivative.

3.3 Conclusion

In summary, an organocatalytic tandem Michael/nitrone formation/intramolecular [3+2] nitrone-olefin cycloaddition reaction strategy for the facile construction of biologically significant, heavily functionalized chiral tetrahydronaphthalene skeletons full of stereogenic centers was developed. This highly stereoselective synthetic

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protocol for construction of complex architecture has very huge potential in medical chemistry and diversity-oriented synthesis. Moreover, the use of water in the strategy is not only environmentally benign, but it also helps to improve the reactivity and stereoselectivity. Further applications of this process in organic synthesis will be reported in due course.

3.4 Experimental section

General experimental conditions (Chapter 2)

3.6.1 Synthesis of substrates 1a, 1b, 1c:

Typical Procedure for the deprotection:

To a solution of **6** (1.10g, 5 mmol) in acetone (30 mL) was added 2 N HCl (10 mL, 20 mmol) at rt and the mixture was stirred for 2 h. The reaction was quenched with 2 N aqueous NaOH and the mixture was extracted with Et₂O (20 mLx 2). The organic layer was washed successively with water and brine, and dried over Na₂SO₄. The solvent was removed under reduced pressure and the residue was purified by washing with hexane to give **7** (0.80 g, 90%).

¹H-NMR (400 MHz, CDCl₃) δ 10.20 (s, 1H), 8.94 (d, *J* = 13.6 Hz, 1H), 7.93 (d, *J* = 7.2 Hz, 1H), 7.74-7.67 (m, 2H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.47 (d, *J* = 13.6 Hz, 1H). ¹³C-NMR (100 MHz, CDCl₃) δ 192.1, 139.8, 136.7, 134.8, 134.5, 134.1, 131.6, 131.1, 128.6. HRMS (ESI) calcd for [M+H] C₉H₈NO₃, *m/z* 178.0504, found 178.0503.

Typical Procedure for the Wittig reaction:

(*E*)-Ethyl 3-(2-((*E*)-2-nitrovinyl)phenyl)acrylate (**1a**)

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To a mixture of **7** (0.71 g, 4 mmol) and **8** (1.40 g, 4 mmol) was added DCM (20 mL) at rt and the mixture was stirred for 5 h. The reaction was quenched with water and the mixture was extracted with DCM (20 mL x 2). The organic layer was washed successively with brine, and dried over Na₂SO₄. The

solvent was removed under reduced pressure and the residue was purified by column chromatography (silica-gel, hexane/EA = 6/1) to give **1a** (0.61 g, 61%).

¹H-NMR (400 MHz, CDCl₃) δ 8.31 (d, *J* = 15.6 Hz, 1H), 7.94 (d, *J* = 16.0 Hz, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.52-7.42 (m, 3H), 6.35 (d, *J* = 7.6 Hz, 1H), 7.47 (d, *J* = 15.6 Hz, 1H), 4.28 (q, *J* = 7.2 Hz, 2H), 1.34 (t, *J* = 7.2 Hz, 3H). ¹³C-NMR (100 MHz, CDCl₃) δ 166.0, 140.2, 139.1, 135.8, 135.7, 131.9, 130.3, 129.4, 128.28, 128.26, 123.3, 60.9, 14.3. HRMS (ESI) calcd for [M+H] C₁₃H₁₄NO₄, *m/z* 248.0923, found 248.0928.

(E)-Benzyl 3-(2-((E)-2-nitrovinyl)phenyl)acrylate (1b)

According to the above typical procedure for the Wittig reaction, **1b** was obtained in 65% yield.

¹H-NMR (400 MHz, CDCl₃) δ 8.34 (d, *J* = 13.6 Hz, 1H), 8.02 (d, *J* = 16.0 Hz, 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.56-7.33 (m, 9H), 6.42 (d, *J* = 7.6 Hz, 1H), 5.29 (s, 2H). ¹³C-NMR (100 MHz, CDCl₃) δ 165.9, 140.8, 139.2, 135.8, 135.5, 131.9, 130.4, 129.5, 128.7, 128.44, 128.39, 128.34, 128.29, 122.9, 66.8. HRMS (ESI) calcd for [M+H] C₁₈H₁₆NO₄, *m/z* 310.1079, found 310.1084.

According to the above typical procedure for the protection, **10** was obtained in 85% yield.

¹H-NMR (400 MHz, CDCl₃) δ 10.16 (s, 1H), 8.91 (d, *J* = 13.2 Hz, 1H), 7.46 (d, *J* = 13.6 Hz, 1H), 7.39 (s, 1H), 7.28 (s, 1H), 7.06 (1H), 6.19 (s, 2H). ¹³C-NMR (100 MHz, CDCl₃) δ 192.1, 139.8, 136.7, 134.8, 134.5, 134.1, 131.6, 131.1, 128.6. HRMS (ESI) calcd for [M+H] C₁₀H₈NO₅, *m/z* 222.0402, found 222.0405.

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According to the above typical procedure for the Wittig reaction, **1c** was obtained in 54% yield.

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

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 8.32 (d, $J = 13.2$ Hz, 1H), 7.94 (d, $J = 15.6$ Hz, 1H), 7.42 (d, $J = 13.2$ Hz, 1H), 7.07 (s, 1H), 7.00 (s, 1H), 6.27 (d, $J = 15.6$ Hz, 1H), 6.10 (s, 2H), 4.29 (q, $J = 7.2$ Hz, 2H), 1.36 (t, $J = 7.2$ Hz, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 166.2, 151.4, 149.8, 139.3, 137.5,

135.1, 131.8, 124.0, 121.8, 107.2, 106.6, 102.6, 60.9, 14.3. HRMS (ESI) calcd for $[\text{M}+\text{H}]$ $\text{C}_{14}\text{H}_{14}\text{NO}_6$, m/z 292.0821, found 292.0824.

Typical Procedure for the Michael/intramolecular [3+2] nitron-olefin cycloaddition reactions:

Aldehyde **2** (0.6 mmol, 3 eq) was added to a suspension of catalyst **I** (2 mol%), benzoic acid (20 mol%), and nitroolefin acrylate **1** (0.2 mmol, 1 eq) in water (1 mL) at room temperature. After the nitroolefin **1** consumed, *N*-hydroxybenzenamine (0.8 mmol, 4 eq) was added, and then stirred for 3-12 hours. After the reaction was complete (monitored by TLC and crude NMR), the mixture was extracted with DCM (5 mL $\times$ 2). The organic layer was washed successively with brine, and dried over Na_2SO_4 . The solvent was removed under reduced pressure and the products were afforded by flash chromatography over silica gel (EtOAc/Hexane = 1/20-1/10).

(1*R*,3*aS*,4*R*,5*S*,9*bR*)-ethyl5-(nitromethyl)-3-phenyl-4-propyl**1,3,3*a*,4,5,9*b*-hexahydronaphtho[2,1-*c*]isoxazole-1-carboxylate (**3a**)**

The title compound was prepared in 73% yield according to the typical procedure, as described above (The first step 5 hours, the second step 3 hours).

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$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.34-7.25 (m, 5H), 7.19 (d, $J = 7.6$ Hz, 2H), 7.09-7.06 (m, 2H), 4.76 (dd, $J = 5.6, 12.0$ Hz, 1H), 4.65-4.63 (m, 1H), 4.43 (d, $J = 7.2$ Hz, 1H), 4.27 (q, $J = 6.8$ Hz, 2H), 4.31-4.23 (m, 1H), 4.10-4.08 (m, 1H), 3.96 (t, $J = 8.4$ Hz, 1H), 2.06-2.02 (m, 1H), 1.53-1.49 (m, 2H), 1.35 (t, $J = 7.2$ Hz, 3H), 1.36-1.27 (m, 2H), 0.96 (t, $J = 7.2$ Hz, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 170.4, 150.3, 134.9, 133.8, 129.7, 128.9, 128.1, 127.7, 127.2, 123.3, 116.4, 84.2, 77.5, 67.3, 61.9, 46.9, 38.7, 37.9, 30.6, 20.2, 14.2, 14.1. HPLC: Chiralpak AD-H (hexane/*i*-PrOH = 80/20, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (major) = 8.1 min, t_R (minor) = 24.7 min; >99% ee. $[\alpha]_D^{24} = 88$ ($c = 0.6$, CH_2Cl_2). HRMS (ESI) calcd for $[\text{M}+\text{H}] \text{C}_{24}\text{H}_{29}\text{N}_2\text{O}_5$, m/z 425.2076, found 425.2075.

(1*R*,3*aS*,4*R*,5*S*,9*bR*)-ethyl4-methyl-5-(nitromethyl)-3-phenyl-1,3,3*a*,4,5,9*b*-hexahydronaphtho[2,1-*c*]isoxazole-1-carboxylate (3b)

The title compound was prepared in 77% yield according to the typical procedure, as described above (The first step 3 hours, the second step 3 hours).

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.34-7.23(m, 5H), 7.21 (d, $J = 7.6$ Hz, 2H), 7.08-7.04 (m, 2H), 4.78-4.68 (m, 2H), 4.42 (d, $J = 7.2$ Hz, 1H), 4.25 (q, $J = 7.2$ Hz, 2H), 4.20 (t, $J = 7.2$ Hz, 1H), 4.10 (dd, $J = 7.2, 11.6$ Hz, 1H), 3.80 (t, $J = 7.2$ Hz, 1H), 2.38-2.33 (m, 1H), 1.31 (t, $J = 7.2$ Hz, 3H), 1.05 (d, $J = 6.8$ Hz, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 170.3, 150.0, 134.3, 133.9, 129.7, 128.9, 128.0, 127.8, 126.6, 123.7, 117.0, 83.7, 77.5, 68.9, 61.9, 47.3, 39.5, 33.0, 14.1, 13.9. HPLC: Chiralpak AD-H (hexane/*i*-PrOH = 80/20, flow rate 1 mL/min, $\lambda = 220$ nm), t_R (major) = 14.5 min, t_R (minor) = 35.5 min; >99% ee. $[\alpha]_D^{24} = 87.3$ ($c = 1.1$, CH_2Cl_2). HRMS (ESI) calcd for $[\text{M}+\text{H}] \text{C}_{22}\text{H}_{25}\text{N}_2\text{O}_5$, m/z 397.1763, found 397.1760.

(1*R*,3*aS*,4*R*,5*S*,9*bR*)-ethyl4-ethyl-5-(nitromethyl)-3-phenyl-1,3,3*a*,4,5,9*b*-hexahydronaphtho[2,1-*c*]isoxazole-1-carboxylate (3c)

The title compound was prepared in 83% yield according to the typical procedure, as described above (The first step 4 hours, the second step 3 hours).

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.32-7.21(m, 5H), 7.16 (d, $J = 8.4$ Hz, 2H), 7.08-7.01 (m, 2H), 4.72 (dd, $J = 5.6, 12.0$ Hz,

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1H), 4.61-4.56 (m, 1H), 4.41 (d, $J = 7.2$ Hz, 1H), 4.25 (q, $J = 6.8$ Hz, 2H), 4.28-4.21 (m, 1H), 4.10-4.08 (m, 1H), 3.96 (t, $J = 8.4$ Hz, 1H), 2.17-2.10 (m, 1H), 1.32 (t, $J = 7.2$ Hz, 3H), 1.34-1.27 (m, 1H), 1.08 (t, $J = 7.2$ Hz, 3H). ^{13}C -NMR (100 MHz, CDCl_3) δ 170.4, 150.4, 134.9, 133.8, 129.6, 128.9, 128.1, 127.7, 127.3, 123.2, 116.2, 84.2, 77.5, 67.1, 61.9, 46.9, 39.8, 38.4, 21.4, 14.1, 11.5. HPLC: Chiralpak AD-H (hexane/*i*-PrOH = 80/20, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (major) = 18.1 min, t_R (minor) = 30.5 min; >99% ee. $[\alpha]_D^{24} = 89.5$ ($c = 0.9$, CH_2Cl_2). HRMS (ESI) calcd for $[\text{M}+\text{H}]$ $\text{C}_{23}\text{H}_{27}\text{N}_2\text{O}_5$, m/z 411.1920, found 411.1916.

(1*R*,3*aS*,4*R*,5*S*,9*bR*)-ethyl4-isopropyl-5-(nitromethyl)-3-phenyl-1,3,3*a*,4,5,9*b*-hexahydronaphtho[2,1-*c*]isoxazole-1-carboxylate (3d)

The title compound was prepared in 48% yield according to the typical procedure, as described above (The first step 10 hours, the second step 12 hours).

^1H -NMR (400 MHz, CDCl_3) δ 7.35-7.23(m, 7H), 7.11-7.06 (m, 2H), 4.72 (dd, $J = 5.6, 12.0$ Hz, 1H), 4.84-4.82 (m, 2H), 4.42 (d, $J = 7.2$ Hz, 1H), 4.27-4.22 (m, 4H), 4.13 (t, $J = 7.2$ Hz, 1H), 2.13-2.10 (m, 1H), 1.88-1.86 (m, 1H), 1.33 (t, $J = 7.2$ Hz, 3H), 1.01 (d, $J = 6.8$ Hz, 3H), 0.92 (d, $J = 5.2$ Hz, 3H). ^{13}C -NMR (100 MHz, CDCl_3) δ 170.2, 149.5, 135.3, 134.4, 129.4, 129.0, 127.9, 127.6, 125.9, 123.8, 117.2, 84.0, 78.1, 65.5, 61.9, 47.9, 44.1, 39.2, 28.2, 22.4, 20.9, 14.1. HPLC: Chiralcel OD-H (hexane/*i*-PrOH = 80/20, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (major) = 7.7 min, t_R (minor) = 13.2 min; >99% ee. $[\alpha]_D^{24} = 93.3$ ($c = 1.5$, CH_2Cl_2). HRMS (ESI) calcd for $[\text{M}+\text{H}]$ $\text{C}_{24}\text{H}_{29}\text{N}_2\text{O}_5$, m/z 425.2076, found 425.2069.

(1*R*,3*aS*,4*R*,5*S*,9*bR*)-ethyl4-hexyl-5-(nitromethyl)-3-phenyl-1,3,3*a*,4,5,9*b*-hexahydronaphtho[2,1-*c*]isoxazole-1-carboxylate (3e)

The title compound was prepared in 71% yield according to the typical procedure, as described above (The first step 6 hours, the second step 5 hours).

^1H -NMR (400 MHz, CDCl_3) δ 7.34-7.23 (m, 5H), 7.19 (d, $J = 8.4$ Hz, 2H), 7.10-7.04 (m, 2H), 4.76 (dd, $J = 5.6, 12.0$ Hz, 1H), 4.65-4.63 (m, 1H), 4.43 (d, $J = 6.8$ Hz,

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1H), 4.31-4.25 (m, 3H), 4.10 (m, 1H), 3.96 (t, $J = 8.4$ Hz, 1H), 2.24-2.20 (m, 1H), 1.53-1.49 (m, 2H), 1.46-1.30 (m, 13H), 0.90 (t, $J = 7.2$ Hz, 3H). ^{13}C -NMR (100 MHz, CDCl_3) δ 170.4, 150.4, 134.9, 133.8, 129.6, 128.9, 128.1, 127.7, 127.1, 123.3, 116.3, 84.2, 77.5, 67.3, 61.9, 46.9, 38.7, 38.0, 31.7, 29.4, 28.4, 26.9, 22.6, 14.1, 14.0. HPLC: Chiralpak AD-H (hexane/*i*-PrOH = 80/20, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (major) = 7.1 min, t_R (minor) = 18.7 min; >99% ee. $[\alpha]_D^{24} = 73.7$ ($c = 0.9$, CH_2Cl_2). HRMS (ESI) calcd for $[\text{M}+\text{H}] \text{C}_{27}\text{H}_{35}\text{N}_2\text{O}_5$, m/z 467.2546, found 467.2543.

(1*R*,3*aS*,4*R*,5*S*,9*bR*)-ethyl-4-benzyl-5-(nitromethyl)-3-phenyl-1,3,3*a*,4,5,9*b*-hexahydronaphtho[2,1-*c*]isoxazole-1-carboxylate (3f)

The title compound was prepared in 72% yield according to the typical procedure, as described above (The first step 5 hours, the second step 3 hours).

^1H -NMR (400 MHz, CDCl_3) δ 7.34-7.14 (m, 10H), 7.01-6.92 (m, 4H), 4.79-4.77 (m, 2H), 4.44 (d, $J = 6.8$ Hz, 1H), 4.30 (t, $J = 7.2$ Hz, 1H), 4.22 (q, $J = 7.2$ Hz, 1H), 4.03-3.97 (m, 2H), 2.58-2.51 (m, 2H), 1.28 (t, $J = 7.2$ Hz, 3H). ^{13}C -NMR (100 MHz, CDCl_3) δ 170.0, 149.8, 138.4, 134.6, 134.0, 129.7, 129.1, 128.9, 1280.8, 128.0, 127.8, 126.8, 126.1, 123.2, 116.5, 83.9, 77.2, 65.7, 61.9, 47.4, 41.3, 37.7, 34.0, 14.1. HPLC: Chiralcel OD-H (hexane/*i*-PrOH = 80/20, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (major) = 12.8 min, t_R (minor) = 43.8 min; >99% ee. $[\alpha]_D^{24} = 132.4$ ($c = 1.4$, CH_2Cl_2). HRMS (ESI) calcd for $[\text{M}+\text{H}] \text{C}_{28}\text{H}_{29}\text{N}_2\text{O}_5$, m/z 473.2076, found 473.2080.

(1*R*,3*aS*,4*R*,5*S*,9*bR*)-ethyl-4-(2-(benzyloxy)ethyl)-5-(nitromethyl)-3-phenyl-1,3,3*a*,4,5,9*b*-hexahydronaphtho[2,1-*c*]isoxazole-1-carboxylate (3g)

The title compound was prepared in 61% yield according to the typical procedure, as described above (The first step 6 hours, the second step 10 hours).

^1H -NMR (400 MHz, CDCl_3) δ 7.38-7.27 (m, 10H), 7.19 (d, $J = 8.0$ Hz, 2H), 7.09-7.00 (m, 2H), 4.80 (dd, $J = 5.2, 8.4$ Hz, 1H), 4.73-4.70 (m, 1H), 4.55-4.53 (m, 2H), 4.44 (d, $J = 6.8$ Hz, 1H), 4.27 (q, $J = 7.2$ Hz, 2H), 4.28-4.23 (m, 1H), 4.17 (m, 1H), 4.07 (t, $J = 8.0$ Hz, 1H), 3.66-3.65 (m, 2H),

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2.47-2.44 (m, 1H), 1.66-1.63 (m, 2H), 1.32 (t, $J = 7.2$ Hz, 3H). ^{13}C -NMR (100 MHz, CDCl_3) δ 170.3, 150.2, 138.1, 134.9, 133.9, 129.6, 128.9, 128.5, 128.0, 127.8, 127.7, 127.0, 123.2, 116.3, 84.1, 77.6, 73.3, 68.2, 61.9, 47.1, 38.9, 36.5, 28.8, 14.1. HPLC: Chiralcel OD-H (hexane/*i*-PrOH = 80/20, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (major) = 13.6 min, t_R (minor) = 42.8 min; >99% ee. $[\alpha]_{\text{D}}^{24} = 65.1$ ($c = 0.4$, CH_2Cl_2). HRMS (ESI) calcd for $[\text{M}+\text{H}]^+ \text{C}_{30}\text{H}_{33}\text{N}_2\text{O}_6$, m/z 517.2339, found 517.2337.

(1*R*,3*aS*,4*R*,5*S*,9*bR*)-benzyl 5-(nitromethyl)-3-phenyl-4-propyl-1,3,3*a*,4,5,9*b*-hexahydronaphtho[2,1-*c*]isoxazole-1-carboxylate (3h)

The title compound was prepared in 63% yield according to the typical procedure, as described above (The first step 6 hours, the second step 4 hours).

^1H -NMR (400 MHz, CDCl_3) δ 7.42 (m, 5H), 7.40-7.19 (m, 4H), 7.17-7.12 (m, 3H), 7.08-7.02 (m, 2H), 5.25 (s, 2H), 4.74 (dd, $J = 5.6, 12.0$ Hz, 1H), 4.60 (m, 1H), 4.47 (d, $J = 7.2$ Hz, 1H), 4.22 (t, $J = 7.2$ Hz, 1H), 4.08 (m, 1H), 3.94 (t, $J = 8.0$ Hz, 1H), 2.25-2.23 (m, 1H), 1.53-1.46 (m, 2H), 1.32-1.27 (m, 2H), 0.95 (t, $J = 7.2$ Hz, 3H). ^{13}C -NMR (100 MHz, CDCl_3) δ 170.2, 150.3, 135.0, 134.8, 133.5, 129.7, 128.9, 128.74, 128.71, 128.66, 128.1, 127.7, 127.2, 123.3, 116.3, 84.1, 77.5, 67.6, 67.5, 46.9, 38.7, 37.8, 30.6, 20.2, 14.2. HPLC: Chiralpak AD-H (hexane/*i*-PrOH = 80/20, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (major) = 13.3 min, t_R (minor) = 37.4 min; >99% ee. $[\alpha]_{\text{D}}^{24} = 38.5$ ($c = 1.5$, CH_2Cl_2). HRMS (ESI) calcd for $[\text{M}+\text{H}]^+ \text{C}_{29}\text{H}_{31}\text{N}_2\text{O}_5$, m/z 487.2233, found 487.2232.

(1*R*,3*aS*,4*R*,5*S*,9*bR*)-benzyl 4-benzyl-5-(nitromethyl)-3-phenyl-1,3,3*a*,4,5,9*b*-hexahydronaphtho[2,1-*c*]isoxazole-1-carboxylate(3i)

The title compound was prepared in 73% yield according to the typical procedure, as described above (The first step 6 hours, the second step 4 hours).

^1H -NMR (400 MHz, CDCl_3) δ 7.38-7.13 (m, 15H), 7.00-6.96 (m, 2H), 6.91-6.89 (m, 2H), 5.22-5.16 (m, 2H), 4.78 (m, 2H), 4.49 (d, $J = 6.8$ Hz, 1H), 4.28 (t, $J = 7.2$ Hz, 1H), 3.98-3.95 (m, 2H), 2.57-2.53 (m, 2H). ^{13}C -NMR (100 MHz, CDCl_3) δ 169.8, 149.6,

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138.3, 135.0, 134.6, 133.8, 129.7, 129.1, 128.9, 128.7, 128.65, 128.0, 127.8, 126.8, 123.2, 116.5, 83.7, 77.2, 67.6, 65.9, 47.5, 41.2, 37.7, 34.0. HPLC: Chiralcel OD-H (hexane/i-PrOH = 80/20, flow rate 1 mL/min, λ = 210 nm), t_R (major) = 20.9 min, t_R (minor) = 28.3 min; >99% ee. $[\alpha]_D^{24}$ = 96.1 (c = 1.0, CH_2Cl_2). HRMS (ESI) calcd for $[\text{M}+\text{H}] \text{C}_{33}\text{H}_{31}\text{N}_2\text{O}_5$, m/z 435.2233, found 535.2227.

(1*R*,3*aS*,4*R*,5*S*,9*bR*)-benzyl4-(2-(benzyloxy)ethyl)-5-(nitromethyl)-3-phenyl-1,3,3*a*,4,5,9*b*-hexahydronaphtho[2,1-*c*]isoxazole-1-carboxylate (3j)

The title compound was prepared in 62% yield according to the typical procedure, as described above (The first step 10 hours, the second step 10 hours).

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.39-7.30 (m, 10H), 7.26-7.13 (m, 7H), 7.08-7.01 (m, 2H), 5.23 (s, 2H), 4.79 (dd, J = 5.2, 12.0 Hz, 1H), 4.70-4.68 (m, 1H), 4.56-4.47 (m,

3H), 4.24 (t, J = 7.2 Hz, 1H), 4.16-4.14 (m, 1H), 4.04 (t, J = 8.0 Hz, 1H), 3.65-3.63 (m, 2H), 2.46-1.43 (m, 1H), 1.98-1.84 (m, 1H), 1.66-1.64 (m, 1H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 170.1, 150.1, 138.1, 135.0, 134.8, 133.6, 129.7, 128.9, 128.7, 128.5, 128.0, 127.8, 127.73, 127.71, 127.0, 123.2, 116.2, 84.0, 77.6, 73.2, 68.2, 67.6, 67.2, 47.2, 38.8, 36.4, 28.8. HPLC: Chiralpak AD-H (hexane/i-PrOH = 80/20, flow rate 1 mL/min, λ = 210 nm), t_R (major) = 17.4 min, t_R (minor) = 29.7 min; >99% ee. $[\alpha]_D^{24}$ = 50.7 (c = 1.3, CH_2Cl_2). HRMS (ESI) calcd for $[\text{M}+\text{H}] \text{C}_{35}\text{H}_{35}\text{N}_2\text{O}_6$, m/z 579.2495, found 579.2488.

General procedure for the domino reaction with different hydroxyamine:

Valeraldehyde **2a** (0.6 mmol, 3 eq) was added to a suspension of catalyst **I** (2 mol%), benzoic acid (20 mol%), and nitroolefin acrylate **1a** (0.2 mmol, 1 eq) in water (1 mL) at room temperature. After 5 hours, the nitroolefin **1a** consumed, hydroxyamine (4-Me-PhNHOH, or 4-Cl-PhNHOH, or 4-Br-PhNHOH, or BnNHOH) (0.8 mmol, 4 eq)

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was added, and then stirred for 3-24 hours. After the reaction was complete (monitored by TLC and crude NMR), the mixture was extracted with DCM (5 mL x 2). The organic layer was washed successively with brine, and dried over Na₂SO₄. The solvent was removed under reduced pressure and the products were afforded by flash chromatography over silica gel (EtOAc/Hexane = 1/20-1/12).

(1*R*,3*aS*,4*R*,5*S*,9*bR*)-ethyl5-(nitromethyl)-4-propyl-3-*p*-tolyl-1,3,3*a*,4,5,9*b*-hexahydronaphtho[2,1-*c*]isoxazole-1-carboxylate (3k)

The title compound was prepared in 74% yield according to the General procedure, as described above (The second step 3 hours).

¹H-NMR (400 MHz, CDCl₃) δ 7.28-7.24 (m, 3H), 7.15-7.07 (m, 5H), 4.76 (dd, *J* = 5.6, 12.0 Hz, 1H), 4.66-4.63 (m, 1H), 4.41 (d, *J* = 7.2 Hz, 1H), 4.29 (q, *J* = 7.2 Hz, 2H), 4.23 (t, *J* = 7.2 Hz, 1H), 4.12 (m, 1H), 3.88 (t, *J* = 8.0 Hz, 1H), 2.33 (s, 3H), 2.18-2.16 (m, 1H), 1.51-1.42 (m, 2H), 1.36 (t, *J* = 7.2 Hz, 3H), 1.29-1.22 (m, 2H), 0.96 (t, *J* = 7.2 Hz, 3H). ¹³C-NMR (100 MHz, CDCl₃) δ 170.5, 147.7, 134.8, 134.0, 133.3, 129.7, 129.5, 128.0, 127.6, 127.0, 117.2, 84.0, 77.5, 67.5, 61.9, 47.0, 38.6, 37.7, 30.4, 20.7, 20.2, 14.2, 14.1. HPLC: Chiralpak AD-H (hexane/*i*-PrOH = 80/20, flow rate 1 mL/min, λ = 210 nm), *t*_R (major) = 10.7 min, *t*_R (minor) = 30.2 min; >99% ee. [α]_D²⁴ = 74.0 (c = 1.0, CH₂Cl₂). HRMS (ESI) calcd for [M+H] C₂₅H₃₁N₂O₅, *m/z* 439.2233, found 439.2234.

(1*R*,3*aS*,4*R*,5*S*,9*bR*)-ethyl3-(4-chlorophenyl)-5-(nitromethyl)-4-propyl-1,3,3*a*,4,5,9*b*-hexahydronaphtho[2,1-*c*]isoxazole-1-carboxylate (3l)

The title compound was prepared in 64% yield according to the General procedure, as described above (The second step 3 hours).

¹H-NMR (400 MHz, CDCl₃) δ 7.29-7.23 (m, 5H), 7.13-7.07 (m, 3H), 4.74 (dd, *J* = 6.0, 12.0 Hz, 1H), 4.67-4.64 (m, 1H), 4.43 (d, *J* = 7.2 Hz, 1H), 4.28 (q, *J* = 7.2 Hz, 2H), 4.22 (t, *J* = 7.2 Hz, 1H), 4.10-4.08 (m, 1H), 3.91 (t, *J* = 8.0 Hz, 1H), 2.23-2.21 (m, 1H), 1.51-1.45 (m, 2H),

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1.34 (t, $J = 7.2$ Hz, 3H), 1.34-1.29 (m, 2H), 0.95 (t, $J = 7.2$ Hz, 3H). ^{13}C -NMR (100 MHz, CDCl_3) δ 170.3, 148.9, 134.7, 133.6, 129.6, 128.9, 128.4, 128.1, 127.8, 127.1, 117.7, 84.2, 77.2, 67.4, 62.0, 47.1, 38.4, 37.8, 30.4, 20.2, 14.2, 14.1. HPLC: Chiralpak AD-H (hexane/*i*-PrOH = 80/20, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (major) = 9.3 min, t_R (minor) = 38.1 min; >99% ee. $[\alpha]_D^{24} = 83.9$ ($c = 1.0$, CH_2Cl_2). HRMS (ESI) calcd for $[\text{M}+\text{H}] \text{C}_{24}\text{H}_{28}\text{N}_2\text{O}_5\text{Cl}$, m/z 459.1687, found 459.1676.

(1*R*,3*aS*,4*R*,5*S*,9*bR*)-ethyl 3-(4-bromophenyl)-5-(nitromethyl)-4-propyl-1,3,3*a*,4,5,9*b*-hexahydronaphtho[2,1-*c*]isoxazole-1-carboxylate (3m)

The title compound was prepared in 67% yield according to the General procedure, as described above (The second step 3 hours).

^1H -NMR (400 MHz, CDCl_3) δ 7.42 (d, $J = 8.8$ Hz, 2H), 7.3-7.25 (m, 3H), 7.08-7.05 (m, 1H), 7.06 (d, $J = 8.8$ Hz, 1H), 4.74 (dd, $J = 6.0, 12.0$ Hz, 1H), 4.67-4.64 (m, 1H), 4.43 (d, $J = 6.8$ Hz, 1H), 4.28 (q, $J = 7.2$ Hz, 2H), 4.22 (t, $J = 7.2$ Hz, 1H), 4.10-4.08 (m, 1H), 3.91 (t, $J = 8.0$ Hz, 1H), 2.23-2.18 (m, 1H), 1.65 (m, 1H), 1.52-1.46 (m, 2H), 1.34 (t, $J = 7.2$ Hz, 3H), 1.29-1.26 (m, 1H), 0.95 (t, $J = 7.2$ Hz, 3H). ^{13}C -NMR (100 MHz, CDCl_3) δ 170.3, 149.5, 134.7, 133.6, 131.8, 129.6, 128.2, 127.8, 127.0, 117.9, 115.8, 84.2, 77.2, 67.3, 62.0, 47.1, 38.5, 37.9, 30.5, 20.2, 14.2, 14.1. HPLC: Chiralpak AD-H (hexane/*i*-PrOH = 80/20, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (major) = 8.7 min, t_R (minor) = 34.0 min; >99% ee. $[\alpha]_D^{24} = 87.5$ ($c = 0.9$, CH_2Cl_2). HRMS (ESI) calcd for $[\text{M}+\text{H}] \text{C}_{24}\text{H}_{28}\text{N}_2\text{O}_5\text{Br}$, m/z 504.3846, found 504.3848.

(1*R*,3*aS*,4*R*,5*S*,9*bR*)-ethyl 3-benzyl-5-(nitromethyl)-4-propyl-1,3,3*a*,4,5,9*b*-hexahydronaphtho[2,1-*c*]isoxazole-1-carboxylate (3n)

The title compound was prepared in 48% yield according to the General procedure, as described above (The second step 24 hours).

^1H -NMR (400 MHz, CDCl_3) δ 7.42 (d, $J = 6.8$ Hz, 2H), 7.36-7.21 (m, 6H), 6.98 (d, $J = 7.6$ Hz, 1H), 4.61 (m, 1H), 4.52 (dd, $J = 6.4, 12.0$ Hz, 1H), 4.37-4.12 (m, 5H), 4.02-4.00

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(m, 2H), 3.24 (t, $J = 7.2$ Hz, 1H), 1.85 (m, 1H), 1.33 (t, $J = 7.2$ Hz, 3H), 1.36-1.30 (m, 3H), 0.93-0.90 (m, 1H), 0.85 (t, $J = 7.2$ Hz, 3H). ^{13}C -NMR (100 MHz, CDCl_3) δ 171.4, 136.9, 134.7, 134.3, 129.7, 129.2, 128.4, 127.8, 127.6, 127.5, 126.3, 83.8, 77.2, 66.2, 61.8, 61.6, 48.3, 37.9, 29.9, 20.2, 14.2, 14.1. HPLC: Chiralpak AD-H (hexane/*i*-PrOH = 80/20, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (major) = 5.7 min, t_R (minor) = 9.3 min; >99% ee. $[\alpha]_D^{24} = -4.6$ ($c = 0.8$, CH_2Cl_2). HRMS (ESI) calcd for $[\text{M}+\text{H}]$ $\text{C}_{25}\text{H}_{31}\text{N}_2\text{O}_5$, m/z 439.2233, found 439.2233.

Experimental procedure:

Propional **2b** (0.6 mmol, 3 eq) was added to a suspension of catalyst **I** (2 mol%), benzoic acid (20 mol%), and nitroolefin acrylate **1c** (0.2 mmol, 1 eq) in water (1 mL) at room temperature. After 5 hours, the nitroolefin **1c** consumed, 4-chloro-*N*-hydroxybenzenamine (0.8 mmol, 4 eq) was added, and then stirred for 4 hours. After the reaction was complete (monitored by TLC and crude NMR), the mixture was extracted with DCM (5 mLx2). The organic layer was washed successively with brine, and dried over Na_2SO_4 . The solvent was removed under reduced pressure and the products were obtained in 61% yield after flash chromatography over silica gel (EtOAc/Hexane = 1/20-1/10).

^1H -NMR (400 MHz, CDCl_3) δ 7.26 (d, $J = 8.8$ Hz, 2H), 7.09 (d, $J = 8.8$ Hz, 1H), 6.72 (s, 1H), 6.55 (s, 1H), 5.95 (s, 2H), 4.70-4.61 (m, 2H), 4.36 (d, $J = 7.2$ Hz, 1H), 4.28 (q, $J = 7.2$ Hz, 2H), 4.03 (t, $J = 7.2$ Hz, 1H), 3.93-3.91 (m, 1H), 3.72 (t, $J = 8.0$ Hz, 1H), 2.33-2.28 (m, 1H), 1.32 (t, $J = 7.2$ Hz, 3H), 1.10 (d, $J = 7.2$ Hz, 3H). ^{13}C -NMR (100 MHz, CDCl_3) δ 170.2, 148.8, 147.5, 147.4, 128.9, 128.5, 127.5, 126.7, 118.0, 109.2, 106.9, 101.4, 84.0, 77.6, 68.7, 62.1, 47.2, 40.2, 32.8, 14.2, 14.1. HPLC: Chiralpak AD-H (hexane/*i*-PrOH = 80/20, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (major) = 16.0 min, t_R (minor) = 35.5 min; >99% ee. $[\alpha]_D^{24} = 86.5$ ($c = 0.5$, CH_2Cl_2). HRMS (ESI) calcd for $[\text{M}+\text{H}]$ $\text{C}_{23}\text{H}_{23}\text{N}_2\text{O}_7\text{Cl}$, m/z 475.1272, found 475.1285.

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General procedure for synthesis of α -hydroxy- γ - amino acid derivative:

(*R*)-ethyl-2-hydroxy-2-((1*R*,2*S*,3*R*,4*S*)-4-(nitromethyl)-2-(phenylamino)

-3-propyl-1,2,3,4-tetrahydronaphthalen-1-yl)acetate (**5**)

10% Pd-C (30 mg) was added to a solution of **3a** (0.1 mmol) in methanol (5 mL) at room temperature. Fill in hydrogen with a H₂ balloon. After 2 hours, the mixture was filtered with celite. And then the solvent was removed under reduced pressure to afford the product in almost quantitative yield.

¹H-NMR (400 MHz, CDCl₃) δ 7.40-7.21 (m, 3H), 7.16 (t, *J* = 7.2 Hz, 1H), 7.04 (d, *J* = 8.0 Hz, 1H), 6.71 (t, *J* = 7.2 Hz, 1H), 6.55 (d, *J* = 8.0 Hz, 2H), 4.65 (s, 1H), 4.60 (dd, *J* = 4.8, 12.0 Hz, 1H), 4.53-4.50 (m, 1H), 4.01-3.92 (m, 4H), 3.78-3.76 (m, 2H), 3.56-3.51 (m, 1H), 3.29 (s, 1H), 2.70-2.68 (m, 1H), 1.56-1.51 (m, 3H), 1.12-0.98 (m, 1H), 1.01 (t, *J* = 7.2 Hz, 3H), 0.94 (t, *J* = 7.2 Hz, 3H). ¹³C-NMR (100 MHz, CDCl₃) δ 174.0, 146.7, 136.3, 135.1, 129.4, 129.0, 127.9, 127.5, 127.4, 117.8, 112.4, 78.4, 75.6, 62.0, 52.3, 42.9, 38.9, 30.2, 20.0, 14.4, 13.9. HPLC: Chiralpak AD-H (hexane/i-PrOH = 90/10, flow rate 0.8 mL/min, λ = 210 nm), *t*_R (minor) = 15.2 min, *t*_R (major) = 17.6 min; >99% ee. [α]₂₄^D = -28.0 (*c* = 1.0, CH₂Cl₂). HRMS (ESI) calcd for [M+H] C₂₄H₃₁N₂O₅, *m/z* 427.2233, found 427.2230.

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Chapter 4

ORGANOCATALYTIC ASYMMETRIC MICHAEL REACTIONS CATALYZED BY BIFUNCTIONAL THIOUREA CATALYST

4.1 Practical Organocatalytic Michael Addition of Dimethyl Malonate to Nitroolefins in Solvent-Free Condition using Bifunctional Cinchonidine Derivatives

The Michael addition reaction is well acknowledged as a notable C-C bond formation reaction.¹ Attracted by its numerous applications, the Michael reaction to nitroolefins has drawn much attention because the strong electron withdrawing nitro group in the adducts offers an easy access to versatile chiral building blocks for the synthesis of important, nitrogen containing bioactive agrochemical and pharmaceutical compounds.²

Recently, organocatalysts has emerged as a new and attractive area in asymmetric synthesis and great efforts have been put into the development of efficient organocatalysts to promote the asymmetric Michael addition of 1,3-dicarbonyl compounds to nitroolefins.³ However, The development of organocatalytic reactions that take place in solvent-free conditions are rarely studied. Moreover, harsh reaction conditions and high catalyst loading are pushed the reaction for a large scale industrial production to a very difficult extent. With these concerns in mind, the development of simple, efficient and easily synthesized organocatalysts that facilitate the asymmetric Michael addition reaction in solvent-free condition is highly desirable.

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Figure 1. Investigated organocatalysts.

Recently, thiourea derivatives serving as active metal-free bifunctional organocatalysts for a wide range of synthetically useful catalysts have been realized.⁴⁻⁵ In particular, thiourea-substituted cinchona alkaloid catalysts which were developed by several research groups have been identified as efficient bifunctional organocatalysts in asymmetric Michael reactions, owing to their special properties.⁶ Herein, we are pleased to present an example of asymmetric organocatalyzed Michael addition reaction of dimethyl malonate to nitroolefins under solvent-free condition using reductive cinchonidine derivative organocatalyst to attain high levels of yield and enantioselectivity. In the absence of solvents, the cost could be significantly reduced and the procedure is simplified to achieve maximum efficiency. Meanwhile reasonable reaction time and easily achieved reaction temperature also allow the procedure to be more effective and controllable. These characteristics make this reaction applicable to the industry.

A series of new bifunctional organocatalysts (Figure 1) were synthesized and screened for their feasibility to promote the asymmetric Michael addition reaction of

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dimethyl malonate and *trans*- β -nitrostyrene in the absence of solvent (Table 1). Our results have shown that, with a small catalyst loading of 10 mol%, all the reactions proceeded smoothly and were complete within a short period of time (3-5 h) to give products with high yield (93-97%) at room temperature. However, with monodentate hydrogen bond donor catalysts (no thiourea group such as **I**, **II**) nearly racemic products were obtained (Table 1, entries 1-2). Thiourea containing catalysts (Table 1, entries 3-7) displayed higher enantioselectivities (73%-92% ee). While, thiourea catalyst **III** led to almost no reactivity. In contrast, replacing 3,5-bis(trifluoromethyl)phenyl group of **V**, with other aryl groups, such as phenyl **IV** and naphthyl **VI**, decreased the enantioselectivity due to the weak hydrogen-bonding

Table 1. Organocatalytic Michael Reaction of Dimethyl Malonate to *trans*- β -nitrostyrene^a

Reaction scheme: **1a** + **2a** $\xrightarrow[\text{Solvent-free}]{10 \text{ mol\% catalysts}}$ **3a**

entry	catalyst	time (h)	T (°C)	yield (%) ^b	ee (%) ^c
1	I	5	23	93	2
2	II	5	23	94	4
3	V	3	23	95	90
4	IV	4	23	96	77
5	VI	4	23	95	73
6	VII	3	23	97	92
7	VIII	3	23	96	90
8 ^d	VII	5	4	97	96
9 ^d	VII	8	4	98	96
10 ^e	VII	27	4	85	94

^a Unless otherwise specified, all the reactions were carried out using **1a** (0.2 mmol, 1 equiv) and **2a** (0.2 mL) with 10 mol% of catalysts. ^b Isolated yields. ^c Determined by chiral HPLC analysis. ^d 5 mol% of catalyst. ^e 2 mol% of catalyst.

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ability (entries 4, 5). Notably, catalyst **VII** which is easily prepared from commercially accessible material, facilitates the reaction with high yield (97%) and excellent enantioselectivity (92% ee) (entry 7). These results demonstrated that the reduction of double bond is essential for higher enantioselectivities. Based on this fact, we reduced the reaction temperature to 4 °C, where higher enantioselectivity was achieved with catalyst **VII** (entry 8). Further optimization showed that the reaction could be performed with as low as 5 mol% of catalyst loading (entry 9) and a comparable result (98% yield, 96% ee) was achieved without an excessive increase in reaction time.

With the optimized reaction condition in hand, the reactions of dimethyl malonate to nitroolefins with various substituents were examined to establish a general utility of this asymmetric Michael addition reaction (Table 2). All the reactions proceeded smoothly and were complete within a relatively short period of time (8-16 hours) at 4°C. The desired adducts were obtained exclusively in yields of 92-99% (almost quantitative) and high enantioselectivity (90-97% ee). The reactions of aromatic nitroolefins, bearing both electron-donating (Table 2, entries 2-6) and electron-withdrawing group (entries 7-9) on the phenyl rings, proceeded efficiently. The heterocyclic thienyl-, furanyl- and naphthyl-substituted nitroolefins (entries 10-13) also participated in this process, giving good yields and enantioselectivities.

However, the substrate with a nitro group on the para position failed to give good enantioselectivities (only 73% ee). To account for this, we envisioned that the *p*-phenyl position substituted nitro group may interfere in the bonding between the catalyst and the nitro group adjacent to the double bond, which may lead to relatively low ee value. Notably, only one Michael adduct was obtained from the reaction of styrene with 92% ee (Entry 14). Theoretically, two positions are possibly attacked due to the two congruous double bonds showing the great regioselectivity and enantioselectivity of this method.

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Table 2. Michael Reaction of Dimethyl Malonate to *trans*-Nitroolefins^a

entry	R	product	time (h)	yield (%) ^b	ee (%) ^c
1	Ph	3a	8	98	96
2	2-OMe-Ph	3b	8	95	92
3	3-OMe-Ph	3c	8	96	93
4	4-OMe-Ph	3d	8	96	96
5	2-Me-Ph	3e	15	92	97
6	4-Me-Ph	3f	12	95	93
7	4-Br-Ph	3g	9	99	91
8	4-Cl-Ph	3h	9	96	95
9	2-Cl-Ph	3i	10	97	96
10	3-Furyl	3j	8	94	91
11	2-Furyl	3k	8	94	90
12	2-Thienyl	3l	9	96	97
13	1-Naphthyl	3m	13	92	93
14	Styrene	3n	16	91	92

^a All the reactions were carried out using **1** (0.2 mmol, 1 equiv) and **2a** (0.2 mL) in the presence of 5 mol% of **VII** at 4°C. ^b Isolated yields. ^c Determined by chiral HPLC analysis.

According to the dual activation model proposed by Takemoto,⁷ the two substrates involved in the reaction are activated simultaneously by the catalyst as shown in Scheme 1. Since nitro compounds are known to form hydrogen bonds with thiourea, nitroolefins have been assumed to interact with the thiourea part of the catalyst via numerous H-bonds, thus increasing the electrophilicity of the reacting carbon center⁸. However, the enolic forms of dione is presumed to interact with the amine, which is followed by deprotonation to give a very nucleophilic enolate species. In this model,

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we predicted the configuration of **3h** to be *S*. X-ray analysis was used to verify the absolute configuration of **3h** (Figure 2).

Scheme 1. Proposed action of catalyst.

Figure 2. Absolute structure of compound **3h** by X-ray analysis.

4.2 Highly Efficient Organocatalytic Michael Addition of 2,4-Pentandione to Nitroalkenes Under Solvent-free Conditions

In recent years, thioureas derived from binaphthyl⁹ have been employed in the Michael addition between 2,4-pentandione and nitroolefins with the usage of solvent. Moderate yields were obtained, even with a long reaction times, thus, indicating the moderate catalytic activity of the catalyst. Moreover, the catalyst is not readily accessible and is expensive. Therefore, there is the need of improvement, particularly with regards to the design of an inexpensive and practical organocatalyst capable of catalyzing the reaction efficiently, even under solvent-free conditions. The results of this investigation revealed that the catalyst proved to be efficient in the carbon-carbon bond forming reaction for a short reaction time, achieving high enantioselectivity under neat condition.

Our study began with six organocatalysts, (Figure 1) which comprise of compounds **II-VII**, were investigated under different temperatures and solvent conditions. It was found that catalysts **II** and **III** displayed poor catalytic activities. Although **II** resulted in good yield, the product **4a** was attained with low enantioselectivity (Table 3, entries 2). Under identical reaction conditions, catalysts **IV-VII** showed high catalytic activities with excellent yield and enantioselectivities (entries 1, 4-6). However, catalyst **VII** showed a shorter reaction time and higher enantioselectivity than the other catalysts. The organocatalyst **VII** has proven to be the best selection for in-depth studies with its short reaction time (0.5 h), high enantioselectivity (95% ee) and yield (almost quantitative). Furthermore, this catalyst

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Table 3. Screening of Organocatalysts for Michael Addition of 2,4-Pentandione and *trans*- β -nitrostyrene ^a

entry	catalyst	solvent	time (h)	yield (%) ^b	ee (%) ^c
1	VII	neat	0.5	98	95
2	II	neat	2	97	20
3	III	neat	10	n.p. ^d	n.d. ^e
4	IV	neat	1	96	85
5	V	neat	0.8	98	92
6	VI	neat	0.8	97	88
7	VII	THF	10	82	89
8	VII	Et ₂ O	10	90	87
9 ^f	VII	neat	3	97	95
10 ^g	VII	neat	1	98	95

^a Unless otherwise specified, the reaction was carried out with dione **2b** (0.2 mL eq) and nitrostyrene (0.2 mmol, 1 eq) in the presence of 10 mol% of catalyst at room temperature. ^b Isolated yields. ^c Enantiomeric excess (ee) determined by chiral HPLC analysis (Chiralpak AS-H). ^d No product. ^e Not determined. ^f reaction at +4 °C. ^g 5 mol% catalyst was used.

is also easily available with the use of inexpensive and commercially-available reactants in a three-step reaction. Solvent screening revealed that numerous solvents were tolerated. Generally, in polar solvents, almost no enantioselectivity for product **4a** was observed because of the destruction of hydrogen bonding interactions between the thiourea and the nitro group in the substrate by strongly H-bonding acceptor solvents. In less polar solvents, high enantioselectivities were obtained (entries 7, 8), but the result is no better than under solvent free condition. Further optimization of this process showed that the reaction could be performed with as low as 5 mol% of catalyst loading (entry 10), where a comparable result (95% ee, 98% yield) was

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achieved without an excessive increase in reaction time. Furthermore, the reaction is also not very sensitive to a change in temperature (entry 9).

Table 4. Results for Michael Addition of 2,4-Pentandione and nitroolefins using catalyst **VII**^a

entry	R	product	time (h)	yield (%) ^b	ee (%) ^c
1	Ph	4a	1	98	95
2	2-OMe-Ph	4b	1	92	99
3	3-OMe-Ph	4c	1	93	93
4	4-OMe-Ph	4d	2	99	96
5	2-Me-Ph	4e	2	93	95
6	3-Me-Ph	4f	2	92	94
7	4-Me-Ph	4g	1	95	96
8	4-Br-Ph	4h	1	99	95
9	4-Cl-Ph	4i	1	96	95
10	1-Naphthyl	4j	2	92	91
11	3-Furan	4k	1	98	95
12	2-Furan	4l	1	94	96
13	2-Thienyl	4m	1	96	94
14	Styrene	4n	4	92	95

^a The reactions were carried out with dione **2b** (0.2 mL) and nitroolefins **1** (0.2 mmol, 1 eq) in the presence of 5 mol% of catalyst **VII** at room temperature. ^bIsolated yield after chromatographic purification. ^c Determined by chiral HPLC analysis.

Encouraged by these results, we investigated the applicability of different substrates. It was discovered that most of the reactions are complete within 1 hour (Table 4, entries 1-10). In addition, most of the reactions showed excellent enantioselectivities (>90%), with the highest being 99% ee. Different aromatic rings

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have a very limited effect on the stereoselection of conjugate additions. Regardless of the types of substituents on the aromatic rings, be it electron- withdrawing (entry 8, 9), –donating (entries 2-7), neutral (entry 1, 10) groups, or heterocyclic compounds (entries 11-13) and substrates containing a variety of substitution (*para*, *meta* and *ortho*) groups participated in this reaction efficiently. The reactions proceeded to give highly enantioselective adducts. To our surprise, if the aromatic ring contains a nitro group, there will be a large decrease in enantiomeric excess (72% ee). This may be attributed to the thiourea group in the catalyst catching the two nitro groups. Notably, only one Michael adduct was obtained from the reaction of styrene with 95% ee value (Entry 14). Theoretically, two positions are possibly attacked due to the two congruous double bonds showing the great regioselectivity and enantioselectivity of this method.

According to the dual activation model proposed by Takemoto⁷, the two substrates involved in the reaction are activated simultaneously by catalyst **VII** as shown in the Scheme 1. Since nitro compounds are known to form hydrogen bonds with thiourea, nitroolefins have been presumed to interact with the thiourea moiety of **VII** via hydrogen bonding, thereby increasing the electrophilicity of the reacting carbon center¹⁰. However, the enolic forms of dione are presumed to interact with the amine, followed by deprotonation to give a very nucleophilic enolate species. (Scheme 2) In this model, we predicted the configuration of the product to be *R*. For one of the products, X-ray crystallography was used to verify that the absolute configuration of **4m** was *R*. (Figure 3)

Scheme 2. Proposed action of catalyst.

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Figure 3. X- ray crystal structure of **4m**.

In summary, an easy and practical method for asymmetric Michael addition reaction of dimethyl malonate or 2,4-pentandione to nitroolefins under solvent-free condition using a bifunctional cinchonidine derived organocatalyst was developed. Such a catalyst is readily accessible and can catalyze the Michael addition efficiently. Moreover, the different optically active nitroalkane derivatives can be synthetically and biologically important by converting them into other valuable substances.² The lack solvent is definitely a green and clean approach compared to using aqueous media or other non-classical solvents.¹¹

4.3 Highly Recyclable Organocatalysis: Enantioselective Michael Addition of 1,3-Diaryl-1,3-propanedione to Nitroolefins

With the dramatically developing interest in organocatalysis, many organocatalytic reactions with high selectivities were easily obtained.^{12,13} It is essential to fully consider the potential limitations and drawbacks related to the use of organocatalysts. Typically, organocatalytic reactions are conducted in organic solvents or in water (need much solvent for extraction) and need a large excess of toxic reactants. Sometime, owing to the desire of complete transformations in an acceptable time frame, usually high catalyst loadings (10-30 mol%) are necessary.^{13,14} Due to these above mentioned, the design and development of recyclable¹⁵ organocatalytic strategies take much attention on recent chemical synthesis. However, to the best of our knowledge, only a few recyclable processes were designed, such as attaching the catalyst to polymers,¹⁶ using recyclable fluorous catalysts¹⁷ and ionic liquids.¹⁸ These processes gave only moderate results. Thus, the development of a highly enantioselective recyclable strategy for the organocatalysis remains a challenging task.

Based on previous reports, there is rarely an example of the use of aromatic ketones as Michael donors. 1,3-Diaryl-1,3-propanedione is normally not considered to be a good Michael donor in organocatalysis due to the conjugation of the phenyl

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groups with carbonyls and it usually requires more harsh reaction conditions and long reaction time. Since the similar reaction using 2,4-pentandione shows good reactivity and enantioselectivity, we envisioned that the problem of using 1,3-diaryl-1,3-propanedione could be overcome by screening suitable organocatalysts.

Catalyst **V** was perceived as a good choice to catalyze the reaction of 1,3-diphenyl-1,3-propanedione (**2c**) and *trans*- β -nitrostyrene (**1a**). The survey of solvents revealed that reactions conducted in THF, hexane and diethyl ether all offered good yields and enantioselectivities (up to 95% ee). Notably, it was found that the Michael adduct was precipitated as a solid in diethyl ether which at the same time gave the highest enantioselectivity. This prompted us to develop a simple and practical methodology through which reusing the catalyst and the excess reactant became possible. Cinchonidine **I** and quinine **II**, together with three other thiourea organocatalysts that were readily prepared, were examined for their catalytic activities. (Figure 1)

As shown in table 5, catalyst **VIII** promoted the reaction with highest enantioselectivity. The enantioselectivity excess was increased to 96% by lowering the temperature to 0 °C, but the reaction time was increased significantly (28 hours, entry 10). Good results were then obtained when 3 equivalents of dione **2c** were used and the reaction was complete within 4 hours at room temperature. In accordance with our prediction, **I** and **II** afforded very low enantioselectivities, which demonstrated that the thiourea group was indispensable to high stereoselectivity.

Table 5. Organocatalytic Asymmetric Michael Addition: Screen conditions^a

entry	catalyst	solvent	time (h)	yield (%) ^b	ee (%) ^c
1	V	Et ₂ O	18	91	94
2	V	hexane	19	87	93
3	V	THF	22	90	94

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4	V	MeOH	25	67	65
5	I	Et ₂ O	11	92	2
6	II	Et ₂ O	11	93	20
7	VI	Et ₂ O	21	92	93
8	VII	Et ₂ O	21	91	94
9	VIII	Et ₂ O	19	91	95
10 ^d	VIII	Et ₂ O	28	86	96
11 ^e	VIII	Et ₂ O	4	97	95

^a Unless otherwise specified, all the reactions were carried out using dione **2c** (0.1 mmol, 1 equiv) and nitrostyrene (**1a**) (0.12 mmol, 1.2 equiv) with 10 mol% of catalysts at rt (23 °C). ^b Isolated yields. ^c Determined by chiral HPLC analysis (chiralpak AS-H). ^d The reaction was carried out at 0 °C. ^e The reaction was conducted using 3 equiv of dione **2c**.

With the optimized reaction condition in hand, various nitroolefin substrates were employed to establish the generality of this method (Table 6). All the reactions proceeded smoothly at room temperature in the presence of 10 mol% of catalyst **VIII** and were completed within 3-8 hours. The desired adducts were obtained exclusively in high yields (91-97%) and excellent enantioselectivities (91% ee to 98% ee). The nitroolefins bearing either neutral (entry 1), electron-donating (entries 2-6), electron-withdrawing (entries 7-9, 14, 15) or heterocyclic compounds (entries 10-12) and substrates containing a variety of substitution (*para*, *meta* and *ortho*) groups participated in this reaction efficiently.

To examine the recyclability of this organocatalysis, the reaction of 3-diphenyl-1,3-propanedione (**2a**) (0.3 mmol, 3 equiv) and nitroolefin (**1a** and **1g**) (0.1 mmol, 1 equiv) in diethyl ether (0.5 mL) was further studied as an example using 10 mol% catalyst **VIII**. Interestingly, the Michael adduct's very poor solubility in diethyl ether could be utilized for separating organocatalyst **VIII** from the product just by simple centrifuge since it was precipitated from the reaction solution.

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Table 6. Michael Addition of 1,3-Diphenyl-1,3-propanedione to *trans*-Nitroolefins Catalyzed by catalyst **VIII**^a

entry	R	product	time (h)	yield (%) ^b	ee (%) ^c
1	Ph	5a	3	97	95
2	4-OMe-Ph	5b	5	93	91
3	3-OMe-Ph	5c	5	92	92
4	2-Me-Ph	5d	5	94	96
5	3-Me-Ph	5e	5	96	95
6	4-Me-Ph	5f	5	94	95
7	4-Br-Ph	5g	3	95	94
8	4-Cl-Ph	5h	4	97	97
9	2-Cl-Ph	5i	3	95	95
10	2-Thienyl	5j	4	97	96
11	2-Furyl	3k	4	95	94
12	3-Furyl	5l	4	96	95
13	1-Naphthyl	5m	5	91	93
14	2-NO ₂ -Ph	5n	4	97	98
15	4-NO ₂ -Ph	5o	4	96	94

^a All the reactions were carried out using **1** (0.1 mmol, 1 equiv) and **2c** (0.3 mmol, 3 equiv) in the presence of 10 mol% **VIII** at rt. ^b Isolated yields. ^c Determined by chiral HPLC analysis.

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Table 7. Recycling of Organocatalytic Michael Reaction^a

cycle	R = Ph (5a)			R = 4-Br-Ph (5g)		
	time (h) ^b	yield ^c	ee (%) ^d	t (h) ^b	yield ^c	ee (%) ^d
1	3		96	3		94
2	3		95	4		94
3	5		95	4		94
4	7	Average	95	4	Average	94
5	7	97%	95	4	95%	94
6	8	for 10	95	6	for 10	94
7	10	recycles	94	7	recycles	97
8	10		95	7		92
9	12		95	10		94
10	15		95	12		98

^a The reactions were carried out using **1a** or **1g** (0.1 mmol, 1 equiv) and **2c** (0.3 mmol, 3 equiv) with 10 mol% of **IV** in cycle 1, and in recycles 2-10 only **1a** or **1g** (0.1 mmol) and **2c** (0.1 mmol) added. ^b Reaction progress was monitored by TLC. ^c Average isolated yields after completion of the reaction. ^d Determined by chiral HPLC analysis.

All the catalyst **VIII** (0.1 equiv) and 2 equivalents of the excess dione **2c** were retained in the filtrate while the isolated solid (from filtration and washing with a small amount of diethyl ether) contained the product exclusively (determined by ¹H-NMR). The excellent enantioselectivity (**5a**: 95% ee, **5g**: 94% ee) was shown in table 3. The filtrate was evaporated to 0.5 mL before the dione **2c** (1 equiv) and nitroolefin (**1a** or

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1g) (1 equiv) were added to the solution for the next round of the Michael reaction. This was to ensure that the reaction condition for each cycle was the same as those previously tried. This process was repeatedly tried and amazingly, the catalyst maintained its high reactivity and efficiency in each reuse, giving almost quantitative yields in each cycle and excellent enantioselectivities even after 10 cycles (Table 7). Based on this easily accessible *product (precipitate)-catalyst (soluble) separation*, the pure product is isolated by a simple filtration and the catalyst which is kept in the filtrate could be reused directly for the next cycle. Hence, a new strategy for recycling the homogeneous organocatalyst was developed (Figure 4).

Figure 4. Recycling Strategy for the Michael Reaction.

The absolute configuration of one Michael adduct **3h** was determined to be *S* (Figure 5).

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Figure 5. X-ray structure of product **5h** (ORTEP).

In summary, we have demonstrated the first example of highly recyclable enantioselective Michael reactions depending on the simple isolation of the desired product by centrifugation. The Michael addition of nitroolefins **1** to dione **2**, which was usually not exploited as a donor, proceeded smoothly at room temperature, giving up to 97% yields and excellent enantioselectivities (up to 98% ee). Making use of the insolubility of the product, the simple strategy for recycling organocatalyst has been developed, which significantly simplified the separation and purification process. This strategy has a great potential in a large industrial scale production because it could greatly reduce the use of chiral catalysts and solvents in the efficient recycling. We hope that this idea could be well addressed and widely applied to facilitate environmentally friendly synthetic and industrial applications.

4.4 Experimental section

General experimental conditions (Chapter 2)

4.4.1 Typical procedure for the Michael reaction of dimethyl malonate to nitroolefins:

To a solution of nitroolefins (**1**) (0.20 mmol) and dimethyl malonate (**2**) (0.2 mL) was added **VII** (5.6 mg, 0.01 mmol) at 4 °C, and the resulting mixture was stirred strongly

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(very important to get high enantioselectivities) for 8-16 hours. Progress of the reaction was monitored by TLC. After completion of the reaction, the excess of **2** was removed under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc = 10/1 to 6/1) to afford **3** in almost quantitative yield. Enantiomeric excess was determined by HPLC analysis.

(S)-Dimethyl 2-(2-nitro-1-phenylethyl)malonate (3a):¹

The title compound was prepared in 98% yield according the typical procedure as described above.

¹H-NMR (400 MHz, CDCl₃) δ 7.36-7.27 (m, 3H), 7.25-7.23 (m, 2H), 4.94 (dd, *J* = 5.2, 13.2 Hz, 1H), 4.89 (dd, *J* = 9.2, 13.2 Hz, 1H), 4.26 (ddd, *J* = 5.2, 9.0, 9.0 Hz, 1H), 3.88 (d, *J* = 9.0 Hz, 1H), 3.77 (s, 3H), 3.57 (s, 3H). ¹³C-NMR (100 MHz, CDCl₃) δ 167.78, 167.18, 136.06, 128.96, 128.35, 121.80, 77.32, 54.67, 52.95, 52.76, 40.86. HPLC: Chiralcel OD-H (hexane/*i*-PrOH = 80/20, flow rate 1 mL/min, λ = 210 nm), *t*_R (major) = 13.7 min, *t*_R (minor) = 15.4 min; 96% ee. [α]_D²⁵ = 4.5 (*c* = 1.1, CHCl₃).

(S)-Dimethyl 2-(1-(2-methoxyphenyl)-2-nitroethyl)malonate (3b):²

The title compound was prepared in 95% yield according the typical procedure as described above.

¹H-NMR (400 MHz, CDCl₃) δ 7.29-7.25 (m, 1H), 7.16-7.14 (m, 1H), 6.91-6.88 (m, 2H), 5.04 (dd, *J* = 9.0, 13.0 Hz, 1H), 4.89 (dd, *J* = 4.6, 13.0 Hz, 1H), 4.41 (ddd, *J* = 4.8, 9.6, 9.6 Hz, 1H), 4.19 (d, *J* = 10.0 Hz, 1H), 3.88 (s, 3H), 3.76 (s, 3H), 3.52 (s, 3H). ¹³C-NMR (100 MHz, CDCl₃) δ 168.29, 167.62, 157.30, 130.55, 129.69, 123.65, 120.85, 111.15, 75.99, 55.45, 52.87, 52.61, 52.53, 40.32. HPLC: Chiralcel OD-H (hexane/*i*-PrOH = 80/20, flow rate 1 mL/min, λ = 254 nm), *t*_R (major) = 7.9 min, *t*_R (minor) = 9.9 min; 92% ee. [α]_D²⁵ = 21.3 (*c* = 1.0, CHCl₃).

(S)-Dimethyl 2-(1-(3-methoxyphenyl)-2-nitroethyl)malonate (3c):²

The title compound was prepared in 96% yield according the typical procedure as described above.

¹H-NMR (400 MHz, CDCl₃) δ 7.28-7.23 (m, 1H), 6.85-6.78 (m,

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3H), 4.96-4.86 (m, 2H), 4.24 (ddd, $J = 5.6, 8.8, 8.8$ Hz, 1H), 3.88 (d, $J = 8.8$ Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 3.61 (s, 3H). ^{13}C -NMR (100 MHz, CDCl_3) δ 167.87, 167.25, 159.89, 137.72, 130.08, 119.84, 113.92, 113.63, 77.32, 55.24, 54.72, 53.03, 52.90, 42.88. HPLC: Chiralcel OD-H (hexane/*i*-PrOH = 80/20, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (minor) = 16.3 min, t_R (major) = 19.1 min; 93% ee. $[\alpha]_{\text{D}}^{25} = 5.3$ ($c = 1.2$, CHCl_3).

(*S*)-Dimethyl 2-(1-(4-methoxyphenyl)-2-nitroethyl)malonate (3d):

The title compound was prepared in 96% yield according to the typical procedure as described above.

^1H -NMR (400 MHz, CDCl_3) δ 7.08 (d, $J = 8.8$ Hz, 2 H), 6.77 (d, $J = 8.8$ Hz, 2 H), 4.83 (dd, $J = 5.0, 13.0$ Hz, 1H), 4.89 (dd, $J = 9.2, 13.0$ Hz, 1H), 4.26 (ddd, $J = 5.0, 9.2, 9.0$ Hz, 1H), 3.76 (d, $J = 9.2$ Hz, 1H), 3.71 (s, 3H), 3.69 (s, 3H), 3.50 (s, 3 H). ^{13}C -NMR (100 MHz, CDCl_3) δ 167.92, 167.31, 159.44, 128.96, 128.02, 127.85, 77.66, 55.21, 54.86, 53.01, 52.84, 42.30. HPLC: Chiralpak AD-H (hexane/*i*-PrOH = 80/20, flow rate 1 mL/min, $\lambda = 236$ nm), t_R (minor) = 14.1 min, t_R (major) = 15.7 min; 94% ee. $[\alpha]_{\text{D}}^{25} = 4.3$ ($c = 1.0$, CHCl_3).

(*S*)-Dimethyl 2-(2-nitro-1-*o*-tolylethyl)malonate (3e):

The title compound was prepared in 92% yield according to the typical procedure as described above.

^1H -NMR (400 MHz, CDCl_3) δ 7.18-7.14 (m, 4H), 4.93 (dd, $J = 5.2, 13.2$ Hz, 1H), 4.88 (dd, $J = 8.8, 13.2$ Hz, 1H), 4.60 (ddd, $J = 5.2, 9.0, 9.0$ Hz, 1H), 3.85 (d, $J = 9.2$ Hz, 1H), 3.78 (s, 3H), 3.55 (s, 3H), 2.46 (s, 3H). ^{13}C -NMR (100 MHz, CDCl_3) δ 168.00, 167.34, 136.99, 134.47, 131.29, 128.10, 126.56, 125.79, 77.34, 54.44, 53.02, 52.80, 37.74, 19.46. HPLC: Chiralcel OD-H (hexane/*i*-PrOH = 80/20, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (minor) = 13.1 min, t_R (major) = 13.9 min; 93% ee. $[\alpha]_{\text{D}}^{25} = 2.8$ ($c = 1.1$, CHCl_3).

(*S*)-Dimethyl 2-(2-nitro-1-*p*-tolylethyl)malonate (3f):³

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The title compound was prepared in 95% yield according the typical procedure as described above.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.08-7.02 (m, 4 H), 6.77 (d, $J = 8.8$ Hz, 2 H), 4.83-4.79 (dd, $J = 5.0, 13.0$ Hz, 2 H), 4.89 (dd, $J = 9.2, 13.0$ Hz, 1H), 4.14 (ddd, $J = 5.2, 9.0, 9.0$ Hz, 1H), 3.78 (d, $J = 9.0$ Hz, 1H), 3.70 (s, 3H), 3.51 (s, 3H), 2.24 (s, 3 H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 167.93, 167.30, 138.19, 133.00, 129.73, 127.68, 77.54, 54.81, 53.01, 52.85, 42.60, 21.10. HPLC: Chiralpak AD-H (hexane/*i*-PrOH = 80/20, flow rate 1 mL/min, $\lambda = 224$ nm), t_R (minor) = 9.8 min, t_R (major) = 11.0 min; 93% ee. $[\alpha]_{\text{D}}^{25} = -5.0$ ($c = 1.6$, CHCl_3).

(S)-Dimethyl 2-(1-(4-bromophenyl)-2-nitroethyl)malonate (3g): ³

The title compound was prepared in 99% yield according the typical procedure as described above.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.44 (d, $J = 8.4$ Hz, 2 H), 7.11 (d, $J = 8.4$ Hz, 2 H), 4.89 (dd, $J = 5.0, 13.2$ Hz, 1H), 4.82 (dd, $J = 9.2, 13.2$ Hz, 1H), 4.26 (ddd, $J = 5.0, 9.0, 9.0$ Hz, 1H), 3.80 (d, $J = 9.0$ Hz, 1H), 3.74 (s, 3H), 3.57 (s, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 167.62, 167.05, 135.18, 132.22, 129.63, 122.57, 77.09, 54.43, 53.14, 53.00, 42.38. HPLC: Chiralcel OD-H (hexane/*i*-PrOH = 80/20, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (major) = 16.4 min, t_R (minor) = 20.3 min; 91% ee. $[\alpha]_{\text{D}}^{25} = 4.2$ ($c = 1.4$, CHCl_3).

(S)-Dimethyl 2-(1-(4-chlorophenyl)-2-nitroethyl)malonate (3h): ³

The title compound was prepared in 96% yield according the typical procedure as described above.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.29 (d, $J = 8.4$ Hz, 2 H), 7.17 (d, $J = 8.4$ Hz, 2 H), 4.92-4.81 (m, 2H), 4.25-4.19 (m, 1H), 3.82 (d, $J = 9.0$ Hz, 1H), 3.76 (s, 3H), 3.58 (s, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 167.64, 167.06, 134.62, 134.43, 129.31, 129.28, 77.17, 54.50, 53.15, 52.99, 42.32. HPLC: Chiralcel OD-H (hexane/*i*-PrOH = 80/20, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (major) = 14.7 min, t_R (minor) = 19.6 min; 95% ee. $[\alpha]_{\text{D}}^{25} = 4.5$ ($c = 1.1$, CHCl_3).

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(S)-Dimethyl 2-(1-(2-chlorophenyl)-2-nitroethyl)malonate (3i): ⁴

The title compound was prepared in 97% yield according the typical procedure as described above.

¹H-NMR (400 MHz, CDCl₃) δ 7.44-7.42 (m, 1H), 7.28-7.24 (m, 3H), 5.14 (dd, J = 8.8, 13.6 Hz, 1H), 4.98 (dd, J = 4.4, 13.6 Hz, 1H), 3.87 (ddd, J = 4.4, 8.4, 8.4 Hz, 1H), 4.13 (d, J = 8.4 Hz, 1H), 3.75 (s, 3H), 3.665 (s, 3H). ¹³C-NMR (100 MHz, CDCl₃) δ 167.79, 167.28, 134.07, 133.60, 130.55, 129.57, 128.58, 127.35, 75.45, 52.84, 39.32. HPLC: Chiralcel OD-H (hexane/*i*-PrOH = 80/20, flow rate 1 mL/min, λ = 210 nm), t_R (major) = 10.8 min, t_R (minor) = 22.3 min; 96% ee. $[\alpha]_D^{25}$ = 4.5 (c = 1.3, CHCl₃).

(S)-Dimethyl 2-(1-(furan-3-yl)-2-nitroethyl)malonate (3j)

The title compound was prepared in 94% yield according the typical procedure as described above.

¹H-NMR (400 MHz, CDCl₃) δ 7.37 (m, 2H), 6.32 (d, J = 1.1 Hz, 1H), 4.86 (dd, J = 5.2, 13.2 Hz, 1H), 4.80 (dd, J = 8.4, 13.2 Hz, 1H), 4.23-4.20 (m, 1 H), 3.83 (d, J = 8.0 Hz, 1H), 3.76 (s, 3H), 3.69 (s, 3H). ¹³C-NMR (100 MHz, CDCl₃) δ 167.82, 167.43, 143.72, 140.71, 120.53, 109.13, 77.13, 54.04, 53.00, 52.95, 34.25. HPLC: Chiralcel OD-H (hexane/*i*-PrOH = 80/20, flow rate 1 mL/min, λ = 254 nm), t_R (major) = 9.6 min, t_R (minor) = 16.8 min; 91% ee. $[\alpha]_D^{25}$ = 5.5 (c = 1.0, CHCl₃).

(R)-Dimethyl 2-(1-(furan-2-yl)-2-nitroethyl)malonate (3k): ³

The title compound was prepared in 94% yield according the typical procedure as described above.

¹H-NMR (400 MHz, CDCl₃) δ 7.26-7.20 (m, 1H), 6.94-6.90 (m, 2H), 4.93-4.91 (m, 2 H), 4.58-4.53 (m, 1 H), 3.90 (d, J = 8.0 Hz, 1H), 3.76(s, 3H), 3.67 (s, 3H). ¹³C-NMR (100 MHz, CDCl₃) δ 167.62, 167.13, 138.39, 127.12, 126.76, 125.67, 77.83, 55.29, 53.11, 53.09, 38.36. $[\alpha]_D^{25}$ = - 5.4 (c = 1.2, CHCl₃).

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(R)-Dimethyl 2-(2-nitro-1-(thiophen-2-yl)ethyl)malonate (3l):³

The title compound was prepared in 96% yield according to the typical procedure as described above.

¹H-NMR (400 MHz, CDCl₃) δ 7.36 (d, *J* = 1.1 Hz, 1H), 6.31 (dd, *J* = 1.8, 3.2 Hz, 1H), 6.24 (d, *J* = 3.2 Hz, 1H), 4.94 (dd, *J* = 8.4, 13.6 Hz, 1H), 4.89 (dd, *J* = 5.2, 13.6 Hz, 1H), 4.41 (ddd, *J* = 5.2, 8.0, 8.0 Hz, 1H), 3.96 (d, *J* = 8.0 Hz, 1H), 3.78 (s, 3H), 3.71 (s, 3H). ¹³C-NMR (100 MHz, CDCl₃) δ 167.54, 167.24, 149.38, 142.88, 110.58, 108.46, 75.28, 53.10, 53.07, 52.66, 36.83. HPLC: Chiralcel OD-H (hexane/*i*-PrOH = 80/20, flow rate 1 mL/min, λ = 246 nm), *t*_R (major) = 10.7 min, *t*_R (minor) = 13.4 min; 97% ee. [α]_D²⁵ = -7.6 (*c* = 1.6, CHCl₃).

(S)-Dimethyl 2-(1-(naphthalen-1-yl)-2-nitroethyl)malonate (3m):⁴

The title compound was prepared in 92% yield according to the typical procedure, as described above.

¹H-NMR (400 MHz, CDCl₃) δ 8.20 (d, *J* = 8.4 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.65-7.62 (m, 1H), 7.57-7.53 (m, 1H), 7.46-7.40 (m, 2H), 5.26-5.17 (m, 1H), 4.09 (dd, *J* = 4.4, 12.8 Hz, 1H), 4.13 (d, *J* = 7.6 Hz, 1H), 3.74 (s, 3H), 3.56 (s, 3H). ¹³C-NMR (100 MHz, CDCl₃) δ 168.24, 167.93, 134.20, 132.26, 130.98, 129.27, 129.06, 127.09, 126.14, 125.14, 123.99, 122.23, 76.65, 54.43, 52.94, 36.83. HPLC: Chiralcel OD-H (hexane/*i*-PrOH = 80/20, flow rate 1 mL/min, λ = 220 nm), *t*_R (major) = 16.4 min, *t*_R (minor) = 23.6 min; 93% ee. [α]_D²⁵ = -3.7 (*c* = 1.0, CHCl₃).

(R,E)-Dimethyl 2-(1-nitro-4-phenylbut-3-en-2-yl)malonate (3n)

The title compound was prepared in 91% yield according to the typical procedure, as described above.

¹H-NMR (400 MHz, CDCl₃) δ 7.36-7.28 (m, 5H), 6.60 (d, *J* = 16.0 Hz, 1H), 6.12 (m, 1H), 4.75 (m, 2H), 3.79-3.73 (m, 8H). ¹³C-NMR (100 MHz, CDCl₃) δ 167.66, 167.57, 135.81, 135.53, 128.58, 128.27, 126.61, 123.25, 77.00, 53.32, 52.93, 52.89, 41.24. HPLC: Chiralpak AS-H (hexane/*i*-PrOH = 85/15, flow rate 1 mL/min, λ = 210 nm), *t*_R (major) = 13.6 min, *t*_R (minor) = 15.2 min; 92% ee. [α]_D²⁵ = 2.3 (*c* = 1.1, CHCl₃).

4.4.2 Typical procedure for the Michael reaction of 2,4-pentanedione to nitroolefin

The catalyst amino-thiourea **VII** (5.6 mg, 0.01 mmol) was added to a vial containing **2b** (0.2 mL, 1.95 mmol) and **nitroolefins** (0.2 mmol) at room temperature. After the reaction was complete (monitored by TLC), the mixture was purified by a flash chromatography to afford the products.

(S)-3-(2-Nitro-1-phenylethyl) pentane-2,4-dione (Table 2, entry 1, 4a)

The title compound was prepared in 98% yield according to the typical procedure as described above.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.35-7.30 (m, 3H), 7.28-7.19 (m, 2H), 4.66-4.64 (m, 2H), 4.39 (d, $J = 10.8$ Hz, 1H), 4.29-4.24 (m, 1H), 2.31 (s, 3H), 1.96 (s, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 201.79, 201.04, 135.98, 129.36, 128.57, 127.95, 78.19, 70.70, 42.79, 30.47, 29.58. HPLC: Chiralpak AS-H (hexane/*i*-PrOH = 85/15, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (major) = 11.1 min, t_R (minor) = 16.4 min; 95% ee. $[\alpha]_D^{25} = 183.1$ ($c = 1.0$, CHCl_3). HRMS (EI) calcd for $\text{C}_{13}\text{H}_{15}\text{NO}_4$, m/z 249.1001, found 249.1004.

(S)-3-(1-(2-Methoxyphenyl)-2-nitroethyl) pentane-2,4-dione (Table 2, entry 2, 4b)

The title compound was prepared in 92% yield according to the typical procedure as described above.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.30-7.25 (m, 1H), 7.10-7.08 (m, 1H), 6.91-6.88 (m, 2H), 4.80 (dd, $J = 8.0, 12.0$ Hz, 1H), 4.63-4.57 (m, 2H), 4.52-4.47 (m, 1H), 3.89 (s, 3H), 2.28 (s, 3H), 1.95 (s, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 202.33, 201.63, 157.02, 130.26, 129.77, 123.50, 121.18, 111.25, 76.56, 68.97, 55.46, 38.98, 30.48, 28.78. HPLC: Chiralcel OD-H (hexane/*i*-PrOH = 85/15, flow rate 1 mL/min, $\lambda = 230$ nm), t_R (major) = 31.5 min, t_R (minor) = 34.0 min; 99% ee. $[\alpha]_D^{25} = 138.3$ ($c = 1.1$, CHCl_3). HRMS (EI) calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_5$, m/z 279.1101, found 279.1099.

(S)-3-(1-(3-Methoxyphenyl)-2-nitroethyl) pentane-2,4-dione (Table 2, entry 3, 4c)

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The title compound was prepared in 93% yield according to the typical procedure as described above.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.28-7.24 (m, 1H), 6.84-6.73 (m, 3H), 4.65-4.63 (m, 2H), 4.38 (d, $J = 10.4$ Hz, 1H), 4.26-4.23 (m, 1H), 3.79 (s, 3H), 2.30 (s, 3H), 1.98 (s, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 201.79, 201.00, 160.07, 137.57, 130.41, 119.91, 114.15, 113.59, 78.15, 70.61, 55.26, 42.77, 30.48, 29.62. HPLC: Chiralpak AS-H (hexane/*i*-PrOH = 85/15, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (major) = 17.0 min, t_R (minor) = 23.8 min; 93% ee. $[\alpha]_D^{25} = 140.8$ ($c = 1.2$, CHCl_3). HRMS (EI) calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_5$, m/z 279.1101, found 279.1110.

(*S*)-3-(1-(4-Methoxyphenyl)-2-nitroethyl)pentane-2,4-dione (Table 2, entry 4, 4d)

The title compound was prepared in 99% yield according to the typical procedure as described above.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.11 (d, $J = 8.8$ Hz, 2H), 6.85 (d, $J = 8.8$ Hz, 2H), 4.61-4.59 (m, 2H), 4.34 (d, $J = 10.8$ Hz, 1H), 4.24-4.18 (m, 1H), 3.78 (s, 3H), 2.29 (s, 3H), 1.95 (s, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 201.89, 201.20, 159.51, 129.08, 127.63, 114.68, 78.46, 70.90, 55.24, 42.12, 30.41, 29.49. HPLC: Chiralpak AD-H (hexane/*i*-PrOH = 85/15, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (major) = 9.5 min, t_R (minor) = 13.8 min; 96% ee. $[\alpha]_D^{25} = 160.0$ ($c = 0.9$, CHCl_3). HRMS (EI) calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_5$, m/z 279.1101, found 279.1100.

(*S*)-3-(2-Nitro-1-*o*-tolylethyl)pentane-2,4-dione (Table 2, entry 5, 4e)

The title compound was prepared in 93% yield according to the typical procedure, as described above.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.28-7.18 (m, 3H), 7.11-7.09 (m, 1H), 4.66-4.54 (m, 3H), 4.43 (d, $J = 10.4$ Hz, 1H), 2.43 (s, 3H), 2.32 (s, 3H), 1.93 (s, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 201.67, 201.01, 136.71, 134.31, 131.64, 128.26, 126.80, 125.99, 77.78, 70.27, 37.68, 30.43, 30.21, 19.55. HPLC: Chiralpak AS-H (hexane/*i*-PrOH = 70/30, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (major) = 7.0 min, t_R (minor) = 9.1 min; 95% ee. $[\alpha]_D^{25} = 121.9$ ($c = 1.5$, CHCl_3).

(S)-3-(2-Nitro-1-*m*-tolylethyl) pentane-2,4-dione (Table 2, entry 6, 4f)

The title compound was prepared in 92% yield according to the typical procedure as described above.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.25-7.21 (m, 1H), 7.12-7.10 (m, 1H), 7.00-6.98 (m, 2H), 4.68-4.59 (m, 2H), 4.38 (d, $J = 10.8$ Hz, 1H), 4.25-4.19 (m, 1H), 2.33 (s, 3H), 2.31 (s, 3H), 1.97 (s, 3H).

$^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 201.90, 201.11, 139.11, 135.90, 129.34, 129.17, 128.72, 124.79, 78.26, 70.75, 42.74, 30.46, 29.54, 21.41. HPLC: Chiralpak AS-H (hexane/*i*-PrOH = 70/30, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (major) = 7.0 min, t_R (minor) = 9.4 min; 94% ee. $[\alpha]_{\text{D}}^{25} = 130.9$ ($c = 1.4$, CHCl_3).

(S)-2-Nitro-1-*p*-tolylethyl)-1-phenylbutane-1,3-dione (Table 2, entry 7, 4g)

The title compound was prepared in 95% yield according to the typical procedure as described above.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.14 (d, $J = 8.0$ Hz, 2H), 7.08 (d, $J = 8.0$ Hz, 2H), 4.66-4.59 (m, 2H), 4.37 (d, $J = 10.8$ Hz, 1H), 4.25-4.19 (m, 1H), 2.31 (s, 3H), 2.30 (s, 3H), 1.95 (s, 3H).

$^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 201.92, 201.18, 138.37, 132.81, 130.01, 127.79, 78.38, 70.81, 42.46, 30.45, 29.50, 21.08. HPLC: Chiralpak AS-H (hexane/*i*-PrOH = 85/15, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (major) = 9.1 min, t_R (minor) = 12.9 min; 96% ee. $[\alpha]_{\text{D}}^{25} = 170.3$ ($c = 1.0$, CHCl_3). HRMS (EI) calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_4$, m/z 263.1152, found 279.1148.

(S)-3-(1-(4-Bromophenyl)-2-nitroethyl) pentane-2,4-dione (Table 2, entry 8, 4h)

The title compound was prepared in 99% yield according to the typical procedure as described above.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.48 (d, $J = 8.4$ Hz, 2H), 7.09 (d, $J = 8.4$ Hz, 2H), 4.64-4.62 (m, 2H), 4.35 (d, $J = 10.8$ Hz, 1H), 4.26-4.20 (m, 1H), 2.31 (s, 3H), 1.99 (s, 3H).

$^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 201.39, 200.59, 135.10, 132.52, 129.65, 122.67, 78.85, 70.43, 42.19, 30.47, 29.72. HPLC: Chiralpak AS-H (hexane/*i*-PrOH = 70/30, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (major) = 8.9 min, t_R (minor) = 14.2 min; 95% ee. $[\alpha]_{\text{D}}^{25} = 119.4$ ($c = 1.4$, CHCl_3).

(S)-3-(1-(4-Chlorophenyl)-2-nitroethyl) pentane-2,4-dione (Table 2, entry 9, 4i)

The title compound was prepared in 96% yield according to the typical procedure as described above.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.32 (d, $J = 8.4$ Hz, 2H), 7.15 (d, $J = 8.4$ Hz, 2H), 4.64-4.62 (m, 2H), 4.35 (d, $J = 10.8$ Hz, 1H), 4.27-4.23 (m, 1H), 2.31 (s, 3H), 1.99 (s, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 201.42, 200.63, 134.56, 129.57, 129.35, 78.92, 70.49, 42.13, 30.48, 29.72. HPLC: Chiralcel OD-H (hexane/*i*-PrOH = 80/20, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (major) = 9.9 min, t_R (minor) = 17.4 min; 95% ee. $[\alpha]_{\text{D}}^{25} = 147.3$ ($c = 1.0$, CHCl_3). HRMS (EI) calcd for $\text{C}_{13}\text{H}_{14}\text{ClNO}_4$, m/z 283.0606, found 283.0607.

(S)-3-(1-(Furan-3-yl)-2-nitroethyl) pentane-2,4-dione (Table 2, entry 10, 4j)

The title compound was prepared in 92% yield according to the typical procedure as described above.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.40 (s, 1H), 7.32 (s, 1H), 6.29 (s, 1H), 4.60-4.58 (m, 2H), 4.27 (d, $J = 10.8$ Hz, 1H), 4.22-4.16 (m, 1H), 2.30 (s, 3H), 2.10 (s, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 201.79, 201.10, 144.12, 140.69, 120.40, 109.03, 77.71, 69.98, 42.46, 33.96, 30.55, 29.46. HPLC: Chiralpak AS-H (hexane/*i*-PrOH = 85/15, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (major) = 16.1 min, t_R (minor) = 19.9 min; 91% ee. $[\alpha]_{\text{D}}^{25} = 167.2$ ($c = 1.2$, CHCl_3). HRMS (EI) calcd for $\text{C}_{11}\text{H}_{13}\text{NO}_5$, m/z 239.0788, found 239.0795.

(R)-3-(1-(Furan-2-yl)-2-nitroethyl) pentane-2,4-dione (Table 2, entry 11, 4k)

The title compound was prepared in 98% yield according to the typical procedure as described above.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.38 (s, 1H), 6.32 (d, $J = 1.6$ Hz, 1H), 6.19 (d, $J = 3.2$ Hz, 1H), 4.69-4.67 (m, 2H), 4.42-4.37 (m, 2H), 2.30 (s, 3H), 2.10 (s, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 201.79, 201.10, 144.12, 140.69, 120.40, 109.03, 77.71, 69.98, 42.46, 33.96, 30.55, 29.46. HPLC: Chiralpak AS-H (hexane/*i*-PrOH = 85/15, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (major) = 13.0 min, t_R (minor) = 16.8 min; 95% ee. $[\alpha]_{\text{D}}^{25} = 160.9$ ($c = 1.2$, CHCl_3). HRMS (EI) calcd for

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$C_{11}H_{13}NO_5$, m/z 239.0788, found 239.0785.

(*R*)-3-(2-Nitro-1-(thiophen-2-yl)ethyl) pentane-2,4-dione (Table 2, entry 12, 4l)

The title compound was prepared in 94% yield according the typical procedure as described above.

1H -NMR (400 MHz, $CDCl_3$) δ 7.25-7.24 (m, 1H), 6.95-6.93 (m, 1H), 6.93-6.90 (m, 1H), 4.68-4.67 (m, 2H), 4.58-4.53 (m, 1H), 4.42 (d, J = 10.0 Hz), 2.30 (s, 3H), 2.09 (s, 3H). ^{13}C -NMR (100 MHz, $CDCl_3$) δ 201.51, 200.72, 138.45, 127.39, 127.01, 125.75, 77.52, 71.00, 38.22, 30.59, 29.69. HPLC: Chiralpak ADS-H (hexane/*i*-PrOH = 90/10, flow rate 1 mL/min, λ = 210 nm), t_R (major) = 17.2 min, t_R (minor) = 24.0 min; 96% ee. $[\alpha]_D^{25}$ = 148.5 (c = 1.2, $CHCl_3$). HRMS (EI) calcd for $C_{11}H_{13}NO_4S$, m/z 255.0560, found 255.0569.

(*S*)-3-(1-(Naphthalen-1-yl)-2-nitroethyl) pentane-2,4-dione (Table 2, entry 13, 4m)

The title compound was prepared in 96% yield according the typical procedure as described above.

1H -NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 8.4 Hz, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.66 (t, J = 8.0 Hz, 1H), 7.57 (d, J = 7.6 Hz, 1H), 7.43 (d, J = 7.6 Hz, 1H), 7.29 (d, J = 8.4 Hz, 1H), 5.23-5.21 (m, 1H), 4.86-4.81 (m, 1H), 4.77-4.71 (m, 2H), 2.34 (s, 3H), 1.89 (s, 3H). ^{13}C -NMR (100 MHz, $CDCl_3$) δ 202.39, 200.85, 134.29, 131.92, 130.80, 129.49, 129.23, 127.39, 126.35, 125.27, 124.77, 121.91, 77.76, 70.43, 36.35, 31.06, 28.68. HPLC: Chiralpak AS-H (hexane/*i*-PrOH = 85/15, flow rate 1 mL/min, λ = 210 nm), t_R (major) = 11.5 min, t_R (minor) = 14.5 min; 94% ee. $[\alpha]_D^{25}$ = 196.9 (c = 1.5, $CHCl_3$). HRMS (EI) calcd for $C_{17}H_{17}NO_4$, m/z 299.1152, found 299.1143.

(*R,E*)-3-(1-Nitro-4-phenylbut-3-en-2-yl) pentane-2,4-dione (Table 2, entry 14, 4n)

The title compound was prepared in 92% yield according the typical procedure as described above.

1H -NMR (400 MHz, $CDCl_3$) δ 7.35-7.28 (m, 5H), 6.57 (d, J = 16.0 Hz, 1H), 6.04 (dd, J = 9.6, 16.0 Hz, 1H), 4.58-4.56

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(m, 2H), 4.10 (d, $J = 10.0$ Hz, 1H), 4.79-4.73 (m, 2H), 2.30 (s, 3H), 2.23 (s, 3H). ^{13}C -NMR (100 MHz, CDCl_3) δ 201.79, 201.10, 144.12, 140.69, 120.40, 109.03, 77.71, 69.98, 42.46, 33.96, 30.55, 29.46. HPLC: Chiralpak AS-H (hexane/*i*-PrOH = 85/15, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (major) = 11.7 min, t_R (minor) = 18.2 min; 95% ee. $[\alpha]_D^{25} = 101.7$ ($c = 1.0$, CHCl_3). HRMS (EI) calcd for $\text{C}_{15}\text{H}_{17}\text{NO}_4$, m/z 275.1152, found 275.1151.

4.4.3 General experimental procedure for the Michael addition of 1,3-diphenyl-1,3-propanedione to nitroolefins

To a solution of 1,3-diphenyl-1,3-propanedione (67.2 mg, 0.3 mmol, 3 eq) and nitroolefin (0.1 mmol, 1eq) in diethyl ether (0.3 mL) was added catalyst **VIII** (**Q-NH₂-Isothio**) (6 mg, 0.01 mmol, 0.1 eq). The resulting mixture was stirred at room temperature (23 °C). After the reaction was complete (monitored by TLC), the products were isolated and purified either by filtration/washing with diethyl ether or by flash chromatography over silica gel (EtOAc:Hexane = 1:10 to 1:3).

(*S*)-2-(2-Nitro-1-phenylethyl)-1,3-diphenylpropane-1,3-dione (**5a**)

Prepared according to the general procedure to provide the title compound (97% yield).

^1H -NMR (400 MHz, CDCl_3) δ 7.89 (d, $J = 8.0$ Hz, 2H), 7.81 (d, $J = 7.6$ Hz, 2H), 7.59-7.51 (m, 2H), 7.43-7.37 (m, 3H), 7.27-7.19 (m, 6 H), 5.85 (d, $J = 8.0$ Hz, 1H), 5.03-5.01 (m, 2H), 4.64 (dd, $J = 7.2$ Hz, 14.4 Hz, 1H). ^{13}C -NMR (100 MHz, CDCl_3) δ 194.24, 193.61, 136.79, 136.19, 135.83, 134.07, 133.80, 128.97, 128.96, 128.84, 128.78, 128.61, 128.26, 128.16, 77.30, 59.88, 44.04. HPLC: Chiralpak AS-H (hexane/*i*-PrOH = 85/15, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (major) = 21.2 min, t_R (minor) = 29.4 min; 95% ee. $[\alpha]_D^{25} = 20.3$ ($c = 1.1$, CH_2Cl_2). HRMS (EI) calcd for $\text{C}_{23}\text{H}_{19}\text{NO}_4$, m/z 373.1308, found 373.1311.

(*S*)-2-(1-(3-Methoxyphenyl)-2-nitroethyl)-1,3-diphenylpropane-1,3-dione (**5b**)

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Prepared according to the general procedure to provide the title compound (93% yield).

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.89 (d, $J = 8.0$ Hz, 2H), 7.82 (d, $J = 8.0$ Hz, 2H), 7.59-7.52 (m, 2H), 7.44-7.37 (m, 4H), 7.16-7.12 (m, 1H), 6.85-6.71 (m, 3H), 5.85 (d, $J = 8.0$ Hz, 1H), 5.02-4.99 (m, 2H), 4.64-4.58 (m, 1H), 3.70 (s, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 194.26, 193.57, 159.81, 138.34, 136.19, 135.82, 134.09, 133.80, 130.03, 128.84, 128.79, 128.62, 128.07, 120.32, 114.26, 113.57, 77.22, 59.70, 55.17, 44.02. HPLC: Chiralpak AD-H (hexane/*i*-PrOH = 85/15, flow rate 1 mL/min, $\lambda = 220$ nm), t_R (major) = 19.8 min, t_R (minor) = 29.5 min; 91% ee. $[\alpha]_{\text{D}}^{25} = 5.0$ ($c = 1.0$, CH_2Cl_2). HRMS (EI) calcd for $\text{C}_{24}\text{H}_{21}\text{NO}_5$, m/z 403.1414, found 403.1412.

(S)-2-(1-(4-Methoxyphenyl)-2-nitroethyl)-1,3-diphenylpropane-1,3-dione (5c)

Prepared according to the general procedure to provide the title compound (92% yield).

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.91 (d, $J = 7.6$ Hz, 2H), 7.81 (d, $J = 7.6$ Hz, 2H), 7.57-7.51 (m, 2H), 7.44-7.36 (m, 4H), 7.17 (d, $J = 8.8$ Hz, 2H), 6.74 (d, $J = 8.8$ Hz, 2H), 5.84 (d, $J = 8.0$ Hz, 1H), 5.00-4.96 (m, 2H), 4.61 (dd, $J = 7.2$ Hz, 14.4 Hz, 1H), 3.72 (s, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 194.33, 193.69, 159.25, 136.21, 135.90, 134.06, 133.76, 129.41, 128.97, 128.84, 128.81, 128.63, 128.52, 114.33, 77.68, 60.13, 55.20, 43.45. HPLC: Chiralpak AD-H (hexane/*i*-PrOH = 70/30, flow rate 1 mL/min, $\lambda = 230$ nm), t_R (major) = 10.7 min, t_R (minor) = 22.5 min; 92% ee. $[\alpha]_{\text{D}}^{25} = 24.5$ ($c = 1.1$, CH_2Cl_2). HRMS (EI) calcd for $\text{C}_{24}\text{H}_{21}\text{NO}_5$, m/z 403.1414, found 403.1411.

(S)-2-(2-Nitro-1-*o*-tolylethyl)-1,3-diphenylpropane-1,3-dione (5d)

Prepared according to the general procedure to provide the title compound (94% yield).

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.89 (d, $J = 7.6$ Hz, 2H), 7.65 (d, $J = 7.6$ Hz, 2H), 7.59-7.47 (m, 2H), 7.43-7.39 (m, 2H), 7.36-7.32 (m, 2H), 7.20-7.18 (m, 1H), 7.10-7.02 (m, 3H), 5.86 (d, $J = 8.0$ Hz, 1H), 5.03-4.98 (m, 2H), 4.88 (dd, $J = 10.0$ Hz, 13.6 Hz, 1H), 2.42 (s, 3H). $^{13}\text{C-NMR}$ (100

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MHz, CDCl₃) δ 194.30, 193.48, 137.01, 136.29, 135.98, 134.81, 133.64, 131.30, 128.94, 128.84, 128.69, 128.55, 127.91, 126.46, 126.34, 77.53, 59.14, 38.77, 19.59. HPLC: Chiralpak AS-H (hexane/*i*-PrOH = 85/15, flow rate 1 mL/min, λ = 210 nm), t_R (major) = 19.1 min, t_R (minor) = 29.3 min; 96% ee. $[\alpha]_D^{25}$ = - 7.4 (c = 1.0, CH₂Cl₂). HRMS (EI) calcd for C₂₄H₂₁NO₄, m/z 387.1466, found 387.1464.

(*S*)-2-(2-Nitro-1-*m*-tolylethyl)-1, 3-diphenylpropane-1, 3-dione (5e)

Prepared according to the general procedure to provide the title compound (96% yield).

¹H-NMR (400 MHz, CDCl₃) δ 7.88 (d, J = 7.6 Hz, 2H), 7.81 (d, J = 7.6 Hz, 2H), 7.60-7.50 (m, 2H), 7.43-7.36 (m, 4H), 7.12-6.97 (m, 4H), 5.84 (d, J = 8.0 Hz, 1H), 5.01-4.99 (m, 2H), 4.59 (dd, J = 8.0 Hz, 13.6 Hz, 1H), 2.22 (s, 3H). ¹³C-NMR (100 MHz, CDCl₃) δ 194.35, 193.69, 138.52, 136.65, 136.24, 135.88, 134.04, 133.75, 129.09, 128.94, 128.90, 128.84, 128.80, 128.61, 125.18, 77.24, 59.81, 43.93, 21.31. HPLC: Chiralpak AS-H (hexane/*i*-PrOH = 85/15, flow rate 1 mL/min, λ = 210 nm), t_R (major) = 16.7 min, t_R (minor) = 24.7 min; 95% ee. $[\alpha]_D^{25}$ = 13.7 (c = 1.1, CH₂Cl₂). HRMS (EI) calcd for C₂₄H₂₁NO₄, m/z 387.1466, found 387.1465.

(*S*)-2-(2-Nitro-1-*p*-tolylethyl)-1, 3-diphenylpropane-1, 3-dione (5f)

Prepared according to the general procedure to provide the title compound (94% yield).

¹H-NMR (400 MHz, CDCl₃) δ 7.90 (d, J = 7.6 Hz, 2H), 7.81 (d, J = 7.6 Hz, 2H), 7.57-7.52 (m, 2H), 7.44-7.37 (m, 4H), 7.14 (d, J = 8.0 Hz, 2H), 7.03 (d, J = 7.6 Hz, 2H), 5.85 (d, J = 8.0 Hz, 1H), 5.00-4.98 (m, 2H), 4.62 (dd, J = 5.2 Hz, 8.0 Hz, 1H), 2.25 (s, 3H). ¹³C-NMR (100 MHz, CDCl₃) δ 194.34, 193.64, 137.90, 136.22, 135.86, 134.05, 133.76, 133.67, 129.64, 128.95, 128.83, 128.81, 128.65, 128.10, 77.53, 60.05, 43.74, 21.01. HPLC: Chiralpak AS-H (hexane/*i*-PrOH = 85/15, flow rate 1 mL/min, λ = 210 nm), t_R (major) = 19.1 min, t_R (minor) = 25.8 min; 95% ee. $[\alpha]_D^{25}$ = 8.7 (c = 1.0, CH₂Cl₂). HRMS (EI) calcd for C₂₄H₂₁NO₄, m/z 387.1466, found 387.1463.

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(S)-2-(1-(4-Bromophenyl)-2-nitroethyl)-1,3-diphenylpropane-1,3-dione (5g)

Prepared according to the general procedure to provide the title compound (95% yield).

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.87-7.85 (m, 2H), 7.77-7.74 (m, 2H), 7.59-7.52 (m, 2H), 7.54-7.47 (m, 2H), 7.41-7.29 (m, 6H), 7.11-7.08 (m, 2H), 5.78 (d, $J = 10.8$ Hz, 1H), 4.93-4.90 (m, 2H), 4.57 (dd, $J = 7.2$ Hz, 19.6 Hz, 1H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 193.96, 193.34, 136.01, 135.81, 135.68, 134.28, 134.02, 132.11, 130.02, 129.06, 128.96, 128.79, 128.61, 122.25, 77.17, 59.63, 43.55. HPLC: Chiralpak AS-H (hexane/*i*-PrOH = 85/15, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (major) = 10.4 min, t_R (minor) = 24.8 min; 94% ee. $[\alpha]_{\text{D}}^{25} = 18.1$ ($c = 1.1$, CH_2Cl_2). HRMS (EI) calcd for $\text{C}_{23}\text{H}_{18}\text{BrNO}_4$, m/z 451.0414, found 451.0410.

(S)-2-(1-(4-Chlorophenyl)-2-nitroethyl)-1,3-diphenylpropane-1,3-dione (5h)

Prepared according to the general procedure to provide the title compound (97% yield).

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.88-7.85 (m, 2H), 7.77-7.74 (m, 2H), 7.54-7.48 (m, 2H), 7.41-7.32 (m, 4H), 7.15 (m, 4H), 5.78 (d, $J = 10.8$ Hz, 1H), 4.93-4.91 (m, 2H), 4.57 (dd, $J = 7.2$ Hz, 19.2 Hz, 1H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 193.97, 193.36, 136.02, 135.70, 135.26, 134.27, 134.11, 134.00, 129.71, 129.15, 129.06, 128.95, 128.79, 128.60, 77.25, 59.70, 43.49. HPLC: Chiralpak AS-H (hexane/*i*-PrOH = 85/15, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (major) = 23.1 min, t_R (minor) = 32.8 min; 97% ee. $[\alpha]_{\text{D}}^{25} = 18.7$ ($c = 1.0$, CH_2Cl_2). HRMS (EI) calcd for $\text{C}_{23}\text{H}_{18}\text{ClNO}_4$, m/z 407.0919, found 407.0912.

(S)-2-(1-(2-Chlorophenyl)-2-nitroethyl)-1,3-diphenylpropane-1,3-dione (5i)

Prepared according to the general procedure to provide the title compound (95% yield).

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.88-7.85 (m, 2H), 7.78-7.75 (m, 2H), 7.53-7.48 (m, 2H), 7.39-7.32 (m, 5H), 7.24-7.18 (m, 1H), 7.13-6.99 (m, 2H), 6.03 (d, $J = 8.4$ Hz, 1H), 5.14-5.05 (m, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 194.47, 193.59, 136.20, 135.60, 134.24, 134.09, 133.97, 133.86, 130.46, 129.56, 129.32, 128.96, 128.91, 128.69, 128.64, 127.26, 75.37, 57.12, 40.31. HPLC:

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Chiralpak AD-H (hexane/*i*-PrOH = 85/15, flow rate 1 mL/min, λ = 230 nm), t_R (major) = 11.4 min, t_R (minor) = 16.1 min; 95% ee. $[\alpha]_D^{25}$ = - 48.3 (c = 1.0, CH₂Cl₂). HRMS (EI) calcd for C₂₃H₁₈ClNO₄, m/z 407.0919, found 407.0915.

(*S*)-2-(1-(Furan-3-yl)-2-nitroethyl)-1,3-diphenylpropane-1,3-dione (5j)

Prepared according to the general procedure to provide the title compound (95% yield).

¹H-NMR (400 MHz, CDCl₃) δ 7.94 (d, J = 7.6 Hz, 2H), 7.88 (d, J = 7.6 Hz, 2H), 7.60-7.57 (m, 2H), 7.46-7.42 (m, 4H), 7.28-7.21 (m, 2H), 6.32 (s, 1H), 5.88 (d, J = 8.0 Hz, 1H), 4.92-4.86 (m, 2H), 4.61 (dd, J = 6.8 Hz, 13.6 Hz, 1H). ¹³C-NMR (100 MHz, CDCl₃) δ 194.19, 193.90, 143.61, 140.87, 136.01, 135.79, 134.14, 133.99, 129.02, 128.99, 128.74, 128.64, 120.97, 109.71, 77.46, 58.73, 35.29. HPLC: Chiralpak AS-H (hexane/*i*-PrOH = 85/15, flow rate 1 mL/min, λ = 210 nm), t_R (major) = 24.5 min, t_R (minor) = 27.7 min; 96% ee. $[\alpha]_D^{25}$ = 77.0 (c = 1.1, CH₂Cl₂). HRMS (EI) calcd for C₂₁H₁₇NO₅, m/z 363.1101, found 363.1100.

(*R*)-2-(1-(Furan-2-yl)-2-nitroethyl)-1,3-diphenylpropane-1,3-dione (5k)

Prepared according to the general procedure to provide the title compound (96% yield).

¹H-NMR (400 MHz, CDCl₃) δ 7.89-7.85 (m, 4H), 7.58-7.55 (m, 2H), 7.45-7.39 (m, 4H), 7.23 (m, 1H), 6.13 (m, 2H), 6.04 (d, J = 7.6 Hz, 1H), 5.01-4.90 (m, 2H), 4.77-4.72 (m, 1H). ¹³C-NMR (100 MHz, CDCl₃) δ 193.74, 149.76, 142.47, 135.87, 135.41, 134.10, 133.93, 128.98, 128.91, 128.62, 110.68, 108.93, 75.55, 56.68, 37.78. HPLC: Chiralpak AS-H (hexane/*i*-PrOH = 85/15, flow rate 1 mL/min, λ = 210 nm), t_R (minor) = 18.7 min, t_R (major) = 22.7 min; 94% ee. $[\alpha]_D^{25}$ = 38.0 (c = 1.0, CH₂Cl₂). HRMS (EI) calcd for C₂₁H₁₇NO₅, m/z 363.1101, found 363.1104.

(*R*)-2-(2-Nitro-1-(thiophen-2-yl)ethyl)-1,3-diphenylpropane-1,3-dione (5l)

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Prepared according to the general procedure to provide the title compound (97% yield).

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.91-7.87 (m, 4H), 7.60-7.56 (m, 2H), 7.45-7.41 (m, 4H), 7.15 (d, $J = 5.2$ Hz, 1 H), 6.90 (d, $J = 3.2$ Hz, 1H), 6.82 (dd, $J = 3.6$ Hz, 5.2 Hz, 1H), 5.98 (d, $J = 7.2$ Hz, 1H), 5.03-5.00 (m, 2H), 4.92 (dd, $J = 6.8$ Hz, 12.8 Hz, 1H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 194.03, 193.50, 139.25, 136.00, 135.60, 134.14, 134.00, 129.00, 128.96, 128.73, 128.68, 127.15, 127.07, 125.43, 77.95, 59.91, 39.47. HPLC: Chiralpak AS-H (hexane/*i*-PrOH = 85/15, flow rate 1 mL/min, $\lambda = 206$ nm), t_R (major) = 20.7 min, t_R (minor) = 23.6 min; 95% ee. $[\alpha]_D^{25} = -15.8$ ($c = 1.0$, CH_2Cl_2). HRMS (EI) calcd for $\text{C}_{21}\text{H}_{17}\text{NO}_4\text{S}$, m/z 379.0873, found 379.0870.

(S)-2-(1-(Naphthalen-1-yl)-2-nitroethyl)-1,3-diphenylpropane-1,3-dione (5m)

Prepared according to the general procedure to provide the title compound (91% yield).

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 8.20 (d, $J = 8.4$ Hz, 2H), 7.86 (d, $J = 7.6$ Hz, 2H), 7.75-7.60 (m, 6H), 7.56-7.40 (m, 3H), 7.33-7.28 (m, 5H), 7.22-7.18 (m, 1H), 6.02 (d, $J = 6.0$ Hz, 1H), 5.66-5.61 (m, 1H), 5.31 (dd, $J = 4.0$ Hz, 14.4 Hz, 1H), 4.61 (dd, $J = 9.2$ Hz, 14.0 Hz, 1H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 194.97, 193.77, 136.22, 135.69, 134.22, 133.72, 132.82, 131.06, 129.28, 128.85, 128.79, 128.75, 128.50, 127.13, 126.12, 124.92, 122.36, 76.54, 58.54, 37.34. HPLC: Chiralpak AS-H (hexane/*i*-PrOH = 85/15, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (major) = 21.4 min, t_R (minor) = 28.9 min; 93% ee. $[\alpha]_D^{25} = -153.7$ ($c = 1.1$, CH_2Cl_2). HRMS (EI) calcd for $\text{C}_{27}\text{H}_{21}\text{NO}_4$, m/z 423.1465, found 423.1466.

(S)-2-(2-Nitro-1-(2-nitrophenyl)ethyl)-1,3-diphenylpropane-1,3-dione (5n)

Prepared according to the general procedure to provide the title compound (97% yield).

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.89-7.84 (m, 5H), 7.60-7.52 (m, 2H), 7.43-7.36 (m, 7H), 6.28 (d, $J = 6.0$ Hz, 1H), 5.28-5.26 (m, 1H), 5.12-5.09 (m, 2H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 194.39, 193.35, 149.97, 136.21, 135.57, 134.33, 133.15, 131.67, 130.14, 129.12, 129.06, 128.94, 128.87,

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128.59, 128.64, 125.43, 75.08, 57.98, 439.04. HPLC: Chiralpak AS-H (hexane/*i*-PrOH = 85/15, flow rate 1 mL/min, λ = 210 nm), t_R (minor) = 16.0 min, t_R (major) = 18.0 min; 98% ee. $[\alpha]_D^{25}$ = - 81.4 (c = 1.1, CH₂Cl₂). HRMS (EI) calcd for C₂₃H₂₈N₂O₆, m/z 418.1159, found 418.1161.

(*S*)-2-(2-Nitro-1-(4-nitrophenyl)ethyl)-1,3-diphenylpropane-1,3-dione (5o)

Prepared according to the general procedure to provide the title compound (96% yield).

¹H-NMR (400 MHz, CDCl₃) δ 8.09 (d, J = 8.4 Hz, 2H), 7.93 (d, J = 7.6 Hz, 2H), 7.82-7.80 (m, 2H), 7.61-7.54 (m, 2H), 7.49-7.39 (m, 6H), 5.87 (d, J = 6.0 Hz, 1H), 5.02-5.00 (m, 2H), 4.78 (dd, J = 7.6 Hz, 14.0 Hz, 1H). ¹³C-NMR (100 MHz, CDCl₃) δ 193.48, 192.92, 147.58, 144.23, 135.76, 135.42, 134.54, 134.32, 129.51, 129.19, 129.10, 128.79, 128.60, 124.08, 76.83, 59.25, 43.73. HPLC: Chiralpak AS-H (hexane/*i*-PrOH = 85/15, flow rate 1 mL/min, λ = 210 nm), t_R (major) = 20.6 min, t_R (minor) = 27.8 min; 94% ee. $[\alpha]_D^{25}$ = 36.8 (c = 1.1, CH₂Cl₂). HRMS (EI) calcd for C₂₃H₂₈N₂O₆, m/z 418.1159, found 418.1158.

1,3-Bis(4-bromophenyl)-2-((*S*)-2-nitro-1-phenylethyl)propane-1,3-dione (5p)

To a solution of dione **2b** (0.1 mmol, 1 eq) and *trans*- β -nitrostyrene **1a** (0.2 mmol, 2eq) in nitrobenzene (0.5 mL) was added catalyst **VIII** (**Q-NH₂-Isothio**) (0.01 mmol, 0.1 eq). The resulting mixture was stirred at room temperature (23 °C). The reaction was complete (monitored by TLC) after 4 hours, the product was isolated by flash chromatography over silica gel (EtOAc:Hexane = 1:10 to 1:6).

¹H-NMR (400 MHz, CDCl₃) δ 7.72 (d, J = 8.4 Hz, 2H), 7.62 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 8.4 Hz, 2H), 7.24-7.19 (m, 5H), 5.73 (d, J = 8.0 Hz, 1H), 5.02-4.91 (m, 2H), 4.64-4.59 (m, 1H). ¹³C-NMR (100 MHz, CDCl₃) δ 193.07, 192.49, 136.29, 134.71, 134.43, 132.40, 132.25, 130.20, 129.96, 129.84, 129.43, 129.14, 128.43, 128.18, 60.05, 43.95. HPLC: Chiralpak AD-H (hexane/*i*-PrOH = 70/30, flow rate 1 mL/min, λ = 254 nm), t_R (major) = 11.4 min, t_R (minor) = 15.9 min; 88% ee. $[\alpha]_D^{25}$ = - 12.5 (c = 1.5, CH₂Cl₂). HRMS (ESI) calcd for C₂₃H₁₇NO₄NaBr₂,

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m/z 551.9422, found 551.9401.

2-((*S*)-2-Nitro-1-phenylethyl)-1,3-dip-tolylpropane-1,3-dione (**5q**)

To a solution of dione **2c** (0.3 mmol, 3 eq) and *trans*- β -nitrostyrene **1a** (0.1 mmol, 1eq) in toluene (0.5 mL) was added catalyst **VIII** (**Q-NH₂-Isothio**) (0.01 mmol, 0.1 eq). The resulting mixture was stirred at room temperature (23 °C). The reaction was complete (monitored by TLC) after 8 hours, the product was isolated by flash chromatography over silica gel (EtOAc:Hexane = 1:10 to 1:6).

¹H-NMR (400 MHz, CDCl₃) δ 7.80 (d, J = 8.0 Hz, 2H), 7.73 (d, J = 8.0 Hz, 2H), 7.28-7.16 (m, 9H), 5.80 (d, J = 8.0 Hz, 1H), 5.01 (d, J = 6.8 Hz, 2H), 4.64 (dd, J = 7.6 Hz, 14.4 Hz, 1H), 2.39 (s, 3H), 2.37 (s, 3H). ¹³C-NMR (100 MHz, CDCl₃) δ 193.83, 193.14, 145.20, 144.87, 137.03, 133.75, 133.30, 129.65, 129.54, 128.96, 128.93, 128.80, 128.26, 128.07, 59.68, 44.07, 21.69, 21.66. HPLC: Chiralpak AD-H (hexane/*i*-PrOH = 70/30, flow rate 1 mL/min, λ = 254 nm), t_R (major) = 11.0 min, t_R (minor) = 27.3 min; 91% ee. $[\alpha]_D^{25}$ = - 1.6 (c = 1.0, CH₂Cl₂). HRMS (ESI) calcd for C₂₅H₂₄NO₄, m/z 402.1705, found 402.1692.

The procedure for the recycling of the Michael addition of 1,3-diphenyl-1,3-propanedione to *trans*- β -nitrostyrene (**1a**) and 1-bromo-4-((*E*)-2-nitrovinyl)benzene (**1g**)

To *trans*- β -Nitrostyrene (1a**):**

To a solution of 1,3-diphenyl-1,3-propanedione (**2c**) (67.2 mg, 0.3 mmol, 3 eq) and *trans*- β -nitrostyrene (**1a**) (14.9 mg, 0.1 mmol, 1eq) in diethyl ether (0.3 mL) was added catalyst **VIII** (**Q-NH₂-Isothio**) (6.0 mg, 0.01 mmol, 0.1 eq). The resulting mixture was stirred at room temperature (23 °C). After the reaction was complete (monitored by TLC), the product **5a** was isolated and purified by centrifuge/washing with diethyl ether (0.5 mL). All the catalyst **VIII** (0.1 equiv) and 2 equivalents of the excess the dione **2c** were retained in the filtrate. The combined ethereal filtrate was evaporated to 0.3 mL before the dione **2c** (1 equiv) and nitrostryene **1a** (1 equiv) were added again to the solution for the next round of the Michael reaction. This was to

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ensure that the reaction condition for each cycle was almost the same as the previous one. The excellent yields (97% in average) and enantioselectivities (95% ee) were achieved in 10 cycles.

To 1-Bromo-4-((*E*)-2-nitrovinyl) benzene (**1g**):

To a solution of 1,3-diphenyl-1,3-propanedione (**2c**) (0.3 mmol, 3 eq) and 1-bromo-4-((*E*)-2-nitrovinyl)benzene (**1g**) (0.1 mmol, 1eq) in diethyl ether (0.5 mL) was added catalyst **VIII** (**Q-NH₂-Isothio**) (6.0 mg, 0.01 mmol, 0.1 eq). The resulting mixture was stirred at room temperature (23 °C). After the reaction was complete (monitored by TLC), the product **5g** was isolated and purified by centrifuge/washing with diethyl ether (0.5 mL). All the catalyst **VIII** (0.1 equiv) and 2 equivalents of the excess the dione **2c** were retained in the filtrate. The combined ethereal filtrate was evaporated to 0.3 mL before the dione **2c** (1 equiv) and **1g** (1 equiv) were added again to the solution for the next round of the Michael reaction. This was to ensure that the reaction condition for each cycle was almost the same as the previous one. The excellent yields (95% in average) and enantioselectivities (94% ee) were achieved in 10 cycles.

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Chapter 5

ORGANOCATALYTIC DOMINO MICHAEL-HENRY REACTION CATALYZED BY THIOUREA CINCHONIA ALKALOID CATALYST

Bicyclo[3.2.1]octanes

Organocatalytic Approach to Chiral Bicyclo[3.2.1]octanes with Two Quaternary Centers: Practical Domino Syntheses and Theoretical Insights into Stereoselectivities

5.1 Background

The bicyclo[3.2.1]octane skeletons exist in various natural products and pharmaceuticals¹ such as Trichorabdol **B**, Kadsurenin **C** and **L**, Piersformoside, Platensimycin, and Platencin (Figure 1). For example, Platencin inhibits bacterial fatty acid formation through coordination with the enzyme FabH.^[2] In 2008, Nicolaou^{2b,c} and Rawal^{2d} reported the total synthesis of this newly discovered and highly promising antibiotic, involving a metal-catalyzed Diels-Alder reaction to construct these that are synthetically challenging, but important compounds.³ It is therefore crucial to devise an efficient synthetic route to this class of compounds.

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Figure 1. Natural products containing bicyclo[3.2.1]octane skeletons.

Domino reactions serve as a powerful tool for the fast and efficient assembly of complex structures with minimal production of waste.⁴ Organocatalytic⁵ enantioselective domino processes⁶ are particularly appealing because of their operational simplicity and environmental friendliness. Although a lot of advancements have been made in organocatalyzed domino reactions,⁷ new methodologies for the generation of molecules with multiple stereogenic carbons including quaternary centers⁸ in a cascade manner remain a big challenge at the forefront of synthetic organic chemistry.

The Michael and Henry reaction are well known C-C bond formation processes as they are versatile tools to assemble multisubstituted carbon skeletons⁹ and transform nitroaldol products into a number of nitrogen and oxygen-containing derivatives.¹⁰ However, to our knowledge, there is no report describing the formation of two quaternary centers in the asymmetric synthesis of bicyclo[3.2.1] motif using domino Michael-Henry reaction strategy with good results. Herein, we disclose an organocatalytic enantioselective domino Michael-Henry reaction to afford highly functionalized bicyclo[3.2.1]octanes with four stereogenic centers including two quaternary carbons in almost complete diastereoselectivities and excellent

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enantioselectivities (85-96% ee). Theoretical calculations on the transition states have been carried out to explain the highly stereo-controlled outcomes. In addition, a novel catalytic model was proposed based on the DFT calculations.

5.2 Results and discussion

Readily accessible cinchona alkaloid and derivatives, which were developed recently in several research groups, have been identified as efficient bifunctional organocatalysts in the asymmetric Michael reactions,¹¹ the Henry reactions,¹² and the tandem Michael-Henry reactions.¹³ These brilliant achievements prompted us to explore the feasibility of employing diamine catalyst **I** to catalyze tandem Michael-Henry

Figure 2. Structures of rational designed substrates.

Figure 3. Structures of cinchona alkaloid derived organocatalyst.

reactions involving a nitroolefin and rationally designed carbon nucleophiles **1c**, **1d**, **1e** to form chiral bicyclic product. (Figure 2) It is very disappointed that these

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substrates didn't afford the expected product any more. The desired product was obtained in moderate yield and enantioselectivity (48% ee) when **1a** was explored catalyzed by catalyst **I**. Encouraged by these initial results, we underwent a detailed optimization investigation. Several cinchona alkaloid-derived catalysts were investigated (Figure 3) and they displayed noteworthy effects on the outcome of the reaction. Thiourea catalysts generally afforded better results in yield and

Table 1. Organocatalytic Tandem Michael-Henry Reactions of Trisubstituted Carbon Nucleophiles and *trans*- β -Nitrostyrene^a

entry	catalyst	Solvent	time (h)	yield (%) ^b	dr ^c	ee (%) ^d
1	I	Toluene	12	73	>99:1	-40
2	II	Toluene	12	78	>99:1	50
3	III	Toluene	4	85	>99:1	-80
4	IV	Toluene	4	90	>99:1	-89
5	V	Toluene	4	87	>99:1	-89
6	VI	Toluene	6	86	>99:1	92
7	VI	Et ₂ O	4	89	>99:1	92
8	VI	<i>m</i> -xylene	4	88	>99:1	90
9	VI	nitrobenzene	4	91	>99:1	90
10	VI	benzonitrile	4	91	>99:1	94
11 ^e	VI	benzonitrile	8	89	>99:1	94
12 ^e	V	benzonitrile	8	86	>99:1	-92
13 ^f	VI	benzonitrile	6	91	>99:1	94
14 ^g	VI	benzonitrile	10	83	>99:1	93

^a Unless otherwise specified, the reactions were carried out using **1a** (0.2 mmol, 2.0 equiv) and **2a** (0.1 mmol, 1.0 equiv) with 10 mol% of catalysts in 0.5 mL of solvent at RT (23 °C). ^b Isolated yields. ^c Determined by NMR and HPLC analysis. ^d Determined by chiral HPLC analysis. ^e Reaction at 4 °C. ^f 5 mol% catalyst. ^g 3 mol% catalyst.

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stereoselectivity. Various solvents were screened and it was found that a more polar solvent resulted in a higher enantioselectivity while maintaining the activity of the catalyst. We next investigated the effect of the reaction temperature and catalyst loading using catalyst **VI**. We observed that this reaction was not affected by changing reaction temperature, unlike most other reactions where lower temperature usually led to higher enantioselectivities and lower reaction rate (Table 1, entries 11 and 12). However, lower catalyst loading did lead to longer reaction time (Table 1, entries 13 and 14), and using catalyst **V** or **VI** could afford both enantiomers.

Table 2. Domino Michael-Henry Reactions of **1a** and Nitroolefins Catalyzed by Catalyst **VI**^a

entry	R	3	t (h)	yield (%) ^b	dr ^c	ee (%) ^d
1	Ph	3a	6	93	>99:1	94
2	3-OMe-Ph	3b	10	84	>99:1	95
3	4-OMe-Ph	3c	10	79	>99:1	90
4	4-Me-Ph	3d	8	91	>99:1	93
5	4-Br-Ph	3e	6	87	>99:1	94
6	2-Cl-Ph	3f	6	86	>99:1	96
7	4-Cl-Ph	3g	6	93	>99:1	95
8	4-F-Ph	3h	6	88	>99:1	94
9	2-Thienyl	3i	8	80	>99:1	92
10	2-Furyl	3j	6	84	>99:1	92
11	1-Naphthyl	3k	12	85	>99:1	94
12	4-NO ₂ -Ph	3l	12	77	>99:1	93

^a All the reactions were carried out using **1a** (0.2 mmol, 2.0 equiv) and **2** (0.1 mmol, 1.0 equiv) in the presence of 5 mol% of **VI** at RT with benzonitrile (0.5 mL). ^b Isolated yields. ^c Determined by NMR and HPLC analysis. ^d Determined by chiral HPLC analysis.

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In our exploratory effort, this new methodology not only provides a facile access to a range of multisubstituted bicyclo[3.2.1]octane derivatives, it is also a facile approach for preparing various substituted bicycles in high enantiomeric excesses (90-96% ee) and excellent diastereoselectivities (>99:1 dr in all cases) (Table 2). The **VI**-promoted tandem Michael-Henry process takes place with a variety of nitroolefin Michael acceptors, which possess neutral, electron-donating, electron-withdrawing groups in the phenyl ring (Table 2, entries 1-8, 11 and 12). It appeared that substituents' electronic and steric nature have minimal influence on efficiency and stereoselectivity of the Michael-Henry reaction. Excellent enantioselectivity was also obtained when heteroaromatic substrates were used (Table 2, entries 9 and 10).

Scheme 1. Domino Michael-Henry Reactions of **1a** with **2m** and **1b** with **2a**

Notably, only one Michael-Henry adduct was obtained from the reaction of nitrodiene **2k** in 97% ee (Scheme 1). Although both β - and δ -positions of **2k** can possibly be attacked due to the congruous two double bonds theoretically, the formation of only one adduct showed the great regioselectivity and enantioselectivity of this methodology. Furthermore, the domino reaction also proceeded smoothly when **1a** was replaced by **1b**, giving good stereoselectivities (85% ee) as displayed in Scheme 1. The stereochemistry was established by X-ray crystallographic determination of **3f** and analysis of NMR data of the products.

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According to the dual activation model proposed by Takemoto,¹⁴ the catalyst simultaneously activates the substrates (Figure 4). Nitroolefins have been presumed to interact with the primary amine moiety of catalyst via hydrogen bonding, which increases the electrophilicity of the electrophile. However, the enolic form is presumed to interact with the tertiary amine group, and a subsequent Henry reaction results in a stereo controlled product. The absolute configuration of **3f** was verified using X-ray crystallography (Figure 5).

Figure 4. Proposed action of the catalyst and substrate before DFT calculation.

Figure 5. X-ray crystallographic determination of **3f**.

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5.3 Theoretical Study of the Transition State Structures and Mechanism Considerations

To provide theoretical insight on the high diastereo- and enantioselectivity of this domino reaction, a systematic conformational analysis of transition states were investigated with density functional theory (DFT) calculations using the Gaussian 03 program and the B3LYP method. Since the Michael addition in domino Michael-Henry step-wise reactions is speculated as the rate determining step, we focused on the search of stationary points relevant to the first C-C bond formation that correlates to the creation of the first two chiral centers. For each proposed transition-state structure, we carried out geometry optimizations at the B3LYP/6-31G(d) level of density functional theory for all atoms except the protons (hydrogen bonding donors) in the amine group in which a more extended basis set 6-31G(d,p) is used to obtain accurate energies. The relative energies of the different transition state were then used to predict the product ratios.¹⁵

Based on a systematic conformational search, as shown in Figure 6, eight possible transition states have been optimized for the Michael addition catalyzed by the catalyst **VI**. The best transition state is **TS-6**, which is accordance with the major product isolated during the experiment. In **TS-6**, both 1,3-dicarbonyl group and nitroolefin were bonded to the catalyst **VI** through hydrogen bond. This catalyst simultaneously activated the two substrates, through a so-called “dual activation model”. However, unlike the Takemoto’s “dual activation model”, the nitro group was activated by the tertiary amine group and the enolic ester part is activated by the thiourea group. The enolic ester part and the thiourea unit showed an almost coplanar structure and this gave rise to a concerted hydrogen bonding network where the steric hindrance is minimized. This was in accordance with the previous theoretical calculation results.¹⁶ More importantly, there was a hydrogen bond between hydrogen in the phenyl group and ester group (O---H 2.058Å). Because of the existence of the two CF₃ groups, the acidity of hydrogen atom in the phenyl group was increased significantly and they were keener to form hydrogen bonds with nucleophilic atoms, such as oxygen. We found out that in the **TS-6**, enolic ester substrate was firmly bound to catalyst **VI** and the proton in the tertiary amine was largely transferred to the nitro group as it shown

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by the N-H bond distance (1.070 Å). The formation of the (*R,S*)-enantiomer was favored by 5.71 kcal/mol, (Table 3) when compared to the (*S,R*)-enantiomer and it supported the high stereoselectivity observed in the experiment. **TS-1** was the best transition state in Takemoto's "dual activation model", as the enolic ester part was bound to the tertiary amine group and the nitro group was bound to the thiourea unit. However, **TS-6** not only has the most number of hydrogen bond between the tertiary amine group and the enolic ester part when compared to the other transition states, it also exhibit the hydrogen bond between hydrogen in the phenyl group and ester group which is critical in the determination of the stereoselectivities of the Michael adduct. These considerations made the 1,3-dicarbonyl substrate in **TS-6** very activated. In addition, we find that a proton transfer from the coordinated enol to the amine group of the catalyst can easily take place, which were displayed clearly in Figure 6.

Table 3. Electronic and Free Energies of the Transition States for the Michael Addition Catalyzed by Catalyst **VI** by DFT Calculations

Transition state	E _{elec} (Hartree)	ΔE _{elec} (kcal/mol)	G (Hartree)	ΔG (Hartree)
TS-1 (<i>S,S</i>)	-3539.2775	8.53	-3538.5237	7.22
TS-2 (<i>S,R</i>)	-3539.2759	9.54	-3538.5181	10.7
TS-3 (<i>R,S</i>)	-3539.2742	10.6	-3538.5174	11.2
TS-4 (<i>R,R</i>)	-3539.2699	13.3	-3538.5130	13.9
TS-5 (<i>R,R</i>)	-3539.2771	8.79	-3538.5225	7.97
TS-6 (<i>R,S</i>)	-3539.2911	0.00	-3538.5352	0.00
TS-7 (<i>S,R</i>)	-3539.2820	5.71	-3538.5265	5.44
TS-8 (<i>S,S</i>)	-3539.2717	12.7	-3538.5169	11.5

Based on the above mentioned and experimental results in Table 1, these results seemed very different compared to the previous reports,^{13,17} in which quinine amine

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catalyst **I** proved to be a better catalyst for the Michael addition. The cyclic substrate might have a large effect in the domino Michael-Henry reactions. In order to demonstrate this phenomenon, we moved on to calculate the eight possible transition states (Figure 7) in the reaction catalyzed by the catalyst **I**. The best transition state was found to be **TS-10**, which was very slightly favored by 0.06 kcal/mol, when compared to **TS-16**. **TS-10** which belongs to conventional “dual activation model” where both substrates were activated led to the (*S,R*) enantiomer. While **TS-16**, which activated only enolic ester part, led to the (*R,S*) enantiomer. However, the catalyst in **TS-16** was less distorted than it was in **TS-10** (the torsion angle N46-C25-C1-N19 is 54.26° in the previous versus 76.76°). Overall, the two transition states were equally favored in the reaction and all the other transition states were less favored by at least 3.26 kcal/mol (Table 4). Our computational results had demonstrated excellent diastereoselectivities in the reactions and they were in accordance with the observed facts in the experiment. The calculation results also uncover the underlying reason for the different enantioselectivities between catalysts **VI** and **I**.

Table 4. Electronic and Free Energies of the Transition States for the Michael Addition Catalyzed by Catalyst **I** by DFT Calculations

Transition state	Eelec (Hartree)	ΔE_{elec} (kcal/mol)	G (Hartree)	ΔG (Hartree)
TS-9 (<i>S,S</i>)	-2142.4939	5.02	-2141.8310	3.45
TS-10 (<i>S,R</i>)	-2142.5019	0.00	-2141.8365	0.00
TS-11 (<i>R,S</i>)	-2142.4948	4.45	-2141.8289	4.77
TS-12 (<i>R,R</i>)	-2142.4967	3.26	-2141.8300	4.08
TS-13 (<i>R,R</i>)	-2142.4925	5.90	-2141.8299	4.14
TS-14 (<i>S,R</i>)	-2142.4922	6.07	-2141.8274	5.71
TS-15 (<i>S,S</i>)	-2142.4961	3.64	-2141.8300	3.45
TS-16 (<i>R,S</i>)	-2142.5018	0.06	-2141.8364	0.06

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Figure 6. Located transition state structures with distant parameters in angstroms using thiourea catalyst VI (most H atoms are removed for clarity).

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Figure 7. Located transition state structures with distant parameters in angstroms using quinine amine catalyst **I** (most H atoms are removed for clarity).

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Based on this theoretical calculation, we proposed a new catalytic model for this domino Michael-Henry reaction (Figure 8). In this model, thiourea group and an acidic proton in phenyl ring activated the 1,3-dicarbonyl substrates together, and at the same time, tertiary amine activated the nitro group, which proceeded the domino reaction smoothly with the excellent stereoselectivity.

Figure 8. Proposed action of the catalyst and substrate after the DFT calculations.

5.4 Further Investigation

For further investigation of the catalyst action, we designed two new catalysts to catalyze this domino reaction (Scheme 2). The poor results demonstrated the aromatic ring with an acidic proton in the thiourea part was crucial to the excellent results.

Scheme 2. Domino Michael-Henry Reaction Using Newly Designed Catalysts

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5.5 Conclusion

The program described above has led to the development of an efficient, highly enantio- and diastereoselective organocatalytic domino Michael-Henry process that can be applied in the construction of practically valuable and medically important bicyclo[3.2.1]octane derivatives. This novel strategy makes use of simple starting materials and low catalyst loading of the cinchona alkaloid derived thiourea catalyst **VI**. Theoretical DFT calculations on the transition states have been carried out to reveal origins of the excellent stereoselectivities. The novel catalytic model will direct the design of some new type of bifunctional catalysts. This approach constitutes our future direction aimed at expanding the scope and applications of these powerful domino processes to total synthesis of natural products.

5.6 Experimental section

General experimental conditions (Chapter 2)

General procedure for the preparation of (**1a**) and (**1b**)

NaHMDS (20 mmol, 2 M in THF) was slowly added to solution of cyclohexane-1,4-dione (20 mmol) in dry THF (30 mL) at -78 °C. After 30 min stirring at the same temperature, a solution of methyl or phenyl chloroformate (20 mmol) was added, and the resulting mixture was stirred for 1 h at -78 °C, and then allowed to warm to room temperature. The reaction was then quenched by addition of sat. NH₄Cl (aq.), and the product extracted with Et₂O (3 x 30 mL). The combined organic phases were then dried over Na₂SO₄, filtered and evaporated under reduced pressure. Purification of the crude mixture by FC (ethyl acetate:*n*-hexane = 1:8), gave the corresponding β -ketoesters **1a** or **1b**.

Methyl 2,5-dioxocyclohexanecarboxylate (**1a**)

The title compound was obtained according to the general procedure as colorless oil (14% yield).

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^1H -NMR (400 MHz, CDCl_3) δ 12.21 (s, 1H), 3.79 (s, 3H), 3.10 (s, 2H), 2.71 (t, $J = 6.8$ Hz, 2H), 2.59 (t, $J = 6.8$ Hz, 2H). (Almost 100% enol form) ^{13}C -NMR (100 MHz, CDCl_3) δ 207.5, 171.7, 170.7, 94.5, 51.8, 37.2, 36.6, 28.3. HRMS (ESI) calcd for $[\text{M}+\text{Na}] \text{C}_8\text{H}_{10}\text{O}_4\text{Na}$, m/z 193.0477, found 193.0477.

Phenyl 2,5-dioxocyclohexanecarboxylate (**1b**)

The title compound was obtained according to the general procedure as colorless oil (25% yield).

^1H -NMR (400 MHz, CDCl_3) δ 12.06 (s, 1H), 7.43 (t, $J = 8.0$ Hz, 2H), 7.31-7.27 (m, 1H), 7.13 (d, $J = 8.0$ Hz, 2H), 3.34 (s, 2H), 2.79 (t, $J = 6.8$ Hz, 2H), 2.66 (t, $J = 6.8$ Hz, 2H). (Almost 100% enol form) ^{13}C -NMR (100 MHz, CDCl_3) δ 207.0, 172.9, 170.0, 150.0, 129.6, 126.2, 121.6, 94.2, 37.1, 36.7, 28.6. HRMS (ESI) calcd for $[\text{M}+\text{H}] \text{C}_{13}\text{H}_{14}\text{O}_4$, m/z 233.0814, found 233.0812.

Typical procedure for the Michael-Henry reactions:

Catalyst **VI** (0.005 mmol, 0.05 eq) was added to a solution of methyl 2,5-dioxocyclohexanecarboxylate **1a** (0.2 mmol, 2 eq) and nitroolefins (0.1 mmol, 1eq) in benzonitrile (0.5 mL) at room temperature. The resulting mixture was stirred vigorously. After the reaction was complete (monitored by TLC and crude NMR), the products were afforded by flash chromatography over silica gel (EtOAc/Hexane = 1/4 to 1/2).

(1*R*,5*S*,6*R*,7*S*)-Methyl-5-hydroxy-6-nitro-2-oxo-7-phenylbicyclo[3.2.1] octane-1-carboxylate (**3a**)

The title compound was prepared according to the typical procedure, as described above in 93% yield.

^1H -NMR (400 MHz, CDCl_3) δ 7.36-7.29 (m, 3H), 7.21 (d, $J = 7.6$ Hz, 2H), 5.27 (d, $J = 5.6$ Hz, 1H), 4.88 (d, $J = 5.6$ Hz, 1H), 3.86 (s, 3H), 3.01 (dd, $J = 3.6, 12.8$ Hz, 1H), 2.64 (brs, 1H), 2.61-2.53 (m, 2H), 2.30-2.17 (m, 2H), 2.13-2.04 (m, 1H). ^{13}C -NMR (100 MHz, CDCl_3) δ 203.4, 169.7, 135.7, 129.0, 127.8, 127.1, 98.6, 76.3, 64.9, 53.0, 52.3, 44.8,

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37.0, 35.2. HPLC: Chiralpak AD-H (hexane/*i*-PrOH = 85/15, flow rate 1 mL/min, λ = 210 nm), t_R (major) = 9.0 min, t_R (minor) = 12.8 min; 94% ee. $[\alpha]_D^{25}$ = - 80.8 (c = 1.8, CH₂Cl₂). HRMS (ESI) calcd for [M+Na] C₁₆H₁₇NO₆Na, m/z 342.0954, found 342.0956.

(1*R*,5*S*,6*R*,7*S*)-Methyl-5-hydroxy-7-(3-methoxyphenyl)-6-nitro-2-oxobicyclo [3.2.1]octane-1-carboxylate (3b)

The title compound was prepared according to the typical procedure, as described above in 84% yield.

¹H-NMR (400 MHz, CDCl₃) δ 7.26-7.22 (m, 1H), 6.83-6.77 (m, 3H), 5.27 (d, J = 5.2 Hz, 1H), 4.86 (d, J = 5.6 Hz, 1H), 3.85 (s, 3H), 3.77 (s, 3H), 3.00 (dd, J = 3.6, 12.8 Hz, 1H), 2.59-2.52 (m, 2H), 2.26-2.77 (m, 3H). ¹³C-NMR (100 MHz, CDCl₃) δ 203.5, 169.8, 159.8, 137.3, 130.0, 119.2, 113.4, 113.0, 98.5, 76.2, 65.0, 55.2, 53.0, 52.2, 44.8, 37.0, 35.2. HPLC: Chiralpak AD-H (hexane/*i*-PrOH = 85/15, flow rate 1 mL/min, λ = 210 nm), t_R (major) = 11.1 min, t_R (minor) = 16.8 min; 95% ee. $[\alpha]_D^{25}$ = - 88.3 (c = 1.0, CH₂Cl₂). HRMS (ESI) calcd for [M+Na] C₁₇H₁₉NO₇Na, m/z 370.1059, found 370.1054.

(1*R*,5*S*,6*R*,7*S*)-Methyl-5-hydroxy-7-(4-methoxyphenyl)-6-nitro-2-oxobicyclo [3.2.1]octane-1-carboxylate (3c)

The title compound was prepared according to the typical procedure, as described above in 79% yield.

¹H-NMR (400 MHz, CDCl₃) δ 7.13 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 8.4 Hz, 2H), 5.23 (d, J = 5.6 Hz, 1H), 4.81 (d, J = 5.6 Hz, 1H), 3.84 (s, 3H), 3.78 (s, 3H), 2.98 (dd, J = 3.6, 12.8 Hz, 1H), 2.96 (brs, 1H), 2.58 (dd, J = 6.8, 16.8 Hz, 1H), 2.53 (d, J = 12.4 Hz, 1H), 2.26-2.07 (m, 3H). ¹³C-NMR (100 MHz, CDCl₃) δ 203.7, 169.9, 158.9, 128.4, 127.4, 114.3, 98.7, 76.2, 65.2, 55.3, 53.0, 51.8, 44.6, 36.7, 35.2. HPLC: Chiralpak AD-H (hexane/*i*-PrOH = 85/15, flow rate 1 mL/min, λ = 210 nm), t_R (major) = 13.9

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min, t_R (minor) = 18.7 min; 90% ee. $[\alpha]_D^{25} = -76.0$ ($c = 1.5$, CH_2Cl_2). HRMS (ESI) calcd for $[\text{M}+\text{Na}] \text{C}_{17}\text{H}_{19}\text{NO}_7\text{Na}$, m/z 370.1059, found 370.1055.

(1*R*,5*S*,6*R*,7*S*)-Methyl-5-hydroxy-6-nitro-2-oxo-7-*p*-tolylbicyclo [3.2.1] octane-1-carboxylate (3d)

The title compound was prepared according to the typical procedure, as described above in 91% yield.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.13 (d, $J = 8.4$ Hz, 2H), 7.08 (d, $J = 8.4$ Hz, 2H), 5.23 (dd, $J = 0.4, 5.6$ Hz, 1H), 4.81 (d, $J = 5.2$ Hz, 1H), 3.84 (s, 3H), 3.00 (dd, $J = 3.6,$

12.4 Hz, 1H), 2.91 (brs, 1H), 2.58-2.51 (m, 3H), 2.32 (s, 3H), 2.26-2.11 (m, 3H).

$^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 203.6, 169.8, 137.5, 132.6, 129.6, 127.0, 98.7, 76.2, 65.0, 53.0, 52.1, 44.7, 37.0, 35.2, 20.9. HPLC: Chiralpak AD-H (hexane/*i*-PrOH = 85/15, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (major) = 9.7 min, t_R (minor) = 12.4 min; 94% ee. $[\alpha]_D^{25} = -94.4$ ($c = 0.9$, CH_2Cl_2). HRMS (ESI) calcd for $[\text{M}+\text{Na}] \text{C}_{17}\text{H}_{19}\text{NO}_6\text{Na}$, m/z 356.1110, found 356.1106.

(1*R*,5*S*,6*R*,7*S*)-Methyl-7-(4-bromophenyl)-5-hydroxy-6-nitro-2-oxo bicyclo [3.2.1] octane-1-carboxylate (3e)

The title compound was prepared according to the typical procedure, as described above in 81% yield.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.46 (d, $J = 8.8$ Hz, 2H), 7.09 (d, $J = 8.0$ Hz, 2H), 5.20 (d, $J = 5.6$ Hz, 1H), 4.80 (d, $J = 5.2$ Hz, 1H), 3.85 (s, 3H), 2.99 (dd, $J = 3.6, 12.8$ Hz,

1H), 2.81 (brs, 1H), 2.63-2.53 (m, 2H), 2.31-2.10 (m, 2H), 2.07-2.00 (m, 1H).

$^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 203.2, 169.7, 134.7, 132.1, 129.0, 122.0, 98.7, 76.2, 65.0, 53.1, 51.8, 44.6, 36.9, 35.2. HPLC: Chiralpak AD-H (hexane/*i*-PrOH = 85/15, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (major) = 11.1 min, t_R (minor) = 14.6 min; 94% ee. $[\alpha]_D^{25} = -70.3$ ($c = 1.2$, CH_2Cl_2). HRMS (ESI) calcd for $[\text{M}+\text{Na}] \text{C}_{16}\text{H}_{16}\text{NO}_6\text{NaBr}$, m/z 420.0059, found 420.0046.

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(1*R*,5*S*,6*R*,7*R*)-Methyl-7-(2-chlorophenyl)-5-hydroxy-6-nitro-2-oxo bicyclo[3.2.1]octane-1-carboxylate (3f)

The title compound was prepared according to the typical procedure, as described above in 86% yield.

¹H-NMR (400 MHz, CDCl₃) δ 7.43 (d, *J* = 8.0 Hz, 1H), 7.27-7.18 (m, 2H), 7.13 (d, *J* = 8.0 Hz, 1H), 5.14 (d, *J* = 6.0 Hz, 1H), 5.08 (d, *J* = 6.0 Hz, 1H), 3.76 (s, 3H), 3.00

(dd, *J* = 3.2, 12.8 Hz, 1H), 2.96 (brs, 1H), 2.81-2.76 (m, 1H), 2.60-2.49 (m, 2H), 2.35-2.25 (m, 2H). ¹³C-NMR (100 MHz, CDCl₃) δ 205.2, 169.0, 134.8, 133.6, 130.8, 129.3, 128.1, 127.0, 97.7, 76.2, 64.8, 52.9, 50.9, 44.0, 36.8, 35.6. HPLC: Chiralpak AD-H (hexane/*i*-PrOH = 85/15, flow rate 1 mL/min, λ = 210 nm), *t*_R (major) = 11.5 min, *t*_R (minor) = 21.8 min; 96% ee. [α]_D²⁵ = - 81.7 (*c* = 0.4, CH₂Cl₂). HRMS (ESI) calcd for [M+Na] C₁₆H₁₆NO₆NaCl, *m/z* 376.0564, found 376.0558.

(1*R*,5*S*,6*R*,7*S*)-Methyl-7-(4-chlorophenyl)-5-hydroxy-6-nitro-2-oxo bicyclo[3.2.1]octane-1-carboxylate (3g)

The title compound was prepared according to the typical procedure, as described above in 93% yield.

¹H-NMR (400 MHz, CDCl₃) δ 7.29 (d, *J* = 8.8 Hz, 2H), 7.16 (d, *J* = 8.4 Hz, 2H), 5.20 (d, *J* = 5.6 Hz, 1H), 4.82 (d, *J* = 5.2 Hz, 1H), 3.85 (s, 3H), 2.99 (dd, *J* = 3.6, 12.8 Hz,

1H), 2.76 (brs, 1H), 2.64-2.54 (m, 2H), 2.32-2.18 (m, 2H), 2.10-2.06 (m, 1H).

¹³C-NMR (100 MHz, CDCl₃) δ 203.2, 169.7, 134.1, 133.9, 129.1, 128.6, 98.3, 76.2, 65.0, 53.1, 51.8, 44.6, 36.9, 35.1. HPLC: Chiralpak AD-H (hexane/*i*-PrOH = 85/15, flow rate 1 mL/min, λ = 210 nm), *t*_R (major) = 10.0 min, *t*_R (minor) = 13.6 min; 95% ee. [α]_D²⁵ = - 95.3 (*c* = 0.9, CH₂Cl₂). HRMS (ESI) calcd for [M+Na] C₁₆H₁₆NO₆NaCl, *m/z* 376.0564, found 376.0556.

(1*R*,5*S*,6*R*,7*S*)-Methyl-7-(4-fluorophenyl)-5-hydroxy-6-nitro-2-oxo bicyclo[3.2.1]

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octane-1-carboxylate (3h)

The title compound was prepared according to the typical procedure, as described above in 88% yield.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.21-7.18 (m, 2H), 7.05-7.00 (m, 2H), 5.22 (d, $J = 5.2$ Hz, 1H), 4.83 (d, $J = 5.6$ Hz, 1H), 3.85 (s, 3H), 2.99 (dd, $J = 3.6, 12.4$ Hz, 1H), 2.91 (brs, 1H), 2.64-2.57 (m, 1H), 2.55 (d, $J = 12.8$ Hz, 1H), 2.29-2.22 (m, 2H), 2.11-2.03 (m, 1H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 203.4, 169.87, 131.4, 129.0, 128.9, 116.0, 115.8, 98.5, 76.2, 65.2, 53.1, 51.7, 44.6, 36.9, 35.2. HPLC: Chiralpak AD-H (hexane/*i*-PrOH = 85/15, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (major) = 8.9 min, t_R (minor) = 13.3 min; 94% ee. $[\alpha]_D^{25} = -105.3$ ($c = 1.0$, CH_2Cl_2). HRMS (ESI) calcd for $[\text{M}+\text{Na}] \text{C}_{16}\text{H}_{16}\text{NO}_6\text{NaF}$, m/z 360.0859, found 360.0848.

(1*R*,5*S*,6*R*,7*S*)-Methyl-5-hydroxy-6-nitro-2-oxo-7-(thiophen-2-yl) bicyclo [3.2.1] octane-1-carboxylate (3i)

The title compound was prepared according to the typical procedure, as described above in 80% yield.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.25 (d, $J = 5.2$ Hz, 1H), 7.04 (d, $J = 3.2$ Hz, 1H), 6.95 (dd, $J = 4.0, 5.2$ Hz, 1H), 5.38 (d, $J = 5.2$ Hz, 1H), 5.02 (d, $J = 5.2$ Hz, 1H), 3.87 (s, 3H), 2.96-2.93 (m, 2H), 2.91 (brs, 1H), 2.64-2.53 (m, 2H), 2.32-2.27 (m, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 202.2, 169.5, 137.4, 127.3, 126.7, 125.6, 97.8, 76.4, 66.3, 53.0, 48.9, 44.1, 36.8, 35.0. HPLC: Chiralpak AD-H (hexane/*i*-PrOH = 85/15, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (major) = 10.3 min, t_R (minor) = 15.0 min; 92% ee. $[\alpha]_D^{25} = -116.8$ ($c = 1.0$, CH_2Cl_2). HRMS (ESI) calcd for $[\text{M}+\text{Na}] \text{C}_{14}\text{H}_{15}\text{NO}_6\text{NaS}$, m/z 348.0518, found 348.0523.

(1*R*,5*S*,6*R*,7*S*)-Methyl-7-(furan-3-yl)-5-hydroxy-6-nitro-2-oxo bicyclo [3.2.1] octane -1-carboxylate (3j)

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The title compound was prepared according to the typical procedure, as described above in 84% yield.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.34 (s, 1H), 6.34-6.31 (m, 2H), 5.43 (d, $J = 5.6$ Hz, 1H), 4.80 (d, $J = 5.2$ Hz, 1H), 3.82 (s, 3H), 2.86 (d, $J = 12.8$ Hz, 1H), 2.80 (brs, 1H), 2.67-2.49 (m, 3H), 2.31-2.26 (m, 2H).

$^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 202.6, 169.1, 146.8, 142.4, 111.1, 109.7, 94.4, 76.4, 64.8, 52.8, 47.4, 43.5, 36.7, 34.3. HPLC: Chiralpak AD-H (hexane/*i*-PrOH = 85/15, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (major) = 9.1 min, t_R (minor) = 12.3 min; 94% ee. $[\alpha]_D^{25} = -85.9$ ($c = 1.5$, CH_2Cl_2). HRMS (ESI) calcd for $[\text{M}+\text{Na}] \text{C}_{14}\text{H}_{15}\text{NO}_7\text{Na}$, m/z 332.0746, found 332.0753.

(1R,5S,6R,7S)-Methyl-5-hydroxy-7-(naphthalen-3-yl)-6-nitro-2-oxo bicyclo[3.2.1]octane-1-carboxylate (3k)

The title compound was prepared according to the typical procedure, as described above in 85% yield.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.82-7.78 (m, 3H), 7.67 (s, 1H), 7.49 (dd, $J = 3.2, 6.0$ Hz, 1H), 7.30-7.28 (m, 1H), 5.36 (d, $J = 5.6$ Hz, 1H), 5.04 (d, $J = 5.6$ Hz, 1H), 3.87 (s, 3H), 3.06 (dd, $J = 3.2, 12.4$ Hz, 1H), 2.90 (brs, 1H), 2.59-2.51 (m, 2H), 2.30-2.06 (m, 3H).

$^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 203.7, 169.9, 133.1, 133.0, 132.4, 128.8, 128.1, 127.5, 126.7, 126.6, 126.1, 124.9, 98.6, 76.3, 65.1, 53.1, 52.4, 44.8, 37.0, 35.3. HPLC: Chiralpak AD-H (hexane/*i*-PrOH = 85/15, flow rate 1 mL/min, $\lambda = 254$ nm), t_R (major) = 11.2 min, t_R (minor) = 21.0 min; 94% ee. $[\alpha]_D^{25} = -77.7$ ($c = 1.2$, CH_2Cl_2). HRMS (ESI) calcd for $[\text{M}+\text{Na}] \text{C}_{20}\text{H}_{19}\text{NO}_6\text{Na}$, m/z 392.1110, found 392.1107.

(1R,5S,6R,7S)-Methyl-5-hydroxy-6-nitro-7-(4-nitrophenyl)-2-oxo bicyclo[3.2.1]octane-1-carboxylate (3l)

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The title compound was prepared according to the typical procedure, as described above in 77% yield.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 8.19 (d, $J = 8.8$ Hz, 2H), 7.41 (d, $J = 9.2$ Hz, 2H), 5.25 (d, $J = 6.0$ Hz, 1H), 4.93 (d, $J = 5.6$ Hz, 1H), 3.86 (s, 3H), 3.00 (dd, $J = 3.6, 12.8$ Hz,

1H), 2.96 (brs, 1H), 2.68-2.58 (m, 2H), 2.36-2.21 (m, 2H), 2.06-1.99 (m, 1H).

$^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 202.8, 169.5, 147.3, 143.0, 128.4, 124.0, 97.8, 76.3, 65.1, 53.3, 52.0, 44.3, 36.8, 35.1. HPLC: Chiralpak AD-H (hexane/*i*-PrOH = 85/15, flow rate 1 mL/min, $\lambda = 254$ nm), t_R (major) = 20.2 min, t_R (minor) = 27.8 min; 94% ee. $[\alpha]_D^{25} = -96.2$ ($c = 0.7$, CH_2Cl_2). HRMS (ESI) calcd for $[\text{M}+\text{Na}] \text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_8\text{Na}$, m/z 387.0804, found 387.0807.

(1R,5S,6R,7S)-Methyl-5-hydroxy-6-nitro-2-oxo-7-styrylbicyclo[3.2.1] octane-1-carboxylate (3m)

The title compound was prepared according to the typical procedure, as described above in 73% yield.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.37-7.28 (m, 5H), 6.67 (d, $J = 16.8$ Hz, 1H), 6.30 (dd, $J = 4.8, 12.0$ Hz, 1H), 5.14 (d, $J = 5.2$ Hz, 1H), 4.26-4.22 (m, 1H), 3.85 (s, 3H), 2.89-2.86 (m, 1H), 2.79 (brs, 1H), 2.70-2.65 (m, 1H), 2.49 (d, $J = 12.4$ Hz, 1H), 2.39-2.24 (m, 3H).

$^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 202.5, 166.9, 149.9, 140.0, 129.6, 129.2, 128.5, 126.1, 121.1, 99.9, 78.1, 77.265.3, 49.1, 44.4, 34.2, 33.0. HPLC: Chiralpak AD-H (hexane/*i*-PrOH = 85/15, flow rate 1 mL/min, $\lambda = 254$ nm), t_R (major) = 10.3 min, t_R (minor) = 14.2 min; 86% ee. $[\alpha]_D^{25} = -37.6$ ($c = 1.5$, CH_2Cl_2). HRMS (ESI) calcd for $[\text{M}+\text{Na}] \text{C}_{18}\text{H}_{19}\text{NO}_6\text{Na}$, m/z 368.1110, found 368.1113.

(1R,5S,6R,7S)-Phenyl-5-hydroxy-6-nitro-2-oxo-7-phenylbicyclo[3.2.1] octane-1-carboxylate (3n)

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Catalyst **VI** (0.005 mmol, 0.05 eq) was added to a solution of phenyl 2,5-dioxocyclohexanecarboxylate **1b** (0.2 mmol, 2 eq) and nitroolefin **2a** (0.1 mmol, 1eq) in diethyl ether (0.5 mL) at room temperature. The resulting mixture was stirred vigorously. After the reaction was complete (monitored by

TLC and crude NMR), the products were afforded by flash chromatography over silica gel (EtOAc/Hexane = 1/4 to 1/2).

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.44-7.38 (m, 5H), 7.22-7.13 (m, 3H), 6.327 (d, $J = 7.6$ Hz, 2H), 5.34 (d, $J = 6.8$ Hz, 1H), 4.58 (d, $J = 6.8$ Hz, 1H), 3.26 (dd, $J = 3.6, 13.6$ Hz, 1H), 3.14 (brs, 1H), 3.11-3.02 (m, 1H), 2.68 (dd, $J = 8.0, 16.8$ Hz, 1H), 2.55 (d, $J = 13.2$ Hz, 1H), 2.30-2.14 (m, 2H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 202.5, 169.5, 135.6, 134.0, 128.7, 128.4, 126.6, 123.1, 95.0, 76.6, 65.0, 52.8, 50.4, 43.1, 36.8, 34.7.

HPLC: Chiralpak AD-H (hexane/*i*-PrOH = 85/15, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (major) = 12.4 min, t_R (minor) = 19.7 min; 85% ee. $[\alpha]_D^{25} = -79.5$ ($c = 1.4$, CH_2Cl_2).

HRMS (ESI) calcd for $[\text{M}+\text{Na}] \text{C}_{21}\text{H}_{19}\text{NO}_6\text{Na}$, m/z 404.1110, found 404.1104.

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Chapter 6

RECYCLABLE ORGANOCATALYSIS: PRIMARY QUININE-AMINE ACT AS HYDROGEN BOND DONOR CATALYST

A Recyclable Enantioselective Michael Addition of 1,3-DiAryl-1,3-propanedione to Nitroolefins by 9-Amino-9-deoxyepiquinine

6.1 Background

Recent years have witnessed a dramatic upsurge in awareness among chemists of the potential utility of asymmetric organocatalysis as a tool for the synthesis of enantiopure molecules under mild and environmentally benign conditions.¹ The Michael addition of 1,3-dicarbonyl nucleophiles to nitroolefins² provides a particularly attractive target for organocatalyst design, largely due to the readily availability, high reactivity of nitroalkenes and the ability of the nitro functionality to accept hydrogen bonds from suitably designed catalyst systems. Thus, reactions of this nature have been reported to proceed in high yield and with good enantioselectivity by the use of various asymmetric catalysts.³ Bifunctional catalysts containing a thiourea group and a tertiary amine in the molecule usually lead to the high yields and enantioselectivities.⁴ Takemoto assumed that a thiourea moiety and a tertiary amino group in the catalyst activated a nitro group and a 1,3-dicarbonyl compound respectively to provide the Michael product with high enantio- and diastereoselectivity.⁵ Recently, 9-epi-amino cinchona alkaloid

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derivatives and diaminocyclohexane derivatives have proved to be efficient organocatalysts to catalyze the Michael reaction,⁶ aldol reaction⁷ and amination.⁸ Based on our recent research⁹ and the comprehension to this type of reaction, using quinine as catalyst, only hydroxy group acted as H-bond donor, the ee is very poor. While using thiourea as H-bond donor, usually obtained high ee for its strong interaction. **we wondered that more readily available primary amine of cinchona alkaloid derivatives can activate nitroolefin through H-bond.** (Figure 1)

Figure 1. Cinchona alkaloid catalysts activating the nitroolefins model.

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Figure 2. Structures of the cinchona alkaloid catalysts.

6.2 Results and discussion

In the initial studies, four cinchona alkaloid catalysts (Figure 2) were tested to catalyze the Michael reaction of **1a** and nitroolefin **2a** (Table 1). Solvent did not influence chemical yields and completed within 17 hours at room temperature. Reactions conducted in THF, toluene and diethyl ether all offered good yields and enantioselectivities (up to 98% ee). Remarkably, the Michael adduct precipitated in solid form in diethyl ether gave the highest ee value. This suggested a route to develop a recyclable and practical methodology to reuse the catalyst and excess reactant.

As shown in Table 1, the reaction promoted by catalyst **IV** gave the highest enantioselectivity and catalyst **III** (with the double bond reduced) gave a slightly lower ee value. Lowering the reaction temperature to 4 °C or reducing the catalyst loading to 10 mol% prolonged the reaction time and decreased the yield, though the ee value remained the same. Examination of the structures of catalysts **I-IV** revealed that both the primary amine groups and the methoxy groups played significant roles in controlling enantioselectivity. The reactions promoted by quinine and cinchonidine which do not contain the primary amine group resulted in very low ee values (reported in chapter IV). Almost racemic adducts were observed for the processes catalyzed by cinchonidine derivatives **I** and **II**, both of which do not contain a methoxy group.

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Table 1. Organocatalytic asymmetric Michael addition of **1a** and nitroolefin **2a**^a

entry	catalyst	solvent	time (h)	yield (%) ^b	ee (%) ^c
1	I	Et ₂ O	8	97	3
2	II	Et ₂ O	8	98	7
3	III	Et ₂ O	8	94	93
4	IV	Et ₂ O	8	96	98
5	IV	MeOH	8	93	65
6	IV	THF	15	82	98
7	IV	Toluene	8	97	95
8 ^d	IV	Et ₂ O	17	94	98
9 ^e	IV	Et ₂ O	12	85	98

^a Unless otherwise specified, the reaction was carried out with dione **1a** (3 eq) and nitrostyrene **2a** (0.1 mmol, 1 eq) dissolved in solvent (0.3 mL) in the presence of 15 mol% of catalyst at room temperature. ^b Isolated yields. ^c Enantiomeric excess (ee) determined by chiral HPLC analysis (Chiralpak AS-H). ^d Reaction at 4 °C. ^e 10 mol% catalyst used.

After we have obtained the optimized reaction conditions of the enantioselective Michael reaction of **1a** to nitroolefins, we next screened a series of analogues bearing different substituents on the aromatic ring (Table 2). All the reactions were carried out efficiently in the presence of 15 mol% of catalyst **IV** and were complete within 8-30 hours regardless of the electronic properties. The desired adducts were obtained exclusively in yields of 86-97% and excellent enantioselectivity (up to >99%). The nitroolefins bearing either neutral (Entries 2-5), electron-withdrawing (Entries 6-7, 12-13) or heterocyclics (Entries 8-10) and contain a variety of substitution (*para*, *meta* and *ortho*) groups all participated in this reaction efficiently. It is noteworthy that different functional group in the benzene ring didn't affect the results (Eqn (1), Scheme 1), and substrate **2o** displayed the great regioselectivity and enantioselectivity of this

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method (Eqn (2), Scheme 1).

Table 2. Michael addition of **1a** and *trans*-nitroolefins catalyzed by catalyst **VI**^a

Entry	R	Product	t (h)	Yield (%) ^b	Ee (%) ^c
1	Ph	3a	8	96	98
2	4-OMe-Ph	3b	12	92	97
3	3-OMe-Ph	3c	16	91	93
4	2-OMe-Ph	3d	16	94	99
5	4-Me-Ph	3e	12	93	98
6	4-Br-Ph	3f	8	96	>99
7	4-Cl-Ph	3g	8	97	>99
8	2-Thienyl	3h	12	92	97
9	2-Furyl	3i	16	91	98
10	3-Furyl	3j	12	91	97
11	1-Naphthyl	3k	16	88	96
12	2-NO ₂ -Ph	3l	12	92	94
13	4-NO ₂ -Ph	3m	24	86	94

^a Unless otherwise specified, the reaction was carried out with dione **1a** (3 eq) and nitrostyrene **2** (0.1 mmol, 1 eq) dissolved in solvent (0.3 mL) in the presence of 15 mol% of catalyst at room temperature. ^b Isolated yields. ^c Enantiomeric excess (ee) determined by chiral HPLC.

Further investigation of the diversity of Michael donor revealed that different substituents in the 1,3-dione have limited influence on the reactivities and enantioselectivities (Eqn (3), Scheme 1).

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Scheme 1. Diversities of Michael donors and acceptors.

According to the dual activation model proposed by Takemoto⁶ the two substrates involved in the reaction are activated simultaneously by catalyst as shown in Figure 3. In this model, we predicted the configuration of **3g** to be *S*. The absolute configuration of **3g** was verified by X-ray analysis.

Figure 3. Proposed action of catalyst.

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Figure 4. X-ray structure of **3g**.

To examine the validity of recyclable homogenous organocatalysis, the reaction of **1a** and nitroolefins (**2a**, **2g**) in diethyl ether was further studied as typical examples using 15 mol% catalyst **IV** (Figure 4). Interestingly, the Michael adducts very poor solubility in diethyl ether could be used to separate organocatalyst **IV** from the product **3a** or **3g** by simple filtration since it was precipitated from the reaction solution. The recyclability of the catalyst was tested in seven times and amazingly, the catalyst kept its high efficiency, giving almost quantitative yields (average 96%) and excellent enantioselectivities in each cycle (Table 3) (also, see ESI†). Based on this operationally simple *product (precipitate)-catalyst (soluble) separation*, the pure product is isolated by filtration from the reaction mixture when the reaction completed and the catalyst which is kept in the filtrate could be reused directly for the next cycle. Hence, the strategy for recyclable homogeneous organocatalysis was developed (Fig. 5).

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Figure 5. Recycling strategy for the organocatalytic Michael addition.

Table 3. Recycling of the organocatalytic Michael addition of 1,3-diphenyl-1,3-propanedione and *trans*- β -nitrostyrene with catalyst **IV**^a

cycle	R = Ph (3a)			R = 4-Cl-Ph (3g)		
	time (h)	yield ^b	ee (%) ^c	time (h)	yield ^b	ee (%) ^c
1	8	74	98	8	76	>99
2	9	83	97	10	82	99
3	10	110	97	11	108	98
4	12	95	96	13	96	97
5	15	109	96	16	114	96
6	19	94	95	19	97	96
7	30	101	94	23	97	95

^a The reaction was carried out using **2a** or **2g** (0.1 mmol, 1 eq.) and dione **1a** (0.3 mmol, 3 eq) with 15 mol% of **IV** in the cycle 1 and in the cycles 2-7 only **2a** or **2g** (0.1 mmol) and **1** (0.1 mmol) were added. ^b Average yield 96%. ^c Determined by chiral

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HPLC analysis.

6.3 Conclusion

In summary, we have demonstrated the first example of highly enantioselective Michael addition reaction with a simple organocatalyst **IV** using recyclable homogenous organocatalysis strategy. 9-Amino-9-deoxyepiquinine (**IV**) has been successfully employed as catalyst to the Michael additions of 1,3-diaryl-1,3-propanedione to various nitroolefins, where the diketone is usually not a good donor. The reactions proceeded smoothly, giving high to excellent yields (81-97%) and stereoselectivities (90->99% ee). Exploiting the use of the insolubility of the adduct, *product (precipitate)-catalyst (soluble) separation* significantly simplified the separation and purification process, and such reactions may be applicable to a large scale industrial production and thus, greatly reduce the cost of catalyst preparation.

6.4 Experimental section

General experimental conditions (Chapter 2)

General experimental procedure for the Michael addition of 1,3-diphenyl-1,3-propanedione to nitroolefins:

To a solution of 1,3-diphenyl-1,3-propanedione (67.2 mg, 0.3 mmol, 3 eq) and nitroolefin (0.1 mmol, 1eq) in diethyl ether (0.3 mL) was added catalyst **IV** (**Q-NH₂**) (0.015 mmol, 0.15 eq). The resulting mixture was stirred at room temperature (23 °C). After the reaction was complete (monitored by TLC), the products were isolated and purified either by filtration/washing with diethyl or by flash chromatography over silica gel (EtOAc:Hexane = 1:10 to 1:3).

(*S*)-2-(2-Nitro-1-phenylethyl)-1,3-diphenylpropane-1,3-dione (**3a**)

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Prepared according to the general procedure to provide the title compound (96% yield).

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.89 (d, $J = 8.0$ Hz, 2H), 7.81 (d, $J = 7.6$ Hz, 2H), 7.59-7.51 (m, 2H), 7.43-7.37 (m, 3H), 7.27-7.19 (m, 6H), 5.85 (d, $J = 8.0$ Hz, 1H), 5.03-5.01 (m, 2H), 4.64 (dd, $J = 7.2, 14.4$ Hz, 1H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 194.24, 193.61, 136.79, 136.19, 135.83, 134.07, 133.80, 128.97, 128.96, 128.84, 128.78, 128.61, 128.26, 128.16, 77.30, 59.88, 44.04. HPLC: Chiralpak AS-H (hexane/*i*-PrOH = 85/15, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (major) = 20.4 min, t_R (minor) = 28.3 min; 98% ee. $[\alpha]_{\text{D}}^{25} = 21.3$ ($c = 1.0$, CH_2Cl_2). MS (ESI, m/z): 374.3 (M+H).

(S)-2-(1-(4-Methoxyphenyl)-2-nitroethyl)-1,3-diphenylpropane-1,3-dione (3b)

Prepared according to the general procedure to provide the title compound (92% yield).

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.91 (d, $J = 7.6$ Hz, 2H), 7.81 (d, $J = 7.6$ Hz, 2H), 7.57-7.51 (m, 2H), 7.44-7.36 (m, 4H), 7.17 (d, $J = 8.8$ Hz, 2H), 6.74 (d, $J = 8.8$ Hz, 2H), 5.84 (d, $J = 8.0$ Hz, 1H), 5.00-4.96 (m, 2H), 4.61 (dd, $J = 7.2, 14.4$ Hz, 1H), 3.72 (s, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 194.33, 193.69, 159.25, 136.21, 135.90, 134.06, 133.76, 129.41, 128.97, 128.84, 128.81, 128.63, 128.52, 114.33, 77.68, 60.13, 55.20, 43.45. HPLC: Chiralpak AD-H (hexane/*i*-PrOH = 70/30, flow rate 1 mL/min, $\lambda = 230$ nm), t_R (major) = 10.7 min, t_R (minor) = 22.5 min; 97% ee. $[\alpha]_{\text{D}}^{25} = 25.1$ ($c = 1.0$, CH_2Cl_2). MS (ESI, m/z): 404.1 (M+H).

(S)-2-(1-(3-Methoxyphenyl)-2-nitroethyl)-1,3-diphenylpropane-1,3-dione (3c)

Prepared according to the general procedure to provide the title compound (91% yield).

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.89 (d, $J = 8.0$ Hz, 2H), 7.82 (d, $J = 8.0$ Hz, 2H), 7.59-7.52 (m, 2H), 7.44-7.37 (m, 4H), 7.16-7.12 (m, 1H), 6.85-6.71 (m, 3H), 5.85 (d, $J = 8.0$ Hz, 1H), 5.02-4.99 (m, 2H),

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4.64-4.58 (m, 1H), 3.70 (s, 3H). ^{13}C -NMR (100 MHz, CDCl_3) δ 194.26, 193.57, 159.81, 138.34, 136.19, 135.82, 134.09, 133.80, 130.03, 128.84, 128.79, 128.62, 128.07, 120.32, 114.26, 113.57, 77.22, 59.70, 55.17, 44.02. HPLC: Chiralpak AD-H (hexane/*i*-PrOH = 85/15, flow rate 1 mL/min, λ = 220 nm), t_R (major) = 19.2 min, t_R (minor) = 32.5 min; 93% ee. $[\alpha]_D^{25}$ = 5.1 (c = 1.1, CH_2Cl_2). HRMS (EI) calcd for $\text{C}_{24}\text{H}_{21}\text{N O}_5$, m/z 403.1414, found 403.1412.

(*S*)-2-(1-(2-Methoxyphenyl)-2-nitroethyl)-1,3-diphenylpropane-1,3-dione (3d)

Prepared according to the general procedure to provide the title compound (94% yield).

^1H -NMR (400 MHz, CDCl_3) δ 7.91-7.87 (m, 4H), 7.55-7.51 (m, 2H), 7.43-7.37 (m, 4H), 7.20-7.13 (m, 2H), 6.81-6.76 (m, 2H), 6.09 (d, J = 8.0 Hz, 1H), 5.25 (dd, J = 9.6, 12.8 Hz, 1H), 4.94 (dd, J = 4.0, 13.2 Hz, 1H), 4.86-4.80 (m, H), 3.87 (s, 3H). ^{13}C -NMR (100 MHz, CDCl_3) δ 194.42, 194.24, 157.09, 136.43, 135.98, 133.81, 133.67, 131.00, 129.35, 128.89, 128.68, 128.61, 128.59, 124.22, 121.06, 110.91, 75.84, 57.17, 55.27, 40.92. HPLC: Chiralpak AD-H (hexane/*i*-PrOH = 85/15, flow rate 1 mL/min, λ = 210 nm), t_R (major) = 16.7 min, t_R (minor) = 23.5 min; 99% ee. $[\alpha]_D^{25}$ = -17.4 (c = 1.0, CH_2Cl_2). HRMS (EI) calcd for $\text{C}_{24}\text{H}_{21}\text{N O}_5$, m/z 403.1414, found 403.1414.

(*S*)-2-(2-Nitro-1-*p*-tolylethyl)-1,3-diphenylpropane-1,3-dione (3e)

Prepared according to the general procedure to provide the title compound (93% yield).

^1H -NMR (400 MHz, CDCl_3) δ 7.90 (d, J = 7.6 Hz, 2H), 7.81 (d, J = 7.6 Hz, 2H), 7.57-7.52 (m, 2H), 7.44-7.37 (m, 4H), 7.14 (d, J = 8.0 Hz, 2H), 7.03 (d, J = 7.6 Hz, 2H), 5.85 (d, J = 8.0 Hz, 1H), 5.00-4.98 (m, 2H), 4.62 (dd, J = 5.2, 8.0 Hz, 1H), 2.25 (s, 3H). ^{13}C -NMR (100 MHz, CDCl_3) δ 194.34, 193.64, 137.90, 136.22, 135.86, 134.05, 133.76, 133.67, 129.64, 128.95, 128.83, 128.81, 128.65, 128.10, 77.53, 60.05, 43.74, 21.01. HPLC: Chiralpak AS-H (hexane/*i*-PrOH = 85/15, flow rate 1 mL/min, λ = 210 nm), t_R (major) = 18.8 min, t_R

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(minor) = 25.5 min; 98% ee. $[\alpha]_{\text{D}}^{25} = 8.6$ ($c = 1.0$, CH_2Cl_2). MS (ESI, m/z): 388.3 (M+H).

(S)-2-(1-(4-Bromophenyl)-2-nitroethyl)-1,3-diphenylpropane-1,3-dione (3f)

Prepared according to the general procedure to provide the title compound (96% yield).

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.87-7.85 (m, 2H), 7.77-7.74 (m, 2H), 7.59-7.52 (m, 2H), 7.54-7.47 (m, 2H), 7.41-7.29 (m, 6H), 7.11-7.08 (m, 2H), 5.78 (d, $J = 10.8$ Hz, 1H), 4.93-4.90 (m, 2H), 4.57 (dd, $J = 7.2$, 19.6 Hz, 1H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 193.96, 193.34, 136.01, 135.81, 135.68, 134.28, 134.02, 132.11, 130.02, 129.06, 128.96, 128.79, 128.61, 122.25, 77.17, 59.63, 43.55. HPLC: Chiralpak AS-H (hexane/*i*-PrOH = 85/15, flow rate 1 mL/min, $\lambda = 210$ nm), t_{R} (major) = 23.8 min, t_{R} (minor) = 33.5 min; >99% ee. $[\alpha]_{\text{D}}^{25} = 17.8$ ($c = 1.3$, CH_2Cl_2). MS (ESI, m/z): 453.3 (M+H).

(S)-2-(1-(4-Chlorophenyl)-2-nitroethyl)-1,3-diphenylpropane-1,3-dione (3g)

Prepared according to the general procedure to provide the title compound (97% yield).

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.88-7.85 (m, 2H), 7.77-7.74 (m, 2H), 7.54-7.48 (m, 2H), 7.41-7.32 (m, 4H), 7.15 (m, 4H), 5.78 (d, $J = 10.8$ Hz, 1H), 4.93-4.91 (m, 2H), 4.57 (dd, $J = 7.2$, 19.2 Hz, 1H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 193.97, 193.36, 136.02, 135.70, 135.26, 134.27, 134.11, 134.00, 129.71, 129.15, 129.06, 128.95, 128.79, 128.60, 77.25, 59.70, 43.49. HPLC: Chiralpak AS-H (hexane/*i*-PrOH = 85/15, flow rate 1 mL/min, $\lambda = 210$ nm), t_{R} (major) = 22.1 min, t_{R} (minor) = 31.2 min; >99% ee. $[\alpha]_{\text{D}}^{25} = 18.9$ ($c = 1.2$, CH_2Cl_2). HRMS (EI) calcd for $\text{C}_{23}\text{H}_{18}\text{ClNO}_4$, m/z 407.0919, found 407.0912.

(R)-2-(2-Nitro-1-(thiophen-2-yl)ethyl)-1,3-diphenylpropane-1,3-dione (3h)

Prepared according to the general procedure to provide the title compound (92% yield).

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^1H -NMR (400 MHz, CDCl_3) δ 7.91-7.87 (m, 4H), 7.60-7.56 (m, 2H), 7.45-7.41 (m, 4H), 7.15 (d, J = 5.2 Hz, 1 H), 6.90 (d, J = 3.2 Hz, 1H), 6.82 (dd, J = 3.6, 5.2 Hz, 1H), 5.98 (d, J = 7.2 Hz, 1H), 5.03-5.00 (m, 2H), 4.92 (dd, J = 6.8, 12.8 Hz, 1H). ^{13}C -NMR (100 MHz, CDCl_3) δ 194.03, 193.50, 139.25, 136.00, 135.60, 134.14, 134.00, 129.00, 128.96, 128.73, 128.68, 127.15, 127.07, 125.43, 77.95, 59.91, 39.47. HPLC: Chiralpak AS-H (hexane/*i*-PrOH = 85/15, flow rate 1 mL/min, λ = 262 nm), t_{R} (major) = 23.4 min, t_{R} (minor) = 27.0 min; 97% ee. $[\alpha]_{\text{D}}^{25}$ = -15.6 (c = 1.4, CH_2Cl_2). MS (ESI, m/z): 380.4 (M+H).

(*R*)-2-(1-(Furan-2-yl)-2-nitroethyl)-1,3-diphenylpropane-1,3-dione (3i)

Prepared according to the general procedure to provide the title compound (91% yield).

^1H -NMR (400 MHz, CDCl_3) δ 7.89-7.85 (m, 4H), 7.58-7.55 (m, 2H), 7.45-7.39 (m, 4H), 7.23 (m, 1H), 6.13 (m, 2H), 6.04 (d, J = 7.6 Hz, 1H), 5.01-4.90 (m, 2H), 4.77-4.72 (m, 1H). ^{13}C -NMR (100 MHz, CDCl_3) δ 193.74, 149.76, 142.47, 135.87, 135.41, 134.10, 133.93, 128.98, 128.91, 128.62, 110.68, 108.93, 75.55, 56.68, 37.78. HPLC: Chiralpak AS-H (hexane/*i*-PrOH = 85/15, flow rate 1 mL/min, λ = 210 nm), t_{R} (minor) = 20.7 min, t_{R} (major) = 25.1 min; 98% ee. $[\alpha]_{\text{D}}^{25}$ = 38.5 (c = 1.1, CH_2Cl_2). MS (ESI, m/z): 364.5 (M+H).

(*S*)-2-(1-(Furan-3-yl)-2-nitroethyl)-1,3-diphenylpropane-1,3-dione (3j)

Prepared according to the general procedure to provide the title compound (91% yield).

^1H -NMR (400 MHz, CDCl_3) δ 7.94 (d, J = 7.6 Hz, 2H), 7.88 (d, J = 7.6 Hz, 2H), 7.60-7.57 (m, 2H), 7.46-7.42 (m, 4H), 7.28-7.21 (m, 2 H), 6.32 (s, 1H), 5.88 (d, J = 8.0 Hz, 1H), 4.92-4.86 (m, 2H), 4.61 (dd, J = 6.8, 13.6 Hz, 1H). ^{13}C -NMR (100 MHz, CDCl_3) δ 194.19, 193.90, 143.61, 140.87, 136.01, 135.79, 134.14, 133.99, 129.02, 128.99, 128.74, 128.64, 120.97, 109.71, 77.46, 58.73, 35.29. HPLC: Chiralpak AS-H (hexane/*i*-PrOH = 85/15, flow rate 1 mL/min, λ = 210 nm), t_{R} (major) = 24.5 min, t_{R} (minor) = 27.7 min; 96% ee. $[\alpha]_{\text{D}}^{25}$ = 74.6 (c = 1.0,

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CH_2Cl_2). MS (ESI, m/z): 364.4 ($M+H$).

(S)-2-(1-(Naphthalen-1-yl)-2-nitroethyl)-1,3-diphenylpropane-1,3-dione (3k)

Prepared according to the general procedure to provide the title compound (88% yield).

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 8.20 (d, $J = 8.4$ Hz, 2H), 7.86 (d, $J = 7.6$ Hz, 2H), 7.75-7.60 (m, 6H), 7.56-7.40 (m, 3H), 7.33-7.28 (m, 5H), 7.22-7.18 (m, 1H), 6.02 (d, $J = 6.0$ Hz, 1H), 5.66-5.61 (m, 1H), 5.31 (dd, $J = 4.0, 14.4$ Hz, 1H), 4.61 (dd, $J = 9.2, 14.0$ Hz, 1H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 194.97, 193.77, 136.22, 135.69, 134.22, 133.72, 132.82, 131.06, 129.28, 128.85, 128.79, 128.75, 128.50, 127.13, 126.12, 124.92, 122.36, 76.54, 58.54, 37.34. HPLC: Chiralpak AS-H (hexane/*i*-PrOH = 85/15, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (major) = 21.8 min, t_R (minor) = 29.6 min; 96% ee. $[\alpha]_D^{25} = -155.4$ ($c = 1.0$, CH_2Cl_2). HRMS (EI) calcd for $\text{C}_{27}\text{H}_{21}\text{N O}_4$, m/z 423.1465, found 423.1466.

(S)-2-(2-Nitro-1-(2-nitrophenyl)ethyl)-1,3-diphenylpropane-1,3-dione (3l)

Prepared according to the general procedure to provide the title compound (92% yield).

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.89-7.84 (m, 5H), 7.60-7.52 (m, 2H), 7.43-7.36 (m, 7H), 6.28 (d, $J = 6.0$ Hz, 1H), 5.28-5.26 (m, 1H), 5.12-5.09 (m, 2H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 194.39, 193.35, 149.97, 136.21, 135.57, 134.33, 133.15, 131.67, 130.14, 129.12, 129.06, 128.94, 128.87, 128.59, 128.64, 125.43, 75.08, 57.98, 439.04. HPLC: Chiralpak AS-H (hexane/*i*-PrOH = 85/15, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (minor) = 16.0 min, t_R (major) = 18.0 min; 94% ee. $[\alpha]_D^{25} = -81.4$ ($c = 1.1$, CH_2Cl_2). MS (ESI, m/z): 419.4 ($M+H$).

(S)-2-(2-Nitro-1-(4-nitrophenyl)ethyl)-1,3-diphenylpropane-1,3-dione (3m)

Prepared according to the general procedure to provide the title compound (86% yield).

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 8.09 (d, $J = 8.4$ Hz, 2H),

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7.93 (d, $J = 7.6$ Hz, 2H), 7.82-7.80 (m, 2H), 7.61-7.54 (m, 2H), 7.49-7.39 (m, 6H), 5.87 (d, $J = 6.0$ Hz, 1H), 5.02-5.00 (m, 2H), 4.78 (dd, $J = 7.6$ Hz, 14.0 Hz, 1H). ^{13}C -NMR (100 MHz, CDCl_3) δ 193.48, 192.92, 147.58, 144.23, 135.76, 135.42, 134.54, 134.32, 129.51, 129.19, 129.10, 128.79, 128.60, 124.08, 76.83, 59.25, 43.73. HPLC: Chiralpak AS-H (hexane/*i*-PrOH = 85/15, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (major) = 20.5 min, t_R (minor) = 28.1 min; 94% ee. $[\alpha]_D^{25} = 36.8$ ($c = 1.1$, CH_2Cl_2). MS (ESI, m/z): 419.4 (M+H).

2-((*S*)-1-(2-Ethynylphenyl)-2-nitroethyl)-1,3-diphenylpropane-1,3-dione (**3n**)

Prepared according to the general procedure to provide the title compound (87% yield).

^1H -NMR (500 MHz, CDCl_3) δ 7.91 (d, $J = 7.5$ Hz, 2H), 7.83 (d, $J = 7.5$, 2H), 7.57-7.52 (m, 3H), 7.40-7.37 (m, 4H), 7.18-7.13 (m, 3H), 6.23 (d, $J = 7.0$ Hz, 1H), 5.26 (dd, $J = 10.5$, 14.5 Hz, 1H), 5.15-5.11 (m, 2H), 3.5 (s, 1H). ^{13}C -NMR (125 MHz, CDCl_3) δ 194.53, 193.61, 139.08, 136.28, 135.74, 134.23, 134.08, 133.86, 129.36, 128.95, 128.80, 128.74, 128.69, 127.86, 121.46, 83.71, 81.83, 75.67, 57.70, 41.95. HPLC: Chiralpak AD-H (hexane/*i*-PrOH = 85/15, flow rate 1 mL/min, $\lambda = 254$ nm), t_R (major) = 18.7 min, t_R (minor) = 21.5 min; 93% ee. $[\alpha]_D^{25} = -45.6$ ($c = 1.0$, CH_2Cl_2). HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{19}\text{NO}_4\text{Na}$, m/z 420.1212, found 420.1209.

2-((*R,E*)-1-Nitro-4-phenylbut-3-en-2-yl)-1,3-diphenylpropane-1,3-dione (**3o**)

To a solution of 1,3-diphenyl-1,3-propanedione (67.2 mg, 0.3 mmol, 3 eq) and nitroolefin **2o** (0.1 mmol, 1eq) in diethyl ether (0.2 mL) was added catalyst **VI** (**Q-NH₂**) (0.03 mmol, 0.3 eq).

The resulting mixture was stirred at room temperature (23 °C) for 30 hours. The products were isolated and purified with diethyl or by flash chromatography over silica gel (EtOAc:Hexane = 1:10 to 1:5) to provide the title compound (81% yield).

^1H -NMR (500 MHz, CDCl_3) δ 8.00-7.97 (m, 4H), 7.62 (t, $J = 7.0$ Hz, 2H), 7.51-7.47 (dd, $J = 7.5$, 13.5 Hz, 4H), 7.29-7.16 (m, 5H), 6.48 (d, $J = 15.5$ Hz, 1H), 6.20 (dd, $J =$

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9.5, 15.5 Hz, 1H), 5.81 (d, $J = 7.0$ Hz, 1H), 4.88-4.80 (m, 2H), 4.06-4.01 (s, 1H). ^{13}C -NMR (125 MHz, CDCl_3) δ 194.49, 194.33, 136.00, 135.87, 135.33, 134.14, 134.03, 129.17, 129.13, 128.70, 128.66, 128.50, 128.14, 126.55, 124.26, 77.58, 57.40, 42.35. HPLC: Chiralpak AS-H (hexane/*i*-PrOH = 85/15, flow rate 1 mL/min, $\lambda = 254$ nm), t_R (major) = 16.4 min, t_R (minor) = 42.0 min; 90% ee. $[\alpha]_D^{25} = 141.1$ ($c = 0.8$, CH_2Cl_2). HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{21}\text{NO}_4\text{Na}$, m/z 422.1368, found 422.1363.

2-((*S*)-2-Nitro-1-phenylethyl)-1,3-dip-tolylpropane-1,3-dione (**3p**)

To a solution of dione **1b** (0.1 mmol, 1 eq) and *trans*- β -nitrostyrene **2a** (0.2 mmol, 2eq) in diethyl ether (0.2 mL) was added catalyst **IV** (**Q-NH₂**) (0.015 mmol, 0.15 eq). The resulting mixture was stirred at room temperature (23 °C) for 24 hours. The product was purified by flash chromatography over silica gel (EtOAc:Hexane = 1:10 to 1:5) to provide the title compound (85% yield).

^1H -NMR (400 MHz, CDCl_3) δ 7.80 (d, $J = 8.0$ Hz, 2H), 7.73 (d, $J = 8.0$ Hz, 2H), 7.28-7.16 (m, 9H), 5.80 (d, $J = 8.0$ Hz, 1H), 5.01 (d, $J = 6.8$ Hz, 2H), 4.64 (dd, $J = 7.6$, 14.4 Hz, 1H), 2.39 (s, 3H), 2.37 (s, 3H). ^{13}C -NMR (100 MHz, CDCl_3) δ 193.83, 193.14, 145.20, 144.87, 137.03, 133.75, 133.30, 129.65, 129.54, 128.96, 128.93, 128.80, 128.26, 128.07, 59.68, 44.07, 21.69, 21.66. HPLC: Chiralpak AD-H (hexane/*i*-PrOH = 70/30, flow rate 1 mL/min, $\lambda = 254$ nm), t_R (major) = 10.7 min, t_R (minor) = 28.0 min; 97% ee. $[\alpha]_D^{25} = -2.6$ ($c = 1.0$, CH_2Cl_2). HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{24}\text{NO}_4$, m/z 402.1705, found 402.1692.

The Procedure for the Recycling of the Michael Addition

To *trans*- β -Nitrostyrene (**2a**):

To a solution of 1,3-diphenyl-1,3-propanedione (**1a**) (67.2 mg, 0.3 mmol, 3 eq) and *trans*- β -nitrostyrene (**1a**) (14.9 mg, 0.1 mmol, 1eq) in diethyl ether (0.3 mL) was added catalyst **IV** (**Q-NH₂**) (0.015 mmol, 0.15 eq). The resulting mixture was stirred at room temperature (23 °C). After the reaction was complete (monitored by TLC), the product **3a** was isolated and purified by centrifuge/washing with diethyl ether (0.5 mL).

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All the catalyst **IV** (0.15 eq) and 2 equivalents of the excess the dione **1a** were retained in the filtrate. The combined ethereal filtrate was evaporated to 0.3 mL before the dione **1a** (1 equiv) and nitrostryene **2a** (1 eq) were added again to the solution for the next round of the Michael reaction. This was to ensure that the reaction condition for each cycle was almost the same as the previous one. The excellent yields (96% in average) and enantioselectivities (>99-95% ee) were achieved in seven cycles.

To 1-chloro-4-((*E*)-2-nitrovinyl) benzene (**2g**):

To a solution of 1,3-diphenyl-1,3-propanedione (**1a**) (0.3 mmol, 3 eq) and 1-chloro-4-((*E*)-2-nitrovinyl)benzene (**2g**) (0.1 mmol, 1eq) in diethyl ether (0.3 mL) was added catalyst **IV** (**Q-NH₂**) (0.015 mmol, 0.15 eq). The resulting mixture was stirred at room temperature (23 °C). After the reaction was complete (monitored by TLC), the product **3g** was isolated and purified by centrifuge/washing with diethyl ether (0.3 mL). All the catalyst **IV** (0.15 equiv) and 2 equivalents of dione **1a** were retained in the filtrate. The combined ethereal filtrate was evaporated to 0.3 mL before dione **1a** (1 eq) and **2g** (1 eq) were added again to the solution for the next round of the Michael reaction. This was to ensure that the reaction condition for each cycle was almost the same as the previous one. The excellent yields (96% in average) and enantioselectivities (98-94% ee) were achieved in seven cycles.

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Chapter 7

ORGANOCATALYTIC ASYMMETRIC DOMINO REACTION CATALYZED BY 9-AMINO-9-DEOXYEPIQUININE

7.1 Organocatalytic Asymmetric Domino Michael-Henry Reactions: A Highly Stereoselective Synthesis of Multifunctionalized Cyclohexanes with Two Quaternary Stereocenters

The asymmetric assembly of quaternary carbon centers has been proven to be one of the most difficult topics in current organic synthesis.^{1,2} One approach towards these challenges is the use of catalytic enantioselective domino reactions,³ which have emerged as powerful tools to give a rapid increase in molecular complexity from simple and readily available starting materials, thus producing enantioenriched complex compounds in a single operation. Of the developed strategies for asymmetric tandem reactions, organocatalysis provided an efficient protocol.⁴ Although several elegant organocatalytic tandem reactions have been reported recently,⁶ the discovery novel approach for the creation of compounds with multiple stereogenic carbons⁵ including quaternary centers in a cascade manner remains a big challenge at the forefront of synthetic chemistry.

The Michael addition reaction provides an important tool for the construction of highly functionalized carbon skeletons.⁷ Until today, there were only a few reports that described the 1,4-adducts containing adjacent quaternary and tertiary chiral centers

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with excellent enantioselectivity and diastereoselectivity in the field of organocatalysis⁸ and there is no report that is related to the formation of two quaternary centers yet.

Figure 1. Cinchona Alkaloid and Derivative Catalysts Tested in the Domino Michael-Henry Reaction.

The Henry reaction also represents a powerful C–C bond-forming tool and the resulting nitro alcohol products can be transformed into a number of nitrogen and oxygen-containing derivatives such as nitroalkenes, aminoalcohols and amino acids.⁹ In addition to substrate-controlled Henry reactions, organocatalytic systems that provide good stereoselectivity have been developed in recent years. However, there are few reports describing the possibility of common ketones used as acceptors with good results. We found a novel facile organocatalyzed enantioselective tandem Michael-Henry reaction that generates multifunctionalized cyclohexane derivatives with four stereogenic centers including two quaternary stereocenters in excellent enantioselectivities (97–>99% ee) and diastereoselectivities (up to 99:1 dr).

Readily accessible cinchona alkaloid and its derivatives, which were developed recently in several research groups, have been identified as efficient bifunctional organocatalysts in asymmetric Michael reactions¹⁰ and Henry reactions.¹¹ These results prompted us to explore the feasibility of employing thiourea catalyst **I** (Figure

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1) to catalyze the tandem Michael-Henry reactions involving a nitroolefin and a carbon nucleophiles **1a** containing three carbonyl groups. To our great delight, the tandem Michael-Henry reaction proceeded smoothly to yield the desired cyclohexane product in high yield (85%) and good enantioselectivity (80% ee) and diastereoselectivity (92:8 dr, Table 1, entry 1). In order to improve the results, different conditions were investigated. However, the results did not change significantly when the process was conducted in solvent or when the reaction temperature was decreased (Table 1, entries 2, 3). As such, we turned our attention to revolutionizing catalysts. After screening the catalysts **II-VII** (Figure 1) at room temperature (23 °C) under neat condition, **VI** and **VII** were found to be excellent candidates to catalyze this tandem reaction with the highest stereoselectivity (92% ee, 95:5 dr) among all the tested cases, as shown in the Table 1. Catalyst **VI**¹² was then chosen as catalyst due to the higher yield obtained and its easy synthesis. Further optimization of the reaction conditions revealed that solvents played a very important role in determining the selectivities of the reaction (in solvent toluene or diethyl ether, >99% ee, 98:2 dr) (Table 1, entries 9-11).

After getting the optimized reaction conditions, we investigated the scope of the tandem Michael-Henry process by using a variety of nitroolefins in diethyl ether at room temperature. It was discovered that most of the reactions are complete within 24 hour with good to excellent yields (85%-94%), excellent enantioselectivities (97%->99% ee) and diastereoselectivities (93:7-98:2 dr). It appeared that the different substituents on aromatic rings have a very limited effect on the stereoselectivities. Regardless of the types of substituents on the aromatic rings, be it electron-withdrawing (Table 2, entries 9 and 10), -donating (entries 2-4), neutral (entry 1) groups and substrates containing a variety of substitution (*para*, *meta* and *ortho*) groups participated in this reaction efficiently and afforded highly enantioselective adducts. To our surprise, the nitro group at the phenyl ring did not cause the enantiomeric excess to decrease. This may be attributed to the primary amine group in the catalyst that can selectively capture the two nitro groups. Notably, only one Michael-Henry adduct was obtained from the reaction of nitrodiene **2k** in

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Table 1. Organocatalytic Domino Michael-Henry Reactions of Ethyl 2-acetyl-5-oxohexanoate **1a** and *trans*- β -Nitrostyrene^a

entry	catalyst	solvent	time (h)	yield (%) ^b	dr ^c	ee (%) ^d
1	I	neat	3	85	92:8	80
2	I	toluene	8	88	93:7	78
3 ^e	I	neat	8	86	93:7	77
4	II	neat	10	92	78:22	65
5	IV	neat	3	95	85:15	26
6	V	neat	3	94	82:18	23
7	VII	neat	18	90	95:5	92
8	VI	neat	10	92	95:5	92
9	VI	toluene	24	88	97:3	>99
10 ^f	VI	toluene	18	92	98:2	>99
11 ^f	VI	Et ₂ O	16	93	98:2	>99
12 ^{f, g}	VI	Et ₂ O	16	93	98:2	>99

^a Unless otherwise specified, all the reactions were carried out using **1a** (0.6 mmol, 1.5 equiv) and **2a** (0.4 mmol, 1.0 equiv) with 10 mol% of catalyst at room temperature (23 °C). ^b Isolated yields. ^c Determined by crude NMR. ^d Determined by chiral HPLC analysis (major isomer). ^e Reaction at 4 °C. ^f 15 mol% catalyst was used. ^g **1a** (0.4 mmol, 1.0 equiv) and **2a** (0.6 mmol, 1.5 equiv) were used.

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Table 2. The Tandem Michael-Henry Reaction of Diketetoester **1a** and Nitroolefin (**2**) Catalyzed by Catalyst **VI**^a

entry	R	3	time (h)	yield (%) ^b	dr ^c	ee (%) ^d
1	Ph	3a	16	93	98:2	>99
2	4-MeO-Ph	3b	24	91	95:5	98
3	4-Me-Ph	3c	24	89	96:4	98
4	3-Me-Ph	3d	24	90	95:5	99
5	4-Br-Ph	3e	30	88	93:7	>99
6	2-Br-Ph	3f	20	90	99:1	97
7	4-Cl-Ph	3g	24	87	93:7	97
8	2-Cl-Ph	3h	24	91	96:4	97
9	2-O ₂ N-Ph	3i	24	94	98:2	97
10	4-CF ₃ -Ph	3j	24	91	95:5	98

^a All the reactions were carried out using **1a** (0.4 mmol, 1.0 equiv) and **2** (0.6 mmol, 1.5 equiv) in the presence of 15 mol % of **VI** at room temperature in diethyl ether (0.4 mL). ^b Isolated yields. ^c Determined by NMR. ^d Determined by chiral HPLC analysis (major isomer).

97% ee value (Scheme 1). Theoretically, both β - and δ -positions of **2k** can possibly be attacked due to the two congruous double bonds, thus demonstrating the great regioselectivity and enantioselectivity of this method. Furthermore, the tandem reaction also proceeded smoothly when **1a** was replaced by either **1b** or **1c**, giving excellent stereoselectivities (99% ee) as displayed in Scheme 1.

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Scheme 1. The Tandem Michael-Henry Reactions of **1a** with **2k** and **1b/1c** with **2a**.

Figure 2. Proposed Action of Catalyst.

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Figure 3. X-ray crystallographic structure **3f**.

According to Takemoto's dual activation action,^{8c} nitroolefins are supposed to cooperate with the primary amine moiety in the **VI** by the use of multiple hydrogen bonds, thus decreasing the LUMO energy of the active double bond. The carboanion (adjacent to the nitro group) generating from the Michael addition then attacks the si-face of the carbonyl group to afford Henry products (Figure 2). The stereochemistry was established by X-ray crystallographic determination of **3f** (CCDC 670273) and analysis of NMR data of the products.

7.2 A Highly Diastereo- and Enantioselective Synthesis of Multisubstituted Cyclopentanes with Four Chiral Carbons by the Organocatalytic Domino Michael-Henry Reaction

After successful development of the enantioselective domino Michael-Henry reaction to afford with four stereogenic centers (two quaternary and two tertiary stereocenters) in high diastereoselectivities and excellent enantioselectivities, we begin to wonder the highly substituted cyclopentane derivatives could be achieved by the same domino strategy. (Scheme 2)

Scheme 2. Organocatalytic synthesis of cycloalkanes using tandem Michael-Henry reactions strategy

These results prompted us to explore the feasibility of employing diamine catalyst **VI** to catalyze domino Michael-Henry reactions involving a nitroolefin and a rationally designed carbon nucleophile **1d** to form chiral cyclopentane (Scheme 1, $n = 0$). To our

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disappointment, the enantioselectivity of the desired product was only 67% ee (Table 3, entry 1). Despite changing the reaction conditions such as catalysts, solvents,

Table 3. Organocatalytic domino Michael-Henry reactions forming cyclopentanes^a

entry	1	catalyst	solvent	time (h)	yield (%) ^b	ee (%) ^c
1	1d	VI	Et ₂ O	18	92	67
2	1d	I	neat	3	94	71
3	1d	I	toluene	10	92	80
4 ^d	1d	I	toluene	18	90	82
5	1e	I	neat	3	92	70
6	1f	I	neat	3	NR ^e	NA ^f
7	1g	I	neat	3	95	75
8	1h	I	neat	3	94	75
9	1g	I	toluene	10	92	80
10 ^d	1g	I	toluene	18	93	83
11	1g	II	toluene	10	94	75
12	1g	V	toluene	18	93	65
13	1g	VI	toluene	18	93	90
14	1g	VI	Et ₂ O	18	92	88
15 ^d	1g	VI	toluene	36	93	95

^a Unless otherwise specified, all the reactions were carried out using **1d** (1.0 mmol, 2.0 equiv) and **2a** (0.5 mmol, 1.0 equiv) with 10 mol% of catalysts at room temperature. ^b Isolated yields. ^c Determined by chiral HPLC analysis. ^d Reaction at 4 °C. ^e No reaction. ^f Not applicable.

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temperature, the highest enantiomeric excess obtained was 82% (Table 3, entries 1-4). In our bid to get better results, we turned our attention to designing substrates. The investigation of various substrates demonstrated that the domino Michael-Henry reaction proceeded very well to give the expected cyclopentane ring products in high yields (92-95%, table 3, entry 5, 7-9) with the exception of the less reactive substrate **1f** (Table 3, entry 6). Surprisingly, only one diastereomer was obtained in all the cases investigated. However, varied enantioselectivities were observed with different substituents on designed substrate **1**. For example, higher enantiomeric excess (75% ee) were observed when **1d** was substituted with **1g** or **1h**. Through much endeavors, the best result achieved was only 83% ee with catalyst **I**. Therefore, it seemed to be essential to change the organocatalysts for much higher enantioselectivity. To our delight, the product was obtained in 93% yield with 90% ee (Table 3, entry 13) when catalyst **VI** was used. When catalyst **V** was used, the lower enantiomeric excess indicated that the OMe group on the catalyst was crucial for stereoselectivity (Table 3, entry 12). Although the reaction time was prolonged to 36 hours, higher ee (95% ee) was afforded when the reaction temperature was lowered to 4 °C (Table 3, entry 15). The domino Michael-Henry reaction indeed proceeded smoothly to yield the desired cyclopentane ring product in excellent yield (95%) and good enantioselectivity (75% ee).

With the optimised reaction conditions, we embarked on the investigation of the generality of the domino Michael-Henry process by using a variety of nitroalkenes. It was observed that all the reactions were completed within 72 hours, giving adducts in excellent yields (90-95%) and with complete diastereoselectivities and excellent enantioselectivities (88-96% ee). It appeared that the different substituents for aromatic rings had a very limited influence on the stereoselectivities of the reactions (Table 4, entries 2-7). Electron-withdrawing (entries 6-7 and 11-12), electron-donating (entries 2-5) and neutral (entries 1 and 10) groups, as well as substrates containing a variety of substitution patterns (*para*, *meta* and *ortho*), participated in this reaction efficiently. The heteroaromatic groups (furyl, thienyl) were also engaged to afford the respective cyclopentane derivatives with excellent enantioselectivity (entries 8 and 9). This demonstrates the point that the primary

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amine group in the catalyst is able to capture one of the two nitro groups selectively. Furthermore, the domino reaction also proceeded smoothly when **1a** was replaced with either **1b** or **1c**, as displayed in Scheme 3.

Table 4. Organocatalytic domino Michael-Henry reactions of **1g** and nitroolefins catalyzed by catalyst **VI**^a

entry	R	4	t (h)	yield (%) ^b	ee (%) ^c
1	Ph	4a	36	93	95
2	3-MeO-Ph	4b	48	91	92
3	4-MeO- Ph	4c	60	93	92
4	2-Me- Ph	4d	48	90	90
5	4-Me- Ph	4e	48	91	95
6	4-Br- Ph	4f	40	94	91
7	4-Cl- Ph	4g	36	95	95
8	2-Thienyl	4h	40	93	93
9	2-Furyl	4i	48	91	92
10	1-Naphthyl	4j	60	91	96
11	4- O ₂ N- Ph	4k	72	90	91
12	4-CF ₃ - Ph	4l	48	95	92

^a All the reactions were carried out using **1g** (1.0 mmol, 2.0 equiv) and **2** (0.5 mmol, 1.0 equiv) in the presence of 10 mol% of **VI** at 4 °C with toluene (0.5 mL). ^b Isolated yields. ^c Determined by chiral HPLC analysis.

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Scheme 3. Organocatalytic domino Michael-Henry reactions of trisubstituted carbon nucleophiles (**1h** or **1i**) to *trans*- β -nitrostyrene catalyzed by catalyst **VI**.

The dual activation model was proposed as shown in the Figure 4, which was very similar to the previous one. The absolute configuration of **4f** was determined by X-ray crystallography (Figure 5, see Supporting Information). The stereochemistry of this domino reaction was then established by analysis of the X-ray crystal structures together with analysis of the NMR data.

Figure 4. Proposed action of catalyst.

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Figure 5. X-ray crystal structure of **4f**.

In summary, we have described a facile organocatalytic, enantioselective synthesis of highly functionalized chiral cyclohexanes or cyclopentanes with four stereogenic centers (two quaternary and two tertiary stereocenters) in excellent, enantioselectivities and complete diastereoselectivities by the domino Michael-Henry reaction strategy. The domino reaction was efficiently catalyzed by readily available catalyst **VI** (9-amino-9-deoxyepiquinine) to give synthetically valuable multifunctionalized chiral cyclopentanes or cyclohexanes, where the organocatalytic *intramolecular* Henry reaction of common ketones was employed for the five or six membered ring closing step in excellent stereoselectivities. This domino synthesis is quite useful in natural product synthesis since we know that there are many types of biologically active natural substances that bear optically active cyclopentane or cyclohexane derivatives. We hope that this strategy of developing a practical and efficient domino Michael-Henry reaction can spark further efforts into the designing of such organocatalytic domino reactions. This approach constitutes our future direction aimed at expanding the scope and applications of these powerful tandem processes.

7.3 Control Four Stereocenters in an Organocatalytic Domino Double Michael Reaction: Efficient Assembly of Multifunctionalized Five-Membered Rings

Efficient asymmetric double Michael reactions¹³ have been achieved by relying on the use of chiral auxiliaries¹⁴ and chiral precursors¹⁵ for stereocontrol. However, the development of organocatalytic enantioselective double reactions proved to be a challenging task, and such processes are elusive, especially the products containing one adjacent quaternary and tertiary chiral centers using α,β -unsaturated esters as Michael acceptors.

Based on the quinine-amine catalyzed domino Michael-Henry reactions reported by our group, we further examined the double Michael reaction involving rationally designed substrates. Herein we wish to report highly stereoselective organocatalytic double Michael reactions, in which four contiguous stereogenic centers (containing one adjacent quaternary and tertiary stereocenters) were constructed by a simple process.

Readily accessible cinchona alkaloid and derivative catalysts, which were developed recently in several research groups, have been identified as efficient bifunctional organocatalysts in asymmetric Michael reactions. To probe the feasibility of the proposed Michael-Michael cascade reaction, we carried out our examination by using nitrostyrene with diethyl 5-acetylhex-2-enedioate **1j** ($E:Z = 6:1$) in the presence of cinchona alkaloid catalyst **IV** (15 mol%). To our great excitement, the reaction proceeded very well, even though the results were not good (Table 5, entry 1). In order to get better yield and enantioselectivity, we investigated several catalysts and solvent.

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Table 5. Organocatalytic Domino Double Michael Reactions of Ethyl 2-Acetyl-5-oxohexanoate **1j** (*E:Z* = 6:1) and *trans*- β -Nitrostyrene^a

entry	catalyst	solvent	time (h)	yield (%) ^b	dr ^c	ee (%) ^d
1	I	neat	5	73	96:4	79
2	I	toluene	8	91	96:4	82
3	I	Et ₂ O	8	90	97:3	83
4	I	Et ₂ O	24	88	97:3	83
5 ^e	II	Et ₂ O	8	90	96:4	80
6	III	Et ₂ O	8	87	96:4	95
7	IV	neat	6	72	94:6	23
8	VI	Et ₂ O	16	91	>99:1	97
9	VII	Et ₂ O	16	91	97:3	95
10 ^f	VI	Et ₂ O	30	85	>99:1	97
11	VI	toluene	36	86	97:3	90
12 ^e	VI	Et ₂ O	24	87	>99:1	96
13 ^g	VI	Et ₂ O	16	82	>99:1	96

^a Unless otherwise specified, all the reactions were carried out using **1j** (0.15 mmol, 1.0 equiv) and **2a** (0.23 mmol, 1.5 equiv) with 15 mol% of catalyst at room temperature (22 °C). ^b Isolated yields. ^c Determined by NMR and HPLC analysis. ^d Determined by chiral HPLC analysis (major isomer). ^e Reaction at 0 °C. ^f 10 mol% catalyst was used. ^g **1j** (0.23 mmol, 1.5 equiv) and **2a** (0.15 mmol, 1.0 equiv) were used.

Catalyst **I** proved to be a very efficient catalyst for the Michael reaction. Therefore, we first chose **I** as the most promising catalyst to screen other conditions. However, the results did not improve significantly when the process was run in solvents or when the reaction temperature was decreased (Table 5, entries 2-5). As such, we turned our attention to changing catalysts (in the Figure 1, **II**, **III**, **VI**, **VII**) at room temperature (22 °C), catalyst **VI** was found to be excellent candidates to catalyze this domino reaction with the highest stereoselectivity (97% ee) among all the tested cases, as

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shown in the Table 1. Further optimization of the reaction conditions elucidated that solvents played a very important role in determining the selectivities of the reaction and yield (diethyl ether, 97% ee, 91% yield) (Table 5, entries 9-11).

Having established the optimal reaction condition, a series of nitroolefins were reacted with dicarbonyl unsaturated esters to investigate the generality of the domino double Michael process by using catalyst **VI** in diethyl ether. It was discovered that most reactions were complete within 36 hour with good to excellent yields (81%-92%), excellent enantioselectivities (90%-97% ee). Significantly, most of the examples showed that different substituents on aromatic rings, have a very limited effect on the stereoselectivities. Regardless of the types of substituents on the aromatic rings, be it electron-withdrawing (Table 2, entries 6, 7, 13), –donating (entries 2-5), neutral (entry 1, 8, 9) groups and substrates containing a variety of substitution (*para*, *meta* and *ortho*) groups participated in this reaction efficiently. The heterocyclic thienyl, furanyl (Table 2, entries 10-12) participated in this process giving good yields and enantioselectivities. This may be attributed to the primary amine group in the catalyst that can selectively capture the two nitro groups. Interestingly, the ratio (*E*:*Z* = 10:1) of **1j** did take no effect on reactivity and selectivity. (Scheme 1, a) The domino reaction also proceeded smoothly when **1j** was replaced by **1k**, giving excellent stereoselectivities (95% ee) as displayed in Scheme 1. Theoretically, both β - and δ -positions of **2o** can possibly be attacked due to the two conjugated double bonds. However, only one double Michael adduct was obtained from the reaction of nitrodiene **2o** in 95% ee value, (Scheme 4, c) thus, showing the great regioselectivity and enantioselectivity of this method.

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Table 2. The Domino Double Michael Reaction of Ethyl 2-Acetyl-5-oxohexanoate **1j** (*E*:*Z* = 6:1) and Nitroolefins (**2**) Catalyzed by Catalyst **VI**^a

entry	R	5	time (h)	yield (%) ^b	dr ^c	ee (%) ^d
1	Ph (2a)	5a	16	91	>99:1	97
2	4-Me-Ph (2b)	5b	24	89	97:3	95
3	3-Me- Ph (2c)	5c	24	85	96:4	95
4 ^e	4-MeO- Ph (2d)	5d	30	83	96:4	94
5 ^e	3-MeO- Ph (2e)	5e	30	81	98:2	90
6	4-Br- Ph (2f)	5f	16	92	>99:1	95
7	4-Cl- Ph (2g)	5g	16	88	98:2	95
8	2-naphthyl (2h)	5h	24	84	95:5	95
9	1-naphthyl (2i)	5i	24	87	97:3	97
10	3-furanyl (2j)	5j	24	86	98:2	97
11	2-furanyl (2k)	5k	24	87	95:5	96
12	2-thienyl (2l)	5l	18	91	>99:1	96
13 ^e	4-NO ₂ - Ph (2m)	5m	36	81	96:4	95

^a Unless otherwise specified, the reactions were carried out using **1j** (0.15 mmol, 1.0 equiv) and **2** (0.23 mmol, 1.5 equiv) in the presence of 15 mol% of **VI** at room temperature in diethyl ether (0.2 mL). ^b Isolated yields. ^c Determined by NMR and HPLC analysis. ^d Determined by chiral HPLC analysis (major isomer). ^e 20 mol% catalyst and 2.0 equiv **2** was used.

The dual activation model shown in Figure 6 was very similar to the previous one. The stereochemistry was established by X-ray crystallographic determination of **5g** (Figure 7) and analysis of NMR data of the products.

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Scheme 4. The Domino Double Michael Reactions of **1j** with **2a** (E:Z = 10:1) and **1k** with **2a/2o**.

Figure 6. Proposed Action of Catalyst.

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Figure 7. X-ray crystal structure of **5g**.

In summary, we have developed a greatly enantioselective and diastereoselective tandem double Michael reaction that prepared multifunctionalized five-membered rings catalyzed by 9-amino-9-deoxyepiquinine.

7.4 Experimental section

General experimental conditions (Chapter 2)

7.4.1 Typical procedure for Michael-Henry reactions of forming cyclohexanes: To a solution of ethyl 2-acetyl-5-oxohexanoate **1a** (0.2 mmol, 1.0 eq) and nitroolefin (0.3 mmol, 1.5 eq) in diethyl ether (0.2 mL) was added catalyst **VI** (**Q-NH₂**) (0.03 mmol, 0.15 eq) at room temperature. The resulting mixture was stirred vigorously. After the reaction was completed (monitored by TLC or crude NMR), the product was afforded by flash chromatography over silica gel (EtOAc:Hexane = 1:10 to 1:5).

(1*R*,2*R*,3*S*,4*R*)-Ethyl-1-acetyl-4-hydroxy-4-methyl-3-nitro-2-phenylecyclohexane carboxylate (**3a**)

The title compound was prepared according to the typical procedure, as described above in 93% yield.

¹H-NMR (400 MHz, CDCl₃) δ 7.39-7.37 (m, 2H), 7.28-7.25 (m, 3H), 5.70 (d, *J* = 12.4 Hz, 1 H), 4.26-4.20 (m, 1H),

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4.14-4.06 (m, 1H), 4.08 (d, $J = 12.4$ Hz, 1H), 2.90 (d, $J = 2.0$ Hz, 1H), 2.56-2.50 (m, 1H), 2.01-1.86 (m, 3H), 1.75 (s, 3H), 1.38 (s, 3H), 1.17 (t, $J = 7.2$ Hz, 3 H). ^{13}C -NMR (100 MHz, CDCl_3) δ 203.19, 171.37, 134.62, 130.07, 128.31, 128.23, 93.19, 69.77, 64.83, 61.44, 46.46, 34.08, 28.83, 27.81, 27.49, 13.75. HPLC: Chiralpak AS-H (hexane/*i*-PrOH = 80/20, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (major) = 10.4 min, t_R (minor) = 28.5 min; >99% ee. $[\alpha]_{\text{D}}^{25} = -91.9$ ($c = 1.0$, CHCl_3).

(1*R*,2*R*,3*S*,4*R*)-Ethyl-1-acetyl-4-hydroxy-2-(4-methoxyphenyl)-4-methyl-3-nitro cyclohexanecarboxylate (3b)

The title compound was prepared according to the typical procedure, as described above in 91% yield.

^1H -NMR (400 MHz, CDCl_3) δ 7.30 (d, $J = 8.8$ Hz, 2H), 6.78 (d, $J = 8.8$ Hz, 2H), 5.67 (d, $J = 12.4$ Hz, 1 H), 4.27-4.21 (m, 1H), 4.14-4.09 (m, 1H), 4.00 (d, $J = 12.8$ Hz, 1H), 3.77 (s, 3H), 2.94 (d, $J = 3.0$ Hz, 1H), 2.57-2.50 (m, 1H), 2.07-1.83 (m, 3H), 1.76 (s, 3H), 1.37 (s, 3H), 1.20 (t, $J = 6.8$ Hz, 3 H). ^{13}C -NMR (100 MHz, CDCl_3) δ 203.49, 171.45, 159.28, 131.20, 126.45, 113.67, 93.34, 69.77, 64.91, 61.43, 55.13, 45.94, 34.07, 28.96, 27.77, 27.49, 13.81. HPLC: Chiralpak AD-H (hexane/*i*-PrOH = 90/10, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (major) = 18.7 min, t_R (minor) = 21.2 min; 98% ee. $[\alpha]_{\text{D}}^{25} = -120.1$ ($c = 1.0$, CHCl_3). HRMS (EI) calcd for $\text{C}_{19}\text{H}_{25}\text{O}_7\text{N}$, m/z 379.1626, found 379.1691.

(1*R*,2*R*,3*S*,4*R*)-Ethyl-1-acetyl-4-hydroxy-4-methyl-3-nitro-2-*p*-tolylcyclohexanecarboxylate (3c)

The title compound was prepared according to the typical procedure, as described above in 89% yield.

^1H -NMR (400 MHz, CDCl_3) δ 7.25 (d, $J = 8.0$ Hz, 2H), 7.06 (d, $J = 8.0$ Hz, 2H), 5.69 (d, $J = 12.8$ Hz, 1 H), 4.28-4.20 (m, 1H), 4.15-4.07 (m, 1H), 4.02 (d, $J = 12.8$ Hz, 1H), 2.93 (d, $J = 2.0$ Hz, 1H), 2.57-2.50 (m, 1H), 2.28 (s, 3H), 2.00-1.85 (m, 3H), 1.75 (s, 3H), 1.36 (s,

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3H), 1.19 (t, $J = 7.2$ Hz, 3 H). ^{13}C -NMR (100 MHz, CDCl_3) δ 203.38, 171.41, 137.92, 131.49, 129.91, 129.02, 93.29, 69.76, 64.87, 61.41, 46.20, 34.08, 28.93, 27.79, 27.50, 21.05, 13.78. HPLC: Chiralpak AD-H (hexane/*i*-PrOH = 90/10, flow rate 1 mL/min, $\lambda = 220$ nm), t_R (major) = 13.0 min, t_R (minor) = 16.3 min; 98% ee. $[\alpha]_D^{25} = -94.1$ ($c = 1.0$, CHCl_3).

(1*R*,2*R*,3*S*,4*R*)-Ethyl-1-acetyl-4-hydroxy-4-methyl-3-nitro-2-*m*-tolylcyclohexanecarboxylate (3d)

The title compound was prepared according to the typical procedure, as described above in 90% yield.

^1H -NMR (400 MHz, CDCl_3) δ 7.21-7.13 (m, 3H), 7.04 (d, $J = 7.2$ Hz, 1H), 5.70 (d, $J = 12.4$ Hz, 1 H), 4.26-4.19 (m, 1H), 4.12-4.08 (m, 1H), 4.04 (d, $J = 12.8$ Hz, 1H), 2.90 (d, $J = 2.4$ Hz, 1H), 2.56-2.49 (m, 1H), 2.30 (s, 3H), 2.00-1.88 (m, 3H), 1.75 (s, 3H), 1.36 (s, 3H), 1.19 (t, $J = 7.2$ Hz, 3 H). ^{13}C -NMR (100 MHz, CDCl_3) δ 203.25, 171.39, 137.78, 134.51, 130.89, 128.96, 128.15, 126.95, 93.22, 69.75, 64.80, 61.39, 46.35, 34.07, 28.87, 27.80, 27.49, 21.40, 13.75.

HPLC: Chiralpak AD-H (hexane/*i*-PrOH = 90/10, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (major) = 11.0 min, t_R (minor) = 16.1 min; 99% ee. $[\alpha]_D^{25} = -100.9$ ($c = 1.0$, CHCl_3).

(1*R*,2*R*,3*S*,4*R*)-Ethyl-1-acetyl-2-(4-bromophenyl)-4-hydroxy-4-methyl-3-nitro cyclohexanecarboxylate (3e)

The title compound was prepared according to the typical procedure, as described above in 88% yield.

^1H -NMR (400 MHz, CDCl_3) δ 7.39 (d, $J = 8.4$ Hz, 2H), 7.26 (d, $J = 8.4$ Hz, 2H), 5.59 (d, $J = 12.4$ Hz, 1 H), 4.27-4.22 (m, 1H), 4.12-4.06 (m, 1H), 4.10 (d, $J = 12.4$ Hz, 1H), 2.85 (d, $J = 2.0$ Hz, 1H), 2.50-2.44 (m, 1H), 2.00-1.91 (m, 3H), 1.83 (s, 3H), 1.36 (s, 3H), 1.19 (t, $J = 7.2$ Hz, 3 H). ^{13}C -NMR (100 MHz, CDCl_3) δ 202.91, 171.26, 133.77, 131.82, 131.42, 122.43, 93.07, 69.75, 64.61, 61.61, 45.68, 34.06, 28.74, 27.74, 27.41, 13.77. HPLC: Chiralpak AD-H (hexane/*i*-PrOH = 90/10, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (minor) = 13.2 min, t_R

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(major) = 14.9 min; >99% ee. $[\alpha]_{\text{D}}^{25} = -82.0$ ($c = 0.9$, CHCl_3). HRMS (EI) calcd for $\text{C}_{18}\text{H}_{22}\text{O}_6\text{NBr}$, m/z 429.0605, found 429.0691.

**(*R*,2*R*,3*S*,4*R*)-Ethyl-1-acetyl-2-(2-bromophenyl)-4-hydroxy-4-methyl-3-nitro
cyclohexanecarboxylate (3f)**

The title compound was prepared according to the typical procedure, as described above in 90% yield.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.99 (dd, $J = 1.2, 8.0$ Hz, 1H), 7.54 (d, $J = 8.0$ Hz, 1H), 7.34-7.28 (m, 1H), 7.15-7.11 (m, 1H), 5.95 (d, $J = 12.4$ Hz, 1H), 4.64 (d, $J = 12.4$ Hz, 1H), 4.24-4.19 (m, 2H), 2.96 (d, $J = 2.0$ Hz, 1H), 2.88-2.82 (m, 1H), 2.03-1.96 (m, 1H), 1.89-1.84 (m, 1H), 1.83 (s, 3H), 1.69-1.61 (m, 1H), 1.37 (s, 3H), 1.23 (t, $J = 7.2$ Hz, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 202.07, 171.09, 134.58, 133.57, 130.53, 129.82, 127.84, 127.56, 93.28, 69.81, 64.69, 61.68, 44.25, 33.86, 28.90, 28.06, 27.43, 13.87. HPLC: Chiralpak AD-H (hexane/*i*-PrOH = 90/10, flow rate 1 mL/min, $\lambda = 210$ nm), t_{R} (minor) = 16.0 min, t_{R} (major) = 20.3 min; 97% ee. $[\alpha]_{\text{D}}^{25} = -134.8$ ($c = 1.1$, CHCl_3). HRMS (EI) calcd for $\text{C}_{18}\text{H}_{22}\text{O}_6\text{NBr}$, m/z 429.0605, found 429.0596.

**(*1R*,2*R*,3*S*,4*R*)-Ethyl-1-acetyl-2-(4-chlorophenyl)-4-hydroxy-4-methyl-3-nitro
cyclohexanecarboxylate (3g)**

The title compound was prepared according to the typical procedure, as described above in 87% yield.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.32 (d, $J = 8.8$ Hz, 2H), 7.24 (d, $J = 8.8$ Hz, 2H), 5.60 (d, $J = 12.4$ Hz, 1H), 4.27-4.21 (m, 1H), 4.13-4.06 (m, 1H), 4.10 (d, $J = 12.8$ Hz, 1H), 2.85 (s, 1H), 2.50-2.43 (m, 1H), 2.01-1.90 (m, 3H), 1.82 (s, 3H), 1.37 (s, 3H), 1.19 (t, $J = 7.2$ Hz, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 202.93, 171.27, 134.19, 133.23, 131.48, 128.47, 93.13, 69.75, 64.66, 61.60, 45.63, 34.06, 28.74, 17.74, 27.42, 13.77. HPLC: Chiralpak AD-H (hexane/*i*-PrOH = 90/10, flow rate 1 mL/min, $\lambda = 210$ nm), t_{R} (minor) = 9.2 min, t_{R} (major) = 10.7 min; 97% ee. $[\alpha]_{\text{D}}^{25} = -101.0$ ($c = 1.0$, CHCl_3).

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(*R*,2*R*,3*S*,4*R*)-Ethyl-1-acetyl-2-(2-chlorophenyl)-4-hydroxy-4-methyl-3-nitro cyclohexanecarboxylate (3h)

The title compound was prepared according to the typical procedure, as described above in 91% yield.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.96 (d, $J = 7.6$ Hz, 1H), 7.34 (d, $J = 7.6$ Hz, 1H), 7.29-7.21 (m, 2H), 5.93 (d, $J = 12.0$ Hz, 1H), 4.64 (d, $J = 12.4$ Hz, 1H), 4.25-4.17 (m, 2H), 2.91 (d, $J = 2.4$ Hz, 1H), 2.87-2.82 (m, 1H), 2.04-1.99 (m, 1H), 1.93-1.86 (m, 1H), 1.75 (s, 3H), 1.68-1.61 (m, 1H), 1.38 (s, 3H), 1.23 (t, $J = 7.2$ Hz, 3 H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 202.16, 171.09, 136.23, 132.90, 130.48, 130.02, 129.52, 127.14, 93.18, 69.82, 64.71, 61.65, 41.47, 33.91, 28.60, 28.01, 27.47, 13.87. HPLC: Chiralpak AD-H hexane/*i*-PrOH = 90/10, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (minor) = 15.0 min, t_R (major) = 18.5 min; 97% ee. $[\alpha]_{\text{D}}^{25} = -123.5$ ($c = 1.2$, CHCl_3).

(*R*,2*R*,3*S*,4*R*)-Ethyl-1-acetyl-4-hydroxy-4-methyl-3-nitro-2-(4-(trifluoromethyl) phenyl) cyclohexanecarboxylate (3i)

The title compound was prepared according to the typical procedure, as described above in 91% yield.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.52 (m, 4H), 5.60 (d, $J = 12.4$ Hz, 1 H), 4.26 (d, $J = 12.4$ Hz, 1H), 4.26-4.21 (m, 1H), 4.08-4.03 (m, 1H), 2.82 (s, 1H), 2.49-2.42 (m, 1H), 2.04-1.98 (m, 3H), 1.84 (s, 3H), 1.38 (s, 3H), 1.15 (t, $J = 6.8$ Hz, 3 H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 202.65, 171.17, 138.95, 130.54, 130.47, 125.09 (q, $J = 3.6$ Hz), 122.49, 93.04, 69.76, 64.56, 61.66, 45.68, 34.09, 28.50, 27.73, 27.37, 13.66. HPLC: Chiralpak AD-H (hexane/*i*-PrOH = 90/10, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (minor) = 9.2 min, t_R (major) = 10.7 min; 97% ee. $[\alpha]_{\text{D}}^{25} = -79.6$ ($c = 1.0$, CHCl_3).

(*R*,2*R*,3*S*,4*R*)-Ethyl-1-acetyl-4-hydroxy-4-methyl-3-nitro-2-(2-nitrophenyl) cyclohexanecarboxylate (3j)

The title compound was prepared according to the typical

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procedure, as described above in 94% yield.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.82 (dd, $J = 1.2, 8.0$ Hz, 1H), 7.69 (dd, $J = 0.8, 8.0$ Hz, 1H), 7.53-7.49 (m, 1H), 7.42-7.38 (m, 1H), 5.65 (d, $J = 12.4$ Hz, 1H), 4.14 (d, $J = 12.4$ Hz, 1H), 4.28-4.20 (m, 1H), 4.07-3.99 (m, 1H), 3.08 (d, $J = 1.6$ Hz, 1H), 2.41-2.37 (m, 1H), 2.13-2.09 (m, 2H), 2.02 (s, 3H), 1.39 (s, 3H), 1.14 (t, $J = 7.2$ Hz, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 202.11, 171.11, 151.62, 131.82, 129.77, 129.57, 128.94, 125.34, 93.23, 69.84, 63.90, 61.77, 38.34, 33.87, 27.88, 27.47, 21.19, 13.66. HPLC: Chiralpak AD-H (hexane/*i*-PrOH = 90/10, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (minor) = 25.9 min, t_R (major) = 37.9 min; 98% ee. $[\alpha]_D^{25} = -302.9$ ($c = 0.5$, CHCl_3).

(1*R*,2*R*,3*S*,4*R*,*E*)-Ethyl-1-acetyl-4-hydroxy-4-methyl-3-nitro-2-styryl cyclohexane carboxylate (3k)

To a solution of ethyl 2-acetyl-5-oxohexanoate **1a** (0.2 mmol, 1.0 eq) and nitroolefin (**2k**) (0.3 mmol, 1.5 eq) in diethyl ether (0.2 mL) was added catalyst **VI** (0.03 mmol, 0.15 eq) at room temperature. The resulting mixture was stirred vigorously.

After 36 hours the reaction was completed (monitored by TLC and crude NMR), the product was afforded by flash chromatography over silica gel in 91% yield.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.33-7.24 (m, 6H), 6.51-6.39 (m, 2H), 5.10 (d, $J = 11.6$ Hz, 1H), 4.31 (q, $J = 7.2$ Hz, 1H), 3.51-3.26 (m, 1H), 3.29 (d, $J = 2.4$ Hz, 1H), 2.53-2.49 (m, 1H), 2.14 (s, 3H), 2.06-1.94 (m, 2H), 1.32 (s, 3H), 1.33 (t, $J = 7.2$ Hz, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 203.44, 171.29, 136.36, 136.08, 128.52, 128.11, 126.70, 122.76, 93.38, 69.22, 64.67, 61.69, 45.78, 34.37, 28.55, 27.38, 26.99, 14.06. HPLC: Chiralpak AD-H (hexane/*i*-PrOH = 90/10, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (major) = 15.2 min, t_R (minor) = 39.6 min; 97% ee. $[\alpha]_D^{25} = -35.4$ ($c = 1.2$, CHCl_3).

(*R*,2*R*,3*S*,4*R*)-Methyl-1-acetyl-4-hydroxy-4-methyl-3-nitro-2-phenyl cyclohexane carboxylate (3l)

To a solution of Methyl 2-acetyl-5-oxohexanoate **1b** (0.2 mmol, 1.0 eq) and nitroolefin (**2a**) (0.3 mmol, 1.5 eq) in diethyl ether

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(0.2 mL) was added catalyst **VI** (0.03 mmol, 0.15 eq) at room temperature. The resulting mixture was stirred vigorously. After 16 hours the reaction was completed (monitored by TLC and crude NMR), the product was afforded by flash chromatography over silica gel in 85% yield.

^1H -NMR (400 MHz, CDCl_3) δ 7.38-7.36 (m, 2H), 7.27-7.24 (m, 3H), 5.67 (d, J = 12.4 Hz, 1 H), 4.11 (d, J = 12.4 Hz, 1H), 3.69 (s, 3H), 2.88 (d, J = 2.0 Hz, 1H), 2.56-2.48 (m, 1H), 2.00-1.86 (m, 3H), 1.76 (s, 3H), 1.33 (s, 3H). ^{13}C -NMR (100 MHz, CDCl_3) δ 202.97, 171.86, 134.53, 130.03, 128.32, 128.28, 93.21, 69.76, 64.79, 52.13, 46.38, 34.12, 28.70, 27.79, 27.46. HPLC: Chiralpak AD-H (hexane/*i*-PrOH = 90/10, flow rate 1 mL/min, λ = 210 nm), t_R (major) = 18.0 min, t_R (minor) = 31.5 min; 99% ee. $[\alpha]_{\text{D}}^{25}$ = -101.3 (c = 1.0, CHCl_3).

(*R*,2*R*,3*S*,4*R*)-Benzyl-1-acetyl-4-hydroxy-4-methyl-3-nitro-2-phenyl cyclohexane carboxylate (3m)

To a solution of benzyl 2-acetyl-5-oxohexanoate **1c** (0.2 mmol, 1.0 eq) and nitroolefin (**2a**) (0.3 mmol, 1.5 eq) in diethyl ether (0.2 mL) was added catalyst **VI** (0.03 mmol, 0.15 eq) at room temperature. The resulting mixture was stirred vigorously.

After 16 hours the reaction was completed (monitored by TLC and crude NMR), the product was afforded by flash chromatography over silica gel in 93% yield.

^1H -NMR (400 MHz, CDCl_3) δ 7.39-7.33 (m, 5H), 7.26-7.19 (m, 5H), 5.70 (d, J = 12.4 Hz, 1 H), 5.23 (d, J = 12.0 Hz, 1H), 5.01 (d, J = 12.0 Hz, 1H), 4.10 (d, J = 12.4 Hz, 1H), 2.90 (s, 1H), 2.57-2.49 (m, 1H), 1.97-1.78 (m, 3H), 1.67 (s, 3H), 1.34 (s, 3H). ^{13}C -NMR (100 MHz, CDCl_3) δ 203.05, 171.15, 134.55, 134.35, 130.05, 128.79, 128.70, 128.57, 128.37, 128.27, 93.15, 69.76, 67.33, 64.94, 46.48, 33.98, 28.91, 27.80, 27.46. HPLC: Chiralpak AS-H (hexane/*i*-PrOH = 80/20, flow rate 1 mL/min, λ = 210 nm), t_R (major) = 11.2 min, t_R (minor) = 38.7 min; 99% ee. $[\alpha]_{\text{D}}^{25}$ = - 83.8 (c = 1.2, CHCl_3).

7.4.2 Typical procedure for the Michael-Henry reactions forming cyclopentanes:

To a solution of ethyl 2-acetyl-4-oxo-4-phenylbutanoate **1g** (1.0 mmol, 2 eq) and

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nitroolefins (0.5 mmol, 1 eq) in toluene (0.5 mL) was added catalyst **VI** (**Q-NH₂**) (0.05 mmol, 0.1 eq) at 4 °C. The resulting mixture was stirred vigorously at 4 °C. After the reaction was complete (monitored by TLC), the products were afforded by flash column chromatography over silica gel (EtOAc:Hexane = 1:10 to 1:6).

(1*R*,2*R*,3*S*,4*S*)-Ethyl-1-acetyl-4-hydroxy-3-nitro-2,4-diphenyl cyclopentane carboxylate (4a)

The title compound was prepared according the typical procedure, as described above in 93% yield.

¹H-NMR (400 MHz, CDCl₃) δ 7.64 (d, *J* = 7.6, 2H), 7.47-7.28 (m, 8H), 5.80 (d, *J* = 12.4 Hz, 1 H), 5.43 (d, *J* = 12.4 Hz, 1H), 3.82-3.76 (m, 2H), 3.50-3.42 (m, 1H), 3.27 (d, *J* = 14.4 Hz, 1H), 2.57 (d, *J* = 14.8 Hz, 1H), 2.26 (s, 3H), 0.76 (t, *J* = 7.2 Hz, 3 H).

¹³C-NMR (100 MHz, CDCl₃) δ 200.38, 170.28, 139.67, 134.29, 128.88, 128.75, 128.59, 128.52, 128.23, 124.90, 93.31, 81.01, 67.82, 62.23, 49.63, 46.44, 26.88, 13.26.

HPLC: Chiralcel OD-H (hexane/*i*-PrOH = 80/20, flow rate 1mL/min, λ = 210 nm), *t_R* (major) = 6.6 min, *t_R* (minor) = 10.7 min; 95% ee. [α]_D²⁵ = 23.1 (*c* = 1.0, CHCl₃).

HRMS (EI) calcd for C₂₂H₂₃NO₆, *m/z* 397.1520, found 397.1524.

(1*R*,2*R*,3*S*,4*S*)-Ethyl-1-acetyl-4-hydroxy-2-(3-methoxyphenyl)-3-nitro-4-phenyl cyclopentanecarboxylate (4b)

The title compound was prepared according the typical procedure, as described above in 91% yield.

¹H-NMR (400 MHz, CDCl₃) δ 7.60(d, *J* = 8.4, 1H), 7.45-7.35 (m, 3H), 7.65-7.63 (m, 3H), 7.24-7.20 (m, 2H), 6.96-6.95 (m, 2H), 6.81 (dd, *J* = 1.6, 8.4 Hz, 1 H), 5.74 (d, *J* = 12.4 Hz, 1H), 5.37 (d, *J* = 12.4 Hz, 1H), 3.85-3.76 (m, 3H), 3.74 (d, *J* = 2.0 Hz, 1H), 3.56-3.48 (m, 1H), 3.25 (dd, *J* = 2.0, 14.4 Hz, 1H), 2.54 (d, *J* = 14.4 Hz, 1H), 2.24 (s, 3H), 0.79 (t, *J* = 7.2 Hz, 3 H).

¹³C-NMR (100 MHz, CDCl₃) δ 200.36, 159.65, 139.65, 135.84, 129.49, 128.87, 128.59, 124.89, 120.53, 114.72, 113.90, 93.43, 81.00, 67.73, 62.25, 55.32, 49.62, 46.48, 26.86, 13.30. HPLC: Chiralcel OD-H (hexane/*i*-PrOH = 80/20,

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flow rate 1 mL/min, $\lambda = 210$ nm), t_R (major) = 7.6 min, t_R (minor) = 11.6 min; 92% ee. $[\alpha]_D^{25} = 28.1$ ($c = 1.0$, CHCl_3). HRMS (EI) calcd for $\text{C}_{23}\text{H}_{25}\text{NO}_7$, m/z 427.1626, found 427.1628.

(1*R*,2*R*,3*S*,4*S*)-Ethyl-1-acetyl-4-hydroxy-2-(4-methoxyphenyl)-3-nitro-4-phenyl cyclopentanecarboxylate (4c)

The title compound was prepared according the typical procedure, as described above in 93% yield.

^1H -NMR (400 MHz, CDCl_3) δ 7.63 (d, $J = 7.6$, 2H), 7.48-7.28 (m, 8H), 5.74 (d, $J = 12.8$ Hz, 1 H), 5.36 (d, $J = 12.8$ Hz, 1H), 3.86-3.80 (m, 2H), 3.79 (s, 3H), 3.56-3.51 (m, 1H), 3.25 (dd, $J = 7.2$, 14.4 Hz, 1H), 2.56 (d, $J = 14.4$ Hz, 1H), 2.27 (s, 3H), 0.83 (t, $J = 7.2$ Hz, 3 H). ^{13}C -NMR (100 MHz, CDCl_3) δ 200.55, 170.44, 159.49, 139.73, 129.90, 128.86, 128.57, 126.03, 124.89, 113.88, 93.46, 88.87, 67.68, 62.22, 55.31, 49.17, 46.39, 26.95, 13.39. HPLC: Chiralcel OD-H (hexane/*i*-PrOH = 80/20, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (major) = 10.8 min, t_R (minor) = 20.7 min; 92% ee. $[\alpha]_D^{25} = 23.3$ ($c = 1.2$, CHCl_3). HRMS (EI) calcd for $\text{C}_{23}\text{H}_{25}\text{NO}_7$, m/z 427.1626, found 427.1629.

(1*R*,2*R*,3*S*,4*S*)-Ethyl-1-acetyl-4-hydroxy-3-nitro-4-phenyl-2-*o*-tolyl cyclopentane carboxylate (4d)

The title compound was prepared according the typical procedure, as described above in 90% yield.

^1H -NMR (400 MHz, CDCl_3) δ 7.60 (d, $J = 7.6$, 2H), 7.48-7.39 (m, 3H), 7.19-7.18 (m, 4H), 5.78 (d, $J = 10.4$ Hz, 1 H), 5.61 (d, $J = 10.8$ Hz, 1H), 3.78-3.72 (m, 1H), 3.65 (s, 1H), 3.43-3.37 (m, 2H), 2.65 (d, $J = 15.2$ Hz, 1H), 2.56 (s, 3H), 2.27 (s, 3H), 0.73 (t, $J = 6.8$ Hz, 3 H). ^{13}C -NMR (100 MHz, CDCl_3) δ 200.61, 169.26, 139.72, 139.02, 135.20, 130.86, 128.86, 128.52, 127.93, 126.61, 126.13, 124.82, 97.39, 81.30, 69.59, 62.14, 46.58, 44.86, 26.32, 20.20, 13.14. HPLC: Chiralcel OD-H (hexane/*i*-PrOH = 80/20, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (major) = 5.6 min, t_R (minor) = 7.2 min; 90% ee.

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$[\alpha]_{\text{D}}^{25} = 18.1$ ($c = 1.0$, CHCl_3). HRMS (EI) calcd for $\text{C}_{23}\text{H}_{25}\text{NO}_6$, m/z 411.1678, found 411.1679.

(1*R*,2*R*,3*S*,4*S*)-Ethyl-1-acetyl-4-hydroxy-3-nitro-4-phenyl-2-*p*-tolyl cyclopentane carboxylate (4e)

The title compound was prepared according the typical procedure, as described above in 91% yield.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.61 (d, $J = 7.6$, 2H), 7.45-7.34 (m, 3H), 7.29-7.27 (m, 2H), 7.11 (d, $J = 8.0$ Hz, 2H), 5.75 (d, $J = 12.4$ Hz, 1 H), 5.36 (d, $J = 12.4$ Hz, 1H), 3.83-3.75 (m, 2H), 3.53-3.45 (m, 1H), 3.24 (dd, $J = 2.0$, 14.4 Hz, 1H), 2.54 (d, $J = 14.8$ Hz, 1H), 2.30 (s, 3H), 2.24 (s, 3H), 0.77 (t, $J = 7.2$ Hz, 3 H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 200.49, 170.35, 139.74, 137.98, 131.10, 129.16, 128.86, 128.60, 128.56, 124.90, 93.42, 80.95, 67.76, 62.20, 49.42, 46.43, 26.93, 21.04, 13.24. HPLC: Chiralcel OD-H (hexane/*i*-PrOH = 80/20, flow rate 1mL/min, $\lambda = 210$ nm), t_{R} (major) = 6.4 min, t_{R} (minor) = 9.4 min; 95% ee. $[\alpha]_{\text{D}}^{25} = 12.1$ ($c = 1.5$, CHCl_3). HRMS (EI) calcd for $\text{C}_{23}\text{H}_{25}\text{NO}_6$, m/z 411.1678, found 411.1682.

(1*R*,2*R*,3*S*,4*S*)-Ethyl-1-acetyl-2-(4-bromophenyl)-4-hydroxy-3-nitro-4-phenyl cyclopentanecarboxylate (4f)

The title compound was prepared according the typical procedure, as described above in 94% yield.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.61 (d, $J = 7.6$, 2H), 7.46-7.42 (m, 4H), 7.38-7.37 (m, 1H), 7.30-7.27 (m, 2H), 5.72 (d, $J = 12.4$ Hz, 1 H), 5.37 (d, $J = 12.4$ Hz, 1H), 3.87-3.79 (m, 1H), 3.76 (d, $J = 2.4$ Hz, 1H), 3.56-3.51 (m, 1H), 3.22 (dd, $J = 2.0$, 14.4 Hz, 1H), 2.53 (d, $J = 14.8$ Hz, 1H), 2.23 (s, 3H), 0.82 (t, $J = 7.2$ Hz, 3 H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 200.28, 170.23, 139.51, 133.35, 131.64, 130.50, 128.92, 128.68, 124.86, 122.35, 92.85, 80.98, 67.55, 62.42, 49.02, 46.46, 26.87, 13.33. HPLC: Chiralcel OD-H (hexane/*i*-PrOH = 80/20, flow rate 1mL/min, $\lambda = 210$ nm), t_{R} (major) = 7.1 min, t_{R} (minor) = 11.6 min; 91% ee. $[\alpha]_{\text{D}}^{25} = 8.1$ ($c = 1.0$, CHCl_3). HRMS (EI)

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calcd for $C_{22}H_{22}BrNO_6$, m/z 475.0626, found 475.0629.

(1*R*,2*R*,3*S*,4*S*)-Ethyl-1-acetyl-2-(4-chlorophenyl)-4-hydroxy-3-nitro-4-phenylcyclopentanecarboxylate (4g)

The title compound was prepared according the typical procedure, as described above in 95% yield.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.62 (d, J = 7.6, 2H), 7.46-7.42 (m, 2H), 7.38-7.35 (m, 3H), 7.30-7.26 (m, 2H), 5.73 (d, J = 12.4 Hz, 1 H), 5.38 (d, J = 12.4 Hz, 1H), 3.87-3.79 (m, 1H), 3.75 (d, J = 3.2 Hz, 1H), 3.57-3.49 (m, 1H), 3.23 (dd, J = 2.0, 14.4 Hz, 1H), 2.53 (d, J = 14.8 Hz, 1H), 2.23 (s, 3H), 0.82 (t, J = 7.2 Hz, 3 H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 200.29, 170.24, 139.51, 134.22, 132.80, 130.18, 128.92, 128.67, 124.86, 92.93, 80.98, 67.59, 62.40, 48.98, 46.45, 26.87, 13.33. HPLC: Chiralcel OD-H (hexane/*i*-PrOH = 80/20, flow rate 1mL/min, λ = 210 nm), t_R (major) = 7.2 min, t_R (minor) = 11.2 min; 95% ee. $[\alpha]_D^{25}$ = 10.4 (c = 1.8, CHCl_3). HRMS (EI) calcd for $C_{22}H_{22}ClNO_6$, m/z 431.1132, found 431.1135.

(1*R*,2*R*,3*S*,4*S*)-Ethyl-1-acetyl-4-hydroxy-3-nitro-4-phenyl-2-(thiophen-2-yl)cyclopentanecarboxylate (4h)

The title compound was prepared according the typical procedure, as described above in 93% yield.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.63 (d, J = 3.6, 2H), 7.48-7.36 (m, 3H), 7.26 (d, J = 4.8 Hz, 1H), 7.05 (d, J = 3.6 Hz, 1H), 6.96 (t, J = 4.4 Hz, 1H), 5.74 (d, J = 12.4 Hz, 1 H), (m, 2H), 5.60 (d, J = 12.4 Hz, 1H), 3.95-3.91 (m, 1H), 3.73-3.68 (m, 2H), 3.26 (dd, J = 2.0, 14.8 Hz, 1H), 2.57 (d, J = 14.8 Hz, 1H), 2.27 (s, 3H), 0.93 (t, J = 7.2 Hz, 3 H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 200.39, 170.54, 139.51, 136.68, 128.89, 128.65, 126.78, 126.48, 125.98, 124.91, 94.42, 80.91, 67.35, 62.54, 46.48, 45.61, 26.91, 13.44. HPLC: Chiralcel OD-H (hexane/*i*-PrOH = 80/20, flow rate 1mL/min, λ = 210 nm), t_R (major) = 8.0 min, t_R (minor) = 12.6 min; 93% ee. $[\alpha]_D^{25}$ = 21.6 (c = 1.8, CHCl_3).

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HRMS (EI) calcd for $C_{20}H_{21}NO_6S$, m/z 403.1086, found 403.1088.

**(1*R*,2*R*,3*S*,4*S*)-Ethyl-1-acetyl-2-(furan-2-yl)-4-hydroxy-3-nitro-4-phenyl
cyclopentanecarboxylate (4i)**

The title compound was prepared according the typical procedure, as described above in 91% yield.

1H -NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 8.0, 2H), 7.47-7.39 (m, 4H), 6.38-6.35 (m, 2H), 5.74 (d, J = 11.6 Hz, 1 H), 5.41 (d, J = 12.0 Hz, 1H), 4.07-4.01 (m, 1H), 3.86-3.80 (m, 1H), 3.66 (s, 1H), 3.25 (d, J = 14.8 Hz, 1H), 2.58 (d, J = 14.8 Hz, 1H), 2.29 (s, 3H), 1.04 (t, J = 7.2 Hz, 3 H). ^{13}C -NMR (100 MHz, $CDCl_3$) δ 200.15, 169.93, 148.62, 142.79, 139.58, 128.85, 128.57, 124.88, 110.84, 109.99, 92.67, 80.85, 66.18, 62.72, 46.29, 44.31, 26.51, 13.62. HPLC: Chiralcel OD-H (hexane/*i*-PrOH = 80/20, flow rate 1 mL/min, λ = 210 nm), t_R (major) = 7.0 min, t_R (minor) = 10.4 min; 92% ee. $[\alpha]_D^{25}$ = 26.0 (c = 1.5, $CHCl_3$). HRMS (EI) calcd for $C_{20}H_{21}NO_7$, m/z 387.1314, found 387.1318.

**(1*R*,2*R*,3*S*,4*S*)-Ethyl-1-acetyl-4-hydroxy-2-(naphthalen-1-yl)-3-nitro-4-phenyl
cyclopentanecarboxylate (4j)**

The title compound was prepared according the typical procedure, as described above in 91% yield.

1H -NMR (400 MHz, $CDCl_3$) δ 8.73 (d, J = 8.4, 1H), 7.84-7.79 (m, 2H), 7.65-7.63 (m, 3H), 7.53-7.37 (m, 6H), 6.42 (d, J = 10.8 Hz, 1 H), 5.85 (d, J = 10.8 Hz, 1H), 3.82 (d, J = 2.4 Hz, 1H), 3.55-3.44 (m, 2H), 3.07-3.02 2.66 (d, J = 14.8 Hz, 1H), 2.26 (s, 3H), 0.21 (t, J = 7.2 Hz, 3 H). ^{13}C -NMR (100 MHz, $CDCl_3$) δ 200.86, 169.30, 139.62, 133.83, 132.95, 128.98, 128.91, 128.62, 128.42, 126.89, 126.16, 124.88, 124.74, 124.35, 96.86, 81.38, 69.59, 61.91, 46.41, 43.93, 26.54, 12.60. HPLC: Chiralcel OD-H (hexane/*i*-PrOH = 80/20, flow rate 1 mL/min, λ = 210 nm), t_R (major) = 6.9 min, t_R (minor) = 8.7 min; 96% ee. $[\alpha]_D^{25}$ = 22.1 (c = 1.0, $CHCl_3$). HRMS (EI) calcd for $C_{26}H_{25}NO_6$, m/z 447.1677, found 447.1678.

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(1*R*,2*R*,3*S*,4*S*)-Ethyl-1-acetyl-4-hydroxy-3-nitro-2-(4-nitrophenyl)-4-phenyl **cyclopentanecarboxylate (4k)**

The title compound was prepared according the typical procedure, as described above in 90% yield.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.18 (d, $J = 8.0$, 2H), 7.64-7.60 (m, 4H), 7.48-7.447 (m, 2H), 7.41-7.37 (m, 1H), 5.80 (d, $J = 12.4$ Hz, 1 H), 5.52 (d, $J = 12.4$ Hz, 1H), 3.93-3.80 (m, 1H), 3.54-3.45 (m, 1H), 3.23 (d, $J = 14.8$ Hz, 1H), 2.58 (d, $J = 14.4$ Hz, 1H), 2.25 (s, 3H), 0.80 (t, $J = 7.2$ Hz, 3 H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 200.02, 170.01, 147.67, 141.96, 139.21, 129.95, 129.02, 128.84, 124.81, 123.54, 92.49, 81.10, 67.66, 62.51, 49.08, 46.59, 26.82, 13.41. HPLC: Chiralcel OD-H (hexane/*i*-PrOH = 65/35, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (major) = 6.8 min, t_R (minor) = 15.6 min; 91% ee. $[\alpha]_D^{25} = 19.3$ ($c = 1.2$, CHCl_3). HRMS (EI) calcd for $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_8$, m/z 442.1371, found 442.1375.

(1*R*,2*R*,3*S*,4*S*)-Ethyl-1-acetyl-4-hydroxy-3-nitro-4-phenyl-2-(4-(trifluoromethyl)phenyl)cyclopentanecarboxylate (4l)

The title compound was prepared according the typical procedure, as described above in 95% yield.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.65-7.58 (m, 6H), 7.49-7.46 (m, 2H), 7.42-7.38 (m, 1H), 5.81 (d, $J = 12.4$ Hz, 1 H), 5.50 (d, $J = 12.4$ Hz, 1H), 3.83-3.77 (m, 1H), 3.73 (d, $J = 2.0$ Hz, 1H), 3.54-3.48 (m, 1H), 3.26 (dd, $J = 2.4, 14.8$ Hz, 1H), 2.58 (d, $J = 14.8$ Hz, 1H), 2.26 (s, 3H), 0.76 (t, $J = 7.2$ Hz, 3 H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 200.04, 170.12, 139.36, 138.50, 130.45 (q), 129.29, 128.97, 128.76, 125.38 (q), 124.83, 92.61, 81.05, 77.22, 67.70, 62.42, 49.22, 46.47, 26.82, 13.15. HPLC: Chiralpak AS-H (hexane/*i*-PrOH = 80/20, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (major) = 6.4 min, t_R (minor) = 14.5 min; 92% ee. $[\alpha]_D^{25} = 23.8$ ($c = 1.0$, CHCl_3). HRMS (EI) calcd for $\text{C}_{23}\text{H}_{22}\text{F}_3\text{NO}_6$, m/z 465.1394, found 465.1395.

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**(1*R*,2*R*,3*S*,4*S*)-Benzyl-1-acetyl-4-hydroxy-3-nitro-2,4-diphenyl
cyclopentanecarboxylate (4m)**

To a solution of benzyl 2-acetyl-4-oxo-4-phenylbutanoate (1.0 mmol, 2 eq) and (*E*)-(2-nitrovinyl)benzene (0.5 mmol, 1 eq) in toluene (0.5 mL) was added catalyst **VI** (0.05 mmol, 0.1 eq) at 4 °C. The resulting mixture was stirred

for 36 hours. The product was afforded by flash column chromatography over silica gel (EtOAc:Hexane = 1:5) in 95% yield.

¹H-NMR (400 MHz, CDCl₃) δ 7.40 (d, *J* = 2.0 Hz, 1H), 7.37-7.24 (m, 11H), 6.90-6.87 (dd, *J* = 2.4, 7.6 Hz, 2H), 5.79 (d, *J* = 12.4 Hz, 1H), 5.43 (d, *J* = 12.4 Hz, 1H), 4.83 (d, *J* = 12.0 Hz, 1H), 4.16 (d, *J* = 12.0 Hz, 1H), 3.80 (s, 1H), 3.26 (d, *J* = 14.8 Hz, 1H), 2.54 (d, *J* = 14.8 Hz, 1H), 2.15 (s, 3H). ¹³C-NMR (100 MHz, CDCl₃) δ 200.17, 170.24, 139.70, 134.23, 133.95, 128.88, 128.72, 128.63, 128.59, 128.53, 128.35, 128.29, 124.91, 93.33, 81.05, 68.07, 67.90, 49.71, 46.56, 26.97.

HPLC: Chiralcel OD-H (hexane/*i*-PrOH = 85/15, flow rate 1 mL/min, λ = 210 nm), *t_R* (major) = 10.4 min, *t_R* (minor) = 13.2 min; 88% ee. [α]_D²⁵ = 15.5 (*c* = 1.0, CHCl₃).

HRMS (EI) calcd for C₂₇H₂₅NO₆, *m/z* 459.1677, found 459.1681.

**(1*R*,2*R*,3*S*,4*S*)-Ethyl-1-acetyl-4-(4-chlorophenyl)-4-hydroxy-3-nitro-2-phenyl
cyclopentanecarboxylate (4n)**

To a solution of ethyl 2-acetyl-4-oxo-4-(4-chlorophenyl)butanoate (1.0 mmol, 2 eq) and (*E*)-(2-nitrovinyl) benzene (0.5 mmol, 1 eq) in toluene (0.5 mL) was added catalyst **VI** (0.05 mmol, 0.1 eq) at 4 °C. The resulting mixture was stirred for 60 hours. The product was afforded by flash column chromatography over silica gel (EtOAc:Hexane = 1:5) in

91% yield.

¹H-NMR (400 MHz, CDCl₃) δ 7.59 (d, *J* = 8.8 Hz, 2H), 7.43-7.28 (m, 7H), 5.74 (d, *J* = 12.4 Hz, 1H), 5.41 (d, *J* = 12.4 Hz, 1H), 3.84 (d, *J* = 1.2 Hz, 1H), 3.82-3.78 (m, 1H), 3.49-3.41 (m, 1H), 3.22 (d, *J* = 15.2 Hz, 1H), 2.54 (d, *J* = 15.2, 1H), 2.25 (s, 3H), 0.76

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(s, 3H). ^{13}C -NMR (100 MHz, CDCl_3) δ 200.33, 170.30, 138.38, 134.59, 134.09, 129.03, 128.67, 128.57, 128.32, 126.52, 93.23, 80.68, 67.62, 62.34, 49.50, 46.52, 26.90, 13.24. HPLC: Chiralcel OD-H (hexane/*i*-PrOH = 85/15, flow rate 1 mL/min, λ = 220 nm), t_R (major) = 6.3 min, t_R (minor) = 9.5 min; 91% ee. $[\alpha]_D^{25}$ = 40.6 (c = 1.5, CHCl_3). HRMS (EI) calcd for $\text{C}_{22}\text{H}_{22}\text{ClNO}_6$, m/z 431.1132, found 431.1137.

7.4.3 Typical procedure for double-Michael reactions:

To a solution of diethyl 5-acetylhex-2-enedioate **1j** (0.15 mmol, 1.0 eq) and nitro olefin (0.23 mmol, 1.5 eq) in diethyl ether (0.2 mL) was added catalyst **VI** (**Q-NH₂**) (0.023 mmol, 0.15 eq) at room temperature (22°C). The resulting mixture was stirred vigorously for 16-36 hours. After the reaction was completed (monitored by TLC and crude NMR), the product was afforded by flash chromatography over silica gel (Et_2O :Hexane = 1:10 to 1:4).

(1*R*,2*R*,3*R*,4*S*)-Ethyl-4-((ethoxycarbonyl)methyl)-1-acetyl-3-nitro-2-phenylcyclopentanecarboxylate (**5a**)

The title compound was prepared according to the typical procedure, as described above in 91% yield.

^1H -NMR (400 MHz, CDCl_3) δ 7.31-7.21 (m, 5H), 5.49 (dd, J = 5.2, 7.6 Hz, 1H), 5.10 (d, J = 4.8 Hz, 1H), 4.26-4.14 (m, 2H), 3.80-3.72 (m, 1H), 3.68-3.58 (m, 1H), 3.41-3.33 (m, 1H), 2.88 (dd, J = 6.8, 12.8 Hz, 1H), 2.50 (dd, J = 7.2, 16.8 Hz, 1H), 2.40 (dd, J = 7.6, 16.8 Hz, 1H), 2.20 (s, 3H), 2.01 (dd, J = 10.8, 12.8 Hz, 1H), 1.30 (t, J = 7.2 Hz, 3H), 0.76 (t, J = 7.2 Hz, 3H). ^{13}C -NMR (100 MHz, CDCl_3) δ 200.09, 170.87, 170.29, 137.16, 128.52, 128.48, 127.80, 94.26, 71.28, 61.77, 61.05, 51.54, 40.27, 37.74, 34.20, 26.98, 14.16, 13.26. HPLC: Chiralcel OD-H (hexane/*i*-PrOH = 80/20, flow rate 1 mL/min, λ = 230 nm), t_R (major) = 6.2 min, t_R (minor) = 8.9 min; 97% ee. $[\alpha]_D^{22}$ = - 3.1 (c = 1.0, CH_2Cl_2). HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{26}\text{NO}_6 + \text{H}$, m/z 392.1709, found 392.1707.

(1*R*,2*R*,3*R*,4*S*)-Ethyl-4-((ethoxycarbonyl)methyl)-1-acetyl-3-nitro-2-*p*-tolyl

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cyclopentanecarboxylate (5b)

The title compound was prepared according to the typical procedure, as described above in 89% yield.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.09 (m, 4H), 5.44 (dd, J = 5.2, 7.6 Hz, 1H), 5.04 (d, J = 5.2 Hz, 1H), 4.24-4.15 (m, 2H), 3.80-3.75 (m, 1H), 3.63-3.57 (m, 1H), 3.45-3.41 (m, 1H), 2.87 (dd, J = 6.8, 12.8 Hz, 1H), 2.46 (dd, J = 7.2, 16.8 Hz, 1H), 2.40 (dd, J = 7.6, 17.2 Hz, 1H), 2.30 (s, 3H), 2.19 (s, 3H), 2.00 (dd, J = 10.8, 12.8 Hz, 1H), 1.29 (t, J = 7.2 Hz, 3H), 0.78 (t, J = 7.2 Hz, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 200.25, 170.89, 170.12, 137.52, 133.97, 129.12, 128.32, 94.28, 71.13, 61.74, 61.02, 51.29, 40.04, 37.77, 34.26, 27.04, 20.99, 14.15, 13.25. HPLC: Chiralcel OD-H (hexane/*i*-PrOH = 80/20, flow rate 1 mL/min, λ = 220 nm), t_R (major) = 6.1 min, t_R (minor) = 8.7 min; 96% ee. $[\alpha]_D^{22}$ = - 5.7 (c = 1.3, CH_2Cl_2). HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{27}\text{NO}_7 + \text{H}$, m/z 406.1866, found 406.1987.

(1R,2R,3R,4S)-Ethyl-4-((ethoxycarbonyl)methyl)-1-acetyl-3-nitro-2-*m*-tolyl

cyclopentanecarboxylate (5c)

The title compound was prepared according to the typical procedure, as described above in 85% yield.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.20-7.17 (m, 1H), 7.10-6.97 (m, 3H), 5.46 (m, 1H), 5.05 (d, J = 5.2 Hz, 1H), 4.24-4.16 (m, 2H), 3.80-3.72 (m, 1H), 3.64-3.58 (m, 1H), 3.45-3.36 (m, 1H), 2.87 (dd, J = 6.8, 12.8 Hz, 1H), 2.48 (dd, J = 6.4, 17.2 Hz, 1H), 2.36 (dd, J = 7.6, 16.8 Hz, 1H), 2.32 (s, 3H), 2.19 (s, 3H), 2.00 (dd, J = 10.8, 12.8 Hz, 1H), 1.30 (t, J = 7.2 Hz, 3H), 0.77 (t, J = 7.2 Hz, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 200.13, 170.88, 170.31, 138.13, 137.06, 129.33, 128.48, 128.41, 125.29, 94.36, 71.24, 61.71, 61.02, 51.53, 40.21, 37.77, 34.23, 26.99, 21.32, 14.16, 13.23. HPLC: Chiralpak AD-H (hexane / *i*-PrOH = 90/10, flow rate 1 mL/min, λ = 210 nm), t_R (minor) = 10.6 min, t_R (major) = 12.0 min; 94% ee. $[\alpha]_D^{22}$ = - 4.2 (c = 1.2, CH_2Cl_2). HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{27}\text{NO}_7 + \text{H}$, m/z 406.1866, found 406.1848.

(1R,2R,3R,4S)-Ethyl-4-((ethoxycarbonyl)methyl)-1-acetyl-2-(4-methoxy phenyl)

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-3-nitrocyclopentanecarboxylate (5d)

To a solution of diethyl 5-acetylhex-2-enedioate **1j** (0.15 mmol, 1.0 eq) and 1-methoxy-4-((*E*)-2-nitrovinyl) benzene (0.3 mmol, 2.0 eq) in diethyl ether (0.2 mL) was added catalyst **VI** (**Q-NH₂**) (0.03 mmol, 0.2 eq) at room temperature (22°C). The resulting mixture was stirred vigorously for 24 hours, continue to react for 6 hours after evaporating the solvent. After the reaction was completed (monitored by TLC and crude NMR), the title product was afforded by flash chromatography over silica gel (Et₂O:Hexane = 1:10 to 1:3) in 83% yield.

¹H-NMR (400 MHz, CDCl₃) δ 7.15 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 5.44 (dd, *J* = 5.6, 7.6 Hz, 1H), 5.02 (d, *J* = 5.2 Hz, 1H), 4.24-4.15 (m, 2H), 3.83-3.76 (m, 1H), 3.78 (s, 3H), 3.63-3.57 (m, 1H), 3.51-3.43 (m, 1H), 2.86 (dd, *J* = 6.8, 12.8 Hz, 1H), 2.48 (dd, *J* = 7.6, 16.8 Hz, 1H), 2.40 (dd, *J* = 7.6, 16.8 Hz, 1H), 2.19 (s, 3H), 2.00 (dd, *J* = 10.8, 12.8 Hz, 1H), 1.30 (t, *J* = 7.2 Hz, 3H), 0.83 (t, *J* = 7.2 Hz, 3H). ¹³C-NMR (100 MHz, CDCl₃) δ 200.36, 170.90, 170.42, 159.14, 129.59, 128.96, 113.85, 94.32, 71.02, 61.77, 61.03, 55.31, 50.97, 39.88, 37.72, 34.27, 27.06, 14.15, 13.39. HPLC: Chiralcel OD-H (hexane/*i*-PrOH = 80/20, flow rate 1 mL/min, λ = 220 nm), *t_R* (major) = 8.1 min, *t_R* (minor) = 12.2 min; 96% ee. [α]_D²² = - 9.0 (*c* = 1.3, CH₂Cl₂). HRMS (ESI) calcd for C₂₁H₂₇NO₈+H, *m/z* 422.1815, found 422.1800.

(1R,2R,3R,4S)-Ethyl-4-((ethoxycarbonyl)methyl)-1-acetyl-2-(2-methoxyphenyl)**-3-nitrocyclopentanecarboxylate (5e)**

To a solution of diethyl 5-acetylhex-2-enedioate **1j** (0.15 mmol, 1.0 eq) and 1-methoxy-2-((*E*)-2-nitrovinyl) benzene (0.3 mmol, 2.0 eq) in diethyl ether (0.2 mL) was added catalyst **VI** (**Q-NH₂**) (0.03 mmol, 0.2 eq) at room temperature (22°C). The resulting mixture was stirred vigorously for 24 hours, continue to react for 6 hours after evaporating the solvent. After the reaction was completed (monitored by TLC and crude NMR), the title product was afforded by flash chromatography over silica gel (Et₂O:Hexane = 1:10 to 1:3) in 81% yield.

¹H-NMR (400 MHz, CDCl₃) δ 7.30-7.21 (m, 2H), 6.90-6.89 (m, 1H), 6.78 (d, *J* = 8.0

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Hz, 1H), 5.55 (dd, $J = 4.0, 7.2$ Hz, 1H), 5.13 (d, $J = 4.0$ Hz, 1H), 4.21-4.13 (m, 2H), 3.90-3.84 (m, 1H), 3.77 (s, 3H), 3.65-3.59 (m, 1H), 3.53-3.45 (m, 1H), 2.89 (dd, $J = 6.4, 12.4$ Hz, 1H), 2.48 (dd, $J = 6.4, 17.2$ Hz, 1H), 2.34 (dd, $J = 8.4, 16.8$ Hz, 1H), 2.14 (s, 3H), 1.95 (m, 1H), 1.28 (t, $J = 7.2$ Hz, 3H), 0.78 (t, $J = 7.2$ Hz, 3H). ^{13}C -NMR (100 MHz, CDCl_3) δ 200.09, 171.03, 170.20, 157.31, 132.03, 129.12, 125.88, 120.85, 110.10, 94.46, 70.76, 61.39, 60.87, 54.90, 50.54, 39.78, 37.88, 34.10, 26.50, 14.19, 13.23. HPLC: Chiralpak AD-H (hexane/*i*-PrOH = 90/10, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (minor) = 12.4 min, t_R (major) = 14.6 min; 95% ee. $[\alpha]_D^{22} = -5.5$ ($c = 1.0$, CH_2Cl_2). HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{27}\text{NO}_8 + \text{H}$, m/z 422.1815, found 422.1823.

(1*R*,2*R*,3*R*,4*S*)-Ethyl-4-((ethoxycarbonyl)methyl)-1-acetyl-2-(4-bromo phenyl)-3-nitrocyclopentanecarboxylate (5f)

The title compound was prepared according to the typical procedure, as described above in 92% yield.

^1H -NMR (400 MHz, CDCl_3) δ 7.43 (d, $J = 8.4$ Hz, 1H), 7.11 (dd, $J = 8.4$ Hz, 1H), 5.44 (dd, $J = 5.6, 7.2$ Hz, 1H), 5.04 (d, $J = 5.2$ Hz, 1H), 4.24-4.16 (m, 2H), 3.86-3.78

(m, 1H), 3.63-3.57 (m, 1H), 3.53-3.45 (m, 1H), 2.86 (dd, $J = 6.8, 13.2$ Hz, 1H), 2.49 (dd, $J = 7.2, 16.8$ Hz, 1H), 2.39 (dd, $J = 7.6, 17.0$ Hz, 1H), 2.19 (s, 3H), 2.00 (dd, $J = 10.4, 12.4$ Hz, 1H), 1.30 (t, $J = 7.2$ Hz, 3H), 0.84 (t, $J = 7.2$ Hz, 3H). ^{13}C -NMR (100 MHz, CDCl_3) δ 199.77, 170.81, 170.12, 136.02, 131.62, 130.21, 121.94, 93.72, 70.99, 61.96, 61.10, 50.93, 39.99, 37.70, 34.17, 26.96, 14.15, 13.33. HPLC: Chiralcel OD-H (hexane/*i*-PrOH = 80/20, flow rate 1 mL/min, $\lambda = 220$ nm), t_R (major) = 7.6 min, t_R (minor) = 11.7 min; 97% ee. $[\alpha]_D^{22} = -19.0$ ($c = 0.8$, CH_2Cl_2). HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{24}\text{BrNO}_7 + \text{H}$, m/z 470.0814, found 470.0798.

(1*R*,2*R*,3*R*,4*S*)-Ethyl-4-((ethoxycarbonyl)methyl)-1-acetyl-2-(4-chloro phenyl)-3-nitrocyclopentanecarboxylate (5g)

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The title compound was prepared according to the typical procedure, as described above in 88% yield.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.28 (d, $J = 6.8$ Hz, 1H), 7.16 (dd, $J = 2.0, 7.8$ Hz, 1H), 5.44 (dd, $J = 5.6, 7.6$ Hz, 1H), 5.05 (d, $J = 5.2$ Hz, 1H), 4.24-4.16 (m, 2H),

3.86-3.78 (m, 1H), 3.64-3.57 (m, 1H), 3.52-3.44 (m, 1H), 2.86 (dd, $J = 6.8, 12.8$ Hz, 1H), 2.48 (dd, $J = 7.4, 17.0$ Hz, 1H), 2.39 (dd, $J = 7.6, 17.0$ Hz, 1H), 2.19 (s, 3H), 2.00 (dd, $J = 10.4, 12.4$ Hz, 1H), 1.30 (t, $J = 7.2$ Hz, 3H), 0.84 (t, $J = 7.2$ Hz, 3H).

$^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 200.03, 170.81, 170.14, 135.49, 133.82, 129.88, 128.64, 93.79, 71.02, 61.92, 61.09, 50.86, 39.97, 37.70, 34.17, 26.97, 14.15, 13.33.

HPLC: Chiralcel OD-H (hexane/*i*-PrOH = 80/20, flow rate 1 mL/min, $\lambda = 254$ nm), t_R (major) = 7.1 min, t_R (minor) = 11.1 min; 96% ee. $[\alpha]_D^{22} = -11.4$ ($c = 1.0$, CH_2Cl_2).

HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{24}\text{ClNO}_7 + \text{H}$, m/z 426.1320, found 426.1312.

(1R,2R,3R,4S)-Ethyl-4-((ethoxycarbonyl)methyl)-1-acetyl-2-(naphthalen-3-yl)-3-nitrocyclopentanecarboxylate (5h)

The title compound was prepared according to the typical procedure, as described above in 84% yield.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.82-7.76 (m, 3H), 7.69 (s, 1H), 7.49-7.47 (m, 2H), 7.34 (d, $J = 8.4$ Hz, 1H),

5.64-5.61 (m, 1H), 5.27 (d, $J = 5.2$ Hz, 1H), 4.26-4.18 (m, 2H), 3.75-3.63 (m, 2H), 3.26-3.18 (m, 1H), 2.93 (dd, $J = 6.8, 12.8$ Hz, 1H), 2.53 (dd, $J = 7.6, 16.8$ Hz, 1H), 2.45 (dd, $J = 7.6, 16.8$ Hz, 1H), 2.21 (s, 3H), 2.45 (dd, $J = 10.8, 12.8$ Hz, 1H), 1.32 (t, $J = 7.2$ Hz, 3H), 0.52 (t, $J = 7.2$ Hz, 3H).

$^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 200.22, 170.91, 170.32, 128.17, 127.89, 127.48, 127.43, 126.40, 126.28, 126.26, 94.23, 71/30, 61.74, 61.08, 51.71, 40.19, 37.86, 34.29, 27.02, 14.18, 13.03.

HPLC: Chiralpak AD-H (hexane/*i*-PrOH = 80/20, flow rate 1 mL/min, $\lambda = 254$ nm), t_R (minor) = 20.5 min, t_R (major) = 33.5 min; 95% ee. $[\alpha]_D^{22} = -31.9$ ($c = 0.6$, CH_2Cl_2).

HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{27}\text{NO}_7 + \text{H}$, m/z 442.1866, found 442.1851.

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(1*R*,2*R*,3*R*,4*S*)-Ethyl-4-((ethoxycarbonyl)methyl)-1-acetyl-2-(naphthalen-1-yl)-3-nitrocyclopentanecarboxylate (5i)

The title compound was prepared according to the typical procedure, as described above in 87% yield.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 8.58 (d, $J = 7.6$ Hz, 1H), 7.82 (d, $J = 8.4$ Hz, 1H), 7.77 (d, $J = 8.4$ Hz, 1H), 7.62-7.59 (m, 1H), 7.52-7.49 (m, 1H), 7.44-7.40 (m, 1H), 7.23 (d, $J = 7.2$ Hz, 1H), 6.03 (d, $J = 2.4$ Hz, 1H), 5.60-5.58 (m, 1H), 4.30-4.17 (m, 2H), 3.76-3.68 (m, 1H), 3.51-3.45 (m, 1H), 3.01 (dd, $J = 6.8, 12.8$ Hz, 1H), 2.88-2.83 (m, 1H), 2.62 (dd, $J = 6.4, 17.2$ Hz, 1H), 2.43 (dd, $J = 8.4, 17.2$ Hz, 1H), 2.19 (s, 3H), 1.16-2.10 (m, 1H), 1.32 (t, $J = 7.2$ Hz, 3H), 0.19 (t, $J = 7.2$ Hz, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 199.62, 170.91, 170.19, 135.23, 133.55, 132.51, 128.57, 126.75, 126.04, 124.99, 124.75, 124.57, 96.98, 72.47, 61.48, 61.11, 46.43, 37.98, 33.91, 26.81, 14.19, 12.51. HPLC: Chiralcel OD-H (hexane/*i*-PrOH = 80/20, flow rate 1 mL/min, $\lambda = 220$ nm), t_R (major) = 7.7 min, t_R (minor) = 10.2 min; 95% ee. $[\alpha]_D^{22} = -29.0$ ($c = 1.0$, CH_2Cl_2). HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{27}\text{NO}_7 + \text{H}$, m/z 442.1866, found 442.1861.

(1*R*,2*R*,3*R*,4*S*)-Ethyl-4-((ethoxycarbonyl)methyl)-1-acetyl-2-(furan-3-yl)-3-nitrocyclopentanecarboxylate (5j)

The title compound was prepared according to the typical procedure, as described above in 86% yield.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.36-7.34 (m, 2H), 6.28 (s, 1H), 5.34-5.31 (m, 1H), 4.82 (d, $J = 6.8$ Hz, 1H), 4.22-4.14 (m, 2H), 4.03-3.95 (m, 1H), 3.88-3.81 (m, 1H), 3.58-3.52 (m, 1H), 2.83 (dd, $J = 7.2, 13.2$ Hz, 1H), 2.41 (d, $J = 7.6$ Hz, 1H), 2.21 (s, 3H), 1.96 (dd, $J = 10.4, 12.8$ Hz, 1H), 1.28 (t, $J = 7.2$ Hz, 3H), 1.02 (t, $J = 7.2$ Hz, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 200.61, 170.86, 170.57, 143.15, 140.79, 120.66, 109.98, 93.37, 69.47, 61.91, 61.04, 43.71, 38.29, 37.85, 34.55, 27.21, 14.14, 13.48. HPLC: Chiralpak AD-H (hexane/*i*-PrOH = 90/10, flow rate 1 mL/min, $\lambda = 254$ nm), t_R (minor) = 17.9 min, t_R (major) = 19.0 min; 94% ee. $[\alpha]_D^{22} = 5.7$ ($c = 1.2$, CH_2Cl_2). HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{23}\text{NO}_8 + \text{H}$, m/z 382.1502, found 382.1495.

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(1*R*,2*R*,3*R*,4*S*)-Ethyl-4-((ethoxycarbonyl)methyl)-1-acetyl-2-(furan-2-yl) 3-nitro cyclopentanecarboxylate (5k)

The title compound was prepared according to the typical procedure, as described above in 87% yield.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.31-7.28 (m, 1H), 6.31-6.26 (m, 2H), 5.45 (dd, $J = 5.6, 7.6$ Hz, 1H), 5.09 (d, $J = 5.6$ Hz, 1H), 4.22-4.15 (m, 2H), 4.04-3.99 (m, 1H), 3.80-3.75 (m, 1H), 3.60-3.53 (m, 1H), 2.88 (dd, $J = 6.8, 13.2$ Hz, 1H), 2.41 (d, $J = 7.6$ Hz, 1H), 2.20 (s, 3H), 1.96-1.90 (m, 1H), 1.28 (t, $J = 7.2$ Hz, 3H), 1.03 (t, $J = 7.2$ Hz, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 199.80, 170.76, 169.98, 149.81, 142.32, 110.73, 108.96, 92.07, 69.40, 62.32, 61.03, 46.32, 38.99, 37.50, 34.29, 26.73, 14.14, 13.60. HPLC: Chiralcel OD-H (hexane/*i*-PrOH = 80/20, flow rate 1 mL/min, $\lambda = 220$ nm), t_R (major) = 7.2 min, t_R (minor) = 11.1 min; 94% ee. $[\alpha]_D^{22} = -6.3$ ($c = 1.1$, CH_2Cl_2). HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{23}\text{NO}_8 + \text{Na}$, m/z 404.1321, found 404.1336.

(1*R*,2*R*,3*R*,4*S*)-Ethyl-4-((ethoxycarbonyl)methyl)-1-acetyl-3-nitro-2-(thiophen-2-yl) cyclopentanecarboxylate (5l)

The title compound was prepared according to the typical procedure, as described above in 91% yield.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.21-7.20 (m, 1H), 6.93-6.92 (m, 2H), 5.52-4.48 (m, 1H), 5.21 (d, $J = 7.2$ Hz, 1H), 4.226-4.14 (m, 2H), 3.96-3.89 (m, 1H), 3.75-3.68 (m, 1H), 3.66-3.57 (m, 1H), 2.89 (dd, $J = 7.2, 12.8$ Hz, 1H), 2.41 (d, $J = 7.6$ Hz, 1H), 2.21 (s, 3H), 1.96 (dd, $J = 10.0, 13.2$ Hz, 1H), 1.29 (t, $J = 7.2$ Hz, 3H), 0.94 (t, $J = 7.2$ Hz, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 200.36, 170.76, 170.21, 138.64, 126.82, 126.27, 125.36, 94.23, 70.46, 62.10, 61.07, 47.35, 38.31, 37.70, 34.55, 27.14, 14.15, 13.48. HPLC: Chiralpak AS-H (hexane/*i*-PrOH = 95/5, flow rate 1 mL/min, $\lambda = 210$ nm), t_R (minor) = 25.0 min, t_R (major) = 28.1 min; 94% ee. $[\alpha]_D^{22} = -4.3$ ($c = 1.2$, CH_2Cl_2). HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{23}\text{NO}_7\text{S} + \text{Na}$, m/z 420.1093, found 420.1151.

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(1*R*,2*R*,3*R*,4*S*)-Ethyl 4-((ethoxycarbonyl)methyl)-1-acetyl-3-nitro-2-(4-nitrophenyl)cyclopentanecarboxylate (5m)

To a solution of diethyl 5-acetylhex-2-enedioate **1j** (0.15 mmol, 1.0 eq) and 1-nitro-4-((*E*)-2-nitrovinyl)benzene (0.3 mmol, 2.0 eq) in diethyl ether (0.2 mL) was added catalyst **VI** (**Q-NH₂**) (0.03 mmol, 0.2 eq) at room temperature

(22°C). The resulting mixture was stirred vigorously for 24 hours, continue to react for 12 hours after evaporating the solvent. After the reaction was completed (monitored by TLC and crude NMR), the title product was afforded by flash chromatography over silica gel (Et₂O:Hexane = 1:10 to 1:3) in 81% yield.

¹H-NMR (400 MHz, CDCl₃) δ 8.17 (d, *J* = 8.8 Hz, 1H), 7.44 (d, *J* = 8.8 Hz, 1H), 5.52-5.49 (m, 1H), 5.19 (d, *J* = 5.6 Hz, 1H), 4.25-4.16 (m, 2H), 3.86-3.80 (m, 1H), 3.69-3.62 (m, 1H), 3.49-3.43 (m, 1H), 2.89 (dd, *J* = 6.8, 13.2 Hz, 1H), 2.51 (dd, *J* = 7.2, 17.2 Hz, 1H), 2.40 (dd, *J* = 7.6, 17.2 Hz, 1H), 2.22 (s, 3H), 2.02 (dd, *J* = 10.8, 12.8 Hz, 1H), 1.30 (t, *J* = 7.2 Hz, 3H), 0.82 (t, *J* = 7.2 Hz, 3H). ¹³C-NMR (100 MHz, CDCl₃) δ 199.79, 170.73, 169.82, 147.41, 144.35, 129.64, 123.60, 93.20, 71.10, 62.07, 61.21, 51.02, 40.01, 37.73, 34.09, 26.91, 14.15, 13.42. HPLC: Chiralpak AS-H (hexane / *i*-PrOH = 80 / 20, flow rate 1 mL / min, λ = 210 nm), *t_R* (major) = 20.9 min, *t_R* (minor) = 25.4 min; 97% ee. [α]_D²² = - 9.7 (*c* = 1.0, CH₂Cl₂).

(1*R*,2*R*,3*R*,4*S*)-benzyl 4-((ethoxycarbonyl)methyl)-1-acetyl-3-nitro-2-phenylcyclopentanecarboxylate (5n)

To a solution of 6-benzyl 1-ethyl 5-acetylhex-2-enedioate **1k** (0.15 mmol, 1.0 eq) and 1-((*E*)-2-nitrovinyl)benzene (0.23 mmol, 1.5 eq) in diethyl ether (0.2 mL) was added catalyst **VI** (**Q-NH₂**) (0.023 mmol, 0.15 eq) at room temperature (22°C). The resulting mixture was stirred

vigorously for 16 hours. After the reaction was completed (monitored by TLC and crude NMR), the title product was afforded by flash chromatography over silica gel (Ethyl acetate:Hexane = 1:10 to 1:4) in 91 % yield.

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$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.54-7.14 (m, 8H), 6.96-6.94 (m, 2H), 5.51 (dd, $J = 5.2$, 7.2 Hz, 1H), 5.11 (d, $J = 5.2$ Hz, 1H), 4.83 (d, $J = 12.0$ Hz, 1H), 4.25-4.16 (m, 2H), 4.10 (d, $J = 12.0$ Hz, 1H), 3.69-3.63 (m, 1H), 2.89 (dd, $J = 6.8$, 13.2 Hz, 1H), 2.49 (dd, $J = 7.6$, 16.8 Hz, 1H), 2.40 (dd, $J = 7.6$, 16.8 Hz, 1H), 2.11 (s, 3H), 2.02 (dd, $J = 10.8$, 12.8 Hz, 1H), 1.30 (t, $J = 7.2$ Hz, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 199.84, 170.86, 170.18, 137.04, 134.09, 128.63, 128.49, 128.45, 128.28, 127.91, 94.23, 71.41, 67.57, 61.07, 51.69, 40.20, 37.81, 34.22, 27.07, 14.17. HPLC: Chiralcel OD-H (hexane/*i*-PrOH = 80/20, flow rate 1 mL/min, $\lambda = 220$ nm), t_R (major) = 7.7 min, t_R (minor) = 11.5 min; 97% ee. $[\alpha]_D^{22} = -5.0$ ($c = 0.9$, CH_2Cl_2). HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{27}\text{NO}_7 + \text{H}$, m/z 454.1866, found 454.1851.

(1*R*,2*R*,3*R*,4*S*)-Benzyl 4-((ethoxycarbonyl)methyl)-1-acetyl-3-nitro-2-styrylcyclopentanecarboxylate (5o)

To a solution of 6-benzyl 1-ethyl 5-acetylhex-2-enedioate **1k** (0.15 mmol, 1.0 eq) and 1-((1*E*,3*E*)-4-nitrobuta-1,3-dienyl)benzene (0.3 mmol, 2.0 eq) in diethyl ether (0.2 mL) was added catalyst **VI** (**Q-NH₂**) (0.03 mmol, 0.2 eq) at room temperature (22°C). The resulting mixture was stirred vigorously for 24 hours. After the reaction was completed (monitored by TLC and crude NMR), the title product was afforded by flash chromatography over silica gel (Et_2O :Hexane = 1:10 to 1:4) in 83% yield.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.32-7.22 (m, 10H), 6.55 (d, $J = 16.0$, 1H), 6.05 (dd, $J = 8.8$, 16.0 Hz, 1H), 5.21-5.17 (m, 1H), 5.18 (d, $J = 12.0$ Hz, 1H), 5.05 (d, $J = 12.0$ Hz, 1H), 4.08 (d, $J = 12.4$ Hz, 1H), 4.26-4.13 (m, 3H), 3.45-3.35 (m, 1H), 2.72 (dd, $J = 7.2$, 13.2 Hz, 1H), 2.43-2.40 (m, 2H), 2.18 (s, 3H), 2.07 (dd, $J = 10.8$, 13.2 Hz, 1H), 1.28 (t, $J = 7.2$ Hz, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 200.66, 170.89, 170.50, 135.91, 135.07, 134.36, 128.75, 128.73, 128.62, 128.60, 128.13, 126.55, 123.69, 92.81, 69.04, 67.85, 61.03, 51.55, 38.04, 37.63, 34.59, 27.64, 14.15. HPLC: Chiralpak AD-H (hexane/*i*-PrOH = 90/10, flow rate 1 mL/min, $\lambda = 254$ nm), t_R (major) = 20.7 min, t_R (minor) = 22.8 min; 95% ee. $[\alpha]_D^{22} = -5.3$ ($c = 1.0$, CH_2Cl_2). HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{29}\text{NO}_7 + \text{H}$, m/z 480.2022, found 480.2007.

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Chapter 8

PYRROLE SYNTHESIS BY ORGANOCATALYTIC DOMINO STRATEGY

Unusual Domino Michael/Aldol Condensation Reactions Employing Oximes as N-Selective Nucleophiles: Synthesis of N-Hydroxy Pyrroles

8.1 Background

As one of the most important heterocycles, pyrroles are not only important building blocks in the synthesis of natural products,¹ but also key structural units in compounds with interesting biological activities.² (Figure 1) Recently it was also found that pyrroles have broad applications in material chemistry.³ Therefore, much consideration has been taken to discover useful approaches for their synthesis. The Paal-Knorr reactions has proven to be a very general way to pyrrole synthesis.⁴ (Scheme 1) However, those approaches usually present significant limitations in terms of substituents introduced, the substitution patterns, or regioselectivities.

Figure 1. The largest selling drug in the world containing pyrrole motif.

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Scheme 1. Paal-Knorr Pyrrole Synthesis.

Although several novel synthetic strategies have been described in recent years,^{5,6} a general, facile and regioselective approach to generate pyrroles with a wide functional group tolerance from readily available precursors is still lacking. Over the past few years, organocatalytic domino reactions have emerged as a powerful synthetic paradigm to prepare many kinds of complex compounds.⁷

In this contribution, we report a catalytic synthesis of multisubstituted *N*-hydroxy pyrroles via the domino reaction of α -carbonyl oxime compounds⁸ and α,β -unsaturated aldehydes in the presence of secondary amine catalysts through iminium activation strategy.^{8a,9} This approach is very different as oximes were employed as *N*-selective nucleophiles in the Michael addition step instead of the more commonly used *O*-selective nucleophiles in organocatalysis.^{8a,8b} There is no report describing the formation of pyrrole derivatives through this simple and mild domino strategy up to now.

Scheme 1. Proposed mechanism of the domino Michael/aldol condensation reaction by iminium activation in pyrrole synthesis.

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8.2 Results and discussion

Amine catalysts perform efficient iminium activation by lowering the LUMO of α,β -unsaturated aldehydes.^{7a,10} Thus, we set out to investigate the use of **IV** as a catalyst for the domino reaction involving sequential Michael addition and intramolecular aldol condensation (Scheme 1). Initially, we chose ethyl 2-(hydroxyimino)-3-oxobutanoate (**1a**) and (*E*)-hex-2-enal (**2a**) as reactants to test the reaction and we were glad to find that the reaction led to the formation of *N*-hydroxy pyrrole smoothly with good yield. After optimizing the reaction conditions by changing the amount of the aldehyde and studying the solvent effect, the yield was improved to 82% (Table 1, entry 4). With these encouraging results at hand, we explored other secondary amine catalysts (**I-VII**). It was observed that the results were influenced by both amine catalysts and solvents (Table 1). It was surprising that no product was obtained when DMSO or DMF was used as solvent. Eventually, we decided to use diisopropylamine (**VII**) as catalyst for following research due to its cheap price, ready availability as well as its higher catalytic efficiency in the reaction (Table 1, entry 7).

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Table 1. Screening of catalysts for the domino reaction^a

entry	catalyst	solvent	time (h)	yield% ^b
1	I	Toluene	10	58
2	II	Toluene	12	61
3	III	Toluene	12	63
4	IV	Toluene	10	82
5	V	Toluene	18	66
6	VI	Toluene	18	67
7	VII	Toluene	18	83
8	VII	CH ₂ Cl ₂	24	79
9	VII	Et ₂ O	24	33
10	VII	DMSO	24	0

^a Unless otherwise specified, all the reactions were carried out using **1a** (0.2 mmol, 1.0 equiv.) and **2a** (0.5 mmol, 2.5 equiv.) with 20 mol % of catalysts in solvent (1.0 mL) at RT (23 °C). ^b Isolated yields.

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Table 2. Synthesis of *N*-hydroxy pyrroles by the domino Michael/aldol condensation reactions^a

entry	oxime 1		enal 2	time (h)	yield ^b of 3 (%)
	R1	R2	R3		
1	EtO	Me	<i>n</i> -Pr	18	3a , 83
2	EtO	Me	Me	18	3b , 83
3	EtO	Me	Et	18	3c , 81
4	EtO	Me	Me(CH ₂) ₄	18	3d , 76
5	EtO	Me	PhCH ₂ CH ₂	24	3e , 82
6	EtO	Me	BnOCH ₂ CH ₂ CH ₂	24	3f , 78
7	MeO	Me	Me	18	3g , 73
8	<i>t</i> -BuO	Me	Me	24	3h , 72
9	BnO	Me	Me	18	3i , 75
10	MeO	Et	Me	24	3j , 77
11	MeO	Et	<i>n</i> -Pr	24	3k , 67
12	MeO	Et	Et	24	3l , 79
13	MeO	Et	Me(CH ₂) ₄	24	3m , 66
14	Me	Me	Me	18	3n , 79
15	Me	Me	<i>n</i> -Pr	18	3o , 81
16	Me	Me	Et	18	3p , 83
17	Me	Me	Me(CH ₂) ₄	18	3q , 77
18	Me	Me	PhCH ₂ CH ₂	18	3r , 82
19	Me	Me	BnOCH ₂ CH ₂ CH ₂	18	3s , 73
20	Me	Me	BocNHCH ₂ CH ₂	24	3t , 61
21 ^c	Ph	Ph	Me	48	3u , 58

^a Unless otherwise specified, all the reactions were carried out using **1** (0.2 mmol, 1.0 equiv.) and **2** (0.5 mmol, 2.5 equiv.) in the presence of 20 mol% of **VII** at RT in toluene (1.0 mL). ^b Isolated yields. ^c 30 mol% catalyst was used.

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After the optimal conditions have been established with catalyst **VII**, the generality of the domino process was investigated. We noticed that good yields could be achieved with many substrates (Table 2, entries 1-19) and several types of R^1 , such as Me, MeO, EtO, *t*-BuO and BnO, did not affect the reaction at all (Table 2, entries 1-9, 14-20). If R^2 group was changed from methyl to ethyl, the yields were almost the same even when different aldehydes were used (Table 2, entries 10-13). When less reactive substrate was used, higher catalytic loading and longer reaction time were required to obtain pyrrole **3u** in 58% yield (entry 21). To our delight, the above reaction proceeded well with different functional groups R^3 , such as phenylethyl, benzyloxypropyl and 2-(*tert*-butoxycarbonylamino)ethyl, attached to the α,β -unsaturated aldehydes (Table 2, entries 5, 6, 18, 19, 20). However, the reaction did not proceed when α,β -unsaturated aldehydes possess beta aromatic substituents such as phenyl group. We believe that this domino reaction could find potential uses in synthetic chemistry laboratories and in industry despite its limitation, since R^3 bearing many different functionalities could be tolerated.

Scheme 2. Regioselectivities of the domino reactions.

It is worth noting that the two theoretically predicted pyrroles (**5** and **6**, Scheme 2) were isolated (Table 3, entries 2 and 3) when oxime compound **4** was subjected to the above reaction conditions. Interestingly, the use of different substituted aldehydes could influence the results significantly. For example, when R^3 was a methyl group, only one product was isolated. This prompted us to investigate the reaction further by changing other conditions in order to achieve higher regioselectivity. Although changing solvent did not improve the results, changing the catalyst (Table 3, 5-7) surprisingly afforded only one major product. The excellent regioselectivity may be attributed to the bulky group in catalyst **IV**.

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Transforming product **3a** into 1*H*-pyrrole under mild conditions with good yield illustrated the synthetically usefulness of such a polyfunctionalized *N*-hydroxy pyrroles. Furthermore, the methyl group can be facilely converted into aldehyde (Scheme 3).¹¹

Table 3. Regioselectivity in the domino reaction of diketone oximes **4** and α,β -unsaturated aldehydes^a

entry	R	catalyst	solvent	pyrrole 5 (yield %) ^b	Pyrrole 6 (yield %) ^b
1	Me	VII	toluene	5a (76)	6a (trace) ^c
2	<i>n</i> -Pr	VII	toluene	5b (62)	6b (13)
3	Me(CH ₂) ₄	VII	toluene	5c (60)	6c (16)
4	Me(CH ₂) ₄	VII	CH ₂ Cl ₂	5c (64)	6c (13)
5	Me(CH ₂) ₄	IV	toluene	5c (71)	6c (trace)
6	Me(CH ₂) ₄	V	toluene	5c (61)	6c (trace)
7	<i>n</i> -Pr	IV	toluene	5b (78)	6b (trace)

^a The reactions were carried out using **4** (0.3 mmol, 1.0 equiv.) and aldehyde (0.6 mmol, 2.0 equiv.) in the presence of 20 mol% of catalyst at RT with solvent (1.0 mL).

^b Isolated yields. ^c Almost can not be detected.

Scheme 3. Transformation into 1*H*-pyrrole.

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The X-ray crystallographic analysis of the domino product **3r** further confirmed the established structure of the product by NMR (Figure 1).¹²

Figure 1. X-ray structure of **3r**.

One-pot multi-component reaction has paid much attention in recent years due to the high efficiencies and other advantages.^[10] Performing such reactions on water^[13] could potentially be give rise to ideal reactions from the green chemistry's perspective. Considering these advantages, we carefully carried out these reactions on water. Fortunately, *N*-hydroxy pyrroles were isolated as major products with moderate yields (Scheme 4). It is noteworthy that lower yields obtained from one-pot synthesis of pyrrole when compared with that from two separate steps with carbonyl compounds could possibly be due to the significant influence of solvent in these reactions.

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Scheme 4. One-pot synthesis of N-hydroxy pyrrole on water.

Figure 2. Preliminary conjecture of mechanism-via intramolecular bonding.

The possible explanation to why the unusual *N*-selective Michael products were obtained with the above reaction protocol could be attributed to the different substrates structure: the ability of the dicarbonyl oxime to form intramolecular hydrogen bond (Figure 2). The intramolecular hydrogen bond could decrease the nucleophilicity of the oxime oxygen, thus relatively increases the nucleophilicity of the oxime nitrogen

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and resulted in the *N*-selectivity. Based on the above deduction, we carried out some controlled experiments. (*E*)-Oxime **8** afforded exclusively *O*-selective Michael adduct and this supported our hypothesis as **8** was unable to form intramolecular hydrogen bonding. Furthermore, when acetyl or methyl-protected oxime **11** or **13** was used in this reaction, surprisingly, the reaction did not proceed at all (Scheme 5). This further strengthens our conjecture that the intramolecular hydrogen bond is the main driving force for producing *N*-selective products.

Scheme 5. Controlled experiments for investigation of *O*/*N*-selectivity.

8.3 Conclusion

In summary, a facile and efficient one-pot synthesis of polyfunctionalized *N*-hydroxy pyrroles has been developed from the readily available carbonyl oxime and α,β -unsaturated aldehydes. Such a one-pot synthesis of polyfunctionalized *N*-hydroxy pyrroles involves sequential Michael addition, intramolecular aldol condensation and aromatization reactions through iminium activation of α,β -unsaturated aldehydes by diisopropylamine. In the domino synthesis, carbonyl oximes were used as unusual *N*-selective nucleophiles in Michael addition steps. This protocol is associated with readily available starting materials, mild conditions, good yields, wide substrate scope, high regioselectivities, dense and flexible substitution patterns as well as the importance of the synthetic potential of products. This approach constitutes our future direction aimed at expanding the scope and applications of these powerful domino processes.

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8.4 Experimental Section

General experimental conditions (Chapter 2)

Typical Procedure for hydroxylpyrrole synthesis: (Table 2, entry 1)

To a solution of oxime compound **1a** (0.2 mmol, 1.0 eq) and (*E*)-hex-2-enal **2a** (0.5 mmol, 2.5 eq) in toluene (1 mL) was added catalyst **VII** (0.04 mmol, 0.2 eq) at room temperature. The resulting mixture was stirred vigorously. After the reaction was completed (monitored by TLC), the mixture were quenched with saturated ammonium chloride extracted with dichloromethane three times, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The product **3a** was afforded by flash chromatography over silica gel (EtOAc/Hexane = 1/15 to 1/10) in 81% yield.

Ethyl 4-formyl-1-hydroxy-3-methyl-5-propyl-1*H*-pyrrole-2-carboxylate (Table2, Entry 1, 3a)

The title compound was prepared according the typical procedure, as described above in 81% yield.

¹H-NMR (400 MHz, CDCl₃) δ 12.37 (s, 1H), 9.96 (s, 1H), 4.45 (q, *J* = 7.2 Hz, 2H), 2.96 (t, *J* = 7.2 Hz, 2H), 2.58 (s, 3H), 1.74-1.68 (m, 2H), 1.44 (t, *J* = 7.2 Hz, 3H), 0.99 (t, *J* = 7.2 Hz, 3H). ¹³C-NMR (100 MHz, CDCl₃) δ 184.80, 165.52, 137.90, 127.80, 115.12, 112.41, 61.60, 24.69, 21.67, 14.28, 113.72, 10.56. HRMS (ESI) [M+H]⁺ calcd for C₁₂H₁₈NO₄, 240.1236, found 240.1228.

Ethyl 4-formyl-1-hydroxy-3,5-dimethyl-1*H*-pyrrole-2-carboxylate (Table2, Entry 2, 3b)

The title compound was prepared according the typical procedure, as described above in 83% yield.

¹H-NMR (400 MHz, CDCl₃) δ 12.36 (brs, 1H), 9.96 (s, 1H), 4.44 (q, *J* = 7.2 Hz, 2H), 2.56 (s, 3H), 2.53 (s, 3H), 1.44 (t, *J* = 7.2 Hz, 3H). ¹³C-NMR (100 MHz, CDCl₃) δ 184.96, 165.43, 133.65, 127.83, 115.30, 112.46, 61.62, 14.27, 10.39, 8.73. HRMS (ESI) [M+H]⁺ calcd for C₁₀H₁₄NO₄, 212.0923, found 212.0924.

Ethyl 5-ethyl-4-formyl-1-hydroxy-3-methyl-1*H*-pyrrole-2-carboxylate (Table2,

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Entry 3, 3c)

The title compound was prepared according the typical procedure, as described above in 81% yield.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 12.32 (brs, 1H), 9.96 (s, 1H), 4.44 (q, $J = 7.2$ Hz, 2H), 3.01 (q, $J = 7.2$ Hz, 2H), 2.56 (s, 3H), 1.44 (t, $J = 7.2$ Hz, 3H), 1.27 (t, $J = 7.2$ Hz, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 184.75, 165.49, 139.08, 127.88, 114.56, 112.39, 61.60, 16.53, 14.28, 12.67, 10.49. HRMS (ESI) $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{11}\text{H}_{16}\text{O}_4$, 226.1079, found 226.1079.

Ethyl-4-formyl-1-hydroxy-3-methyl-5-pentyl-1H-pyrrole-2-carboxylate (Table2, Entry 4, 3d)

The title compound was prepared according the typical procedure, as described above in 76% yield.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 12.36 (brs, 1H), 9.95 (s, 1H), 4.44 (q, $J = 7.2$ Hz, 2H), 2.97 (t, $J = 7.2$ Hz, 2H), 2.58 (s, 3H), 1.68-1.64 (m, 2H), 1.44 (t, $J = 7.2$ Hz, 3H), 1.36-1.35 (m, 3H), 0.90 (t, $J = 7.2$ Hz, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 184.78, 165.51, 138.17, 127.81, 114.98, 112.40, 61.59, 31.38, 27.98, 22.85, 22.36, 14.28, 13.93, 10.57. HRMS (ESI) $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{14}\text{H}_{22}\text{NO}_4$, 268.1549, found 268.1549.

Ethyl 4-formyl-1-hydroxy-3-methyl-5-phenethyl-1H-pyrrole-2-carboxylate (Table2, Entry 5, 3e)

The title compound was prepared according the typical procedure, as described above in 82% yield.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 12.39 (s, 1H), 9.87 (s, 1H), 7.33-7.21 (m, 5H), 4.45 (q, $J = 7.2$ Hz, 2H), 3.30-3.26 (m, 2H), 2.98-2.94 (m, 2H), 2.57 (s, 3H), 1.45 (t, $J = 7.2$ Hz, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 184.73, 165.46, 140.59, 136.63, 128.50, 128.46, 127.80, 126.31, 115.14, 112.45, 61.68, 34.16, 25.29, 14.29, 10.46. HRMS (ESI) $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{20}\text{NO}_4$, 302.1392, found 302.1432.

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Ethyl 5-(3-(benzyloxy)propyl)-4-formyl-1-hydroxy-3-methyl-1*H*-pyrrole-2-carboxylate (Table2, Entry 6, 3f)

The title compound was prepared according the typical procedure, as described above in 78% yield.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 12.36 (s, 1H), 9.97 (s, 1H), 7.36-7.29 (m, 5H), 4.51 (s, 2H), 4.44 (q, $J = 7.2$

Hz, 2H), 3.54 (t, $J = 7.2$ Hz, 3H), 3.11 (t, $J = 7.2$ Hz, 3H), 2.57 (s, 3H), 2.04-1.97 (m, 2H), 1.45 (t, $J = 7.2$ Hz, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 184.93, 165.43, 138.38, 137.36, 128.34, 127.75, 127.69, 127.53, 115.21, 112.59, 72.89, 69.25, 61.62, 28.07, 19.87, 14.29, 10.58.

Methyl 4-formyl-1-hydroxy-3,5-dimethyl-1*H*-pyrrole-2-carboxylate (Table2, Entry 7, 3g)

The title compound was prepared according the typical procedure, as described above in 73% yield.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 12.27 (s, 1H), 9.98 (s, 1H), 3.98 (s, 3H), 2.56 (s, 3H), 2.55 (s, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 184.92, 165.80, 137.78, 127.95, 115.36, 112.37, 52.24, 10.41, 8.77. HRMS (ESI) $[\text{M}+\text{H}]^+$ calcd for $\text{C}_9\text{H}_{12}\text{NO}_4$, 198.0766, found 198.0774.

***tert*-Butyl 4-formyl-1-hydroxy-3,5-dimethyl-1*H*-pyrrole-2-carboxylate (Table2, Entry 8, 3h)**

The title compound was prepared according the typical procedure, as described above in 72% yield.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 12.62 (s, 1H), 9.95 (s, 1H), 2.522 (s, 3H), 2.518 (s, 3H), 1.63 (s, 9H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 184.98, 165.12, 133.14, 127.15, 115.03, 113.18, 84.06, 28.42, 10.39, 8.67. HRMS (ESI) $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{12}\text{H}_{18}\text{NO}_4$, 240.1236, found 240.0958.

Benzyl 4-formyl-1-hydroxy-3,5-dimethyl-1*H*-pyrrole-2-carboxylate (Table2, Entry 9, 3i)

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The title compound was prepared according the typical procedure, as described above in 75% yield.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 12.22 (brs, 1H), 9.96 (s, 1H), 7.44-7.41 (m, 5H), 5.42 (s, 2H), 2.56 (s, 3H), 2.54 (s, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 184.93, 165.12, 135.00, 133.93, 128.78, 128.68, 128.22, 115.41, 112.36, 67.10, 10.52, 8.80. HRMS (ESI) $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{16}\text{NO}_4$, 274.1079, found 274.1079.

Methyl 3-ethyl-4-formyl-1-hydroxy-5-methyl-1H-pyrrole-2-carboxylate (Table2, Entry 10, 3j)

The title compound was prepared according the typical procedure, as described above in 77% yield.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 12.26 (brs, 1H), 9.93 (s, 1H), 3.96 (s, 3H), 3.00 (q, $J = 10.0$ Hz, 2H), 2.51 (s, 3H), 1.18 (t, $J = 10.0$ Hz, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 184.70, 165.61, 134.80, 133.82, 114.41, 111.54, 52.28, 17.809, 16.38, 8.84. HRMS (ESI) $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{10}\text{H}_{14}\text{NO}_4$, 212.0923, found 212.0927.

Methyl 3,5-diethyl-4-formyl-1-hydroxy-1H-pyrrole-2-carboxylate (Table2, Entry 11, 3k)

The title compound was prepared according the typical procedure, as described above in 67% yield.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 12.29 (s, 1H), 9.96 (s, 1H), 3.98 (s, 3H), 3.06-2.98 (m, 4H), 1.26 (t, $J = 7.6$ Hz, 3H), 1.21 (t, $J = 7.6$ Hz, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 184.54, 165.70, 139.22, 134.87, 113.66, 111.47, 52.28, 17.99, 16.65, 16.32, 12.61. HRMS (ESI) $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{11}\text{H}_{16}\text{NO}_4$, 226.1079, found 226.1087.

Methyl 3-ethyl-4-formyl-5-propyl-1H-pyrrole-2-carboxylate (Table2, Entry 12, 3l)

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The title compound was prepared according the typical procedure, as described above in 79% yield.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 12.29 (s, 1H), 9.95 (s, 1H), 3.99 (s, 3H), 3.07-2.95 (m, 4H), 1.73-1.66 (m, 2H), 1.21 (t, J = 7.6 Hz, 3H), 0.99 (t, J = 7.6 Hz, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 184.60, 165.72, 138.10, 134.80, 114.20, 111.52, 52.29, 24.81, 21.64, 18.03, 16.26, 13.77. HRMS (ESI) $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{12}\text{H}_{18}\text{NO}_4$, 240.1236, found 240.1271.

Methyl 3-ethyl-4-formyl-1-hydroxy-5-pentyl-1H-pyrrole-2-carboxylate (Table2, Entry 13, 3m)

The title compound was prepared according the typical procedure, as described above in 60% yield.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 12.29 (s, 1H), 9.95 (s, 1H), 3.98 (s, 3H), 3.06-2.95 (m, 4H), 1.68-1.65 (m, 2H), 1.37-1.35 (m, 4H), 1.20 (t, J = 7.6 Hz, 3H), 0.90 (t, J = 6.8 Hz, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 184.57, 165.71, 138.37, 134.81, 114.07, 111.51, 52.28, 31.44, 27.94, 22.98, 22.36, 18.04, 16.26, 13.94. HRMS (ESI) $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{14}\text{H}_{22}\text{NO}_4$, 268.1549, found 268.1542.

5-Acetyl-1-hydroxy-2,4-dimethyl-1H-pyrrole-3-carbaldehyde (Table2, Entry 14, 3n)

The title compound was prepared according the typical procedure, as described above in 79% yield.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 14.18 (s, 1H), 9.99 (s, 1H), 2.64 (s, 3H), 2.54 (s, 3H), 2.51 (s, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 192.35, 184.85, 134.63, 128.96, 121.74, 115.84, 28.38, 11.47, 8.47. HRMS (ESI) $[\text{M}+\text{H}]^+$ calcd for $\text{C}_9\text{H}_{12}\text{NO}_3$, 182.0817, found 182.0824.

5-Acetyl-1-hydroxy-2-ethyl-4-methyl-1H-pyrrole-3-carbaldehyde (Table2, Entry 15, 3o)

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The title compound was prepared according to the typical procedure, as described above in 81% yield.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 14.15 (s, 1H), 10.00 (s, 1H), 2.98 (q, $J = 7.6$ Hz, 2H), 2.65 (s, 3H), 2.54 (s, 3H), 1.24 (t, $J = 7.6$ Hz, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 192.51, 184.69, 139.89, 129.06, 121.63, 115.10, 28.46, 16.23, 12.36, 11.57. HRMS (ESI) $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{10}\text{H}_{14}\text{NO}_3$, 196.0974, found 196.0968.

5-Acetyl-1-hydroxy-4-methyl-2-propyl-1H-pyrrole-3-carbaldehyde (Table2, Entry 16, 3p)

The title compound was prepared according to the typical procedure, as described above in 83% yield.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 14.15 (s, 1H), 9.98 (s, 1H), 2.94 (t, $J = 7.6$ Hz, 2 H), 2.65 (s, 3H), 2.54 (s, 3H), 1.72-1.66 (m, 2H), 0.98 (t, $J = 7.2$ Hz, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 192.51, 184.76, 138.76, 128.96, 121.68, 115.61, 28.46, 24.37, 21.42, 13.77, 11.62. HRMS (ESI) $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{11}\text{H}_{16}\text{NO}_3$, 210.1130, found 210.1133.

5-Acetyl-1-hydroxy-4-methyl-2-pentyl-1H-pyrrole-3-carbaldehyde (Table2, Entry 17, 3q)

The title compound was prepared according to the typical procedure, as described above in 77% yield.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 14.15 (s, 1H), 9.99 (s, 1H), 2.95 (t, $J = 7.6$ Hz, 2H), 2.65 (s, 3H), 2.54 (s, 3H), 1.67-1.63 (m, 2H), 1.35-1.34 (m, 4H), 0.98 (t, $J = 7.2$ Hz, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 192.48, 184.74, 139.03, 128.98, 121.67, 115.50, 31.41, 28.45, 27.69, 22.54, 22.33, 13.91, 11.63. HRMS (ESI) $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{13}\text{H}_{20}\text{NO}_3$, 238.1443, found 238.1435.

5-Acetyl-1-hydroxy-4-methyl-2-phenethyl-1H-pyrrole-3-carbaldehyde (Table2, Entry 18, 3r)

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The title compound was prepared according the typical procedure, as described above in 82% yield.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 14.21 (s, 1H), 9.89 (s, 1H), 7.32-7.23 (m, 5H), 3.29-3.25 (m, 2H), 2.96 (t, $J = 8.0$ Hz, 2H), 2.65 (s, 3H), 2.56 (s, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 192.60, 184.67, 140.43, 137.50, 128.94, 128.49, 128.48, 126.39, 121.67, 115.67, 33.79, 28.50, 24.98, 11.55. HRMS (ESI) $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{18}\text{NO}_3$, 272.1287, found 272.1287.

5-Acetyl-1-hydroxy-2-(3-(benzyloxy)propyl)-4-methyl-1H-pyrrole-3-carbaldehyde
(Table2, Entry 19, 3s)

The title compound was prepared according the typical procedure, as described above in 73% yield.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 14.15 (s, 1H), 10.00 (s, 1H), 7.37-7.28 (m, 5H), 4.50 (s, 2H), 3.54 (t, $J = 6.0$ Hz, 2H), 3.10 (t, $J = 7.2$ Hz, 2H), 2.64 (s, 3H), 2.53 (s, 3H), 2.04-1.97 (m, 2H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 192.53, 184.94, 138.36, 138.29, 128.91, 128.34, 127.67, 127.54, 121.80, 115.71, 72.88, 69.25, 28.50, 27.79, 19.65, 11.64.

5-Benzoyl-1-hydroxy-2-methyl-4-phenyl-1H-pyrrole-3-carbaldehyde (Table2, Entry 20, 3t)

To a solution of oxime compound (2-(hydroxyimino)-1,3-diphenylpropane-1,3-dione, **1g**) (0.2 mmol, 1.0 eq) and (*E*)-but-2-enal **2b** (0.5 mmol, 2.5 eq) in toluene (1 mL) was added catalyst **VII** (0.06 mmol, 0.3 eq) at room temperature. The resulting mixture was stirred vigorously. After the reaction was completed (monitored by TLC), the product **3a** was afforded by flash chromatography over silica gel (EtOAc/Hexane = 1/15 to 1/10) in 58% yield.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 13.79 (s, 1H), 9.64 (s, 1H), 7.33-7.23 (m, 3H), 7.15-6.99 (m, 7H), 2.72 (s, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 190.27, 187.18, 136.33, 135.39, 134.55, 131.82, 131.11, 130.78, 128.83, 127.83, 127.78, 127.56, 120.16, 115.84, 9.57. HRMS (ESI) $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{16}\text{NO}_3$, 306.1130, found

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306.0910.

5-Benzoyl-1-hydroxy-2,4-dimethyl-1*H*-pyrrole-3-carbaldehyde (Table 3, 5a)

The title compound was prepared according the typical procedure, as described above in 76% yield.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 13.30 (brs, 1H), 9.98 (s, 1H), 7.67-7.60 (m, 3H), 7.53-7.50 (m, 2H), 2.60 (s, 3H), 2.10 (s, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 189.95, 184.94, 137.95, 136.07, 132.52, 129.87, 128.63, 128.53, 122.11, 116.23, 11.97, 8.81. HRMS (ESI) $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{14}\text{H}_{14}\text{NO}_3$, 244.0974, found 244.0977.

5-Acetyl-1-hydroxy-4-phenyl-2-propyl-1*H*-pyrrole-3-carbaldehyde (Table 3, 6b)

The title compound was prepared according the typical procedure, as described above in 13% yield.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 14.20 (brs, 1H), 9.44 (s, 1H), 7.49-7.48 (m, 3H), 7.402-7.395 (m, 2H), 3.07 (t, $J = 7.6$ Hz, 2H), 1.97 (s, 3H), 1.79-1.74 (m, 2H), 1.04 (t, $J = 7.6$ Hz, 2H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 193.32, 186.37, 1137.15, 134.79, 131.62, 130.47, 128.85, 128.52, 120.34, 116.42, 27.49, 25.05, 20.99, 13.95.

5-Benzoyl-1-hydroxy-4-methyl-2-propyl-1-hydroxy-pyrrole-3-carbaldehyde (Table 3, 5b)

The title compound was prepared according the typical procedure, as described above in 62% yield.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 13.28 (brs, 1H), 9.97 (s, 1H), 7.68-7.60 (m, 3H), 7.54-7.50 (m, 2H), 3.54 (t, $J = 7.6$ Hz, 2H), 2.11 (s, 3H), 1.80-1.74 (m, 2H), 1.04 (t, $J = 7.6$ Hz, 2H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 190.07, 184.83, 140.20, 138.01, 132.50, 129.89, 128.61, 128.55, 122.04, 116.01, 24.72, 21.58, 13.87, 12.18. HRMS (ESI) $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{18}\text{NO}_3$, 272.1287, found 272.1287.

5-Acetyl-1-hydroxy-2-pentyl-4-phenyl-1*H*-pyrrole-3-carbaldehyde (Table 3,6c)

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The title compound was prepared according the typical procedure, as described above in 16% yield.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 14.20 (s, 1H), 9.45 (s, 1H), 7.49-7.48 (m, 3H), 7.40-7.39 (m, 2H), 3.08 (t, $J = 8.0$ Hz, 2H), 1.97 (s, 3H), 1.74-1.70 (m, 2H), 1.41-1.39 (m, 4H), 0.93 (t, $J = 6.8$ Hz, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 193.30, 186.36, 137.40, 134.80, 131.63, 130.47, 128.84, 128.52, 120.33, 116.32, 31.60, 27.48, 27.20, 23.21, 22.39, 13.98.

5-Benzoyl-1-hydroxy-4-methyl-2-pentyl-1H-pyrrole-3-carbaldehyde (Table 3, 5c)

The title compound was prepared according the typical procedure, as described above in 60% yield.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 13.29 (s, 1H), 9.97 (s, 1H), 7.68-7.66 (m, 2H), 7.62-7.60 (m, 1H), 7.54-7.50 (m, 2H), 3.03 (t, $J = 8.0$ Hz, 2H), 2.11 (s, 3H), 1.75-1.71 (m, 2H), 1.42-1.39 (m, 4H), 0.93 (t, $J = 6.8$ Hz, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 190.07, 184.82, 140.46, 138.01, 132.50, 129.95, 128.61, 128.55, 122.02, 115.89, 31.51, 27.85, 22.88, 22.38, 13.96, 12.20. HRMS (ESI) $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{22}\text{NO}_3$, 300.1600, found 300.1588.

One-pot synthesis of 1-hydroxypyrrole:

To a solution of ethyl acetoacetate (0.5 mmol) in acetic acid (0.6 mmol) were added sodium nitrite (0.6 mmol) in water (1 mL) dropwise. After stirred at room temperature for 30 minutes, then added (*E*)-hex-2-enal **2a** (1.25 mmol) in one portion, followed by adding catalyst **VII** (0.1 mmol) in water (1 mL). The resulting mixture was stirred vigorously. After the reaction was completed (monitored by TLC), the mixture were quenched with saturated ammonium chloride extracted with dichloromethane three times, dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. The product **3a** was afforded by flash chromatography over silica gel in 65% yield.

Conversion into 1H-pyrrole (Ethyl-4-formyl-3-methyl-5-propyl-1H-pyrrole-2-carboxylate):

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To a solution of **3a** (48 mg, 0.2 mmol) in dichloromethane (5 mL), added zinc dust (130 mg, 2.0 mmol) and acetic acid (0.2 mL), stirred at room temperature for 4 hours. The

reaction was completed (monitored by TLC), the mixture were quenched with water, extracted with dichloromethane three times, dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. The product **1H-pyrrole** was afforded by flash chromatography over silica gel in 85% yield.

^1H -NMR (400 MHz, CDCl_3) δ 10.03 (s, 1H), 9.23 (brs, 1H), 4.38 (q, $J = 7.2$ Hz, 2H), 2.92 (t, $J = 8.0$ Hz, 2H), 2.11 (s, 3H), 1.76-1.70 (m, 4H), 1.40 (t, $J = 7.2$ Hz, 3H), 1.00 (t, $J = 7.2$ Hz, 3H). ^{13}C -NMR (100 MHz, CDCl_3) δ 186.05, 161.75, 144.78, 130.18, 121.28, 118.79, 60.60, 28.55, 22.64, 14.48, 13.75, 10.57. HRMS (ESI) $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{12}\text{H}_{18}\text{NO}_3$, 224.1287, found 224.1281.

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Appendix

Outlook and Summary

- Organocatalysis is acknowledged as fairly robust chemistry, because the catalysts are generally non-toxic and easily available and, recently, scale-up and low catalyst loading are being studied and developed. Hopefully new and exciting results will provide good reasons for using organocatalysis in industry, beside the few processes already were carried out. We have seen, in the past chapters, how aldehydes, ketones and β -ketoesters can be easily functionalized affording new and interesting compounds. Eventually, the combination of various activation concepts will make the synthesis of important and complex products simpler and more flexible. I predicted that more and more natural products and pharmaceuticals will be synthesized using organocatalysis especially organocatalytic domino reactions as key steps. Hayashi's¹ three "one-pot" operations synthesis **Tamiflu** and List's² one-pot total synthesis **Ricciocarpin A** fully symbolized the singnificance of the organocatalytic domino reactions. Maybe the total synthesis of Tamiflu and Lipitor will be reported in our group in the near future.

Appendix

- This research fully demonstrates the versatility and potentiality of organocatalysis. Obviously, it is just a small piece in the jigsaw puzzle of Science. Confidently, once it will be more complete, we will have a more definite and general view on organocatalysis.

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Appendix

Appendix

List of Symbols and Abbreviations

δ	NMR chemical shift/ppm
J	NMR coupling constant/Hz
λ	Wavelength/nm
Ac	Acetyl
AcOH	Acetic acid
Ar	Arene
Bn	Benzyl
Boc	<i>t</i> -Butyloxycarbonyl
Bu	Butyl
Bz	Benzoyl
c	Concentration
Cbz	Carbobenzyloxy
Cat.	Catalyst
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexyl Carbodiimide
DCM	Dichloromethane
de	Diastereomeric excess
dr	Diastereomeric ratio
DFT	Density functional theory
DIPEA	<i>N</i> -Ethyl- <i>N,N</i> -Diisopropylamine
DMAP	4-Dimethylaminopyridine
DMF	<i>N,N</i> -Dimethylformamide
DMSO	Dimethyl sulfoxide
ee	Enantiomeric excess
eq	equivalent
Et ₃ N	Triethylamine
GC	Gas chromatography
GC-MS	Gas chromatography coupled with a mass spectrometer
HOMO	The highest occupied molecular orbital
HPLC	High Performance Liquid Chromatography
IPA	<i>iso</i> -Propyl alcohol
LUMO	The lowest unoccupied molecular orbital
<i>m</i>	<i>meta</i>
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser Effect
Ph	Phenyl
ppm	Parts per million
PTC	Phase Transfer Catalysis
R	arbitrary substituent

Appendix

rt	Room temperature
SOMO	The singly occupied molecular orbital
TFA	2,2,2-Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
t_R	Retention time
Ts	Tosyl

Appendix

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Submitted

Submitted