ASYMMETRIC SYNTHESIS OF FURAN AND OXINDOLE DERIVATIVES WITH BIFUNCTIONAL AND MULTIFUNCTIONAL ORGANIC CATALYSTS

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NATIONAL UNIVERSITY OF SINGAPORE

2013

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A THESIS SUBMITTED FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

NATIONAL UNIVERSITY OF SINGAPORE

2013

Thesis Declaration

I hereby declare that this thesis is my original work and it has been written by me in its entirety under the supervision of A/P Lu Yixin, Chemistry Department, National University of Singapore, between 08/2009 and 07/2013.

I have duly acknowledged all the sources of information which have been used in the thesis.

This thesis has not been submitted for any degree in any university previously.

The content of the thesis has been partly published in:

1. **Xiaowei Dou**, Xiaoyu Han, Yixin Lu. *Chem. Eur. J.* **2012**, *18*, 85.

2. **Xiaowei Dou**, Fangrui Zhong, Yixin Lu. *Chem. Eur. J.* **2012**, *18*, 13945.

3. **Xiaowei Dou**, Yixin Lu. *Chem. Eur. J.* **2012**, *18*, 8315.

4. **Xiaowei Dou**, Yixin Lu. *Org. Biomol. Chem.* **2013**, *11*, 5217.

5. **Xiaowei Dou**, Weijun Yao, Bo Zhou, Yixin Lu. *Chem. Commun.* **2013**, *49*, 9224.

6. **Xiaowei Dou**, Bo Zhou, Weijun Yao, Fangrui Zhong, Chunhui Jiang, Yixin Lu. *Org. Lett.* **2013**, *15*, 4920.

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Name	Signature	Date

Acknowledgements

I would like to express my whole-hearted gratitude to all the people who have helped and inspired me during my PhD studies in the past 4 years. This thesis could not have been accomplished without their supports.

Foremost, my deepest appreciation and respect go to my supervisor, Prof. Lu Yixin, for his constant support and guidance throughout my studies. His profound knowledge, invaluable suggestions and encouragement benefit me a lot and will always accompany me in my future career.

Every member of Prof. Lu's group has been extremely supportive and I really appreciate their support and encouragement. I especially thank Dr. Wang Youqing, Dr. Xie Xiaoan, Dr. Wang Haifei, Dr. Wang Suxi, Dr. Yao Weijun, Dr. Wang Tianli, Dr. Vasudeva Rao Gandi, Dr. Zhu Qiang, Dr. Han Xiao, Dr. Liu Xiaoqian, Dr. Luo Jie, Dr. Liu Chen, Dr. Chen Guoying, Dr. Zhong Fangrui, Dr. Han Xiaoyu, Jolin Foo, Jacek Kwiatkowski, Liu Guannan, Jiang Chunhui, Wen Shan, Wong Yee Lin, Zhou Xin, Zhou Bo and other labmates for their help during my PhD studies. They are not only co-workers in chemistry, but also good friends in life.

I also want to thank NUS for the research scholarship and financial support. Thanks also go to all the staff in department of chemistry for their help: I especially thank Madam Han Yanhui and Dr. Wu Ji'en (NMR analysis), Ms Tan Geok Kheng and Ms Hong Yimian (X-ray crystallography analysis), Madam Wong Lai Kwai and Madam Lai Hui Ngee (Mass analysis) for their great help.

Last but not least, I am extremely grateful to my parents and my sister who give me their unconditional love and support. Finally, I thank my beloved wife, Li Yingying, for always being there for me, understanding and believing in me. My gratitude also goes to my parents–in–law for their endless love and support.

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Summary

This thesis describes the development of asymmetric synthesis of furan and oxindole derivatives with tertiary amine thiourea organocatalysts, including enantioselective synthesis of 3(2*H*)-furanones and 2,3-dihydrofurans with novel L-threonine derived bifunctional catalysts, asymmetric formation of 3-spirocyclopropyl-2-oxindoles and 3-heteroatom-substituted-oxindoles with L-threonine-incorporating multifunctional catalysts, and a quinine-derived bifunctional catalyst catalyzed chiral 3-fluorooxindoles synthesis.

Chapter 1 gave a brief introduction and development of asymmetric organocatalysis. Particularly, chiral hydrogen bonding based organocatalysis is introduced in detail. Selected examples showing recent advancements in this field of catalysis are described.

Chapter 2 described the first organocatalytic asymmetric synthesis of 3(2*H*)-furanones derivatives. In the presence of L-threonine-based bifunctional tertiary amine thiourea catalysts, a highly enantioselective modified Feist–Bénary reaction between ethyl 4-bromoacetoacetate and nitroolefins afforded optically enriched 3(2*H*)-furanone derivatives. Moreover, the furanone derivatives could be easily transformed into tetronic acid and γ-lactam derivatives.

Chapter 3 further studied the utilization of modified Feist–Bénary reaction for furan derivative synthesis. L-Threonine-based bifunctional tertiary amine thiourea catalysts promoted the reaction between acyclic β-ketoesters and β,β-bromonitrostyrenes, affording synthetically useful 2,3-dihydrofurans with excellent enantioselectivities and complete *trans*-diastereoselectivity.

Chapter 4 disclosed the first direct asymmetric cyclopropanation reaction of oxindoles. By engaging DABCO as a nucleophilic catalyst, a stereochemically retentative conversion of different diastereomers of cyclopropyl spirooxindoles was discovered. Highly diastereodivergent and enantioselective synthesis of 3-spirocyclopropyl-2-oxindoles was achieved by using L-threonine-incorporating multifunctional tertiary amine thiourea catalysts.

Chapter 5 presented a novel method to conveniently access various 3-heteroatom-substituted oxindoles from 3-chlorooxindoles. With the employment of L-threonine-incorporating multifunctional catalysts, the Michael addition of oxindoles containing various 3-heteroatom substituents to nitroolefins proceeded in a highly stereoselective manner, leading to the formation of oxindoles with a 3-heteroatom-substituted quaternary center in high diastereoselectivity (up to >25:1 dr) and excellent enantioselectivity (up to 99% ee). Synthetic values of the oxindole adducts were demonstrated, and useful oxindoles, indolines and indole derivatives were asymmetrically prepared.

Chapter 6 showed the first asymmetric conjugate addition of prochiral 3-fluorinated oxindoles to vinyl sulfones catalyzed by quinine-derived bifunctional tertiary amine thiourea catalyst, furnishing biologically important chiral 3-fluoro-3-substituted oxindoles in high yields and with high enantioselectivities.

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List of Schemes

List of Abbreviations

Ac	Acetyl
Å	ångström
Aq	Aqueous
Ar	Aromatic
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
br	broad
Bz	Benzoyl
Bu	Butyl
Cat.	Catalysts
Conc.	Concentrated
DABCO	1,4-diazabicyclo[2.2.2]octane
DCE	1,2-Dichloroethylene
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DIPA	Diisopropylamine
d	doublet
d.r.	Diastereomeric ratio
ee	Enantiomeric excess
Et	Ethyl
EWG	Electron-withdrawing group

h	Hour
HPLC	High performance liquid chromatography
IPA	*iso*-Propanol
m	multiplet
m/z	mass-to-charge ratio
mmol	millimole
MBH	Morita–Bayliss–Hillman
Me	Methyl
Ms	Methyl sulfonyl
μL	microlitre
NR	No reaction
Nu	nucleophile
Ph	Phenyl
Pr	Propyl
ppm	parts per million
q	quartet
RT	Room temperature
s	singlet
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TDS	thexyldimethylsilyl
TEA	Triethylamine
TFA	Trifluoromethylacetic acid
THF	Tetrahydrofuran

TIPB	1,3,5-Triisopropylphenyl
TPS	Triphenylsilane
TS	Transition state
Ts (Tos)	*p*-Toluenesulfonyl
t	triplet
vs	versus

List of Publications

1. **Xiaowei Dou**, Fangrui Zhong, Yixin Lu. "A Highly Enantioslective Synthesis of Functionalized 2,3-Dihydrofurans by a Modified Feist–Bénary Reaction", *Chem. Eur. J.* **2012**, *18*, 13945.

2. **Xiaowei Dou**, Yixin Lu. "Diastereodivergent Synthesis of 3-Spirocyclopropyl-2-oxindoles through Direct Enantioselective Cyclopropanation of Oxindoles", *Chem. Eur. J.* **2012**, *18*, 8315.

3. **Xiaowei Dou**, Xiaoyu Han, Yixin Lu. "From Feist–Bénary Reaction to Organocatalytic Domino Michael–Alkylation Reaction: Asymmetric Synthesis of 3(2*H*)-Furanones", *Chem. Eur. J.* **2012**, *18*, 85.

4. **Xiaowei Dou**, Yixin Lu. "Enantioselective Conjugate Addition of 3-Fluoro-Oxindoles to Vinyl Sulfone: An Organocatalytic Access to Chiral 3-Fluoro-3-substituted Oxindoles", *Org. Biomol. Chem.* **2013**, *11*, 5217.

5. **Xiaowei Dou**, Bo Zhou, Weijun Yao, Fangrui Zhong, Chunhui Jiang, Yixin Lu. "A Facile Approach for the Asymmetric Synthesis of Oxindoles with a 3-Sulfenyl-substituted Quaternary Stereocenter", *Org. Lett.* **2013**, *15*, 4920.

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7. Fangrui Zhong, **Xiaowei Dou**, Xiaoyu Han, Weijun Yao, Qiang Zhu, Yuezhong Meng, Yixin Lu. "Chiral Phosphine-Catalyzed Asymmetric Michael Addition of Oxindoles", *Angew. Chem. Int. Ed.* **2013**, *52*, 943. **(highlighted in *SYNFACTS* 2013, 216**)

8. Chen Liu, **Xiaowei Dou**, Yixin Lu. "Organocatalytic Asymmetric Aldol Reaction of Hydroxyacetone with β,γ-Unsaturated α-Keto Esters: Facile Access to Chiral Tertiary Alcohols", *Org. Lett.* **2011**, *13*, 5248.

9. Fangrui Zhong, Weijun Yao, **Xiaowei Dou**, Yixin Lu. "Enantioselective Construction of 3-Hydroxy Oxindoles via Decarboxylative Addition of β-Ketoacids to Isatins", *Org. Lett.* **2012**, *14*, 4018.

10. Fangrui Zhong, Jie Luo, Guo-Ying Chen, **Xiaowei Dou**, Yixin Lu. "Highly Enantioselective Regiodivergent Allylic Alkylations of MBH Adducts with

Phthalides", *J. Am. Chem. Soc.* **2012**, *134*, 10222. **(highlighted in *SYNFACTS* 2012, 906)**.

11. Ru Wang, Ling-Chen Kang, Jing Xiong, **Xiaowei Dou**, Xiao-Yu Chen, Jing-Lin Zuo, Xiao-Zen You. "Structures and Physical Properties of Oligomeric and Polymeric Metal Complexes Based on Bis(pyridyl)-substituted TTF Ligands and an Inorganic Analogue", *Dalton Trans.* **2011**, *40*, 919.

Chapter 1 Introduction

1.1 Asymmetric Organocatalysis

1.1.1 Introduction

Chiral molecules are optically active compounds that lack an internal plane of symmetry and have a non-superimposable mirror image.[1] Such molecules are extremely important in human life. Firstly, they play a critical role in biological systems. Secondly, molecular chirality has shown its great importance in pharmaceutical industry.[2] Enantiopure molecules provide unique pharmacological activities as well as pharmacokinetic and pharmacodynamic effects, compared with their racemic counterparts, and thus lead to different therapeutic activities.[3] Hence, preparation of enantiopure molecules has now become an extremely important topic in organic synthesis.

Due to the importance of chiral molecules, synthetic methods leading to their synthesis have been intensively studied over the last several decades. In the early days, resolution of racemic compounds and employment of chiral auxiliaries[4] were the main approaches to access chiral molecules. However, both approaches suffered from severe drawbacks, the former yielded only up to 50% of the desired enantiomer, while the latter required stoichiomeric amounts of suitable chiral auxiliaries and the

[1] M. A. Fox, J. K. Whitesell, Eds. *Organic Chemistry* (3rd Edition), Jones & Bartlett Publishers, **2004**.
[2] a) M. Gardner, *The New Ambidextrous, 3rd Rev. Ed,* W. H. Freeman & Co: New York, **1990**; b) E. Francotte, W. Lindner, Eds. *Chirality in drug research*, Wiley-VCH, Weinheim, **2006**.
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auxiliaries need be cleaved after the reaction. Furthermore, both approaches have limited applications in terms of substrate scopes and reaction types. Asymmetric catalysis has emerged as a more effective and promising method for the synthesis of optically enriched molecules.[5] In general, only a catalytic amount of chiral catalyst is required, which temporarily binds to the substrates to induce chirality. Based on the catalyst used, asymmetric catalysis can be further divided into three catagories: enzyme catalysis, metal-based catalysis and organocatalysis.

Enzymes are proteins that are capable of producing small molecules in enantiomerically pure form. Therefore, enzyme catalysis becomes a choice for preparation of chiral compounds in organic synthesis.[6] However, the types of available enzymes are quite limited, and specific reaction conditions are required when enzymes are employed as the catalysts, which limites their application in organic synthesis.

Transition metal based catalysis is widely used nowadays by chemists for the preparation of optically pure compounds. Great progress has been made since the 1980s, thanks to the contributions made by Sharpless,[7] Noyori,[8] Jacobsen[9] and

[5] a) R. Noyori, R. *Asymmetric Catalysis in Organic Synthesis*, Wiley: New York, **1994**; b) E. N. Jacobsen, A. Pfaltz, H. Yamamoto, Eds. *Comprehensive Asymmetric Catalysis*, 1st Ed, Springer: Berlin, **1999**; c) I. Ojima, *Catalytic Asymmetric Synthesis*, 2nd Ed. Wiely-VCH: New York, **2000**.
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[8] a) A. Miyashita, A. Yasuda, H. Takaya, K. Toriumi, T. Ito, T. Souchi, R. Noyori, *J. Am. Chem. Soc.* **1980**, *102*, 7932; b) T. Ohta, H. Takaya, M. Kitamura, K. Nagai, R. Noyori, *J. Org. Chem.* **1987**, *52*, 3174; c) H. Takaya, T. Ohta, N. Sayo, H. Kumobayashi, S. Akutagawa, S. Inoue, I. asahara, R. Noyori, *J. Am. Chem. Soc.* **1987**, *109*, 1596; d) R. Noyori, T. Ohkuma, M. Kitamura, H. Takaya, N. Sayo, H. Kumobayashi, S. Akutagawa, *J. Am. Chem. Soc.* **1987**, *109*, 5856; e) M. Kitamura, T. Ohkuma, S. Inoue, N. Sayo, H. Kumobayashi, S. Akutagawa, T. Ohta, H. Takaya, R. Noyori, *J. Am. Chem. Soc.* **1987**, *109*, 1596.
[9] W. Zhang, J. L. Loebach, S. R. Wilson, E. N. Jacobsen, *J. Am. Chem. Soc.* **1990**, *112*, 2801.

others.[10] Metal catalysis succeeded in almost all types of reactions, and good selectivities can often be achieved by combining chiral ligands and suitable metals. However, high cost and toxicity of the metals, and stringent reaction conditions are the key drawbacks of metal-based catalytic methods.

Organocatalysis has emerged as as another important method for the asymmetric preparation of chiral molecules in the past decade.[11] Organocatalysis is the acceleration of chemical reactions with a substoichiometric amount of an organic compound which does not contain a metal atom.[3b] The advantages of organic catalysts are notable: they are usually non-toxic, readily available from natural products, inexpensive, insensitive to reaction conditions in most cases. Furthermore, multi-component, tandem or domino multi-step reactions are also suitable in organocatalysis, allowing rapid and enantioselective constructions of structurally complex products. All these advantages make organocatalysis an indispensable method for the synthesis of chiral compounds.

1.1.2 Development of Asymmetric Organocatalysis

The asymmetric organocatalytic reactions have a rich history.[12] However, considerably less attention had been paid to this approach, and asymmetric

[10] a) R. E. Lowenthal, A. Abiko, S. Masamune, *Tetrahedron Lett.* **1990**, *31*, 6005; b) D. A. Evans, M. M. Faul, M. T. Bilodeau, B. A. Anderson, D. M. Barnes, *J. Am. Chem. Soc.* **1993**, *115*, 5328; c) D. S. La, J. B. Alexander, D. R. Cefalo, D. D. Graf, A. H. Hoveyda, R. R. Schrock, *J. Am. Chem. Soc.* **1998**, *120*, 9720; d) A. El-Qisairi, O. Hamed, P. M. Henry, *J. Org. Chem.* **1998**, *63*, 2790; e) D. A. Evans, M. C. Kozlowski, J. A. Murry, C. S. Burgey, K. R. Campos, B. T. Connell, R. J. Staples, *J. Am. Chem. Soc.* **1999**, *121*, 669.

[11] a) A. Berkessel, H. Gröger, *Asymmetric organocatalysis: from biomimetic concepts to applications in asymmetric synthesis*, Wiley-VCH, Weinheim, **2005**; b) P. I. Dalko, *Enantioselective organocatalysis*, Wiley-VCH, Weinheim, **2006**; c) C. E. Song, *Cinchona alkaloids in synthesis and catalysis*, Wiley-VCH, Weinheim, **2009**; d) B. List, S. Arseniyadis, *Asymmetric organocatalysis*, Springer, **2010**.

[12] a) G. Breding, R. W. Balcom, *Ber. Deutsch. Chem. Ger.* **1908**, *41*, 740; b) G. Breding, P. S. Fiske, *Biochem. Z.* **1912**, *46*, 7; c) M. M. Vavon, P. Peignier, *Bull Soc. Fr.* **1929**, *45*, 293; d) H. Pracejus, *Justus Liebigs Ann. Chem.* **1960**, *643*, 9; e) G. Stork, R. Terrell, J. Szmuszkovicz, *J. Am. Chem. Soc.* **1954**, *76*, 2029; f) G. Stork, H. Landesman, *J. Am. Chem. Soc.* **1956**, *78*, 5128; g) U. Eder, G. Sauer, R. Wiechert, *Angew. Chem. Int. Ed.* **1971**, *10*, 496; h) Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1615.

organocatalytic reactions were considered to be inefficient and limited in scope for a long time. The revival of modern asymmetric organocatalysis did not begin until the late 1990s and 2000s. The research groups of Jacobsen,[13] Denmark,[14] List and Barbas,[15] MacMillan,[16] Maruoka[17] developed a number of different organic catalysts to mediate various types of reactions. Inspired by their elegant studies, the interest in the field of organocatalysis has increased spectacularly in the past decade. To date, organoatalysis has developed into its own subdiscipline within organic chemistry and organocatalytic reactions are becoming powerful tools in the construction of enantioly pure compounds and complex molecular skeletons.

As one of the core issues in organocatalysis, the development of different organic catalysts is always the focus and therefore numerous organic catalysts have appeared in the past few years, and some selected examples are shown in Figure 1.1. The known organic catalysts can be divided into the following categories according to their activation modes and structural specialty.

[13] a) M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 4901; b) M. S. Sigman, P. Vachal, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2000**, *39*, 1279; c) P. Vachal, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 10012; d) P. Vachal, E. N. Jacobsen, *Org. Lett.* **2000**, *2*, 867.
[14] a) S. E. Denmark, R. A. Stavenger, T. K. Wong, X. P. Su, *J. Am. Chem. Soc.* **1999**, *121*, 4982; b) S. E. Denmark, J. P. Fu, *J. Am. Chem. Soc.* **2000**, *122*, 12021; c) S. E. Denmark, R. A. Stavenger, *Acc. Chem. Res.* **2000**, *33*, 432; d) S. E. Denmark, J. P. Fu, *Org. Lett.* **2002**, *4*, 1951.
[15] a) B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395; b) B. List, *J. Am. Chem. Soc.* **2000**, *122*, 9336; c) B. List, *Synlett* **2001**, 1675; d) B. List, *J. Am. Chem. Soc.* **2002**, *124*, 5656; e) B. List, *Tetrahedron* **2002**, *58*, 5573.
[16] a) K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243; b) N. A. Paras, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2001**, *123*, 4370; c) N. A. Paras, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 7894.
[17] a) O. Ooi, M. Kameda, K. Maruoka, *J. Am. Chem. Soc.***1999**, *121*, 6519; b) O. Ooi, E. Tayama, K. Doda, M. Takeuchi, K. Maruoka, *Synlett* **2000**, 1500; c) O. Ooi, M. Takeuchi, K. Maruoka, *Synthesis* **2001**, 1716; d) O. Ooi, Y. Uematsu, M. Kameda, K. Maruoka, *Angew. Chem. Int. Ed.* **2002**, *41*, 1551; e) O. Ooi, M. Kameda, K. Maruoka, *J. Am. Chem. Soc.* **2003**, *125*, 5139.

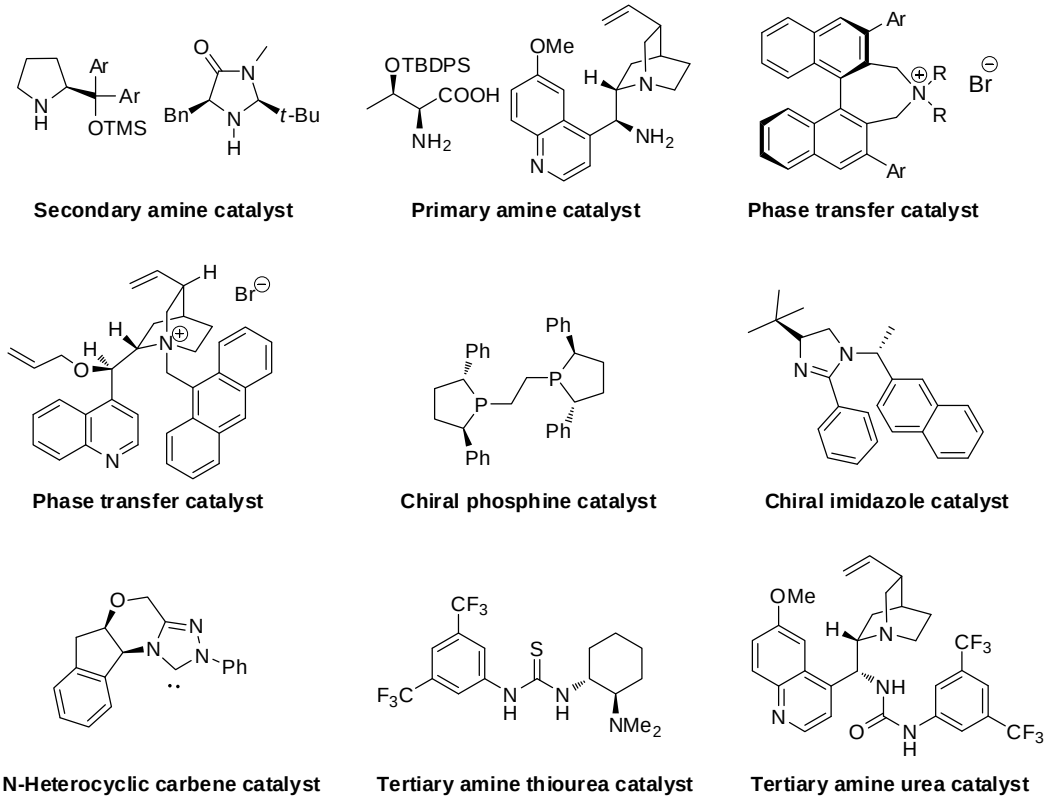


Figure 1.1 Selected examples of chiral organocatalysts

a) Aminocatalysts that contain a secondary amine or primary amine moiety. The activation modes for this type of catalysts are mainly through enamine or iminium activation, and aldehydes and ketones are the typical substrates used in this catalytic system.

b) Phase transfer catalysts (PTC). The PTC catalysts are normally chiral quaternary ammonium and phosphonium salts derived from cinchona alkaloids or binaphthyl derivatives. The enantiomeric control of the reaction is usually mediated by an ion-pairing interaction between the catalyst and substrate.

c) Nucleophilic amine catalysts. Examples of these catalysts include DMAP type catalysts, imidazole type catalysts and some cinchona alkaloid derivatives. The nucleophilic nature of amine was utilized for acylation reactions, resolution of

alcohols, amines and other reactions.

d) Organic phosphine catalysts. The difference in nucleophilicity and Brønsted basicity of the trivalent phosphines compared to the amine function makes them unique and powerful catalysts in a number of reactions, including various cycloaddition reactions, Morita-Baylis-Hillman reaction and its aza-counterpart, kinetic resolution reactions, as well as Michael additions and γ-additions.

e) N-Heterocyclic carbene (NHC) catalysts. The NHC catalysts can induce inversion of the classical reactivity (e.g. conjugate umpolung of α,β-unsaturated aldehydes), which opens up new synthetic pathways. NHC catalysis has found wide applications in many useful transformations like benzoin condensation, Stetter reaction and 1,2-additions.

f) Hydrogen bonding based organic catalysts. In this catalytic system, hydrogen bonding interaction is essential for both of substrate activation and the high selectivity. The chiral catalysts usually contain hydrogen bond donors such as alcohols, urea or thiourea moiety.

In the following sections of this Chapter, typical hydrogen bonding based organocatalytic methods will be reviewed, and focuses will be given to thiourea/urea based hydrogen bonding organocatalysts and their applications in organic synthesis.

1.2 Chiral Hydrogen Bonding Based Organocatalysis

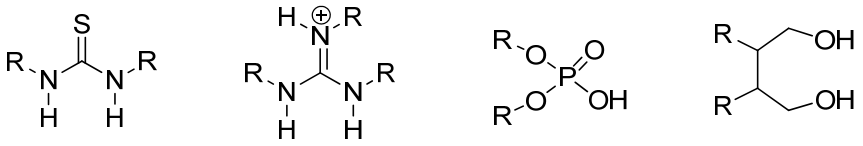
1.2.1 Introduction

Although the importance of hydrogen bonding interactions has been recognized in the scientific community for a long time, the term 'hydrogen bond' was not coined

until the year of 1931 in Pauling's seminal paper on the nature of the chemical bond.[18] Desipite its wide existence in chemical and biological systems, hydrogen bonding has been rarely used as the design principle for asymmetric catalysts. The enormous potential of hydrogen bonding as an activating interaction and its application in asymmetric synthesis has only been recognized recently.[19] It was found that hydrogen bonding interactions constitute a major driving force in the formation of specific molecular and complex geometries in the transition states. Nowadays hydrogen bonding based organocatalysis has emerged as a frontier in the field of asymmetric catalysis.

Although a large number of hydrogen bonding based organic catalysts appeared in the past few years, the vast majority of them contains certain hydrogen bond donors like thiourea/urea, alcohols, guanidinium ions and strong Brønsted acid (e.g. phosphoric acid, phenols) (Scheme 1.1). Moreover, they were mainly derived from some 'priviledged' chiral scaffold such as amino acids, 1,2-diaminocyclohexane, cinchona alkaloids, binaphthyl, TADDOL, indane and others. In the following part, hydrogen bonding based organocatalysts and their applications in asymmetric transformations will be reviewed based on the hydrogen bond donors. In particular, thiourea/urea based organocatalysis will be reviewed in detail according to the chiral scaffold of the catalysts.

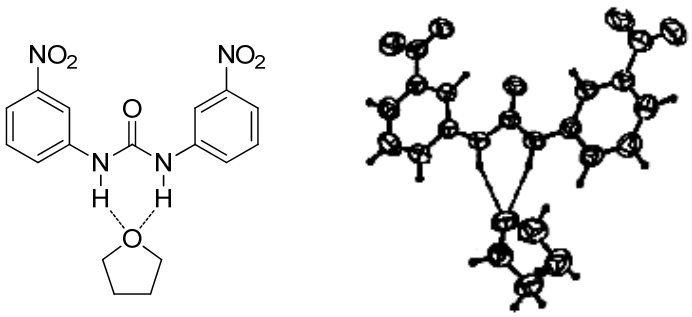
[18] L. Pauling, *J. Am. Chem. Soc.* **1931**, *53*, 1367.
[19] P. M. Pinko, *Hydrogen Bonding in Organic Synthesis*, Wiley, Weinhein, **2009**.



Scheme 1.1 Typical hydrogen bond donors in organocatalysts

1.2.2 Hydrogen Bonding Organocatalysis Based on Thiourea/Urea

The systematic study of thiourea/urea as the hydrogen bond donors for the promotion of racemic organic reactions began in the 1980s. The Etter group reported that achiral diaryl ureas were good complexing agents for a number of proton acceptors, and well-defined crystalline complexs were formed. They proposed that the stability of the complex derived from a two-point hydrogen bonding interactions between the urea N-H bonds and the oxygen (Scheme 1.2).[20]

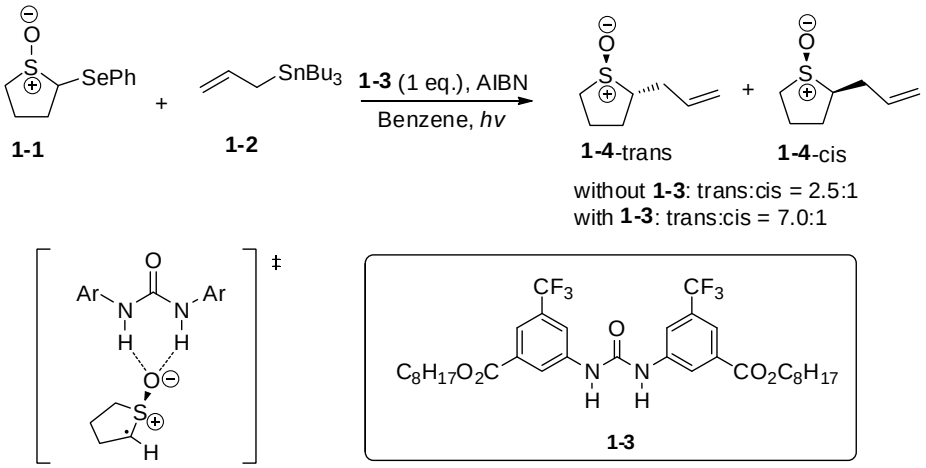


Scheme 1.2 Etter's urea mediated hydrogen bonding interactions

In 1994, the first report on the application of Etter's ureas as Lewis acids was disclosed by Curran and co-workers. They showed that the outcome of radical allylation reactions could be altered in the presence of ureas. The activation of the radical intermediate through hydrogen bonding interactions was believed to be

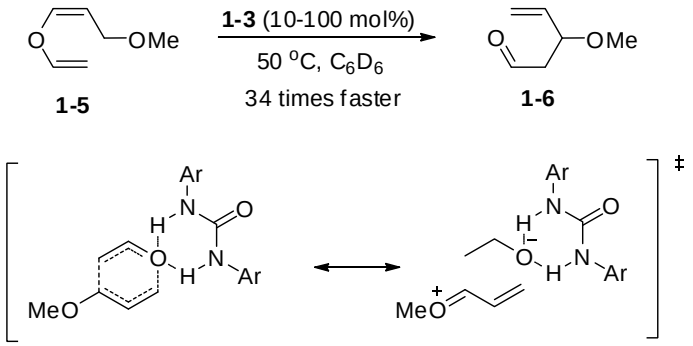
[20] a) M. C. Etter, T. W. Panunto, *J. Am. Chem. Soc.* **1988**, *110*, 5896; b) M. C. Etter, *Acc. Chem. Res.* **1990**, *23*, 120; c) M. C. Etter, Z. Urbanczyk-Lipkowska, M. Zia-Ebrahimi, T. W. Panunto, *J. Am. Chem. Soc.* **1990**, *112*, 8415.

essential for the stereochemistry and the rate acceleration (Scheme 1.3).[21]



Scheme 1.3 Urea catalyzed radical allylation reaction

Shortly after, the same group reported the dipolar Claisen rearrangement using diaryl urea as catalyst. The reaction was found to be accelerated *via* the bis-hydrogen bonded transition state (Scheme 1.4).[22]



Scheme 1.4 Urea catalyzed Claisen rearrangement

Other examples appeared in the early 2000, the Schreiner group used the Etter-type ureas for the promotion of Diels-Alder reactions.[23] The utilization of

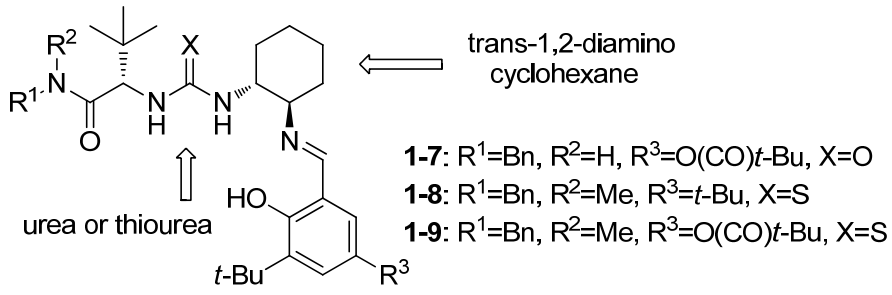
[21] D. P. Curran, L. H. Kuo, *J. Org. Chem.* **1994**, *59*, 3259.
[22] D. P. Curran, L. H. Kuo, *Tetrahedron Lett.* **1995**, *36*, 6647.
[23] P. R. Schreiner, A. Wittkopp, *Org. Lett.* **2002**, *4*, 217.

thioureas for the activation of nitrones was also reported by Takemoto and co-workers.[24]

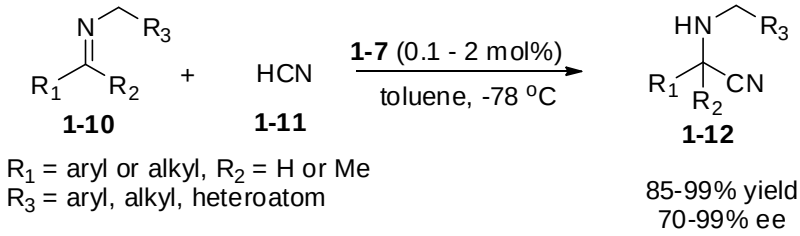
Numerous chiral organic catalysts containg a thiourea/urea as the hydrogen bond donor were prepared in the past few years, and they were mainly derived from the 'priviledged' chiral scaffold such as 1,2-diaminocyclohexane, amino acids, cinchona alkaloids, binaphthyl, indane and others.

1.2.2.1 Diamines Derived Thiourea/Urea Organocatalysts

One early success in the field of hydrogen bonding based organocatalysis came from Jacobsen and co-workers. In 1998, a library of *trans*-1,2-diaminocyclohexane derived Schiff base thiourea/urea catalysts were introduced.[25] These catalysts were initially designed as ligands for metal-based catalysis, but the study revealed that the catalysts themselves were efficient for the asymmetric Strecker reaction of hydrogen cyanide with *N*-allylaldimine (Scheme 1.5). The computational and experimental studies indicated that the hydrogen bonding between the imine lone electron pair and the acidic thiourea/urea N–H proton was formed as the activation model.[26]

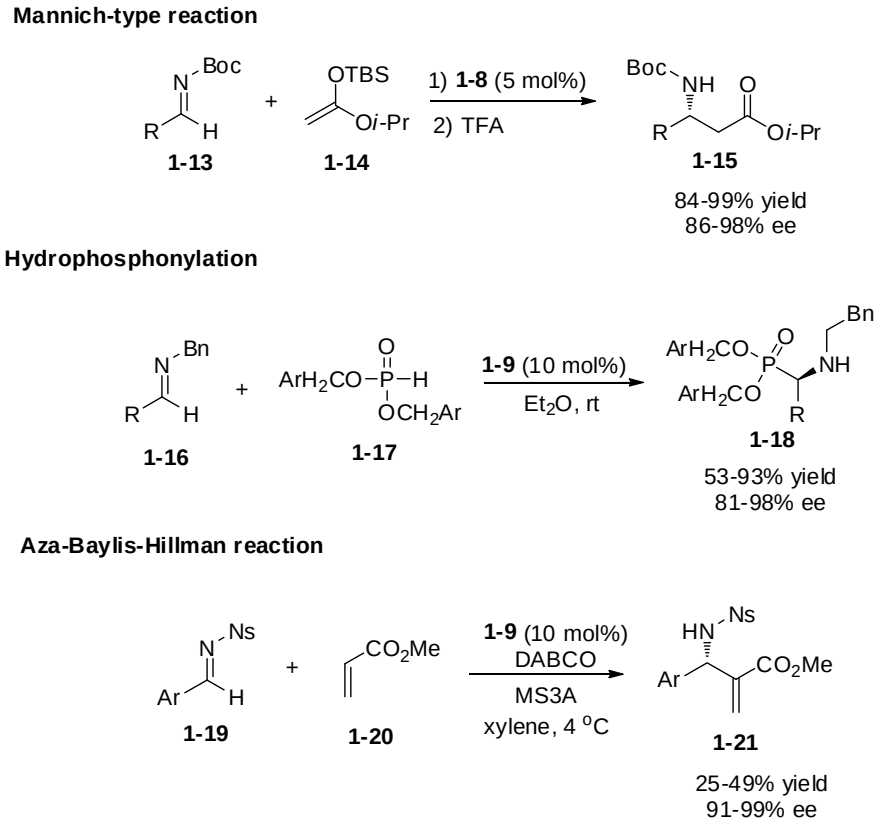


[24] T. Okino, Y. Hoashi, Y. Takemoto, *Tetrahedron Lett.* **2003**, *44*, 2817.
[25] a) M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 4901; b) M. S. Sigman, P. Vachal, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2000**, *39*, 1279; c) P. Vachal, E. N. Jacobsen, *Org. Lett.* **2000**, *2*, 867; d) J. T. Su, P. Vachal, E. N. Jacobsen, *Adv. Synth. Catal.* **2001**, *343*, 197.
[26] P. Vachal, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 10012.



Scheme 1.5 Jacobsen's thiourea/urea catalyst and its application in Strecker reaction

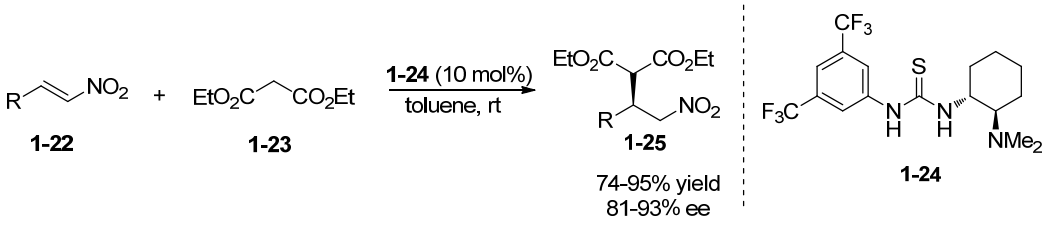
Subsequently, these catalysts were found to be also applicable to other types of reactions, such as Mannich-type reaction of *N*-Boc-aldimines with ketene silyl acetals,[27] hydrophosphonylation of aldimines[28] and *aza*-Baylis-Hillman reaction[29] (Scheme 1.6)



Scheme 1.6 Jacobsen's thiourea/urea catalysts catalyzed reactions

[27] A. G. Wenzel, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 12964.
[28] G. D. Joly, E. N. Jacobsen, *J. Am. Chem. Soc.* **2004**, *126*, 4102.
[29] I. T. Raheem, E. N. Jacobsen, *Adv. Synth. Catal.* **2005**, *347*, 1701.

In contrast to most organometallic catalysts, the vast majority of the efficient catalysts currently used in organocatalysis have more than one active center. In thiourea/urea based organocatalysts, most of them are bifunctional and have another functional site, commonly a Lewis base center. Such catalysts are able to activate both the donor and acceptor and thus increase the reaction rate and selectivity. The first elegant example of bifunctional thiourea tertiary amine catalyst was developed by Takemoto in 2003. [30] The catalyst was derived from chiral *trans*-1,2-diaminocyclohexane with one amino group transformed to thiourea while the other converted to tertiary amine. Such a bifunctional catalyst was found to be highly efficient for the enantioselective Michael addition of malonate esters to nitroolefins (Scheme 1.7).

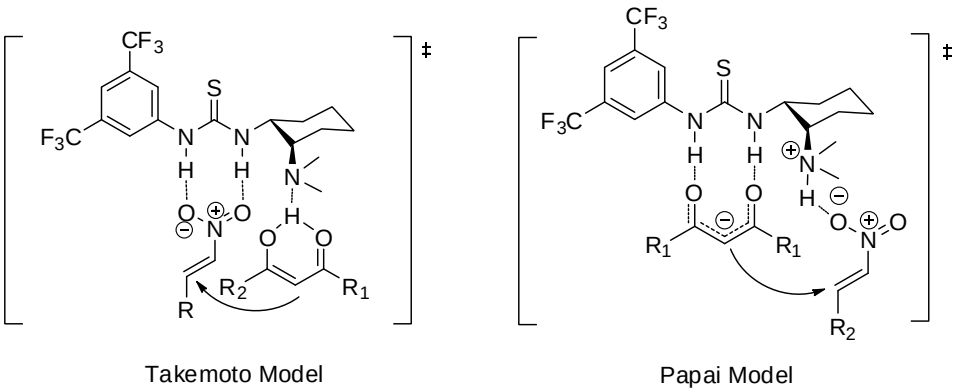


Scheme 1.7 Michael addition reaction catalyzed by Takemoto's bifunctional catalyst

In Takemoto's initial report, the high selectivity was attributed to two hydrogen bonding interactions, one between thiourea moiety and the nitro goup, and another one resulted from tertiary amine moiety and the enol form of malonate ester (Scheme 1.8). Pápai *et al* proposed an alternative mode of this reaction based on density

[30] a) T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672; b) T. Okino, Y. Hoashi, T. Furukawa, X. Xu, Y. Takemoto, *J. Am. Chem. Soc.* **2005**, *127*, 119.

functional theory calculations in 2006.[31] They believed that the electrophile nitro olefin was activated via hydrogen bonding with the protonated tertiary amine, and the nucleophile enolate was activated by thiourea group through double hydrogen bonding interaction (Scheme 1.8). Interestingly, predictions by both activation modes lead to the same experimental outcome of the reaction.



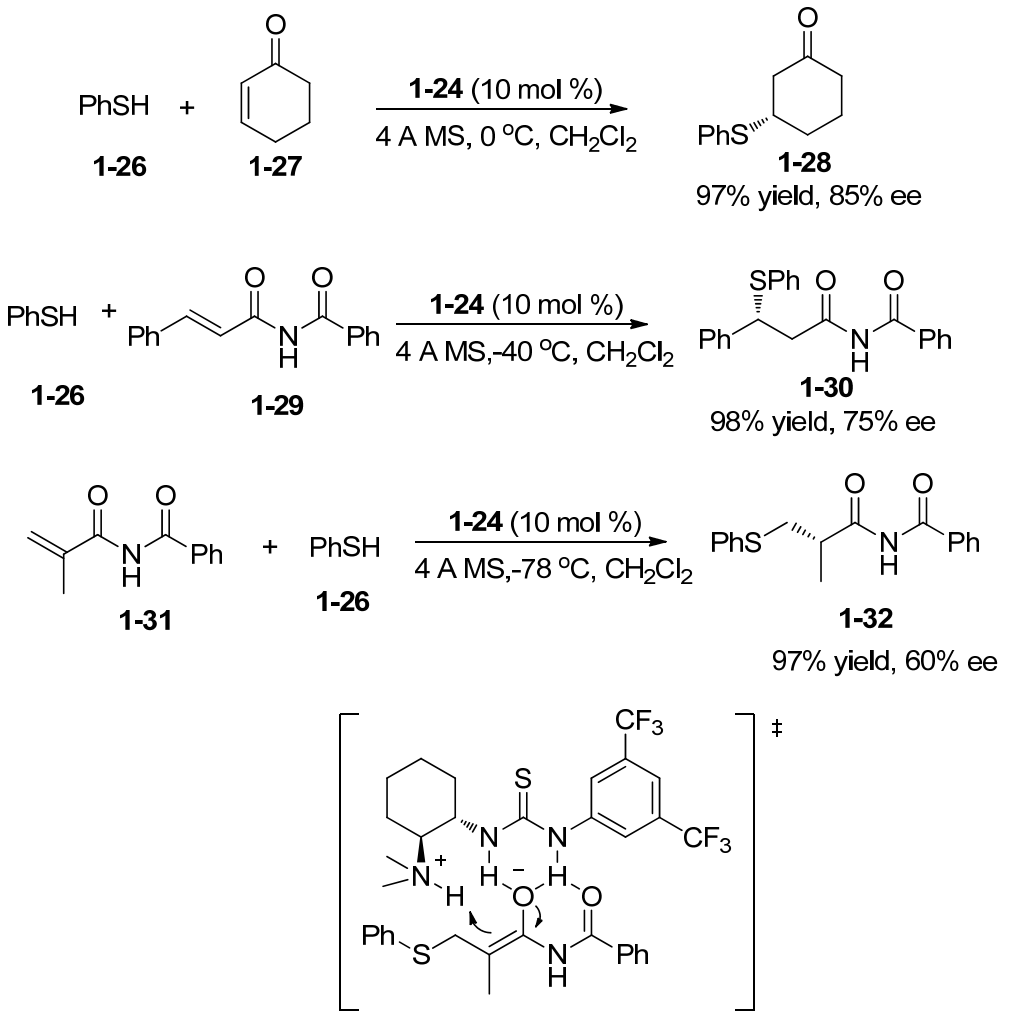
Scheme 1.8 Proposed activation models for Takemoto catalyst

The Takemoto group also demonstrated the applications of bifunctional tertiary amine thiourea catalyst **1-24** in other reactions, including 1,4-addition of malonitrile to α,β-unsaturated imides,[32] *aza*-Henry reactions[33] and conjuate addition of γ,δ-unsaturated β-ketoesters to nitroolefins.[34]

The Takemoto catalyst was also employed by other research groups for a variety of reactions. Representative examples include asymmetric 1,4-addition of aryl thiols to α,β-unsaturated cyclic enones and imides, conjugate addition/asymmetric

[31] A. Hamza, G. Schubert, T. Soós, I. Pápai, *J. Am. Chem. Soc.* **2006**, *128*, 13151.
[32] a) Y. Hoashi, T. Okino, Y. Takemoto, *Angew. Chem. Int. Ed.* **2005**, *44*, 4032; b) T. Inokuma, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2006**, *128*, 9413.
[33] a) T. Okino, S. Nakamura, T. Furukawa, Y. Takemoto, *Org. Lett.* **2004**, *6*, 625; b) X. Xu, T. Furukawa, T. Okino, H. Miyabe, Y. Takemoto, *Chem. Eur. J.* **2006**, *12*, 466.
[34] Y. Hoashi, T. Yabuta, P. Yuan, H. Miyabe, Y. Takemoto, *Tetrahedron Lett.* **2006**, *62*, 365.

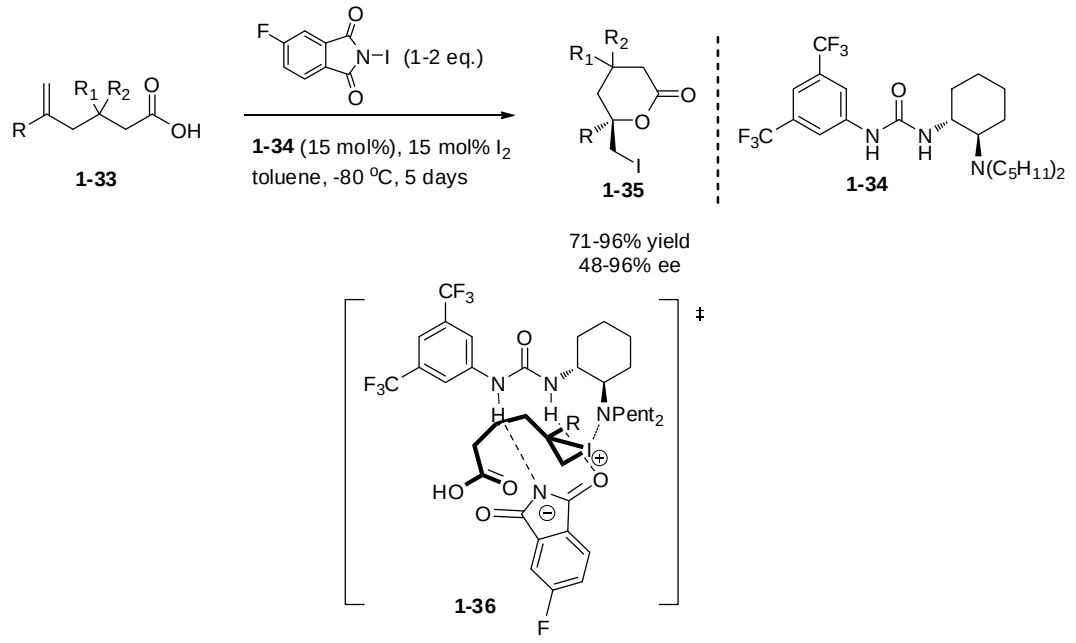
protonation of α-prochiral imide.[35] In the latter case, the ammonium group of the catalyst serves as a chiral proton source for the stablized enone intermediate after initial 1,4-addition of the thiol group (Scheme 1.9).



Scheme 1.9 Various reactions catalyzed by Takemoto catalyst

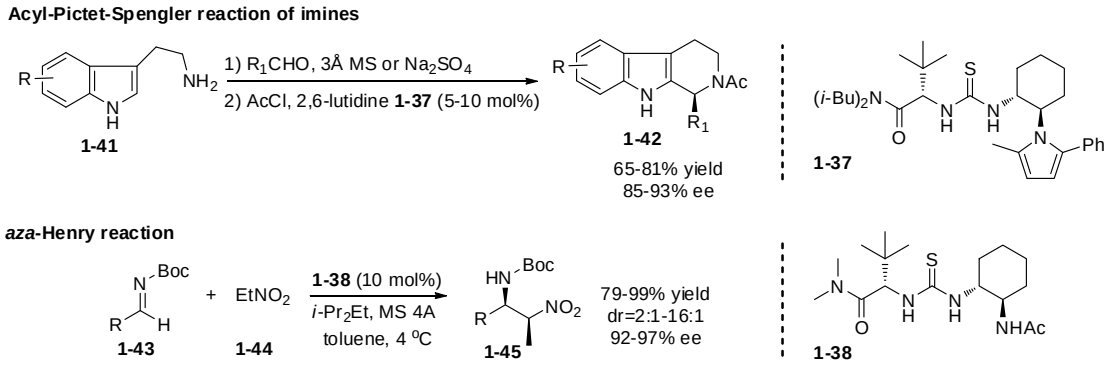
Jacobsen also prepared Takemoto-type urea catalyst **1-34** to promote enantioselective iodolactonization reaction of hexenoic acid derivatives. Preliminary computational studies supported the intermediacy of an iodonium ion complex **1-36**, which maintained a tertiary amino-iodonium ion interaction (Scheme 1.10).[36]

[35] B. J. Li, L. Jiang, M. Liu, Y. C. Chen, L. S. Ding, Y. Wu, *Synlett* **2005**, 603.
[36] G. E. Veitch, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2010**, *49*, 7332.

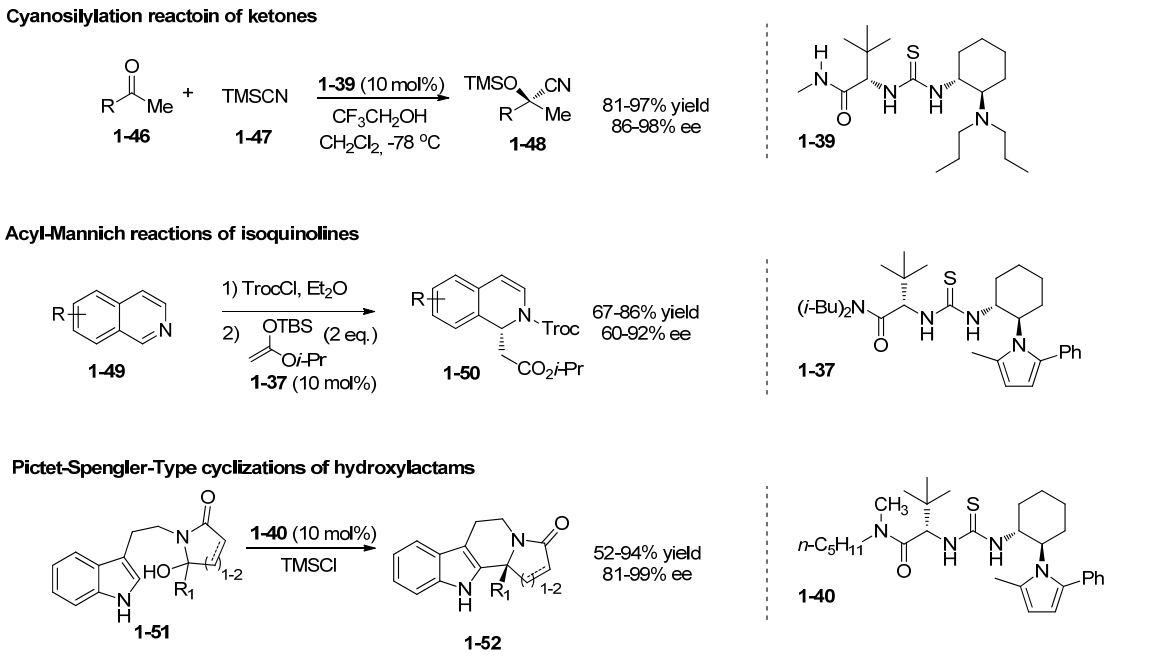


Scheme 1.10 Enantioselective iodolactonization reaction catalyzed by Takemoto type catalyst

Other bifunctional thiourea catalysts based on *trans*-1,2-diaminocyclohexane were also developed by the Jacobsen group, and they were versatile catalysts in acyl-Pictet-Spengler reaction of imines,[37] *aza*-Henry reaction,[38] cyanosilylation of ketones,[39] acyl-Mannich reactions of isoquinolines[40] and Pictet-Spengler-type cyclizations of hydroxylactams[41] (Scheme 1.11).

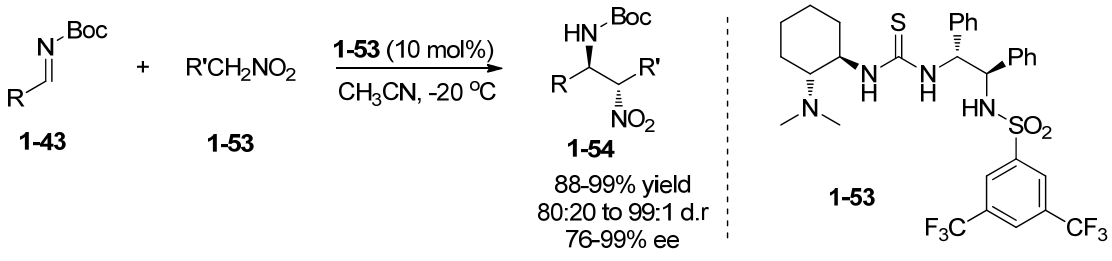


[37] M. S. Taylor, E. N. Jacobsen, *J. Am. Chem. Soc.* **2004**, *126*, 10558.
[38] T. P. Yoon, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2005**, *44*, 466.
[39] D. E. Fuerst, E. N. Jacobsen, *J. Am. Chem. Soc.* **2005**, *127*, 8964.
[40] M. S. Taylor, N. Tokunaga, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2005**, *44*, 6700.
[41] I. T. Raheem, P. S. Thiara, E. A. Peterson, E. N. Jacobsen, *J. Am. Chem. Soc.* **2007**, *129*, 13404.



Scheme 1.11 Jacobsen's bifuntional thiourea catalysts and application

Multifunctional tertiary amine thiourea catalyst based on *trans*-1,2-diaminocyclohexane was developed in 2008. Wang and co-workers reported a highly *anti*-selective asymmetric nitro-Mannich reaction catalyzed by a Multifunctional thiourea catalyst (Scheme 1.12).[42] The multiple hydrogen bonding interactions in the catalysis were important for the observed high selectivity.

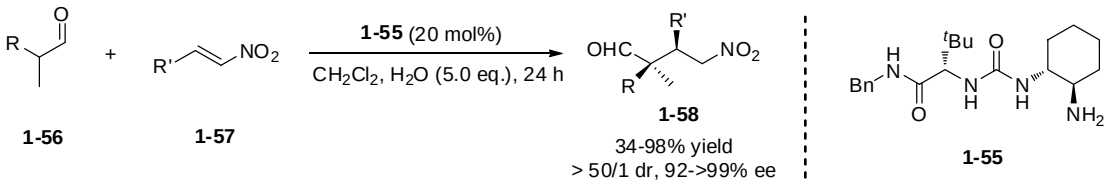


Scheme 1.12 Nitro-Mannich reaction catalyzed by a multifunctional catalyst

Functionalities other than the tertiary amino group were also introduced to the

[42] C.-J. Wang, X.-Q. Dong, Z.-H. Zhang, Z.-Y. Xue, H.-L. Teng, *J. Am. Chem. Soc.* **2008**, *130*, 8606.

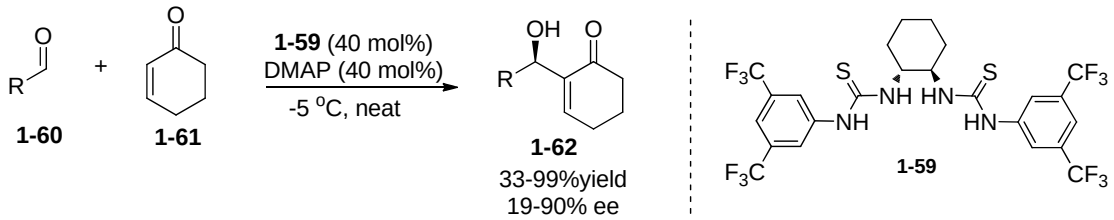
diamine based thiourea/urea catalytic systems. In 2006, bifunctional primary amine urea catalyst **1-55** was reported by Jacobsen for the conjugate addition of branched aldehydes to nitroolfeins, affording the adducts in excellent diastereoselectivities (up to >50:1 dr) and very high enantioselectivities (up to 99% ee) (Scheme 1.13). It was hypothesized that nitroolefin was activated by the hydrogen bonding interaction between the urea function and the nitro moiety, and the aldehyde was activated *via* the enamine intermediate. The observed stereochemical control was believed due to the simultaneous activations of both reactants.[43]



Scheme 1.13 Bifunctional primary amine urea catalyst mediated conjugate addition

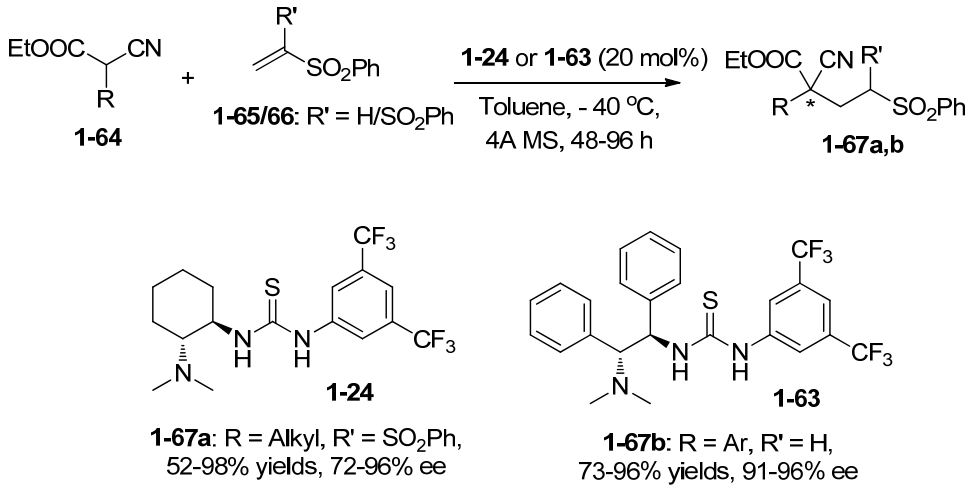
In 2004, Nagasawa *el al.* reported the use of diamine based chiral bis-thiourea **1-59** as a co-catalyst with DMAP to promote the Morita–Baylis–Hillman addition of cyclohexenone to aldehydes (Scheme 1.14).[44] The observed high enantioselectivity was apparently due to the chiral bis-thiourea catalyst since non-chiral DMAP was employed, it was proposed that bis-thiourea moiety interacting with the substrate during the transition state of the reaction.

[43] M. P. Lalonde,Y. Chen, E. N. Jacobsen, *Angew. Chem. Int. Ed.*, **2006**, *45*, 6366.
[44] Y. Sohtome, A. Tanatani, Y. Hashimoto, K. Nagasawa, *Tetrahedron Lett.* **2004**, *45*, 5589.



Scheme 1.14 Bis-thiourea catalyst mediated MBH reaction

In addition to *trans*-1,2-diaminocyclohexane, other diamines were also used as the chiral diamine framework for construction of thiourea/urea organocatalysts. Chen reported the conjugate addition of α-substituted α-cyanoacetates to vinyl sulfone catalyzed by catalyst **1-63** (Scheme 1.15).[45] With the Takemoto catalyst **1-24**, the addition of α-substituted α-cyanoacetates **1-64** to vinyl sulfone **1-65** proceeded well. However, catalyst **1-63** led to better results when α-aliphatic substituted α-cyanoacetates were used. It was believed that double hydrogen bonding interactions were involved between thiourea function and vinyl sulfone substrate.



Scheme 1.15 Different diamine based bifunctional catalyst mediated conjugate addition

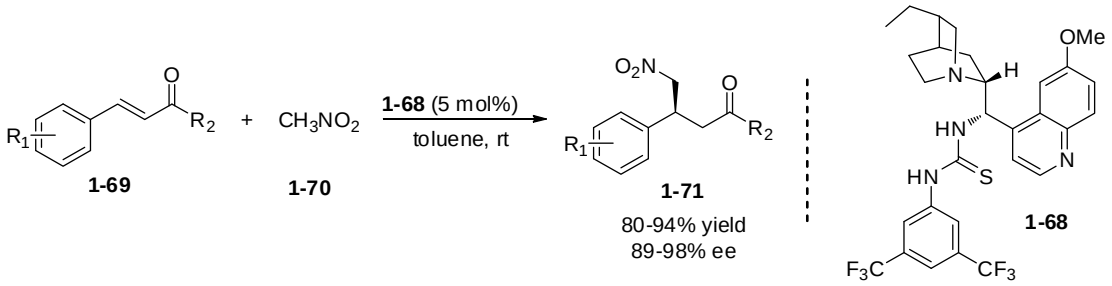
1.2.2.2 Cinchona Alkaloids Derived Thiourea/Urea Organocatalysts

Recently, cinchona alkaloids derived bifunctional thiourea/urea organocatalysts

[45] T.-Y. Liu, J. Long, B.-J. Li, L. Jiang, R. Li, Y. Wu, L. Ding, Y.-C. Chen, *Org. Biomol. Chem.* **2006**, *4*, 2097.

have been developed. In such catalytic systems the thiourea/urea moiety serves as the hydrogen bond donor, and the teitiary amine from the alkaloid is a Lewis base functional center.

The first cinchona alkaloids derived thiourea catalyst was developed by Soós and co-workers in 2005. Enantioselective conjugate addition of nitromethane to *trans*-chalcones was efficiently promoted by hydroquinine-derived thiourea catalyst **1-68**, and high yields and high enantioselectivities were attainable (Scheme 1.16).[46] The synergistic interplay in the spatial orientation of the thiourea-enone complex and the ammonium nitronate nucleophile was crucial for obtaining high selectivity.

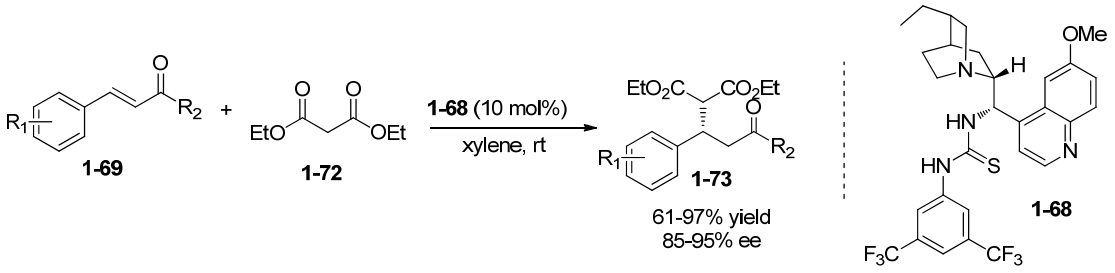


Scheme 1.16 Conjugate addition catalyzed by cinchona alkaloid derived thiourea catalyst

In 2006, the Wang group utilized the hydroquinine derived thiourea catalyst to catalyze conjugate addition of a broad spectrum of nucleophilic enol species to enones. Excellent enantioselectivities and high yields were obtained for a diverse array of nucleophiles, including malonate esters, ketoesters, 1,3-diketones, nitroesters and malonitrile. Conjugate addition reaction of diethyl malonate to different enones was thoroughly studied, and consistently high yields as well as good enantioselectivities

[46] B. Vakulya, S. Varga, A. Csámpai, T. Soós, *Org. Lett.* **2005**, *7*, 1967.

were attainable (Scheme 1.17).[47]

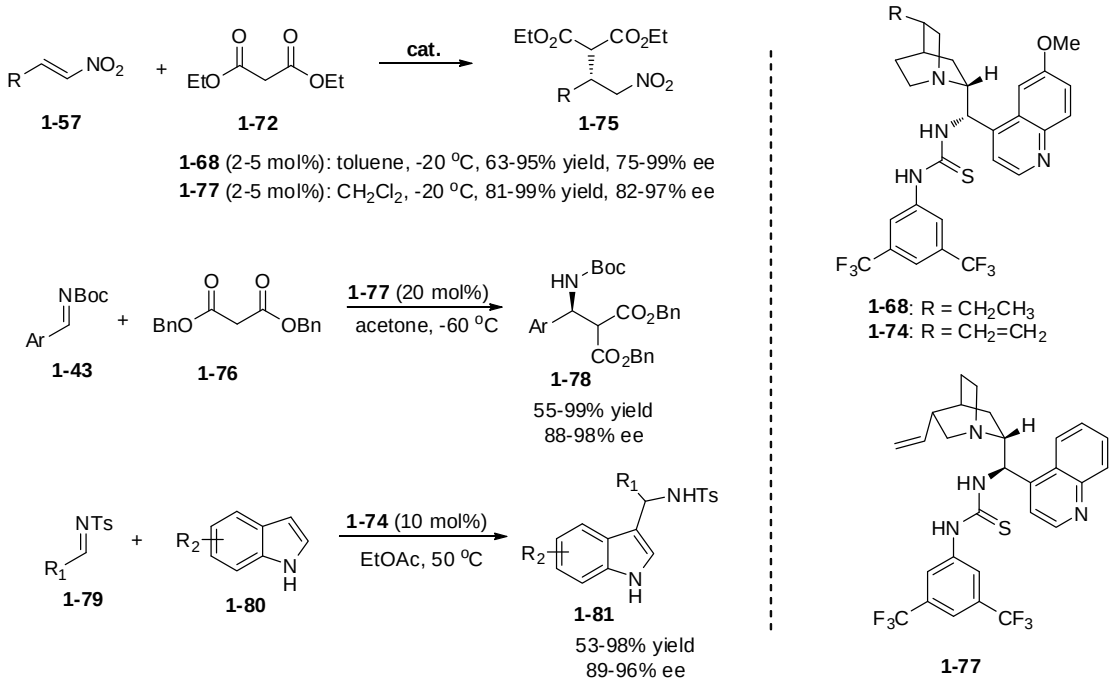


Scheme 1.17 Conjugate addition of malonate ester to enones catalyzed by cinchona alkaloid derived thiourea catalyst

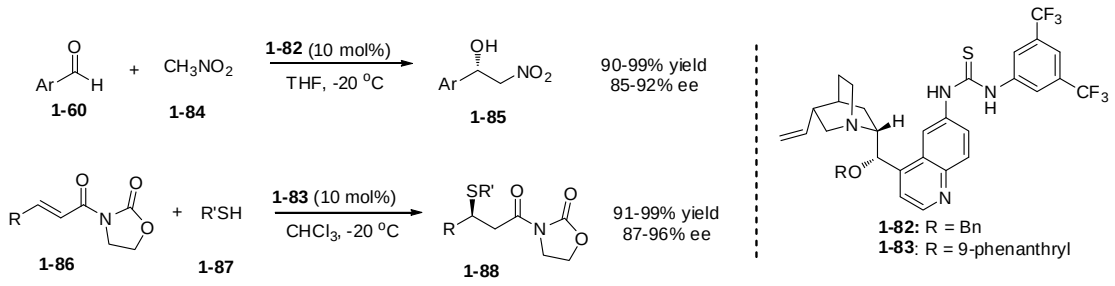
Dixon and Connon independently reported 1,4-addition of malonate esters to nitroolefins with the same catalysts in 2005.[48] One year later, Deng disclosed enantioselective addition of malonate esters and indoles to imines[49] (Scheme 1.18).

Hiemstra and co-workers developed another type of thiourea catalyst from cinchona alkaloid; hydrogen bond donor was placed at the C6' positionby by replacing the phenolic group with a thiourea. Henry reaction between aromatic aldehydes and nitromethane could be protmoted efficiently and high yields and good enantiomeric excesses were obtained (Scheme 1.19).[50] Subsequently, the Deng grioup employed the same catalyst for the asymmetric conjugate addition of simple alkyl thiols to α,β-unsaturated *N*-acylated oxazolidin-2-ones (Scheme 1.19).[51]

[47] J. Wang, H. Li, L. Zu, W. Jiang,, H. Xie, W. Duan, W. Wang, *J. Am. Chem. Soc.* **2006**, *128*, 12652.
[48] a) J. Ye, D. J. Dixon, P. S. Hynes, *Chem. Commun.* **2005**, 4481; b) S. H. McCooey, S. J. Connon, *Angew. Chem. Int. Ed.* **2005**, *44*, 6367.
[49] a) J. Song, Y. Wang, L. Deng, *J. Am. Chem. Soc.* **2006**, *128*, 6048; b) Y.-Q. Wang, J. Song, R. Hong, H. Li, L. Deng, *J. Am. Chem. Soc.* **2006**, *128*, 8156.
[50] T. Marcelli, R. N. S. Haas, J. H. Maarseveen, H. Hiemstra, *Angew. Chem. Int. Ed.* **2006**, *45*, 929.
[51] Y. Liu, B. Sun, B. Wang, M. Wakem, L. Deng, *J. Am. Chem. Soc.* **2009**, *131*, 418.



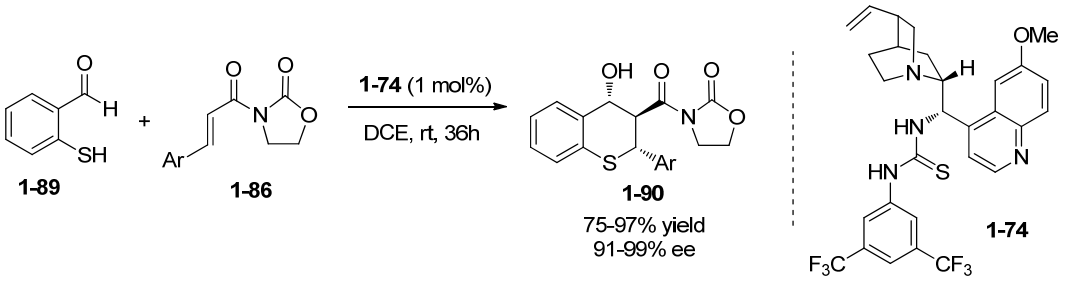
Scheme 1.18 Various reactions catalyzed by cinchona alkaloid derived thiourea catalyst



Scheme 1.19 A new type of cinchona alkaloid derived thiourea catalyst and application

The cinchona alkaloid derived thiourea catalysts were also efficient in the domino type reactions. In an example reported by Wang *et al.* in 2007, bifunctional thiourea catalyst **1-74** was shown to effectively promote the cascade Michael–aldol reaction between 2-mercaptobenzaldehyde and α,β-unsaturated oxazolidinones.[52] In the presence of only 1 mol % catalyst, the product was formed as a single diastereoisomer and with excellent enantioselectivity (Scheme 1.20).

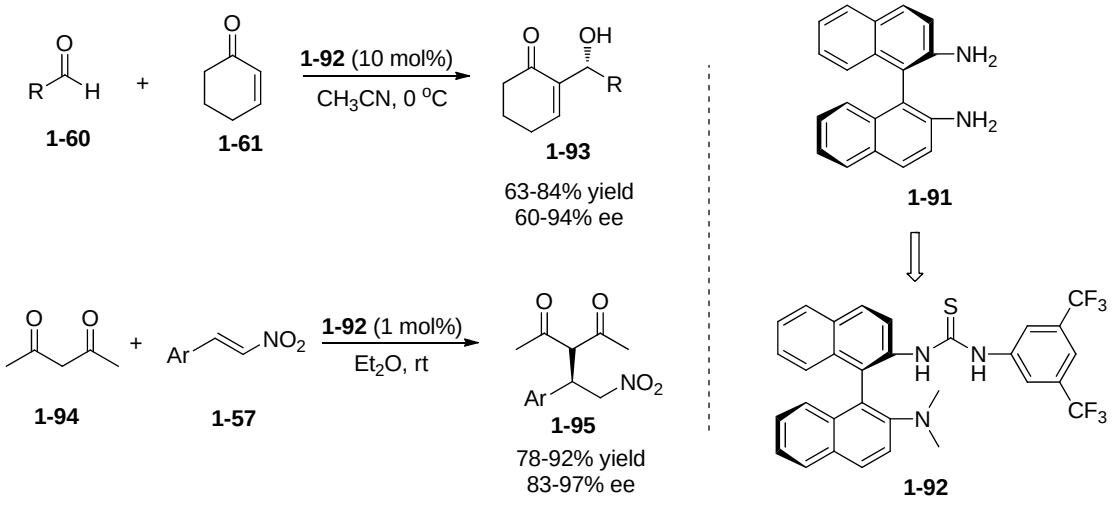
[52] L. Zu, J. Wang, H. Li, H. Xie, W. Jiang, W. Wang, *J. Am. Chem. Soc.* **2007**, *129*, 1036.



Scheme 1.20 Cinchona alkaloid derived thiourea catalyst mediated cascade reaction

1.2.2.3 Binaphthyl Derived Thiourea/Urea Organocatalysts

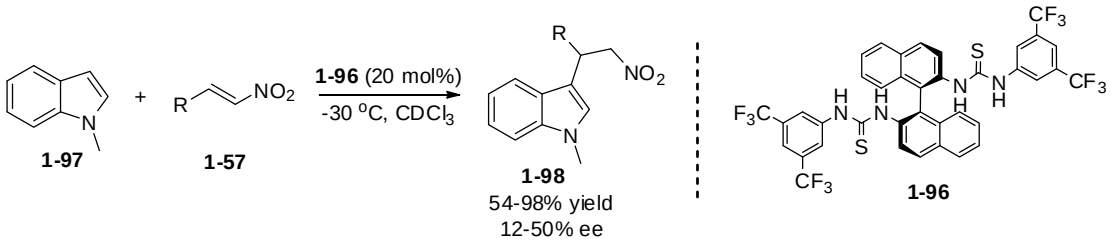
As one of the best chiral scaffolds in the design of chiral ligands, binaphthyl derivatives were well studied in metal based asymmetric catalysis. However, their application as chiral motifs for construction of organic thiourea/urea catalysts was only explored recently. In 2005, Wang and co-workers devised novel chiral amine-thiourea bifucntional catalysts **1-92** from (*R*)-binaphtyl diamine **1-91**, which was demonstrated to promote the asymmetric MBH reactions of cyclohexenone with a variety of aldehydes..[53] Catalyst **1-92** was also found to be useful in enantioselective Michael addition of 2,4-pentadione to nitroolefins (Scheme 1. 21).[54]



Scheme 1.21 Binaphthyl derived thiourea amine catalyst

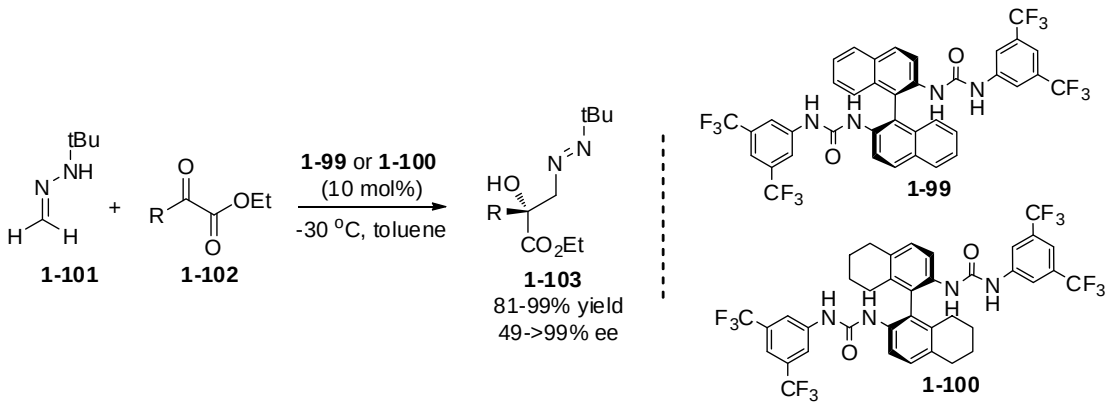
[53] J. Wang, H. Li, X. Yu, L. Zu, W. Wang, *Org. Lett.* **2005**, *7*, 4293.
[54] J. Wang, H. Li, W. Duan, L. Zu, W. Wang, *Org. Lett.* **2005**, *7*, 4713.

Application of binaphthyl derived bis-thiourea catalyst as organocatalyst was also investigated. Conon *et al.* utilized catalyst **1-96** to the asymmetric Friedel–Crafts addition of *N*-methyl indole to nitroolefins.[55] Although only low enantioselectivity (up to 50% ee) was obtained, high reactivity was observed, and the application of this type catalyst as a new chiral Lewis acid catalyst was demonstrated (Scheme 1.22).



Scheme 1.22 Binaphthyl derived bis-thiourea catalyst mediated Friedel–Crafts reaction

The value of bis-urea catalyst was demonstrated very recently in asymmetric formal carbonyl-ene reaction. The binaphthyl derived bis-urea **1-99** and **1-100** allowed highly enantioselective addition of *tert*-butyl hydrazone to aromatic α-ketoesters for the synthesis of densely functionalized tertiary carbinols (Scheme 1.23).[56]



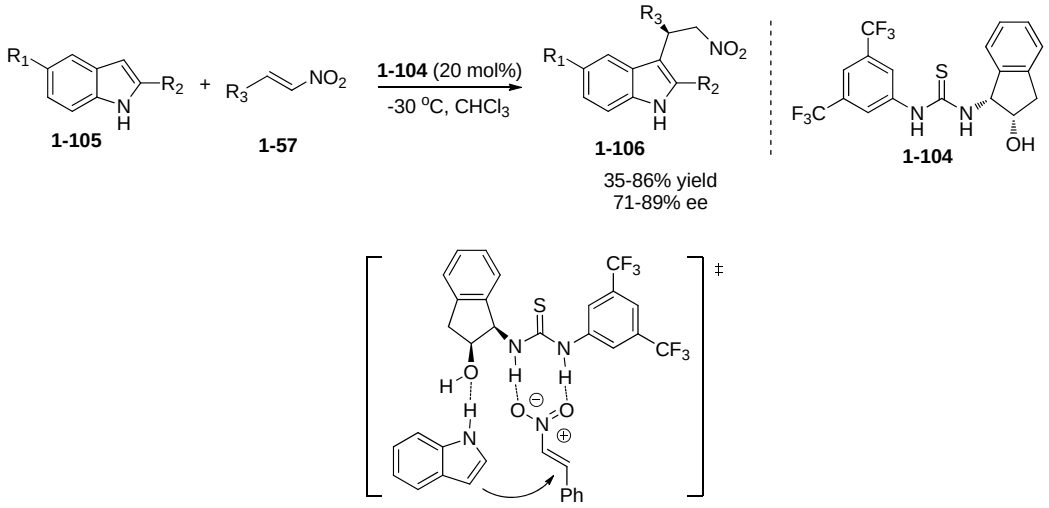
Scheme 1.23 Binaphthyl derived bis-urea catalyst mediated formal carbonyl-ene reaction

[55] E. M. Fleming, T. Macabe, S. J. Connon, *Tetrahedron Lett.* **2006**, *47*, 7073.
[56] A. Crespo-Peña, D. Monge, E. Martín-Zamora, E. Álvarez, R. Fernández, J. M. Lassaletta, *J. Am. Chem. Soc.* **2012**, *134*, 12912.

1.2.2.4 Indane Derived Thiourea/Urea Organocatalysts

Chiral indane amino alcohol is another useful structure employed in the design of organocatalysts. In 2005, novel indane thiourea catalysts were introduced by Ricci's group *via* simple derivatization of commercially available chiral indane amino alcohols. The hydrogen bonding interactions between thiourea and nitro group as well as free alcohol and indole proton were proved to be crucial for the observed high reactivity and selectivity (Scheme 1.24).[57]

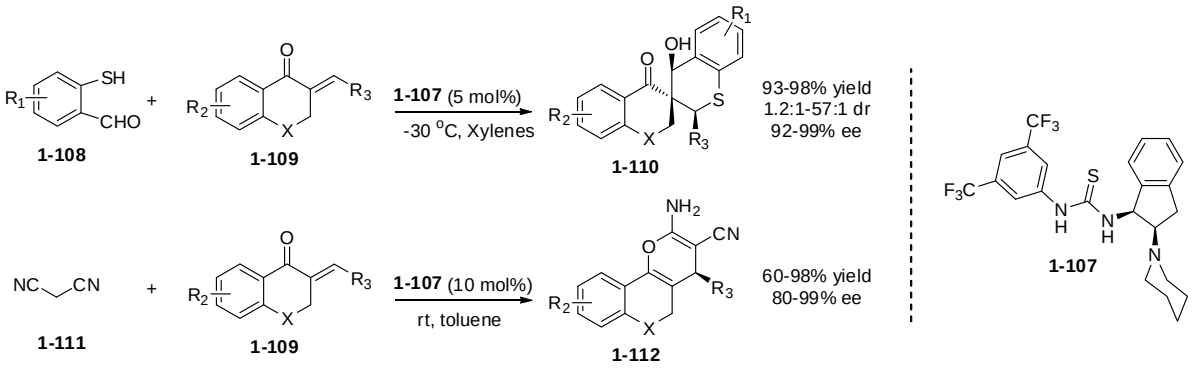
Recently, Wang and co-workers developed a series of chiral indane amino alcohol derived tertiary amine thiourea catalysts. These catalyst were found superior to other traditional bifunctional catalysts in the domino reactions of benzylidenechroman-4-ones with 2-mercaptobenzaldehydes, **1-107** showed the best selectivity and afford spiro chromanone-thiochroan complexes with high yields and excellent selectivities (Scheme 1.25).[58]



Scheme 1.24 Chiral indane thiourea catalyst mediated Friedel–Crafts reaction

[57] R. P. Herrera, V. Sgarzani, L. Bernardi, A. Ricci, *Angew. Chem. Int. Ed.* **2005**, *44*, 6576.
[58] Y. Gao, Q. Ren, H. Wu, M. Li, J. Wang, *Chem. Commun.* **2010**, *46*, 9232.

Subsequent study of the same group showed that indane amino thiourea **1-107** was also the most efficient catalyst in the cascade Micheal-oxa-Michael-tautomerization reactions of malononitrile to enones, the densely functionalized chiral pyranochromenes were obtained in high yields and with high to excellent enantioselectivities (up to 99% ee) (Scheme 1.25).[59]



Scheme 1.25 Wang's chiral indane tertiary amine thiourea catalyst

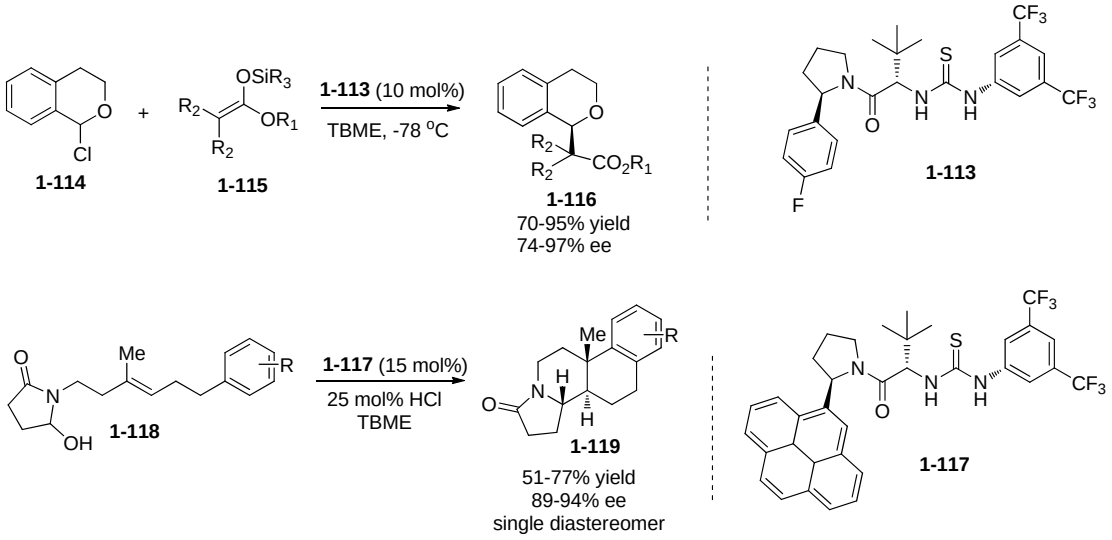
1.2.2.5 Amino Acids Derived Thiourea/Urea Organocatalysts

Amino acids are arguably the most abundant chiral compounds from the existing chiral pools, and the revival of organocatalysis could also be attributed to L-proline mediated enamine catalysis. As one of the privileged scaffold, the amino acids derived thiourea/urea system was also investigated in recent years.

Jacobsen and co-workers developed the thiourea amide catalysts from unnatural amino acid L-*tert*-leucine, these catalysts were successfully applied in the enantioselective additions to oxocarbenium ions and cationic polycyclization reaction (Scheme 1.26). It is believed the anion binding ability of thiourea group and cation-π interactions from the aromatic moiety of catalyst are essential for the

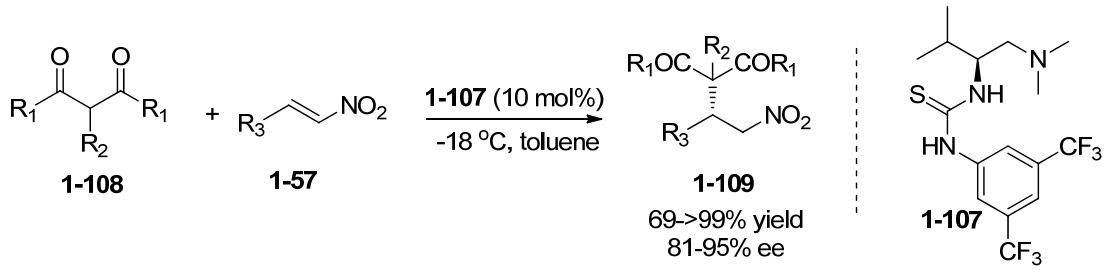
[59] Q. Ren, Y. Gao, J. Wang, *Chem. Eur. J.* **2010**, *16*, 13594.

observed high enantioselectivities.[60]



Scheme 1.26 Jacobsen's thiourea catalyzed reactions of cationic species

In 2008, Pedrosa first disclosed amino acids based thiourea tertiary amine catalysts. A series of bifunctional amino thiourea/urea catalysts were prepared from amino acids, and L-valine derived catalyst **1-107** was identified as one of the best catalysts to promote the asymmetric nitro-Michael reaction of malonates and diketones (Scheme 1.27).[61]

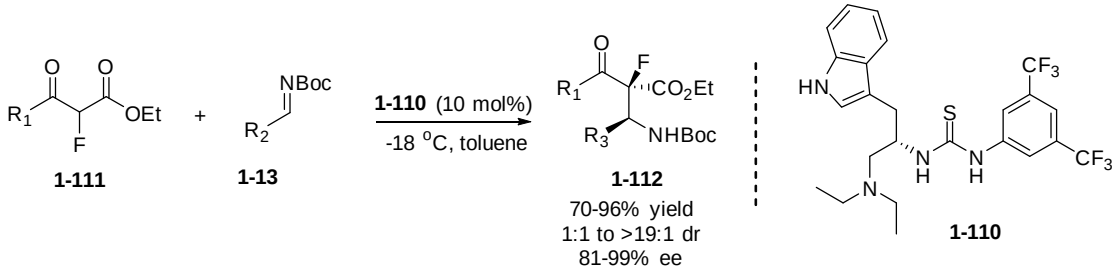


Scheme 1.27 L-Valine derived bifunctional thiourea catalyst

In the following year, our group developed a tryptophan derived bifunctional

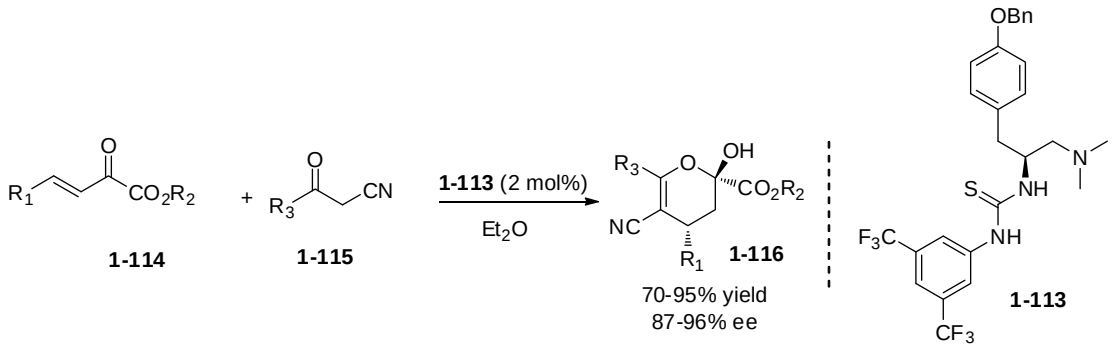
[60] a) S. E. Reisman, A. G. Doyle, E. N. Jacobsen, *J. Am. Chem. Soc.* **2008**, *130*, 7198; b) R. P. Knowles, S. Lin, E. N. Jacobsen, *J. Am. Chem. Soc.* **2010**, *132*, 5030.
[61] J. M. Andrés, R. Manzano, R. Pedrosa, *Chem. Eur. J.* **2008**, *14*, 5116.

thiourea catalyst **1-110** and applied it successfully to the asymmetric Mannich reaction of fluorinated ketoesters (Scheme 1.28). The indole moiety of tryptophan was found to crucial for the observed high selectivity, an additional N–H--O hydrogen bonding interaction was believed to assist the thiourea moiety in binding the ketoenolate.[62]



Scheme 1.28 L-Tryptophan derived bifunctional thiourea catalyst

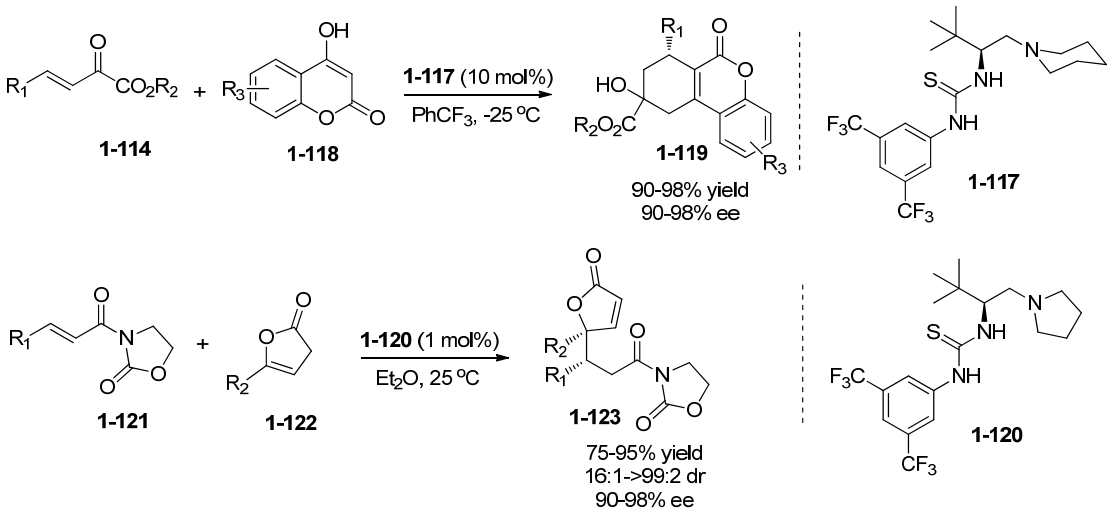
The tyrosine derived amino thiourea catalyst **1-113** was reported by Zhao *et al*., which promoted an asymmetric Michael addition of α-substituted cyano ketones to β,γ-unsaturated α-ketoesters. The desired dihydropyrans were obtained in high yields (up to 95% yield) and with high selectivities (single isomer, up to 96% ee) (Scheme 1.29).[63]



Scheme 1.29 L-Tyrosine derived bifunctional thiourea catalyst

[62] X. Han, J. Kwiatkowski, F. Xue, K.-W. Huang, Y. Lu, *Angew. Chem. Int. Ed.* **2009**, *48*, 7604.
[63] S.-L. Zhao, C.-W. Zheng, H.-F. Wang, G. Zhao, *Adv. Synth. Catal.* **2009**, *351*, 2811.

Other examples of amino acids derived thiourea catalysts include Wang's asymmetric coumarin synthesis[64] and Jiang's asymmetric vinylogous conjugate additions of γ-aryl- and alkyl-substituted butenolides[65] (Scheme 1.30).



Scheme 1.30 L-*tert*-Leucine derived bifunctional thiourea catalyst

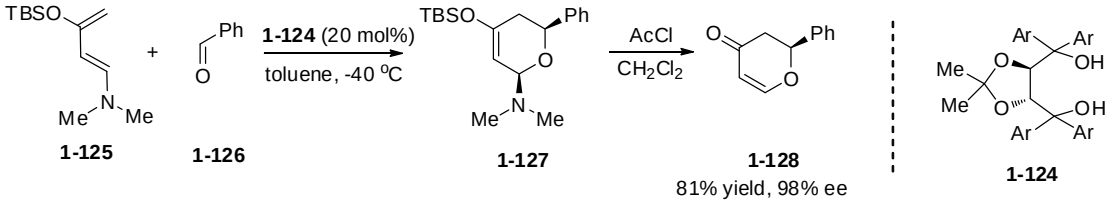
1.2.3 Hydrogen Bonding Organocatalysis Based on Other H-Bond Donors

Hydrogen bonding donors such as alcohols, guanidinium ions, phenols, acids and amides were also intensively investigated in the field of hydrogen bonding based organocatalysis over the past years. In this section, the representative examples will be discussed.

Alcohol is one of the earliest studied hydrogen bond donors in hydrogen bonding based organocatalysis. In 2003, Rawal *et al.* reported a TADDOL-derived **1-124** catalyzed hetero-Diels-Alder reaction of aminosiloxydiene and benzaldehyde, and cycloadduct **1-127** was formed as a single diastereomer. Treatment of **1-127** with AcCl afforded hetero-Diels-Alder product in good yield and with excellent

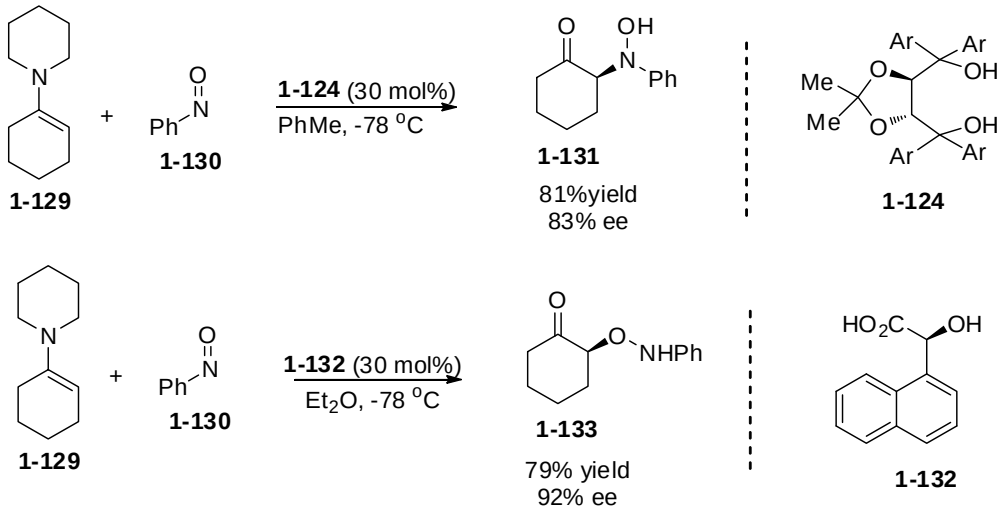
[64] Y. Gao, Q. Ren, L. Wang, J. Wang, *Chem. Eur. J.* **2010**, *16*, 13068.
[65] W. Zhang, D. Tan, R. Lee, G. Tong, W. Chen, B. Qi, K.-W. Huang, C.-H. Tan, Z. Jiang, *Angew. Chem. Int. Ed.* **2012**, *51*, 10069.

enantioselectivity (Scheme 1.31).[66]



Scheme 1.31 TADDOL catalyst and its application in hetero-Diels-Alder reaction

In 2005, the nitroso aldol reaction between nitrosobenzene and enamines catalyzed by TADDOL catalyst was reported by Yamamoto and co-workers, TADDOL catalyst **1-124** gave *N*-Nitroso aldol product in 77-91% ee. Very interestingly, *O*-Nitroso aldol products could also be selectively formed when the reactions were performed by using glycolic acid alcohol **1-132** as the catalyst (Scheme 1.32).[67]

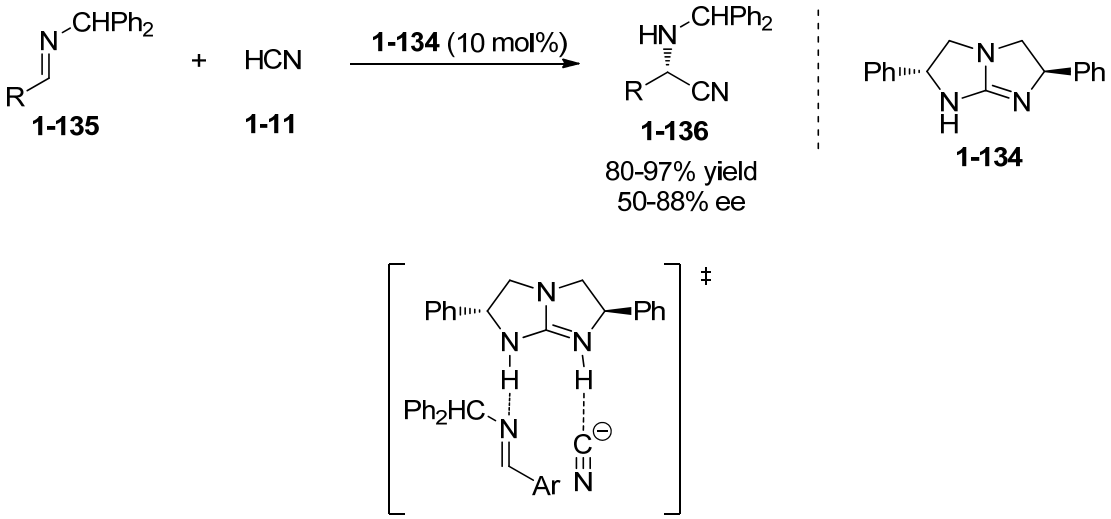


Scheme 1.32 Nitroso aldol reaction of enamine

Guanidinium ions represent another important class of hydrogen bonding donor.

[66] Y. Huang, A. K. Unni, A. N. Thadani, V. H. Rawal, *Nature* **2003**, *424*, 146.
[67] N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* **2005**, *127*, 1080.

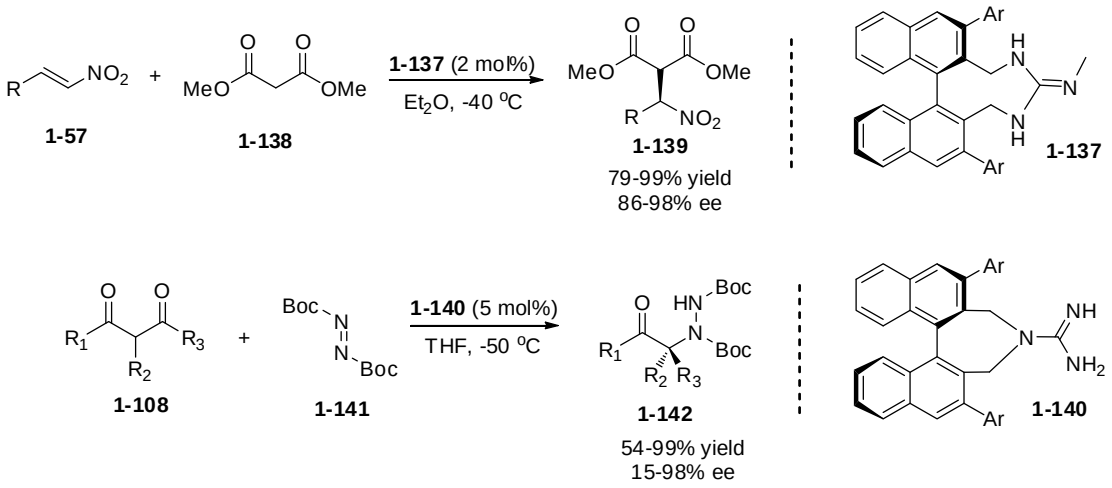
In 1999, Corey first disclosed a C_2-symmetric guanidine catalyst **1-134** and applied it in Strecker reaction of imine, and (*S*)-amino nitriles were obtained in high yields and with good nantioselectivities. In the proposed transitional state, a guanidinium cyanide salt was believed to provide hydrogen bonding interactions to activate the aldimine (Scheme 1.33).[68]



Scheme 1.33 Corey's chiral guanidine catalyst

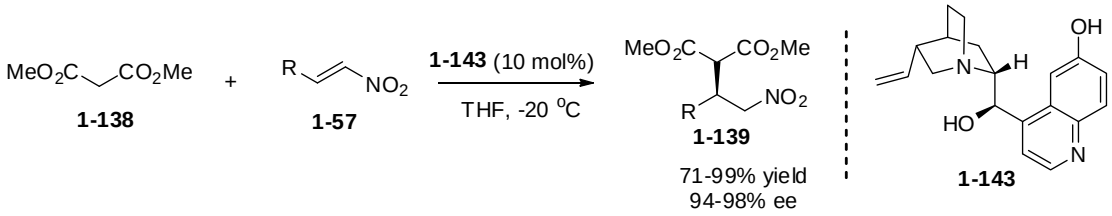
Guanidines derived from binaphthyl were also developed. In 2006, Terada and co-workers designed axially chiral guanidine **1-137**, which was successfully applied to highly enantioselective Michael addition of 1,3-dicarbonyl compounds to nitroolefins. In the same year, the same group developed electrophilic amination reactions of ketoesters and di-ketones catalyzed by axially chiral guanidine **1-140** (Scheme 1.34).[69]

[68] E. J. Coery, M. Grogan, *Org. Lett.* **1999**, *1*, 157.
[69] a) M. Terada, H. Ube, Y. Yaguchi, *J. Am. Chem. Soc.* **2006**, *128*, 1454; b) M. Terada, M. Nakano, H. Ube, *J. Am. Chem. Soc.* **2006**, *128*, 16044.



Scheme 1.34 Binaphthyl derived guanidine catalysts

Strong Brønsted acids are no doubt good hydrogen bonding donors, and chiral catalysts making use of strong Brønsted acids are certainly valuable. In 2004, Deng and co-worekers modified chichona alkaloid and prepared catalyst **1-143**, which effectively promoted asymmetric Michael addition of malonate ester to nitroolefins (Scheme 1.35). Based on the observation that 6'-hydroxyquinoline derived catalysts gave significantly higher reaction rates and enantioselectivities when compared to the corresponding 6'-methoxyquinoline derivative, the authors suggested that the phenolic hydroxyl functioned as a hydrogen bond donor in the organization of the transition state assembly.[70]

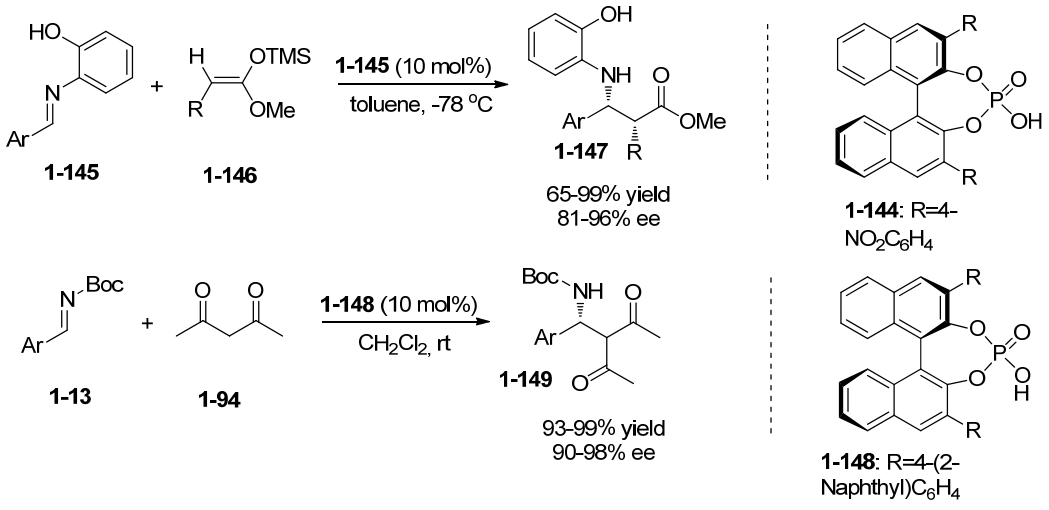


Scheme 1.35 Cinchona alkaloid derivative mediated Michael addition

[70] H. M. Li, Y. Wang, L. Tang, L. Deng, *J. Am. Chem. Soc.* **2004**, *126*, 9906.

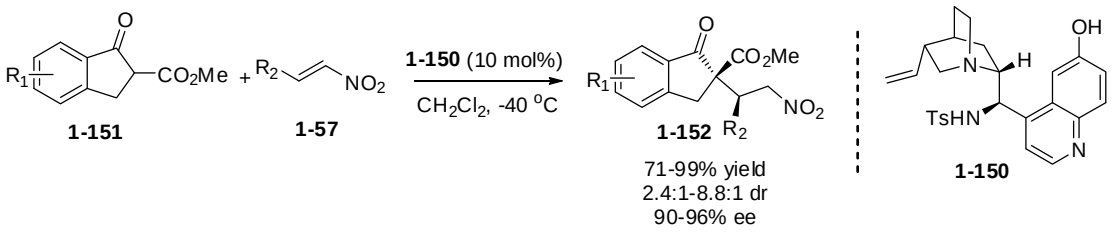
In the same year, Akiyama and Terada independently reported that chiral phosphoric acids could mediate highly enantioselective Mannich reactions. The phosphoric acids were shown to be superior catalysts for Mannich reactions of aldimines with silyl enolates,[71] and acetyl acetone to *N*-Boc-protected arylimines[72] (Scheme 1.36). These seminal contributions demonstrated that modifications on the 3,3'-bisaryl substituents of the catalysts could have immense effects on asymmetric induction, which had opened up a new avenue in catalyst design .

Recently, our group developed the sulfonamide catalysts from the cinchona alkaloid, these catalysts were utilized to promote Michael addition of bicyclic α-substituted β-ketoesters to nitroolefins. The desired Michael adducts with all-carbon quaternary centers were constructed in high yields and with excellent enantioselectivities (Scheme 1.37).[73]



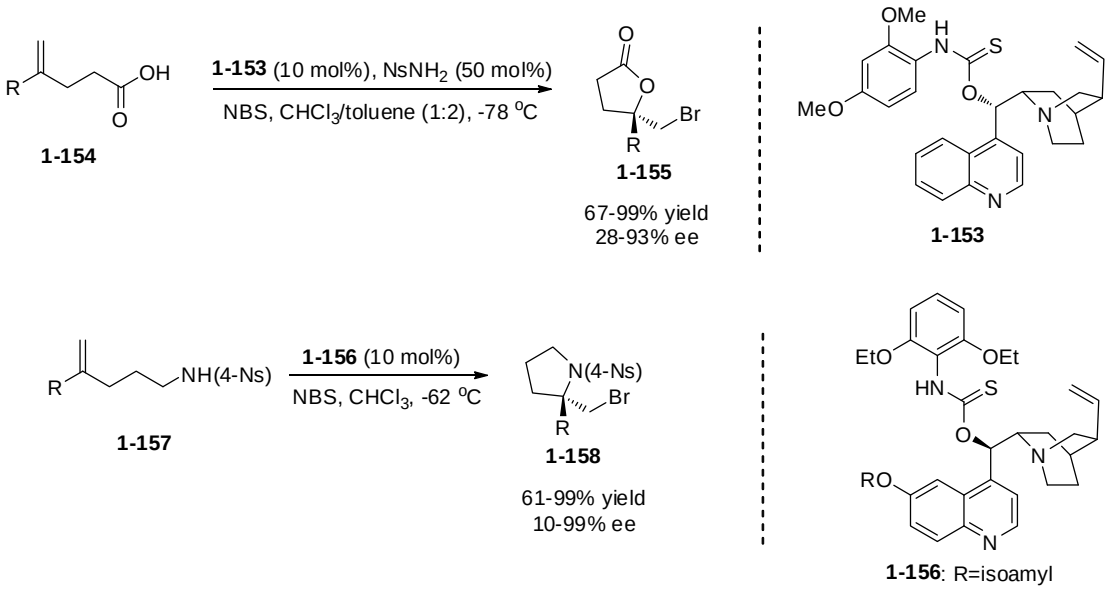
Scheme 1.36 Chiral phosphoric acids mediated Mannich reaction

[71] T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem. Int. Ed.* **2004**, *43*, 1566.
[72] D. Uraguchi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 5356.
[73] J. Luo, L.-W. Xu, R. A. S. Hay, Y. Lu, *Org. Lett.* **2009**, *11*, 437.



Scheme 1.37 Cinchona alkaloid derived sulfonamide catalyst

Catalyst **1-153** with the amino–thiocarbamate moiety as hydrogen bonding donor and sulfur Lewis base was recently designed by Yeung and co-workers. This catalyst was utilized in the bromolactonization of unsaturated carboxylic acids, and γ-lactones were obtained in up to 99% yield and 93% ee.[74] Enantioselective bromoaminocyclization of unsaturated sulfonamides were also efficiently promoted by catalyst **1-156**, and enantioenriched pyrrolidines were obtaind in very high yields and with nearly perfect enantioselectivities[75] (Scheme 1.38).



Scheme 1.38 Amino–thiocarbamate mediated bromocyclization reactions

[74] L. Zhou, C. K. Tan, X. Jiang, F. Chen, Y.-Y. Yeung, *J. Am. Chem. Soc.* **2010**, *132*, 15474.
[75] L. Zhou, J. Chen, C. K. Tan, Y.-Y. Yeung, *J. Am. Chem. Soc.* **2011**, *133*, 9164.

1.3 Project Objectives

The field of hydrogen bonding based organocatalysis has advanced rapidly in the past decade. Particularly, bifunctional and multifunctional organic molecules containing a tertiary amino group and a thiourea moiety are remarkably useful organic catalysts. A wide range of enantioselective transformations were discovered, which provide access to many useful synthetic building blocks.

Natural amino acids are obviously ideal chiral building blocks for design of organocatalysts.[76] Our group has keen interests in designing novel organocatalysts from natural amino acids. In particular, we have successfully uncovered primary amine catalysts and phosphine catalysts that are based on L-threonine, and demonstrated their effectiveness in a number of asymmetric reactions. Some of the catalysts developed by our group are shown in Figure 1.2.[77]

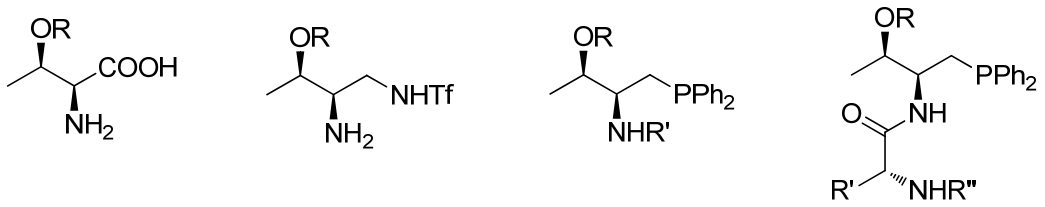


Figure 1.2 Organocatalysts based on L-threonine developed by the Lu group

As a further extension of our L-threonine based organocatalytic systems, the main aim of this project was to design and synthesize bifunctional or multifunctional

[76] For related reviews, see: a) L.-W. Xu, J. Luo, Y. Lu, *Chem. Commun.* **2009**, 1807; b) L.-W. Xu, Y. Lu, *Org. Biomol. Chem.* **2008**, *6*, 2047; c) F. Peng, Z. Shao, *J. Mol. Catal. A* **2008**, *285*, 1; d) E. A. C. Davie, S. M. Mennen, Y. Xu, S. J. Miller, *Chem. Rev.* **2007**, *107*, 5759.

[77] a) L.Cheng, X. Han, H. Huang, M. W. Wong, Y. Lu, *Chem. Commun.* **2007**, 4143; b) L. Cheng, X. Wu, Y. Lu, *Org. Biomol. Chem.* **2007**, *5*, 1018; c) X. Wu, Z. Jiang, H.-M. Shen, Y. Lu, *Adv. Synth. Catal.* **2007**, *349*, 812; d) Q. Zhu, Y. Lu, *Chem. Commun.* **2010**, *46*, 2235; e) X. Han, Y. Wang, F. Zhong, Y. Lu, *J. Am. Chem. Soc.* **2011**, *133*, 1726; f) X. Han, F. Zhong, Y. Wang, Y. Lu, *Angew. Chem. Int. Ed.* **2012**, *51*, 767; g) F. Zhong, Y. Wang, X. Han, K.-W. Huang, Y. Lu, *Org. Lett.* **2011**, *13*, 1310; h) F. Zhong, X. Han, Y. Wang, Y. Lu, *Angew. Chem. Int. Ed.* **2011**, *50*, 7873; i) F. Zhong, X. Han, Y. Wang, Y. Lu, *Chem. Sci.* **2012**, *3*, 1231; j) F. Zhong, J. Luo, G.-Y. Chen, X. Dou, Y. Lu, *J. Am. Chem. Soc.* **2012**, *134*, 10222; k) F. Zhong, X. Dou, X. Han, W. Yao, Q. Zhu, Y. Meng, Y. Lu, *Angew. Chem. Int. Ed.* **2013**, *52*, 943.

tertiary amine thiourea catalysts that are based on privileged L-threonine structure, and employ them in the enantioselective synthesis of biologically useful furan and oxindole derivatives. We will demonstrate in the following Chapters that different types of bifunctional or multifunctional L-threonine-based catalysts are superior to many tertiary amine thiourea catalysts reported in the literature, and our methods represent novel enantioselective preparations of chiral 3-2(*H*)-furanones, 2,3-dihydrofurans, 3-spirocyclopropyl-2-oxindoles and different 3-heteroatom-substituted oxindoles.

Chapter 2 From the Feist-Bénary Reaction to Organocatalytic Domino Michael-Alkylation Reactions: Asymmetric Synthesis of 3(2*H*)-Furanones

2.1 Introduction

3(2*H*)-Furanones are well known as basic structural motifs of many natural products and medicinally important agents (Figure 2.1).[1] Over the past few decades, a number of approaches toward the synthesis of 3(2*H*)-furanones have been established, including: metal-mediated cyclizations of alkynyl substrates,[2] transformations from furans,[3] cyclization of dienes or alkynes[4] and cycloisomerization of allenes.[5] However, most of the above reactions required the employment of specific substrates, and the reaction conditions were often harsh. Moreover, to the best of our knowledge, an organocatalytic asymmetric synthesis of chiral furanone derivatives has not been reported to date. Thus, there clearly exists a need to devise an efficient and mild

[1] a) For recent review: T. T. Haug, S. F. Kirsch, *Targets in Heterocyclic Syntems, vol.13* (Ed.: O. A. Attanasi, D. Spinelli), Royal Society of Chemistry, London, **2009**, p. 57; b) S. M. Kupchan, C. W. Sigel, M. J. Matz, C. J. Gilmore, R. F. Bryan, *J. Am. Chem. Soc.* **1976**, *98*, 2295; c) A. B. Smith, III, M. A. Guaciaro, S. R. Schow, P. M. Wovkulich, B. H. Toder, T. W. Hall, *J. Am. Chem. Soc.* **1981**, *103*, 219; d) P. K. Chowdhury, R. P. Sharma, G. Thyagarajan, *J. Org. Chem.* **1980**, *45*, 4993; e) R. A. Mack, W. I. Zazulak, L. A. Radov, J. E. Baer, J. D. Stewart, P. H. Elzer, C. R. Kinsolving, V. S. Gerrgiev, *J. Med. Chem.* **1988**, *31*, 1910; f) K. Takao, H. Ochiai, K. Yoshida, T. Hashizuka, H. Koshimura, K. Tadano, S. Ogawa, *J. Org. Chem.* **1995**, *60*, 8179; g) G. Comte. D. P. Allais, A. J. Chulia, *Tetrahedron Lett.* **1996**, *37*, 2995; h) R. J. M. Goss, J. Fuchser, D. O'Hagan, *Chem. Commun.* **1999**, 2255; i) P. G. Steel, *Chem. Commun.* **1999**, 2257; i) K. C. Nicolaou, D. Sarlah, D. M. Shaw, *Angew. Chem. Int. Ed.* **2007**, *46*, 4708.

[2] a) H. Saimoto, T. Hiyama, H. Nozaki, *J. Am. Chem. Soc.* **1981**, *103*, 4975; b) Y. Liu, M. Liu, S. Guo, H. Tu, Y. Zhou, H. G, *Org. Lett.* **2006**, *8*, 3445; c) S. F. Kirsch, J. T. Binder, C. Liébert, H. Menz, *Angew. Chem. Int. Ed.* **2006**, *45*, 5878; d) B. Crone, S. F. Kirsch, *J. Org. Chem.* **2007**, *72*, 5435; e) M. Egi, K. Azechi, M. Saneto, K. Shimizu, S. Akai, *J. Org. Chem.* **2010**, *75*, 2123.

[3] a) D. W. Henry, R. M. Silverstein, *J. Org. Chem.* **1966**, *31*, 2391; b) R. Antonioletti, F. Bonadies, T. Prencipe, A. Scettri, *J. Chem. Soc. Chem. Commun.* **1988**, 850.

[4] a) P. Langer, T. Krummel, *Chem. Commun.* **2000**, 967; b) P. Langer, T. Krummel, *Chem. Eur. J.* **2001**, *7*, 1720; c) C. M. Marson, E. Edaan, J. M. Morrell, S. J. Coles, M. B. Hursthouse, D. T. Davies, *Chem. Commun.* **2007**, 2494; e) B. A. Trofimov, O. A. Shemyakina, A. G. Mal'kina, I. A. Ushakov, O. N. Kazheva, G. G. Alexandrov, O. A. Dyachenko, *Org. Lett.* **2010**, *12*, 3200.

[5] M. Poonoth, N. Krause, *J. Org. Chem.* **2011**, *76*, 1934

synthetic strategy to access this important class of compounds in optically enriched form.

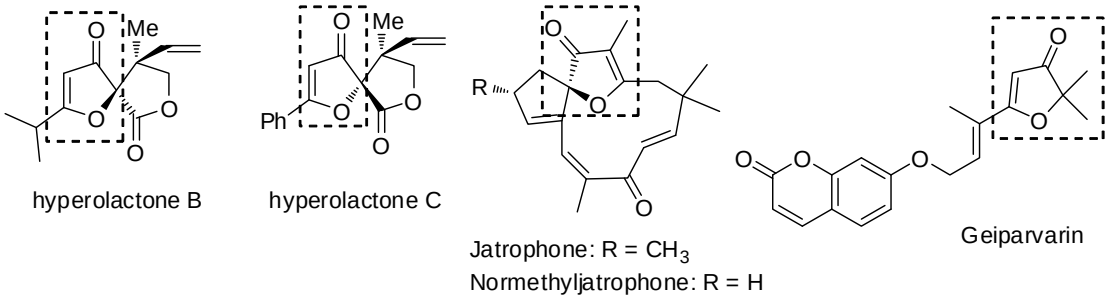
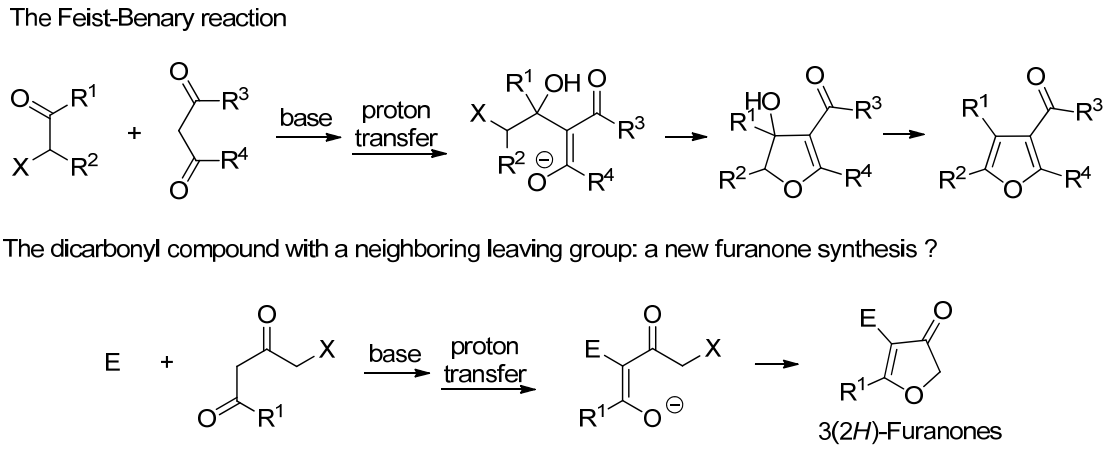


Figure 2.1 Natural products containing a 3(2*H*)-furanone motif

The Feist–Bénary reaction is a base-catalyzed condensation between α-halogen ketones and β-dicarbonyl compounds for the preparation of substituted furans.[6] The Feist–Bénary synthesis can also be viewed as a domino aldol–alkylation reaction, in which the ketone electrophile plays a key role in the proton transfer, and the presence of halogen atom is crucial for the cyclization step. Except its application in furan synthesis, this name reaction was considerly less explored. We envisioned that a modified Feist–Bénary reaction employing other reaction partners may provide a new route for thesis of some interesting furan derivatives. Since furanones are furan derivatives, a modified Feist–Bénary reaction that can provide a straightforward method for the synthesis of furanones became our interest. By employing a γ-halogenated-β-dicarbonyl compound and a suitable electrophile, a modified

[6] a) F. Feist, *Chem. Ber.* **1902**, *35*, 1537; b) E. Bénary, *Chem. Ber.* **1911**, *44*, 489. For recent selected examples, see: c) M. A. Calter, R. M. Phillips, C. Flaschenriem, *J. Am. Chem. Soc.* **2005**, *127*, 14566; d) E. Holtz, P. Langer, *Synlett* **2004**, 1805; e) G. Mross, E. Holtz, P. Langer, *J. Org. Chem.* **2006**, *71*, 8045.

Feist–Bénary reaction via a Michael–alkylation cascade sequence[7] is anticipated to generate 3(2*H*)-furanones (Scheme 2.1).



Scheme 2.1 Synthesis of furanones through a modified Feist–Bénary reaction

2.2 Results and Discussion

2.2.1 Catalyst Design and Synthesis

Our group has been investigating amino acid-based asymmetric organocatalysis in the past few years, and asymmetric amino catalysis and asymmetric phosphine catalysis based on different amino acids have been established as powerful and versatile tools in asymmetric synthesis.[8] In our previous studies, L-threonine based catalysts[9] showed to be previliged among all the natural amino acids tested due to its unique stucuture. To further expand the L-threonine-based asymmetric organocatalysis system, we were interested in establishing novel bifunctional

[7] For recent reviews on asymmetric domino reactions, see: a) D. J. Ramón, M. Yus, *Angew. Chem. Int. Ed.* **2005**, *44*, 1602; b) D. Tejedor, D. G. Cruz, A. S. Expósito, J. J. M. Tellado, P. D. Armas, F. G. Tellado, *Chem. Eur. J.* **2005**, *11*, 3502; c) H.-C. Guo, J.-A. Ma, *Angew. Chem. Int. Ed.* **2006**, *45*, 354; d) H. Pellissier, *Tetrahedron* **2006**, *62*, 2143; e) D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem. Int. Ed.* **2007**, *46*, 1570; f) G. Guillena, D. J. Ramón, M. Yus, *Tetrahedron: Asymmetry* **2007**, *18*, 693; g) C. J. Chapman, C. G. Frost, *Synthesis* **2007**, *1*, 1; h) X. Yu, W. Wang, *Org. Biomol. Chem.* **2008**, *6*, 2037; i) C. Grondal, M. Jeanty, D. Enders, *Nature Chem.* **2010**, *2*, 167.

[8] For reviews on asymmetric catalysis mediated by amino acids, see: a) L.-W. Xu, J. Luo, Y. Lu, *Chem. Commun.* **2009**, 1807; b) L.-W. Xu, Y. Lu, *Org. Biomol. Chem.* **2008**, *6*, 2047; c) E. A. C. Davie, S. M. Mennen, Y. Xu, S. J. Miller, *Chem. Rev.* **2007**, *107*, 5759.

[9] see Chapter 1, ref 77.

tertiary amine thiourea catalysts based on L-threonine scaffold. We envisioned that novel bifunctional tertiary amine thiourea catalysts can be easily derived from L-threonine, and the catalyst design is ilustrated in Figure 2.2. Simple transformations convert the acid group into a tertiary amine, and the thiourea site for the bifunctional catalysts can be easily derived from the amine moiety. Proper selection of protecting groups on the hydroxy moiety then provides steric tuning to the structures of the catalysts. Using L-threonine as starting chiral source, bifunctional tertiary amine thiourea catalysts **2-8a** and **2-8b** were prepared through several steps transformations.

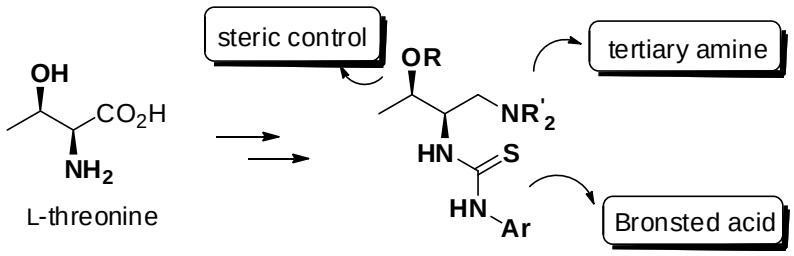


Figure 2.2 Novel bifunctional tertiary amine thiourea catalysts based on L-threonine

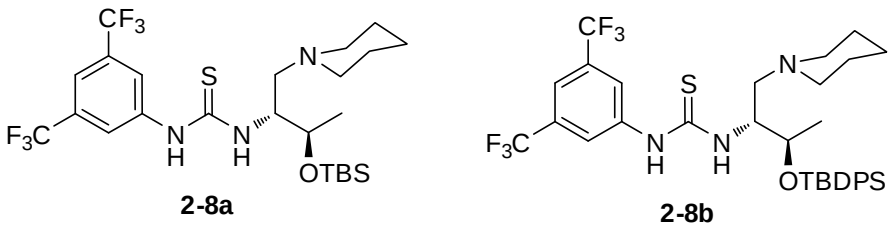
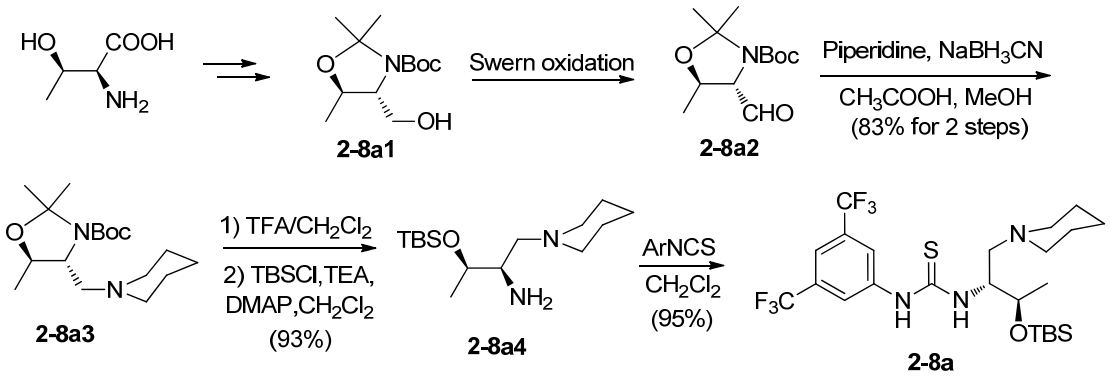


Figure 2.3 Structures of bifunctional catalysts synthesized from L-threonine

Synthetic route for bifunctional tertiary amine thiourea **2-8a** from L-threonine is illustrated in Scheme 2.2. Alcohol **2-8a1**[10] was oxidized to aldehyde **2-8a2** *via* Swern oxidation. Subsequent reductive amination yielded tertiary amine **2-8a3**, which

[10] K. Kawamura, H. Fukuzawa, M. Hayashi, *Org. Lett.* **2008**, *10*, 3509.

underwent subsequent deprotection and selective protection of hydroxy group to afford primary amine **2-8a4**. Catalyst **2-8a** was prepared upon reaction of **2-8a4** with the corresponding isothiocyanate.



Scheme 2.2 Synthetic route for preparation of catalyst **2-8a**

2.2.2 Reaction Optimization

To test the feasibility of our proposal for the synthesis of 3(2*H*)-furanones, we chose nitroolefins as potential electrophiles, since they are readily available and versatile electrophiles in the conjugate addition.[11] For the selection of the catalysts, except the novel L-threonine-derived bifunctional catalysts, we also tested other bifunctional amino catalysts containing a Brønsted acid moiety;[12] promotion of the modified Feist–Bénary reaction could be realized through the interactions of the

[11] For selected examples of Michael reaction between β-dicarbonyl compound and nitroolefin, see: a) J. Ji, D. M. Barnes, J. Zhang, S. A. King, S. J. Steven, H. E. Morton, *J. Am. Chem. Soc.* **1999**, *121*, 10215; b) D. M. Barnes, J. Ji, M. G. Fickes, M. A. Fitzgerald, S. A. King, H. E. Morton, F. A. Fpagge, M. Preskill, S. H. Wagaw, S. J. Wittenberger, J. Zhang, *J. Am. Chem. Soc.* **2002**, *124*, 13097; c) T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672; d) H. Li, Y. Wang, L. Tang, L. Deng, *J. Am. Chem. Soc.* **2004**, *126*, 9906; e) S. H. McCooey, S. J. Connon, *Angew. Chem. Int. Ed.* **2005**, *44*, 6367; f) T. Okino, Y. Hoashi, T. Furukawa, X. Xu, Y. Takemoto, *J. Am. Chem. Soc.* **2005**, *127*, 119; g) D. A. Evans, D. Seidel, *J. Am. Chem. Soc.* **2005**, *127*, 9958; h) M. Terada, H. Ube, Y. Yaguchi, *J. Am. Chem. Soc.* **2006**, *128*, 1454; i) C.-J. Wang, Z.-H. Zhang, X.-Q. Dong, X.-J. Wu, *Chem. Commun.* **2008**, 1431; j) H. Li, S. Zhang, C. Yu, X. Song, W. Wang, *Chem. Commun.* **2009**, 2136; k) Z. Yu, X. Liu, L. Zhou, L. Lin, X. Feng, *Angew. Chem. Int. Ed.* **2009**, *48*, 5195; l) Q. Zhu, H. Huang, D. Shi, Z. Shen, C. Xia, *Org. Lett.* **2009**, *11*, 4536.

[12] For reviews, see: a) P. R. Schreiner, *Chem. Soc. Rev.* **2003**, *32*, 289; b) M. S. Taylor, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2006**, *45*, 1520; c) T. Akiyama, J. Itoh, K. Fuchibe, *Adv. Synth. Catal.* **2006**, *348*, 999; d) X. Yu, W. Wang, *Chem. Asian J.* **2008**, *3*, 516; f) S. J. Connon, *Chem. Commun.* **2008**, 2499; g) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713.

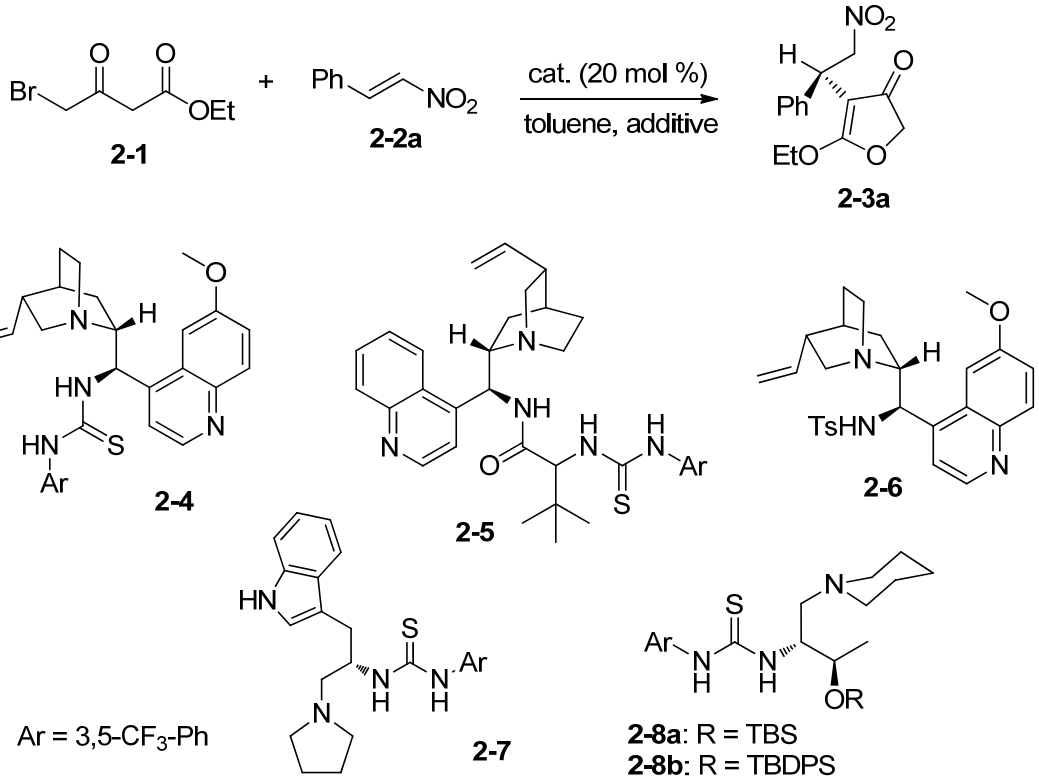
catalysts with both substrates in a cooperative manner. The domino reaction between ethyl 4-bromoacetoacetate **2-1** and nitrostyrene **2-2a** was selected as a model reaction, and the results are summarized in Table 2.1.

When quinidine-derived tertiary amine-thiourea catalyst **2-4** was used, the reaction proceeded with very low conversion (entry 1). This result is not surprising, and it suggested that the catalyst was probably quenched by HBr generated during the reaction. To circumvent this problem, we next introduced a stoichiometric amount of base as an additive to capture HBr released. The inclusion of Et_3N or K_2CO_3 into the reaction system proved to be beneficial, the desired products were obtained in very high yields, however, the enantioselectivities were very poor (entries 2–3). Suspecting the above bases were strong enough to induce undesired background reactions, $(NH_4)_2CO_3$ was then introduced as a HBr scavenger. Gratifyingly, the desired furanone **2-3a** was obtained in good yield and with moderate enantioselectivity in the presence of $(NH_4)_2CO_3$ (entry 4). To further improve the enantioselectivity of the reaction, we turned our attention to different types of tertiary amine-thiourea catalysts with an amino acid structural scaffold, including our group recently developed tryptophan-derived tertiary amine-thiourea catalysts[13] and amino acid-incorporating trifunctional catalysts.[14] While cinchonidine-derived multifunctional catalyst **2-5** and quinidine-derived sulfonamide[15] **2-6** gave moderate enantioselectivity (entries 5–6), tryptophan-based **2-7** turned out to be an excellent

[13] a) X. Han, J. Kwiatkowski, F. Xue, K.-W. Huang, Y. Lu, *Angew. Chem. Int. Ed.* **2009**, *48*, 7604; b) J. Luo, H. Wang, X. Han, L.-W. Xu, J. Kwiatkowski, K.-W. Huang, Y. Lu, *Angew. Chem. Int. Ed.* **2011**, *50*, 1861.
[14] Q. Zhu, Y. Lu, *Angew. Chem. Int. Ed.* **2010**, *49*, 7753.
[15] J. Luo, L.-W. Xu, R. A. S. Hay, Y. Lu, *Org. Lett.* **2009**, *11*, 437.

catalyst, furnishing the desired product with very good enantioselectivity (entry 7). Gratifyingly, L-threonine-derived tertiary amine–thiourea catalysts **2-8** proved to be the most efficient catalysts, and the desired 3(2*H*)-furanones **2-3a** was obtained in excellent yield and with very high enantioselectivity (entries 8–9).

Table 2.1 Domino Michael–Alkylation Reaction for the Synthesis of 3(2*H*)-Furanone **2-3a**[a]



entry	cat.	additive	t (h)	yield (%)[b]	ee (%)[c]
1	**2-4**	none	24	<10	-
2	**2-4**	Et_3N	0.5	95	-10
3	**2-4**	K_2CO_3	1	86	-16
4	**2-4**	$(NH_4)_2CO_3$	16	73	-65
5	**2-5**	$(NH_4)_2CO_3$	8	82	75
6	**2-6**	$(NH_4)_2CO_3$	24	60	-61
7	**2-7**	$(NH_4)_2CO_3$	24	84	95

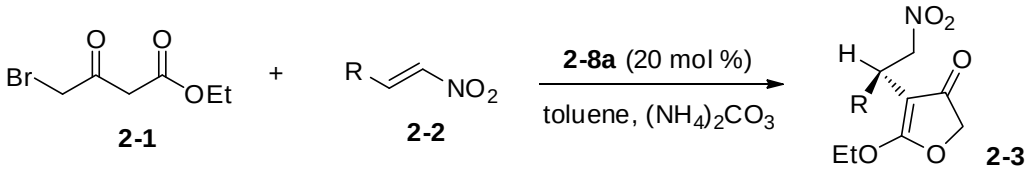
8	**2-8a**	$(NH_4)_2CO_3$	24	90	90
9	**2-8b**	$(NH_4)_2CO_3$	24	85	90

[a] Reactions were performed with **2-1** (0.05 mmol), **2-2a** (0.05 mmol), the additive (0.05 mmol) and the catalyst (0.01 mmol) in toluene (0.5 mL) at room temperature. [b] Isolated yield. [c] Determined by HPLC analysis on a chiral stationary phase.

2.2.3 Substrate Scope

The substrate scope for this novel domino Michael–alkylation reaction was subsequently examined (Table 2.2). Consistently high yields and excellent enantioselectivities were observed for a wide range of aryl nitroolefins (entries 1–10). Nitroolefins with different halide substitutions, substitution groups with different electronic properties and subsitution positions were all well tolerated (entries 2–8). Furyl and thienyl substituted nitroolefins could also be employed (entries 9–10). Moreover, alkyl nitroolefins were also suitable substrates, and high yields and ee values were attainable (entries 11–13). The absolute configurations of the 3(2*H*)-furanones were determined on the basis of the X-ray crystal structure of **2-3d**.

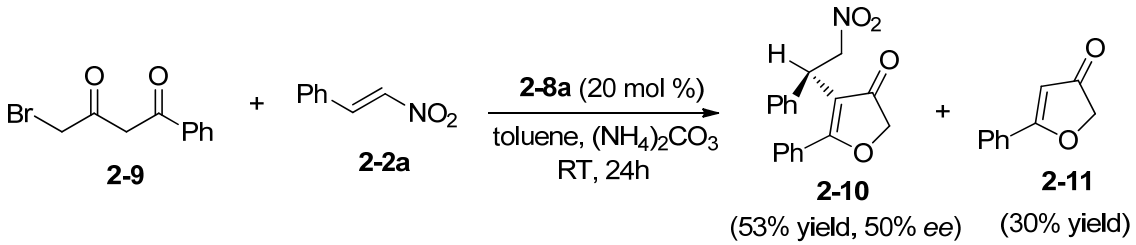
Table 2.2 Enantioselective Synthesis of 3(2*H*)-Furanones *via* a **2-8a**-Catalyzed Domino Michael–Alkylation Reaction[a]



entry	product (R)	t (h)	yield (%)[b]	ee (%)[c]
1	**2-3a** (C_6H_5)	24	90	90
2	**2-3b** (2-F-C_6H_4)	24	89	94
3	**2-3c** (2-Cl-C_6H_4)	24	88	96

4	**2-3d** (2-Br-C_6H_4)	24	83	96
5	**2-3e** (2-Me-C_6H_4)	30	85	94
6	**2-3f** (3-NO_2-C_6H_4)	24	86	88
7	**2-3g** (4-Cl-C_6H_4)	24	78	91
8	**2-3h** (4-CN-C_6H_4)	24	84	95
9	**2-3i** (2-furyl)	24	85	91
10	**2-3j** (2-thienyl)	30	75	90
11	**2-3k** (cyclohexyl)	48	72	87
12	**2-3l** (*n*-butyl)	48	81	91
13	**2-3m** (*iso*-butyl)	48	78	93

[a] Reaction were performed with **2-1** (0.05 mmol), **2-2** (0.05 mmol), $(NH_4)_2CO_3$ (0.05 mmol) and **2-8a** (0.01 mmol) in toluene (0.5 mL) at room temperature. [b] Isolated yield. [c] Determined by chiral phase HPLC analysis.



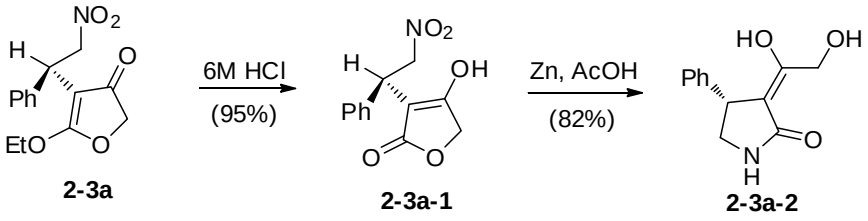
Scheme 2.3 Synthesis of furanone employing bromodiketone

In an attempt to broaden the substrate scope, bromodiketone **2-9** was examined, as illustrated in Scheme 2.3. Under the optimized reaction conditions established in our previous experiments, the desired furanone **2-10** was obtained in moderate yield and with only 50% ee. Meanwhile, furanone **2-11**, resulted from the self-cyclization of **2-9**, was obtained in 30% yield. When **2-9** was treated with triethylamine alone (2 eq.), product **2-11** was isolated in 89% yield, which clearly demonstrated the high tendency of such substrates to undergo rapid cyclization reaction. However, when **2-1** was treated with triethylamine alone without adding nitroolefin **2-2**, decomposition of

2-1 was observed, and only trace amount of the cyclization product was observed after 1h, and the vast majority of **2-1** remained unreacted. The same was observed under the optimal reaction conditions.

2.2.4 Synthetic Manipulations of the 3(2*H*)-Furanone Product

The 3(2*H*)-furanone products **2-3** are valuable molecules due to the importance of the furanone core in natural product and medicinal chemistry.[1] Moreover, such structures are also valuable synthetic intermediates. As illustrated in Scheme 2.4, treatment with HCl readily elaborated furanone **2-3a** to tetronic acid **2-3a-1**,[16] a core structural skeleton that has been found in many bioactive natural products.[17] Furthermore, reducing the nitro group of the teronic acid resulted in spontaneous formation of α-alkylidene-lactam **2-3a-2**, an intriguing structural motif possessing a wide variety of biological activities.[18]

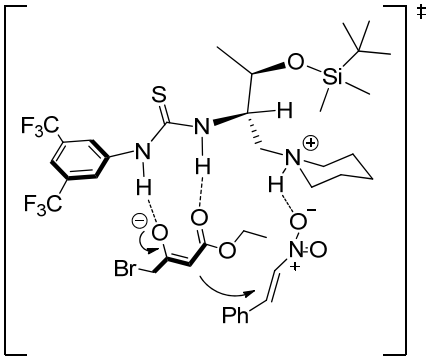


Scheme 2.4 Preparation of tetronic acid and γ-lactam from furanone **2-3a**

2.2.5 Proposed Transition State

[16] E. Wenkert, A. J. Marsaioli, P. D. R. Moeller, *J. Chromatogr.* **1988**, *440*, 449.
[17] a) Y. S. Rao, *Chem. Rev.* **1976**, *76*, 625; b) M. Sodeoka, R. Sampe, S. Kojima, Y. Baba, T. Usui, K. Ueda, H. Osada, *J. Med. Chem.* **2001**, *44*, 3216; c) H. Bühler, A. Bayer, F. Effenberger, *Chem. Eur. J.* **2000**, *6*, 2564; d) J. Wu, Q. Zhu, L. Wang, R. Fathi, Z. Yang, *J. Org. Chem.* **2003**, *68*, 670; e) D. T. Aragon, G. V. Lopez, F. G. Tellado, J. J. M. Tellado, P. D. Armas, D. Terrero, *J. Org. Chem.* **2003**, *68*, 3363; f) T. L. Trullinger, J. Qi, W. R. Roush, *J. Org. Chem.* **2006**, *71*, 6915; g) D. Tejedor, A. S. Exposito, F. G. Tellado, *Synthlett* **2006**, *10*, 1607; h) R. K. Boeckman, Jr., P. Shao, S. T. Wrobleski, D. J. Boehmler, G. R. Heintzelman, A. J. Barbosa, *J. Am. Chem. Soc.* **2006**, *128*, 10572; i) K. C. Nicolaou, S. T. Harrison, *J. Am. Chem. Soc.* **2007**, *129*, 429; j) A. Mallinger, T. L. Gall, C. Mioskowski, *Synthlett* **2008**, *3*, 386.
[18] a) W. Xu, A. Kong, X. Lu, *J. Org. Chem.* **2006**, *71*, 3854; b) R. L. Vezouet, A. J. P. White, J. N. Burrows, A. G. M. Barrett, *Tetrahedron* **2006**, *62*, 12252; c) H. Wang, X. Han. X. Lu, *Tetrahedron* **2010**, *66*, 9129; d) Y.-C. Jeong, M. G. Mooney, *J. Org. Chem.* **2011**, *76*, 1342; e) S. Tekkam, M. A. Alam, S. C. Jonnalagadda, V. R. Mereddy, *Chem. Commun.* **2011**, *47*, 3219.

The detailed mechanism of the reaction is not investigated at this stage. A plausible transition state model is shown in Scheme 2.5. The tertiary amine group of the catalyst deprotonates the β-ketoester to form an enolate, which engages in hydrogen bonding interactions with the thiourea moiety of the catalyst. The ionic interaction between positively charged ammonium with nitroolefin is believed to be important for the substrate binding. Such a proposal is consistent with the theoretical studies carried out in the literature for similar systems.[19]



Scheme 2.5 A plausible transition state model

2.3 Conclusions

In summary, we have designed a modified Feist–Bénary reaction employing a domino Michael–alkylation sequence for the enantioselective preparation of 3(2*H*)-furanones, synthetically useful structural motifs with significant biological importance. We have also prepared L-threonine-derived tertiary amine–thiourea catalysts for the first time; such catalysts promoted the designed domino Michael–alkylation reactions efficiently, affording 3(2*H*)-furanones in high yields and with excellent enantioselectivities. Further development of practical synthetic

[19] A. Hamza, G. Schubert, T. Soós, I. Pápai, *J. Am. Chem. Soc.* **2006**, *128*, 13151.

methods based on the Feist–Bénary reaction to access biologically significant molecules is currently ongoing in our laboratory.

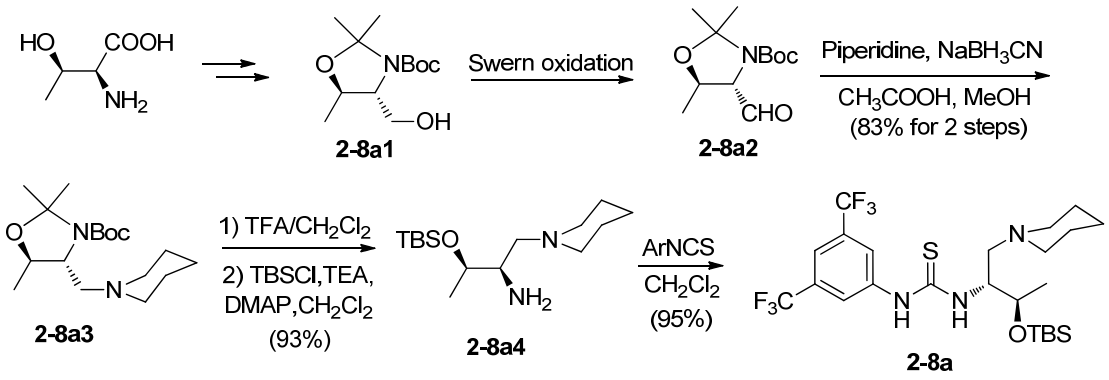
2.4 Experimental section

2.4.1 Material and General Methods

All the starting materials were obtained from commercial sources and used without further purification unless otherwise stated. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ACF300 or AMX500 (500 MHz) spectrometer. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (chloroform δ 7.26), carbon (chloroform δ 77.0). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), br (broad singlet). Coupling constants were reported in Hertz (Hz). Low resolution mass spectra were obtained on a Finnigan/MAT LCQ spectrometer in ESI mode, and a Finnigan/MAT 95XL- T mass spectrometer in EI mode. All high resolution mass spectra were obtained on a Finnigan/MAT 95XL- T spectrometer. For thin layer chromatography (TLC), Merck pre- coated TLC plates (Merck 60 F254) were used, and compounds were visualized with a UV light at 254 nm. Further visualization was achieved by staining with iodine, or ceric ammonium molybdate followed by heating on a hot plate. Flash chromatographic separations were performed on Merck 60 (0.040- 0.063 mm) mesh silica gel. The enantiomeric excesses of products were determined by chiral-phase HPLC analysis.

2.4.2 Catalysts Preparation

Preparation of L-threonine-derived bifunctional catalyst 2-8a



(4R,5R)-tert-Butyl-2,2,5-trimethyl-4-(piperidin-1-ylmethyl)oxazolidine-3-carboxylate **2-83a**

Alcohol **2-8a1** was oxidized to aldehyde **2-8a2** (0.5 mmol, 122 mg) *via* Swern oxidation, and the crude aldehyde was added directly to a stirred solution of piperidine (0.6 mmol, 51 mg) in methanol (5 mL). The resulting mixture was stirred at RT for 2 h, and then $NaBH_3CN$ (2 mmol, 160 mg) was added. The reaction mixture was further stirred for 6 h, during which acetic acid was added periodically to maintain the pH of the solution at 5–6. Ammonia solution was introduced, and white precipitate was formed. The mixture was concentrated under reduced pressure, and the residue was taken up in dichloromethane (20 mL), washed with brine and dried over Na_2SO_4. After filtration and concentration, the residue was purified by column chromatography (hexane/ethyl acetate = 5/1 to ethyl acetate) to afford **2-8a3** as a colorless oil (125 mg, 83%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (d, J = 6.2 Hz, 3H), 1.37-1.51 (m, 21H), 2.23-2.42 (m, 6H), 3.42-3.57 (m, 2H), 4.01-4.12 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0,

21.4, 24.2, 25.8, 25.9, 26.9, 28.1, 28.2, 28.3, 55.3, 61.3, 77.2, 79.4, 93.6, 93.8, 151.7; HRMS (ESI) m/z calcd for $C_{17}H_{33}N_2O_3$ $[M+H]^+$ = 313.2486, found = 313.2477.

(2*R*,3*R*)-3-((*tert*-Butyldimethylsilyl)oxy)-1-(piperidin-1-yl)butan-2-amine 2-**8a4**

To a stirred solution of TFA (0.3 mL) in CH_2Cl_2 (1.2 mL) was added 2-**8a3** (123 mg, 0.4 mmol), and the resulting solution was stirred overnight. The solvent was then removed under reduced pressure and the residue was further dried under vacuum. The residue was dissolved in anhydrous CH_2Cl_2 (1 mL), followed by addition of triethylamine (2 mmol, 202 mg) and DMAP (0.08 mmol, 10 mg). *t*-Butyldimethylsilyl chloride (0.4 mmol) in anhydrous CH_2Cl_2 (0.5 mL) was introduced to the reaction mixture dropwise. After stirring at room temperature for 24 h, the reaction mixture was concentrated and the residue was purified by flash column chromatography (CH_2Cl_2/MeOH = 50/1 to 5/1) to afford amine **2-8a4** as a yellow oil (105 mg, 93%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (d, *J* = 2.6 Hz, 6H), 0.86 (s, 9H), 1.14 (d, *J* = 6.2 Hz, 3H), 1.38-1.44 (m, 2H), 1.54-1.58 (m, 4H), 2.21-2.32 (m, 4H), 2.47 (d, *J* = 5.3 Hz, 2H), 2.75-2.81 (m, 1H), 3.42 (br s, 2H), 3.68-3.76 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.0, -4.3, 17.9, 20.6, 24.2, 25.7, 25.7, 53.5, 54.8, 62.6, 69.8; HRMS (ESI) m/z calcd for $C_{15}H_{35}N_2OSi$ $[M+H]^+$ = 287.2513, found = 287.2506.

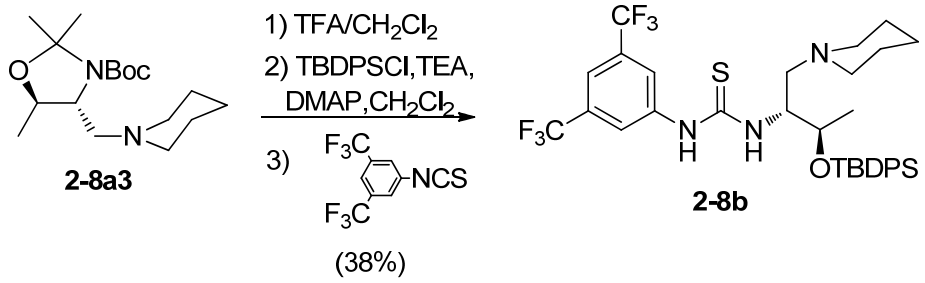
1-(3,5-Bis(trifluoromethyl)phenyl)-3-((2*R*,3*R*)-3-((*tert*-butyldimethylsilyl)oxy)-1-(piperidin-1-yl)butan-2-yl)thiourea **2-8a**

Amine 2-**8a4** (100 mg, 0.35 mmol) was dissolved in CH_2Cl_2 (3 mL), and

3,5-bis(trifluoromethy)-phenylisothiocyanate (95 mg, 0.35 mmol) was then added. After stirring for 4 h, the reaction mixture was concentrated and subjected to flash chromatographic separation (CH_2Cl_2 to CH_2Cl_2/MeOH = 10/1) to afford catalyst **2-8a** as a yellow oil (185 mg, 95%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.09 (d, *J* = 4.3 Hz, 6H), 0.90 (s, 9H), 1.26 (d, *J* = 6.1 Hz, 4H), 1.54 (d, *J* = 17.6 Hz, 6H), 2.45-2.72 (m, 6H), 3.60 (s, 1H), 3.92 (s, 1H), 6.68 (s, 1H), 7.61 (s, 1H), 8.04 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.0, -4.2, 17.8, 21.1, 23.3, 25.5, 25.6, 55.1, 59.7, 65.3, 69.4, 117.9, 124.4, 131.3, 131.7, 141.8, 184.0; HRMS (ESI) m/z calcd for $C_{24}H_{38}F_6N_3OSSi$ $[M+H]^+$ = 558.2404, found = 558.2380.

Preparation of L-threonine-derived bifunctional catalyst 2-8b



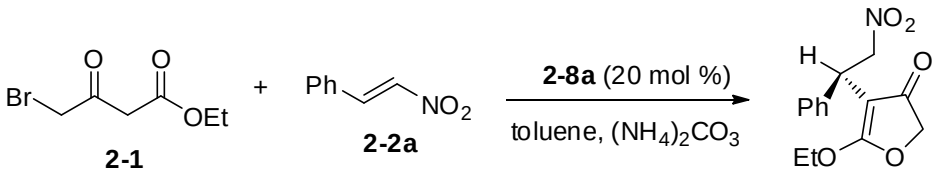
1-(3,5-Bis(trifluoromethyl)phenyl)-3-((2*R*,3*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-1-(piperidin-1-yl)butan-2-yl)thiourea **2-8b**

To a stirred solution of TFA (0.15 mL) in CH_2Cl_2 (0.6 mL) was added amine 2-**8a3** (62 mg, 0.2 mmol), and the resulting solution was stirred overnight. The solvent was then removed under reduced pressure and the residue was further dried under vacuum. The residue was dissolved in anhydrous CH_2Cl_2 (1 mL), followed by addition of triethylamine (1 mmol, 101 mg) and DMAP (0.04 mmol, 5 mg). *t*-Butyldiphenylsilyl

chloride (0.2 mmol) in anhydrous CH_2Cl_2 (0.25 ml) was introduced to the reaction mixture dropwise. After stirring at room temperature for 24 h, the reaction mixture was concentrated and further dried under vacuum. The residue was then dissolved in CH_2Cl_2 (2.5 mL), and 3,5-bis(trifluoromethy)-phenylisothiocyanate (54 mg, 0.2 mmol) was added. After stirring for 4 h, the reaction mixture was washed with water and concentrated under reduced pressure to afford the crude product, which was subjected to flash chromatographic separation (ethyl acetate/hexanes = 1/5 to 1/1) to afford catalyst **2-8b** as a yellow oil (52 mg, 38% for 3 steps).

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.00-1.27 (m, 13H), 1.36-1.53 (m, 6H), 2.25-2.67 (m, 6H), 3.51 (s, 1H), 3.90 (d, *J* = 6.9 Hz, 1H), 6.68 (s, 1H), 7.39-7.46 (m, 7H), 7.63-7.69 (m, 5H), 8.02 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 19.2, 20.6, 20.9, 23.4, 24.3, 25.5, 26.0, 27.0, 52.9, 54.7, 59.1, 68.0, 118.1, 124.5, 127.7, 130.1, 132.8, 132.9, 135.9, 184.1; HRMS (ESI) m/z calcd for $C_{34}H_{42}F_6N_3OSSi$ $[M+H]^+$ = 682.2717, found = 682.2758.

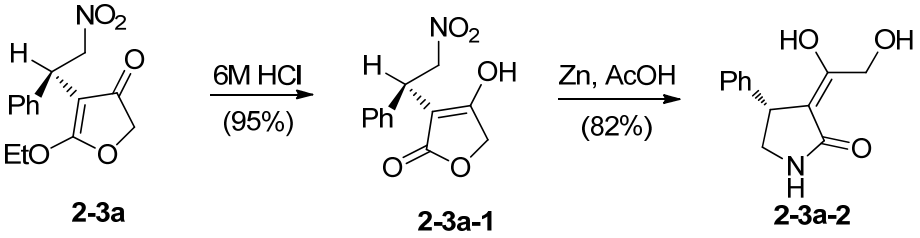
2.4.3 Representative Procedure



Ethyl 4-bromoacetoacetate **2-1** (10.5 mg, 0.05 mmol) was added to a mixture of **2-2a** (7.5 mg, 0.05 mmol), $(NH_4)_2CO_3$ (4.8 mg, 0.05 mmol) and **2-8a** (5.6 mg, 0.01 mmol) in anhydrous toluene (0.5 mL) in a sample vial. The vial was then sealed and the

resulting mixture was stired at room temperature for 24 h. The reaction mixture was concentrated *in vacuo*, and the crude was purified by flash column chromatography (ethyl acetate/hexane = 1/5 to 1/1) to afford furanone **2-3a** (12.5 mg, 90% yield). The enantiomeric excess of **2-3a** was determined by chiral HPLC analysis.

2.4.4 Derivatizations of the 3(2*H*)-Furanone Product



2-3a **2-3a-1** **2-3a-2**

Synthesis of 4-hydroxy-3-(2-nitro-1-phenylethyl)furan-2(5*H*)-one **2-3a-1**

5-Ethoxy-4-(2-nitro-1-phenylethyl)furan-3(2*H*)-one **2-3a** (111 mg, 0.4 mmol) was dissolved in THF (4 mL), then 6 M HCl (4 mL) was added in to the solution, and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated in *vacuo*, the residue was extracted with ethyl acetate several times (5 mL x 3), and the combined organic extracts were dried, filtered and concentrated. Purification by flash chromatography (ethyl acetate/hexane = 1/1 to 10/1) afforded tetronic acid **2-3a-1** as a yellow solid (95 mg, 95%).

^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 4.64-4.72 (m, 3H), 5.11 (dd, *J* = 7.0 Hz, 13.2Hz, 1H), 5.29 (dd, *J* = 8.9 Hz, 13.3Hz, 1H), 7.26 (t, *J* = 7.0 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.45 (d, *J* = 7.6 Hz, 2H), 11.05 (br s, 1H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 38.3, 66.5, 76.2, 99.5, 127.5, 127.8, 128.7, 138.8, 173.4, 173.9; HRMS (ESI) m/z calcd for $C_{12}H_{11}NNaO_5$ $[M+Na]^+$ = 272.0529, found = 272.0539.

Synthesis of (*E*)-3-(1,2-dihydroxyethylidene)-4-phenylpyrrolidin-2-one **2-3a-2**

4-Hydroxy-3-(2-nitro-1-phenylethyl)furan-2(5H)-one **2-3a-1** (0.34 mmol, 85 mg) was dissolved in a mixture of THF (2 mL) and AcOH (1.5 mL), Zn dust (3.4 mmol, 222mg) was then added, and the resulting mixture was stirred at room temperature for 24 h. The reaction mixture was filtered through celite, and the filtrate was concentrated in *vacuo*. The residue was purified by flash chromatography (CH_2Cl_2/MeOH = 5/1 to CH_2Cl_2/MeOH/TEA=5/1/1) to afford γ-lactam **2-3a-2** as an orange solid (61 mg, 82%).

^{1}H NMR (500 MHz, CD_3OD) δ 3.29 (dd, *J* = 4.4 Hz, 12.3Hz, 1H), 3.56 (dd, *J* = 7.6 Hz, 12.3Hz, 1H), 4.00 (dd, *J* = 3.8 Hz, 7.6Hz, 1H), 4.40 (dd, *J* = 15.2 Hz, 19.6Hz, 2H), 7.24 (t, *J* = 7.6 Hz, 1H),7.32-7.38 (m, 4H); ^{13}C NMR (125 MHz, CD_3OD) δ 38.8, 43.9, 69.9, 91.0, 126.7, 127.6, 128.4, 140.5, 181.0, 189.8; HRMS (ESI) m/z calcd for $C_{12}H_{13}NNaO_3$ $[M+Na]^+$ = 242.0788, found = 242.0796.

2.4.5 X-Ray Crystallographic Analysis and Determination of Configurations of the 3(2*H*)-Furanone Products

The absolute configuration of the product **2-3d** (*S*) was assigned based on the X-ray crystallographic analysis of a single crystal of **2-3d** (Figure 2.4). The configurations of other 3(*2H*)-furanone products were assigned by analogy.

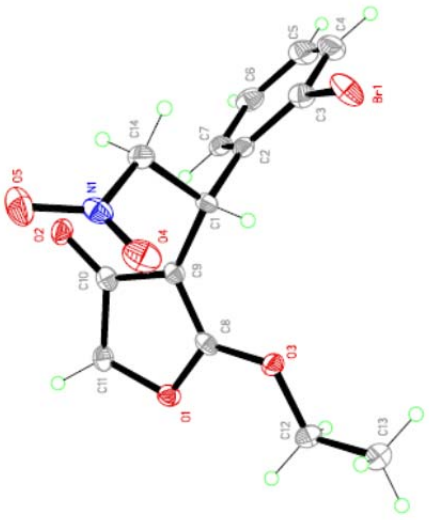


Figure 2.4 X-ray structure of **2-3d**

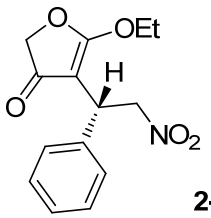
Table 2.3 Crystal Data and Structure Refinement for A435.

Identification code	a435	
Empirical formula	C_{14} H_{14} Br N O_5	
Formula weight	356.17	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 9.9607(14) Å	□= 90°.
	b = 6.8788(9) Å	□= 94.974(3)°.
	c = 10.6438(14) Å	□ = 90°.
Volume	726.54(17) $Å^3$	
Z	2	
Density (calculated)	1.628 Mg/m^3	

Absorption coefficient	2.850 mm^{-1}
F(000)	360
Crystal size	0.60 x 0.26 x 0.14 mm^3
Theta range for data collection	1.92 to 27.49°.
Index ranges	-8<=h<=12, -8<=k<=8, -13<=l<=13
Reflections collected	4995
Independent reflections	3071 [R(int) = 0.0213]
Completeness to theta = 27.49°	99.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.6911 and 0.2797
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3071 / 1 / 191
Goodness-of-fit on F^2	0.967
Final R indices [I>2sigma(I)]	R1 = 0.0256, wR2 = 0.0590
R indices (all data)	R1 = 0.0268, wR2 = 0.0594
Absolute structure parameter	0.011(6)
Largest diff. peak and hole	0.514 and -0.275 $e.Å^{-3}$

2.4.6 Analytical Data of the 3(2*H*)-Furanone Products

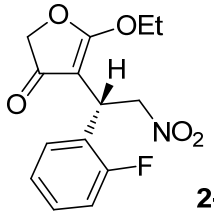
(*R*)-5-Ethoxy-4-(2-nitro-1-phenylethyl)furan-3(2*H*)-one **2-3a**



2-3a

A light yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43 (t, *J* = 7.6 Hz, 3H), 4.41-4.49 (m, 3H), 4.55 (dd, *J* = 16.4 Hz, 19.5 Hz, 2H), 4.86 (dd, *J* = 6.9 Hz, 12.6 Hz, 1H), 5.23 (dd, *J* = 8.8 Hz, 12.9 Hz, 1H), 7.24-7.32 (m, 3H), 7.39 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.7, 37.9, 66.7, 74.9, 76.5, 92.4, 127.6, 127.7, 128.9, 139.2, 181.2, 194.5; The ee value is 90%, t_R (minor) = 27.83 min, t_R (major) = 42.52 min (Chiralcel IC, λ = 254 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{14}H_{15}NNaO_5$ $[M+Na]^+$ = 300.0842, found = 300.0836; $[\alpha]^{27}_D$ = -30.8 (c 0.80, $CHCl_3$).

(*S*)-5-Ethoxy-4-(1-(2-fluorophenyl)-2-nitroethyl) furan-3(2*H*)-one **2-3b**

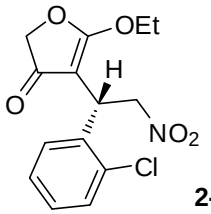


2-3b

A light yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.42 (t, *J* = 7.0 Hz, 3H), 4.20-4.49 (m, 2H), 4.57 (dd, *J* = 15.8 Hz, 18.9 Hz , 2H), 4.79-4.85 (m, 2H), 5.22-5.28 (m, 1H), 7.01-7.11 (m, 2H), 7.22-7.26 (m, 1H), 7.48-7.52 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.6, 30.7 (d, *J* = 3.6 Hz), 30.9, 66.8, 74.9, 75.1, 91.1, 115.6 (d, *J* = 22.8 Hz), 124.5 (d, *J* = 3.6 Hz), 125.5 (d, *J* = 13.7 Hz), 129.3 (d, *J* = 8.2 Hz), 129.5 (d, *J* =

2.7 Hz), 160.0 (d, *J* = 246.0 Hz), 181.4, 194.6; The ee value is 94%, t_R (minor) = 26.56 min, t_R (major) = 35.92 min (Chiralcel IC, λ = 254 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{14}H_{14}FNNaO_5$ $[M+Na]^+$ = 318.0748, found = 318.0739; $[\alpha]^{27}_D$ = -26.8 (c 0.60, $CHCl_3$).

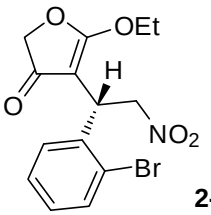
(*S*)-4-(1-(2-Chlorophenyl)-2-nitroethyl)-5-ethoxyfuran-3(2*H*)-one **2-3c**



2-3c

A yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (t, *J* = 7.1 Hz, 3H), 4.42-4.58 (m, 4H), 4.74-4.80 (m, 1H), 5.00 (dd, *J* = 5.8 Hz, 9.9 Hz, 1H), 5.24-5.32 (m, 1H), 7.19-7.26 (m, 2H), 7.35-7.38 (m, 1H), 7.60 (d, *J* = 2.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6, 34.3, 66.8, 74.9, 75.0, 91.0, 127.4, 128.8, 129.5, 129.8, 133.2, 136.1, 181.6, 194.7; The ee value is 96%, t_R (minor) = 26.46 min, t_R (major) = 36.16 min (Chiralcel IC, λ = 254 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{14}H_{14}ClNNaO_5$ $[M+Na]^+$ =334.0453, found = 334.0450; $[\alpha]^{27}_D$ = -56.0 (c 0.40, $CHCl_3$).

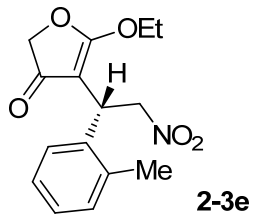
(*S*)-4-(1-(2-Bromophenyl)-2-nitroethyl)-5-ethoxyfuran-3(2*H*)-one **2-3d**



2-3d

A yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (t, *J* = 7.1 Hz, 3H), 4.40-4.50 (m, 2H), 4.52-4.63 (m, 2H), 4.74 (dd, *J* = 5.6 Hz, 12.8 Hz, 1H), 4.97 (dd, *J* = 5.6 Hz, 10.1 Hz, 1H), 5.23-5.31 (m, 1H), 7.08-7.13 (m, 1H), 7.24-7.30 (m, 1H), 7.54 (d, *J* = 8.1 Hz, 1H), 7.60 (d, *J* = 1.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.5, 37.0, 66.7, 74.9, 74.9, 91.0, 123.7, 127.9, 129.0, 129.6, 133.1, 137.7, 181.6, 194.6; The ee value is 96%, t_R (minor) = 27.71 min, t_R (major) = 37.04 min (Chiralcel IC, λ = 254 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{14}H_{14}{}^{79}BrNNaO_5$ $[M+Na]^+$ = 377.9948, found = 377.9932; $[\alpha]^{27}{}_D$ = -33.3 (c 0.15, $CHCl_3$).

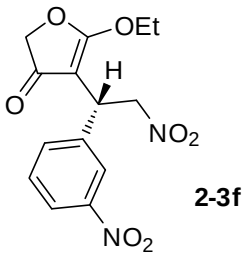
(*R*)-5-Ethoxy-4-(2-nitro-1-(o-tolyl)ethyl)furan-3(2*H*)-one **2-3e**



2-3e

A yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (t, *J* = 7.1 Hz, 3H), 2.46 (s, 3H), 4.41-4.55 (m, 4H), 4.69-4.82 (m, 2H), 5.20-5.29 (m, 1H), 7.13-7.18 (m, 3H), 7.51-7.54 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6, 19.5, 33.2, 66.6, 74.9, 75.9, 92.4, 126.5, 127.3, 127.4, 130.6, 135.4, 137.4, 181.3, 194.7; The ee value is 90%, t_R (minor) = 17.19 min, t_R (major) = 19.18 min (Chiralcel AD-H, λ = 254 nm, 8% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{15}H_{17}NNaO_5$ $[M+Na]^+$ = 314.0999, found = 314.0991; $[\alpha]^{27}{}_D$ = -20.2 (c 0.80, $CHCl_3$).

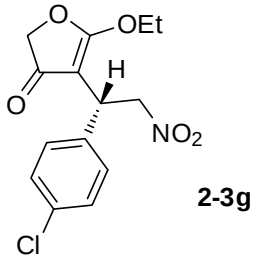
(*R*)-5-Ethoxy-4-(2-nitro-1-(3-nitrophenyl)ethyl)furan-3(2*H*)-one **2-3f**



2-3f

An orange oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.47 (t, *J* = 6.9 Hz, 3H), 4.49-4.60 (m, 5H), 4.99 (dd, *J* = 7.6 Hz, 13.3 Hz, 1H), 5.15 (dd, *J* = 8.2 Hz, 13.3 Hz, 1H), 7.50 (t, *J* = 8.2 Hz, 1H), 7.80 (d, *J* = 7.6 Hz, 1H), 8.12 (d, *J* = 8.2 Hz, 1H), 8.24 (t, *J* = 1.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.7, 37.4, 67.2, 75.1, 75.9, 91.4, 122.7, 129.9, 134.0, 141.1, 148.5, 152.5, 181.2, 194.2; The ee value is 88%, t_R (minor) = 36.78 min, t_R (major) = 53.55 min (Chiralcel IC, λ = 254 nm, 40% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{14}H_{14}N_2NaO_7$ $[M+Na]^+$ = 345.0693, found = 345.0683; $[\alpha]^{27}_D$ = -12.4 (c 0.45, $CHCl_3$).

(*R*)-4-(1-(4-Chlorophenyl)-2-nitroethyl)-5-ethoxyfuran-3(2*H*)-one **2-3g**

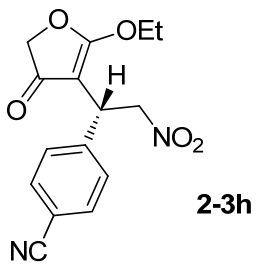


2-3g

A yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.42 (t, *J* = 7.6 Hz, 3H), 4.37-4.58 (m, 5H), 4.87 (dd, *J* = 6.9 Hz, 12.6 Hz, 1H), 5.13-5.175 (dd, *J* = 8.8 Hz, 12.6 Hz, 1H), 7.27 (t, *J* = 8.2 Hz, 1H), 7.33 (d, *J* = 8.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.7, 37.3, 66.9, 75.0, 76.3, 92.1, 129.1, 133.5, 137.7, 153.5, 181.2, 194.4; The ee value is

91%, t_R (minor) = 24.00 min, t_R (major) = 34.58 min (Chiralcel IC, λ = 254 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{14}H_{14}ClNNaO_5$ $[M+Na]^+$ =334.0453, found = 334.045; $[\alpha]^{27}_D$ = -30.8 (c 0.50, $CHCl_3$).

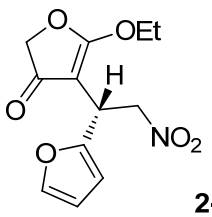
(*R*)-4-(1-(2-Ethoxy-4-oxo-4,5-dihydrofuran-3-yl)-2-nitroethyl)benzonitrile **2-3h**



2-3h

An orange oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (t, *J* = 7.1 Hz, 3H), 4.42-4.62 (m, 5H), 4.96 (dd, *J* = 7.7 Hz, 13.1 Hz, 1H), 5.13 (dd, *J* = 8.2 Hz, 13.0 Hz, 1H), 7.49-7.52 (m, 2H), 7.57-7.60 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6, 37.7, 67.0, 75.0, 75.6, 91.3, 111.5, 118.4, 128.5, 132.6, 144.3, 181.1, 194.2; The ee value is 95%, t_R (major) = 62.83 min, t_R (minor) = 69.27 min (Chiralcel AD-H, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1.0 mL/min);HRMS (ESI) m/z calcd for $C_{15}H_{14}N_2NaO_5$ $[M+Na]^+$ = 325.0795, found = 325.0785; $[\alpha]^{27}_D$ = -22.7 (c 0.60, $CHCl_3$).

(*R*)-5-Ethoxy-4-(1-(furan-2-yl)-2-nitroethyl)furan-3(2*H*)-one **2-3i**

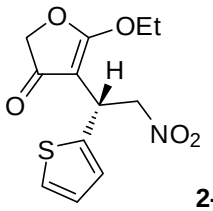


2-3i

A red oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.42 (t, *J* = 7.0 Hz, 3H), 4.45-4.49 (m, 2H),

4.58-4.64 (m, 3H), 4.89 (dd, *J* = 7.0 Hz, 13.3 Hz, 1H), 5.03 (dd, *J* = 8.8 Hz, 12.6 Hz, 1H), 6.16 (d, *J* = 3.2 Hz, 1H), 6.28 (dd, *J* = 1.9 Hz, 3.1 Hz, 1H), 7.32 (d, *J* = 1.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.7, 31.3, 66.8, 74.6, 75.0, 89.8, 106.9, 110.5, 142.0, 150.8, 181.4, 194.1; The ee value is 91%, t_R (minor) = 17.27 min, t_R (major) = 19.66 min (Chiralcel AD-H, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{12}H_{13}NNaO_6$ $[M+Na]^+$ = 290.0635, found = 290.0626; $[\alpha]^{27}_D$ = -14.0 (c 0.10, $CHCl_3$).

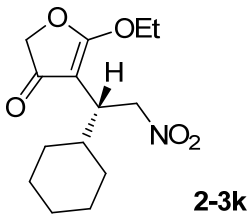
(*R*)-5-Ethoxy-4-(2-nitro-1-(thiophen-2-yl)ethyl)furan-3(2*H*)-one **2-3j**



2-3j

A red oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (t, *J* = 7.1 Hz, 3H), 4.45-4.60 (m, 4H), 4.76 (dd, *J* = 6.9 Hz, 8.7 Hz, 1H), 4.86 (dd, *J* = 6.7 Hz, 12.5 Hz, 1H), 5.11-5.29 (m, 1H), 6.90-6.93 (m, 1H), 7.00-7.02 (m, 1H), 7.15-7.17 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6, 32.5, 66.8, 74.9, 76.5, 92.1, 124.6, 125.4, 127.0, 141.0, 180.9, 193.8; The ee value is 90%, t_R (minor) = 32.93 min, t_R (major) = 42.36 min (Chiralcel IC, λ = 254 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{12}H_{13}NNaO_5S$ $[M+Na]^+$ = 306.0407, found = 306.0396; $[\alpha]^{27}_D$ = -25.5 (c 0.40, $CHCl_3$).

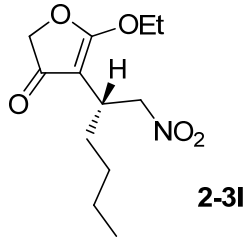
(*R*)-4-(1-Cyclohexyl-2-nitroethyl)-5-ethoxyfuran-3(2*H*)-one **2-3k**



2-3k

A colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89-1.25 (m, 5H), 1.42 (t, *J* = 7.1 Hz, 3H), 1.64-1.74 (m, 6H), 2.96-3.04 (m, 1H), 4.40-4.47 (m, 2H), 4.54-4.62 (m, 3H), 4.89 (dd, *J* = 10.5 Hz, 11.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.6, 25.9, 26.0, 26.1, 30.4, 31.0, 38.0, 38.7, 66.3, 74.6, 75.4, 90.9, 181.9, 195.1; The ee value is 87%, t_R (minor) = 34.95 min, t_R (major) = 43.60 min (Chiralcel IC, λ = 254 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{14}H_{21}NNaO_5$ $[M+Na]^+$ = 306.1312, found = 306.1302; $[\alpha]^{27}_D$ = 11.7 (c 0.10, $CHCl_3$).

(*R*)-5-Ethoxy-4-(1-nitrohexan-2-yl)furan-3(2*H*)-one **2-3l**

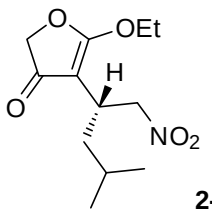


2-3l

A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (t, *J* = 7.0 Hz, 3H), 1.22-1.32 (m, 4H), 1.41-1.53 (m, 4H), 1.64-1.74 (m, 1H), 3.15-3.21 (m, 1H), 4.42-4.54 (m, 5H), 4.71 (dd, *J* = 8.8 Hz, 12.0 Hz, 1H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 14.7, 22.3, 29.3, 29.7, 32.2, 66.4, 74.7, 91.4, 181.7, 195.0; The ee value is 91%, t_R (major) = 34.70 min, t_R (minor) = 36.47 min (Chiralcel IC, λ = 254 nm, 20% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{12}H_{19}NNaO_5$ $[M+Na]^+$ =

280.1155, found = 280.1149; $[\alpha]^{27}_{D}$ = -29.0 (c 0.10, $CHCl_3$).

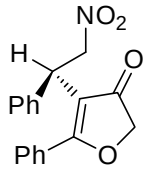
(*R*)-5-Ethoxy-4-(4-methyl-1-nitropentan-2-yl)furan-3(2*H*)-one **2-3m**



2-3m

A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88-0.90 (m, 6H), 1.18-1.25 (m, 1H), 1.40-1.48 (m, 4H), 1.67-1.77 (m, 1H), 3.25-3.30 (m, 1H), 4.42-4.56 (m, 5H), 4.69 (dd, *J* = 8.9 Hz, 11.4Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.7, 21.4, 23.2, 25.7, 30.3, 38.6, 66.4, 74.7, 77.5, 91.3, 181.7, 195.0; The ee value is 93%, t_R (major) = 53.09 min, t_R (minor) = 56.30 min (Chiralcel IC, λ = 254 nm, 15% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{12}H_{19}NNaO_5$ $[M+Na]^+$ = 280.1155, found = 280.1149; $[\alpha]^{27}_{D}$ = 6.8 (c 0.25, $CHCl_3$).

(*R*)-4-(2-Nitro-1-phenylethyl)-5-phenylfuran-3(2*H*)-one **2-10**

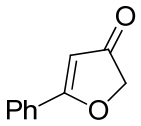


2-10

A light yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.64-4.69 (m, 3H), 4.84 (dd, *J* = 5.7 Hz, 12.9Hz, 1H), 5.52 (dd, *J* = 9.5 Hz, 12.9Hz, 1H), 7.29-7.37 (m, 3H), 7.42 (d, *J* = 2.6 Hz, 2H), 7.49-7.59 (m, 3H), 7.62 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 40.5, 74.1, 76.6, 113.2, 127.9, 128.0, 129.0, 129.2, 129.3, 132.3, 138.6, 185.5, 202.4;

The ee value is 50%, t_R (major) = 53.09 min, t_R (minor) = 56.30 min (Chiralcel IC, λ = 254 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min)

5-Phenylfuran-3(2*H*)-one **2-11**



2-11

A light yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.64-4.69 (m, 3H), 4.84 (dd, *J* = 5.7 Hz, 12.9Hz, 1H), 5.52 (dd, *J* = 9.5 Hz, 12.9Hz, 1H), 7.29-7.37 (m, 3H), 7.42 (d, *J* = 2.6 Hz, 2H), 7.49-7.59 (m, 3H), 7.62 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 75.4, 101.5, 127.1, 128.8, 128.9, 132.8, 187.0, 202.2. MS (ESI) m/z calcd for $C_{10}H_7O_2$ $[M-H]^-$ = 159.1, found = 159.1

Chapter 3 A Highly Enantioslective Synthesis of Functionalized 2,3-Dihydrofurans by a Modified Feist-Bénary Reaction

3.1 Introduction

2,3-Dihydrofurans distribute widely in many natural products, and also serve as useful synthetic intermediates.[1] In particular, enantiomerically enriched 2,3-dihydrofurans have attracted much attention as they are important precursors for the asymmetric synthesis of tetrahydrofurans,[2] and many synthetic strategies employing chiral auxiliaries and precursors[3] or metal-containing catalysts[4] have been devised toward this end. On the other hand, organocatalytic approaches to access chiral 2,3-dihydrofurans are very limited.[5] Recently, Rueping[5c] and Xie[5e] reported the synthesis of 2,3-dihydrofurans from cyclic diketones. A practical and general strategy employing acyclic β-ketoester for the asymmetric preparation of 2,3-dihydrofurans is still lacking, thus it is our goal to develop an efficient asymmetric synthetic method to access chiral 2,3-dihydrofurans.

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[1] a) O. R. Gottlied, *New Natural Products and Plant Drugs with Pharmacological, Biological, or Therapeutical Activity;* Springer-Verlag: Berlin-Heidelberg, Germany, **1987**; p 227; b) B. M. Fraga, *Nat. Prod. Rep.,* **1992**, *9*, 217; c) A. T. Merrit, S. B. Ley, *Nat. Prod. Rep.,* **1992**, *9*, 243.

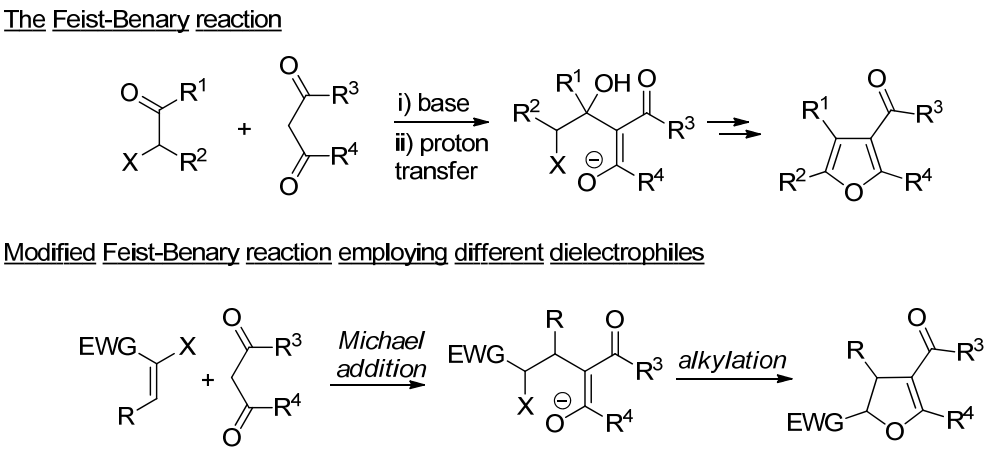
[2] a) B. H. Lipshutz, *Chem. Rev.,* **1986**, *86*, 795; b) M. M. Faul, B. E. Huff, *Chem. Rev.,* **2000**, *100*, 2407.

[3] a) H. J. Gais, L. R. Reddy, G. S. Babu, G. Raabe, *J. Am. Chem. Soc.,* **2004**, *126*, 4859; b) F. Garzino, A. Méou, P. Brun, *Eur. J. Org. Chem.,* **2003**, 1410; c) W. Xia, C. Yang, B. O. Patrick, J. R. Scheffer, C. Scott, *J. Am. Chem. Soc.,* **2005**, *127*, 2725; d) R. K. Bowman, J. S. Jonhson, *Org. Lett.,* **2006**, *8*, 573; e) J.-C. Zheng, C.-Y. Zhu, X.-L. Sun, Y. Tang, L.-X. Dai, *J. Org. Chem.,* **2008**, *73*, 6909.

[4] a) D. A. Evans, Z. K. Sweeney, T. Rovis, J. S. Tedrow, *J. Am. Chem. Soc.,* **2001**, *123*, 12095; b) S. Son, G. C. Fu, *J. Am. Chem. Soc.,* **2007**, *129*, 1046; c) H. M. L. Davies, G. Ahmed, R. L. Calvo, M. R. Churchill, D. G. Churchill, *J. Org. Chem.,* **1998**, *63*, 2641; d) F. Ozawa, A. Kubo, Y. Matsumoto, T. Hayashi, *Organometallics,* **1993**, *12*, 4188; e) P. Müller, G. Bernardinelli, Y. F. Allenbach, M. Ferri, S. Grass, *Synlett,* **2005**, *9*, 1397.

[5] a) F. Silva, M. Sawicki, V. Gouverneur, *Org. Lett.,* **2006**, *8*, 5417; b) L. Albrecht, L. K. Ransborg, B. Gschwend, K. A. Jørgensen, *J. Am. Chem. Soc.,* **2010**, *132*, 17886; c) M. Rueping, A. Parra, U. Uria, F. Besselièvre, E. Merino, *Org. Lett.,* **2010**, *12*, 5680; d) M. Rueping, M.-Y. Lin, *Chem. Eur. J.,* **2010**, *16*, 4169; e) L.-P. Fan, P. Li, X.-S. Li, D.-C. Xu, M.-M. Ge, W.-D. Zhu, J.-W. Xie, *J. Org. Chem.,* **2010**, *75*, 8716; f) T. G. Kilroy, T. P. O'Sullivan, P. J. Guiry, *Eur. J. Org. Chem.,* **2005**, 4929; g) Z. Chen, J. Zhang, *Chem. Asian J.,* **2010**, *5*, 1542.

The Feist–Bénary reaction is a base catalyzed reaction between α-halogenated ketones and 1,3-dicarbonyl compounds for the synthesis of substituted furans. Synthetic methods based on the Feist–Bénary reaction could lead to effective formation of various furan derivatives.[6] In Chapter 2, we have shown that a modified Feist–Bénary reaction could be utilized for a convenient synthesis of chiral 3(2*H*)-furanone derivatives. After that, we tried to employ the modified Feist–Bénary reaction to prepare other useful furan derivatives. Herein, we describe a modified Feist–Bénary reaction for an enantioselective synthesis of functionalized 2,3-dihydrofurans.



Scheme 3.1 Modified Feist–Bénary reaction for synthesis of functionalized 2,3-dihydrofurans

The Feist–Bénary synthesis can be regarded as a domino aldol–alkylation reaction, in which the α-halogenated ketones are used as a dielectrophile and 1,3-dicarbonyl compounds as a dinucleophile. By employing halogen-substituted electron-deficient olefins and β-ketoesters as a dielectrophile and a dinucleophile, respectively, we reasoned that such modified Feist–Bénary reaction could be utilized

[6] See Chapter 2, ref. 6.

for the asymmetric synthesis of highly functionalized 2,3-dihydrofuran products (Scheme 3.1).

3.2 Results and Discussion

3.2.1 Reaction Optimization

The domino Michael–alkylation reaction between β-ketoesters **3-4** and (*E*)-β,β-bromonitrostyrene[7] **3-5a** was chosen as a model reaction (Table 3.1). For the selection of the catalysts, we still focused on the amino catalysts containing a Brønsted acid moiety; it is anticipated that high stereoselectivity could be achieved via cooperative interactions between the catalysts and the substrates. Since HBr would be generated during the reaction, $(NH_4)_2CO_3$ was thus introduced as a HBr scavenger, and this strategy was proven to be effective in our previous 3(2*H*)-furanone synthesis system in Chapter 2. In the presence of quinine-derived bifunctional tertiary amine thiourea catalyst **3-1a**, the desired product was obtained with moderate enantioselectiviy (entry 1). Our recently developed multifunctional catalyst **3-1b**[8] gave similar results (entry 2). Quinidine-derived sulfonamide **3-2** also led to moderate enantioselectivity (entry 3). To our delight, threonine structural motif proved to be privileged again. L-Threonine-derived tertiary amine-thiourea catalysts **3-3** were found to be effective, diastereomerically pure products **3-6** were obtained in good yields and with high enantioselectivities, and the ester moiety had little influence on the reaction (entries 4–5). Performing reaction with excess ketoester under dilute reaction

[7] W. E. Parham, J. L. Bleasdale, *J. Am. Chem. Soc.*, 1951, **73**, 4664.
[8] a) Q. Zhu, Y. Lu, *Angew. Chem. Int. Ed.* **2010**, *49*, 7753; b) X. Dou, Y. Lu, *Chem. Eur. J.* **2012**, *18*, 8315; c) J. Luo, H. Wang, F. Zhong, J. Kwiatkowski, L.-W. Xu, Y. Lu, *Chem. Commun.* **2012**, *48*, 4707; d) F. Zhong, J. Luo, G.-Y. Chen, X. Dou, Y. Lu, *J. Am. Chem. Soc.* **2012**, *134*, 10222.

conditions resulted in further improvement (entries 6–7). By lowering the temperature, 2,3-dihydrofuran **3-6** was obtained in high yield and with excellent enantioselectivity (entry 8). It should be highlighted that threonine-based bifunctional catalysts are not only effective in asymmetric induction, but also structurally highly tunable; fine tuning was achieved in the above study by simply utilizing TBDPS instead of TBS as a protective group (entry 9).

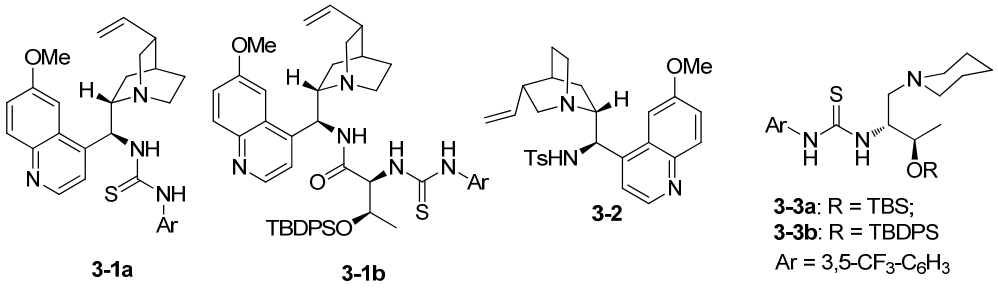
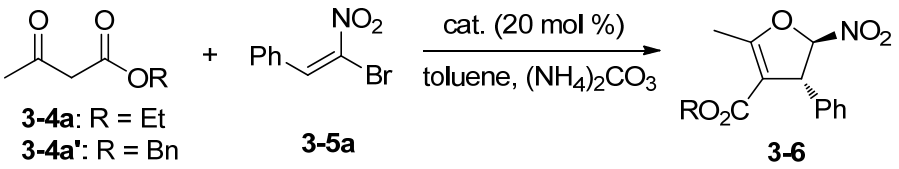


Figure 3.1 Organic catalysts examined

Table 3.1 Domino Michael–Alkylation Reaction between β-Ketoester and Bromonitroolefin[a]



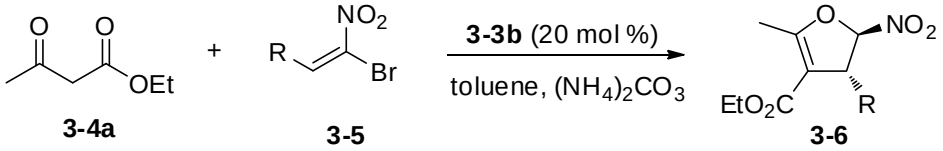
entry	cat.	R	t (h)	yield (%)[b]	ee(%)[c]
1	**3-1a**	Et	18	71	63
2	**3-1b**	Et	18	75	65
3	**3-2**	Et	18	62	52
4	**3-3a**	Et	18	65	84
5	**3-3a**	Bn	18	72	84
6[d]	**3-3a**	Et	18	87	88
7[d]	**3-3a**	Bn	18	91	86
8[d,e]	**3-3a**	Et	36	82	92
9[d,e]	**3-3b**	Et	36	86	94

[a] Reactions were performed with **3-4** (0.04 mmol), **3-5a** (0.04 mmol), $(NH_4)_2CO_3$ (0.04 mmol) and the catalyst (20 mol %) in toluene (0.4 mL) at room temperature. [b] Yield of the isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. [d] 0.8 mL toluene and 0.2 mmol **3-4** were used. [e] The reaction was performed at -20 °C.

3.2.2 Substrate Scope

With the optimized reaction conditions in hand, the substrate scope of 1,2-dihydrofuran synthesis was then investigated. This domino reaction is applicable to various aryl-substituted bromonitroolefins, high yields and excellent enantioselectivities were attainable (Table 3.2, entries 1–10). A large scale synthesis of **3-6a** was achieved in 67% yield and with 90% ee (Table 3.2, entry 1, 3 mmol scale). In addition, the reaction also tolerated well with bromonitroolefin with an alkyl group, which is a difficult substrate and was not reported before (entry 11).

Table 3.2 Substrate Scope of the Asymmetric Synthesis of 2,3-Dihydrofurans *via* a **3-3b**-Catalyzed Domino Michael–Alkylation Reaction[a]

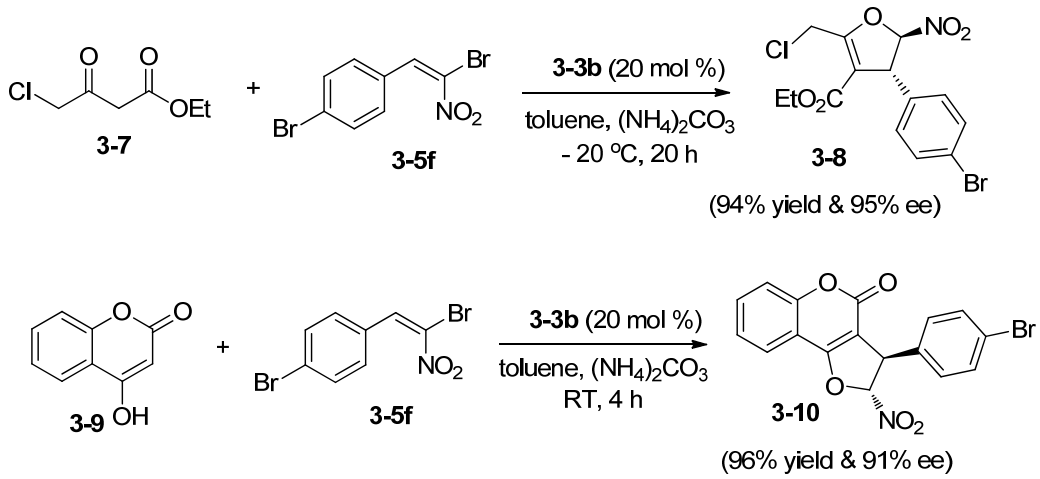


3-4a **3-5** **3-6**

entry	R (**3-6**)	t (h)	yield (%)[b]	*ee* (%)[d]
1	C_6H_5 (**3-6a**)	36	80 (67)[e]	93 (90)[e]
2	2-F-C_6H_4 (**3-6b**)	20	82	91
3	2-Me-C_6H_4 (**3-6c**)	72	70	96
4	3-Br-C_6H_4 (**3-6d**)	36	83	88
5	4-F-C_6H_4 (**3-6e**)	36	77	91
6	4-Br-C_6H_4 (**3-6f**)	36	74	91
7	4-Me-C_6H_4 (**3-6g**)	72	78	92

8	4-OMe-C_6H_4 (**3-6h**)	96	68	99
9	2-thienyl (**3-6i**)	96	73	95
10	1-naphthyl (**3-6j**)	96	75	91
11[d]	n-butyl (**3-6k**)	96	59	91

[a] Reactions were performed with **3-4a** (2.5 mmol), **3-5** (0.5 mmol), $(NH_4)_2CO_3$ (0.5 mmol) and the catalyst (0.1 mmol) in toluene (10 mL) at -20 °C. [b] Isolated yield [c] Determined by HPLC analysis on a chiral stationary phase. [d] Benzyl acetoacetate was used and reaction was performed at room temperature. [e] Reaction was performed on a 3.0 mmol scale.



Scheme 3.2 Versatile domino Michael-alkylation reaction

Our reaction system was also suitable for other β-ketoester substrates. Interestingly, when 4-chloro ethyl acetoacetate **3-7** was used in the reaction, 2,3-dihydrofuran **3-8** was obtained in 94% yield and with 95% ee, and no competing 3(2*H*)-furanone product was observed. Employment of coumarin **3-9** led to tricyclic coumarin **3-10** in 96% yield and with 91% ee (Scheme 3.2). The absolute configurations of 2,3-dihydrofuran products were assigned on the basis of the absolute configuration of **3-10**.[5e]

Complete *trans*-diastereoselectivity was observed for all the examples examined in this study. The observed diastereoselectivity may be a result from a stereospecific

protonation of the nitronate anion, following the initial Michael addition of keto enolate to nitroolefin. Alternatively, the abromo nitro intermediates may readily epimerize with only one of the epimers being converted to the diastereomerically pure products. We cannot draw a definite conclusion at the moment. However, a stereospecific protonation seems unlikely under the reaction conditions, and based on the high acidity of the a-proton of bromo nitro compounds, the epimerization pathway seems plausible.

3.3 Conclusions

In conclusion, we have employed acyclic β-ketoesters in a modified Feist–Bénary reaction for the enantioselective preparation of 2,3-dihydrofurans, which are synthetically useful molecules. We have also prepared L-threonine-derived tertiary amine thiourea bifunctional catalysts; such catalysts promoted the designed domino Michael–alkylation reactions efficiently, affording highly functionalized 2,3-dihydrofurans in good yields and with excellent enantioselectivities. Further development of practical synthetic methods based on the Feist–Bénary reaction to access biologically significant heterocyclic compounds is currently ongoing in our laboratory.

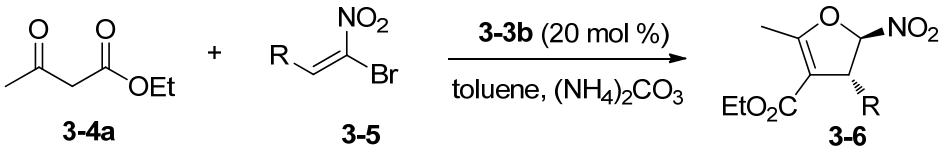
3.4 Experimental Section

3.4.1 Material and General Methods

All the starting materials were obtained from commercial sources and used without further purification unless otherwise stated. ^{1}H and ^{13}C NMR spectra were

recorded on a Bruker ACF300 or AMX500 (500 MHz) spectrometer. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (chloroform δ 7.26), carbon (chloroform δ 77.0). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), br (broad singlet). Coupling constants were reported in Hertz (Hz). Low resolution mass spectra were obtained on a Finnigan/MAT LCQ spectrometer in ESI mode, and a Finnigan/MAT 95XL- T mass spectrometer in FAB mode. All high resolution mass spectra were obtained on a Finnigan/MAT 95XL- T spectrometer. For thin layer chromatography (TLC), Merck pre- coated TLC plates (Merck 60 F254) were used, and compounds were visualized with a UV light at 254 nm. Further visualization was achieved by staining with iodine, or ceric ammonium molybdate followed by heating on a hot plate. Flash chromatographic separations were performed on Merck 60 (0.040- 0.063 mm) mesh silica gel. The enantiomeric excesses of products were determined by chiral-phase HPLC analysis.

3.4.2 Representative Procedure



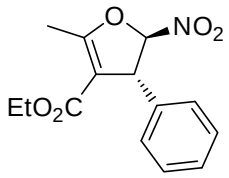
3-4a **3-5** **3-6**

Ethyl acetoacetate **3-4a** (316 μl, 2.5 mmol**)** was added to a mixture of **3-5a** (114 mg, 0.5 mmol) and $(NH_4)_2CO_3$ (48 mg, 0.5 mmol) in anhydrous toluene (9.4 mL) in a 25 mL RBF under N_2. The reaction mixture was cooled down to -20 ^oC and a 0.29 M

solution of **3-3b** in anhydrous toluene (345 μl, 0.1 mmol) was then added to the reaction mixture. The resulting mixture was stirred at -20 ^{o}C until the TLC analysis showed complete consumption of **3-5a**. The reaction mixture was then filtered and the filtrate was concentrated *in vacuo*, the crude was purified by flash column chromatography (ethyl acetate/hexane = 1/8) to afford the desired adduct **3-6**. The enantiomeric excess of **3-6** was determined by chiral HPLC analysis. Catalyst **3-3b** was washed out the column and recovered by changing the eluent to dichloromethane/MeOH = 5/1.

3.4.3 Analytical Data of the 2,3-Dihydrofuran Products

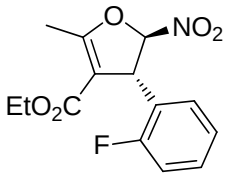
(4*R*,5*R*)-Ethyl 2-methyl-5-nitro-4-phenyl-4,5-dihydrofuran-3-carboxylate **3-6a**



3-6a

A light yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.11 (t, *J* = 7.3 Hz, 3H), 2.51 (d, *J* = 1.9 Hz, 3H), 4.01-4.11 (m, 2H), 4.60 (s, 1H), 5.78 (d, *J* = 1.9 Hz, 1H), 7.22 (t, *J* = 6.9 Hz, 2H), 7.31-7.38 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.7, 14.0, 55.8, 60.3, 107.8, 109.6, 127.1, 128.3, 129.1, 138.0, 163.4, 167.0; The ee value is 93% (0.5 mmol scale), 90% (3 mmol scale), t_R (major) = 31.48 min, t_R (minor) = 24.89 min (Chiralcel IC, λ = 254 nm, 0.8% *i*PrOH/hexanes, flow rate = 0.5 mL/min); HRMS (EI) m/z calcd for $C_{14}H_{15}O_3$ [M-NO_2] = 231.1021, found = 231.1020; $[\alpha]^{27}_D$ = -17.6 (c 0.85, $CHCl_3$).

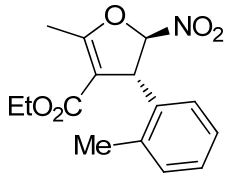
(4*S*,5*R*)-Ethyl 4-(2-fluorophenyl)-2-methyl-5-nitro-4,5-dihydrofuran-3-carboxylate **3-6b**



3-6b

A light yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.11 (t, *J* = 7.3 Hz, 3H), 2.50 (d, *J* = 1.3 Hz, 1H), 4.01-4.11 (m, 2H), 4.89 (s, 1H), 5.85 (d, *J* = 1.9 Hz, 1H), 7.08-7.15 (m, 3H), 7.29-7.34 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.7, 13.9, 49.3(d, *J* = 2.7 Hz), 60.3, 106.4, 108.8, 116.0 (d, *J* = 21.9 Hz), 124.5(d, *J* = 3.6 Hz), 124.8 (d, *J* = 13.7 Hz), 128.7 (d, *J* = 3.7 Hz), 130.1(d, *J* = 8.2 Hz), 160.4 (d, *J* = 246.9 Hz), 163.2, 167.6; The ee value is 91%, t_R (major) = 36.31 min, t_R (minor) = 31.82 min (Chiralcel IC, λ = 254 nm, 0.6 % *i*PrOH/hexanes, flow rate = 0.5 mL/min); HRMS (EI) m/z calcd for $C_{14}H_{14}O_3F$ [M-NO_2] = 249.0927, found = 249.0926; $[\alpha]^{27}_D$ = -25.1 (c 0.80, $CHCl_3$).

(4*R*,5*R*)-Ethyl 2-methyl-5-nitro-4-(o-tolyl)-4,5-dihydrofuran-3-carboxylate **3-6c**

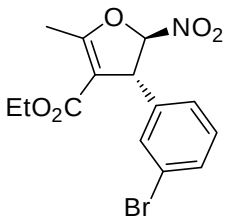


3-6c

A light yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.10 (t, *J* = 7.0 Hz, 3H), 2.53 (d, 6H), 4.04 (dd, *J* = 7.0 Hz, 14.5 Hz, 2H), 4.86 (d, *J* = 1.9 Hz, 1H), 5.71 (d, *J* = 0.8 Hz, 1H), 6.94 (d, *J* = 7.4 Hz, 1H), 7.16-7.24 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.7,

13.9, 51.6, 60.2, 108.3, 109.5, 125.7, 126.7, 128.1, 130.9, 135.9, 136.2, 163.3, 167.0; The ee value is 96%, t_R (major) = 14.81 min, t_R (minor) = 13.28 min (Chiralcel IC, λ = 254 nm, 0.8% *i*PrOH/hexanes, flow rate = 0.5 mL/min); HRMS (EI) m/z calcd for $C_{15}H_{17}O_3$ [M-NO_2] = 245.1178, found = 245.1174; $[\alpha]^{27}_D$ = -15.0 (c 0.80, $CHCl_3$).

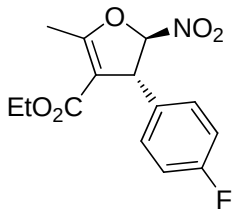
(4*R*,5*R*)-Ethyl 4-(3-bromophenyl)-2-methyl-5-nitro-4,5-dihydrofuran-3-carboxylate **3-6d**



3-6d

A light yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.17 (t, *J* = 7.3 Hz, 3H), 2.54 (d, *J* = 1.3 Hz, 3H), 4.05-4.16 (m, 2H), 4.58 (s, 1H), 5.79 (d, *J* = 1.9 Hz, 1H), 7.19 (d, *J* = 7.6 Hz, 1H), 7.28 (t, *J* = 3.8 Hz, 1H), 7.38 (d, *J* = 1.9 Hz, 1H), 7.49 (d, *J* = 4.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 14.0, 55.3, 60.4, 107.4, 109.0, 123.1, 125.9, 130.1, 130.7, 131.5, 140.1, 163.1, 167.5; The ee value is 88%, t_R (major) = 88.43 min, t_R (minor) = 72.60 min (Chiralcel IC, λ = 254 nm, 0.2 % *i*PrOH/hexanes, flow rate = 0.5 mL/min); HRMS (EI) m/z calcd for $C_{14}H_{14}O_3$ ^{81}Br [M-NO_2] = 311.0106, found = 311.0096; $[\alpha]^{27}_D$ = -17.3 (c 1.00, $CHCl_3$).

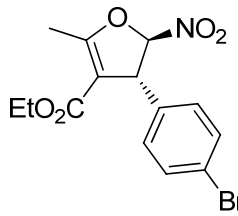
(4*R*,5*R*)-Ethyl 4-(4-fluorophenyl)-2-methyl-5-nitro-4,5-dihydrofuran-3-carboxylate **3-6e**



3-6e

A light yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.12 (t, *J* = 7.3 Hz, 3H), 2.50 (d, *J* = 1.3 Hz, 3H), 4.03-4.10 (m, 2H), 4.58 (s, 1H), 5.74 (d, *J* = 1.3 Hz, 1H), 7.04-7.07 (m, 2H), 7.18-7.21 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 14.0, 55.1, 60.4, 107.8, 109.4, 116.1 (d, *J* = 21.9 Hz), 128.7(d, *J* = 8.2 Hz), 133.7 (d, *J* = 3.7 Hz) , 162.6 (d, *J* = 246.0 Hz), 163.2, 167.1; The ee value is 91%, t_R (major) = 26.70 min, t_R (minor) = 21.85 min (Chiralcel IA, λ = 254 nm, 0.8 % *i*PrOH/hexanes, flow rate = 0.5 mL/min); HRMS (EI) m/z calcd for $C_{14}H_{14}O_3F$ [M-NO_2] = 249.0927, found = 249.0926; $[\alpha]^{27}_D$ = -17.8 (c 0.70, $CHCl_3$).

(4*R*,5*R*)-Ethyl 4-(4-bromophenyl)-2-methyl-5-nitro-4,5-dihydrofuran-3-carboxylate **3-6f**

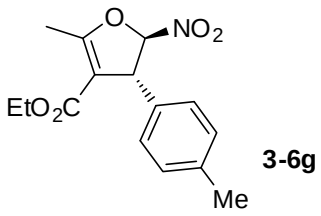


3-6f

A light yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.13 (t, *J* = 7.3 Hz, 3H), 2.50 (d, *J* = 1.9 Hz, 3H), 4.04-4.09 (m, 2H), 4.56 (s, 1H), 5.73 (d, *J* = 1.9 Hz, 1H), 7.10 (dd, *J* = 2.2 Hz, 6.6Hz, 2H), 7.49 (dd, *J* = 1.9 Hz, 7.0Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 14.0, 55.2, 60.4, 107.5, 109.1, 122.3, 128.8, 132.3, 136.9, 163.2, 167.3; The ee

value is 91%, t_R (major) = 35.21 min, t_R (minor) = 43.44 min (Chiralcel IC, λ = 254 nm, 1.0 % *i*PrOH/hexanes, flow rate = 0.5 mL/min); HRMS (EI) m/z calcd for $C_{14}H_{14}O_3{}^{81}Br$ [M-NO_2] = 311.0106, found = 311.0096; $[\alpha]^{27}_D$ = -15.8 (c 0.80, $CHCl_3$).

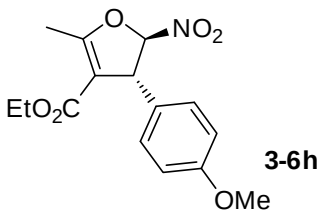
(4*R*,5*R*)-Ethyl 2-methyl-5-nitro-4-(p-tolyl)-4,5-dihydrofuran-3-carboxylate **3-6g**



3-6g

A light yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.13 (t, *J* = 6.9 Hz, 3H), 2.35 (s, 3H), 2.50 (d, *J* = 1.9 Hz, 3H), 4.06 (dd, *J* = 7.0 Hz, 14.5 Hz, 2H), 4.56 (s, 1H), 5.76 (d, *J* = 1.9 Hz, 1H), 7.10 (d, *J* = 8.2 Hz, 2H), 7.17 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.7, 14.0, 21.1, 55.5, 60.2, 107.9, 109.7, 126.9, 129.7, 134.9, 138.0, 163.4, 166.8; The ee value is 92%, t_R (major) = 24.96 min, t_R (minor) = 21.87 min (Chiralcel IC, λ = 254 nm, 0.8 % *i*PrOH/hexanes, flow rate = 0.5 mL/min); HRMS (EI) m/z calcd for $C_{15}H_{17}O_3$ [M-NO_2] = 245.1178, found = 245.1174; $[\alpha]^{27}_D$ = -15.6 (c 0.95, $CHCl_3$).

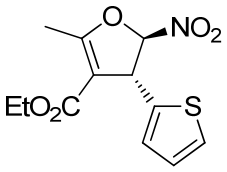
(4*R*,5*R*)-Ethyl 4-(4-methoxyphenyl)-2-methyl-5-nitro-4,5-dihydrofuran-3-carboxylate **3-6h**



3-6h

A light yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.13 (t, *J* = 7.0 Hz, 3H), 2.50 (d, *J* = 1.3 Hz, 3H), 3.80 (s, 3H), 4.02-4.11 (m, 2H), 4.55 (s, 1H), 5.75 (d, *J* = 1.9 Hz, 1H), 6.88 (d, *J* = 8.2 Hz, 2H), 7.49 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.7, 14.0, 55.2, 55.3, 60.2, 108.0, 109.8, 114.5, 128.1, 130.0, 159.6, 163.4, 166.7; The ee value is 99%, t_R (major) = 30.11 min, t_R (minor) = 26.69 min (Chiralcel IA, λ = 254 nm, 1.2 % *i*PrOH/hexanes, flow rate = 0.5 mL/min); HRMS (EI) m/z calcd for $C_{15}H_{17}O_6N$ [M] = 307.1056, found = 307.1041; $[\alpha]^{27}_D$ = -18.8 (c 0.85, $CHCl_3$).

(4*R*,5*R*)-Ethyl 2-methyl-5-nitro-4-(thiophen-2-yl)-4,5-dihydrofuran-3-carboxylate **3-6i**

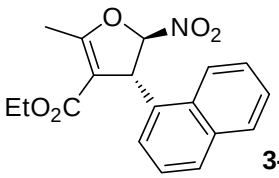


3-6i

An orange oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.17 (t, *J* = 6.9 Hz, 3H), 2.49 (d, *J* = 1.3 Hz, 3H), 4.07-4.17 (m, 2H), 4.91 (s, 1H), 5.83 (d, *J* = 1.3 Hz, 1H), 6.99-7.00 (m, 2H), 7.27 (d, *J* = 5.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 14.0, 50.9, 60.4, 107.8, 109.2, 125.5, 127.4, 140.9, 163.1, 167.3; The ee value is 95%, t_R (major) = 18.42 min, t_R (minor) = 16.76 min (Chiralcel IC, λ = 254 nm, 0.8 % *i*PrOH/hexanes, flow rate = 0.5 mL/min); HRMS (EI) m/z calcd for $C_{12}H_{13}O_3S$ [M-NO_2] = 237.0585, found = 237.0585; $[\alpha]^{27}_D$ = -22.0 (c 0.80, $CHCl_3$).

(4*R*,5*R*)-Ethyl 2-methyl-4-(naphthalen-1-yl)-5-nitro-4,5-dihydrofuran-

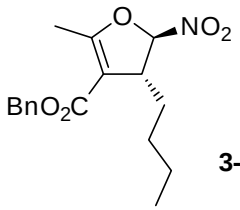
3-carboxylate **3-6j**



3-6j

A brown oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.03 (t, *J* = 7.3 Hz, 3H), 2.60 (d, *J* = 1.9 Hz, 3H), 4.02-4.06 (m, 2H), 5.46 (s, 1H), 5.77 (s, 1H), 7.21 (d, *J* = 7.0 Hz, 1H), 7.43 (t, *J* = 7.9 Hz, 1H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.68 (t, *J* = 8.2 Hz, 1H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.93 (d, *J* = 8.2 Hz, 1H), 8.45 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 14.0, 60.3, 107.1, 109.3, 123.1, 125.3, 126.2, 127.1, 129.1, 129.2, 131.1, 132.8, 134.2, 163.5, 167.9; The ee value is 91%, t_R (major) = 18.75 min, t_R (minor) = 16.69 min (Chiralcel IC, λ = 254 nm, 1.0 % *i*PrOH/hexanes, flow rate = 0.5 mL/min); HRMS (EI) m/z calcd for $C_{18}H_{17}O_3$ [M-NO_2] = 281.1636, found = 281.1632; $[\alpha]^{27}_D$ = -11.3 (c 1.00, $CHCl_3$).

(4*R*,5*R*)-Benzyl 4-butyl-2-methyl-5-nitro-4,5-dihydrofuran-3-carboxylate **3-6k**

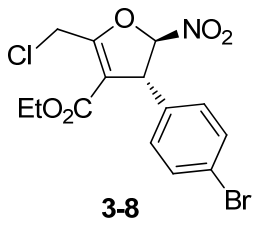


3-6k

A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.83-0.93 (m, 3H), 1.24-1.36 (m, 6H), 2.37(d, *J* = 1.3 Hz, 3H), 3.41-3.44 (m, 1H), 5.13 (d, *J* = 12.6 Hz, 1H), 5.22 (d, *J* = 12.6 Hz, 1H), 5.68 (d, *J* = 1.9 Hz, 1H), 7.33-7.39 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 13.9, 22.2, 28.1, 31.5, 50.7, 66.1, 107.2, 107.9, 128.2, 128.3, 128.6,

135.8, 163.6, 166.7; The ee value is 93%, t_R (major) = 43.54 min, t_R (minor) = 53.51 min (Chiralcel OJ, λ = 254 nm, 0.8 % *i*PrOH/hexanes, flow rate = 0.5 mL/min); HRMS (EI) m/z calcd for $C_{17}H_{21}O_3$ [M-NO_2] = 273.1482, found = 273.1480; $[\alpha]^{27}_D$ = 4.1 (c 0.60, $CHCl_3$).

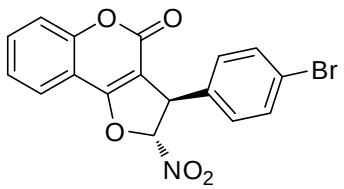
(4*R*,5*R*)-Ethyl 4-(4-bromophenyl)-2-(chloromethyl)-5-nitro-4,5-dihydrofuran-3-carboxylate **3-8**



3-8

A light yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15 (t, *J* = 7.3 Hz, 3H), 4.11 (dd, *J* = 7.2 Hz, 14.2 Hz, 2H), 4.61 (t, *J* = 5.4 Hz, 2H), 4.90 (d, *J* = 12.0 Hz, 1H), 5.83 (d, *J* = 1.9 Hz, 1H), 7.10-7.13 (m, 2H), 7.51-7.54 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 34.5, 55.2, 61.2, 108.7, 110.6, 122.8, 128.7, 132.5, 135.8, 161.8, 162.8; The ee value is 95%, t_R (major) =55.66 min, t_R (minor) = 50.53 min (Chiralcel AD-H, λ = 254 nm, 0.6 % *i*PrOH/hexanes, flow rate = 0.5 mL/min); HRMS (EI) m/z calcd for $C_{14}H_{13}ClO_3{}^{81}Br$ [M-NO_2] = 345.4554, found = 345.4551; $[\alpha]^{27}_D$ = -23.7 (c 1.00, $CHCl_3$).

(2*R*,3*R*)-3-(4-Bromophenyl)-2-nitro-2H-furo[3,2-c]chromen-4(3H)-one **3-10**



3-10

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.92 (d, *J* = 1.9 Hz, 1H), 6.21 (d, *J* = 2.5 Hz, 1H), 7.16 (d, *J* = 8.2 Hz, 2H), 7.42-7.48 (m, 2H), 7.53 (d, *J* = 8.2 Hz, 2H), 7.69-7.73 (m, 1H), 7.87 (dd, *J* = 1.3 Hz, 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 53.1, 104.3, 110.9, 111.0, 117.3, 123.1, 123.2, 124.8, 128.8, 132.7, 134.0, 134.5, 155.6, 157.9, 165.8; The ee value is 91%, t_R (major) =37.16 min, t_R (minor) = 22.23 min (Chiralcel IC, λ = 254 nm, 20 % *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{17}H_{10}NO_5BrNa$ [M+Na] = 409.9638, found = 409.9635; $[\alpha]^{27}_D$ = -11.6 (c 0.80, $CHCl_3$).

Chapter 4 Diastereodivergent Synthesis of 3-Spirocyclo -propyl-2-oxindoles through Direct Enantioselective Cyclopropanation of Oxindoles

4.1 Introduction

Oxindoles are structural motifs that are widely present in natural products and medicinally important agents.[1] In particular, spirocyclic oxindoles bearing a quaternary stereogenic center at the 3-position possess significant biological profiles.[2] In this context, syntheses of 3-spirocyclic oxindoles bearing a five[3] or six-membered[4] ring system have been intensively investigated due to the biological importance of these molecules. Spiro cyclopropyl oxindoles have shown remarkable biological activities (Figure 4.1),[5] moreover, they are also molecules of high synthetic values.[6]

[1] For selected reviews, see: a) C. Marti, E. M. Carreira, *Eur. J. Org. Chem.* **2003**, 2209; b) A. B. Dounay, L. E. Overman, *Chem. Rev.* **2003**, *103*, 2945; c) C. V. Galliford, K. A. Scheidt, *Angew. Chem. Int. Ed.* **2007**, *46*, 8748; d) B. M. Trost, M. K. Brennan, *Synthesis*, **2009**, *18*, 3003.

[2] G. S. Singh, Z. Y. Desta, *Chem. Rev.* **2012**, *112*, 6104; (b) R. Dalpozzo, G. Bartoli, G. Bencivenni, *Chem. Soc. Rev.* **2012**, *41*, 7247; (c) N. R. Ball-Jones, J. J. Badillo, A. K. Franz, *Org. Biomol. Chem.* **2012**, *10*, 5165; (d) L. Hong, R. Wang, *Adv. Synth. Catal.* **2013**, *355*, 1023.

[3] For representative examples, see: a) S. Edmondson, S. J. Danishefsky, S.-L. Laura, N. Rosen, *J. Am. Chem. Soc.* **1999**, *121*, 2147; b) P. R. Sebahar, R. M. Williams, *J. Am. Chem. Soc*. **2000**, *122*, 5666; c) C. Marti, E. M. Carreira, *J. Am. Chem. Soc.* **2005**, *127*, 11505; d) K. Ding, Y. Lu, N.-C. Zaneta, S. Qiu, Y. Ding, W. Gao, J. Stuckey, K. Krajewski, P. P. Roller, Y. Tomita, D. A. Parrish, J. R. Deschamps, S. Wang, *J. Am. Chem. Soc.* **2005**, *127*, 10130; e) A. K. Franz, P. D. Dreyfuss, S. L. Schreiber, *J. Am. Chem. Soc.* **2007**, *129*, 1020; f) B. M. Trost, N. Cramer, S. M. Silverman, *J. Am. Chem. Soc.* **2007**, *129*, 12396; g) B. M. Trost, N. Cramer, H. Bernsmann, *J. Am. Chem. Soc.* **2007**, *129*, 3086; h) X.-H. Chen,W. Wei, S.-W. Luo, H. Xiao, L.-Z. Gong, *J. Am. Chem. Soc.* **2009**, *131*, 13819.

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Surprisingly, methods for the preparation of 3-spirocyclopropane-2-oxindoles are very limited.[7] To the best of our knowledge, only one example describing enantioselective construction of cyclopropyl spirooxindoles was reported recently; Bartoli and Bencivenni utilized a Michael–alkylation cascade to realize enantioselective nitrocyclopropanation of 3-alkylidene oxindoles.[8] As part of our ongoing efforts towards efficient creation of quaternary stereogenic centers and chiral spirooxindole derivatives,[9] we became interested in developing an enantioselective synthetic method for the direct cyclopropanation of oxindole substrates.

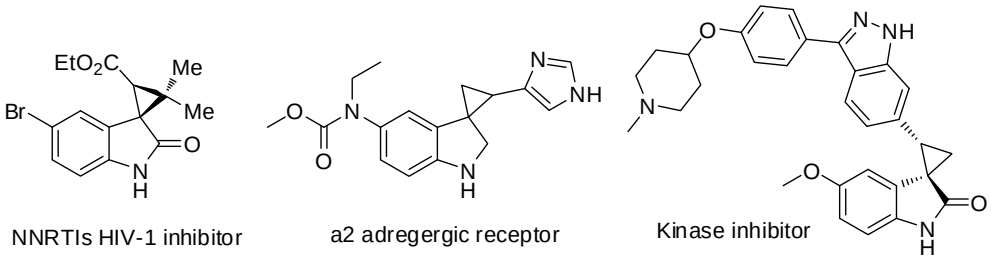

Figure 4.1 Bioactive molecules containing a spiro cyclopropyl oxindole/indoline motif

The asymmetric cyclopropanation reactions have fascinated organic chemists for decades as the cyclopropane motif is both synthetically useful and biologically important.[10] The well-established synthetic strategies for asymmetric

[7] For the preparation of non-chiral spiro cyclopropyl oxindoles, see: a) M. K. Eberle, G. G. Kahle, M. J. Shapiro, *J. Org. Chem.* **1982**, *47*, 2210; b) P. Shanmugam, V. Caithiyanathan, B. Viswambharan, *Tetrahedron* **2006**, *62*, 4342; c) S. R. Yong, A. T. Ung, S. G. Pyne, B. W. Skelton, A. H. White, *Tetrahedron* **2007**, *63*, 1191; d) S. Muthusamy, D. Azhagan, B. Gnanaprakasam, E. Suresh, *Tetrahedron Lett.* **2010**, *51*, 5662; e) H. Yu, Y. Liu, H. Zhang, J. Chen, H. Deng, M. Shao, Z. Ren, W. Cao, *Tetrahedron* **2010**, *66*, 2598; f) S. Jaegli, J.-P. Vors, L. Neuville, J. Zhu, *Tetrahedron* **2010**, *63*, 8911.

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[9] a) X. Han, Y. Wang, F. Zhong, Y. Lu, *J. Am. Chem. Soc.* **2011**, *133*, 1726; (b) F. Zhong, X. Han, Y. Wang, Y. Lu, *Angew. Chem. Int. Ed.* **2011**, *50*, 7837; c) Q. Zhu, Y. Lu, *Angew. Chem. Int. Ed.* **2010**, *49*, 7753; d) X. Han, J. Kwiatkowski, F. Xue, K.-W. Huang, Y. Lu, *Angew. Chem. Int. Ed.* **2009**, *48*, 7604; e) Q. Zhu, Y. Lu, *Chem. Commun.* **2010**, *46*, 2235; f) Z. Jiang, Y. Lu, *Tetrahedron Lett.* **2010**, *51*, 1884; g) J. Luo, L.-W. Xu, R. A. S. Hay, Y. Lu, *Org. Lett.* **2009**, *11*, 437; h) X. Han, J. Luo, C. Liu, Y. Lu, *Chem. Commun.* **2009**, 2044; i) X. Han, F. Zhong, Y. Lu, *Adv. Synth. Catal.* **2010**, *352*, 2778; j) F. Zhong, G.-Y. Chen, Y. Lu, *Org. Lett.* **2011**, *13*, 82.

[10] For selected reviews, see: a) M.-N. Roy, V. N. G. Lindsay, A. B. Charette, *Science of Synthesis, Stereoselective synthesis* **2011**, *1*, 731; b) A. B. Charette, A. Beauchemin, *Org. React.* **2001**, *58*, 1; c) H. Lebel, J.-F. Marcoud, C. Molinaro, A. B. Charette, *Chem. Rev.* **2003**, *103*, 977; d) H. Pellissier, *Tetrahedron* **2008**, *64*, 7041; e) C. A. Carson, M. A. Kerr, *Chem. Soc. Rev.* **2009**, *38*, 3051; f) M. J. Campbell, J. S. Johnson, A. T. Parsons, P. D. Pohlhaus, S. D.

cyclopropanation include Simmons–Smith reaction,[11] transition metal-catalyzed decomposition of diazoalkanes,[12] Michael-initiated ring closure reactions,[13] and others.[14] In the past few years, organocatalytic cyclopropanations have emerged as a powerful approach for the construction of chiral cyclopropanes.[15] However, a direct cyclopropanation method to access spiro cyclopropyl oxindoles has yet to be developed. In the reported organocatalytic cyclopropanation approaches, α-halogenated carbonyl compounds are commonly utilized as a C1 synthon, which contains a nucleophilic/electrophilic center for the construction of cyclopropanes. From a practical viewpoint, it would be ideal if simple oxindoles can be used directly as a C1 synthon for the synthesis of cyclopropyl spirooxindoles. We envisioned that employment of oxindoles containing a dinucleophilic center as a C1 synthon, in combination with a suitable dielectrophilic C2 synthon (e.g. halogenated

Sanders, *J. Org. Chem.* **2010**, *75*, 6317.

[11] a) H. E. Simmons, R. D. Smith, *J. Am. Chem. Soc.* **1959**, *81*, 4256. For recent examples, see: b) M.-C. Lecasse, C. Poulard, A. B. Charette, *J. Am. Chem. Soc.* **2005**, *127*, 12440; c) H. Shitama, T. Katsuki, *Angew. Chem. Int. Ed.* **2008**, *47*, 2450.; d) L. E. Zimmer, A. B. Charette, *J. Am. Chem. Soc.* **2009**, *131*, 15624; e) S. R. Goudreau, A. B. Charette, *J. Am. Chem. Soc.* **2009**, *131*, 15633; f) J. A. Bull, A. B. Charette, *J. Am. Chem. Soc.* **2010**, *132*, 1895.

[12] For recent selected examples, see: a) S. Zhu, J. V. Ruppel, H. Lu, L. Wojtas, X. P. Zhang, *J. Am. Chem. Soc.* **2008**, *130*, 5042; b) D. Marcoux, A. B. Charette, *Angew. Chem. Int. Ed.* **2008**, *47*, 10155; c) S. Zhu, J. A. Perman, X. P. Zhang, *Angew. Chem. Int. Ed.* **2008**, *47*, 8460; d) D. Marcoux, S. Azzi, A. B. Charette, *J. Am. Chem. Soc.* **2009**, *131*, 6970; e) V. N. G. Lindsay, W. Lin, A. B. Charette, *J. Am. Chem. Soc.* **2009**, *131*, 16383; f) M. Ichinose, H. Suematsu, T. Katsuki, *Angew. Chem. Int. Ed.* **2009**, *48*, 3121; g) S. Zhu, X. Xu, J. A. Perman, X. P. Zhang, *J. Am. Chem. Soc.* **2010**, *132*, 12796; h) T. Nishimura, Y. Maeda, T. Hayashi, *Angew. Chem. Int. Ed.* **2010**, *49*, 7324; i) V. N. G. Lindsay, C. Nicolas, A. B. Charette, A. B. *J. Am. Chem. Soc.* **2011**, *133*, 8972.

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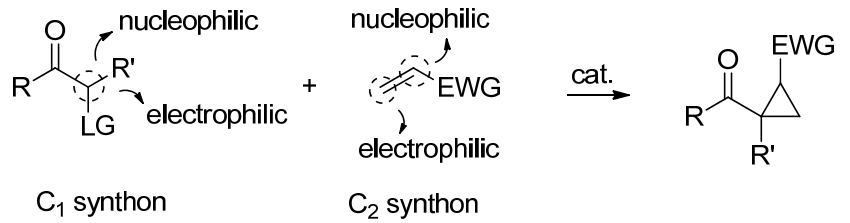
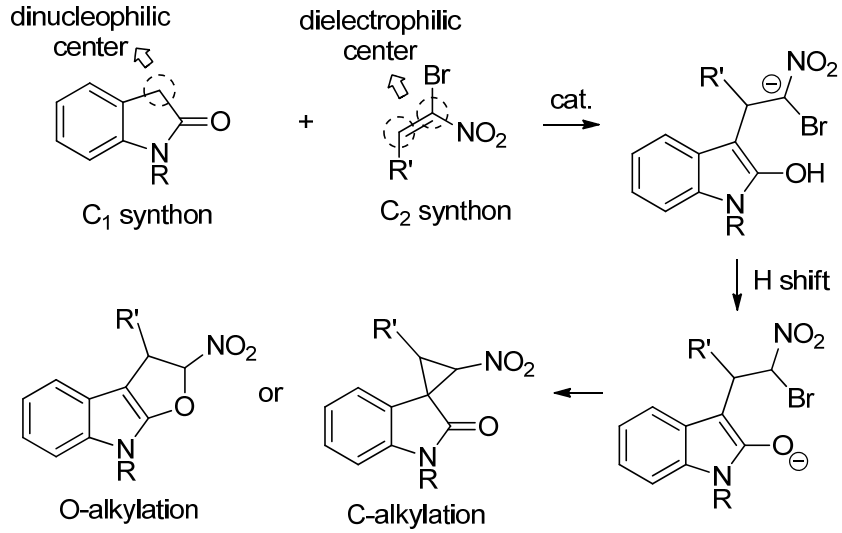
[14] a) B. Moreau, A. B. Charette, *J. Am. Chem. Soc.* **2005**, *127*, 18014; b) R. Shintani, S. Park, T. Hayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 14866; c) W. Liu, D. Chen, X.-Z. Zhu, X.-L. Wan, X.-L. Hou, *J. Am. Chem. Soc.* **2009**, *131*, 8734; d) H. Y. Kim, L. Salvi, P. J. Carroll, P. J. Walsh, *J. Am. Chem. Soc.* **2010**, *132*, 402.

[15] a) C. D. Papageorgiou, S. V. Ley, M. J. Gaunt, *Angew. Chem. Int. Ed.* **2003**, *42*, 828; b) C. D. Papageorgiou, M. A. C. Dios, S. V. Ley, M. J. Gaunt, *Angew. Chem. Int. Ed.* **2004**, *43*, 4641; c) N. Bremeyer, S. C. Smith, S. V. Ley, M. J. Gaunt, *Angew. Chem. Int. Ed.* **2004**, *43*, 2681; d) R. K. Kunz, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 3240; e) C. C. C. Johansson, N. Bremeyer, S. V. Ley, D. R. Owen, S. C. Smith, M. J. Gaunt, *Angew. Chem. Int. Ed.* **2006**, *45*, 6024; f) S. H. McCooey, T. McCabe, S. J. Connon, *J. Org. Chem.* **2006**, *71*, 7494; g) H. Xie, L. Zu, H. Li, J. Wang, W. Wang, *J. Am. Chem. Soc.* **2007**, *129*, 10886; h) R. Rios, H. Sundén, J. Vesely, G.-L. Zhao, P. Dziedzic, A. Córdova, *Adv. Synth. Catal.* **2007**, *349*, 1028; i) I. Ibrahem, G.-L. Zhao, R. Rios, J. Vesely, H. Sundén, P. Dziedzic, A. Córdova, *Chem. Eur. J.* **2008**, *14*, 7867; j) Y. Xuan, S. Nie, L. Dong, J. Zhang, M. Yan, *Org. Lett.* **2009**, *11*, 1583; k) V. Terrasson, A. Lee, R. M. Figueiredo, J. M. Campagne, *Chem. Eur. J.* **2010**, *16*, 7875; l) Y. Cheng, J. An, L.-Q. Lu, L. Luo, Z.-Y. Wang, J.-R. Chen, W.-J. Xiao, *J. Org. Chem.* **2011**, *76*, 281.

nitroolefines), may provide a straightforward cyclopropanation strategy. In the presence of a suitable catalyst, oxindole can readily add to nitroolefin. Followed by intramolecular proton transfer, an S_N2 substitution is expected to generate the cyclopropane core. Apparently, the O-alkylation product may also be formed, in addition to the desired C-alkylation product (Scheme 4.1). It is noteworthy that utilization of a dinucleophilic C1 synthon in asymmetric organocatalytic cyclopropanation is unknown, and the use of halogenated nitroolefins in asymmetric cyclopropanation has also not been disclosed. Notably, Connon and co-workers described a stereoselective synthesis of functioanlized nitrocyclopropanes employing nitroolefins as a reaction component. However, their attempt of utilizing halogenated nitroolefin in the asymmetric cyclopropanantion led to disappointing results.[15f] Herein, we describe the first direct highly diastereoselective and enantioselective cyclopropanation of oxindoles by employing oxindoles as readily available C1 synthon and (*E*)-β,β-bromo nitroolefins as a convenient C2 synthon.



Reported organocatalytic cyclopropanation approach



Synthesis of cyclopropyl spirooxindoles employing dinucleophilic/electrophilic synthons

Scheme 4.1 Organocatalytic approaches to access cyclopropanes and cyclopropyl spirooxindoles

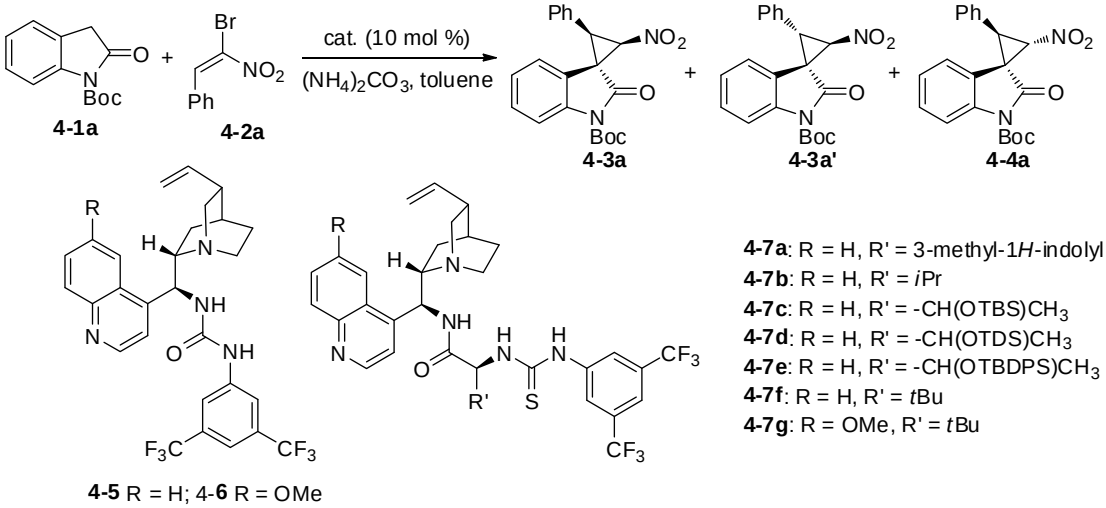
4.2 Results and Discussion

4.2.1 Reaction Optimization

We initiated our study by examining the reaction between N-Boc-protected oxindole **4-1a** and (*E*)-β,β-bromo nitrostyrene **4-2a** (Table 4.1). Tertiary amine~thiourea catalysts were selected to promote the projected reaction. As HBr would be generated during the reaction process, thus a stoichiometric amount of $(NH_4)_2CO_3$ was used as HBr scavenger, since $(NH_4)_2CO_3$ could capture the released HBr and not induce undesired background reaction. Cinchona alkaloid-derived **4-5**

and **4-6** promoted the reaction efficiently, furnishing three diastereomers **4-3a**, **4-3a'**[16] and **4-4a** in high yields and with excellent enantioselectivities, but with very poor diastereoselectivities (Table 4.1, entries 1–2). To further improve the results, we chose to employ our recently developed amino acid-incorporating multifunctional catalysts. All the multifunctional catalysts could efficiently promote the reaction, affording the desired C-alkylation products **4-3a**, **4-3a'** and **4-4a** in high yields. Fine tuning the side chain of the amino acid moiety of the catalysts led to formation of **4-3a** and **4-4a** with excellent enantioselectivity and diastereoselectivity. However, the selectivity between **4-3a** and **4-4a** remained poor (Table 4.1, entries 3–9).

Table 4.1 Cyclopropanation of Oxindole **4-1a** Catalyzed by Different Tertiary Amine Thiourea Catalysts[a]



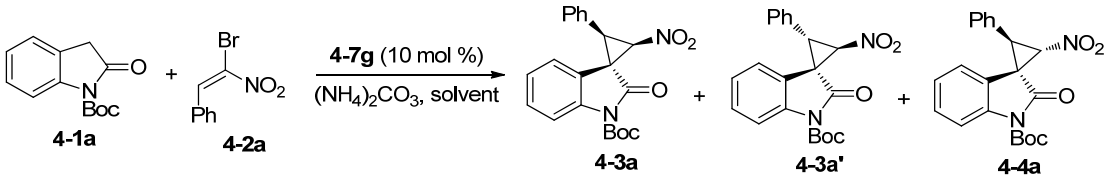
entry	cat	yield (%)[b]	**4-3a**:**4-3a'**:**4-4a**[c]	*ee* (%)[d] **4-3a**	**4-3a'**	**4-4a**
1	**4-5**	95	28:58:14	90	93	n.d.
2	**4-6**	97	44:44:12	88	93	n.d.
3	**4-7a**	82	46:12:42	57	n.d.	80

[16] 3a' is a known compound reported in reference 8.

4	**4-7b**	85	43:14:43	75	n.d.	87
5	**4-7c**	95	45:6:49	72	n.d.	85
6	**4-7d**	95	45:5:50	78	n.d.	86
7	**4-7e**	97	39:4:57	85	n.d.	86
8	**4-f**	98	52:6:42	96	n.d.	92
9	4-g	98	53:5:42	97	n.d.	92

[a] Reactions were performed with **4-1a** (0.05 mmol), **4-2a** (0.06 mmol) , $(NH_4)_2CO_3$ (0.05 mmol) and the catalyst (0.005 mmol, 10 mol %) in toluene (1.0 mL) at room temperature for 3h. Products **4-3a**, **4-3a'** was obtained as a mixture and **4-4a** were easily separated by column chromatography. [b] Combined isolated yield of three stereoisomers. [c] Determined by ^{1}H NMR analysis of the crude products. [d] Determined by HPLC analysis on a chiral stationary phase. (n.d.: not determined)

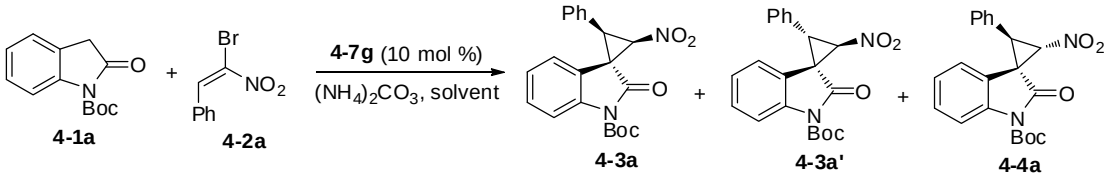
Table 4.2 Solvent Effects on the **4-7g** Catalyzed Asymmetric Cyclopropanation of Oxindole **4-1a**[a]



entry	solvent	yield (%)[b]	**4-3a**:**4-3a'**:**4-4a**[c]	*ee* (%)[d] **4-3a**
1	Hexane	95	43:7:50	n.d.
2	Xylene	97	51:4:45	92
3	THF	93	28:58:14	n.d.
4	Et_2O	88	50:6:44	n.d.
5	$CHCl_3$	98	57:11:32	96
6	CH_2Cl_2	98	61:11:28	93
7	DCE	97	53:18:29	n.d.

[a] Reactions were performed with **4-1a** (0.05 mmol), **4-2a** (0.06 mmol) , $(NH_4)_2CO_3$ (0.05 mmol) and **4-7g** (0.005 mmol, 10 mol %) in solvent (1.0 mL) at room temperature for 3h. [b] Combined isolated yield of three stereoisomers. [c] Determined by ^{1}H NMR analysis of the crude products. [d] ee values of **4-3a**, determined by HPLC analysis on a chiral stationary phase. (n.d.: not determined; DCE: Dichloroethane)

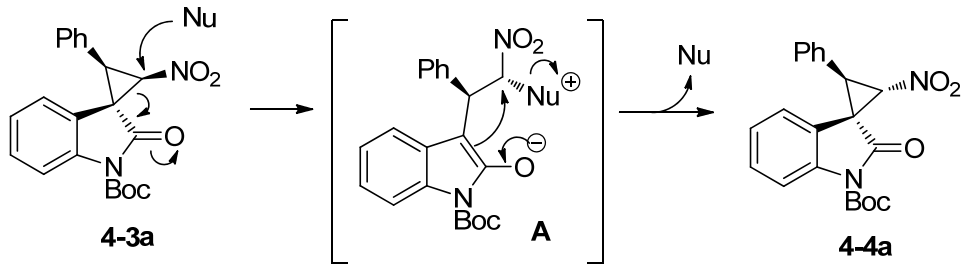
Table 4.3 Survey of Additives, Temperature and Catalyst Loading Effects on **4-7g** Catalyzed Asymmetric Cyclopropanation of Oxindole **4-1a**[a]



entry	solvent	conditions	yield (%)[b]	**4-3a**:**4-3a'**:**4-4a**[c]	*ee* (%)[d] **4-3a**
1	$CHCl_3$	4 Å MS, rt	98	63:13:24	95
2	CH_2Cl_2	4 Å MS, rt	97	65:13:22	92
3	$CHCl_3$	3 Å MS, rt	98	66:10:24	95
4	$CHCl_3$	5 Å MS, rt	98	67:9:24	97
5	$CHCl_3$	5 Å MS, -20°C	87	64:11:25	95
6	$CHCl_3$	5 mol % cat, rt	95	53:13:34	94

[a] Reactions were performed with **4-1a** (0.05 mmol), **4-2a** (0.06 mmol) , $(NH_4)_2CO_3$ (0.05 mmol) and **4-7g** (0.005 mmol, 10 mol %) in solvent (1.0 mL) at room temperature for 3h. [b] Combined isolated yield of three stereoisomers. [c] Determined by ^{1}H NMR analysis of the crude products. [d] ee values of **4-3a**, determined by HPLC analysis on a chiral stationary phase. (n.d.: not determined)

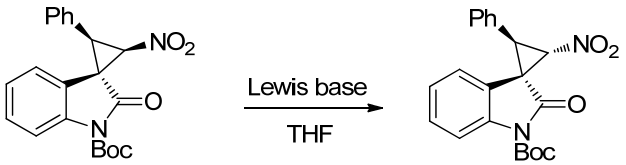
Solvent studies showed that CH_2Cl_2 and $CHCl_3$ were superior to other for **4-3a** synthesis (Table 4.2). Gratifyingly, further extensive additive studies resulted in promising results; when the reaction was performed in chloroform in the presence of 5 Å molecular sieves, cyclopropyl spirooxindole **4-3a** was obtained in good yield and excellent *ee* value (Table 4.3, entry 4). Further optimization did not help to improve the results, lower the reaction temperature or catalyst loading led to decline of selectivities (Table 4.3, entries 5−6).



Scheme 4.2 Conversion of **4-3a** to **4-4a** *via* nucleophilic catalyst-initiated cyclopropane ring opening–closing process

Having stereoselectively obtained spirocyclopropanes **4-3a**, our next task was to devise a diastereodivergent approach to selectively access cyclopropanes **4-4a**. It is well-established that the activated cyclopropanes can be readily opened by nucleophiles,[17] we therefore considered the possibility of converting **4-3a** to **4-4a** via cyclopropane opening–closing process. We reasoned that the employment of a suitable nucleophile may lead to the opening of the cyclopropane ring **4-3a**, highly stabilized oxindole enolate makes the opening at the α-position of the nitro group favorable, and the subsequent ring closure may yield **4-4a** (Scheme 4.2).

Table 4.4 Lewis Base-initiated Conversion of **4-3a** to **4-4a**[a]



4-3a (95% ee) **4-4a**

entry	base	t (h)	yield (%)[b]	dr[c]	*ee* (%)[d] **4-4a**

[17] For selected examples on nucleophilic openings of activated nitrocyclopropanes: a) R. K. Dieter, S. Pounds, *J. Org. Chem.* **1982**, *47*, 3174; b) R. P. Wurz, A. B. Charette, *Org. Lett.* **2005**, *7*, 2313; c) E. M. Budynina, O. A. Ivanova, E. B. Averina, T. S. Kuznetsova, N. S. Zefirov, *Tetrahedron Lett.* **2006**, *47*, 647; d) O. Lifchits, A. B. Charette, *Org. Lett.* **2008**, *10*, 2809; e) O. Lifchits, D. Alberico, I. Zakharian, A. B. Charette, *J. Org. Chem.* **2008**, *73*, 6838.

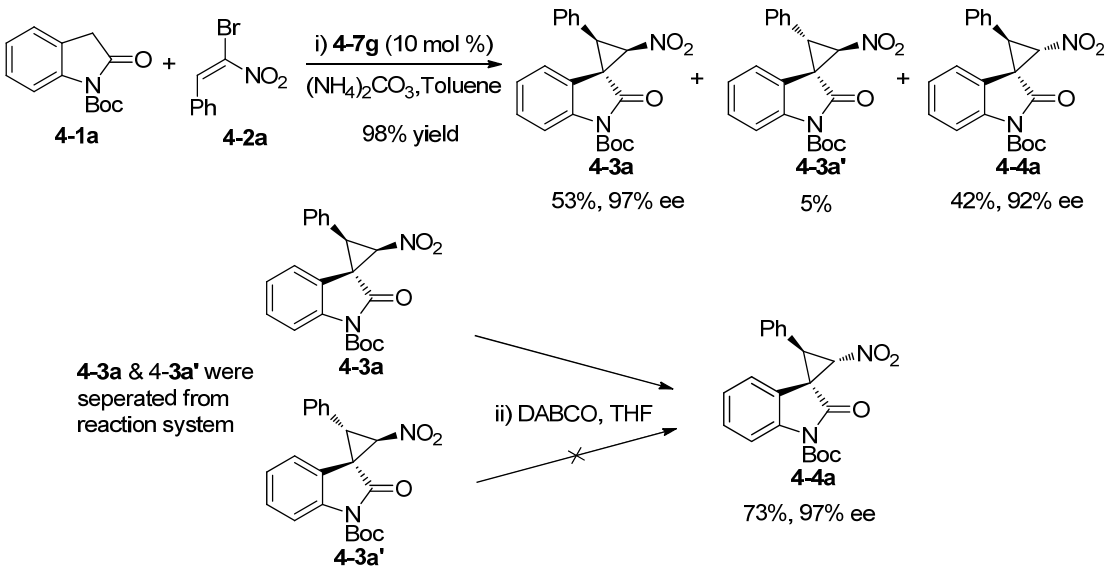
1	DIPEA	12	trace	-	-
2	Et_3N	6	42	>20:1	94
3	DMAP	24	47	>20:1	95
4	DABCO	6	73	>20:1	95
5	PPh_3	24	-	-	-
6	Quinine	6	22	>20:1	86

[a] Reactions were performed with **4-3a** (0.05 mmol), base (0.05 mmol) in THF (0.5 mL) at room temperature. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis. [d] ee values of **4-4a**, determined by HPLC analysis on a chiral stationary phase.

The feasibility of converting **4-3a** to **4-4a** in the presence of a number of Lewis bases was studied (Table 4.4). When diisopropylethylamine (DIPEA) was used, only trace amount of **4-4a** was observed, suggesting the importance of the nucleophilicity of the promoting base (entry 1). Both triethylamine and dimethylaminopyridine (DMAP) could promote conversion of **4-3a** to **4-4a** without affecting the *ee* values, however, yields were unsatisfactory (entries 2–3). DABCO was found to be the most effective promoter, leading to the formation of **4-4a** in good yield, and the enantiomeric excess of the product was maintained (entry 4). Triphenylphosphine, however, was found to be completely ineffective (entry 5). A chiral base quinine was also introduced to the epimerization process, however, low conversion and lower ee value were observed (entry 6). It is noteworthy that **4-3a'** remained unchanged in the epimerization process of **3a**. We believe that the conversion of **4-3a** to **4-4a** was initiated by the nucleophilic attack of the nucleophilic amine on the cyclopropane ring, as the ammonium enolate intermediate[18] (Scheme 4.2, **A**: Nu = DABCO) was

[18] HRMS (ESI) m/z calcd for $C_{27}H_{33}N_4O_5$ $[M+H]^+$= 493.2445, found 493.2450, see the experimental section for the MS spectrum. For an excellent review on the uses of ammonium enolate, see: M. J. Gaunt, C. C. C. Johansson, *Chem. Rev.* **2007**, *107*, 5596.

observed in mass spectroscopy during the reaction process.



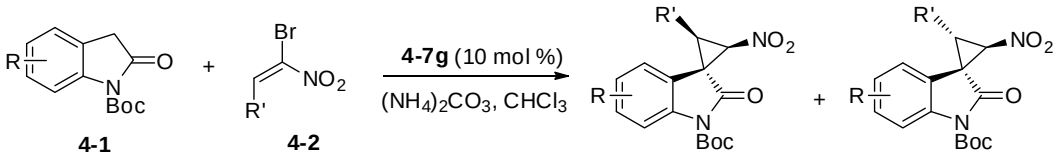
Scheme 4.3 Reaction sequence for the synthesis of cyclopropyl spirooxindoles **4-4a**

With the effective method for the creation of **4-4a** from **4-3a** in hand, we then proceeded to directly prepare cyclopropanes **4-4a** from oxindoles **4-1a** and bromonitroolefins **4-2a** (Scheme 4.3). Following the reaction conditions we had established (Table 4.1, entry 9), **4-3a** and **4-3a'** were separated from the reaction system and obtained as a mixture (**4-3a**:**4-3a'** = 53:3, **3a** 97% ee) while **4-4a** was obtained in 92% ee. DABCO was then introduced to effect the conversion of **4-3a** to **4-4a**. The epimerization from **4-3a** lead to the formation of **4-4a** in high yield and the enantiomeric excess of the product was maintained. The final products **4-4a** were derived from two sources; via direct cyclopropanation reaction and epimerization from **4-3a**, and it was obtained in 82% overall yield and 95% ee.

4.2.2 Substrate Scope

With the optimized reaction condition in hand, the generality of **4-7g** catalyzed asymmetric cyclopropanation of oxindoles was then investigated. The substrate scope for preparation of spirocyclopropyl oxindoles **4-3** was first investigated (Table 4.5). Both oxindoles and bromonitroolefins could be varied, and cyclopropyl spiroxindoles **4-3** were obtained in good diastereomeric ratios and excellent enantioselectivities (entries 1–10). When alkyl bromonitroolefin **4-2q** was employed, product with high *ee* was attainable, although only with moderate yield and poor diastereoselectivity (entry 11). When the reaction was performed at a larger scale, similar results were obtained (entry 12).

Table 4.5 The Substrate Scope of the Direct Cyclopropanation Reaction for Preparation of Spirooxindoles **4-3**[a]



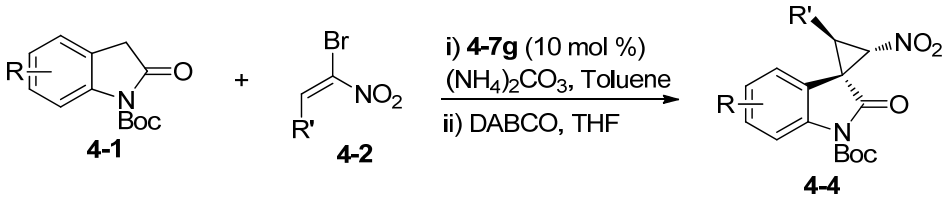
entry	R/R'	t (h)	**4-3**	dr (**4-3**:**4-3'**)[b]	yield (%)[c]	ee (%)[d]
1[e]	H/C_6H_5	12	**4-3a**	87:13	72	97
2[e]	H/3-Br-C_6H_4	12	**4-3c**	81:19	81	90
3[e]	H/4-Br-C_6H_4	24	**4-3d**	81:19	75[f]	95
4[e]	H/2-F-C_6H_4	72	**4-3g**	86:14	63[f]	96
5	H/4-F-C_6H_4	36	**4-3h**	82:18	76[f]	97
6	H/4-Cl-C_6H_4	24	**4-3f**	82:18	68[f]	98
7	H/2-Me-C_6H_4	36	**4-3i**	>20:1	60	97
8	H/4-Me-C_6H_4	36	**4-3j**	88:12	72[f]	98
9[e]	6-Cl/C_6H_5	12	**4-3s**	88:12	68	93
10	6-Cl/2-BrC_6H_4	12	**4-3o**	92:8	45	99

11	H/phenethyl	36	**4-3q**	57:43	46	93
12[e,g]	H/C_6H_5	12	**4-3a**	85:15	68	95

[a] Reactions were performed with **4-1** (0.05 mmol), **4-2** (0.06 mmol), $(NH_4)_2CO_3$ (0.05 mmol) and **4-7g** (0.005 mmol, 10 mol %) in $CHCl_3$ (1.0 mL) at room temperature. [b] Determined by ^{1}H NMR analysis of the crude products. [c] Isolated yield of **4-3** and **4-3'**. [d] ee values of **4-3**, determined by HPLC analysis on a chiral stationary phase. [e] Molecular sieve (5 Å, 10 mg) was added. [f] Two diastereoisomers could be separated by silica gel column chromatography. [g] Reaction was performed with 0.5 mmol oxindole **4-1**.

Following the same procedure as preparation of **4-4a**, the substrate scope of synthesis of cyclopropyl spirooxindoles **4-4** was then investigated (Table 4.6). Consistently high chemical yields, excellent diastereoselectivities and enantioselectivities were attainable for a wide range of aryl bromonitroolefins (entries 1–13). Variation of the substitutions on the oxindole rings was also tolerated (entries 14–15). Alkyl bromonitroolefins were suitable for the reaction, high ee values, chemical yields, and moderate diastereoselectivities were attainable (entries 16–17). The reaction repeated well at a larger scale (entry 18). The products **4-4** were derived from two sources; via direct cyclopropanation reaction and epimerization from **4-3**. Thus the ee values in Table 4.6 differed slightly from those shown in Table 4.5.

Table 4.6 The Substrate Scope of the Direct Cyclopropanation Reaction for Preparation of Spirooxindoles **4-4**[a]



entry	R/R'	**4-3**	dr[b]	yield (%)[c]	ee (%)[d]
1	H/C_6H_5	**4-4a**	>20:1	82	95
2	H/2-Br-C_6H_4	**4-4b**	>20:1	92	94

3	H/3-Br-C_6H_4	**4-4c**	>20:1	84	95
4	H/4-Br-C_6H_4	**4-4d**	>20:1	80	96
5	H/2-Cl-C_6H_4	**4-4e**	>20:1	85	95
6	H/4-Cl-C_6H_4	**4-4f**	>20:1	81	94
7	H/2-F-C_6H_4	**4-4g**	>20:1	88	94
8	H/4-F-C_6H_4	**4-4h**	>20:1	71	96
9	H/2-Me-C_6H_4	**4-4i**	>20:1	90	90
10	H/4-Me-C_6H_4	**4-4j**	>20:1	72	95
11	H/1-naphthyl	**4-4k**	>20:1	77	97
12	H/2-naphthyl	**4-4l**	>20:1	74	96
13	H/2,4-Cl-C_6H_3	**4-4m**	>20:1	86	94
14	5-Cl/2-Br-C_6H_4	**4-4n**	>20:1	91	98
15	6-Cl/2-Br-C_6H_4	**4-4o**	>20:1	95	97
16[e]	H/*iso*-butyl	**4-4p**	4:1	69	92
17[e]	H/phenethyl	**4-4q**	3:1	82	92
18[f]	6-Cl/2-Br-C_6H_4	**4-4o**	>20:1	93	96

[a] Reactions were performed with **4-1** (0.05 mmol), **4-2** (0.06 mmol) , $(NH_4)_2CO_3$ (0.05 mmol) and **4-7g** (0.005 mmol, 10 mol %) in toluene (1.0 mL) at room temperature for 6 h; in the subsequent step, crude **4-3** was separated and treated with DABCO (0.05 mmol) in THF (0.5 mL) at room temperature for 3 h. **4-4** was obtained as a sum of the **4-4** obtained in the first step and **4-4** obtained after epimerization [b] Determined by ^{1}H NMR analysis. [c] Isolated combined yield. [d] Determined by HPLC analysis on a chiral stationary phase, ee value of the final combined product. [e] Reaction time was 18 h. [f] Reaction was performed with 0.5 mmol oxindole **4-1**.

4.3 Conclusions

In summary, we have developed the first direct asymmetric cyclopropanation reaction of oxindoles. In our novel cyclopropanation strategy, we employed oxindoles with a dinucleophilic center as a C_1 synthon, and we also used bromonitroolefins containing a dielectrophilic center as a unique C_2 synthon. We believed the cyclopropanation strategy reported herein will find wide applications in synthetic

organic chemistry. By engaging DABCO as a nucleophilic catalyst, a stereochemically retentative conversion of different diastereomers of cyclopropyl spirooxindoles was discovered. We achieved highly diastereodivergent and enatioselective synthesis of 3-spirocyclopropyl-2-oxindoles, which are classes of compounds of great biological significance. Currently we are extending such novel cyclopropanation approach to prepare other cyclopropanes, and the biological evaluation of the prepared cyclopropyl spirooxindoles is underway.

4.4 Experimental Section

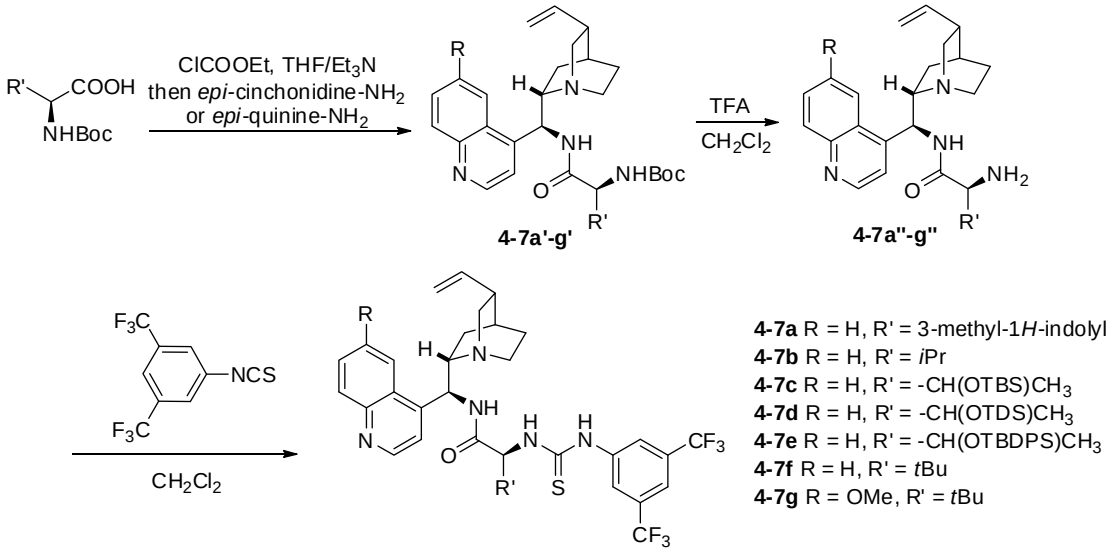
4.4.1 Material and General Methods

All the starting materials were obtained from commercial sources and used without further purification unless otherwise stated. THF and diethyl ether were dried and distilled from sodium benzophenone ketyl prior to use. $CHCl_3$ and CH_2Cl_2 were distilled from CaH_2 prior to use. ^1H and ^{13}C NMR spectra were recorded on a Bruker ACF300 or AMX500 (500 MHz) spectrometer. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (chloroform δ 7.26), carbon (chloroform δ 77.0). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), br (broad singlet). Coupling constants were reported in Hertz (Hz). Low resolution mass spectra were obtained on a Finnigan/MAT LCQ spectrometer in ESI mode, and a Finnigan/MAT 95XL- T mass spectrometer in FAB mode. All high resolution mass spectra were obtained on a Finnigan/MAT 95XL- T spectrometer. For thin layer chromatography (TLC), Merck pre-coated TLC plates (Merck 60 F254)

were used, and compounds were visualized with a UV light at 254 nm. Further visualization was achieved by staining with iodine, or ceric ammonium molybdate followed by heating on a hot plate. Flash chromatographic separations were performed on Merck 60 (0.040-0.063 mm) mesh silica gel. The enantiomeric excesses of products were determined by chiral-phase HPLC analysis.

The catalysts **4-7a**, **4-7b**, **4-7c**,**4-7f** were prepared following the literature procedure.[19]

4.4.2 Preparation of Multifunctional Catalysts



tert-Butyl-((2*S*,3*R*)-3-(((2,3-dimethylbutan-2-yl)dimethylsilyl)oxy)-1-oxo-1-(((*S*)-quinolin-4-yl((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)amino)butan-2-yl) carbamate 4-**7d'**

To a stirred solution of acid (181 mg, 0.5 mmol) in anhydrous tetrahydrofuran (8

[19] Q. Zhu, Y. Lu, *Angew. Chem. Int. Ed.* **2010**, *49*, 7753.

mL) and triethylamine (174 μL, 1.25 mmol) was added ethylchloroformate (60 mg, 0.22 mmol) under N_2 at 0 ^oC. After stirring for 1 h, (*S*)-quinolin-4-yl((2*S*) -8-vinylquinuclidin-2-yl) methanamine(epi-cinchonidine-NH_2, 147 mg, 0.2 mmol) was added. The reaction mixture was warmed to room temperature and stirred for 2 h. After concentration, water (15 mL) was added to the residue, and the resulting mixture was extracted with dichloromethane (15 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (ethyl acetate /hexanes = 1:2 to ethyl acetate to ethyl acetate/methanol = 20:1) to afford **4-7d'** (250 mg, 80% yield) as a colorless oil.

^1H NMR (500 MHz, $CDCl_3$) δ 0.07 (s, 3H), 0.15 (s, 3H), 0.86 (s, 3H), 0.87 (s, 3H), 0.92 (d, *J* = 5.7 Hz, 6H), 1.11 (d, *J* = 6.3 Hz, 3H), 1.37 (m, 12H), 1.56-1.63 (m, 4H), 2.26 (s, 1H), 2.63-2.71 (m, 2H), 3.07 (br, 2H), 3.18-3.23 (m, 1H), 4.04 (s, 1H), 4.20 (s, 1H), 4.91-4.96 (m, 2H), 5.43 (br, 2H), 5.66-5.73 (m, 1H), 7.36 (s, 1H), 7.60 (br, 1H), 7.68-7.71 (m, 1H), 8.04 (br, 1H), 8.1 (d, *J* = 8.2 Hz, 1H), 8.38 (br, 1H), 8.86 (d, *J* = 4.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -3.0, -2.7, 14.2, 17.9, 18.6, 18.7, 20.1, 20.2, 24.9, 26.1, 27.5, 27.9, 28.3, 34.1, 39.6, 40.8, 56.1, 59.0, 68.4, 77.3, 79.4, 114.4, 123.2, 126.7, 129.0, 130.5, 141.4, 150.0, 155.4, 170.1; HRMS (ESI) *m/z* calcd for $C_{36}H_{56}N_4O_4Si$ $[M+H]^+$ = 637.4144, found = 637.4143.

(2*S*,3*R*)-2-(3-(3,5-bis(Trifluoromethyl)phenyl)thioureido)-3-(((2,3-dimethylbutan-2-yl)dimethylsilyl)oxy)-N-((*S*)-quinolin-4-yl((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)meth yl)butanamide **4-7d**

To a stirred solution of **4-7d'** (64 mg, 0.10 mmol) in dichloromethane (4.0 mL) was added trifluoroacetic acid (0.4 mL). After stirring at room temperature for 12 h, aqueous $NaHCO_3$ (15 mL) was added. The resulting mixture was then extracted with dichloromethane (10 mL x 3), and the organic extracts were combined, dried over Na_2SO_4, filtered and concentrated. The crude product was used directly dissolved in dichloromethane (5.0 mL) at room temperature and was treated with 1-isothiocyanato-3,5-bis(trifluoromethyl)benzene (27 mg, 0.10 mmol). After stirring for 2 h, the reaction mixture was concentrated under reduced pressure to afford the crude product, which was subjected to flash chromatographic separation (ethyl acetate /hexanes = 1:2 to ethyl acetate) to afford product **4-7d** (69.8 mg, 86% for two steps) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.24 (s, 3H), 0.27 (s, 3H), 0.95 (m, 13H), 1.19 (d, J = 5.7 Hz, 3H), 1.32-1.37 (m, 1H), 1.58-1.72 (m, 4H), 2.28 (s, 1H), 2.66-2.74 (m, 2H), 3.08 (br, 2H), 3.20-3.25 (m, 1H), 4.45 (s, 1H), 4.95-5.02 (m, 3H), 5.52 (br, 1H), 5.67-5.74 (m, 1H), 7.28 (d, J = 4.4 Hz, 1H), 7.47-7.62 (m, 6H), 7.99 (d, J = 8.2 Hz, 1H), 8.22 (d, J = 7.6 Hz, 1H), 8.34 (br, 2H), 8.76 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -2.6, -2.3, 17.7, 18.6, 18.7, 20.2, 20.3, 25.0, 26.0, 27.4, 27.9, 34.1, 39.5, 40.1, 56.0, 62.1, 68.1, 114.6, 118.6, 121.8, 122.7, 123.5, 124.0, 126.7, 129.2, 130.6, 131.9, 132.2, 139.3, 141.2, 150.0, 170.4; HRMS (ESI) *m/z* calcd for $C_{40}H_{51}F_6N_5O_2SSi$ $[M+H]^+$ = 808.3510, found = 808.3510.

Catalysts **4-7e** & **4-7g** were prepared following the same procedures described for the preparation of **4-7d**

tert-Butyl-((2*S*,3*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-1-oxo-1-(((*S*)-quinolin-4-yl((*1S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)amino)butan-2-yl)carbamate **4-7e'**

A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02 (d, *J* = 6.3 Hz, 3H), 1.05 (s, 9H), 1.36 (m, 12H), 1.64 (m, 3H), 2.04 (br, 1H), 2.25 (m, 1H), 2.72-2.78 (m, 1H), 3.12-3.14 (m, 3H), 4.23-4.27 (m, 2H), 4.91-4.94 (m, 2H), 5.33 (m, 1H), 5.65-5.67 (m, 1H), 7.32-7.46 (m, 6H), 7.62 (br, 1H), 7.71-7.72 (m, 6H), 8.13-8.15 (m, 2H), 8.43 (br, 1H), 8.86 (d, *J* = 4.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.1, 19.2, 27.0, 27.5, 27.9, 28.2, 39.5, 40.9, 55.9, 59.2, 70.2, 79.4, 114.4, 123.2, 126.7, 127.5, 127.7, 129.1, 129.7, 129.9, 130.5, 132.5, 134.0, 135.8, 136.1, 141.4, 150.1, 155.2, 170.0; HRMS (ESI) *m/z* calcd for $C_{44}H_{56}N_4O_4Si$ $[M+H]^+$ = 733.4132, found = 733.4139.

(2*S*,3*R*)-2-(3-(3,5-Bis(trifluoromethyl)phenyl)thioureido)-3-((*tert*-butyldiphenylsilyl)oxy)-N-((*S*)-quinolin-4-yl((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl) butanamide **4-7e**

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.14 (d, *J* = 6.3 Hz, 3H), 1.22 (s, 9H), 1.27 (m, 2H), 1.54-1.60 (m, 3H), 2.25 (s, 1H), 2.49-2.52 (m, 1H), 2.74 (m, 1H), 3.03 (br, 2H), 3.08-3.13 (m, 1H), 4.29-4.31 (m, 1H), 4.91-4.95 (m, 2H), 5.44 (br, 2H), 5.62-5.69 (m, 1H), 7.20 (br, 1H), 7.27 (s, 1H), 7.38 (s, 2H), 7.43-7.53 (m, 9H), 7.57 (m, 1H), 7.79-7.81 (m, 4H), 7.87 (d, *J* = 8.2 Hz, 1H), 8.15 (d, *J* = 8.6 Hz, 1H), 8.47 (br, 1H), 8.67 (d, *J* = 3.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.8, 19.2, 27.2, 27.3, 27.8, 39.3, 40.9, 56.5, 61.8, 69.9, 114.6, 118.2, 121.8, 122.2, 122.2, 122.3, 122.4, 123.3, 124.0, 126.6, 127.7, 127.9, 129.1, 130.0, 130.3, 130.5, 131.3, 131.6, 132.0, 133.6, 135.9, 136.3, 139.3, 141.1, 149.9, 171.2, 181.1. HRMS (ESI) *m/z* calcd for $C_{48}H_{51}F_6N_5O_2SSi$

$[M+H]^+$ = 904.3510, found = 904.3498.

tert-Butyl-((*S*)-1-(((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)amino)-3,3-dimethyl-1-oxobutan-2-yl)carbamate **4-7g'**

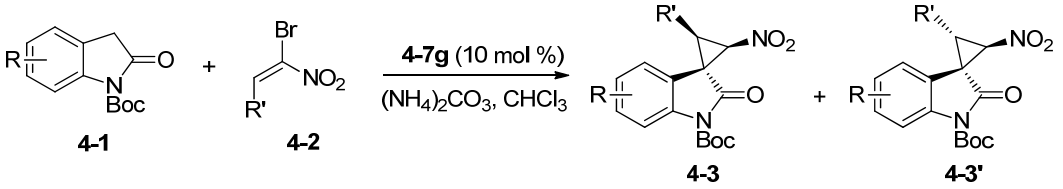
A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.83-1.04 (m, 12H), 1.22-1.42 (m, 12H), 1.58 (s, 2H), 1.65 (s, 1H), 2.27 (s, 1H), 2.68 (s, 2H), 2.99 (br, 1H), 3.13-3.21 (m, 2H), 3.80 (s, 1H), 3.94 (s, 3H), 4.94 (m, 2H), 5.07 (br, 1H), 5.36 (br, 1H), 5.70 (br, 1H), 7.05 (br, 1H), 7.32 (s, 2H), 7.56 (br, 1H), 7.98 (d, *J* = 8.9 Hz, 1H), 8.66 (d, *J* = 3.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 21.0, 23.4, 25.9, 26.5, 27.4, 28.2, 34.3, 39.5, 41.0, 42.0, 50.4, 55.6, 55.8, 60.4, 60.6, 62.4, 76.8, 79.5, 101.7, 114.7, 118.5, 121.6, 128.4, 128.5, 131.7, 131.9, 132.0, 141.2, 144.6, 145.3, 147.5, 155.8, 157.9, 170.7;HRMS (ESI) *m/z* calcd for $C_{31}H_{45}N_4O_4$ $[M+H]^+$ = 537.3435, found = 537.3418.

(*S*)-2-(3-(3,5-Bis(trifluoromethyl)phenyl)thioureido)-N-((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)-3,3-dimethylbutanamide **4-7g**

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.80-1.05 (m, 15H), 1.23-1.25 (m, 2H), 1.60-1.68 (m, 4H), 2.28 (s, 1H), 2.71 (m, 2H), 2.90-3.12 (m, 2H), 3.20-3.24 (m, 2H), 3.79 (s, 1H), 3.93 (s, 3H), 4.84-4.91 (m, 3H), 5.26 (br, 1H), 5.67 (br, 1H), 7.24-7.50 (m, 7H), 7.72-7.79 (m, 2H), 8.16 (br, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.4, 26.7, 27.1, 27.3, 27.7, 27.8, 29.7, 34.4, 35.4, 39.8, 41.2, 55.5, 55.8, 56.0, 60.8, 61.3, 65.5, 100.6, 101.6, 114.9, 118.4, 119.7, 121.5, 121.9, 123.1, 124.1, 125.2, 125.6, 126.3, 127.9, 128.7, 130.4, 130.7, 131.0, 131.2, 131.7, 131.9, 132.0, 139.0, 141.0, 144.0, 144.7, 146.6, 147.6, 157.3, 157.9, 172.2, 172.8, 181.8, 182.5; HRMS (ESI) *m/z* calcd for $C_{35}H_{40}F_6N_5O_2S$ $[M+H]^+$ = 708.2801, found = 708.2808.

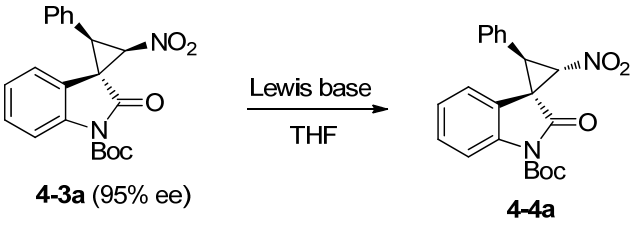
4.4.3 Representative Procedure

Asymmetric Synthesis of Spiro Cyclopropyl Oxindole **4-3**



Oxindole **4-1** (0.05 mmol) was added to a mixture of nitrostyrene **4-2** (0.06 mmol), $(NH_4)_2CO_3$ (4.8 mg, 0.05 mmol), catalyst **4-7g** (3.5 mg, 0.005 mmol) and 5 Å molecular sieves (10 mg) in $CHCl_3$ (1.0 mL) in a sample vial, and the resulting mixture was sealed and stirred at room temperature for the time specified in Table 4.5. At the end of the reaction, the reaction mixture was filtered and concentrated *in vacuo* to yield the crude product, which was purified by flash column chromatography (ethyl acetate/hexane = 1:7) to afford the desired adducts as a mixture (if not separatable by column chromatography) of **4-3** and **4-3'** (46%-81% yield). The enantiomeric excessess of **4-3** were determined by chiral HPLC analysis.

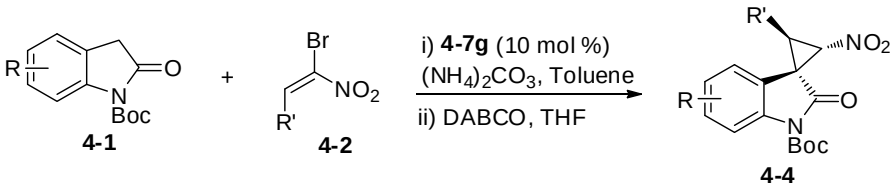
Lewis Base-initiated Conversion of **4-3a** to **4-4a**



Enantioenriched **4-3a** (95% ee, 0.05 mmol, 19 mg) was dissolved in THF (0.5 mL), the Lewis base (0.05 mmol) was added and the resulting solution was stirred at room temperature for the time specified (6–24 h). The reaction mixture was concentrated *in vacuo* to yield the crude product, which was purified by flash column

chromatography (ethyl acetate/hexane = 1:5) to afford the desired adduct **4-4a**.

Asymmetric Synthesis of Spiro Cyclopropyl Oxindole **4-4**



Oxindole **4-1** (0.05 mmol) was added to a mixture of nitrostyrene **4-2** (0.06 mmol), $(NH_4)_2CO_3$ (4.8 mg, 0.05 mmol) and catalyst **4-7g** (3.5 mg, 0.005 mmol) in toluene (1.0 mL) in a sealed sample vial and the resulting mixture was stirred at room temperature. After 6 h, the reaction mixture was concentrated *in vacuo* to yield the crude product, which was purified by flash column chromatography (ethyl acetate/hexane = 1:7) to afford the adducts **4-3** and **4-4**. DABCO (0.05 mmol) was added to the THF solution (0.5 mL) of **4-3** and the resulting solution was stirred at room temperature for 3 h. The reaction solution was concentrated and then purified by flash column chromatography (ethyl acetate/hexane = 1:7) to afford the adduct **4-4**, which was combined with adduct **4-4** from the first step to give the final product (69%-95% yield). The enantiomeric excess of **4-4** was determined by chiral HPLC analysis.

4.4.4 MS Spectrum of Ammonium Enolate Intermediate

Mass Spectrum SmartFormula Report

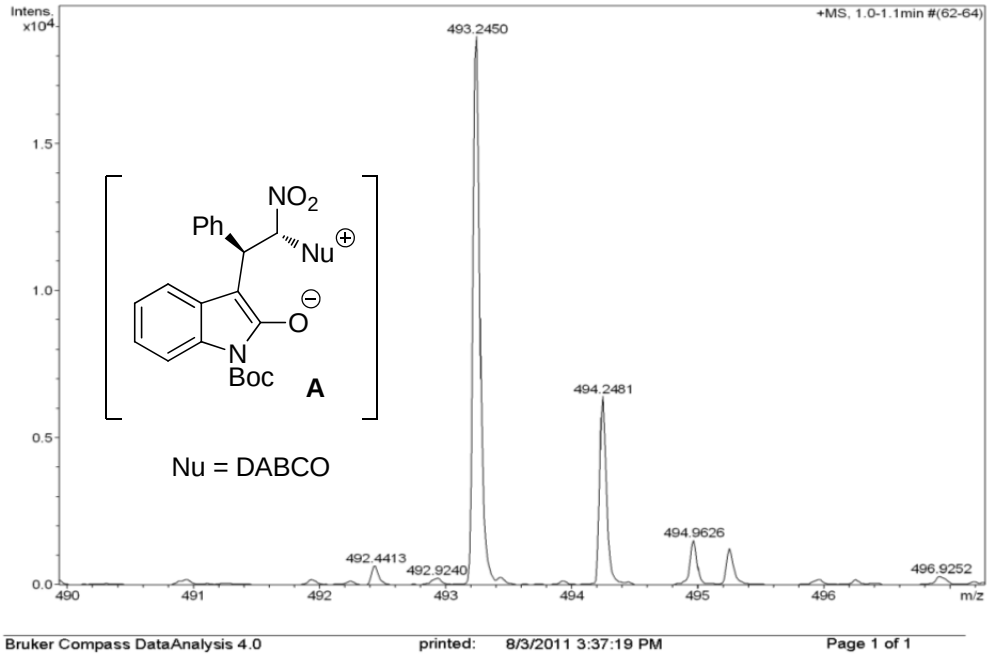
Analysis Info

Analysis Name	D:\Data\Chemistry\2011 Sample\aug2011_Sample\DABCO.d	Acquisition Date	8/3/2011 3:32:54 PM
Method	tune_low_pos_200ul.m	Operator	default user
Sample Name	DABCO	Instrument / Ser#	micrOTOF-Q II 10269
Comment	A/P LU YIXIN		

Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	2.0 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	200 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	5.0 l/min
Scan End	1100 m/z	Set Collision Cell RF	120.0 Vpp	Set Divert Valve	Waste

Meas. m/z	#	Formula	m/z	err [ppm]	rdb	e⁻ Conf	z
493.2450	1	C 27 H 33 N 4 O 5	493.2445	-0.9	13.5	even	1+

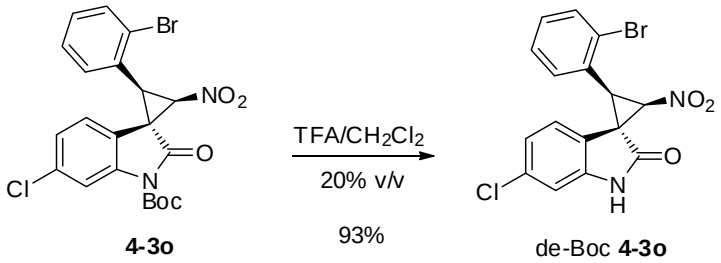


Bruker Compass DataAnalysis 4.0 printed: 8/3/2011 3:37:19 PM Page 1 of 1

4.4.5 X-Ray Crystallographic Analysis and Determination of Configurations of the Spirooxindole Products

X-Ray Crystallographic Analysis of **4-3o**

The absolute configuration of the product **3o** was assigned based on the X-ray crystallographic analysis of a single crystal of de-Boc **3o** (Figure S1). The configurations of other products **4-3** were assigned by analogy.



4-3o de-Boc **4-3o**

4-3o (49.2 mg, 0.1 mmol) in CH_2Cl_2 (1.6 mL) was added TFA (0.4 mL) at 0 ^oC, the resulting solution was then stirred at 0 ^oC to room temperature for 6 h. The reaction was then diluted with CH_2Cl_2 (5 mL) and washed with aqueous saturated $NaHCO_3$ solution (5 mL) and brine (5 mL). The organic phase was then dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to yield the crude product, which was purified by flash column chromatography (ethyl acetate/hexane = 1:2) to afford the deprotected pruduct de-Boc **4-3o** as a light yellow solid (36.5 mg, 93% yield).

^1H NMR (500 MHz, $CDCl_3$) δ 3.64 (d, *J* = 8.9 Hz, 1H), 5.26 (d, *J* = 8.2 Hz, 1H), 6.76 (d, *J* = 8.2 Hz, 1H), 6.92-6.94 (m, 1H), 7.07-7.09 (m, 2H), 7.27-7.33 (m, 2H), 7.63-7.65 (m, 1H), 8.97 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.8, 39.9, 70.3, 111.1, 118.7, 122.7, 125.9, 127.2, 127.8, 128.3, 130.1, 131.2, 133.2, 135.3, 143.0, 174.2; HRMS (ESI) m/z calcd for $C_{16}H_9N_2O_3{}^{79}BrCl$ $[M-H]^-$ = 390.9491, found = 390.9481; calcd for $C_{16}H_9N_2O_3{}^{81}BrCl$ $[M-H]^-$ = 392.9470, found = 392.9473.

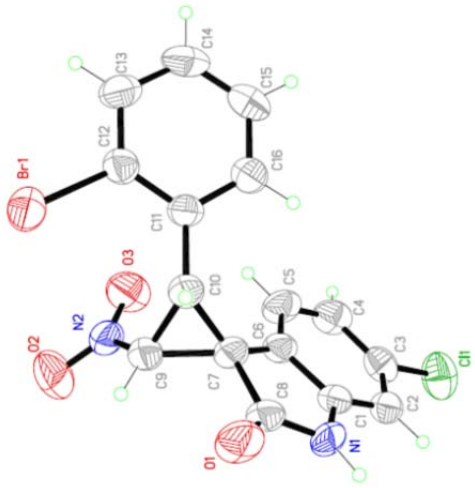


Figure 4.2 X-ray structure of de-Boc **4-3o**

Table 4.7 Crystal Data and Structure Refinement for B559.

Identification code	b559	
Empirical formula	C_{16} H_{10} Br Cl N_2 O_3	
Formula weight	393.62	
Temperature	223(2) K	
Wavelength	0.71073 Å	
Crystal system	Tetragonal	
Space group	P4(3)2(1)2	
Unit cell dimensions	a = 8.3189(4) Å	□= 90°.
	b = 8.3189(4) Å	□= 90°.
	c = 43.947(4) Å	□ = 90°.
Volume	3041.3(3) $Å^3$	
Z	8	
Density (calculated)	1.719 Mg/m^3	
Absorption coefficient	2.895 mm^{-1}	

F(000)	1568
Crystal size	0.60 x 0.54 x 0.10 mm^3
Theta range for data collection	1.85 to 27.50°.
Index ranges	-10<=h<=10, -10<=k<=10, -47<=l<=57
Reflections collected	21393
Independent reflections	3486 [R(int) = 0.0511]
Completeness to theta = 27.50°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7606 and 0.2755
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3486 / 1 / 212
Goodness-of-fit on F^2	1.030
Final R indices [I>2sigma(I)]	R1 = 0.0457, wR2 = 0.1034
R indices (all data)	R1 = 0.0611, wR2 = 0.1096
Absolute structure parameter	0.022(12)
Largest diff. peak and hole	0.675 and -0.500 e.$Å^{-3}$

X-Ray Crystallographic Analysis of **4-4b**

The absolute configuration of the product **4-4b** was assigned based on the X-ray crystallographic analysis of a single crystal of **4-4b** (Figure 4.3). The configurations of other products **4-4** were assigned by analogy.

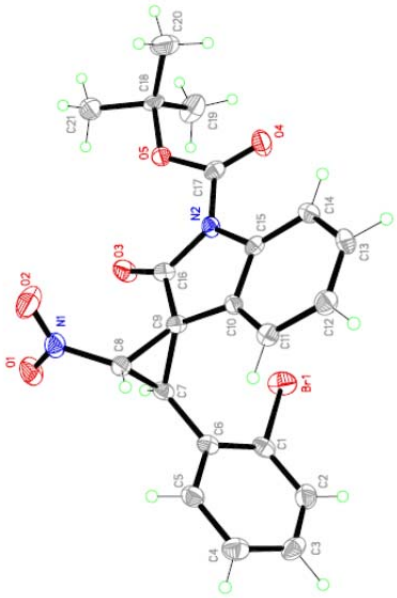


Figure 4.3 X-ray structure of de-Boc **4-4b**

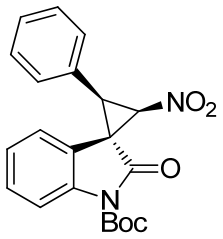
Table 4.8 Crystal Data and Structure Refinement for b350.

Identification code	b350	
Empirical formula	C_{21} H_{19} Br N_2 O_5	
Formula weight	459.29	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 13.3854(19) Å	□= 90°.
	b = 10.8817(16) Å	□= 91.611(4)°.
	c = 14.380(2) Å	□ = 90°.
Volume	2093.6(5) Å^3	
Z	4	

Density (calculated)	1.457 Mg/m^3
Absorption coefficient	1.997 mm^{-1}
F(000)	936
Crystal size	0.66 x 0.28 x 0.24 mm^3
Theta range for data collection	2.05 to 27.49°.
Index ranges	-16<=h<=17, -13<=k<=14, -18<=l<=14
Reflections collected	14931
Independent reflections	8928 [R(int) = 0.0277]
Completeness to theta = 27.49°	99.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.6457 and 0.3523
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	8928 / 140 / 569
Goodness-of-fit on F^2	0.973
Final R indices [I>2sigma(I)]	R1 = 0.0382, wR2 = 0.0805
R indices (all data)	R1 = 0.0451, wR2 = 0.0826
Absolute structure parameter	0.009(5)
Largest diff. peak and hole	0.792 and -0.346 $e.Å^{-3}$

4.4.6 Analytical Data of the Spirooxindole Products

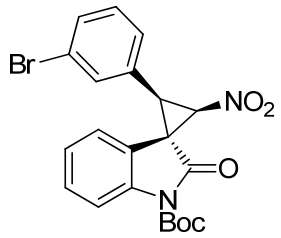
(1*S*,2*R*,3*R*)-*tert*-Butyl-2-nitro-2'-oxo-3-phenylspiro[cyclopropane-1,3'-indoline]-1'-carboxylate **4-3a**



4-3a

A light yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.69 (s, 9H), 3.81 (d, *J* = 8.9 Hz, 1H), 5.14 (d, *J* = 8.2 Hz, 1H), 6.76 (d, *J* = 7.6 Hz, 1H), 7.00-7.05 (m, 3H), 7.32-7.39 (m, 4H), 8.00 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.1, 36.7, 39.6, 70.6, 85.4, 114.9, 118.8, 124.0, 127.1, 127.4, 128.4, 128.6, 129.2, 130.0, 141.0, 148.6, 171.5; The ee value was 97%, t_R (minor) = 20.25 min and 35.81 min, t_R (major) = 20.08 min and 29.68 min (Chiralcel AD-H + IA, λ = 254 nm, 2% *i*PrOH/hexanes, flow rate = 0.8 mL/min); HRMS (ESI) m/z calcd for $C_{21}H_{20}N_2O_5Na$ $[M+Na]^+$ = 403.1267, found = 403.1279.

(1*S*,2*R*,3*R*)-*tert*-Butyl-2-(3-bromophenyl)-3-nitro-2'-oxospiro[cyclopropane-1,3'-indoline]-1'-carboxylate **4-3c**

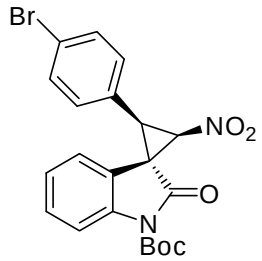


4-3c

A light yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.68 (s, 9H), 3.74 (d, *J* = 8.9 Hz, 1H), 5.11 (d, *J* = 8.2 Hz, 1H), 6.77-6.79 (m, 1H), 6.99 (d, *J* = 6.9 Hz, 1H), 7.05 (dd, *J* = 6.9 Hz, 11.7 Hz, 1H), 7.19-7.26 (m, 2H), 7.34-7.51 (m, 2H), 8.01 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.1, 35.6, 39.3, 70.2, 85.5, 115.1, 118.4, 122.4, 124.1, 126.8, 128.8, 129.5, 129.7, 130.1, 131.6, 133.1, 141.1, 148.5, 171.2; The ee

value is 90%, t_R (minor) = 12.73 min and 14.34 min, t_R (major) = 12.07 min and 23.63 min (Chiralcel IC + AD-H, λ = 254 nm, 15% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{21}H_{19}N_2O_5Na^{79}Br$ $[M+Na]^+$ = 481.0370, found = 481.0383; calcd for $C_{21}H_{19}N_2O_5Na^{81}Br$ $[M+Na]^+$ = 483.0367, found = 483.0349.

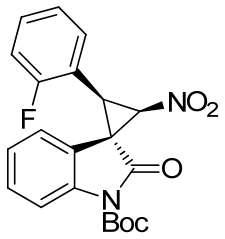
(1*S*,2*R*,3*R*)-*tert*-Butyl-2-(4-bromophenyl)-3-nitro-2'-oxospiro[cyclopropane-1,3'-indoline]-1'-carboxylate **4-3d**



4-3d

A light yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.68 (s, 9H), 3.70 (d, *J* = 8.9 Hz, 1H), 5.12 (d, *J* = 8.9 Hz, 1H), 6.73 (d, *J* = 8.2 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 2H), 7.03-7.06 (m, 1H), 7.34-7.46 (m, 1H), 7.47-7.49 (m, 2H), 8.01 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.1, 35.9, 39.3, 70.3, 85.4, 115.1, 118.5, 122.7, 124.1, 126.8, 129.4, 130.6, 131.7, 131.9, 141.0, 148.5, 171.2; The ee value is 95%, t_R (minor) = 19.51 min and 25.99 min, t_R (major) = 22.29 min and 30.42 min (Chiralcel IB + IA, λ = 254 nm, 5% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{21}H_{19}N_2O_5Na^{79}Br$ $[M+Na]^+$ = 481.0370, found = 481.0383; calcd for $C_{21}H_{19}N_2O_5Na^{81}Br$ $[M+Na]^+$ = 483.0367, found = 483.0349.

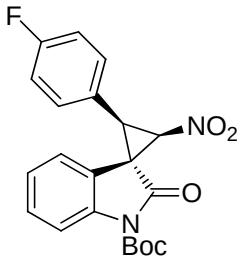
(1*S*,2*S*,3*R*)-*tert*-Butyl-2-(2-fluorophenyl)-3-nitro-2'-oxospiro[cyclopropane-1,3'-indoline]-1'-carboxylate **4-3g**



4-3g

A light yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.69 (s, 9H), 3.63 (d, *J* = 8.2 Hz, 1H), 5.17 (d, *J* = 8.2 Hz, 1H), 6.80 (d, *J* = 7.6 Hz, 1H), 6.94 (t, *J* = 7.6 Hz, 1H), 7.02 (t, *J* = 8.2 Hz, 1H), 7.10 (dd, *J* = 10.8 Hz, 17.6 Hz, 2H), 7.26-7.40 (m, 2H), 8.00 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.1, 31.5, 38.8, 70.1, 85.5, 115.1, 115.2, 115.3, 115.8, 115.9, 118.8, 123.9, 124.0, 124.1, 126.3, 129.4, 130.5, 131.7, 141.1, 148.5, 171.2; The ee value is 96%, t_R (minor) = 26.89 min, t_R (major) = 18.34 min (Chiralcel AD-H, λ = 254 nm, 2% *i*PrOH/hexanes, flow rate = 0.5 mL/min); HRMS (ESI) m/z calcd for $C_{21}H_{19}N_2O_5FNa$ $[M+Na]^+$ = 421.1170, found = 421.1184.

(1*S*,2*R*,3*R*)-*tert*-Butyl-2-(4-fluorophenyl)-3-nitro-2'-oxospiro[cyclopropane-1,3'-indoline]-1'-carboxylate **4-3h**

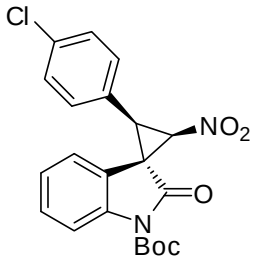


4-3h

A light yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.68 (s, 9H), 3.73 (d, *J* = 8.2 Hz, 1H), 5.12 (d, *J* = 8.9 Hz, 1H), 6.74 (d, *J* = 8.9 Hz, 1H), 7.01-7.05 (m, 5H), 7.35-7.41 (m, 1H), 8.00 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.1, 35.9, 39.5, 70.5, 85.4, 115.1, 115.7, 115.9, 118.6, 124.0, 126.8, 129.3, 131.9 (d, *J* = 8.2 Hz),

141.0, 148.5, 162.6 (d, J = 246.9 Hz), 171.3; The ee value is 97%, t_R (minor) = 10.12 min and 14.11 min, t_R (major) = 12.57 min and 20.45 min (Chiralcel IB, λ = 254 nm, 3% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{21}H_{19}N_2O_5FNa$ $[M+Na]^+$ = 421.1170, found = 421.1184.

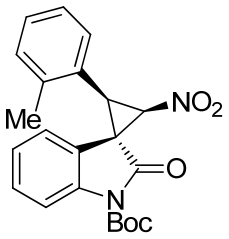
(1*S*,2*R*,3*R*)-*tert*-Butyl-2-(4-chlorophenyl)-3-nitro-2'-oxospiro[cyclopropane-1,3'-indoline]-1'-carboxylate **4-3f**



4-3f

A light yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.68 (s, 9H), 3.72 (d, J = 8.2 Hz, 1H), 5.12 (d, J = 8.8 Hz, 1H), 6.75 (d, J = 8.2 Hz, 1H), 6.98 (d, J = 8.2 Hz, 2H), 7.04 (t, J = 7.6 Hz, 1H), 7.30-7.40 (m, 3H), 8.00 (d, J = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.1, 35.9, 39.4, 70.3, 85.5, 115.1, 118.5, 124.1, 125.9, 126.8, 128.9, 129.4, 131.4, 134.6, 141.0, 148.5, 171.2; The ee value is 98%, t_R (minor) = 17.60 min and 22.06 min, t_R (major) = 20.24 min and 26.16 min (Chiralcel IB+IA, λ = 254 nm, 5% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{21}H_{19}N_2O_5ClNa$ $[M+Na]^+$ = 437.0875, found = 437.0883.

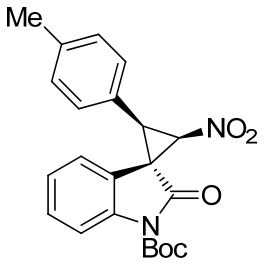
(1*S*,2*R*,3*R*)-*tert*-Butyl-2-nitro-2'-oxo-3-(o-tolyl)spiro[cyclopropane-1,3'-indoline]-1'-carboxylate **4-3i**



4-3i

A light yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.69 (s, 9H), 2.02 (s, 3H), 3.66 (d, *J* = 8.8 Hz, 1H), 5.18 (d, *J* = 8.9 Hz, 1H), 6.78 (d, *J* = 7.6 Hz, 1H), 6.96 (d, *J* = 7.6 Hz, 1H), 7.01 (t, *J* = 7.6 Hz, 1H), 7.13 (t, *J* = 8.2 Hz, 1H), 7.20 (d, *J* = 6.9 Hz , 1H), 7.29 (d, *J* = 7.6 Hz , 1H), 7.35-7.39 (m, 1H), 7.99 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.4, 28.1, 36.2, 39.6, 70.9, 85.4, 115.0, 119.2, 124.1, 125.8, 126.2, 126.3, 128.6, 129.2, 129.6, 130.6, 138.3, 140.8, 148.6, 171.5; The ee value was 97%, t_R (minor) = 12.70 min and 16.88 min, t_R (major) = 8.77 min and 14.98 min (Chiralcel IC, λ = 254 nm, 3% *i*PrOH/hexanes, flow rate = 1.0 mL/min); $[\alpha]^{24}_D$ = -91.5 (c 0.81, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{22}H_{22}N_2O_5Na$ $[M+Na]^+$ = 417.1421, found = 417.1428.

(1*S*,2*R*,3*R*)-*tert*-Butyl-2-nitro-2'-oxo-3-(p-tolyl)spiro[cyclopropane-1,3'-indoline]-1'-carboxylate **4-3j**

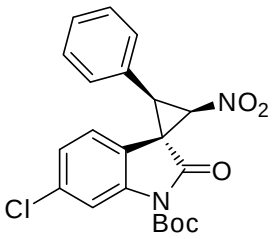


4-3j

A light yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.68 (s, 9H), 2.36 (s, 3H), 3.76 (d, *J* = 8.8 Hz, 1H), 5.12 (d, *J* = 8.9 Hz, 1H), 6.79 (d, *J* = 7.6 Hz, 1H), 6.91 (d, *J* = 7.6 Hz,

2H), 7.02 (t, *J* = 7.0 Hz, 1H), 7.13 (d, *J* = 8.2 Hz, 2H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.99 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2, 28.1, 36.6, 39.6, 70.7, 85.3, 118.9, 123.9, 124.2, 127.2, 128.8, 129.1, 129.3, 129.8, 138.3, 140.9, 148.6, 171.5; The ee value was 98%, t_R (minor) = 17.46 min and 23.29 min, t_R (major) = 16.59 min and 18.88 min (Chiralcel IB+IA, λ = 254 nm, 3% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{22}H_{22}N_2O_5Na$ $[M+Na]^+$ = 417.1421, found = 417.1428.

(1*S*,2*R*,3*R*)-*tert*-Butyl-6'-chloro-2-nitro-2'-oxo-3-phenylspiro[cyclopropane-1,3'-indoline]-1'-carboxylate **4-3s**

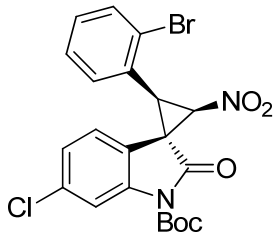


4-3s

A light yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.68 (s, 9H), 3.80 (d, *J* = 8.9 Hz, 1H), 5.14 (d, *J* = 8.2 Hz, 1H), 6.67 (d, *J* = 8.8 Hz, 1H), 6.99-7.02 (m, 3H), 7.28-7.39 (m, 3H), 8.08 (d, *J* = 1.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.0, 36.8, 39.4, 70.5, 85.9, 115.7, 117.2, 124.1, 127.1, 128.0, 128.6, 128.8, 129.9, 135.4, 141.8, 148.3, 171.1; The ee value was 93%, t_R (minor) = 10.34 min and 10.93 min, t_R (major) = 8.87 min and 23.01 min (Chiralcel IC, λ = 254 nm, 5% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{21}H_{19}N_2O_5ClNa$ $[M+Na]^+$ = 437.0875, found = 437.0883.

(1*S*,2*S*,3*R*)-*tert*-Butyl-2-(2-bromophenyl)-6'-chloro-3-nitro-2'-oxospiro[cyclopropan

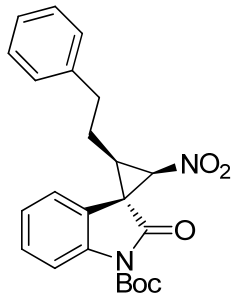
e-1,3'-indoline]-1'-carboxylate **4-3o**



4-3o

A light yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.68 (s, 9H), 3.63 (d, *J* = 8.2 Hz, 1H), 5.20 (d, *J* = 8.2 Hz, 1H), 6.68 (d, *J* = 8.2 Hz, 1H), 6.99-7.03 (m, 2H), 7.25-7.29 (m, 2H), 7.60 (d, *J* = 7.0 Hz, 1H), 8.08 (d, *J* = 1.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.0, 37.4, 39.8, 70.8, 85.9, 115.9, 117.4, 124.3, 126.0, 126.8, 127.2, 127.9, 130.2, 131.2, 133.2, 135.6, 141.9, 148.3, 170.7; The ee value is 99%, t_R (minor) = 5.90 min and 9.14 min, t_R (major) = 7.44 min and 8.18 min (Chiralcel IA, λ = 254 nm, 2% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{21}H_{18}N_2O_5Na^{79}BrCl$ $[M+Na]^+$ = 514.9980, found = 515.0000; calcd for $C_{21}H_{18}N_2O_5Na^{81}BrCl$ $[M+Na]^+$ = 516.9959, found = 516.9977.

(1*S*,2*R*,3*R*)-*tert*-Butyl-2-nitro-2'-oxo-3-phenethylspiro[cyclopropane-1,3'-indoline]-1'-carboxylate **4-3q**

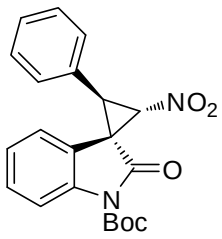


4-3q

A light yellow oil. ^{1}H NMR (mixture of two diastereoisomers, 500 MHz, $CDCl_3$) δ

1.65 (s, 9H), 2.28-2.38 (m, 1H), 2.55-2.80 (m, 3H), 2.91-2.97 (m, 1H), 4.73-4.86 (1H, 4.73-4.75 (major, d, *J* = 6.3 Hz), 4.85-4.86 (minor, d, *J* = 7.6 Hz)), 6.98-7.10 (m, 2H), 7.13-7.24 (m, 3H), 7.28-7.38 (m, 3H), 7.82-7.92 (1H, 7.82-7.84 (major, d, *J* = 8.2 Hz), 7.90-7.92 (minor, d, *J* = 8.2 Hz)); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.9, 24.1, 28.1, 31.1, 34.8, 34.9, 35.3, 37.2, 37.8, 39.8, 60.7, 69.7, 73.7, 84.8, 85.0, 115.1, 115.4, 120.1, 121.4, 123.6, 124.4, 124.6, 126.2, 126.3, 126.6, 128.2, 128.3, 128.6, 128.7, 128.8, 128.9, 139.4, 139.5, 140.2, 140.7, 148.5, 169.4, 171.7; The ee value is 93%, t_R (minor) = 28.15 min and 41.17 min, t_R (major) = 17.20 min and 23.92 min (Chiralcel OD-H, λ = 254 nm, 2.5% *i*PrOH/hexanes, flow rate = 0.8 mL/min); HRMS (ESI) m/z calcd for $C_{23}H_{24}N_2O_5Na$ $[M+Na]^+$ = 431.1577, found = 431.1579.

(1*S*,2*S*,3*R*)-*tert*-Butyl-2-nitro-2'-oxo-3-phenylspiro[cyclopropane-1,3'-indoline]-1'-carboxylate **4-4a**

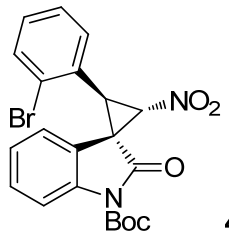


4-4a

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.66 (s, 9H), 4.45 (d, *J* = 6.3 Hz, 1H), 5.09 (d, *J* = 6.3 Hz, 1H), 5.97 (d, *J* = 7.6 Hz, 1H), 6.85 (t, *J* = 7.6 Hz, 1H), 7.19 (t, *J* = 3.2 Hz, 2H), 7.27 (d, *J* = 8.2 Hz, 1H), 7.33 (dd, *J* = 2.6 Hz, 16.4 Hz, 3H), 7.96 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.1, 39.8, 40.4, 71.5, 85.1, 115.4, 121.1, 122.1, 124.0, 128.8, 129.0, 129.1, 129.3, 129.4, 140.4, 148.9, 168.4; The ee value is 95%, t_R (minor) = 13.06 min, t_R (major) = 17.21 min (Chiralcel IC, λ = 254 nm, 30%

*i*PrOH/hexanes, flow rate = 1.0 mL/min); $[\alpha]^{24}_D$ = +144.5 (c 0.80, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{21}H_{20}N_2O_5Na$ $[M+Na]^+$ = 403.1267, found = 403.1279.

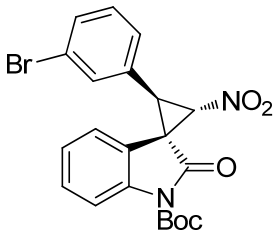
(1*S*,2*S*,3*S*)-*tert*-Butyl-2-(2-bromophenyl)-3-nitro-2'-oxospiro[cyclopropane-1,3'-indoline]-1'-carboxylate **4-4b**



4-4b

A colorless crystal; ^1H NMR (500 MHz, $CDCl_3$) δ 1.65 (s, 9H), 4.33 (d, *J* = 7.0 Hz, 1H), 5.12 (d, *J* = 6.3 Hz, 1H), 5.89 (d, *J* = 8.2 Hz, 1H), 6.82 (t, *J* = 7.6 Hz, 1H), 7.25-7.31 (m, 2H), 7.40 (d, *J* = 4.4 Hz, 2H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.95 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.1, 40.0, 41.3, 71.4, 85.1, 115.4, 119.9, 121.9, 124.0, 126.4, 127.8, 129.1, 129.7, 130.2, 130.5, 133.4, 140.5, 148.9, 168.0; The ee value is 94%, t_R (minor) = 10.86 min, t_R (major) = 9.12 min (Chiralcel IC, λ = 254 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min); $[\alpha]^{24}_D$ = +102.6 (c 0.91, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{21}H_{19}N_2O_5Na^{79}Br$ $[M+Na]^+$ = 481.0370, found = 481.0383; calcd for $C_{21}H_{19}N_2O_5Na^{81}Br$ $[M+Na]^+$ = 483.0367, found = 483.0349.

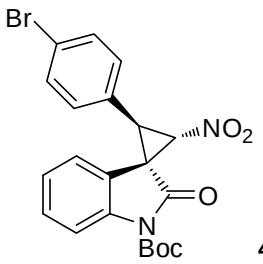
(1*S*,2*R*,3*S*)-*tert*-Butyl-2-(3-bromophenyl)-3-nitro-2'-oxospiro[cyclopropane-1,3'-indoline]-1'-carboxylate **4-4c**



4-4c

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.66 (s, 9H), 4.40 (d, *J* = 7.0 Hz, 1H), 5.06 (d, *J* = 6.3 Hz, 1H), 6.01 (d, *J* = 7.6 Hz, 1H), 6.92 (t, *J* = 7.6 Hz, 1H), 7.09 (d, *J* = 7.6 Hz, 1H), 7.22 (t, *J* = 7.6 Hz, 1H), 7.32 (t, *J* = 8.2 Hz, 1H), 7.39 (s, 1H), 7.50 (d, *J* = 8.2 Hz, 1H), 7.98 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.1, 39.5, 39.6, 71.1, 85.3, 115.6, 121.1, 121.5, 123.1, 124.3, 128.1, 129.3, 130.6, 131.5, 132.1, 132.3, 140.4, 148.8, 168.2; The ee value is 95%, t_R (minor) = 20.69 min, t_R (major) = 10.91 min (Chiralcel IB, λ = 254 nm, 5% *i*PrOH/hexanes, flow rate = 1.0 mL/min); $[\alpha]^{24}_{D}$ = +114.1 (c 0.85, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{21}H_{19}N_2O_5Na^{79}Br$ $[M+Na]^+$ = 481.0370, found = 481.0383; calcd for $C_{21}H_{19}N_2O_5Na^{81}Br$ $[M+Na]^+$ = 483.0367, found = 483.0349.

(1*S*,2*R*,3*S*)-*tert*-Butyl-2-(4-bromophenyl)-3-nitro-2'-oxospiro[cyclopropane-1,3'-indoline]-1'-carboxylate **4-4d**

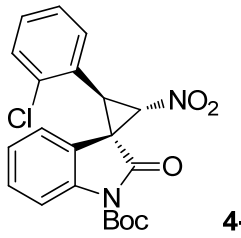


4-4d

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.65 (s, 9H), 4.36 (d, *J* = 6.9 Hz, 1H), 5.04 (d, *J* = 6.3 Hz, 1H), 5.99 (d, *J* = 7.6 Hz, 1H), 6.91 (t, *J* = 7.6 Hz, 1H), 7.07 (d, *J* = 8.2 Hz, 2H), 7.30-7.33 (m, 1H), 7.49 (d, *J* = 8.2 Hz, 2H), 7.97 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.1, 39.5, 39.6, 71.2, 85.3, 115.5, 121.1, 121.6, 123.1, 124.3, 128.3, 129.2, 131.0, 132.3, 140.4, 148.8, 168.2; The ee value is 96%, t_R (minor) = 11.96 min, t_R (major) = 15.07 min (Chiralcel IC, λ = 254 nm, 30% *i*PrOH/hexanes,

flow rate = 1.0 mL/min); $[\alpha]^{24}_D$ = +84.8 (c 0.78, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{21}H_{19}N_2O_5Na^{79}Br$ $[M+Na]^+$ = 481.0370, found = 481.0383; calcd for $C_{21}H_{19}N_2O_5Na^{81}Br$ $[M+Na]^+$ = 483.0367, found = 483.0349.

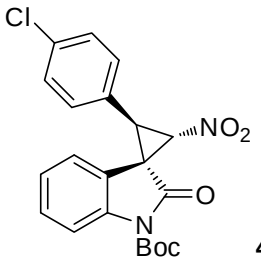
(1*S*,2*S*,3*S*)-*tert*-Butyl-2-(2-chlorophenyl)-3-nitro-2'-oxospiro[cyclopropane-1,3'-indoline]-1'-carboxylate **4-4e**



4-4e

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.65 (s, 9H), 4.35 (d, *J* = 6.3 Hz, 1H), 5.12 (d, *J* = 6.3 Hz, 1H), 5.90 (d, *J* = 7.6 Hz, 1H), 6.82 (t, *J* = 7.6 Hz, 1H), 7.27-7.40 (m, 5H), 7.95 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.1, 39.1, 39.7, 71.1, 85.1, 115.4, 119.9, 121.9, 124.0, 127.2, 127.9, 129.1, 130.0, 130.1, 130.4, 136.2, 140.4, 148.9, 168.1; The ee value is 95%, t_R (minor) = 8.89 min, t_R (major) = 10.57 min (Chiralcel IC, λ = 254 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min); $[\alpha]^{24}_D$ = +140.5 (c 0.74, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{21}H_{19}N_2O_5ClNa$ $[M+Na]^+$ = 437.0875, found = 437.0883.

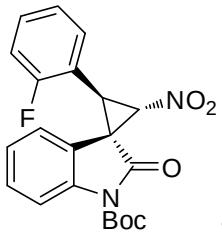
(1*S*,2*R*,3*S*)-*tert*-Butyl-2-(4-chlorophenyl)-3-nitro-2'-oxospiro[cyclopropane-1,3'-indoline]-1'-carboxylate **4-4f**



4-4f

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.65 (s, 9H), 4.38 (d, *J* = 6.3 Hz, 1H), 5.05 (d, *J* = 6.3 Hz, 1H), 5.99 (d, *J* = 7.6 Hz, 1H), 6.90 (t, *J* = 7.6 Hz, 1H), 7.13 (d, *J* = 8.2 Hz, 2H), 7.30-7.34 (m, 3H), 7.97 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.1, 39.6, 71.3, 85.3, 115.5, 121.1, 121.7, 124.2, 127.8, 129.2, 129.4, 130.8, 135.0, 140.4, 148.8, 168.3; The ee value is 94%, t_R (minor) = 11.58 min, t_R (major) = 14.26 min (Chiralcel IC, λ = 254 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min); $[\alpha]^{24}_{D}$ = +132.8 (c 0.69, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{21}H_{19}N_2O_5ClNa$ $[M+Na]^+$ = 437.0875, found = 437.0883.

(1*S*,2*S*,3*S*)-*tert*-Butyl-2-(2-fluorophenyl)-3-nitro-2'-oxospiro[cyclopropane-1,3'-indoline]-1'-carboxylate **4-4g**

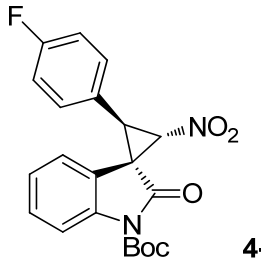


4-4g

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.66 (s, 9H), 4.31 (d, *J* = 7.0 Hz, 1H), 5.12 (d, *J* = 6.3 Hz, 1H), 6.01 (d, *J* = 7.6 Hz, 1H), 6.87 (t, *J* = 7.6 Hz, 1H), 7.03 (t, *J* = 8.8 Hz, 1H), 7.17 (t, *J* = 7.6 Hz, 1H), 7.24-7.38 (m, 4H), 7.97 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.1, 35.2, 39.2, 70.8, 85.1, 115.5, 116.2 (d, *J* = 21.0 Hz),

117.1 (d, *J* = 13.7 Hz), 120.2, 122.0, 124.1, 124.6 (d, *J* = 3.7 Hz), 129.1, 130.6 (d, *J* = 2.7 Hz), 131.0 (d, *J* = 8.2 Hz), 140.4, 148.9, 161.7 (d, *J* = 248.7 Hz), 168.1; The ee value is 94%, t_R (minor) = 12.97 min, t_R (major) = 8.07 min (Chiralcel IB, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1.0 mL/min); $[\alpha]^{24}_D$ = +151.0 (c 0.73, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{21}H_{19}N_2O_5FNa$ $[M+Na]^+$ = 421.1170, found = 421.1184.

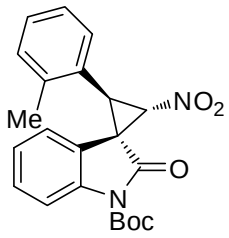
(1*S*,2*R*,3*S*)-*tert*-Butyl-2-(4-fluorophenyl)-3-nitro-2'-oxospiro[cyclopropane-1,3'-indoline]-1'-carboxylate **4-4h**



4-4h

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.65 (s, 9H), 4.39 (d, *J* = 6.3 Hz, 1H), 5.06 (d, *J* = 7.0 Hz, 1H), 5.97 (d, *J* = 7.6 Hz, 1H), 6.910 (t, *J* = 7.6 Hz, 1H), 7.02-7.07 (m, 2H), 7.17 (dd, *J* = 5.1 Hz, 7.9 Hz, 2H), 7.30 (t, *J* = 8.2 Hz, 1H), 7.96 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.1, 39.6, 39.7, 71.5, 85.3, 115.5, 116.3 (d, *J* = 21.8 Hz), 121.1, 121.8, 124.2, 125.1 (d, *J* = 2.7 Hz), 129.2, 131.2 (d, *J* = 8.2 Hz), 140.4, 148.8, 162.8 (d, *J* = 247.8 Hz), 168.3; The ee value is 96%, t_R (minor) = 11.72 min, t_R (major) = 13.96 min (Chiralcel IC, λ = 254 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min); $[\alpha]^{24}_D$ = +130.8 (c 1.11, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{21}H_{19}N_2O_5FNa$ $[M+Na]^+$ = 421.1170, found = 421.1184.

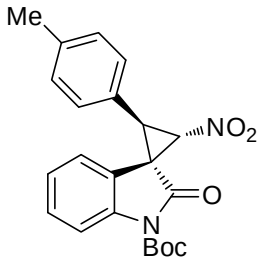
(1*S*,2*S*,3*R*)-*tert*-Butyl-2-nitro-2'-oxo-3-(o-tolyl)spiro[cyclopropane-1,3'-indoline]-1'-carboxylate **4-4i**



4-4i

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.66 (s, 9H), 1.89 (s, 3H), 4.30 (d, *J* = 6.3 Hz, 1H), 5.13 (d, *J* = 7.0 Hz, 1H), 5.91 (d, *J* = 7.6 Hz, 1H), 6.83 (t, *J* = 7.6 Hz, 1H), 7.11 (d, *J* = 7.6 Hz, 1H), 7.27-7.33 (m, 4H), 7.95 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.3, 28.1, 39.6, 71.6, 85.2, 115.3, 120.3, 122.1, 124.2, 126.4, 127.9, 128.3, 129.0, 129.1, 130.8, 138.7, 140.0, 148.9, 168.3; The ee value is 90%, t_R (minor) = 10.71 min, t_R (major) = 11.47 min (Chiralcel IC, λ = 254 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min); $[\alpha]^{24}_D$ = +148.6 (c 0.74, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{22}H_{22}N_2O_5Na$ $[M+Na]^+$ = 417.1421, found = 417.1428.

(1*S*,2*S*,3*R*)-*tert*-Butyl-2-nitro-2'-oxo-3-(p-tolyl)spiro[cyclopropane-1,3'-indoline]-1'-carboxylate **4-4j**

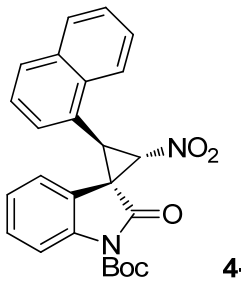


4-4j

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.65 (s, 9H), 2.35 (s, 3H), 4.41 (d, *J* = 7.0 Hz, 1H), 5.07 (d, *J* = 6.3 Hz, 1H), 6.01 (d, *J* = 7.6 Hz, 1H), 6.87 (t, *J* = 7.6 Hz, 1H), 7.06 (d, *J* = 7.6 Hz, 2H), 7.14 (d, *J* = 7.6 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 1H), 7.95 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2, 28.1, 39.7, 40.3, 71.6, 85.1,

115.3, 121.2, 122.2, 124.1, 126.1, 128.9, 129.2, 129.8, 138.8, 140.2, 148.9, 168.5; The ee value is 95%, t_R (minor) = 12.36 min, t_R (major) = 20.13 min (Chiralcel IC, λ = 254 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min); $[\alpha]^{24}_D$ = +161.2 (c 1.10, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{22}H_{22}N_2O_5Na$ $[M+Na]^+$ = 417.1421, found = 417.1428.

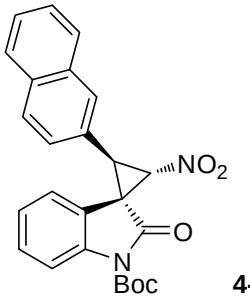
(1*S*,2*R*,3*S*)-*tert*-Butyl-2-(naphthalen-1-yl)-3-nitro-2'-oxospiro[cyclopropane-1,3'-indoline]-1'-carboxylate **4-4k**



4-4k

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.69 (s, 9H), 4.73 (d, *J* = 7.0 Hz, 1H), 5.26 (d, *J* = 7.0 Hz, 1H), 5.93 (d, *J* = 7.6 Hz, 1H), 6.68 (t, *J* = 7.6 Hz, 1H), 7.17 (t, *J* = 7.9 Hz, 1H), 7.40-7.50 (m, 4H), 7.69 (d, *J* = 8.2 Hz, 1H), 7.83 (d, *J* = 8.2 Hz, 1H), 7.89 (t, *J* = 7.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.1, 38.8, 40.0, 71.8, 85.3, 115.3, 120.4, 122.2, 123.0, 124.1, 124.9, 125.6, 126.5, 126.8, 127.3, 128.8, 129.0, 129.8, 132.2, 133.7, 140.1, 148.9, 168.5; The ee value is 97%, t_R (minor) = 13.30 min, t_R (major) = 11.14 min (Chiralcel IC, λ = 254 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min); $[\alpha]^{24}_D$ = +49.5 (c 0.68, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{25}H_{22}N_2O_5Na$ $[M+Na]^+$ = 453.1421, found = 453.1433.

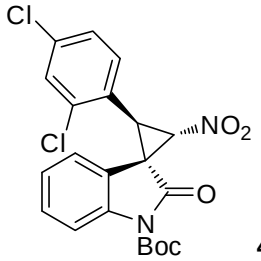
(1*S*,2*R*,3*S*)-*tert*-Butyl-2-(naphthalen-2-yl)-3-nitro-2'-oxospiro[cyclopropane-1,3'-indoline]-1'-carboxylate **4-4l**



4-4l

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.67 (s, 9H), 4.59 (d, *J* = 7.0 Hz, 1H), 5.22 (d, *J* = 7.0 Hz, 1H), 5.86 (d, *J* = 8.2 Hz, 1H), 6.74 (dd, *J* = 1.9 Hz, 8.2 Hz, 1H), 7.17 (dd, *J* = 1.9 Hz, 8.2 Hz, 1H), 7.54-7.55 (m, 2H), 7.75 (s, 1H), 7.80-7.82 (m, 4H), 8.05 (d, *J* = 1.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.1, 39.5, 40.7, 71.4, 85.7, 116.2, 120.4, 121.8, 124.3, 126.4, 126.5, 127.0 127.1, 127.8, 127.9, 128.4, 129.3, 133.1, 133.2, 135.1, 141.1, 148.7, 168.1; The ee value is 96%, t_R (minor) = 14.13 min, t_R (major) = 22.39 min (Chiralcel IC, λ = 254 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min); $[\alpha]^{24}_D$ = +235.4 (c 0.65, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{25}H_{22}N_2O_5Na$ $[M+Na]^+$ = 453.1421, found = 453.1433.

(1*S*,2*S*,3*S*)-*tert*-Butyl-2-(2,4-dichlorophenyl)-3-nitro-2'-oxospiro[cyclopropane-1,3'-indoline]-1'-carboxylate **4-4m**

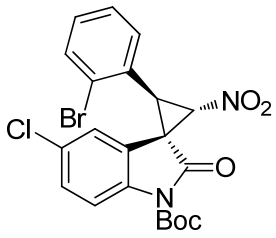


4-4m

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.65 (s, 9H), 4.27 (d, *J* = 6.9 Hz, 1H), 5.10 (dd, *J* = 2.5 Hz, 6.6 Hz, 1H), 5.94 (d, *J* = 7.6 Hz, 1H), 6.88 (t, *J* = 7.6 Hz, 1H),

7.30-7.35 (m, 4H), 7.95 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.1, 38.4, 39.6, 70.9, 85.2, 115.6, 119.9, 121.6, 124.2, 126.6, 127.6, 129.3, 130.1, 130.9, 135.8, 136.9, 140.4, 148.8, 168.0; The ee value is 94%, t_R (minor) = 9.99 min, t_R (major) = 7.61 min (Chiralcel IC, λ = 254 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min); $[\alpha]^{24}_D$ = +109.1 (c 0.87, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{21}H_{18}N_2O_5Cl_2Na$ $[M+Na]^+$ = 471.0485, found = 471.0497.

(1*S*,2*S*,3*S*)-*tert*-Butyl-2-(2-bromophenyl)-5'-chloro-3-nitro-2'-oxospiro[cyclopropane-1,3'-indoline]-1'-carboxylate **4-4n**

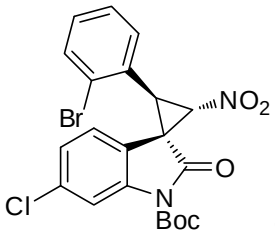


4-4n

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.64 (s, 9H), 4.33 (d, *J* = 6.3 Hz, 1H), 5.13 (d, *J* = 6.3 Hz, 1H), 5.81 (d, *J* = 2.5 Hz, 1H), 7.24-7.31 (m, 2H), 7.41-7.46 (m, 2H), 7.54 (d, *J* = 8.2 Hz, 1H), 7.91 (d, *J* = 8.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.1, 39.5, 41.6, 71.3, 85.5, 116.6, 120.2, 123.7, 126.4, 128.0, 129.0, 129.1, 129.5, 130.1, 130.8, 133.5, 139.0, 148.7, 167.5; The ee value is 98%, t_R (minor) = 9.95 min, t_R (major) = 6.50 min (Chiralcel IC, λ = 254 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min); $[\alpha]^{24}_D$ = +93.4 (c 1.10, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{21}H_{18}N_2O_5Na^{79}BrCl$ $[M+Na]^+$ = 514.9980, found = 515.0000; calcd for $C_{21}H_{18}N_2O_5Na^{81}BrCl$ $[M+Na]^+$ = 516.9959, found = 516.9977.

(1*S*,2*S*,3*S*)-*tert*-Butyl-2-(2-bromophenyl)-6'-chloro-3-nitro-2'-oxospiro[cyclopropane

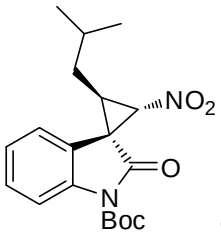
-1,3'-indoline]-1'-carboxylate **4-4o**



4-4o

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.65 (s, 9H), 4.31 (d, *J* = 6.9 Hz, 1H), 5.13 (d, *J* = 7.0 Hz, 1H), 5.79 (d, *J* = 8.2 Hz, 1H), 6.81 (dd, *J* = 1.9 Hz, 8.2 Hz, 1H), 7.28 (t, *J* = 4.1 Hz, 1H), 7.40-7.42 (m, 2H), 7.52 (d, *J* = 8.2 Hz, 1H), 8.02 (d, *J* = 1.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.1, 39.6, 41.5, 71.2, 85.7, 116.3, 120.3, 120.6, 124.1, 126.4, 127.9, 129.4, 130.1, 130.7, 133.5, 135.2, 141.2, 148.7, 167.7; The ee value is 97%, t_R (minor) = 10.86 min, t_R (major) = 6.65 min (Chiralcel IC, λ = 254 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min); $[\alpha]^{24}_D$ = +146.3 (c 1.13, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{21}H_{18}N_2O_5Na^{79}BrCl$ $[M+Na]^+$ = 514.9980, found = 515.0000; calcd for $C_{21}H_{18}N_2O_5Na^{81}BrCl$ $[M+Na]^+$ = 516.9959, found = 516.9977.

(1*S*,2*R*,3*S*)-*tert*-Butyl-2-isobutyl-3-nitro-2'-oxospiro[cyclopropane-1,3'-indoline]-1'-carboxylate **4-4p**

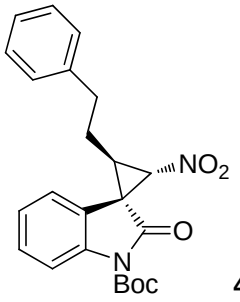


4-4p

A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.82 (d, *J* = 7.0 Hz, 1H), 0.90-0.93 (m, 5H), 1.67 (s, 9H), 3.04-3.09 (m, 1H), 4.60 (d, *J* = 7.0 Hz, 1H), 6.94 (d, *J* = 7.6 Hz,

1H), 7.17-7.20 (m, 1H), 7.37-7.41 (m, 1H), 8.00 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.0, 22.2, 27.9, 28.1, 33.3, 36.6, 36.8, 37.1, 38.4, 69.8, 72.6, 84.4, 85.0, 115.1, 115.3, 115.7, 118.0, 120.9, 122.9, 123.2, 124.2, 124.6, 128.1, 128.7, 128.9, 140.4, 141.0, 148.9, 149.2, 169.1, 173.2; The ee value is 92%, t_R (minor) = 6.39 min and 7.02 min, t_R (major) = 7.71 min and 15.96 min (Chiralcel IC, λ = 254 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{19}H_{24}N_2O_5Na$ $[M+Na]^+$ = 383.1577, found = 383.1578.

(1*S*,2*S*,3*R*)-*tert*-Butyl-2-nitro-2'-oxo-3-phenethylspiro[cyclopropane-1,3'-indoline]-1'-carboxylate **4-4q**



4-4q

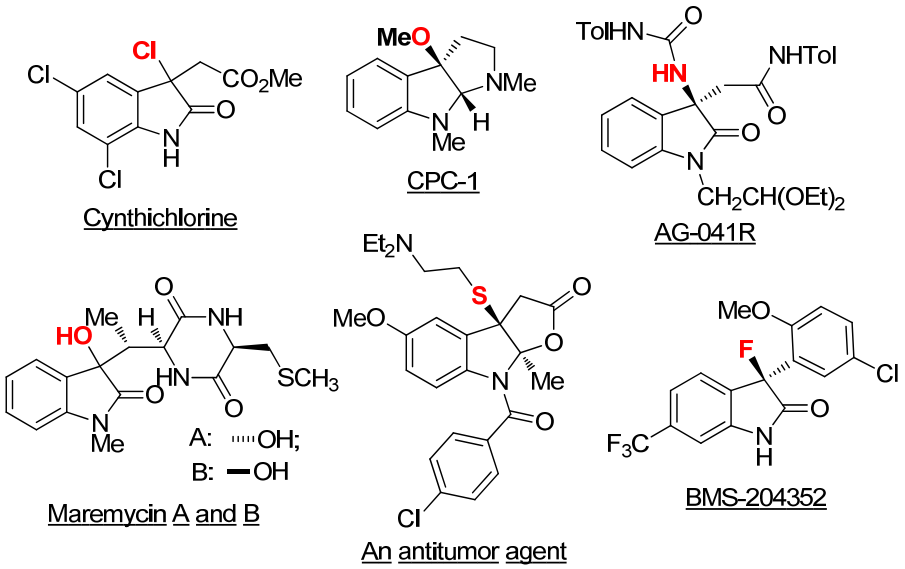
A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.63 (s, 9H), 1.88-1.96 (m, 1H), 2.14-2.21 (m, 1H), 2.59-2.69 (m, 1H), 2.75-2.79 (m, 1H), 3.04-3.08 (m, 1H), 4.50 (d, *J* = 6.9 Hz, 1H), 6.86 (d, *J* = 7.6 Hz, 1H), 7.02-7.07 (m, 2H), 7.12-7.17 (m, 4H), 7.35 (t, *J* = 4.1 Hz, 1H), 7.92 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.5, 26.0, 28.1, 34.5, 35.4, 37.4, 37.6, 38.3, 69.6, 71.8, 84.6, 84.9, 115.3, 115.7, 120.7, 122.5, 124.1, 124.4, 128.3, 128.5, 128.6, 128.9, 139.4, 139.6, 139.7, 140.3, 148.8, 168.8; The ee value is 91%, t_R (minor) = 7.98 min and 14.03 min, t_R (major) = 11.98 min and 15.29 min (Chiralcel IC, λ = 254 nm, 30% *i*PrOH/hexanes, flow rate = 1.0

mL/min); HRMS (ESI) m/z calcd for $C_{23}H_{24}N_2O_5Na$ $[M+Na]^+$ = 431.1577, found = 431.1579.

Chapter 5 A Facile and Versatile Approach for the Asymmetric Synthesis of Oxindoles with a 3-Heteroatom -substituted Quaternary Stereocenter

5.1 Introduction

3,3-Disubstituted oxindoles are widely present in natural products and biologically significant molecules.[1] In particular, oxindoles bearing a 3-heteroatom-substituted quaternary stereogenic center are extremely important in medicinal chemistry (Figure 5.1),[2] and thus their asymmetric synthesis has attracted tremendous attention in recent years.



[1] For reviews, see: a) C. V. Galliford, K. A. Scheidt, *Angew. Chem., Int. Ed.* **2007**, *46*, 8748; b) A. B. Dounay,L. E. Overman, *Chem. Rev.* **2003**, *103*, 2945; c) G. S. Singh, Z. Y. Desta, *Chem. Rev.* **2012**, *112*, 6104; d) R. Dalpozzo, G. Bartoli, G. Bencivenni, *Chem. Soc. Rev.* **2012**, *41*, 7247; e) K. Shen, X. Liu, L. Lin, X. Feng, *Chem. Sci.* **2012**, *3*, 327; f) F. Zhou, Y.-L. Liu, J. Zhou, *Adv. Synth. Catal.* **2010**, *352*, 1381; g) B. M. Trost, M. K. Brennan, *Synthesis* **2009**, *18*, 3003; h) C. Marti, E. M. Carreira, *Eur. J. Org. Chem.* **2003**, 2209.

[2] For selected examples, see: (a) A. Abourriche, Y. Abboud, S. Maoufoud, H. Mohou, T. Seffaj, M. Charrouf, N. Chaib, A. Benamara, N. Bontemps, C. Francisco, *Farmaco* **2003**, *58*, 1351;. b) V. K. Gribkoff, D. J. Post-Munson, S. W. Yeola, C. G. Boissard, P. Hewawasam, PCT Int. Appl. WO 2002/030868, **2002**; c) K. Bernard,S. Bogliolo, J.Ehrenfeld, *Br. J. Pharmacol.* **2005**, *144*, 1037; d) G. Gilles, S. L. Claudine, *Stress* **2003**, *6*, 199; e) N. Shibata, T. Ishimaru, E. Suzuki, K. L. Kirk, *J. Org. Chem.* **2003**, *68*, 2494; f) M. Kitajima, I. Mori, K. Arai, N. Kogure, H. Takayama, *Tetrahedron Lett.* **2006**, *47*, 3199; g) J. J. Badillo, N. V. Hanhan, A. K. Franz, *Curr. Opin. Drug Discovery Dev.* **2010**, *13*, 758; h) P. Gross, G. Sperl, R. Pamukcu, K. Brendel, PCT Int. Appl. WO 96/03987, **1996**.

Figure 5.1 Biologically important oxindoles/indoline with a 3-heteroatom-substituted quaternary center

A range of synthetic methods have been developed for catalytic asymmetric synthesis of 3-substituted-3-heteroatom oxindoles such as 3-aminooxindoles,[3] 3-hydroxyoxindoles,[4] 3-fluorooxindoles,[5] 3-sulfenyloxindoles,[6] 3-chlorooxindoles[7] and 3-selenooxindoles.[8] The vast majority of the above examples relied on the employment of common 3-aryl or alkyl-substituted oxindoles, which were then subjected to different heteroatom-inducing catalytic processes. Asymmetric introduction of a specific heteroatom to the oxindole core is not trivial, which highly depends on the nature of the incoming heteroatom. Therefore, a diverse set of reaction conditions and catalytic systems are apparently required. Moreover, the 3-alkyl or

[3] For amination of pro-chiral oxindoles, see: a) S. Mouri, Z. Chen, H. Mitsunuma, M. Furutachi, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2010**, *132*, 1255; b) T. Bui, M. Borregan, C. F. Barbas III, *J. Org. Chem.* **2009**, *74*, 8935; c) L. Cheng, L. Liu, D. Wang, Y.-J. Chen, *Org. Lett.* **2009**, *11*, 3874; d) Z.-Q. Qian, F. Zhou, T.-P. Du, B.-L. Wang, M. Ding, X.-L. Zhao, J. Zhou, *Chem. Commun.* **2009**, 6753. For addition to isatin-derived ketimines, see: e) J. Feng, W. Yan, D. Wang, P. Li, Q. Sun, R. Wang, *Chem. Commun.* **20012**, *48*, 8003; f) N. Hara, S. Nakamura, M. Sano, R. Tamura, Y. Funahashi, N. Shibata, *Chem. Eur. J.* **2012**, *18*, 9726.

[4] For examples using isatins as the electrophile, see: a) Y.-L. Liu, J. Zhou, *Chem. Commun.* **2012**, *48*, 1919; b) J. Guang, Q. Guo, J. C.-G. Zhao, *Org. Lett.* **2012**, *14*, 3174; c) L. Liu, S. Zhang, F. Xue, G. Lou, H. Zhang, S. Ma, S.; W. Duan, W. Wang, *Chem. Eur. J.* **2011**, *17*, 7791; d) Y.-L. Liu, B.-L. Wang, J.-J. Cao, L. Chen, Y.-X. Zhang, C. Wang, J. Zhou, *J. Am. Chem. Soc.* **2010**, *132*, 15176; e) J. Itoh, S. B. Han, M. J. Krische, *Angew. Chem. Int. Ed.* **2009**, *48*, 6313; f) D. Tomita, K. Yamatsugu, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 6946; g) T. Itoh, H. Ishikawa, Y. Hayashi, *Org. Lett.* **2009**, *11*, 3854; h) R. Shintani, M. Inoue, T. Hayashi, *Angew. Chem. Int. Ed.* **2006**, *45*, 3353. For hydroxylation of benzoyloxylation of pro-chiral oxindoles, see: i) Y.-H. Liao, Z.-J. Wu, W.-Y. Han, X.-M. Zhang, W.-C. Yuan, *Chem. Eur. J.* **2012**, *18*, 8916; j) Z. Zhang, W. Zheng, J. C. Antilla, *Angew. Chem. Int. Ed.* **2011**, *50*, 1135; k) T. Bui, N. R. Candeias, C. F. Barbas III, *J. Am. Chem. Soc.* **2010**, *132*, 5574; l) T. Ishimaru, N. Shibata, J. Nagai, S. Nakamura, T. Toru, S. Kanemasa, *J. Am. Chem. Soc.* **2006**, *128*, 16488. For examples employing 3-OH-oxindoles, see: m) G. Bergonzini, P. Melchiorre, *Angew. Chem. Int. Ed.* **2012**, *51*, 971; n) M. Retini, G. Bergonzini, P. Melchiorre, *Chem. Commun.* **20012**, *48*, 3336.

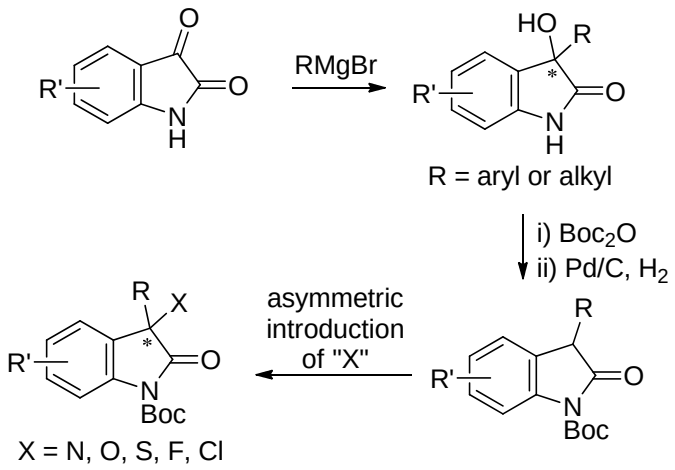
[5] a) L. Wu, L. Falivene, E. Drinkel, S. Grant, A. Linden, L. Cavallo, R. Dorta, *Angew. Chem. Int. Ed.* **2012**, *51*, 2870; b) Y. Li, Y. Cai, W. Chen, X. Liu, L. Lin, X. Feng, *J. Org. Chem.* **2012**, *77*, 9148; c) Q.-H. Deng, H. Wadepohl, L. H. Gade, *Chem. Eur. J.* **2011**, *17*, 14922; d) T. Ishimaru, N. Shibata, T. Horikawa, N. Yasuda, S. Nakamura, T. Toru, M. Shiro, *Angew. Chem. Int. Ed.* **2008**, *47*, 4157; e) Y. Hamashima, T. Suzuki, H. Takano, Y. Shimura, M. Sodeoka, *J. Am. Chem. Soc.* **2005**, *127*, 10164; f) N. Shibata, J. Kohno, K. Takai, T. Ishimaru, S. Nakamura, T. Toru, S. Kanemasa, *Angew. Chem. Int. Ed.* **2005**, *44*, 4204; g) L. Zoute, C. Audouard, J.-C. Plaquevent, D. Cahard, *Org. Biomol. Chem.* **2003**, *1*, 1833; h) N. Shibata, E. Suzuki, T. Asahi, M. Shiro, *J. Am. Chem. Soc.* **2001**, *123*, 7001.

[6] a) C. Wang, X. Yang, C. C. J. Loh, G. Raabe, D. Enders, *Chem. Eur. J.* **2012**, *18*, 11531; b) X. Li, C. Liu, X.-S. Xue, J.-P. Cheng, *Org. Lett.* **2012**, *14*, 4374; c) Z. Han, W. Chen, S. Dong, C. Yang, H. Liu, Y. Pan, L. Yan, Z. Jiang, *Org. Lett.* **2012**, *14*, 4670; d) Y. Cai, J. Li, W. Chen, M. Xie, X. Liu, L. Lin, X. Feng, *Org. Lett.* **2012**, *14*, 2726.

[7] a) W. Zheng, Z. Zhang, M. J. Kaplan, J. C. Antilla, *J. Am. Chem. Soc.* **2011**, *133*, 3339; b) D. Wang, J.-J. Jiang, R. Zhang, M. Shi, *Tetrahedron: Asymmetry* **2011**, *22*, 1133; c) M.-X. Zhao, Z.-W. Zhang, M.-X. Chen, W.-H. Tang, M. Shi, *Eur. J. Org. Chem.* **2011**, 3001. Also see ref. 5f.

[8] V. Marcos, J. Alemán,J. L. G. Ruano, F. Marini, M. Tiecco, *Org. Lett.* **2011**, *13*, 3052.

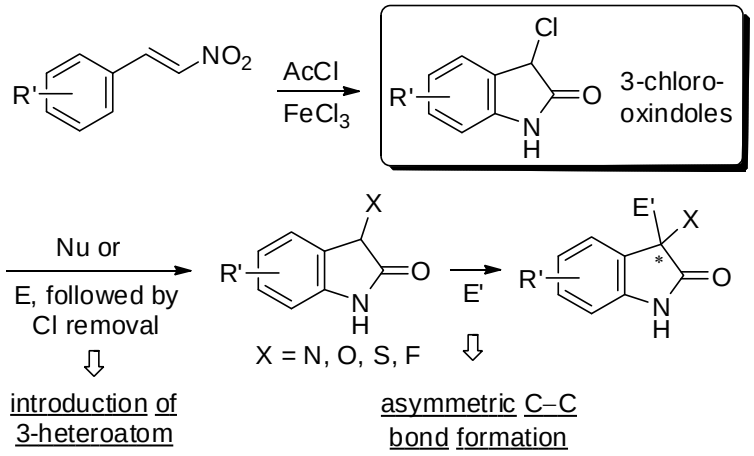
aryl-substituted prochiral oxindoles are commonly prepared from isatins. Such a preparation suffers from several key drawbacks,[9] including: employment of expensive isatins, poor functional group tolerance under Grignard conditions, as well as limited availability of Grignard reagents (Scheme 5.1).



Scheme 5.1 Common methods for the synthesis of 3-heteroatom-substituted oxindoles

Our group has been actively investigating asymmetric synthesis of chiral oxindole derivatives, particularly those bearing a quaternary stereogenic center. Given the biological significance of oxindoles containing a 3-heteroatom-substituted quaternary carbons, we became very interested in developing an efficient and versatile synthetic strategy to access a variety of these heteroatom containing chiral oxindoles. To make our method practical and synthetically useful, employment of cheap and readily available starting materials would be desirable. Moreover, asymmetry-inducing processes should ideally be promoted by similar catalytic systems.

[9] For a representative preparation of 3-alkyl/aryl-substituted oxindoles from isatins, see the Supporting Information of ref. 5e.



Scheme 5.2 Our approach to access 3-heteroatom-3-substituted oxindoles

With the above designing principles in mind, we turned our attention to 3-chlorooxindoles as a key intermediate. Various 3-chlorooxindoles could be readily derived from nitroolefins,[10] a method was reported more than 30 years ago, but did not draw much attention from the synthetic community. Ready availability and inexpensive nature of nitroolefins make the derivatization of the corresponding 3-chlorinated oxindoles highly economical. We hypothesize their reactions with nucleophiles would install different heteroatoms at the 3-position of oxindoles. Alternatively, reactions of 3-chlorooxindoles with electrophiles, followed by reductive de-chlorination would also allow for the incorporation of the heteroatoms at the 3-position. The reactions of different 3-heteroatom substituted oxindoles with carbon electrophiles then create the desired quaternary chiral centers in the oxindole structures. Presumably, when a given electrophilic reaction partner is employed, the projected carbon~carbon bond forming reactions of different 3-heteroatom-substituted

[10] a) P. Demerseman, J. Guillaumel, J.-M. Clavel, R. Royer, *Tetrahedron Lett.* **1978**, *23*, 2011; b) J. Guillaumel, P. Demerseman, J.-M. Clavel, R. Royer, *Tetrahedron* **1980**, *36*, 2459; c) J. Guillaumel, P. Demerseman, J.-M. Clavel, R. Royer, *J. Heterocyclic Chem.* **1980**, *17*, 1531.

oxindoles may be promoted by similar catalytic systems (Scheme 5.2), which will make this approach highly versatile. Herein, we describe preparation of various 3-heteroatom-substituted (including Cl, O, S, F, N) oxindoles, and their catalytic reactions with nitroolefins[11] for the facile asymmetric synthesis of oxindoles bearing a heteroatom-containing quaternary stereogenic center.

5.2 Results and Discussion

5.2.1 Reaction Optimization for the Synthesis of Chiral 3-Chlorooxindoles

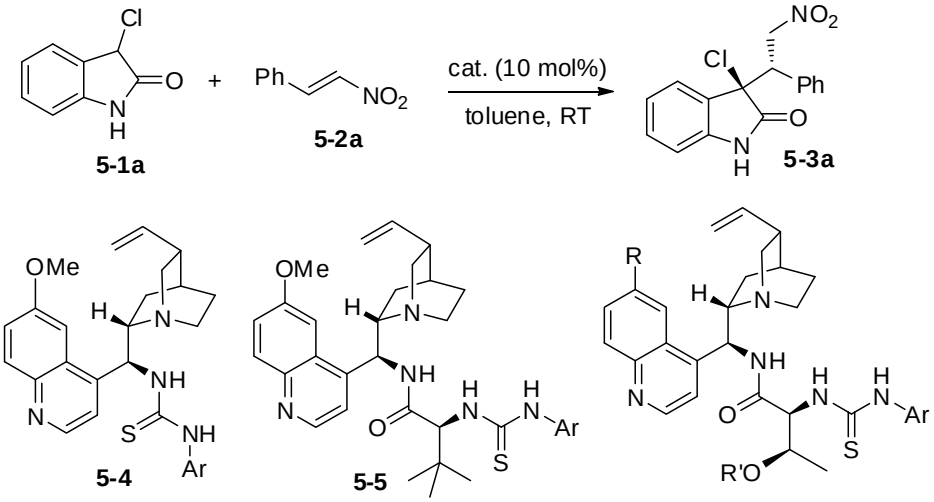
We first examined the conjugate addition of unprotected 3-chlorooxindole **5-1a** to nitroolefin **5-2a** in the presence of different bifunctional catalysts, and the results are summarized in Table 5.1. For the selection of organic catalysts, we firstly tested the bifunctional tertiary amine thiourea catalyst. When quinine-derived tertiary amine-thiourea catalyst **5-4** was used, the reaction was fast, however, both diastereoselectivity and enantioselectivity were modest (entry 1). To further improve the results, we chose to employ our recently developed amino acid incorporating multifunctional catalysts.[12] Gratifyingly, all the multifunctional catalysts could efficiently promote the reaction, affording the desired products in high yields and with very high diastereoselectivities. Incorporation of silylated L-threonine backbone to the catalyst structure resulted in a series of multifunctional catalysts, essential for further

[11] For examples of conjugate addition of 3-alkyl or aryl-substituted oxindoles to nitroolefins, see: a) M. Ding, F. Zhou, Y.-L. Liu, C.-H. Wang, X.-L. Zhao, J. Zhou, *Chem. Sci.* **2011**, *2*, 2035; b) Y.-Y. Han, Z.-J. Wu, W.-B. Chen, X.-L. Du, X.-M. Zhang, W.-C. Yuan, *Org. Lett.* **2011**, *13*, 5064; c) X. Li, B. Zhang, Z.-G. Xi, S. Luo, J.-P. Cheng, *Adv. Synth. Catal.* **2010**, *352*, 416; d) M. Ding, F. Zhou, Z.-Q. Qian, J. Zhou, *Org. Biomol. Chem.* **2010**, *8*, 2912; e) T. Bui, S. Syed, C. F. Barbas III, *J. Am. Chem. Soc.* **2009**, *131*, 8758; f) Y. Kato, M. Furutachi, Z. Chen, H. Mitsunuma, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 9168; g) R. He, S. Shirakawa, K. Maruoka, *J. Am. Chem. Soc.* **2009**, *131*, 16620.

[12] a) Q. Zhu, Y. Lu, *Angew. Chem. Int. Ed.* **2010**, *49*, 7753; b) X. Dou, Y. Lu, *Chem. Eur. J.* **2012**, *18*, 8315; c) F. Zhong, J. Luo, G.-Y. Chen, X. Dou,Y. Lu, *J. Am. Chem. Soc.* **2012**, *134*, 10222; d) J. Luo, H. Wang, F. Zhong, J. Kwiatkowski, L.-W. Xu, Y. Lu, *Chem. Commun.* **2012**, *48*, 4707.

improvement of the enantioselectivity. It should be noted that the multifunctional catalysts utilized are structurally highly tunable, which is crucial for achieving the optimal interactions with different substrates during the reaction. Catalyst **5-9** which contains an *O*-TBDPS-L-threonine moiety turned out to be the best catalyst, affording **5-3a** in quantitative yield, excellent diastereoselectivity and enantioselectivity (entry 6). When the reaction was performed at 0 ^{o}C in the presence of 5 mol% **5-9** under the optimized reaction conditions, adduct **5-3a** was obtained in 98% yield, with >20:1 dr and 97% ee (entry 8).

Table 5.1 Conjugate Addition of 3-Chlorooxindole **5-1a** to Nitroolefin **5-2a** Catalyzed by Different Organic Catalysts[a]



entry	cat.	t (h)	yield (%)[b]	dr[c]	ee (%)[d]
1	**5-4**	2	94	4:1	68
2	**5-5**	1	90	19:1	74
3	**5-6**	2	85	>20:1	84
4	**5-7**	2.5	91	20:1	75

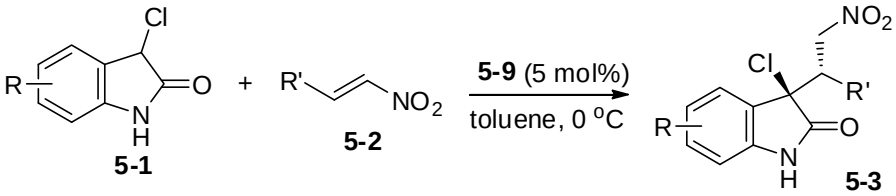
5	**5-8**	1	97	>20:1	94
6	**5-9**	1	99	>20:1	95
7[e]	**5-9**	5	98	>20:1	95
8[e,f]	**5-9**	8	98	>20:1	97

[a] Reactions were performed with **5-1a** (0.1 mmol), **5-2a** (0.12 mmol) and the catalyst (0.01 mmol) in toluene (1.0 mL) at room temperature. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis of the crude products. [d] The ee values of the major isomer, determined by HPLC analysis on a chiral stationary phase. [e] 5 mol % **5-9** was used. [f] Reaction was performed at 0 ^{o}C.

5.2.2 Substrate Scope for the Synthesis of Chiral 3-Chlorooxindoles

With the optimized reaction conditions in hand, the substrate scope was next examined (Table 5.2). Different aryl nitroolefins could be employed, including aromatic rings with different halogen substitutions, substituents with different electronic nature, as well as different substitution patterns (entries 1–12). Moreover, aryls other than phenyls could also be employed in the nitroolefin structures (entries 13–16). The reaction was also applicable to 3-chlorooxindoles containing different aromatic moieties (entries 17–19). Alkyl nitroolefin could also be employed, the desired product was obtained with excellent diastereoselectivity and enantioselectivity, although the reaction was substantially slower and the yield was moderate (entry 20). In all the examples examined, nearly perfect diastereoselectivities and enantioselectivities were attainable. In addition, synthesis of **5-3a** was scaled up to 2 mmol, and the yield, diastereo- and enantio- selectivities of the reaction were maintained (entry 1a). The absolute configurations of 3-chloro-3-substituted oxindole products were determined on the basis of the X-ray crystal structure of **5-3b**.

Table 5.2 Substrate Scope of the Conjugate Addition of 3-Chlorooxindoles to Nitroolefins[a]



entry	R/R', **5-3**	t (h)	yield/%[b]	dr[c]	ee/%[d]
1	H/C_6H_5, **5-3a**	8	98	>20:1	97
1a[e]	H/C_6H_5, **5-3a**	12	96	>20:1	95
2	H/2-Br-C_6H_4, **5-3b**	8	99	>20:1	96
3	H/3-Br-C_6H_4, **5-3c**	12	94	>20:1	96
4	H/4-Br-C_6H_4, **5-3d**	10	98	>20:1	93
5	H/2-Cl-C_6H_4, **5-3e**	10	95	>20:1	94
6	H/3-Cl-C_6H_4, **5-3f**	16	91	>20:1	98
7	H/4-Cl-C_6H_4, **5-3g**	10	99	>20:1	98
8	H/4-F-C_6H_4, **5-3h**	12	99	>20:1	94
9	H/2-Me-C_6H_4, **5-3i**	22	98	>20:1	98
10	H/4-Me-C_6H_4, **5-3j**	12	98	>20:1	99
11	H/3,4-OMeC_6H_3, **5-3k**	24	99	>20:1	97
12	H/4-CN-C_6H_4, **5-3l**	8	99	>20:1	98
13	H/1-naphthyl, **5-3m**	20	98	>20:1	99
14	H/2-naphthyl, **5-3n**	18	99	>20:1	96
15	H/2-furyl, **5-3o**	18	95	>20:1	99
16	H/2-thienyl, **5-3p**	18	99	>20:1	97
17	4-Cl/C_6H_5, **5-3q**	24	95	12:1	99
18	5-Cl/ C_6H_5, **5-3r**	12	97	>20:1	99
19	5-Cl/2-Br-C_6H_4, **5-3s**	12	99	>20:1	98
20[f]	H/phenethyl, **5-3t**	48	53	13:1	99

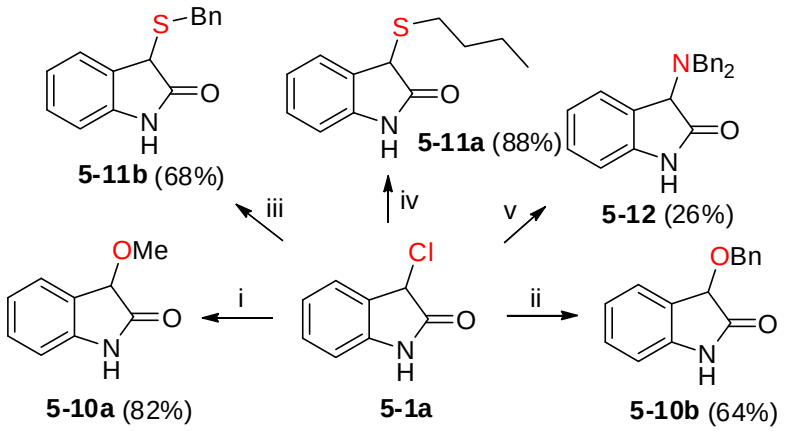
[a] Reactions were performed with **5-1** (0.1 mmol), **5-2** (0.12 mmol) and the catalyst **5-9** (0.005 mmol) in toluene (1.0 mL) at 0 °C. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis of the crude products. [d] Determined by HPLC analysis on a chiral stationary phase, *ee* value of the major isomer. [e] Reaction was performed on a 2.0 mmol scale. [f] 10 mol % **5-9** was used and reaction was performed at room temperature.

5.2.3 Facile Synthesis of Various 3-Heteroatom-substituted Oxindoles

Having demonstrated that 3-chloro-substituted oxindoles could be asymmetrically added to nitroolefins, our next goal was to show that similar asymmetric processes may be applicable to various 3-heteroatom-substituted oxindole pronucleophiles. We envisioned that 3-chlorooxindole could serve as a versatile starting material to derivatize various 3-heteroatom containing oxindoles. It is noteworthy that a general method for the preparation of pronucleophilic oxindoles with a 3-substituted heteroatom is unknown in the literature.[13] As illustrated in Scheme 5.3, when 3-chlorooxindole **5-1a** reacted with a range of nucleophiles, nucleophilic substitutions took place readily to afford 3-sulfur, oxygen, or nitrogen substituted oxindoles (**5-10**–**5-12**). For the synthesis of 3-fluorooxindole, 3-chlorooxindole **5-1a** was subjected to an electrophilic fluorination, followed by reductive cleavage of the chlorine atom to yield 3-fluoro-substituted oxindoles (**5-14** and **5-16**).

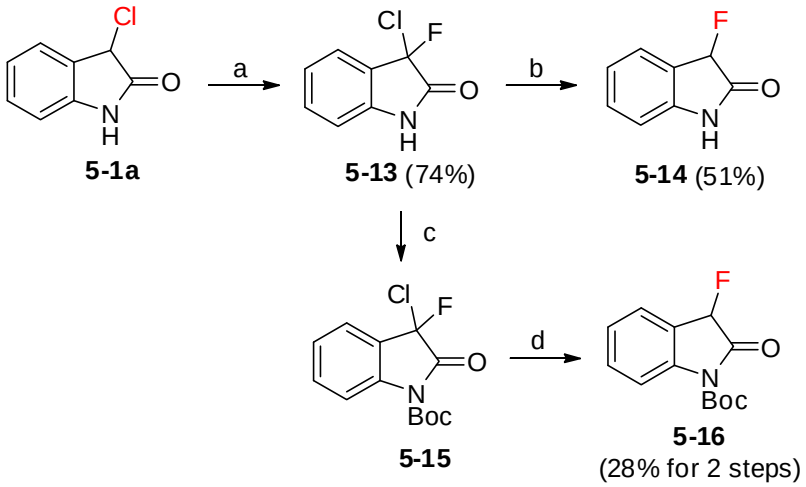
[13] For some isolated examples, see: a) P. L. Creger, *J. Org. Chem.* **1965**, *30*, 3610; b) L. A. McAllister, S. Brand, R. Gentile, D. J. Procter, *Chem. Commun.* **2003**, 2380; c) M. Miller, W. Tsang, A. Merritt, D. J. Procter, *Chem. Commun.* **2007**, 498.

Via Nucleophilic Substitution



i: MeOH, reflux, 10 h; ii: BnOH, 100 ^{o}C, 3 h; iii: BnSH, K_2CO_3, DMF, 50 ^{o}C, 40 min; iv: *n*-BuSH, K_2CO_3, DMF, 60 ^{o}C, 1 h; v: Bn_2NH, CH_3CN, reflux, 3 h.

Via Nucleophilic Addition–Dechlorination



a: NFSI, DBU, CH_2Cl_2, 5 min; b: Pd/C, H_2, EtOAc, 1 h;
c: Boc_2O/DMAP, CH_2Cl_2,15 min; d: Pd/C, H_2, EtOAc, 30 min.

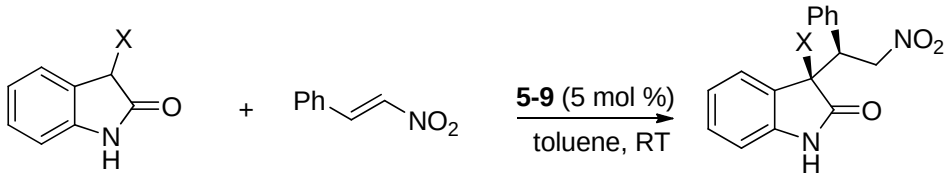
Scheme 5.3 Synthesis of various 3-heteroatom-substituted prochiral oxindoles

5.2.4 Substrate Scope for the Synthesis of Chiral 3-Heteroatomoxindoles

5-9 Catalyzed asymmetric conjugate additions of various above-prepared 3-heteroatom-substituted oxindoles to nitroolefin **5-2a** were then tested, and the results are summarized in Table 5.3. When 3-oxygenated oxindole **5-10a** was employed, excellent yield, high diastereoselectivity and enantioselectivity were

attainable, although the reaction took 30 hours to complete (entry 1). With the employment of 3-OBn oxindole **5-10b**, the reactivity was substantially improved**,** and product was obtained with very high diastereomeric ratio and nearly perfect ee value (entry 2). Sulfur-containing oxindoles also proved to be suitable pronucleophiles, and they reacted with nitroolefin to furnish the desired Michael products in high chemical yields, excellent diastereomeric and enantiomeric selectivities (entries 3–4). 3-Fluoro-substituted oxindoles were found to be difficult substrates. With the employment of 3-F-oxindole **5-14**, the adduct was obtained in high yield and with high diastereoselectivity, however, virtually no enantioselectivity was observed (entry 5). With the employment of 3-fluorinated *N*-Boc protected oxindole **5-16**, moderate enantioselectivity and decreased diastereoselectivity were obtained (entry 6). Another substrate unsuitable for the current catalytic system was 3-nitrogen-oxindole **5-12**, and no reaction was observed, probably due to the low reactivity of **5-12** (entry 7).

Table 5.3 Substrate Scope of the Conjugate Addition of 3-Heteroatom-substituted Oxindoles to Nitroolefins[a]



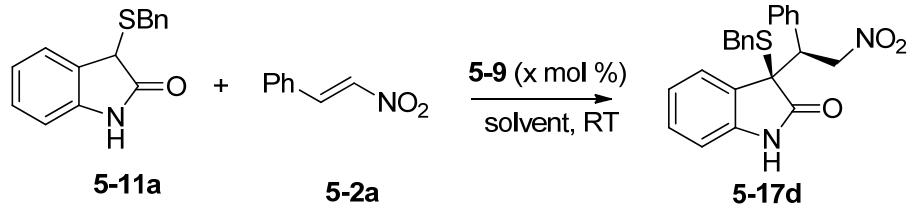
entry	X, **5-17**	t (h)	yield (%)[b]	dr[c]	ee (%)[d]
1[e]	OMe, **5-17a**	30	94	9:1	86
2	OBn, **5-17b**	3	96	>20:1	98
3	*n*-BuS, **5-17c**	2	95	>20:1	91

4	BnS, **5-17d**	1.5	98	19:1	97
5[e]	F, **5-17e**	48	92	10:1	3
6[f]	F, **5-17f**	4	87	4:1	55
7[g]	Bn_2N	24	-	-	-

[a] Reactions were performed with 3-X-oxindole (0.1 mmol), **5-2** (0.12 mmol) and the catalyst **5-9** (0.005 mmol) in toluene (1.0 mL) at room temperature. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis of the crude products. [d] Determined by HPLC analysis on a chiral stationary phase, *ee* value of the major isomer. [e] 10 mol % **5-9** was used. [f] **5-16** was used in the reaction. [g] No reaction took place after 24 h.

Sulfur-containing oxindoles showed the best reactivity and further study was conducted to optimize the reaction conditions (Table 5.4). Solvent screening showed CH_2Cl_2 and xylene were slightly inferior to toluene in terms of reaction time (entry 1) or enantioselectivity (entry 3). Surprisingly, THF showed to be unsuitable in this reaction, there was only very low conversion after 12 h (entry 2). Additive studies proved 4 Å molecular sieves was beneficial and could slightly improve the diastereoselectivity while maintain the ee value (entries 4–6). Catalyst loading could be reduced to as low as 1 mol % to promote the reaction efficiently without sacrificing the diastereoselectivity and enantioselectivity (entries 7–8). Even lower catalyst loading 0.5 mol % could be reached with slightly lower dr and ee values (entry 9).

Table 5.4 Asymmetric Conjugate Addition of 3-Sulfenyloxindole **5-11b** to Nitroolefin **5-2a** under Different Conditions[a]



5-11a **5-2a** **5-17d**

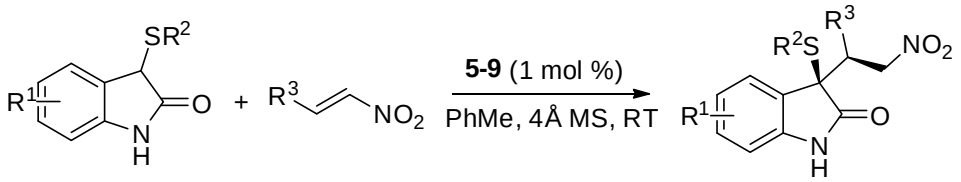
entry	x	solvent	additive	t (h)	yield (%)[b]	dr[c]	ee (%)[d]
1	5	CH_2Cl_2	none	4	93	>20:1	97
2	5	THF	none	12	88	<10	n.d.
3	5	xylene	none	1.5	96	>20:1	96
4	5	toluene	3Å MS	1.5	75	19:1	97
5	5	toluene	4Å MS	1.5	72	>20:1	97
6	5	toluene	5Å MS	1.5	78	>20:1	96
7	2.5	toluene	4Å MS	3	85	>20:1	97
8	1	toluene	4Å MS	8	96	>20:1	97
9	0.5	toluene	4Å MS	15	97	19:1	95

[a] Reactions were performed with **5-11a** (0.1 mmol), **5-2a** (0.12 mmol), and the **5-9** (x mol %) in solvent (1.0 mL) at room temperature [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] Determined by HPLC analysis on a chiral stationary phase, *ee* value of the major isomer.

With the optimal reaction conditions in hand, we next examined the substrate scope of the conjugate addition of 3-sulfenyloxindole to nitroolefins **5-2**. As shown in Table 5.5, different aryl nitroolefins could be employed, including aromatic rings with different halogen substitutions, substituents of different electronic nature, as well as different substitution patterns (entries 1–5). Aryls other than phenyls could also be employed in the nitroolefin structures (entries 6–7). The reaction was also applicable to 3-sulfenyloxindoles containing different aromatic moieties (entries 8–9) and thio substitutions (entries 10–11). Moreover, alkyl nitroolefin could also be employed, and the desired product was obtained with excellent diastereoselectivity and enantioselectivity, although the yield was slightly lower (entry 12–13). In all the

examples examined, very high diastereoselectivities (14:1 to >20:1 dr) and enantioselectivities (up to 99% *ee*) were attainable.

Table 5.5 The Scope of Asymmetric Conjugate Addition of 3-Sulfenyloxindoles **5-11** to Nitroolefins **5-2**[a]



5-11 **5-2** **5-17**

entry	$R^1/R^2/R^3$, **5-17**	t (h)	yield (%)[b]	dr[c]	ee (%)[d]
1	H/Bn/C_6H_5, **5-17d**	8	98	>20:1	97
2	H/Bn/2-Br-C_6H_4, **5-17e**	10	95	14:1	99
3	H/Bn/3-Br-C_6H_4, **5-17f**	12	98	>20:1	97
4	H/Bn/4-Cl-C_6H_4, **5-17g**	12	98	>20:1	97
5	H/Bn/4-Me-C_6H_4, **5-17h**	16	97	>20:1	97
6	H/Bn/2-naphthyl, **5-17i**	10	99	>20:1	98
7	H/Bn/2-furyl, **5-17j**	12	96	19:1	96
8	5-Me/Bn/C_6H_5, **5-17k**	12	97	>20:1	98
9	6-Cl/Bn/C_6H_5, **5-17l**	10	95	19:1	96
10	H/*n*-Bu/C_6H_5, **5-17c**	12	95	>20:1	91
11	H/*n*-Bu/3-Br-C_6H_4, **5-17m**	12	97	>20:1	90
12[e]	H/Bn/*n*-butyl, **5-17n**	12	81	19:1	98
13[e]	H/Bn/phenethyl, **5-17o**	12	84	16:1	98

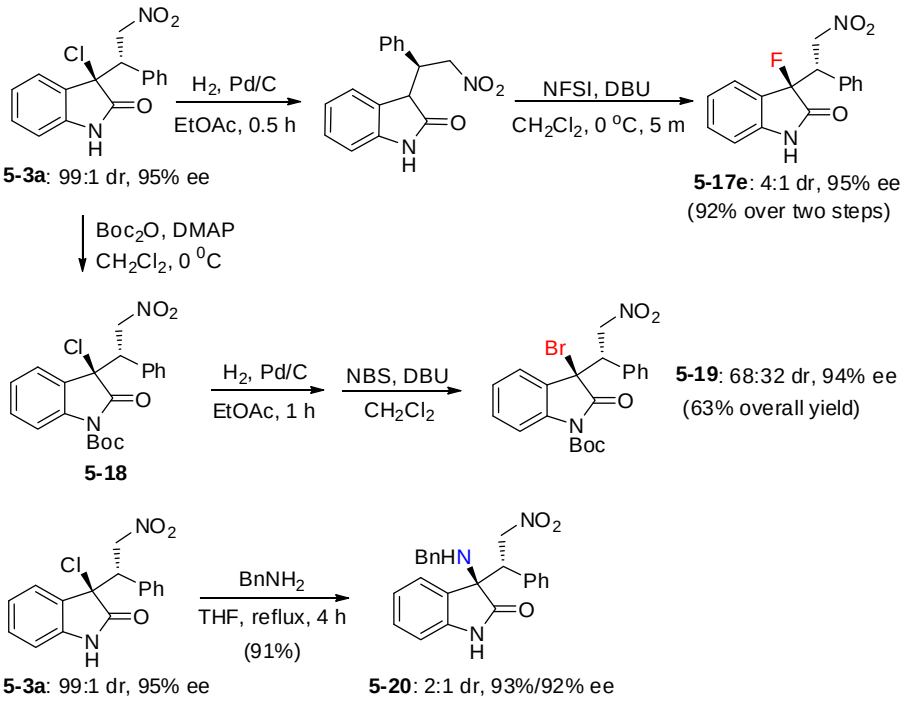
[a] Reactions were performed with **5-11** (0.1 mmol), **5-2** (0.12 mmol), **5-9** (0.001 mmol) and 4Å MS (10 mg) in toluene (1 mL) at room temperature. [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] Determined by HPLC analysis on a chiral stationary phase, *ee* value of the major isomer. [e] 5 mol % catalyst loading.

5.2.5 Introducing a Heteroatom to 3-Chlorinated Oxindole Adduct

We reasoned the Michael adduct **5-3a**, which contains a chlorine atom at the 3-quaternary carbon, may be utilized to construct oxindoles with other heteroatoms, especially for those structures not accessible through the previous attempts (Table 5.3, entries 5–7). The chloride at the 3-position may undergo an S_N2 displacement to yield other heteoatom-substituted oxindoles.[14] Alternatively, the chlorine atom may be reductively cleaved, followed by reaction with a suitable electrophile for the installation of the desired heteroatom. As illustrated in Sheme 5.4, when chloride **5-3a** was treated under hydrogenation conditions, cleavage of the chlorine atom occurred smoothly, and the subsequent reaction with electrophilic fluorinating NFSI yielded 3-fluoro-substituted oxindole **5-17e** with a 4:1 diastereomeric ratio and a 95% ee. Similarly, *N*-Boc-3-Cl-oxindole **5-18** was converted to 3-bromo-substituted oxindole **5-19**. Although **19** was obtained with a low dr ratio, but the diastereomers could be separated, and ee value was excellent. This type of 3-Br-oxindoles is a highly useful synthetic intermediate.[15] The nucleophilic substitution of 3-chlorooxindole **5-3a** with benzyl amine took place readily, furnishing oxindole **5-20** with a nitrogen-containing quaternary stereocenter at the 3-position (Scheme 5.4)

[14] For a recent report on S_N2 displacement of tertiary chlorides, see: K. Shibatomi, Y. Soga, A. Narayama, I. Fujisawa, S. Iwasa, *J. Am. Chem. Soc.* **2012**, *134*, 9836.

[15] a) L. Furst, J. M. R. Narayanam, C. R. J. Stephenson, *Angew. Chem. Int. Ed.* **2011**, *50*, 9655; b) M. Movassaghi, O. K. Ahmad, S. P. Lathrop, *J. Am. Chem. Soc.* **2011**, *133*, 13002; c) V. R. Espejo, X.-B. Li, J. D. Rainier, *J. Am. Chem. Soc.* **2010**, *132*, 8282.



Scheme 5.4 Introducing different heteroatoms to 3-chlorooxindole adduct **5-3a**

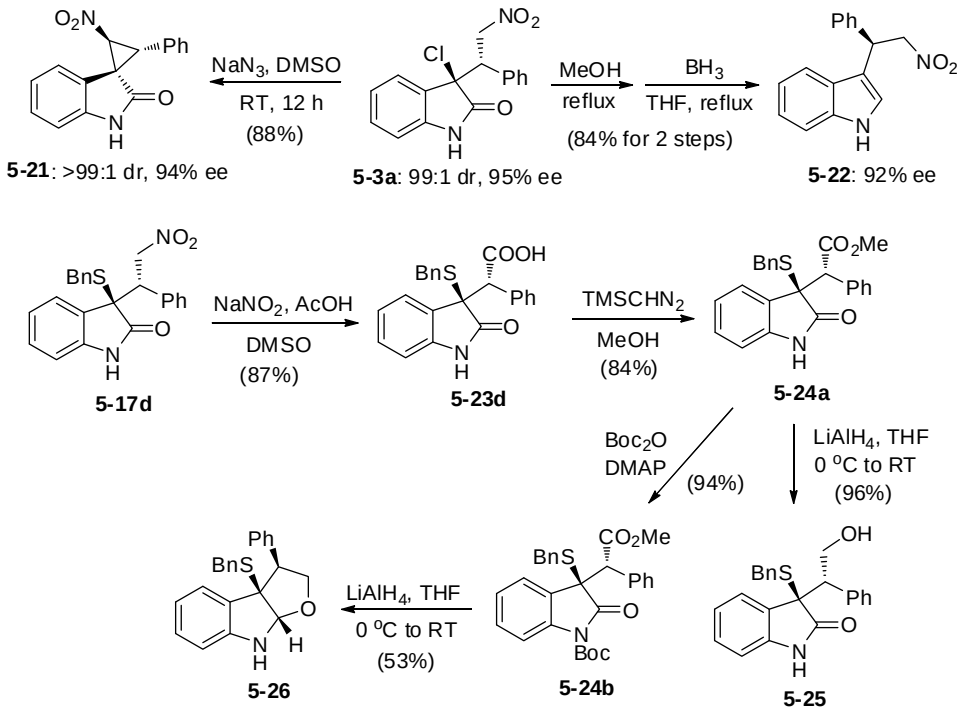
5.2.6 Synthetic Elaborations of Oxindoles with a 3-Substituted Heteroatom

In addition to their potential biological significance in medicinal chemistry, the oxindole adducts containing a 3-heteroatom-substituted quaternary stereocenter are valuable synthetic intermediates.[16] We carried out some simple derivatizations to demonstrate the values of these molecules in synthesis, which are summarized in Scheme 5.5. Treatment of 3-chlorooxindole **5-3a** with sodium azide failed to produce the corresponding S_N2 displacement product,[14] but instead yielded spriocyclopropyl oxindole **5-21**, a class of molecules of great biological significance.[12b] The reaction proceeded in excellent yield, and with complete retention of diastereoselectivity and enantioselectivity. Nucleophilic substitution of **5-3a** with methanol yielded the 3-OMe-oxindole, which was subjected directly to borane reduction to furnish

[16] a) S. Ma, X. Han, S. Krishnan, S. C. Virgil, B. M. Stoltz, *Angew. Chem. Int. Ed.* **2009**, *48*, 8037; b) C. D. Grant, M. J. Krische, *Org. Lett.* **2009**, *11*, 4485; c) S. Krishnan, B. M. Stoltz, *Tetrahedron Lett.* **2007**, *48*, 7571.

3-substituted indole **5-22** in high yield and excellent enantiomeric excess.[17] It is noteworthy that this transformation represents a new synthetic route to asymmetrically access 3-substitued indole derivatives, which are normally synthesized via Friedel–Crafts alkylation reactions of indoles.[18] The 3-heteroatom-substituted oxindoles can be further manipulated easily, pending on the need of inclusion of a specific atom in the bio-relevant molecules. As an illustrative example, the 3-BnS-substituted product **5-17d** was subjected to further transformations. As the reduction of nitro group in oxindole adducts have been well practiced in the literature,[11e,11g] we oxidized **5-17d** to the corresponding acid **5-23d**,[19] and the subsequent esterification followed by reduction then afforded hydroxy group containing oxindole **5-25**. However, the cyclization of hydroxyl with the amide carbonyl could not be realized. Alternatively, installation of a Boc group on the NH group of **5-24a**, in combination with the subsequent $LiAlH_4$ reduction, resulted in a smooth cyclization[20] to yield furoindoline derivative **5-26**, which is a core structure of an antitumor agent.[2h]

[17] W. Wierenga, J. Griffin, M. A. Warpehoski, *Tetrahedron Lett.* **1983**, *24*, 2437.
[18] For selected reviews, see: a) S.-L. You, Q. Cai, M. Zeng, *Chem. Soc. Rev.* **2009**, *38*, 2190; b) M. Bandini, A. Eichholzer, *Angew. Chem. Int. Ed.* **2009**, *48*, 9608; c) T. B. Poulsen, K. A. Jorgensen, *Chem. Rev.* **2008**, *108*, 2903.
[19] C. Matt, A. Wagner, C. Mioskowski, *J. Org. Chem.* **1997**, *62*, 234.
[20] For a similar transformation, see: Z.-J. Jia, H. Jiang, J.-L. Li, B. Gschewnd, Q.-Z. Li, X. Yin, J. Grouleff, Y.-C. Chen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2011**, *133*, 5053.



Scheme 5.5 Synthetic manipulations of oxindoles with a 3-substituted heteroatom

5.3 Conclusions

In conclusion, we have devised a convenient method to access various pronucleophilic 3-heteroatom-substituted oxindoles from 3-chlorooxindoles, which were readily prepared from the corresponding nitroolefins. By utilizing our amino acid-incorporating multifunctional catalysts, we showed that Michael addition of oxindoles containing 3-heteroatoms with nitroolefins proceeded in a highly stereoselective manner, affording the oxindoles with a 3-heteroatom-substituted quaternary stereogenic center in good diastereoselectivities and excellent enantioselectivities, and the synthetic values of oxindole adducts have also been demonstrated. The general implication of this report is that by careful selection of catalytic systems, chiral oxindoles with a 3-heteroatom containing quaternary centers

can be readily created by reactions of heteroatom substituted oxindole pronulceophiles with different electrophilic reaction partners, and progress in this direction is underway. Given the high importance of heteroatom-containing oxindole structures, synthetic potential of our methodology can be enormous, and we anticipate that our method could be used for practical asymmetric preparation of novel oxindole structures with a 3-heteroatom-substituted quaternary stereocenter.

5.4 Experimental Section

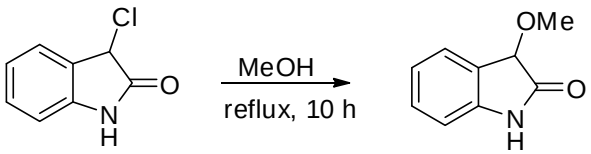
5.4.1 Material and General Methods

All the starting materials were obtained from commercial sources and used without further purification unless otherwise stated. THF and diethyl ether were dried and distilled from sodium benzophenone ketyl prior to use. $CHCl_3$ and CH_2Cl_2 were distilled from CaH_2 prior to use. ^1H and ^{13}C NMR spectra were recorded on a Bruker ACF300 or AMX500 (500 MHz) spectrometer. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (chloroform δ 7.26), carbon (chloroform δ 77.0). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), br (broad singlet). Coupling constants were reported in Hertz (Hz). Low resolution mass spectra were obtained on a Finnigan/MAT LCQ spectrometer in ESI mode, and a Finnigan/MAT 95XL- T mass spectrometer in FAB mode. All high resolution mass spectra were obtained on a Finnigan/MAT 95XL- T spectrometer. For thin layer chromatography (TLC), Merck pre- coated TLC plates (Merck 60 F254) were used, and compounds were visualized with a UV light at 254 nm. Further

visualization was achieved by staining with iodine, or ceric ammonium molybdate followed by heating on a hot plate. Flash chromatographic separations were performed on Merck 60 (0.040- 0.063 mm) mesh silica gel. The enantiomeric excesses of products were determined by chiral-phase HPLC analysis.

3-Cl-Oxindoles were synthesized following the literature procedure.[10]

5.4.2 Preparation of the Prochiral 3-Heteroatom Oxindoles

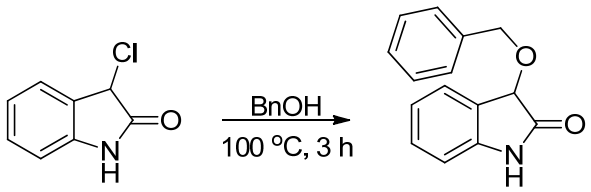


5-1a **5-10a**

3-Methoxyindolin-2-one **5-10a**

3-Cl-Oxindole **5-1a** (167.5 mg, 1.0 mmol) was dissolved in methanol (5 mL), and the resulting solution was heated to reflux for 10 h. After removal of the solvent under reduced pressure, the residue was directly subjected to flash column chromatography (hexane/ethyl acetate = 2/1) to afford **5-10a** as a light yellow solid (133.6 mg, 82% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.52 (s, 3H), 4.91 (s, 1H), 6.90 (d, *J* = 8.2 Hz, 1H), 7.07 (t, *J* = 7.6 Hz, 1H), 7.28 (t, *J* = 7.6 Hz, 1H), 7.38 (d, *J* = 7.6 Hz, 1H), 9.06 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.9, 77.3, 110.5, 122.9, 125.1, 125.6, 130.0, 141.6, 177.1; HRMS (ESI) m/z calcd for $C_9H_8NO_2$ $[M-H]^-$ = 162.0408, found = 162.0412.

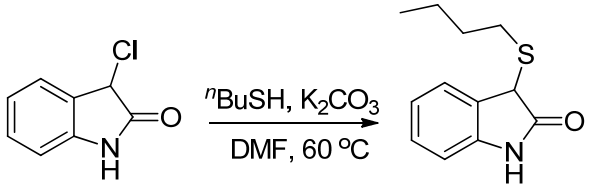


5-1a **5-10b**

3-(Benzyloxy)indolin-2-one **5-10b**

3-Cl-Oxindole **5-1a** (167.5 mg, 1.0 mmol) was dissolved in benzyl alcohol (5 mL), and the resulting solution was heated to 100 °C for 3 h. The excess benzyl alcohol was removed by distillation under reduced pressure, and the residue was directly subjected to flash column chromatography (hexane/ethyl acetate = 2/1) to afford **5-10b** as a light yellow solid (153.1 mg, 64% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.70 (s, 2H), 5.15 (s, 1H), 6.89 (d, *J* = 7.9 Hz, 1H), 7.10 (t, *J* = 7.6 Hz, 1H), 7.27-7.42 (m, 7H), 8.85 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.9, 65.3, 110.6, 123.4, 125.9, 126.2, 127.0, 127.6, 128.5, 130.5, 140.8, 141.0, 174.4; HRMS (EI) m/z calcd for $C_{15}H_{13}NO_2$ $[M]^+$ = 239.0946, found = 239.0948.



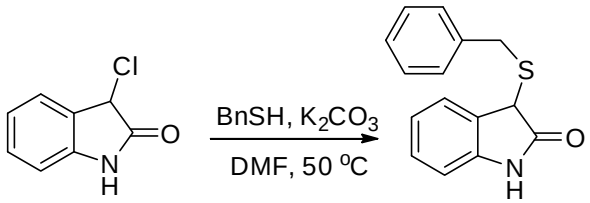
5-1a **5-11a**

3-(Butylthio)indolin-2-one **5-11a**

3-Cl-Oxindole (167.5 mg, 1.0 mmol) and 1-butanethiol (215 μL, 2 equiv.) were dissolved in anhydrous DMF (5 mL) under N_2 protection, K_2CO_3 (138 mg, 1 equiv.)

was added and the resulting mixture was heated at 60 ^{o}C for 1 h. After cooling to room temperature, water (20 mL) was added and the mixture was extracted with ethyl acetate (20 mL x 2). The combined organic phases were washed with brine (20 mL x3), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/ethyl acetate = 3/1) to afford **5-11a** as a yellow solid (194.5 mg, 88% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.84 (t, *J* = 7.6 Hz, 3H), 1.25-1.39 (m, 2H), 1.48-1.55 (m, 2H), 2.44-2.50 (m, 1H), 2.65-2.70 (m, 1H), 4.30 (s, 1H), 6.92 (d, *J* = 7.6 Hz, 1H), 7.06 (t, *J* = 7.3 Hz, 1H), 7.24 (t, *J* = 7.6 Hz, 1H), 7.36 (d, *J* = 7.6 Hz, 1H), 9.27 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.5, 21.9, 29.2, 31.0, 45.7, 110.1, 122.8, 125.2, 126.8, 128.9, 141.3, 178.4; HRMS (ESI) m/z calcd for $C_{12}H_{14}NOS$ $[M-H]^-$ = 220.0802, found = 220.0794.



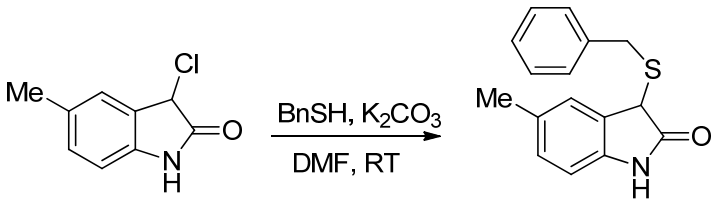
5-1a **5-11b**

3-(Benzylthio)indolin-2-one **5-11b**

3-Cl-Oxindole (167.5 mg, 1.0 mmol) and benzyl thiol (176 μL, 1.5 equiv.) were dissolved in anhydrous DMF (5 mL) under N_2 protection, K_2CO_3 (138 mg, 1 equiv.) was then added and the resulting mixture was heated to 50 ^{o}C for 40 min. After cooling to room temperature, water (20 mL) was added and the mixture was extracted with ethyl acetate (20 mL x 2). The combined organic phases were washed

with brine (20 mL x3), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/ethyl acetate = 3/1) to afford **5-11b** as a yellow solid (173.4 mg, 68% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.73 (d, *J* = 13.2 Hz, 1H), 4.09 (d, *J* = 12.6 Hz, 1H), 4.23 (s, 1H), 6.91 (d, *J* = 7.6 Hz, 1H), 7.04 (t, *J* = 7.6 Hz, 1H), 7.19-7.34 (m, 7H), 9.11 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.2, 44.4, 110.1, 122.7, 125.2, 126.1, 127.3, 128.4, 129.0, 129.2, 137.1, 141.5, 178.3; HRMS (ESI) m/z calcd for $C_{15}H_{12}NOS$ $[M-H]^-$ = 254.0645, found = 254.0639.

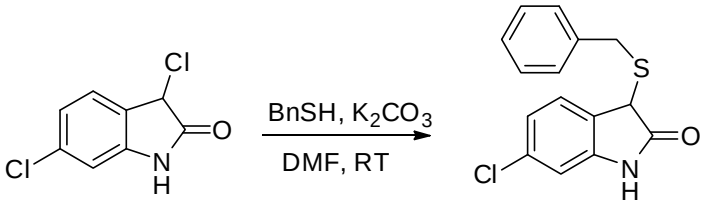


5-11c

3-(Benzylthio)-5-methylindolin-2-one **5-11c**

5-Me-3-Cl-Oxindole (91 mg, 0.5 mmol) and benzyl thiol (88 μL, 1.5 equiv.) were dissolved in anhydrous DMF (2.5 mL) under N_2 protection, K_2CO_3 (69 mg, 1 equiv.) was then added and the resulting mixture was stirred at room temperature for 1.5 h. Water (10 mL) was added and the mixture was extracted with ethyl acetate (10 mL x 2). The combined organic phases were washed with brine (10 mL x3), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/ethyl acetate = 3/1) to afford **5-11c** as a yellow solid (108.9 mg, 81% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.30 (s, 3H), 3.73 (d, *J* = 13.3 Hz, 1H), 4.11 (d, *J* = 13.3 Hz, 1H), 4.18 (s, 1H), 6.78 (t, *J* = 3.8 Hz, 1H), 7.03 (d, *J* = 8.2 Hz, 1H), 7.07 (s, 1H), 7.21 (t, *J* = 7.3 Hz, 1H), 7.28 (d, *J* = 6.9 Hz, 2H), 7.33 (d, *J* = 7.0 Hz, 2H), 5.56 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.9, 34.2, 44.2, 109.7, 125.9, 126.0, 127.2, 128.3, 129.2, 129.3, 132.3, 137.1, 138.8, 178.0; HRMS (ESI) m/z calcd for $C_{16}H_{14}NOS$ $[M-H]^-$ = 268.0802, found = 268.0800.

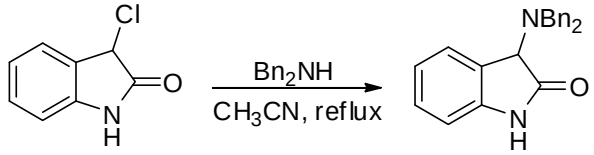


5-11d

3-(Benzylthio)-6-chloroindolin-2-one **5-11d**

Same procedure as preparation of **5-11c**. 70% yield, white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.74 (d, *J* = 13.2 Hz, 1H), 4.08 (d, *J* = 13.3 Hz, 1H), 4.20 (s, 1H), 6.84 (d, *J* = 7.6 Hz, 1H), 7.20-7.23 (m, 3H), 7.28 (d, *J* = 7.0 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 2H), 9.45 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.5, 44.4, 111.2, 125.7, 127.5, 128.0, 128.2, 128.5, 129.1, 129.2, 136.8, 140.0, 178.3; HRMS (ESI) m/z calcd for $C_{15}H_{11}ClNOS$ $[M-H]^-$ = 288.0255, found = 288.0257.

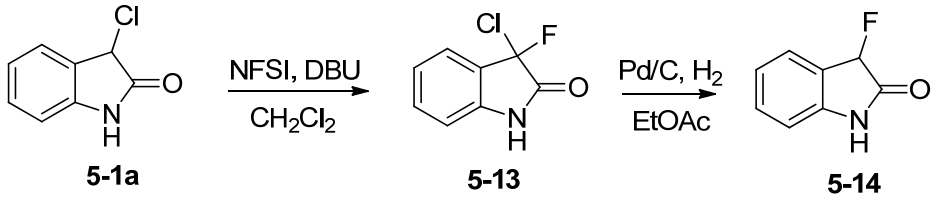


5-1a **5-12**

3-(Dibenzylamino)indolin-2-one **5-12**

To a stirred solution of 3-Cl-oxindole **5-1a** (167.5 mg, 1.0 mmol) in CH_3CN (5 mL) was added Bn_2NH (970 μL, 5 equiv.), and the resulting solution was brought to reflux for 3 h. Solvent was removed under reduced pressure, and the residue was purified by column chromatography (hexane/ethyl acetate = 4/1) to afford **5-12** as a light yellow solid (85.3 mg, 26% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.73 (d, *J* = 13.3 Hz, 2H), 4.02 (d, *J* = 13.3 Hz, 2H), 4.36 (s, 1H), 6.86 (d, *J* = 7.6 Hz, 1H), 7.07 (t, *J* = 7.3 Hz, 1H), 7.21-7.25 (m, 3H), 7.32-7.35 (m, 4H), 7.44-7.49 (m, 5H), 8.55 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 54.1, 61.1, 109.7, 122.6, 125.0, 127.1, 127.7, 128.3, 128.7, 128.9, 139.2, 141.6, 178.9; HRMS (ESI) m/z calcd for $C_{22}H_{19}N_2O$ $[M-H]^-$ = 327.1503, found = 327.1515.



5-1a **5-13** **5-14**

3-Chloro-3-fluoroindolin-2-one **5-13**

To a stirred solution of 3-Cl-oxindole **5-1a** (167.5 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) was added NFSI (347 mg, 1.1 equiv.), followed by addition of DBU (164 μL, 1.1 equiv.). The resulting solution was stirred at room temperature for 5 min. Solvent was removed under reduced pressure, and the residue was directly subjected to flash column chromatography (CH_2Cl_2) to afford **5-13** as a white solid (136.5 mg, 74% yield).

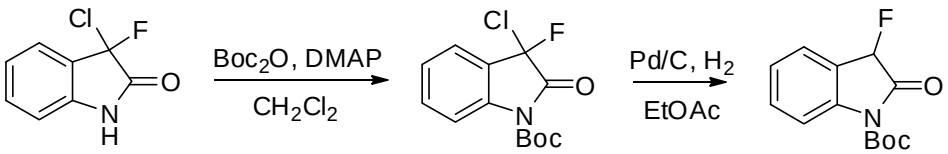
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.00 (d, *J* = 8.2 Hz, 1H), 7.17 (t, *J* = 7.6 Hz, 1H),

7.41 (t, *J* = 7.9 Hz, 1H), 7.58 (d, *J* = 7.6 Hz, 1H), 9.04 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 99.6 (d, *J* = 254.2 Hz), 111.6, 124.2 (d, *J* = 1.8 Hz), 125.1 (d, *J* = 20.0 Hz), 125.2, 133.0 (d, *J* = 1.8 Hz), 139.4 (d, *J* = 5.5 Hz), 169.2 (d, *J* = 25.5 Hz); ^{19}F NMR (282.38 MHz, $CDCl_3$) δ -42.5 (s); HRMS (ESI) m/z calcd for C_8H_4ClFNO $[M-H]^-$ = 183.9971, found = 183.9966.

3-Fluoroindolin-2-one **5-14**

To a solution of 3-Cl-3-F-oxindole **5-13** (55.6 mg, 0.3 mmol) in ethyl acetate (5 mL) was added Pd/C (11 mg, 20%) and charged with hydrogen gas using a hydrogen balloon. The resulting mixture was stirred at room temperature for 1 h. The mixture was then filtered through celite, and the filtrate was concentrated and purified by column chromatography (hexane/ethyl acetate = 3/1) to afford **5-14** as a pink solid (45.2 mg, 51% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.70 (d, *J* = 51.1 Hz, 1H), 6.92 (d, *J* = 8.2 Hz, 1H), 7.10 (t, *J* = 7.6 Hz, 1H), 7.34 (t, *J* = 7.9 Hz, 1H), 7.45 (d, *J* = 7.0 Hz, 1H), 8.90 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 85.9 (d, *J* = 187.7 Hz), 110.8, 123.2 (d, *J* = 16.4 Hz), 123.3 (d, *J* = 2.7 Hz), 126.3, 131.5 (d, *J* = 3.7 Hz), 141.9 (d, *J* = 5.5 Hz), 173.2 (d, *J* = 18.2 Hz); ^{19}F NMR (282.38 MHz, $CDCl_3$) δ -117.8 (d, *J* = 50.5 Hz); HRMS (ESI) m/z calcd for C_8H_5FNO $[M-H]^-$ = 150.0361, found = 150.0357



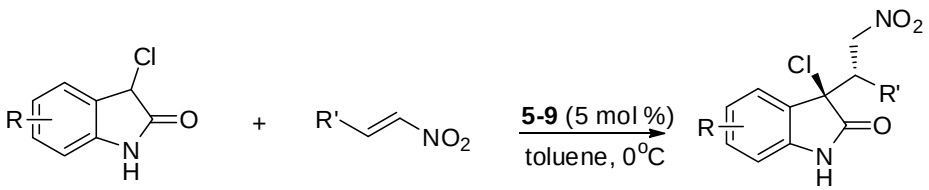
5-13 **5-15** **5-16**

tert-Butyl 3-fluoro-2-oxoindoline-1-carboxylate **5-16**

To a stirred solution of 3-Cl-3-F-oxindole **5-13** (55.6 mg, 0.3 mmol) in CH_2Cl_2 (2.5 mL) under N_2 protection were added DMAP (3.5 mg, 10 mol %) and Boc_2O (72.0 mg in 0.5 mL CH_2Cl_2, 1.1 equiv.). After stirring at room temperature for 15 min, the reaction solution was subjected to a short pad of silica gel (using CH_2Cl_2 as eluent). The filtrate was concentrated, and the residue was used for next step without further purification. The residue was dissolved in ethyl acetate (5 mL), Pd/C (17 mg, 20%) was added and the reaction mixture was charged with hydrogen gas using a hydrogen balloon. The resulting mixture was stirred at room temperature for 0.5 h. The mixture was filtered through celite and the filtrate was concentrated and purified by column chromatography (hexane/ethyl acetate = 8/1) to afford **5-16** as a white solid (21.1 mg, 28% yield for two steps).

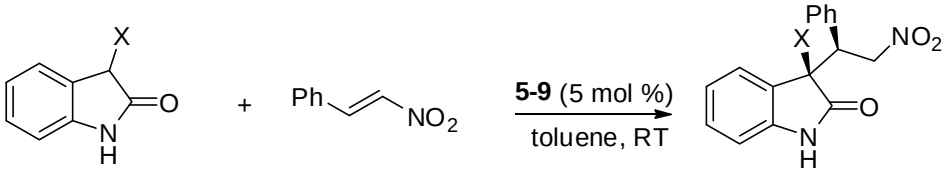
A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.63 (s, 9H), 5.70 (d, J = 51.1 Hz, 1H), 7.22 (t, J = 7.6 Hz, 1H), 7.43 (t, J = 7.9 Hz, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.87 (d, J = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.0, 85.0 (d, J = 187.7 Hz), 85.1, 115.6, 121.8 (d, J = 16.4 Hz), 125.0 (d, J = 2.7 Hz), 125.9, 131.7 (d, J = 2.7 Hz), 140.9 (d, J = 4.6 Hz), 148.7, 169.0 (d, J = 17.3 Hz); ^{19}F NMR (282.38 MHz, $CDCl_3$) δ -111.1 (d, J = 51.6 Hz); HRMS (ESI) m/z calcd for $C_{13}H_{14}FNO_3Na$ $[M+Na]^+$ = 274.0850, found = 274.0860.

5.4.3 Representative Procedure



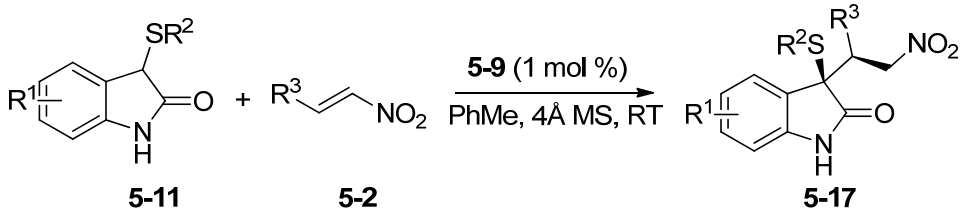
5-1 **5-2** **5-3**

3-Cl-Oxindole **5-1** (0.1 mmol) was added to a solution of nitroolefin **5-2** (0.12 mmol) and catalyst **5-9** (4.7 mg, 0.005 mmol) in toluene (1.0 mL) in a sample vial at 0°C, and the resulting mixture was sealed and stirred at 0 °C for the time specified in Table 5.2. At the end of the reaction, the reaction solution was concentrated *in vacuo* to yield the crude product, which was purified by flash column chromatography (hexane/ethyl acetate = 5:2) to afford the desired adducts **5-3** (53%–99% yield). The enantiomeric excessess of **5-3** were determined by chiral HPLC analysis.



5-2a **5-17**

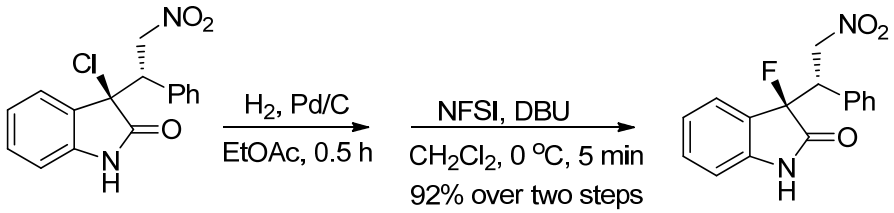
3-X-Oxindole (0.1 mmol) was added to a solution of nitroolefin **5-2a** (0.12 mmol) and catalyst **5-9** (5 mol %) in toluene (1.0 mL) in a sample vial at room temperature, and the resulting mixture was sealed and stirred for the time specified in Table 5.3. At the end of the reaction, the reaction solution was concentrated *in vacuo* to yield the crude product, which was purified by flash column chromatography to afford the desired adducts 3-X-3-R-oxindoles **5-17**. The enantiomeric excessess of products were determined by chiral HPLC analysis.



5-11 **5-2** **5-17**

3-S-Oxindole **5-11** (0.1 mmol) was added to a mixture of nitroolefin **5-2** (0.12 mmol), 4Å molecular seives (10 mg) and catalyst **5-9** (1 mol %) in toluene (1.0 mL) in a sample vial at room temperature, and the resulting mixture was sealed and stirred for the time specified in Table 5.5. At the end of the reaction, the reaction mixture was directly subjected to flash column chromatography (CH_2Cl_2 as the eluent) to afford the desired adducts 3-S-3-R-oxindoles **5-17**. The enantiomeric excessess of products were determined by chiral HPLC analysis.

5.4.4 Synthetic Manipulation of 3-Heteroatom Oxindole Products



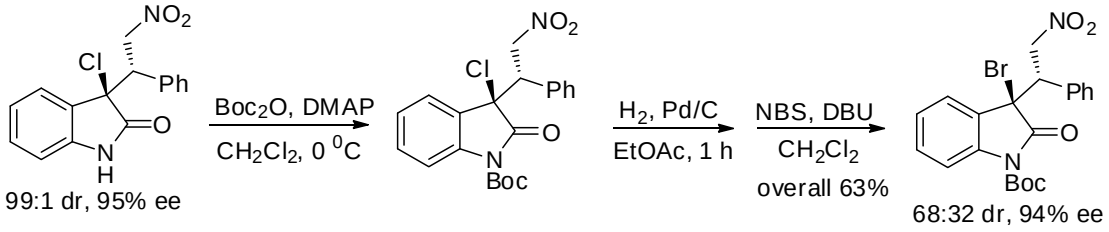
99:1 dr, 95% ee
5-3a

4:1 dr, 95% ee
5-17e

3-Cl-Oxindole **5-3a** (31.6 mg, 0.1 mmol) in ethyl acetate (2 mL) was added Pd/C (6 mg, 20%) and charged with hydrogen gas using a hydrogen balloon. The resulting mixture was stirred at room temperature for 0.5 h. The mixture was filtered through celite, the filtrate was concentrated and used for next step without further purification. The residue was dissolved in CH_2Cl_2 (1 mL) and the resulting solution was cooled to 0 °C, NFSI (34.7 mg, 1.1 equiv.) was added to the solution, followed by the addition

of DBU (16.5 μL, 1.1 equiv.). After stirred at 0 ^{o}C for 5 min, the solution was concentrated and purified by column chromatography (hexane/ethyl acetate = 3/1) to afford **5-17e** as a white solid (27.6 mg, 92% yield for two steps).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.09-4.16 (m, 1H), 5.06 (dd, *J* = 10.1 Hz, 13.6 Hz, 1H), 5.67 (dd, *J* = 4.5 Hz, 13.9 Hz, 1H), 6.57 (d, *J* = 7.6 Hz, 1H), 6.83 (d, *J* = 7.6 Hz, 1H), 6.93 (t, *J* = 7.6 Hz, 1H), 7.05-7.13 (m, 2H), 7.23-7.33 (m, 4H), 8.32 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 48.6, 48.7, 74.2 (d, *J* = 3.6 Hz), 93.3 (d, *J* = 196.8 Hz), 110.8, 123.1 (d, *J* = 2.7 Hz), 123.7 (d, *J* = 19.1 Hz), 126.4, 128.7, 128.9, 129.4 (d, *J* = 1.8 Hz), 131.8 (d, *J* = 2.7 Hz), 132.5, 140. 9 (d, *J* = 6.4 Hz) 173.5 (d, *J* = 24.6 Hz); ^{19}F NMR (282.38 MHz, $CDCl_3$) δ -88.9 (d, *J* = 21.6 Hz); The ee value was 95%, t_R (minor) = 25.98, 32.77 min, t_R (major) = 19.49, 29.03 min (Chiralcel OD-H, λ = 254 nm, 5% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{16}H_{12}N_2O_3F$ $[M-H]^-$ = 299.0837, found = 299.0835.



5-3a **5-18** **5-19**

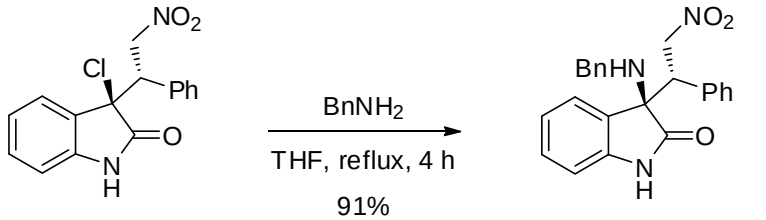
Under N_2 protection, to a stirred solution of **5-3a** (63.2 mg, 0.2 mmol) in CH_2Cl_2 (2.5 mL) at 0 ^{o}C were added DMAP (2.4 mg, 10 mol %) and Boc_2O (48.0 mg in 0.5 mL CH_2Cl_2, 1.1 equiv.). After stirring at 0 ^{o}C for 15 min, the reaction solution was concentrated and purified by column chromatography (hexane/ethyl acetate = 7:1) to afford the **5-18** as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.52 (s, 9H), 4.32 (dd, *J* = 3.2 Hz, 11.4 Hz, 1H), 5.11 (dd, *J* = 11.4 Hz, 13.3 Hz, 1H), 5.59 (dd, *J* = 3.8 Hz, 13.3 Hz, 1H), 6.87 (d, *J* = 7.6 Hz, 2H), 7.00 (d, *J* = 7.6 Hz, 1H), 7.13-7.18 (m, 3H), 7.23 (t, *J* = 7.6 Hz, 1H), 7.36-7.39 (m, 1H), 7.70 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.8, 51.6, 66.5, 75.1, 77.2, 85.1, 115.4, 124.8, 125.2, 128.4, 129.0, 129.2, 131.1, 131.8, 139.1, 147.9, 170.3; HRMS (ESI) m/z calcd for $C_{21}H_{21}ClN_2O_5Na$ $[M+Na]^+$ = 439.1031, found = 439.1021.

The Boc-protected product was dissolved in ethyl acetate (2 mL), Pd/C (17 mg, 20%) was added and the reaction mixture was charged with hydrogen gas using a hydrogen balloon. The resulting mixture was stirred at room temperature for 1 h. The mixture was filtered through celite and the filtrate was concentrated to afford the de-chlorinated intermediate. The crude intermediate was used for next step without further purification. The residue was dissolved in CH_2Cl_2 (2 mL), DBU (3 μL, 10 mol %) was added followed by the addition of NBS (53.4 mg, 1.5 equiv.). After stirring at room temperature for 30 min, the reaction mixture was concentrated and purified by column chromatography (hexane/ethyl acetate = 6:1) to afford the **5-19** as a light yellow oil (58.0 mg, 63% yield for three steps).

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.62 (s, 9H), 4.48 (dd, *J* = 3.8 Hz, 11.3 Hz, 1H), 5.51-5.62 (m, 2H), 7.00 (d, *J* = 6.9 Hz, 2H), 7.06-7.10 (m, 3H), 7.16-7.22 (m, 2H), 7.53 (t, *J* = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.0, 52.2, 57.3, 77.1, 115.3, 124.6, 124.9, 125.1, 127.4, 128.7, 129.3, 130.7, 132.4, 138.1, 148.2, 171.2; The ee

value was 94%, t_R (minor) = 10.11 min, t_R (major) = 9.06 min (Chiralcel ID, λ = 254 nm, 5% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{21}H_{21}{}^{79}BrNaN_2O_5$ $[M+Na]^+$ = 483.0526, found = 483.0527; HRMS (ESI) m/z calcd for $C_{21}H_{21}{}^{81}BrNaN_2O_5$ $[M+Na]^+$ = 485.0506, found = 485.0515.



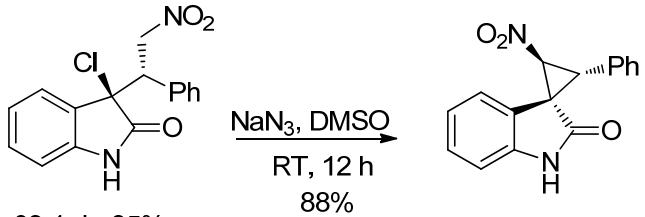
99:1 dr, 95% ee
5-3a

2:1 dr, 93%, 92% ee
5-20

To a stirred solution of **5-3a** (0.1 mmol, 31.6 mg) in THF (2.0 mL) in a round bottom flask under N_2 was added benzyl amine (55 μL, 5 equiv.), and the resulting solution was brought to reflux for 4 h. The solution was diluted with ethyl acetate (5 mL) and washed with brine (5 mL x 3). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated, and the residue was purified by column chromatography (hexane/ethyl acetate = 2:1) to afford the **5-20** as a light yellow oil (35.2 mg, 91% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ (mixture of diastereoisomers) (0.0–6.0 ppm) major isomer: 2.06 (br s, 1H), 3.34 (d, *J* = 12.5 Hz, 2H), 4.14 (dd, *J* = 5.0 Hz, 10.1 Hz, 1H), 5.18 (dd, *J* = 10.1 Hz, 13.2 Hz, 1H), 5.44 (dd, *J* = 4.7 Hz, 13.5 Hz, 1H); minor isomer: 2.33 (br s, 1H), 3.43 (t, *J* = 10.4 Hz, 2H), 4.03 (dd, *J* = 4.7 Hz, 10.4 Hz, 1H), 4.93 (dd, *J* = 10.4 Hz, 12.9 Hz, 1H), 5.64 (dd, *J* = 4.7 Hz, 12.9 Hz, 1H); (6.0–10.0 ppm) 6.68 (d, *J* = 7.6 Hz, 1H), 6.73-6.76 (m, 3H), 7.03-7.14 (m, 10H), 7.19-7.36 (m, 16H), 7.44 (d,

J = 6.9 Hz, 1H), 8.11 (br s, 1H, minor isomer), 8.34 (br s, 1H, major isomer); ^{13}C NMR (125 MHz, $CDCl_3$) δ (mixture of diastereoisomers) 48.6, 48.7, 50.7, 50.9, 69.0, 70.0, 74.8, 76.0, 110.1, 110.6, 122.8, 122.9, 124.3, 125.2, 125.9, 127.2, 127.3, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.7, 128.9, 129.4, 130.1, 133.5, 139.1, 139.3, 140.3, 141.6, 178.6, 179.5; The ee value was 92% for major isomer, t_R (minor) = 10.65, 46.11 min, t_R (major) = 13.24, 15.87 min (Chiralcel IB, λ = 254 nm, 7.5% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{23}H_{20}N_3O_3$ $[M-H]^-$ = 386.1510, found = 386.1516.



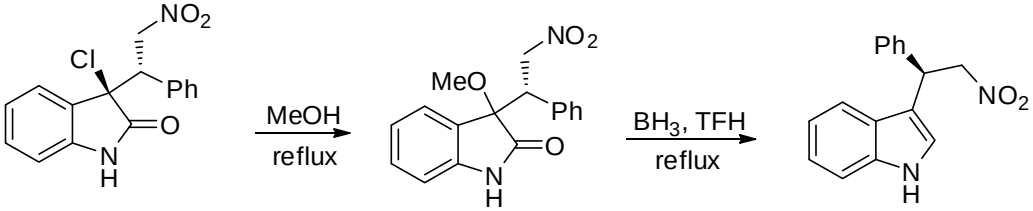
99:1 dr, 95% ee
5-3a

>99:1 dr, 94% ee
5-21

To a stirred solution of **5-3a** (0.1 mmol, 31.6 mg) in DMSO (1.2 mL) in a sample vial was added NaN_3 (19.5 mg, 3 equiv.), and the resulting mixture was stirred at room temperature for 12 h. The solution was diluted with ethyl acetate (5 mL) and washed with brine (5 mL x 3). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated, and the residue was purified by column chromatography (hexane/ethyl acetate = 2:1) to afford the 3-spirocyclopropyl-2-oxindole **5-21** as a white solid (24.6 mg, 93% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.35 (d, *J* = 7.0 Hz, 1H), 5.46 (d, *J* = 7.0 Hz, 1H), 6.89 (d, *J* = 7.6 Hz, 1H), 7.10 (t, *J* = 7.6 Hz, 1H), 7.29-7.34 (m, 6H), 7.38 (d, *J* = 7.6 Hz, 1H), 8.29 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 40.4, 41.8, 72.0, 110.3, 122.5,

123.0, 123.4, 128.4, 128.6, 128.9, 129.1, 129.8, 141.4, 171.4; The ee value was 94%, t_R (minor) = 8.35 min, t_R (major) = 9.20 min (Chiralcel ID, λ = 254 nm, 20% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{16}H_{11}N_2O_3$ $[M-H]^-$ = 279.0775, found = 279.0766.



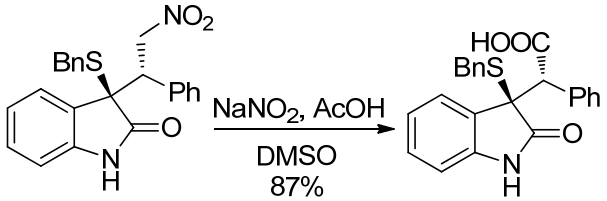
99:1 dr, 95% ee
5-3a

92% ee
5-22

3-Cl-Oxindole **5-3a** (31.6 mg, 0.1 mmol) was dissolved in MeOH (5 mL) and the resulting solution was heated to reflux for 36 h. After removal of the solvent, the residue was purified by column chromatography (hexane/ethyl acetate = 2/1) to afford 3-OMe-oxindole intermediate as a colorless oil. 3-OMe-oxindole was dissolved in THF (1.8 mL) and a solution of borane dimethyl sulfide complex (0.2 mL, 2M solution in THF) was added at 0 ^oC. The resulting solution was then brought to reflux for 3 h. After cooled down to room temperature, the reaction was quenched by addition of MeOH and the solution was diluted with ethyl acetate (5 mL) and washed with brine (5 mL x 3). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated, and the residue was purified by column chromatography (hexane/ethyl acetate = 3:1) to afford **5-22** as a light yellow oil (22.3 mg, 84% yield for two steps).

^1H NMR (500 MHz, $CDCl_3$) δ 4.95 (dd, *J* = 8.5 Hz, 12.3 Hz, 1H), 5.08 (dd, *J* = 2.5 Hz, 10.1 Hz, 1H), 5.21 (t, *J* = 8.2 Hz, 1H), 6.99 (s, 1H), 7.10 (t, *J* = 8.1 Hz, 1H),

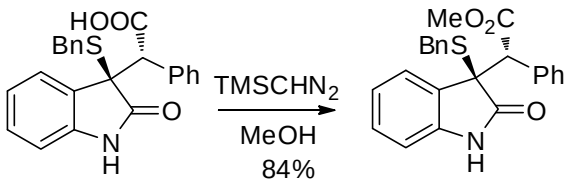
7.20-7.24 (m, 1H), 7.27 (t, *J* = 3.2 Hz, 1H), 7.28-7.35 (m, 5H), 7.47 (d, *J* = 7.6 Hz, 1H), 8.08 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 41.5, 79.5, 111.4, 114.2, 118.8, 119.9, 121.6, 122.6, 126.0, 127.5, 127.7, 128.9, 136.4, 139.1. The ee value was 92%, t_R (minor) = 5.56 min, t_R (major) = 6.26 min (Chiralcel IC, λ = 254 nm, 20% *i*PrOH/hexanes, flow rate = 1.0 mL/min).



5-17d **5-23d**

5-17d (121.2 mg, 0.3 mmol) was dissolved in DMSO (0.75 mL) at room temperature under Ar protection, $NaNO_2$ (62.1 mg, 3 equiv.) was added, followed by the addition of acetic acid (190 μL, 10 equiv.). The resulting mixture was heated to 40 ^{o}C and stirred at that temperature for 16 h. 1N aqueous HCl (6 mL) was added to the mixture, and the resulting mixture was extracted with ethyl acetate (10 mL x 3). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, concentrated and purified by column chromatography (hexane/ethyl acetate = 2:1) to afford the acid **5-23d** as a white solid (101.5 mg, 87% yield).

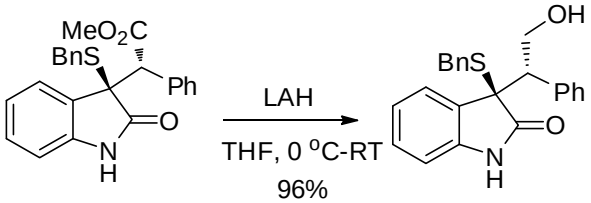
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.93 (dd, *J* = 11.4 Hz, 17.1 Hz, 2H), 4.63 (s, 1H), 6.69 (d, *J* = 7.6 Hz, 1H), 7.06-7.23 (m, 12H), 7.96 (d, *J* = 7.6 Hz, 1H), 8.28 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.8, 55.3, 56.6, 110.0, 123.0, 126.9, 127.2, 127.3, 128.1, 128.3, 128.4, 129.3, 129.4, 129.9, 132.2, 135.9, 140.3, 174.7, 177.0; HRMS (ESI) m/z calcd for $C_{23}H_{18}NO_3S$ $[M-H]^-$ = 388.1013, found = 388.1019.



5-23d **5-24a**

Acid **5-23d** (77.8 mg, 0.2 mmol) was dissolved in MeOH (1.5 mL) and the resulting solution was cooled to 0 ^{o}C, and $TMSCHN_2$ (1.0 mL, 2M solution in hexane, 10 equiv.) was added by portions (100 μL every 15 min, 10 times). The reaction mixture was diluted with ethyl acetate (10 mL) and water (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (8 mL x 2). The combined organic phases were washed with brine and dried over anhydrous Na_2SO_4, filtered and concentrated, and the residue was purified by column chromatography (hexane/ethyl acetate = 3:1) to afford the methyl ester **5-24a** as a yellow solid (67.7 mg, 84% yield).

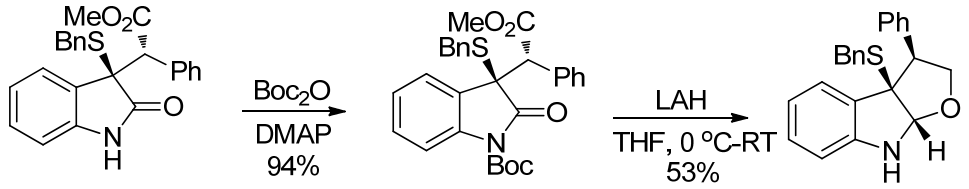
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.75 (s, 3H), 3.90 (dd, *J* = 12.0 Hz, 15.8 Hz, 2H), 4.60 (s, 1H), 6.70 (d, *J* = 7.6 Hz, 1H), 7.05-7.07 (m, 2H), 7.11-7.23 (m, 10H), 8.01 (d, *J* = 7.6 Hz, 1H), 8.51 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.0, 52.1, 54.9, 56.8, 109.8, 122.7, 126.8, 127.2, 127.4, 127.9, 128.0, 128.3, 129.3, 129.7, 132.4, 136.1, 140.5, 171.0, 176.5; HRMS (ESI) m/z calcd for $C_{24}H_{20}NO_3S$ $[M-H]^-$ = 402.1169, found = 402.1171.



5-24a **5-25**

5-24a (20.2 mg, 0.05 mmol) was dissolved in THF (1.0 mL) under Ar protection and the resulting solution was cooled to 0 ^{o}C, $LiAlH_4$ (9.5 mg, 5 equiv.) was then introduced. The resulting mixture was warmed up to room temperature and stirred for 3 h. The reaction was quenched by addition of 1N NaOH and extracted with ethyl acetate (5 mL x 3). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated, and the residue was purified by column chromatography (hexane/ethyl acetate = 2:1) to afford the alcohol **5-25** as a colorless oil (18.0 mg, 96% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.60 (dd, *J* = 5.0 Hz, 9.5 Hz, 1H), 3.70 (d, *J* = 12.0 Hz, 1H), 4.18 (t, *J* = 10.2 Hz, 1H), 4.61 (dd, *J* = 5.0 Hz, 11.0 Hz, 1H), 6.69 (d, *J* = 7.6 Hz, 1H), 6.89 (d, *J* = 7.6 Hz, 2H), 7.01-7.24 (m, 10H), 7.35 (d, *J* = 7.6 Hz, 1H), 7.70 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.6, 51.8, 58.1, 63.2, 110.0, 122.7, 125.8, 127.3, 127.7, 128.0, 128.2, 128.4, 129.3, 129.4, 136.3, 136.4, 140.5, 145.6, 177.0; HRMS (ESI) m/z calcd for $C_{23}H_{20}NO_2S$ $[M-H]^-$ = 374.1220, found = 374.1217.



5-24a **5-24b** **5-26**

5-24a (40.3 mg, 0.1 mmol) was dissolved in CH_2Cl_2 (2.0 mL) under N_2 protection at room temperature, Boc_2O (26.2 mg, 1.2 equiv.) was added, followed by the addition of DMAP (1.2 mg, 10 mol %). The resulting mixture was stirred at room temperature for 30 min. The reaction mixture was then concentrated and the

residue was purified by column chromatography (hexane/ethyl acetate = 7:1) to afford **5-24b** as a colorless oil (47.3mg, 94% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.56 (s, 9H), 3.73 (s, 3H), 3.79 (d, *J* = 12.0 Hz, 1H), 3.87 (d, *J* = 12.0 Hz, 1H), 4.61 (s, 1H), 7.11-7.31 (m, 12H), 7.61 (d, *J* = 8.2 Hz, 1H), 7.98 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.0, 34.3, 52.2, 56.0, 56.6, 77.2, 114.7, 124.4, 125.4, 126.5, 127.3, 128.0, 128.2, 128.4, 129.3, 129.5, 130.0, 132.2, 135.9, 139.4, 148.5, 170.7, 172.4; HRMS (ESI) m/z calcd for $C_{29}H_{29}NO_5SNa$ $[M+Na]^+$ = 526.1659, found = 526.1674.

5-24b (25.2 mg, 0.05 mmol) was dissolved in THF (1.0 mL) under Ar protection and the resulting solution was cooled to 0 ^{o}C. $LiAlH_4$ (9.5 mg, 5 equiv.) was then introduced. The resulting mixture was warmed up room temperature and stirred for 4 h. The reaction was quenched by addition of 1N NaOH and extracted with ethyl acetate (5 mL x 3). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated, and the residue was purified by column chromatography (hexane/ethyl acetate = 6:1) to afford **5-26** as a yellow solid (9.5 mg, 53% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.15 (d, *J* = 12.6 Hz, 1H), 3.26 (d, *J* = 12.6 Hz, 1H), 3.62 (d, *J* = 3.8 Hz, 1H), 3.97 (dd, *J* = 5.4 Hz, 9.2 Hz, 1H), 4.11 (dd, *J* = 1.9 Hz, 8.9 Hz, 1H), 4.49 (s, 1H), 5.61 (s, 1H), 6.65 (d, *J* = 8.2 Hz, 1H), 6.90-6.95 (m, 3H), 7.13-7.18 (m, 4H), 7.31-7.37 (m, 3H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.50 (t, *J* = 4.1 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.5, 57.6, 67.2, 73.0, 100.8, 109.2, 120.0, 124.6,

126.8, 127.5, 128.0, 128.1, 129.0, 129.1, 130.2, 137.7, 139.5, 149.6; HRMS (ESI) m/z calcd for $C_{23}H_{21}NNaSO$ $[M+Na]^+$ = 382.1236, found = 382.1238.

5.4.5 X-Ray Crystallographic Analysis and Determination of Configurations of the 3-Chlorooxindole and 3-Sulfenyloxindole Products

X-Ray Crystallographic Analysis of **5-3b**

The absolute configuration of the product **5-3b** was assigned based on the X-ray crystallographic analysis of a single crystal of **5-3b** (Figure 5.2). The configurations of other Michael addition products were assigned by analogy.

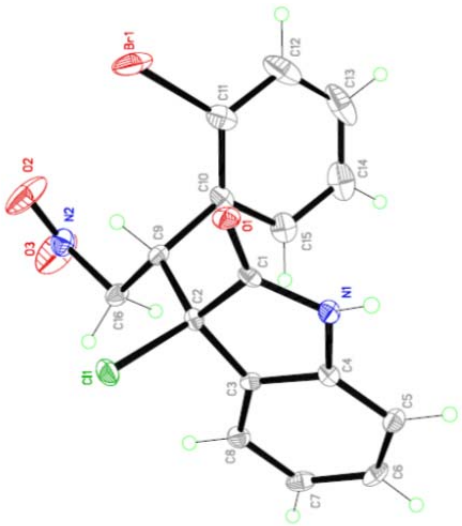


Figure 5.2 X-ray structure of **5-3b**

Table 5.6 Crystal Data and Structure Refinement for C321.

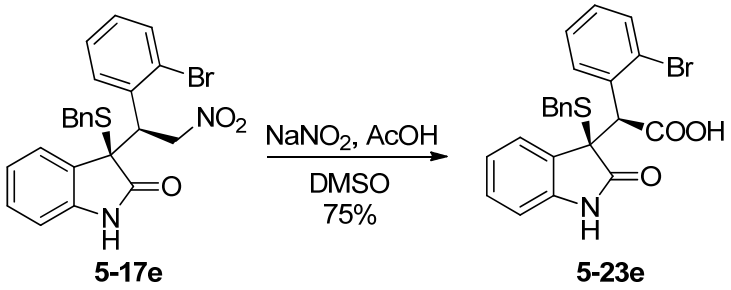
Identification code	c321
Empirical formula	C_{16} H_{12} Br Cl N_2 O_3

Formula weight	395.64	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 8.3011(7) Å	□= 90°.
	b = 14.7678(12) Å	□= 90°.
	c = 25.328(2) Å	□ = 90°.
Volume	3104.9(4) $Å^3$	
Z	8	
Density (calculated)	1.693 Mg/m^3	
Absorption coefficient	2.836 mm^{-1}	
F(000)	1584	
Crystal size	0.52 x 0.51 x 0.28 mm^3	
Theta range for data collection	1.60 to 27.50°.	
Index ranges	-10<=h<=10, -19<=k<=16, -31<=l<=32	
Reflections collected	22091	
Independent reflections	7096 [R(int) = 0.0409]	
Completeness to theta = 27.50°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.5040 and 0.3202	
Refinement method	Full-matrix least-squares on F^2	

Data / restraints / parameters	7096 / 0 / 423
Goodness-of-fit on F^2	0.976
Final R indices [I>2sigma(I)]	R1 = 0.0303, wR2 = 0.0607
R indices (all data)	R1 = 0.0356, wR2 = 0.0619
Absolute structure parameter	0.002(5)
Largest diff. peak and hole	0.724 and -0.493 e.Å^{-3}

X-Ray Crystallographic Analysis of **5-17e**

The absolute configuration of the product **5-17e** was assigned based on the X-ray crystallographic analysis of a single crystal of a **5-23e-THF** complex (Figure 5.3). The configurations of other products **5-17** were assigned by analogy.



5-17e **5-23e**

Following the procedure for preparation of **5-23a**. 0.2 mmol scale, 75% yield.

^{1}H NMR (500 MHz, d_6-DMSO) δ 3.49 (d, *J* = 11.4 Hz, 1H), 3.66 (d, *J* = 11.4 Hz, 1H), 5.15 (s, 1H), 6.83 (d, *J* = 7.6 Hz, 1H), 7.07-7.09 (m, 3H), 7.17-7.30 (m, 5H), 7.43-7.45 (m, 1H), 7.56 (d, *J* = 7.0 Hz, 1H), 7.63-7.65 (m, 1H), 10.56(s, 1H), 12.99 (br s, 1H); ^{13}C NMR (125 MHz, d_6-DMSO) δ 33.2, 54.1, 55.6, 110.2, 122.3, 125.2, 126.8, 127.5, 127.7, 128.9, 129.0, 129.6, 129.9, 130.3, 131.8, 133.1, 134.4, 136.4,

142.3, 171.3, 175.7; HRMS (ESI) m/z calcd for $C_{23}H_{17}{}^{79}BrNO_3S$ $[M-H]^-$ = 466.0118, found = 466.0118; calcd for $C_{23}H_{17}{}^{81}BrNO_3S$ $[M-H]^-$ = 468.0098, found = 468.0111.

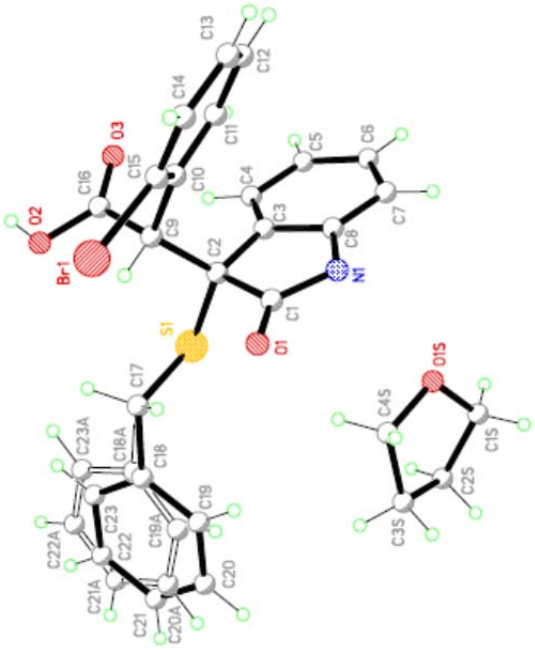


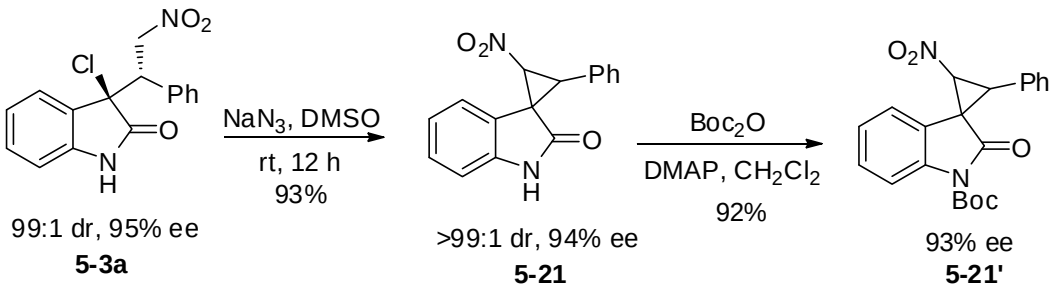
Figure 5.3 X-ray structure of **5-23e-THF** complex

Table 5.7 Crystal Data and Structure Refinement for D375.

Identification code	d375	
Empirical formula	C_{27} H_{26} Br N O_4 S	
Formula weight	540.46	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 9.2559(4) Å	□= 90°.
	b = 7.6278(4) Å	□= 95.990(2)°.

	c = 17.5660(9) Å □ = 90°.
Volume	1233.43(10) $Å^3$
Z	2
Density (calculated)	1.455 Mg/m^3
Absorption coefficient	1.785 mm^{-1}
F(000)	556
Crystal size	0.41 x 0.39 x 0.25 mm^3
Theta range for data collection	2.21 to 27.49°.
Index ranges	-12<=h<=11, -9<=k<=9, -22<=l<=22
Reflections collected	28018
Independent reflections	5548 [R(int) = 0.0255]
Completeness to theta = 27.49°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7457 and 0.6211
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5548 / 164 / 340
Goodness-of-fit on F^2	1.041
Final R indices [I>2sigma(I)]	R1 = 0.0244, wR2 = 0.0585
R indices (all data)	R1 = 0.0259, wR2 = 0.0589
Absolute structure parameter	0.011(5)
Largest diff. peak and hole	0.524 and -0.261 $e.Å^{-3}$

Absolute Configuration Assignment of Spirooxindole Product **5-21**



99:1 dr, 95% ee
5-3a

>99:1 dr, 94% ee
5-21

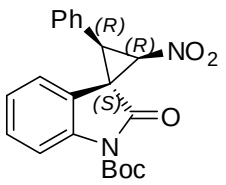
93% ee
5-21'

To determine the absolute configuration of **5-21**, the chiral **5-21** was transformed to the literature reported compound **5-21'**. To a stirred solution of **5-21** (0.05 mmol, 14.0 mg) in CH_2Cl_2 (1.0 mL) in a sample vial were added Boc_2O (13.1 mg, 1.2 equiv.) and DMAP (1.2 mg, 20 mol %), and the resulting mixture was stirred at room temperature for 15 min. The solution was concentrated, and the residue was purified by column chromatography (hexane/ethyl acetate = 7:1) to afford the 3-spirocyclopropyl-2-oxindole **5-21'** as a colorless oil (17.5 mg, 92% yield).

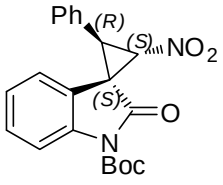
A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.59 (s, 9H), 4.33 (d, *J* = 6.9 Hz, 1H), 5.49 (d, *J* = 6.9 Hz, 1H), 7.21-7.24 (m, 1H), 7.30-7.42 (m, 7H), 7.93 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.0, 41.3, 41.9, 72.8, 85.1, 115.3, 121.6, 120.0, 124.8, 128.5, 128.6, 128.9, 129.1, 129.3, 140.5, 148.6, 167.8; MS (ESI) m/z calcd for $C_{21}H_{20}N_2O_5Na$ $[M+Na]^+$ = 403.1, found = 403.1.

NMR data showed **5-21'** is a diastereoisomer of our reported spirocyclopropane-oxindole product **5-21-1** & **5-21-2**[12b] and it has the same ^{1}H

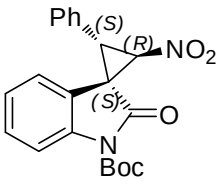
NMR data as the reported spirocyclopropane-oxindole product **5-21-3**.[21]



5-21-1



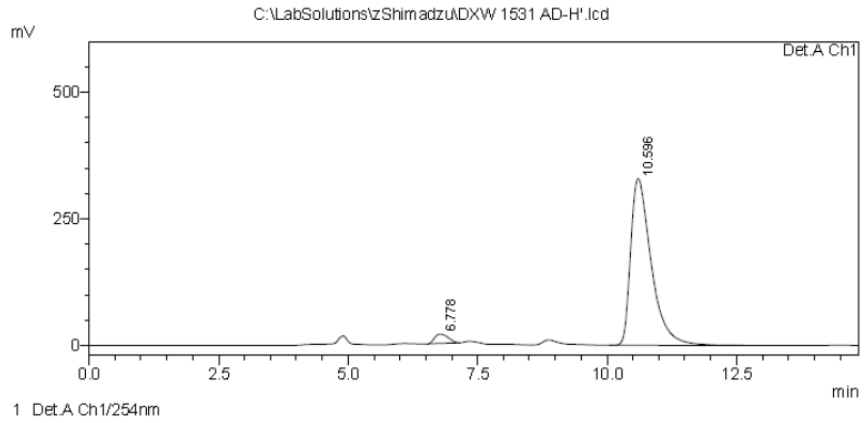
5-21-2



5-21-3

The reported HPLC conditions (Daicel Chiralpak AD-H column, 90/10 hexane/*i*-PrOH, flow rate 0.750 mL/min, λ = 254 nm: t_{major} = 6.88 min, t_{minor} = 11.22 min) were followed for the analysis of compound **5-21'**.

<Chromatogram>



PeakTable

Detector A Ch1 254nm

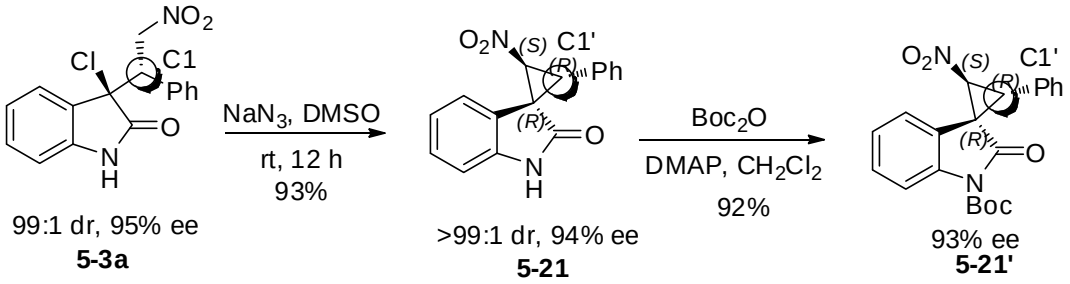
Peak#	Ret. Time	Area	Height	Area %	Height %
1	6.778	335979	18351	3.560	5.281
2	10.596	9102581	329134	96.440	94.719
Total		9438560	347485	100.000	100.000

(enantiomerically enriched **5-21'**)

HPLC analysis showed that **5-21'** is the enantiomer of **5-21-3**. The absolute configuration of **5-21'** was then assigned. This assignment is in agreement with the absolute configuration of **5-3a**, as the chiral center at C1 of **5-3a** did not change during the cyclopropane formation, thus the chiral center at C1' of **5-21** should be *R*,

[21] See Chapter 4, ref. 8.

which agrees with the assigned absolute configuration of **5-21'**.



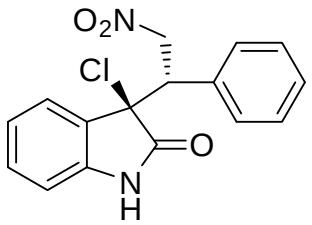
99:1 dr, 95% ee
5-3a

>99:1 dr, 94% ee
5-21

93% ee
5-21'

5.4.6 Analytical Data of the 3-Heteroatom Oxindole Products

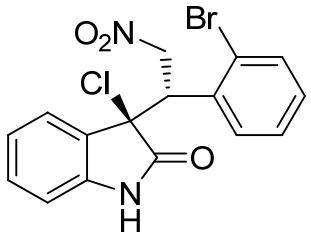
(*R*)-3-Chloro-3-((*S*)-2-nitro-1-phenylethyl)indolin-2-one **5-3a**



5-3a

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.27 (dd, *J* = 3.5 Hz, 11.0 Hz, 1H), 5.14 (dd, *J* = 11.3 Hz, 13.2 Hz, 1H), 5.67 (dd, *J* = 3.2 Hz, 13.2 Hz, 1H), 6.82 (d, *J* = 8.2 Hz, 1H), 6.86 (d, *J* = 7.0 Hz, 1H), 6.98-7.05 (m, 3H), 7.15-7.32 (m, 4H), 8.55 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 50.5, 66.1, 75.5, 110.9, 123.3, 125.8, 127.1, 128.5, 129.0, 129.3, 131.0, 132.6, 139.9, 174.4; The ee value was 97%, t_R (minor) = 27.23, 41.15 min, t_R (major) = 36.62, 48.54 min (Chiralcel OD-H, λ = 254 nm, 4% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{16}H_{13}ClN_2O_3Na$ $[M+Na]^+$ = 339.0507, found = 339.0523.

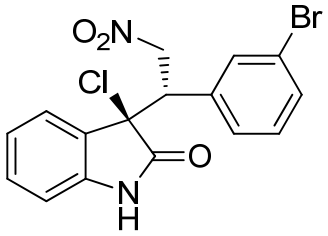
(*R*)-3-((*S*)-1-(2-Bromophenyl)-2-nitroethyl)-3-chloroindolin-2-one **5-3b**



5-3b

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.88 (dd, *J* = 3.2 Hz, 10.7 Hz, 1H), 5.15 (dd, *J* = 5.7 Hz, 14.5 Hz, 1H), 5.87 (dd, *J* = 3.8 Hz, 13.9 Hz, 1H), 6.06 (d, *J* = 7.6 Hz, 1H), 6.83 (t, *J* = 7.6 Hz, 1H), 6.92 (d, *J* = 8.2 Hz, 1H), 7.22-7.30 (m, 2H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.50 (d, *J* = 8.2 Hz, 1H), 7.66 (d, *J* = 7.6 Hz, 1H), 8.64 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 46.3, 65.8, 74.7, 110.6, 123.3, 126.1, 127.4, 127.7, 128.4, 128.7, 130.4, 130.9, 133.2, 133.3, 139.4, 174.6; The ee value was 96%, t_R (minor) = 18.54 min, t_R (major) = 30.18 min (Chiralcel OD-H, λ = 220 nm, 14% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{16}H_{11}{}^{79}BrClN_2O_3$ $[M-H]^-$ = 392.9647, found = 392.9639; HRMS (ESI) m/z calcd for $C_{16}H_{11}{}^{81}BrClN_2O_3$ $[M-H]^-$ = 394.9627, found = 394.9613.

(*R*)-3-((*S*)-1-(3-Bromophenyl)-2-nitroethyl)-3-chloroindolin-2-one **5-3c**

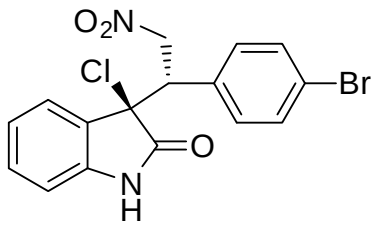


5-3c

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.28 (dd, *J* = 3.5 Hz, 11.1 Hz, 1H), 5.10 (dd, *J* = 10.8 Hz, 13.6 Hz, 1H), 5.68 (dd, *J* = 3.8 Hz, 13.2 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 6.92 (d, *J* = 7.6 Hz, 1H), 6.97 (d, *J* = 7.6 Hz, 1H), 7.08-7.12 (m, 2H), 7.14 (s,

1H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.42-7.44 (m, 1H), 8.06 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 50.2, 65.7, 75.2, 110.9, 122.4, 123.5, 125.8, 126.7, 128.1, 130.0, 131.3, 132.3, 132.4, 135.0, 139.8, 173.6; The ee value was 96%, t_R (minor) = 19.22, 20.81 min, t_R (major) = 24.05, 28.35 min (Chiralcel IB, λ = 254 nm, 4% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{16}H_{11}{}^{79}BrClN_2O_3$ $[M-H]^-$ = 392.9647, found = 392.9639; HRMS (ESI) m/z calcd for $C_{16}H_{11}{}^{81}BrClN_2O_3$ $[M-H]^-$ = 394.9627, found = 394.9613.

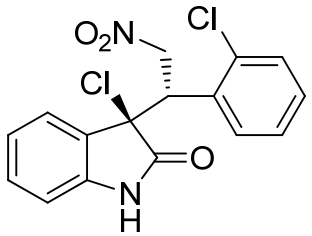
(*R*)-3-((*S*)-1-(4-Bromophenyl)-2-nitroethyl)-3-chloroindolin-2-one **5-3d**



5-3d

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.27 (dd, *J* = 3.5 Hz, 11.0 Hz, 1H), 5.08 (dd, *J* = 11.4 Hz, 13.3 Hz, 1H), 5.65 (dd, *J* = 3.5 Hz, 13.6 Hz, 1H), 6.83-6.86 (m, 3H), 6.94 (d, *J* = 7.0 Hz, 1H), 7.07 (t, *J* = 7.6 Hz, 1H), 7.31-7.34 (m, 3H), 8.52 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 50.0, 65.7, 75.2, 111.0, 123.3, 123.5, 125.7, 126.7, 130.9, 131.2, 131.5, 131.7, 139.9, 174.0; The ee value was 93%, t_R (minor) = 23.66, 36.37 min, t_R (major) = 28.22, 39.63 min (Chiralcel OD-H, λ = 254 nm, 5% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{16}H_{11}{}^{79}BrClN_2O_3$ $[M-H]^-$ = 392.9647, found = 392.9639; HRMS (ESI) m/z calcd for $C_{16}H_{11}{}^{81}BrClN_2O_3$ $[M-H]^-$ = 394.9627, found = 394.9613.

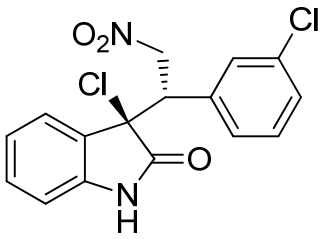
(*R*)-3-Chloro-3-((*S*)-1-(2-chlorophenyl)-2-nitroethyl)indolin-2-one **5-3e**



5-3e

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.89 (dd, *J* = 3.5 Hz, 11.0 Hz, 1H), 5.14 (dd, *J* = 10.7 Hz, 13.9 Hz, 1H), 5.85 (dd, *J* = 3.8 Hz, 13.9 Hz, 1H), 6.12 (d, *J* = 7.0 Hz, 1H), 6.85 (t, *J* = 7.6 Hz, 1H), 6.90-6.93 (m, 1H), 7.27-7.34 (m, 4H), 7.60 (t, *J* = 5.7 Hz, 1H), 8.33-8.61 (br, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 43.7, 65.8, 74.7, 110.6, 123.3, 125.9, 127.1, 127.5, 128.6, 130.0, 130.2, 130.9, 131.6, 136.9, 139.4, 174.5; The ee value was 94%, t_R (minor) = 15.17 min, t_R (major) = 27.37 min (Chiralcel OD-H, λ = 254 nm, 14% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{16}H_{11}Cl_2N_2O_3$ $[M-H]^-$ = 349.0152, found = 349.0156.

(*R*)-3-Chloro-3-((*S*)-1-(3-chlorophenyl)-2-nitroethyl)indolin-2-one **5-3f**

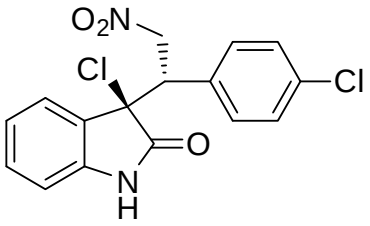


5-3f

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.28 (dd, *J* = 3.8 Hz, 11.4 Hz, 1H), 5.11 (dd, *J* = 11.4 Hz, 13.2 Hz, 1H), 5.69 (dd, *J* = 3.5 Hz, 13.9 Hz, 1H), 6.86 (d, *J* = 7.6 Hz, 1H), 6.91 (d, *J* = 7.6 Hz, 1H), 7.00 (s, 1H), 7.09-7.17 (m, 2H), 7.27 (s, 1H), 7.34-7.37 (m, 1H), 8.09 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 50.2, 65.7, 75.2, 110.9, 123.5, 125.8, 126.8, 127.6, 129.3, 129.5, 129.7, 131.3, 134.4, 134.7, 139.8, 173.6; The ee

value was 98%, t_R (minor) = 20.82 min, t_R (major) = 14.88, 25.52 min (Chiralcel OD-H, λ = 254 nm, 5% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{16}H_{11}Cl_2N_2O_3$ $[M-H]^-$ = 349.0152, found = 349.0156.

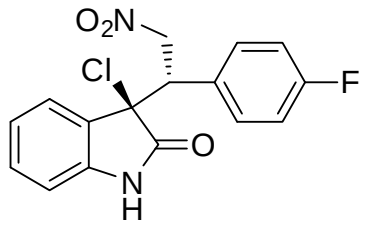
(*R*)-3-Chloro-3-((*S*)-1-(4-chlorophenyl)-2-nitroethyl)indolin-2-one **5-3g**



5-3g

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.28 (dd, *J* = 3.2 Hz, 11.4 Hz, 1H), 5.09 (t, *J* = 12.6 Hz, 1H), 5.65 (dd, *J* = 2.8 Hz, 13.6 Hz, 1H), 6.82 (d, *J* = 7.6 Hz, 1H), 6.91-6.93 (m, 3H), 7.06-7.17 (m, 3H), 7.33 (t, *J* = 7.9 Hz, 2H), 8.02 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 50.1, 65.8, 75.3, 110.9, 123.5, 125.8, 126.8, 128.8, 130.7, 131.1, 131.2, 135.2, 139.8, 173.6; The ee value was 98%, t_R (minor) = 21.24, 25.70 min, t_R (major) = 34.54, 37.13 min (Chiralcel OD-H, λ = 254 nm, 5% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{16}H_{11}Cl_2N_2O_3$ $[M-H]^-$ = 349.0152, found = 349.0156.

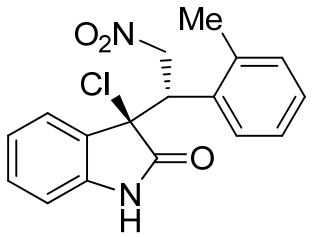
(*R*)-3-Chloro-3-((*S*)-1-(4-fluorophenyl)-2-nitroethyl)indolin-2-one **5-3h**



5-3h

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.29 (dd, *J* = 2.6 Hz, 11.1 Hz, 1H), 5.08 (t, *J* = 12.3 Hz, 1H), 5.64 (dd, *J* = 3.5 Hz, 13.5 Hz, 1H), 6.81 (d, *J* = 8.2 Hz, 1H), 6.86 (t, *J* = 8.5 Hz, 2H), 6.93-6.97 (m, 3H), 7.08 (t, *J* = 7.6 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 8.02 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 49.9, 65.9, 75.5, 110.8, 115.7 (d, *J* = 21.0 Hz), 123.5, 125.8, 126.8, 128.3, 131.1, 131.2 (d, *J* = 7.3 Hz), 139.8, 162.9 (d, *J* = 247.8 Hz), 173.7; The ee value was 94%, t_R (minor) = 10.41, 14.22 min, t_R (major) = 11.97, 14.80 min (Chiralcel IB, λ = 254 nm, 7.5% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{16}H_{11}FClN_2O_3$ $[M-H]^-$ = 333.0448, found = 333.0437.

(*R*)-3-Chloro-3-((*S*)-2-nitro-1-(o-tolyl)ethyl)indolin-2-one **5-3i**

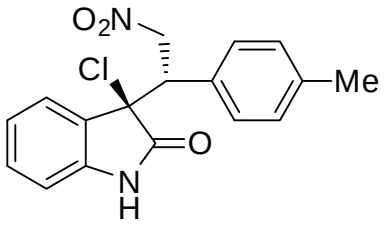


5-3i

A yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.00 (s, 3H), 4.54 (dd, *J* = 3.5 Hz, 11.0 Hz, 1H), 5.13 (dd, *J* = 11.1 Hz, 13.6 Hz, 1H), 5.76 (dd, *J* = 3.8 Hz, 13.9 Hz, 1H), 6.42 (d, *J* = 7.6 Hz, 1H), 6.85 (d, *J* = 7.6 Hz, 1H), 6.91 (t, *J* = 7.6 Hz, 1H), 7.07 (d, *J* = 7.6 Hz, 1H), 7.12 (t, *J* = 7.3 Hz, 1H), 7.19-7.22 (m, 2H), 7.27-7.31 (m, 1H), 8.33 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.6, 43.9, 66.2, 75.7, 110.6, 123.3, 126.1, 126.6, 127.5, 128.8, 130.9, 131.9, 139.0, 139.5, 174.6; The ee value was 98%, t_R (minor) = 8.73, 10.44 min, t_R (major) = 9.74, 11.81 min (Chiralcel IB, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{17}H_{15}ClN_2O_3Na$

$[M+Na]^+$ = 353.0663, found = 353.0654.

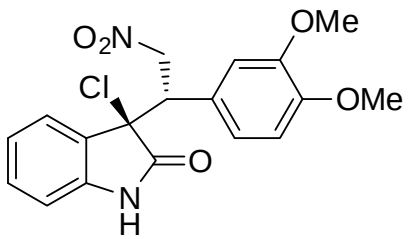
(*R*)-3-Chloro-3-((*S*)-2-nitro-1-(p-tolyl)ethyl)indolin-2-one **5-3j**



5-3j

A yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.99 (s, 3H), 4.53 (dd, *J* = 3.5 Hz, 10.7 Hz, 1H), 5.14 (dd, *J* = 10.7 Hz, 13.9 Hz, 1H), 5.77 (dd, *J* = 3.2 Hz, 13.6 Hz, 1H), 6.41 (d, *J* = 7.6 Hz, 1H), 6.86 (d, *J* = 7.6 Hz, 1H), 6.92 (t, *J* = 7.6 Hz, 1H), 7.07 (d, *J* = 7.6 Hz, 1H), 7.12 (t, *J* = 7.6 Hz, 1H), 7.19-7.22 (m, 2H), 7.27-7.31 (m, 1H), 8.33 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.6, 43.9, 66.2, 75.7, 110.6, 123.3, 126.1, 126.6, 127.5, 128.8, 130.9, 131.9, 139.0, 139.5, 174.6; The ee value was 99%, t_R (minor) = 22.08, 26.88 min, t_R (major) = 19.10, 27.70 min (Chiralcel IB, λ = 254 nm, 3% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{17}H_{15}ClN_2O_3Na$ $[M+Na]^+$ = 353.0663, found = 353.0654.

(*R*)-3-Chloro-3-((*S*)-1-(3,4-dimethoxyphenyl)-2-nitroethyl)indolin-2-one **5-3k**

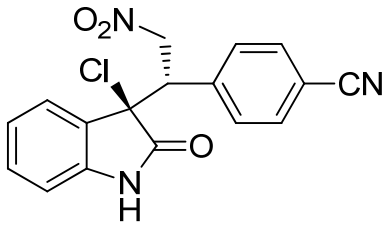


5-3k

A yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.55 (s, 3H), 3.79 (s, 3H), 4.26 (dd, *J* =

3.2 Hz, 11.4 Hz, 1H), 5.08 (dd, *J* = 11.4 Hz, 12.6 Hz, 1H), 5.61 (dd, *J* = 3.8 Hz, 13.3 Hz, 1H), 6.32 (d, *J* = 1.3 Hz, 1H), 6.57-6.60 (m, 1H), 6.66 (d, *J* = 8.9 Hz, 1H), 6.78 (d, *J* = 8.2 Hz, 1H), 7.04-7.10 (m, 2H), 7.29-7.32 (m, 1H) 7.94 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 50.4, 55.6, 55.7, 66.1, 75.8, 110.8, 110.9, 111.5, 122.4, 123.3, 124.5, 125.8, 127.3, 131.0, 140.2, 148.5, 149.3, 173.7; The ee value was 97%, t_R (minor) = 24.55 min, t_R (major) = 20.83 min (Chiralcel IA, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{18}H_{16}ClN_2O_5$ $[M-H]^-$ = 375.0753, found = 375.0767.

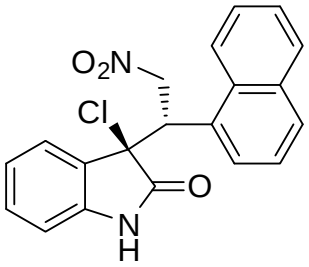
4-((*S*)-1-((*R*)-3-Chloro-2-oxoindolin-3-yl)-2-nitroethyl)benzonitrile **5-3l**



5-3l

A light yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.37 (dd, *J* = 3.8 Hz, 11.4 Hz, 1H), 5.12 (dd, *J* = 11.7 Hz, 13.9 Hz, 1H), 5.68 (dd, *J* = 3.8 Hz, 13.9 Hz, 1H), 6.82 (d, *J* = 7.6 Hz, 1H), 6.93 (d, *J* = 7.6 Hz, 1H), 7.08-7.14 (m, 3H), 7.32-7.36 (m, 1H), 7.41-7.50 (m, 2H), 7.80 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 50.5, 65.3, 74.9, 111.0, 113.2, 118.0, 123.7, 125.7, 126.4, 130.2, 131.5, 132.2, 138.0, 139.7, 173.0; The ee value was 98%, t_R (minor) = 45.33 min, t_R (major) = 57.71 min (Chiralcel IB, λ = 254 nm, 5% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{17}H_{11}CClN_3O_3$ $[M-H]^-$ = 340.0494, found = 340.0479.

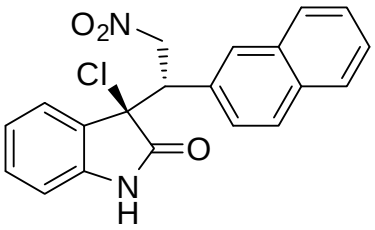
(*R*)-3-Chloro-3-((*S*)-1-(naphthalen-1-yl)-2-nitroethyl)indolin-2-one **5-3m**



5-3m

A yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.22-5.31 (m, 2H), 5.82 (dd, *J* = 2.8 Hz, 12.9 Hz, 1H), 6.55 (d, *J* = 7.6 Hz, 1H), 6.74-6.79 (m, 2H), 7.19-7.22 (m, 2H), 7.28 (t, *J* = 7.6 Hz, 1H), 7.40-7.44 (m, 2H), 7.79 (d, *J* = 7.6 Hz, 1H), 7.94 (d, *J* = 8.2 Hz, 1H), 8.06 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 42.9, 66.4, 76.2, 110.6, 123.0, 123.2, 124.5, 125.1, 125.9, 126.5, 127.3, 128.6, 129.4, 129.7, 130.8, 132.5, 133.7, 139.8, 174.1; The ee value was 99%, t_R (minor) = 23.09 min, t_R (major) = 34.53 min (Chiralcel IA, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{20}H_{14}ClN_2O_3$ $[M-H]^-$ = 365.0698, found = 365.0699.

(*R*)-3-Chloro-3-((*S*)-1-(naphthalen-2-yl)-2-nitroethyl)indolin-2-one **5-3n**

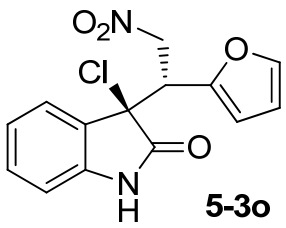


5-3n

A yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.45 (dd, *J* = 3.2 Hz, 10.8 Hz, 1H), 5.25 (t, *J* = 12.3 Hz, 1H), 5.72 (dd, *J* = 2.9 Hz, 13.6 Hz, 1H), 6.73 (d, *J* = 7.6 Hz, 1H), 6.95 (d, *J* = 7.0 Hz, 1H), 7.03 (t, *J* = 7.3 Hz, 2H), 7.29 (t, *J* = 7.9 Hz, 1H), 7.42-7.49 (m, 3H), 7.63 (t, *J* = 4.1 Hz, 1H), 7.75 (d, *J* = 7.6 Hz, 1H), 7.87 (br s, 1H); ^{13}C NMR (125

MHz, $CDCl_3$) δ 50.7, 66.1, 75.6, 110.8, 123.3, 125.9, 126.2, 126.4, 126.8, 127.2, 127.5, 128.1, 128.2, 129.4, 130.0, 131.0, 132.8, 133.2, 139.8, 173.7; The ee value was 96%, t_R (minor) = 40.64 min, t_R (major) = 36.78 min (Chiralcel AD-H, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 0.5 mL/min); HRMS (ESI) m/z calcd for $C_{20}H_{14}ClN_2O_3$ $[M-H]^-$ = 365.0698, found = 365.0699.

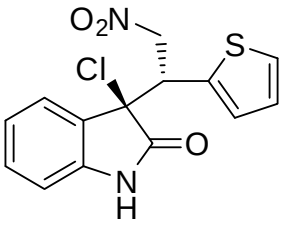
(*R*)-3-Chloro-3-((*R*)-1-(furan-2-yl)-2-nitroethyl)indolin-2-one **5-3o**



5-3o

A light yellow oil; ^1H NMR (500 MHz, $CDCl_3$) δ 4.43 (dd, *J* = 3.2 Hz, 10.7 Hz, 1H), 5.16 (dd, *J* = 11.0 Hz, 13.5 Hz, 1H), 5.64 (dd, *J* = 3.7 Hz, 13.6 Hz, 1H), 6.23 (d, *J* = 3.2 Hz, 1H), 6.27 (t, *J* = 1.6 Hz, 1H), 6.79 (d, *J* = 7.6 Hz, 1H), 6.88 (d, *J* = 7.6 Hz, 1H), 7.03 (t, *J* = 7.6 Hz, 1H), 7.28-7.32 (m, 2H), 8.32-8.50 (br, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 44.4, 64.8, 73.7, 110.7, 110.8, 123.5, 125.6, 127.4, 131.0, 139.4, 143.1, 146.8, 174.1; The ee value was 99%, t_R (minor) = 29.76, 36.05 min, t_R (major) = 38.09, 39.36 min (Chiralcel IB, λ = 254 nm, 5% *i*PrOH/hexanes, flow rate = 0.5 mL/min); HRMS (ESI) m/z calcd for $C_{14}H_{10}ClN_2O_4$ $[M-H]^-$ = 305.0335, found = 305.0340.

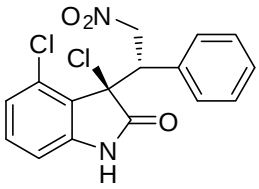
(*R*)-3-Chloro-3-((*R*)-2-nitro-1-(thiophen-2-yl)ethyl)indolin-2-one **5-3p**



5-3p

A yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.63 (dd, *J* = 3.5 Hz, 11.0 Hz, 1H), 5.02 (dd, *J* = 10.7 Hz, 13.2 Hz, 1H), 5.70 (dd, *J* = 3.2 Hz, 13.3 Hz, 1H), 6.81 (d, *J* = 3.8 Hz, 1H), 6.84-6.86 (m, 2H), 6.94 (d, *J* = 7.6 Hz, 1H), 7.08 (t, *J* = 7.6 Hz, 1H), 7.19 (d, *J* = 5.1 Hz, 1H),7.32-7.36 (m, 1H), 8.00 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 46.6, 65.4, 76.7, 110.8, 123.5, 125.9, 126.6, 126.7, 126.9, 129.4, 131.3, 134.4, 140.1, 173.5; The ee value was 97%, t_R (minor) = 29.66 min, t_R (major) = 25.88 min (Chiralcel IA, λ = 254 nm, 5% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{14}H_{10}ClN_2O_3S$ $[M-H]^-$ = 321.0106, found = 321.0113.

(*R*)-3,4-Dichloro-3-((*S*)-2-nitro-1-phenylethyl)indolin-2-one **5-3q**

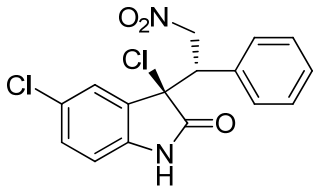


5-3q

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.55 (dd, *J* = 3.2 Hz, 12.0 Hz, 1H), 5.38 (t, *J* = 11.3 Hz, 1H), 5.50 (dd, *J* = 3.2 Hz, 13.3 Hz, 1H), 6.65 (d, *J* = 8.2 Hz, 1H), 6.95 (d, *J* = 7.6 Hz, 2H), 7.10-7.15 (m, 3H), 7.19-7.27 (m, 2H), 8.45-8.53 (br, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.1, 66.8, 77.6, 109.4, 124.1, 125.0, 128.5, 128.9, 129.1, 131.8, 132.2, 142.1, 173.6; The ee value was 99%, t_R (minor) = 22.09, 24.79 min, t_R

(major) = 20.73, 34.34 min (Chiralcel OD-H, λ = 254 nm, 5% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{16}H_{11}Cl_2N_2O_3$ $[M-H]^-$ = 349.0152, found = 349.0156.

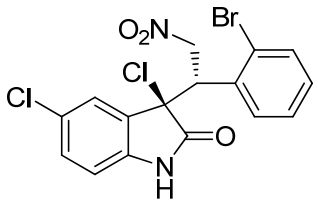
(*R*)-3,5-Dichloro-3-((*S*)-2-nitro-1-phenylethyl)indolin-2-one **5-3r**



5-3r

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.22 (dd, *J* = 3.5 Hz, 11.1 Hz, 1H), 5.12 (dd, *J* = 10.7 Hz, 13.2 Hz, 1H), 5.65 (dd, *J* = 3.5 Hz, 13.6 Hz, 1H), 6.68 (s, 1H), 6.78 (d, *J* = 8.2 Hz, 1H), 7.03 (d, *J* = 7.6 Hz, 2H), 7.21-7.33 (m, 4H), 8.60 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 50.1, 65.7, 75.1, 111.8, 126.4, 128.6, 128.7, 128.8, 129.3, 129.4, 131.0, 132.3, 138.2, 174.1; The ee value was 99%, t_R (minor) = 12.75, 16.85 min, t_R (major) = 11.91, 16.85 min (Chiralcel ID, λ = 254 nm, 5% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{16}H_{11}Cl_2N_2O_3$ $[M-H]^-$ = 349.0152, found = 349.0156.

(*R*)-3-((*S*)-1-(2-Bromophenyl)-2-nitroethyl)-3,5-dichloroindolin-2-one **5-3s**

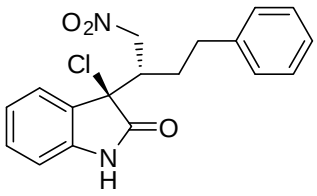


5-3s

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.87 (dd, *J* = 3.8 Hz, 10.1 Hz, 1H), 5.15

(dd, *J* = 10.4 Hz, 14.2 Hz, 1H), 5.84 (m, 2H), 6.89 (d, *J* = 8.9 Hz, 1H), 7.21-7.31 (m, 2H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.56 (d, *J* = 10.1 Hz, 1H), 7.70 (d, *J* = 6.3 Hz, 1H), 8.89-9.07 (br, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 46.0, 65.4, 74.3, 111.7, 126.6, 127.9, 128.4, 128.6, 128.7, 128.8, 130.7, 130.8, 132.7, 133.4, 137.8, 174.7; The ee value was 98%, t_R (minor) = 13.54 min, t_R (major) = 16.55 min (Chiralcel ID, λ = 254 nm, 5% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{16}H_{10}Cl_2{}^{79}BrN_2O_3$ $[M-H]^-$ = 426.9257, found = 426.9248, calcd for $C_{16}H_{10}Cl_2{}^{81}BrN_2O_3$ $[M-H]^-$ = 428.9237, found = 428.9236.

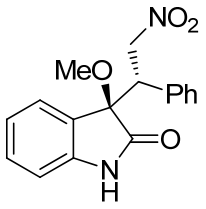
(*R*)-3-Chloro-3-((*S*)-1-nitro-4-phenylbutan-2-yl)indolin-2-one **5-3t**



5-3t

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.62-1.66 (m, 1H), 1.91-1.98 (m, 1H), 2.60 (t, *J* = 8.2 Hz, 2H), 3.30-3.35 (m, 1H), 4.57 (dd, *J* = 7.6 Hz, 13.3 Hz, 1H), 5.12 (dd, *J* = 4.1 Hz, 13.6 Hz, 1H), 6.93 (d, *J* = 8.2 Hz, 1H), 7.07 (d, *J* = 7.0 Hz, 2H), 7.17 (t, *J* = 7.6 Hz, 1H), 7.17-7.25 (m, 3H), 7.30 (t, *J* = 9.2 Hz, 1H), 7.34 (dd, *J* = 1.3 Hz, 7.6 Hz, 1H), 8.02 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.3, 33.4, 44.5, 66.3, 75.8, 111.1, 123.8, 125.1, 126.4, 127.5, 128.3, 128.6, 131.1, 139.8, 140.3, 174.2; The ee value was 99%, t_R (minor) = 23.71, 45.93 min, t_R (major) = 21.81, 36.32 min (Chiralcel OD-H, λ = 254 nm, 5% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{18}H_{16}ClN_2O_3$ $[M-H]^-$ = 343.0855, found = 343.0849.

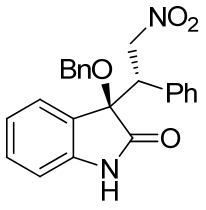
(*R*)-3-Methoxy-3-((*S*)-2-nitro-1-phenylethyl)indolin-2-one **5-17a**



5-17a

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.08 (s, 3H), 3.94 (dd, *J* = 4.4 Hz, 10.7 Hz, 1H), 5.00 (dd, *J* = 10.4 Hz, 13.6 Hz, 1H), 5.58 (dd, *J* = 4.4 Hz, 13.3 Hz, 1H), 6.60 (d, *J* = 7.6 Hz, 1H), 6.81 (d, *J* = 7.6 Hz, 1H), 6.94-7.00 (m, 3H), 7.15 (t, *J* = 7.6 Hz, 2H), 7.22-7.29 (m, 2H), 8.47 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 50.1, 53.6, 75.0, 84.3, 110.6, 122.7, 124.1, 126.0, 128.0, 128.1, 128.2, 128.4, 128.8, 129.5, 130.6, 133.9, 141.1, 176.9; The ee value was 86%, t_R (minor) = 12.34, 21.05 min, t_R (major) = 30.31, 44.03 min (Chiralcel IC, λ = 254 nm, 5% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{17}H_{15}N_2O_4$ $[M-H]^-$ = 311.1037, found = 311.1043.

(*R*)-3-(Benzyloxy)-3-((*S*)-2-nitro-1-phenylethyl)indolin-2-one **5-17b**

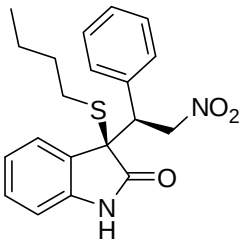


5-17b

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.27 (dd, *J* = 3.8 Hz, 11.4 Hz, 1H), 4.69 (s, 2H), 5.14 (dd, *J* = 11.4 Hz, 13.3 Hz, 1H), 5.66 (dd, *J* = 3.5 Hz, 13.6 Hz, 1H), 6.76

(d, *J* = 8.2 Hz, 1H), 6.87 (d, *J* = 7.6 Hz, 1H), 6.98 (d, *J* = 7.6 Hz, 2H), 7.03 (t, *J* = 7.6 Hz, 1H), 7.17 (t, *J* = 7.6 Hz, 2H), 7.24-7.32 (m, 3H), 7.36 (d, *J* = 4.5 Hz, 4H), 8.37 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 50.5, 65.2, 66.1, 75.5, 110.8, 123.2, 125.8, 127.0, 127.1, 127.6, 128.4, 128.5, 129.0, 129.3, 131.0, 132.5, 139.9, 140.8, 174.1; The ee value was 98%, t_R (minor) = 14.32, 17.22 min, t_R (major) = 18.24, 21.01 min (Chiralcel IB, λ = 254 nm, 5% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{23}H_{19}N_2O_4$ $[M-H]^-$ = 387.1351, found = 387.1366.

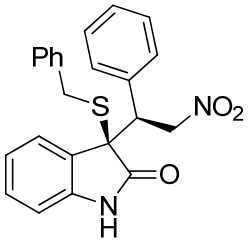
(*R*)-3-(Butylthio)-3-((*S*)-2-nitro-1-phenylethyl)indolin-2-one **5-17c**



5-17c

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.84 (t, *J* = 7.6 Hz, 3H), 1.30-1.38 (m, 2H), 1.43-1.50 (m, 2H), 2.60-2.66 (m, 2H), 4.22 (dd, *J* = 3.2 Hz & 12.0 Hz, 1H), 5.08 (t, *J* = 12.4 Hz, 1H), 5.63 (dd, *J* = 3.2 Hz, 12.6 Hz, 1H), 6.77 (d, *J* = 8.1 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 7.04-7.11 (m, 2H), 7.13-7.19 (m, 2H), 7.27 (d, *J* = 7.6 Hz, 1H), 7.29 (dd, *J* = 1.3 Hz & 7.6 Hz, 1H), 8.29 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.5, 21.9, 28.0, 30.5, 47.6, 56.7, 76.5, 110.4, 122.9, 124.8, 124.9, 127.3, 128.2, 128.4, 128.9, 129.0, 129.8, 133.7, 140.4, 176.9; The ee value was 91%, $[\alpha]^{27}_D$ = -78.2 (c = 0.85, CH_2Cl_2), t_R (minor) = 10.07, 11.96 min, t_R (major) = 13.49, 23.77 min (Chiralcel OD-H, λ = 254 nm, 5% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{20}H_{21}N_2O_3S$ $[M-H]^-$ = 369.1278, found = 369.1277.

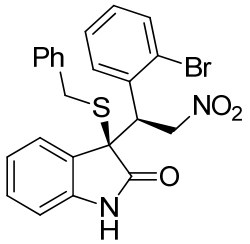
(*R*)-3-(Benzylthio)-3-((*S*)-2-nitro-1-phenylethyl)indolin-2-one **5-17d**



5-17d

A white foam; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.91 (d, *J* = 12.0 Hz, 1H), 3.96 (d, *J* = 12.0 Hz, 1H), 4.27 (dd, *J* = 3.2 Hz, 12.0 Hz, 1H), 5.07 (t, *J* = 12.6 Hz, 1H), 5.62 (dd, *J* = 3.5 Hz, 12.9 Hz, 1H), 6.79 (d, *J* = 7.6 Hz, 1H), 6.87 (d, *J* = 7.6 Hz, 2H), 7.06 (t, *J* = 7.6 Hz, 2H), 7.14 (dd, *J* = 7.6 Hz, 15.2 Hz, 2H), 7.20-7.25 (m, 6H), 7.30 (t, *J* = 7.9 Hz, 1H), 8.59 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.3, 47.3, 57.2, 76.3, 110.4, 123.0, 124.9, 126.7, 127.5, 128.2, 128.4, 128.6, 129.0, 129.2, 130.0, 133.6, 135.9, 140.5, 176.1; The ee value was 97%, $[\alpha]^{27}_D$ = -26.4 (c = 1.02, CH_2Cl_2), t_R (minor) = 11.74, 14.32 min, t_R (major) = 9.69, 16.22 min (Chiralcel IB, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{23}H_{19}N_2O_3S$ $[M-H]^-$ = 403.1122, found = 403.1117.

(*R*)-3-(Benzylthio)-3-((*S*)-1-(2-bromophenyl)-2-nitroethyl)indolin-2-one **5-17e**

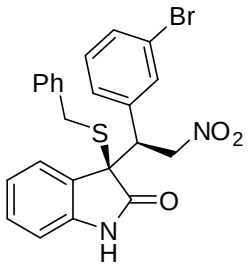


5-17e

A light yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.71 (d, *J* = 12.0 Hz, 1H), 3.82 (d, *J*

= 12.0 Hz, 1H), 4.98 (dd, *J* = 10.4 Hz, 18.0 Hz, 2H), 5.61-5.66 (m, 1H), 6.79 (d, *J* = 7.6 Hz, 2H), 6.89 (d, *J* = 7.6 Hz, 1H), 7.00-7.23 (m, 9H), 7.30-7.33 (m, 1H), 7.48 (dd, *J* = 1.6 Hz, 7.9 Hz, 1H), 8.48 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.6, 45.2, 57.2, 75.9, 110.5, 123.1, 125.2, 126.8, 127.3, 127.5, 127.7, 128.5, 129.2, 129.9, 130.0, 133.4, 134.2, 135.6, 140.5, 176.7; The ee value was 99%, $[\alpha]^{27}_D$ = -70.1 (c = 1.07, CH_2Cl_2), t_R (minor) = 14.93, 15.93 min, t_R (major) = 13.69, 22.47 min (Chiralcel IC, λ = 254 nm, 20% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{23}H_{18}{}^{79}BrN_2O_3S$ $[M-H]^-$ = 481.0227, found = 481.0223; calcd for $C_{23}H_{18}{}^{81}BrN_2O_3S$ $[M-H]^-$ = 483.0215, found = 483.0207.

(*R*)-3-(Benzylthio)-3-((*S*)-1-(3-bromophenyl)-2-nitroethyl)indolin-2-one **5-17f**

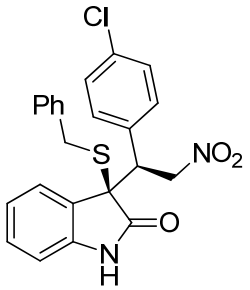


5-17f

A yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.92 (d, *J* = 12.0 Hz, 1H), 3.98 (d, *J* = 12.0 Hz, 1H), 4.22 (dd, *J* = 2.6 Hz, 11.4 Hz, 1H), 5.00 (t, *J* = 12.6 Hz, 1H), 5.58-5.61 (m, 1H), 6.82 (dd, *J* = 5.1 Hz, 7.0 Hz, 2H), 6.95 (t, *J* = 7.9 Hz, 1H), 7.01 (d, *J* = 1.9 Hz, 1H), 7.14 (t, *J* = 7.6 Hz, 1H), 7.20-7.34 (m, 8H), 8.34 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.4, 46.9, 57.1, 76.0, 77.3, 110.8, 122.2, 123.2, 124.8, 126.3, 127.6, 127.7, 128.7, 129.2, 129.8, 130.3, 131.7, 132.2, 135.8, 136.0, 140.5, 176.2; The ee value was 97%, $[\alpha]^{27}_D$ = -8.3 (c = 1.15, CH_2Cl_2), t_R (minor) = 14.36, 25.17 min, t_R

(major) = 15.73, 17.96 min (Chiralcel ID, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{23}H_{18}{}^{79}BrN_2O_3S$ $[M-H]^-$ = 481.0227, found = 481.0223; calcd for $C_{23}H_{18}{}^{81}BrN_2O_3S$ $[M-H]^-$ = 483.0215, found = 483.0207.

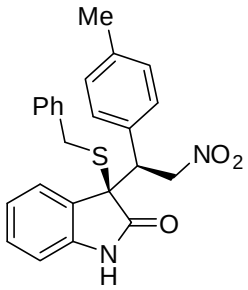
(*R*)-3-(Benzylthio)-3-((*S*)-1-(4-chlorophenyl)-2-nitroethyl)indolin-2-one **5-17g**



5-17g

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.93 (d, *J* = 12.0 Hz, 1H), 3.99 (d, *J* = 12.0 Hz, 1H), 4.26 (dd, *J* = 3.2 Hz, 11.4 Hz, 1H), 5.01 (t, *J* = 12.6 Hz, 1H), 5.60 (dd, *J* = 3.2 Hz, 13.2 Hz, 1H), 6.80 (dd, *J* = 8.2 Hz, 13.3 Hz, 2H), 7.08 (d, *J* = 8.2 Hz, 2H), 7.14 (t, *J* = 7.6 Hz, 1H), 7.22-7.27 (m, 6H), 7.32 (t, *J* = 7.6 Hz, 1H), 8.13 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.3, 46.7, 57.0, 76.0, 77.2, 110.7, 123.1, 124.8, 126.3, 127.6, 128.5, 128.6, 129.1, 130.1, 130.3, 132.1, 134.4, 135.8, 140.4, 176.0; The ee value was 97%, $[\alpha]^{27}{}_D$ = -19.4 (c = 1.03, CH_2Cl_2) t_R (minor) = 12.36, 13.73 min, t_R (major) = 10.25, 20.62 min (Chiralcel IB, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{23}H_{18}ClN_2O_3S$ $[M-H]^-$ = 437.0732, found = 437.0750.

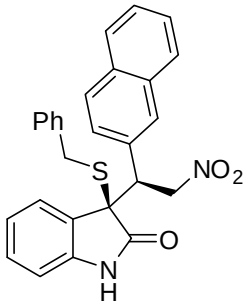
(*R*)-3-(Benzylthio)-3-((*S*)-2-nitro-1-(p-tolyl)ethyl)indolin-2-one **5-17h**



5-17h

A white foam; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.2 (s, 3H), 3.92 (d, *J* = 12.0 Hz, 1H), 3.97 (d, *J* = 12.0 Hz, 1H), 4.25 (dd, *J* = 3.2 Hz, 11.4 Hz, 1H), 5.05 (t, *J* = 12.6 Hz, 1H), 5.60 (dd, *J* = 3.5 Hz, 12.9 Hz, 1H), 6.77 (d, *J* = 7.6 Hz, 3H), 6.89 (d, *J* = 7.6 Hz, 2H), 7.11 (t, *J* = 7.6 Hz, 1H), 7.21-7.30 (m, 7H), 8.14 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.1, 33.3, 47.0, 57.3, 76.5, 110.6, 123.0, 125.0, 126.9, 127.5, 128.6, 128.9, 129.0, 129.2, 129.9, 130.6, 135.9, 138.2, 140.6, 176.4; The ee value was 97%, $[\alpha]^{27}_{D}$ = -30.9 (c = 0.94, CH_2Cl_2), t_R (minor) = 16.46, 19.56 min, t_R (major) = 20.21, 22.63 min (Chiralcel ID, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{24}H_{21}N_2O_3S$ $[M-H]^-$ = 417.1278, found = 417.1284.

(*R*)-3-(Benzylthio)-3-((*S*)-1-(naphthalen-2-yl)-2-nitroethyl)indolin-2-one **5-17i**

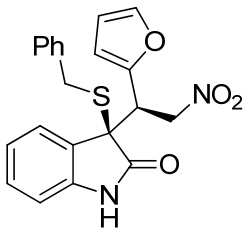


5-17i

A white foam; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.94 (d, *J* = 12.0 Hz, 1H), 4.01 (d, *J* = 12.7 Hz, 1H), 4.42 (dd, *J* = 3.2 Hz, 12.0 Hz, 1H), 5.14 (t, *J* = 12.6 Hz, 1H), 5.64 (dd, *J*

= 3.2 Hz, 12.6 Hz, 1H), 6.65 (d, *J* = 8.2 Hz, 1H), 6.94 (d, *J* = 8.2 Hz, 1H), 7.12 (t, *J* = 7.6 Hz, 1H), 7.19-7.28 (m, 7H), 7.36-7.42 (m, 3H), 7.51 (d, *J* = 8.2 Hz, 1H), 7.57 (d, *J* = 8.2 Hz, 1H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.85 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.4, 47.5, 57.2, 76.4, 77.3, 110.6, 123.0, 125.0, 126.1, 126.2, 126.5, 126.8, 127.5, 127.6, 128.0, 128.1, 128.7, 129.0, 129.3, 130.0, 131.2, 132.8, 133.0, 135.9, 140.5, 176.1; The ee value was 98%, $[\alpha]^{27}_D$ = -18.7 (c = 0.97, CH_2Cl_2), t_R (minor) = 18.83, 26.31 min, t_R (major) = 20.56, 29.15 min (Chiralcel IA, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{27}H_{21}N_2O_3S$ $[M-H]^-$ = 453.1278, found = 453.1295.

(*R*)-3-(Benzylthio)-3-((*R*)-1-(furan-2-yl)-2-nitroethyl)indolin-2-one **5-17j**

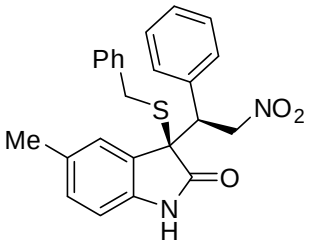


5-17j

A white foam; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.93 (d, *J* = 12.6 Hz, 1H), 3.97 (d, *J* = 12.6 Hz, 1H), 4.46 (dd, *J* = 1.3 Hz, 11.4 Hz, 1H), 5.08-5.14 (m, 1H), 5.56-5.59 (m, 1H), 5.99 (d, *J* = 3.2 Hz, 2H), 6.12 (d, *J* = 1.9 Hz, 1H), 6.84 (dd, *J* = 2.2 Hz, 7.9 Hz, 1H), 7.04-7.08 (m, 3H), 7.19-7.28 (m, 6H), 8.64 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.2, 41.3, 56.3, 74.3, 109.5, 110.4, 110.5, 123.0, 124.8, 127.0, 127.6, 128.6, 129.2, 129.8, 135.7, 140.2, 142.7, 148.0, 176.6; The ee value was 96%, $[\alpha]^{27}_D$ = -21.4 (c = 1.01, CH_2Cl_2), t_R (minor) = 15.13, 21.03 min, t_R (major) = 11.65, 13.82 min (Chiralcel IC, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI)

m/z calcd for $C_{21}H_{17}N_2O_4S$ $[M-H]^-$ = 393.0915, found = 393.0918.

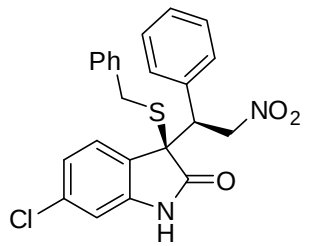
(*R*)-3-(Benzylthio)-5-methyl-3-((*S*)-2-nitro-1-phenylethyl)indolin-2-one **5-17k**



5-17k

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.37 (s, 3H), 3.92 (d, *J* = 12.6 Hz, 1H), 3.98 (d, *J* = 12.0 Hz, 1H), 4.25 (dd, *J* = 3.2 Hz, 12.0 Hz, 1H), 5.06 (t, *J* = 12.6 Hz, 1H), 5.59 (dd, *J* = 3.2 Hz, 13.2 Hz, 1H), 6.66 (d, *J* = 8.2 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 2H), 6.99 (s, 1H), 7.05-7.10 (m, 3H), 7.15 (t, *J* = 7.3 Hz, 1H), 7.20-7.25 (m, 5H), 8.10 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.3, 33.4, 47.4, 57.3, 76.4, 110.3, 125.5, 126.8, 127.5, 128.2, 128.4, 128.6, 129.1, 129.2, 130.4, 132.6, 133.7, 136.1, 138.1, 176.3; The ee value was 98%, $[\alpha]^{27}_D$ = -49.9 (c = 0.90, CH_2Cl_2), t_R (minor) = 27.82, 37.31 min, t_R (major) = 19.96, 32.74 min (Chiralcel IB, λ = 254 nm, 3% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{24}H_{21}N_2O_3S$ $[M-H]^-$ = 417.1278, found = 417.1284.

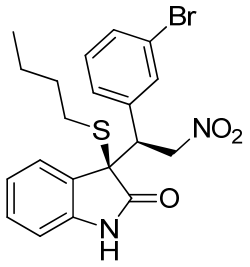
(*R*)-3-(Benzylthio)-6-chloro-3-((*S*)-2-nitro-1-phenylethyl)indolin-2-one **5-17l**



5-17l

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.90 (d, *J* = 12.6 Hz, 1H), 3.96 (d, *J* = 12.0 Hz, 1H), 4.23 (dd, *J* = 3.5 Hz, 11.7 Hz, 1H), 5.04 (d, *J* = 12.6 Hz, 1H), 5.57 (dd, *J* = 3.5 Hz, 12.9 Hz, 1H), 6.70 (d, *J* = 8.2 Hz, 1H), 6.89 (d, *J* = 7.6 Hz, 1H), 7.09-7.12 (m, 3H), 7.17-7.27 (m, 7H), 8.25 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.5, 47.3, 57.4, 75.9, 111.4, 125.3, 127.7, 128.3, 128.4, 128.5, 128.6, 129.0, 129.1, 130.0, 133.2, 135.5, 138.9, 176.0; The ee value was 96%, $[\alpha]^{27}_D$ = -46.0 (c = 0.98, CH_2Cl_2), t_R (minor) = 21.47, 31.19 min, t_R (major) = 16.42, 27.19 min (Chiralcel IB, λ = 254 nm, 5% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{23}H_{18}ClN_2O_3S$ $[M-H]^-$ = 437.0732, found = 437.0750.

(*R*)-3-((*S*)-1-(3-Bromophenyl)-2-nitroethyl)-3-(butylthio)indolin-2-one **5-17m**

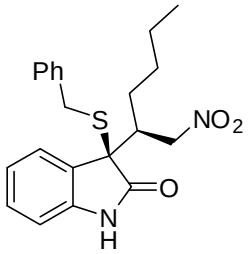


5-17m

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (t, *J* = 7.6 Hz, 3H), 1.31-1.39 (m, 2H), 1.44-1.50 (m, 2H), 2.62-2.71 (m, 2H), 4.20 (dd, *J* = 3.2 Hz, 12.0 Hz, 1H), 5.02 (t, *J* = 12.6 Hz, 1H), 5.62 (dd, *J* = 3.2 Hz, 13.2 Hz, 1H), 6.81 (d, *J* = 7.6 Hz, 2H), 6.95 (t, *J* = 7.9 Hz, 1H), 7.00 (s, 1H), 7.14 (d, *J* = 7.6 Hz, 1H), 7.19 (d, *J* = 6.9 Hz, 1H), 7.30 (dd, *J* = 7.0 Hz & 13.3 Hz, 2H), 8.16 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.5, 22.0, 28.0, 30.4, 47.1, 56.4, 76.2, 110.6, 122.1, 123.1, 124.8, 126.8, 127.6, 129.7, 130.1, 131.6, 132.1, 136.0, 140.3, 176.4; The ee value was 90%, $[\alpha]^{27}_D$ = -63.9 (c =

0.88, CH_2Cl_2), t_R (minor) = 17.40, 20.11 min, t_R (major) = 11.35, 13.58 min (Chiralcel AD-H, λ = 254 nm, 20% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{20}H_{20}{}^{79}BrN_2O_3S$ $[M-H]^-$ = 447.0383, found = 447.0384; HRMS (ESI) m/z calcd for $C_{20}H_{20}{}^{81}BrN_2O_3S$ $[M-H]^-$ = 449.0357, found = 449.0362.

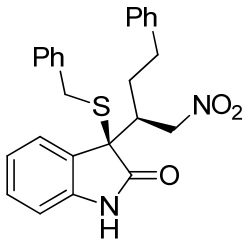
(*R*)-3-(Benzylthio)-3-((*S*)-1-nitrohexan-2-yl)indolin-2-one **5-17n**



5-17n

A light yellow oil; ^1H NMR (500 MHz, $CDCl_3$) δ 0.77 (t, *J* = 7.0 Hz, 3H), 1.17-1.23 (m, 5H), 1.37-1.40 (m, 1H), 3.26-3.30 (m, 1H), 3.94 (d, *J* = 11.5 Hz, 1H), 4.05 (d, *J* = 11.4 Hz, 1H), 4.55 (dd, *J* = 8.8 Hz, 13.2 Hz, 1H), 5.50 (dd, *J* = 2.5 Hz, 13.3 Hz, 1H), 6.96 (d, *J* = 8.2 Hz, 1H), 7.04-7.11 (m, 2H), 7.20-7.31 (m, 6H), 8.54 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.7, 22.6, 29.1, 30.3, 32.8, 40.7, 57.4, 77.2, 110.6, 123.1, 124.3, 127.0, 127.4, 128.6, 129.3, 129.7, 135.6, 140.4, 177.1; The ee value was 98%, $[\alpha]^{27}{}_D$ = -22.1 (c = 1.05, CH_2Cl_2), t_R (minor) = 7.89 min, t_R (major) = 6.72 min (Chiralcel IC, λ = 254 nm, 20% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{21}H_{23}N_2O_3S$ $[M-H]^-$ = 383.1435, found = 383.1441.

(*R*)-3-(Benzylthio)-3-((*S*)-1-nitro-4-phenylbutan-2-yl)indolin-2-one **5-17o**



5-17o

A light yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.47-1.55 (m, 1H), 1.69-1.76 (m, 1H), 2.50-2.61 (m, 2H), 3.33-3.38 (m, 1H), 3.94 (d, *J* = 12.0 Hz, 1H), 4.04 (d, *J* = 12.0 Hz, 1H), 4.63 (dd, *J* = 8.8 Hz, 13.3 Hz, 1H), 5.52 (dd, *J* = 2.8 Hz, 12.9 Hz, 1H), 6.94 (d, *J* = 7.6 Hz, 1H), 7.01-7.08 (m, 2H), 7.12-7.31 (m, 11H), 8.65 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 32.6, 32.8, 33.4, 40.7, 57.3, 77.1, 110.8, 123.2, 124.4, 126.2, 126.8, 127.5, 128.2, 128.4, 128.6, 129.3, 129.9, 135.6, 140.4, 140.6, 177.0; The ee value was 98%, $[\alpha]^{27}_{D}$ = -28.8 (c = 1.05, CH_2Cl_2), t_R (minor) = 10.42 min, t_R (major) = 11.81 min (Chiralcel IB, λ = 254 nm, 20% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{25}H_{23}N_2O_3S$ $[M-H]^-$ = 431.1435, found = 431.1442.

Chapter 6 Enantioselective Conjugate Addition of 3-Fluoro-Oxindoles to Vinyl Sulfone: An Organocatalytic Access to Chiral 3-Fluoro-3-substituted Oxindoles

6.1 Introduction

Fluorinated molecules are of great importance in pharmaceutical industry, and their distinctive characteristics are mainly due to unique properties of the fluorine atom and resulting C–F bonds.[1] Not surprisingly, asymmetric synthesis of fluorinated molecules has drawn enormous attention from synthetic community in recent years.[2]

Oxindoles are widely present in natural products and bioactive molecules, and oxindoles bearing a 3-fluorinated quaternary stereogenic center are structural motifs that have important applications in pharmaceutical industry.[3] Various synthetic strategies have been devised to target this important molecular structure over the years. In 2001, Shibata et al. described an enantioselective fluorination strategy by using a combination of stoichiometric amounts of cinchona alkaloid and Selectfluor.[4] Shortly after, the Shibata group, and the Cahard group, independently reported an asymmetric synthesis of BMS-204352 (Figure 6.1) by using a stoichiometric amount of cinchona

[1] For general reviews on fluorinated compounds in medicinal chemistry, see a) K. Muller, C. Faeh, F. Diederich, *Science*, **2007**, *317*, 1881; b) K. L. Kirk, *Org. Process. Res. Dev.*, **2008**, *12*, 305.
[2] For reviews, see: a) H. Ibrahim, A. Togni, *Chem. Commun.*, **2004**, 1147; b) K. Mikami, Y. Itoh, M. Yamanaka, *Chem. Rev.*, **2004**, *104*, 1; c) M. Oestreich, *Angew. Chem. Int. Ed.*, **2005**, *44*, 2324; d) P. M. Pihko, *Angew. Chem. Int. Ed.*, **2006**, *45*, 544; e) G. K. S. Prakash, P. Beier, *Angew. Chem. Int. Ed.*, **2006**, *45*, 2172; f) V. A. Brunet, D. O'Hagan, *Angew. Chem. Int. Ed.*, **2008**, *47*, 1179; g) J.-A. Ma, D. Cahard, *Chem. Rev.*, **2008**, *108*, 1; h) C. Hollingworth, V. Gouverneur, *Chem. Commun.*, **2012**, *48*, 2929.
[3] a) V. K. Gribkff, J. E. Starrett Jr., S. L. Dworetzky, P. Hewawasam, C. G. Boissard, D. A. Cook, S. W. Frantz, K. Heman, J. R. Hibbard, K. Huston, G. Johnson, B. S. Krishnan, G. G. Kinney, L. A. Lombardo, N. A. Meanwell, P. B. Molinoff, R. A. Myers, S. L. Moon, A. Ortiz, L. Pajor, R. L. Pieschl, D. J. Post-Munson, L. J. Signor, N. Srinivas, M. T. Taber, G. Thalody, J. T. Trojnacki, H. Wiener, K. Yeleswaram, S. W. Yeola, *Nat. Med. (N. Y.)*, **2001**, *7*, 471; b) P. Hewawasam, V. K. Gribkoff, Y. Pendri, S. I. Dworetzky, N. A. Meanwell, E. Martinez, C. G. Boissard, D. J. Post-Munson, J. T. Trojnacki, K. Yeleswaram, L. M. Pajor, J. Knipe, Q. Gao, R. Perrone, J. E. Starrett Jr., *Bioorg. Med. Chem. Lett.*, **2002**, *12*, 1023.
[4] N. Shibata, E. Suzuki, T. Asahi, M. Shiro, *J. Am. Chem. Soc.*, **2001**, *123*, 7001.

alkaloid-derived fluorinating reagent.[5] Metal-based catalytic systems have been developed recently for the asymmetric fluorination of oxindoles, including: Shibata's dbfoxPh/Ni(II) complex, [6] Sodeoka's (*S*)-DM-BINAP-Pd complex, [7] Gade's boxmi-Ni(II),[8] Feng's Sc(III)-*N,N'*-dioxide complex,[9] and Dorta's chiral NHC-Pd complex. [10] On the other hand, advance of organocatalytic enantioselective fluorination methods lagged well behind compared with their transition metal counterparts. To the best of our knowledge, there is only one such report in the literature. Shibata and co-workers employed bis-cinchona alkaloid as the catalyst to achieve enantioselective fluorination of oxindoles.[11] The reported reaction, however, suffered from long reaction time, and there was also room for the improvement of enantioselectivity.

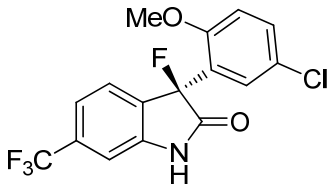


Figure 6.1 Structure of BMS-204352

Recently, organocatalytic synthetic methods utilizing fluorinated substrates for the C–C bond formation have been shown to a viable approach for the synthesis of chiral fluorine-containing molecules. The true advantage of this approach is that challenging asymmetric construction of C–F bond is turned into C–C bond formation,

[5] a) N. Shibata, T. Ishimaru, E. Suzuki, K. L. Kirk, *J. Org. Chem.*, **2003**, *68*, 2494; b) L. Zoute, C. Audouard, J.-C. Plaquevent, D. Cahard, *Org. Biomol. Chem.*, **2003**, *1*, 1833.
[6] N. Shibata; J. Kohno, K. Takai, T. Ishimaru, S. Nakamura, T. Toru, S. Kanemasa, *Angew. Chem. Int. Ed.*, **2005**, *44*, 4204.
[7] Y. Hamashima, T. Suzuki, H. Takano, Y. Shimura, M. Sodeoka, *J. Am. Chem. Soc.*, **2005**, *127*, 10164.
[8] Q.-H. Deng, H. Wadepohl, L. H. Gade, *Chem. Eur. J.*, **2011**, *17*, 14922.
[9] J. Li, Y. Cai, W. Chen, X. Liu, L. Lin, X. Feng, *J. Org. Chem.*, **2012**, *77*, 9148.
[10] L. Wu, L. Falivene, E. Drinkel, S. Grant, A. Linden, L. Cavallo, R. Dorta, *Angew. Chem. Int. Ed.*, **2012**, *51*, 2870.
[11] T. Ishimaru, N. Shibata, T. Horikawa, N. Yasuda, S. Nakamura, T. Toru, M. Shiro, *Angew. Chem. Int. Ed.*, **2008**, *47*, 4157.

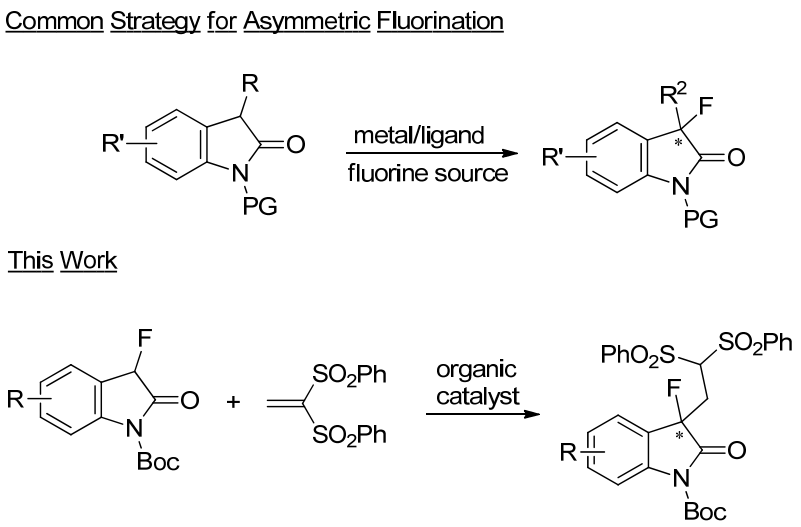
which is very well studied and much easier to control in modern organic synthesis. In this context, we and others have developed a range of asymmetric reactions for the synthesis of fluorine-containing stereogenic centers using fluorinated pronucleophiles.[12] To align with our interest of synthesizing biologically important structural scaffolds containing a quaternary stereogenic center, we became interested in developing an efficient strategy to access 3-fluoro-3-substituted oxindoles. Vinyl sulfones are valuable acceptors for conjugate addition reactions, mainly due to the high electron withdrawing ability of the sulfone group, and a variety of well-established post-synthetic manipulations of the sulfone functionality.[13] Our group has recently developed a number of asymmetric conjugate additions by utilizing vinyl sulfones as an acceptor.[14] We envisioned that a conjugate addition of 3-fluoro-substituted oxindoles to 1,1-bis(benzenesulfonyl)ethylene may represent a straightforward method to access enantiomerically enriched 3-fluoro-3-substituted oxindoles (Scheme 6.1). In this communication, we document the first organocatalytic

[12] a) X. Han, J. Luo, C. Liu, Y. Lu, *Chem. Commun.*, **2009**, 2044; b) H. Li, S. Zhang, C. Yu, X. Song, W. Wang, *Chem. Commun.*, **2009**, 2044; c) Z. Jiang, Y. Pan, Y. Zhao, T. Ma, R. Lee, Y. Yang, K.-W. Huang, M. W. Wang, C.-H. Tan, *Angew. Chem. Int. Ed.*, **2009**, *48*, 3627; d) X. Han, J. Kwiatkowski, F. Xue, K.-W. Huang, Y. Lu, *Angew. Chem. Int. Ed.*, **2009**, *48*, 7604; e) G. K. S. Prakash, F. Wang, T. Stewart, T. Mathew, G. A. Olah, *Proc. Natl. Acad. Sci. USA*, **2009**, *106*, 4090; f) B. K. Kwon, S. M. Kim, D. Y. Kim, *J. Fluorine Chem.*, **2009**, *130*, 759; g) C. Ding, K. Maruoka, *Synlett*, **2009**, *4*, 664; h) X. Han, F. Zhong, Y. Lu, *Adv. Synth. Catal.*, **2010**, *352*, 2778; i) M. Kamlar, N. Bravo, A.-N. R. Alba, S. Hybelbauerová, I. Císarová, J. Veselý, A. Moyano, R. Rios, *Eur. J. Org. Chem.*, **2010**, 5464; j) S. Hong, J. Lee, M. Kim, Y. Park, C. Park, M. Kim, S. Jew. H. Park, *J. Am. Chem. Soc.*, **2011**, *133*, 4924; k) Y. Pan, Y. Zhao, T. Ma, Y. Yang, H. Liu, Z. Jiang, C.-H. Tan, *Chem. Eur. J.*, **2010**, *16*, 779; l) H.-F. Cui, P. Li, X.-W. Wang, S.-Z. Zhu, G. Zhao, *J. Fluorine Chem.*, **2012**, *133*, 120.

[13] For reviews, see: a) N. S. Simpkins, *Tetrahedron*, **1990**, *44*, 6951; b) C. Najera, M. Yus, *Tetrahedron*, **1999**, *55*, 10547; c) M. Nielsen, C. B. Jacobsen, N. Holub, M. W. Paixão, K. A. Jørgesen, *Angew. Chem., Int. Ed.,* **2010**, *49*, 2668; d) Q. Zhu, Y. Lu, *Aus. J. Chem.,* **2009**, *62*, 951. For recent examples, see: e) H. Li, J. Song, X. Liu, L. Deng, *J. Am. Chem. Soc.,* **2005**, *127*, 8948; f) H. Li, J. Song, L. Deng, *Tetrahedron,* **2009**, *65*, 3139; g) S. Mossé, A. Alexakis, *Org. Lett.,* **2005**, *7*, 4361; h) A. Quintard, C. Bournaud, A. Alexakis, *Chem. Eur. J.,* **2008**, *14*, 7504; i) A. Quintard, A. Alexakis, *Chem. Eur. J.,* **2009**, *15*, 11109; j) S. Sulzer-Mossé, A. Alexakis, J. Mareda, G. Bollot, G. Bernardinelli, Y. Filinchuk, *Chem. Eur. J.,* **2009**, *15*, 3204; k) A. Quintard, S. Belot, M. Sebastien, E. Marchal, A. Alexakis, *Eur. J. Org. Chem.,* **2010**, 927; l) A. Quintard, A. Alexakis, *Chem. Commun.,* **2010**, *46*, 4085; m) A. Landa, M. Maestro, C. Masdeu, A. Puente, S. Vera, M. Oiarbide, C. Palomo, *Chem. Eur. J.,* **2009**, *15*, 1562; n) T. -Y. Liu, J. Long, B. -J. Li, L. Jiang, R. Li, Y. Wu, L. -S. Ding, Y. -C. Chen, *Org. Biomol. Chem.,* **2006**, *4*, 2097; o) A.-N. R.Alba, X. Companyo, G. Valero, A. Moyano, R. Rios, *Chem. Eur. J.,* **2010**, *16*, 5354.

[14] a) Q. Zhu, Y. Lu, *Org. Lett.,* **2008**, *10*, 4803; b) Q. Zhu, L. Cheng, Y. Lu, *Chem. Commun.,* **2008**, 6315; c) Q. Zhu, Y. Lu, *Org. Lett.,* **2009**, *11*, 1721; d) Q. Zhu, Y. Lu, *Chem. Commun.,* **2010**, *46*, 2235; e) Q. Zhu, Y. Lu, *Angew. Chem. Int. Ed.,* **2010**, *49*, 7753.

asymmetric conjugate addition of 3-fluoro-substituted oxindoles to a vinyl sulfone.



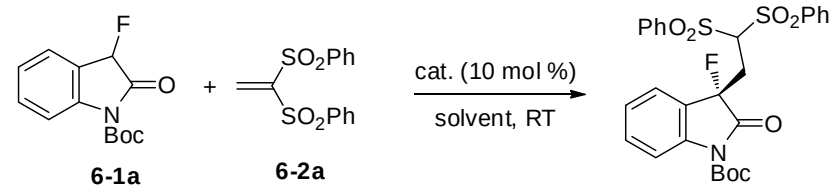
Scheme 6.1 Catalytic asymmetric synthesis of 3-fluoro-3-substituted oxindoles

6.2 Results and Discussion

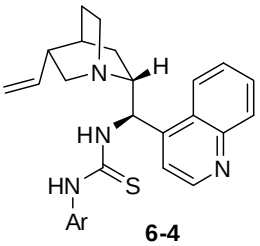
6.2.1 Reaction Optimization

To promote the projected conjugate addition, tertiary amine catalysts with a Brønsted acid moiety are apparently excellent choice. We chose conjugate addition of 3-fluorinated oxindole **6-1a** to vinyl sulfone **6-2a** as a model reaction, and examined the catalytic effects of a number of tertiary amine (thio)urea catalysts. The results are summarized in Table 6.1.

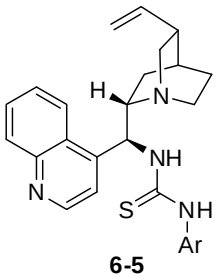
Table 6.1 Conjugate Addition of 3-Fluorooxindole **6-1a** to Vinyl Sulfone **6-2a** Catalyzed by Different Organic Catalysts[a]



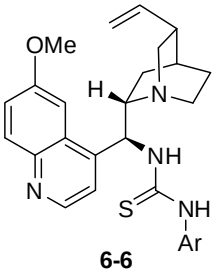
6-1a **6-2a** **6-3a**



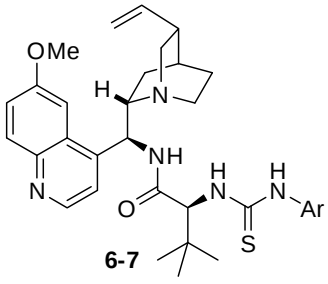
6-4



6-5

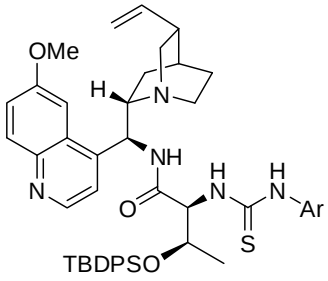


6-6

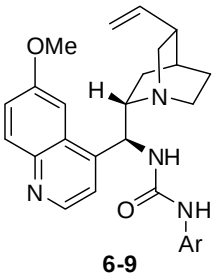


6-7

Ar = 3,5-$CF_3C_6H_3$



6-8



6-9

entry	cat.	solvent	t (min)	yield (%)[b]	ee (%)[c]
1	**6-4**	toluene	30	>95	-68
2	**6-5**	toluene	10	>95	81
3	**6-6**	toluene	5	>95	84
4	**6-7**	toluene	5	54	86
5	**6-8**	toluene	5	52	85
6	**6-9**	toluene	5	>95	69
7[d]	**6-6**	toluene	8	>95	86
8[d,e]	**6-6**	toluene	60	>95	80
9[d]	**6-6**	xylene	10	>95	81
10[d]	**6-6**	THF	60	>95	82
11[d]	**6-6**	CH_2Cl_2	30	>95	87
12[d]	**6-6**	$CHCl_3$	15	>95	90
13[d]	**6-6**	DCE	15	>95	83
14[d,f]	**6-6**	$CHCl_3$	15	>95	91

15[d,g]	**6-6**	$CHCl_3$	15	>95	93
16[d,h]	**6-6**	$CHCl_3$	15	>95	92
17[d,g,i]	**6-6**	$CHCl_3$	25	>95	93
18[d,g,j]	**6-6**	$CHCl_3$	120	>95	90

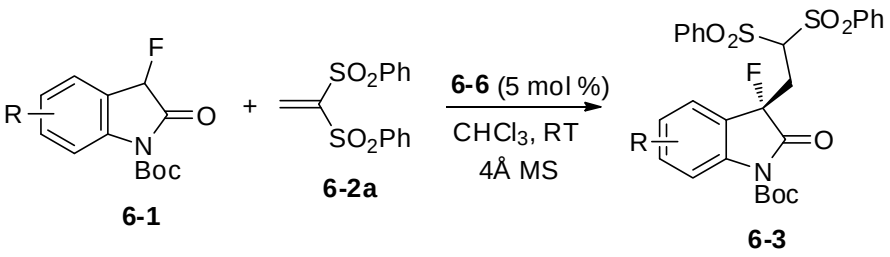
[a] Reactions were performed with **6-1a** (0.05 mmol), **6-2a** (0.05 mmol) and the catalyst (0.005 mmol) in solvent (0.5 mL) at room temperature. [b] Isolated yield. [c] Determined by HPLC analysis on a chiral stationary phase. [d] 1.0 mL solvent was used. [e] Reaction was performed at 0 °C. [f] 3Å Molecular sieves (10 mg) was added. [g] 4Å Molecular sieves (10 mg) was added. [h] 5Å Molecular sieves (10 mg) was added. [i] Catalyst loading was 5 mol %. [j] Catalyst loading was 2 mol %.

Cinchonine-derived ficunctional tertiary amine–thiourea catalyst **6-4** was found to be very effective, affording the desired product in excellent yield and with moderate *ee* (entry 1). Cinchonidine and quinine-derived catalysts **6-5** and **6-6** were more efficient, and the reactions proceeded faster and the desired adducts were obtained with higher enantioselectivities (entries 2–3). When our multifunctional catalysts were employed, slightly higher *ee* values could be obtained, the reaction, however, suffered from low yield (entries 4–5). Quinine-derived tertiary amine urea **6-9** proved to be inferior to catalyst **6-6** (entry 6). Overall, catalyst **6-6** offered the best results. Further optimizations using **6-6** as the catalyst of choice were then performed. Dilution of the reaction mixture was beneficial, and lowering temperature turned out to be detrimental (entries 7–8). Solvent screening revealed that chloroform was the best solvent (entries 9–13). Additive study led to further enhancement; **3a** was obtained in >95% yield and with 93% *ee* when 4 Å molecular sieves were added (entries 14–16). Moreover, the catalyst loading could be reduced to 5 mol % without sacrificing the enantioselectivity (entries 17–18).

6.2.2 Substrate Scope

With the optimal reaction conditions in hand, the substrate scope of this conjugate addition reaction was then investigated. As summarized in Table 6.2, fluorinated oxindoles with diverse substitution groups at different positions were examined, and consistent high yields and enantioselectivities could be obtained. Different halide substitutions on the aromatic ring were well tolerated (entries 2–6), and oxindoles with electron donating substitution groups as well as bis-substituted oxindole were also suitable substrates (entries 7–9). In general, all the reactions went to completion within one hour, affording the desired adducts in high yields and excellent *ee* values. The absolute configurations of the 3-fluoro-3-substituted oxindoles were assigned on the basis of the X-ray crystallographic analysis of **6-3e**.

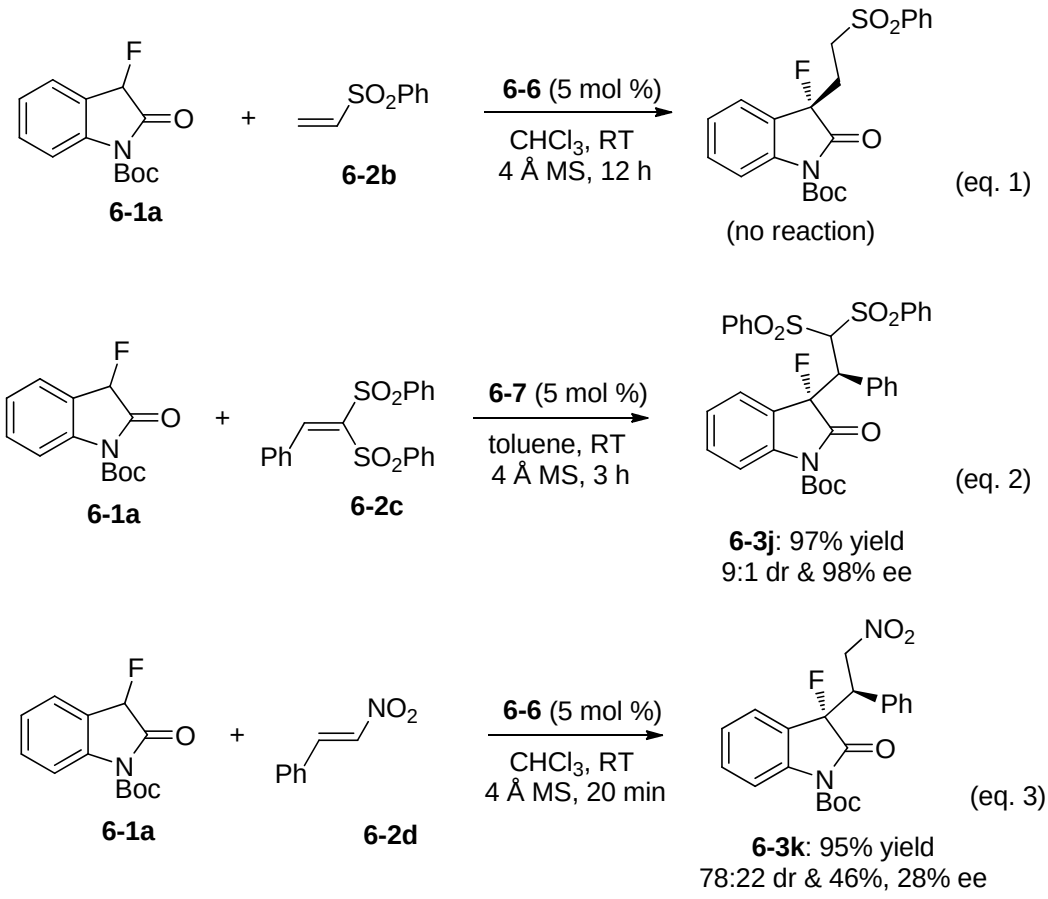
Table 6.2 Substrate Scope of the Conjugate Addition of 3-Fluorooxindoles **6-1** to Vinyl Sulfone **6-2a**[a]



entry	R (**6-3**)	t (min)	yield (%)[b]	ee (%)[c]
1	H (**6-3a**)	25	>95	93
2	5-Cl (**6-3b**)	20	>95	93
3	6-Cl (**6-3c**)	25	>95	91
4	5-Br (**6-3d**)	30	>95	93
5	7-F (**6-3e**)	20	>95	89
6	7-Cl (**6-3f**)	30	>95	87
7	5-Me (**6-3g**)	45	>95	89

8	5-OMe (**6-3h**)	50	>95	90
9	5,7-Me (**6-3i**)	60	>95	89

[a] Reactions were performed with **6-1** (0.05 mmol), **6-2a** (0.05 mmol), **6-6** (0.0025 mmol) and 4Å molecular sieves (10 mg) in $CHCl_3$ (1.0 mL) at room temperature. [b] Isolated yield. [c] Determined by HPLC analysis on a chiral stationary phase.



Scheme 6.2 Reaction of 3-fluorooxindole with different electrophiles

Different electrophiles were also tested. Olefin **6-2b** with mono-sulfone activation was found to be unsuitable for the reaction (eq. 1). Substituted vinyl sulfone **6-2c** was a good substrate. In the presence of multifunctional catalyst **6-7**, the conjugate addition of **6-1a** to **6-2b** took place readily, affording the desired product in high yield, with high dr and near perfect *ee* value (eq. 2). Although mono-sulfone activated olefin showed no reactivity, mono-activated nitroolefin was reactive enough and applicable as the Michael acceptor. Bifunctional catalyst **6-6** catalyzed Michael

addition of 3-fluoro-oxindole **6-1a** to nitroolefin **6-2d** completed in twenty minutes and afforded the Michael product in high yield, moderate diastereoselectivity and enantioselectivity (eq. 3).

6.3. Conclusions

In summary, we have developed the first asymmetric conjugate addition of 3-fluoro oxindoles to vinyl sulfones, promoted by tertiary amine~thiourea bifunctional catalysts. The desired 3-fluoro-3-substituted oxindoles were prepared in excellent chemical yields and with very high enantiomeric excesses. The reported method is simple and efficient, representing a promising approach to access biologically important chiral oxindoles containing a 3-fluoro-quaternary stereogenic center.

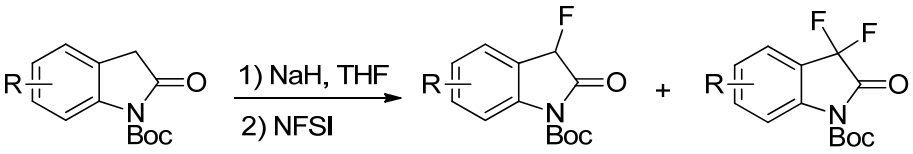
6.4 Experimental Section

6.4.1 Material and General Methods

All the starting materials were obtained from commercial sources and used without further purification unless otherwise stated. THF were dried and distilled from sodium benzophenone ketyl prior to use. $CHCl_3$ and CH_2Cl_2 were distilled from CaH_2 prior to use. ^1H and ^{13}C NMR spectra were recorded on a Bruker ACF300 or AMX500 (500 MHz) spectrometer. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (chloroform δ 7.26), carbon (chloroform δ 77.0). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), br (broad singlet). Coupling constants were reported in Hertz (Hz). Low

resolution mass spectra were obtained on a Finnigan/MAT LCQ spectrometer in ESI mode, and a Finnigan/MAT 95XL- T mass spectrometer in FAB mode. All high resolution mass spectra were obtained on a Finnigan/MAT 95XL- T spectrometer. For thin layer chromatography (TLC), Merck pre- coated TLC plates (Merck 60 F254) were used, and compounds were visualized with a UV light at 254 nm. Further visualization was achieved by staining with iodine, or ceric ammonium molybdate followed by heating on a hot plate. Flash chromatographic separations were performed on Merck 60 (0.040- 0.063 mm) mesh silica gel. The enantiomeric excesses of products were determined by chiral-phase HPLC analysis, using a Daicel Chiralcel IC-H column (250 x 4.6 mm), or Chiralpak OD-H ncolumn, or IA column (250 x 4.6 mm).

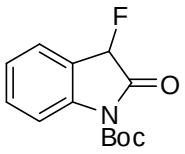
6.4.2 Synthesis of Substrates



The substrates **6-1** were synthesized following the general procudure: Boc-protected oxindole (1 mmol) was dissolved in dry THF (5 mL) under N_2 protection and the solution was cooled to 0 ^oC. NaH (1 mmol) was added and the mixture was stirred at 0 ^oC for 30 min. NFSI (1 mmol) was added to the mixture in one portion and the resulting mixture was stirred at 0 ^oC to room temperature for 15 min. The reaction mixture was quenched by addition of water (10 mL) and the mixture was extracted with CH_2Cl_2 (15 mL×3). The combined organic phase was dried over $MgSO_4$, filtered

and concentrated *in vacuo*, which was purified by flash column chromatography (ethyl acetate/hexane = 1:7) to afford the desired monofluorinated product (38-46% yield), the bisfluorinated side product (8-13% yield) and the recovered Boc-protected oxindole (23-41% recovered).

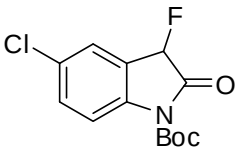
tert-Butyl 3-fluoro-2-oxoindoline-1-carboxylate **6-1a**



6-1a

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.63 (s, 9H), 5.70 (d, *J* = 51.1 Hz, 1H), 7.22 (t, *J* = 7.6 Hz, 1H), 7.43 (t, *J* = 7.9 Hz, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.87 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.0, 85.0 (d, *J* = 187.7 Hz), 85.1, 115.6, 121.8 (d, *J* = 16.4 Hz), 125.0 (d, *J* = 2.7 Hz), 125.9, 131.7 (d, *J* = 2.7 Hz), 140.9 (d, *J* = 4.6 Hz), 148.7, 169.0 (d, *J* = 17.3 Hz); ^{19}F NMR (282.38 MHz, $CDCl_3$) δ -111.1 (d, *J* = 51.6 Hz); HRMS (ESI) m/z calcd for $C_{13}H_{14}FNO_3Na$ $[M+Na]^+$ = 274.0850, found = 274.0860.

tert-Butyl 5-chloro-3-fluoro-2-oxoindoline-1-carboxylate **6-1b**

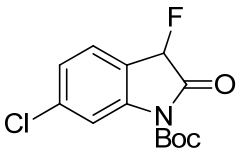


6-1b

A white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.63 (s, 9H), 5.68 (d, *J* = 50.9 Hz, 1H), 7.40-7.44 (m, 1H), 7.48 (s, 1H), 7.85 (dd, *J* = 1.3 Hz, 8.7 Hz, 1H); ^{13}C NMR (125

MHz, $CDCl_3$) δ 28.0, 84.6 (d, *J* = 190.4 Hz), 85.4, 117.0, 123.3 (d, *J* = 16.4 Hz), 126.1, 130.6 (d, *J* = 2.7 Hz), 131.7 (d, *J* = 2.7 Hz), 139.4 (d, *J* = 4.6 Hz), 148.5, 168.1 (d, *J* = 18.2 Hz); ^{19}F NMR (282.38 MHz, $CDCl_3$) δ -112.2 (d, *J* = 52.6 Hz); HRMS (ESI) m/z calcd for $C_{13}H_{13}FClNO_3Na$ $[M+Na]^+$ = 308.0460, found = 308.0452.

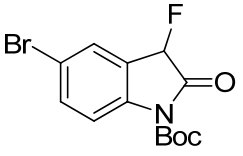
tert-Butyl 6-chloro-3-fluoro-2-oxoindoline-1-carboxylate **6-1c**



6-1c

A white solid; ^1H NMR (300 MHz, $CDCl_3$) δ 1.64 (s, 9H), 5.68 (d, *J* = 51.1 Hz, 1H), 7.21-7.24 (m, 1H), 7.43 (dd, *J* = 1.1 Hz, 7.9 Hz, 1H), 7.97 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.0, 84.4 (d, *J* = 189.5 Hz), 85.6, 116.5, 120.0 (d, *J* = 16.4 Hz), 125.2 (d, *J* = 2.7 Hz), 126.8, 137.8 (d, *J* = 3.7 Hz), 141.9 (d, *J* = 4.6 Hz), 148.4, 168.4 (d, *J* = 18.2 Hz); ^{19}F NMR (282.38 MHz, $CDCl_3$) δ -110.8 (d, *J* = 51.6 Hz); HRMS (ESI) m/z calcd for $C_{13}H_{13}FClNO_3Na$ $[M+Na]^+$ = 308.0460, found = 308.0452.

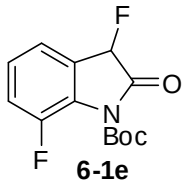
tert-Butyl 5-bromo-3-fluoro-2-oxoindoline-1-carboxylate **6-1d**



6-1d

A white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.63 (s, 9H), 5.69 (d, *J* = 50.9 Hz, 1H), 7.55-7.59 (m, 1H), 7.63 (s, 1H), 7.76-7.82 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.0, 84.4 (d, *J* = 190.4 Hz), 85.5, 117.1, 117.3, 123.6 (d, *J* = 16.4 Hz), 128.9 (d, *J* = 34.6 Hz), 134.7 (d, *J* = 3.7 Hz), 139.9, 148.5, 168.1 (d, *J* = 21.0 Hz); ^{19}F NMR (282.38 MHz, $CDCl_3$) δ -112.1 (dd, *J*= 2.1 Hz, 27.3 Hz); HRMS (ESI) m/z calcd for $C_{13}H_{13}F^{79}BrNO_3Na$ $[M+Na]^+$ = 351.9951, found = 351.9926, $C_{13}H_{13}F^{81}BrNO_3Na$ $[M+Na]^+$ = 353.9937, found = 353.9918.

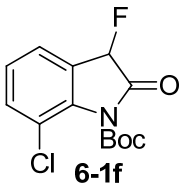
tert-Butyl 3,7-difluoro-2-oxoindoline-1-carboxylate **6-1e**



6-1e

A white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.61 (s, 9H), 5.75 (d, *J* = 50.8 Hz, 1H), 7.17-7.24 (m, 2H), 7.31-7.34 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.6, 76.5, 84.6 (d, *J* = 160.4 Hz), 86.1 (d, *J* = 2.2 Hz), 119.8 (d, *J* = 3.3 Hz), 120.1 (d, *J* = 2.7 Hz), 121.8 (d, *J* = 3.3 Hz), 124.7 (d, *J* = 15.3 Hz), 126.2 (d, *J* = 2.7 Hz), 126.3, 146.7 (d, *J* = 14.2 Hz), 150.2, 168.4 (d, *J* = 18.5 Hz); ^{19}F NMR (282.38 MHz, $CDCl_3$) δ -111.0 (d, *J* = 50.5 Hz), (-42.2) (t, *J* =7.2 Hz); HRMS (ESI) m/z calcd for $C_{13}H_{13}F_2NO_3Na$ $[M+Na]^+$ = 292.0761, found = 292.0753.

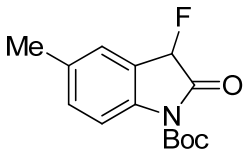
tert-Butyl 7-chloro-3-fluoro-2-oxoindoline-1-carboxylate **6-1f**



6-1f

A white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.63 (s, 9H), 5.74 (d, *J* = 50.8 Hz, 1H), 7.15-7.21 (m, 1H), 7.41-7.44 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.7, 85.1 (d, *J* = 191.3 Hz), 86.3, 119.5, 124.5, 125.0 (d, *J* = 21.9 Hz), 125.8, 133.3, 138.2, 147.1, 169.2 (d, *J* = 20.0 Hz); ^{19}F NMR (282.38 MHz, $CDCl_3$) δ -112.5 (d, *J* = 50.5 Hz); HRMS (ESI) m/z calcd for $C_{13}H_{13}FClNO_3Na$ $[M+Na]^+$ = 308.0460, found = 308.0452.

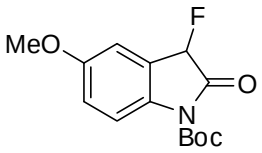
tert-Butyl 3-fluoro-5-methyl-2-oxoindoline-1-carboxylate **6-1g**



6-1g

A colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.63 (s, 9H), 2.37 (s,3H), 5.68 (d, *J* = 51.3 Hz, 1H), 7.24 (d, *J* = 8.4 Hz, 1H), 7.31 (s, 1H), 7.74 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8, 28.0, 84.8, 85.1 (d, *J* = 187.6 Hz), 115.3 (d, *J* = 1.6 Hz), 121.6 (d, *J* = 16.4 Hz), 126.3, 132.1 (d, *J* = 3.3 Hz), 134.8 (d, *J* = 2.7 Hz), 138.4 (d, *J* = 5.5 Hz), 148.6, 169.0 (d, *J* = 17.5 Hz); ^{19}F NMR (282.38 MHz, $CDCl_3$) δ -110.8 (d, *J* = 51.6 Hz); HRMS (ESI) m/z calcd for $C_{14}H_{16}FNO_3Na$ $[M+Na]^+$ = 288.1006, found = 288.1020.

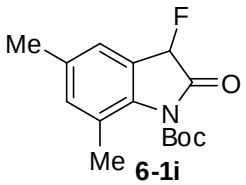
tert-Butyl 3-fluoro-5-methoxy-2-oxoindoline-1-carboxylate **6-1h**



6-1h

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.63 (s, 9H), 3.83 (s,3H), 5.69 (d, *J* = 51.1 Hz, 1H), 6.95-6.98 (m, 1H), 7.06 (s, 1H), 7.79 (dd, *J* = 1.3 Hz, 8.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.1, 55.8, 84.9, 85.2 (d, *J* = 188.6 Hz), 111.4, 116.7, 117.0 (d, *J* = 3.6 Hz), 122.8 (d, *J* = 16.4 Hz), 134.1 (d, *J* = 3.6 Hz), 148.7, 157.2 (d, *J* = 3.7 Hz), 169.0 (d, *J* = 19.1 Hz); ^{19}F NMR (282.38 MHz, $CDCl_3$) δ -111.4 (t, *J* = 25.8 Hz); HRMS (ESI) m/z calcd for $C_{14}H_{16}FNO_4Na$ $[M+Na]^+$ = 304.0956, found = 304.0965.

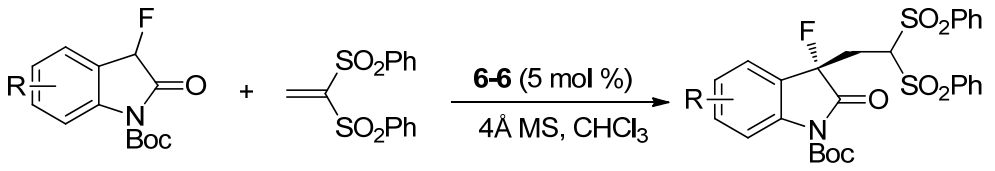
tert-Butyl 3-fluoro-5,7-dimethyl-2-oxoindoline-1-carboxylate **6-1i**



6-1i

A white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.62 (s, 9H), 2.19 (s, 3H), 2.32 (s, 3H), 5.67 (d, *J* = 51.3 Hz, 1H), 7.05 (s, 1H), 7.14 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.3, 20.7, 27.7, 85.1, 85.6 (d, *J* = 188.7 Hz), 123.0 (d, *J* = 16.4 Hz), 124.0, 124.2 (d, *J* = 1.6 Hz), 134.7 (d, *J* = 3.3 Hz), 135.0 (d, *J* = 3.3 Hz), 136.8 (d, *J* = 4.9 Hz), 148.5, 170.1 (d, *J* = 17.5 Hz); ^{19}F NMR (282.38 MHz, $CDCl_3$) δ -110.6 (d, *J* = 51.6 Hz); HRMS (ESI) m/z calcd for $C_{15}H_{17}FNO_3$ $[M-H]^-$ = 278.0810, found = 278.0818.

6.4.3 Representative Procedure for the Conjugate Addition Reactions



6-1 **6-2a** **6-3**

Oxindole **6-1** (0.05 mmol) was at room temperature added to a mixture of vinylsulfone **6-2a** (0.05 mmol), catalyst **6-6** (1.5 mg, 0.0025 mmol) and 4 Å molecular sieves (10 mg) in $CHCl_3$ (1.0 mL) in a sample vial, and the resulting mixture was sealed and stirred at room temperature for the time specified in Table 6.2. At the end of the reaction, the reaction mixture was filtered and concentrated *in vacuo* to yield the crude product, which was purified by flash column chromatography (ethyl acetate/hexane = 1:2) to afford the desired adducts **6-3**. The enantiomeric excessess of **6-3** were determined by chiral HPLC analysis.

6.4.4 X-Ray Crystallographic Analysis and Determination of Configurations of the Conjugate Addition Products

The absolute configuration of the product **6-3e** was assigned based on the X-ray crystallographic analysis of a single crystal of **6-3e** (Figure 6.2). The configurations of other products **6-3** were assigned by analogy.

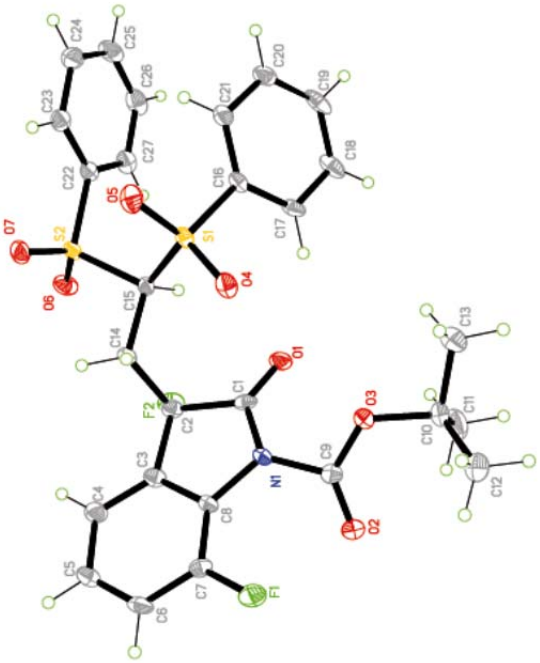


Figure 6.2 X-ray structure of **6-3e**

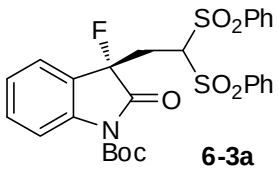
Table 6.3 Crystal Data and Structure Refinement for c009.

Identification code	c009	
Empirical formula	C_{27} H_{25} F_2 N O_7 S_2	
Formula weight	577.60	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 8.2718(7) Å	□= 90°.
	b = 13.6799(13) Å	□= 90°.
	c = 23.831(2) Å	□ = 90°.
Volume	2696.7(4) $Å^3$	
Z	4	

Density (calculated)	1.423 Mg/m^3
Absorption coefficient	0.258 mm^{-1}
F(000)	1200
Crystal size	0.60 x 0.20 x 0.08 mm^3
Theta range for data collection	1.71 to 27.50°.
Index ranges	-10<=h<=10, -17<=k<=14, -28<=l<=30
Reflections collected	19152
Independent reflections	6196 [R(int) = 0.0465]
Completeness to theta = 27.50°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7457 and 0.6628
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6196 / 0 / 355
Goodness-of-fit on F^2	1.028
Final R indices [I>2sigma(I)]	R1 = 0.0402, wR2 = 0.0883
R indices (all data)	R1 = 0.0458, wR2 = 0.0910
Absolute structure parameter	0.12(6)
Largest diff. peak and hole	0.472 and -0.260 $e.Å^{-3}$

6.4.5 Analytical Data of the Conjugate Addition Products

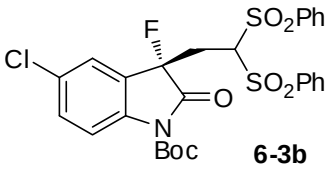
(*S*)-*tert*-Butyl 3-(2,2-bis(phenylsulfonyl)ethyl)-3-fluoro-2-oxoindoline-1-carboxylate **6-3a**



6-3a

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.62 (s, 9H), 3.00-3.08 (m, 1H), 3.10-3.23 (m, 1H), 5.38 (t, *J* = 4.4 Hz, 1H), 7.24 (d, *J* = 7.6 Hz, 1H), 7.36 (d, *J* = 7.6 Hz, 1H), 7.48 (t, *J* = 7.9 Hz, 1H), 7.51-7.58 (m, 4H), 7.65-7.71 (m, 2H), 7.86 (d, *J* = 7.6 Hz, 2H), 7.93 (d, *J* = 8.2 Hz, 1H), 8.01-8.03 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.0, 31.2 (d, *J* = 31.0 Hz), 76.8, 85.0, 89.2 (d, *J* = 189.5 Hz), 116.1, 123.7 (d, *J* = 18.2 Hz), 124.0, 125.2, 129.1 (d, *J* = 23.7 Hz), 129.7 (d, *J* = 1.8 Hz), 132.2 (d, *J* = 2.7 Hz), 134.6 (d, *J* = 30.1 Hz), 137.0, 138.3, 140.0 (d, *J* = 4.6 Hz), 148.3, 170.1 (d, *J* = 22.8 Hz); ^{19}F NMR (282.38 MHz, $CDCl_3$) δ -75.6 (dd, *J* = 11.3 Hz, 32.0 Hz); The ee value was 93%, t_R (minor) = 17.52 min, t_R (major) = 20.04 min (Chiralcel AD-H, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{27}H_{26}FNO_7S_2Na$ $[M+Na]^+$ = 582.1027, found = 582.1025; $[\alpha]^{27}_D$ = +21.2 (c = 0.95, $CHCl_3$).

(*S*)-*tert*-Butyl-3-(2,2-bis(phenylsulfonyl)ethyl)-5-chloro-3-fluoro-2-oxoindoline-1-carboxylate **6-3b**

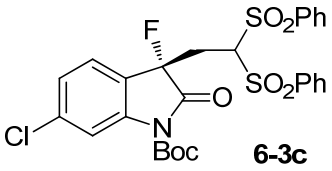


6-3b

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.62 (s, 9H), 2.98-3.09 (m, 1H), 3.13-3.19 (m, 1H), 5.32 (t, *J* = 4.4 Hz, 1H), 7.30 (t, *J* = 1.9 Hz, 1H), 7.45 (d, *J* = 8.2 Hz, 1H), 7.54-7.59 (m, 4H), 7.68-7.72 (m, 2H), 7.88-7.92 (m, 3H), 8.02 (d, *J* = 8.2 Hz, 1H); ^{13}C

NMR (125 MHz, $CDCl_3$) δ 28.0, 31.3 (d, *J* = 31.0 Hz), 85.4, 88.9 (d, *J* = 192.3 Hz), 117.6, 124.2, 125.3 (d, *J* = 18.2 Hz), 129.2 (d, *J* = 23.7 Hz), 129.7 (d, *J* = 10.9 Hz), 130.8 (d, *J* = 2.7 Hz), 132.2 (d, *J* = 1.8 Hz), 134.7 (d, *J* = 31.9 Hz), 136.8, 138.3, 138.5 (d, *J* = 4.6 Hz), 148.2, 169.5 (d, *J* = 22.8 Hz); ^{19}F NMR (282.38 MHz, $CDCl_3$) δ -76.5 (dd, *J* = 11.9 Hz, 31.4 Hz); The ee value was 93%, t_R (minor) = 14.51 min, t_R (major) = 15.43 min (Chiralcel AD-H, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{27}H_{25}FClNO_7S_2Na$ $[M+Na]^+$ = 616.0637, found = 616.0613; $[\square]^{27}_D$ = +23.4 (c = 1.20, $CHCl_3$).

(*S*)-*tert*-Butyl-3-(2,2-bis(phenylsulfonyl)ethyl)-6-chloro-3-fluoro-2-oxoindoline-1-carboxylate **6-3c**

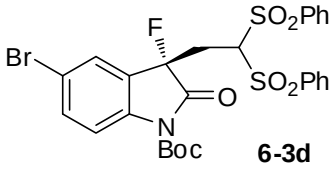


6-3c

A white solid; ^1H NMR (300 MHz, $CDCl_3$) δ 1.62 (s, 9H), 2.94-3.23 (m, 2H), 5.33 (t, *J* = 4.5 Hz, 1H), 7.22-7.32 (m, 2H), 7.51-7.59 (m, 4H), 7.65-7.73 (m, 2H), 7.84-7.87 (m, 2H), 7.99-8.03 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.0, 31.3 (d, *J* = 31.9 Hz), 76.8, 85.6, 89.0 (d, *J* = 190.4 Hz), 117.0, 122.1 (d, *J* = 19.1 Hz), 125.0, 125.4 (d, *J* = 2.7 Hz), 129.2 (d, *J* = 23.7 Hz), 129.7 (d, *J* = 2.7 Hz), 134.7 (d, *J* = 28.2 Hz), 137.1, 138.3, 138.4 (d, *J* = 3.7 Hz), 141.0 (d, *J* = 4.6 Hz), 148.2, 169.7 (d, *J* = 22.8 Hz); ^{19}F NMR (282.38 MHz, $CDCl_3$) δ -75.2 (dd, *J* = 11.4 Hz, 32.0 Hz); The ee value was 91%, t_R (minor) = 17.20 min, t_R (major) = 20.55 min (Chiralcel IA, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{27}H_{25}FClNO_7S_2Na$ $[M+Na]^+$ = 616.0637, found =

616.0613; $[\alpha]^{27}_D$ = +16.0 (c = 0.80, $CHCl_3$).

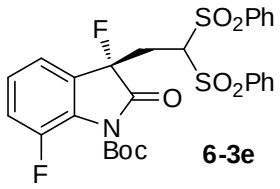
(*S*)-*tert*-Butyl-3-(2,2-bis(phenylsulfonyl)ethyl)-5-bromo-3-fluoro-2-oxoindoline-1-carboxylate **6-3d**



6-3d

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.62 (s, 9H), 2.99-3.19 (m, 2H), 5.30 (t, *J* = 4.7 Hz, 1H), 7.44 (t, *J* = 1.9 Hz, 1H), 7.55-7.62 (m, 5H), 7.68-7.73 (m, 2H), 7.85-7.90 (m, 3H), 8.01-8.03 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.0, 31.3 (d, *J* = 31.0 Hz), 85.5, 88.9 (d, *J* = 191.3 Hz), 117.9, 118.1 (d, *J* = 2.7 Hz), 125.7 (d, *J* = 17.3 Hz), 127.0, 129.2 (d, *J* = 22.8 Hz), 129.7 (d, *J* = 14.6 Hz), 134.8 (d, *J* = 32.8 Hz), 135.2, 136.8, 138.3, 139.1 (d, *J* = 5.5 Hz), 148.2, 169.4 (d, *J* = 21.9 Hz); ^{19}F NMR (282.38 MHz, $CDCl_3$) δ -76.2 (dd, *J* = 12.4 Hz, 32.0 Hz); The ee value was 93%, t_R (minor) = 15.53 min, t_R (major) = 17.34 min (Chiralcel IA, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{27}H_{25}F^{79}BrNO_7S_2Na$ $[M+Na]^+$ = 660.0132, found = 660.0109, $C_{27}H_{25}F^{81}BrNO_7S_2Na$ $[M+Na]^+$ = 662.0112, found = 662.0091; $[\alpha]^{27}_D$ = +15.5 (c = 0.75, $CHCl_3$).

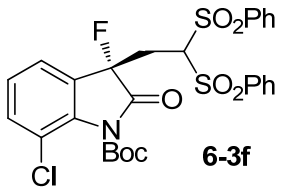
(*S*)-*tert*-Butyl 3-(2,2-bis(phenylsulfonyl)ethyl)-3,7-difluoro-2-oxoindoline-1-carboxylate **6-3e**



6-3e

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.59 (s, 9H), 3.02-3.13 (m, 1H), 3.19-3.25 (m, 1H), 5.36 (t, *J* = 4.4 Hz, 1H), 7.18 (t, *J* = 3.2 Hz, 1H), 7.25 (d, *J* = 6.9 Hz, 2H), 7.52-7.59 (m, 4H), 7.65-7.72 (m, 2H), 7.86 (d, *J* = 7.6 Hz, 2H), 8.00 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.6, 31.3 (d, *J* = 31.9 Hz), 77.2, 85.7, 89.6 (d, *J* = 194.0 Hz), 119.9 (d, *J* = 3.7 Hz), 120.5, 120.7 (d, *J* = 2.7 Hz), 126.7 (d, *J* = 4.6 Hz), 126.9 (d, *J* = 10.0 Hz), 127.0, 129.1 (d, *J* = 18.2 Hz), 129.7 (d, *J* = 9.1 Hz), 134.7 (d, *J* = 23.7 Hz), 137.1, 138.1, 146.3, 148.0, 150.6, 169.7 (d, *J* = 22.8 Hz); ^{19}F NMR (282.38 MHz, $CDCl_3$) δ -75.1 (dd, *J* = 12.1 Hz, 32.0 Hz), -40.1 (t, *J* = 7.7 Hz); The ee value was 89%, t_R (minor) = 26.71 min, t_R (major) = 31.00 min (Chiralcel IA, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{27}H_{25}F_2NO_7S_2Na$ $[M+Na]^+$ = 600.0933, found = 600.0943; $[\square]^{27}_D$ = +15.8 (c = 0.84, $CHCl_3$).

(*S*)-*tert*-Butyl-3-(2,2-bis(phenylsulfonyl)ethyl)-7-chloro-3-fluoro-2-oxoindoline-1-carboxylate **6-3f**

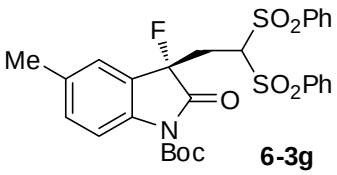


6-3f

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.60 (s, 9H), 3.01-3.12 (m, 1H), 3.19-3.25 (m, 1H), 5.40 (t, *J* = 4.4 Hz, 1H), 7.21 (t, *J* = 7.6 Hz, 1H), 7.29 (d, *J* = 7.6 Hz, 1H), 7.48 (d, *J* = 8.2 Hz, 1H), 7.51-7.58 (m, 4H), 7.65-7.72 (m, 2H), 7.86 (dd, *J* = 1.3 Hz, 8.2 Hz, 2H), 8.00 (t, *J* = 4.1 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.6, 31.4 (d, *J* = 31.0 Hz), 76.7, 86.1, 89.7 (d, *J* = 193.1 Hz), 120.6, 122.6, 126.2, 127.2 (d,

J = 19.1 Hz), 129.2 (d, *J* = 22.8 Hz), 129.7 (d, *J* = 17.3 Hz), 133.9 (d, *J* = 2.7 Hz), 134.7 (d, *J* = 23.7 Hz), 137.3, 138.2, 146.5, 170.3 (d, *J* = 22.8 Hz); ^{19}F NMR (282.38 MHz, $CDCl_3$) δ -76.7 (dd, *J* = 11.3 Hz, 33.0 Hz); The ee value was 87%, t_R (minor) = 27.51 min, t_R (major) = 36.01 min (Chiralcel IA, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{27}H_{25}FClNO_7S_2Na$ $[M+Na]^+$ = 616.0637, found = 616.0613; $[\alpha]^{27}_D$ = +12.4 (c = 1.10, $CHCl_3$).

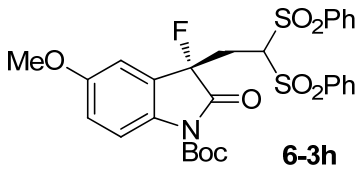
(*S*)-*tert*-Butyl-3-(2,2-bis(phenylsulfonyl)ethyl)-3-fluoro-5-methyl-2-oxoindoline-1-carboxylate **6-3g**



6-3g

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.62 (s, 9H), 2.38 (s, 3H), 2.98-3.23 (m, 2H), 5.39 (t, *J* = 4.4 Hz, 1H), 7.14 (s, 1H), 7.28 (s, 1H), 7.52-7.58 (m, 4H), 7.65-7.71 (m, 2H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.86-7.88 (m, 2H), 8.01-8.03 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.0, 28.0, 31.3 (d, *J* = 31.0 Hz), 76.9, 84.9, 89.4 (d, *J* = 190.4 Hz), 116.0, 123.7 (d, *J* = 18.2 Hz), 124.4, 129.1 (d, *J* = 22.8 Hz), 129.7 (d, *J* = 2.7 Hz), 132.7 (d, *J* = 1.8 Hz), 134.6 (d, *J* = 29.2 Hz), 135.2 (d, *J* = 2.7 Hz), 137.3, 137.7 (d, *J* = 4.6 Hz), 138.5, 148.5, 170.3 (d, *J* = 22.8 Hz); ^{19}F NMR (282.38 MHz, $CDCl_3$) δ -75.3 (dd, *J* = 10.3 Hz, 32.0 Hz); The ee value was 89%, t_R (minor) = 19.79 min, t_R (major) = 22.86 min (Chiralcel IA, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{28}H_{28}FNO_7S_2Na$ $[M+Na]^+$ = 596.1183, found = 596.1175; $[\alpha]^{27}_D$ = +17.3 (c = 0.98, $CHCl_3$).

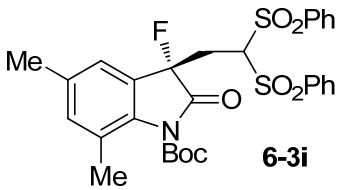
(*S*)-*tert*-Butyl-3-(2,2-bis(phenylsulfonyl)ethyl)-3-fluoro-5-methoxy-2-oxoindoline-1-carboxylate **6-3h**



6-3h

A white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.62 (s, 9H), 2.96-3.25 (m, 2H), 3.85 (s, 3H), 5.41 (t, *J* = 4.4 Hz, 1H), 6.92-7.01 (m, 2H), 7.50-7.58 (m, 4H), 7.61-7.73 (m, 2H), 7.83-7.92 (m, 3H), 7.95-8.02 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.0, 31.3 (d, *J* = 31.0 Hz), 55.9, 76.9, 84.9, 89.4 (d, *J* = 191.3 Hz), 109.8, 117.3 (d, *J* = 3.6 Hz), 124.9 (d, *J* = 17.3 Hz), 129.1 (d, *J* = 23.7 Hz), 129.7 (d, *J* = 1.8 Hz), 133.1 (d, *J* = 4.6 Hz), 134.6 (d, *J* = 31.9 Hz), 137.2, 138.4, 148.5, 157.4 (d, *J* = 2.7 Hz), 170.2 (d, *J* = 22.8 Hz); ^{19}F NMR (282.38 MHz, $CDCl_3$) δ -76.2 (dd, *J* = 11.3 Hz, 31.9 Hz); The ee value was 90%, t_R (minor) = 26.12 min, t_R (major) = 32.68 min (Chiralcel IA, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{28}H_{28}FNO_8S_2Na$ $[M+Na]^+$ = 612.1133, found = 611.1127; $[\alpha]^{27}_D$ = +24.8 (c = 0.85, $CHCl_3$).

(*S*)-*tert*-Butyl-3-(2,2-bis(phenylsulfonyl)ethyl)-3-fluoro-5,7-dimethyl-2-oxoindoline-1-carboxylate **6-3i**

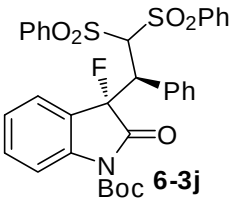


6-3i

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.60 (s, 9H), 2.22 (s, 3H), 2.33 (s, 3H), 2.98-3.22 (m, 2H), 5.39 (t, *J* = 4.4 Hz, 1H), 6.96 (s, 1H), 7.08 (s, 1H), 7.51-7.58 (m, 4H), 7.64-7.71 (m, 2H), 7.87 (d, *J* = 7.6 Hz, 2H), 8.02 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.8, 20.8, 27.8, 31.5 (d, *J* = 31.9 Hz), 85.1, 90.1 (d, *J* = 189.5 Hz), 121.9, 125.1 (d, *J* = 17.3 Hz), 125.5, 129.1 (d, *J* = 23.7 Hz), 129.7 (d, *J* = 9.1 Hz), 134.6 (d, *J* = 26.4 Hz), 135.3 (d, *J* = 2.7 Hz), 135.7 (d, *J* = 2.7 Hz), 136.1 (d, *J* = 5.5 Hz), 137.4, 138.5, 148.1, 171.3 (d, *J* = 22.8 Hz); ^{19}F NMR (282.38 MHz, $CDCl_3$) δ -75.2 (dd, *J* = 11.4 Hz, 21.7 Hz); The ee value was 89%, t_R (minor) = 17.12 min, t_R (major) = 19.55 min (Chiralcel IA, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{29}H_{30}FNO_7S_2Na$ $[M+Na]^+$ = 610.1340, found = 610.1346; $[\alpha]^{27}_D$ = +16.8 (c = 0.78, $CHCl_3$).

(*S*)-*tert*-Butyl 3-fluoro-2-oxo-3-((*S*)-1-phenyl-2,2-bis(phenylsulfonyl)ethyl)indoline-1-carboxylate

6-3j

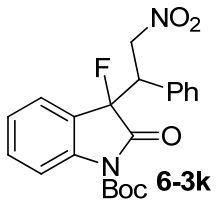


6-3j

A white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.62 (s, 9H), 4.66 (dd, *J* = 2.5 Hz, 31.5 Hz, 1H), 6.39 (d, *J* = 1.9 Hz, 1H), 6.77 (d, *J* = 7.6 Hz, 1H), 6.95 (t, *J* = 7.6 Hz, 1H), 7.28 (d, *J* = 6.9 Hz, 3H), 7.35-7.41 (m, 4H), 7.43-7.49 (m, 3H), 7.55-7.61 (m, 3H), 7.85 (d, *J* = 7.6 Hz, 2H), 7.93 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.0, 48.0 (d, *J* = 26.4 Hz), 77.2, 80.6, 85.1, 92.4 (d, *J* = 199.5 Hz), 115.6, 123.5 (d, *J*

= 19.1 Hz), 124.5 (d, *J* = 1.8 Hz), 126.3, 128.0, 128.5, 128.9 (d, *J* = 30.1 Hz), 129.3 (d, *J* = 31.0 Hz), 129.9, 131.8 (d, *J* = 7.3 Hz), 133.3 (d, *J* = 2.7 Hz), 133.8, 134.1, 138.3, 139.7, 140.0 (d, *J* = 18.3 Hz), 148.4, 170.7 (d, *J* = 22.8 Hz); ^{19}F NMR (282.38 MHz, $CDCl_3$) δ -40.4 (d, *J* = 20.6 Hz); The ee value was 98%, t_R (minor) = 30.69 min, 52.43 min t_R (major) = 27.33 min, 33.48 min (Chiralcel AD-H, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1.0 mL/min); HRMS (ESI) m/z calcd for $C_{33}H_{30}FNO_7S_2Na$ $[M+Na]^+$ = 658.1340, found = 658.1348.

tert-Butyl- 3-fluoro-3-(2-nitro-1-phenylethyl)-2-oxoindoline-1-carboxylate **6-3k**



6-3k

A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) The major isomer: δ 1.59 (s, 9H), 4.12-4.19 (m, 1H), 5.06 (dd, *J* = 10.4 Hz, 13.6 Hz, 1H), 5.55 (dd, *J* = 4.7 Hz, 13.6 Hz, 1H), 6.69 (d, *J* = 7.6 Hz, 1H), 7.00-7.14 (m, 3H), 7.22-7.31 (m, 3H), 7.40 (t, *J* = 15.8 Hz, 1H), 7.77 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) The major isomer: δ 28.0, 49.4 (d, *J* = 24.6 Hz), 73.9 (d, *J* = 3.6 Hz), 85.2, 92.9 (d, *J* = 198.6 Hz), 115.4 (d, *J* = 16.4 Hz), 124.6, 125.1 (d, *J* = 2.7 Hz), 125.6, 128.7 (d, *J* = 9.1 Hz), 129.2 (d, *J* = 39.2 Hz), 131.7 (d, *J* = 3.7 Hz), 132.0 (d, *J* = 2.7 Hz), 140.1, 148.0, 170.0 (d, *J* = 22.8 Hz); ^{19}F NMR (282.38 MHz, $CDCl_3$) The major isomer: δ -85.5 (d, *J* = 19.6 Hz); The ee value was 46% (major isomer), 28% (minor isomer), t_R (minor) = 10.26 min, 11.78 min t_R (major) = 15.26 min, 17.90 min (Chiralcel ID, λ = 254 nm, 3% *i*PrOH/hexanes, flow rate = 1.0 mL/min); MS (ESI) m/z calcd for $C_{21}H_{21}FN_2O_5Na$ $[M+Na]^+$ = 423,

found = 423.1.