DEVELOPMENT OF ENANTIOSELECTIVE ORGANOCATALYSIS BY BIFUNCTIONAL INDANE AMINE-THIOUREA CATALYST

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NATIONAL UNIVERSITY OF SINGAPORE

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To my parents

for their endless love, support and encouragement

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 Wang Jian, Chemistry Department, National University of Singapore, between 08/2009 and 09/2013.

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

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

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2. **Qiao Ren,** Jiayao Huang, Lei Wang, Wenjun Li, Hui Liu, Xuefeng Jiang, Jian Wang. *ACS Catal.* **2012**, *2*, 2622.

3. **Qiao Ren,** Woon-Yew Siau, Zhiyun Du, Kun Zhang, Jian Wang. *Chem. –Eur. J.* **2011**, *17*, 7781.

4. **Qiao Ren,** Yaojun Gao, Jian Wang. *Org. Biomol. Chem.* **2011**, *9*, 5297.

5. **Qiao Ren,** Yaojun Gao, Jian Wang. *Chem. –Eur. J.* **2010**, *16*, 13594.

Ren Qiao	Ren Qiao	2014/03/07
Name	Signature	Date

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Table of Contents

Summary

Organocatalysis has emerged as a powerful tool to synthesize chiral pharmaceutical important natural products because of its advantages in comparison with transition metal catalysis. Among different modes of organocatalysis, hydrogen-bond-mediated asymmetric catalysis has made astounding advances in the synthetic chemistry in the past few decades. Urea and thiourea catalysts have paved the way for the development of hydrogen-bonding catalysis mode in asymmetric organocatalysis. Although huge contributions have been made by various chiral scaffold based urea/thiourea catalysts, it is still highly desirable to discover novel and simple chiral structure scaffolds. The aim of this dissertation was to develop some novel and easily synthesized bifunctional indane amine-thiourea catalysts to promote unique enantioselective cascade reactions, resulting in assembling some densely functionalized privileged medicinal scaffolds.

Chapter 1 gave a brief introduction of the enantioselective hydrogen bonding catalysis mediated by urea and thiourea derivatives. Various chiral scaffolds based urea/thiourea derivatives were successfully applied in a wide range of novel and particularly interesting enantioselective transformations, such as Strecker reaction, Michael reaction, Mannich reaction, Henry reaction, acyl-Pictect Spenger reaction, Morita-Baylis-Hillman (MBH) reaction, petasis-type reaction and so on.

Chapter 2 described a surprising example of enantioselective cascade Michael–*oxa*-Michael–tautomerization reaction of malononitrile and benzylidenechromanones. In this case, malononitrile functioned as both nucleophile and electrophile. Meanwhile, a simple bifunctional indane amine–thiourea catalyst was discovered to promote this process to afford high yields (up to 99%) and high to excellent enantiomeric excesses (81–99% *ee*).

Chapter 3 disclosed a novel and highly stereoselective Michael–enolation–cyclization cascade reaction catalyzed by a chiral bifunctional indane amine-thiourea catalyst. A broad substrate scope of chiral dihydro-2H-pyran complexes that contained two stereogenic centers were obtained in one-pot manner in good to excellent yields (72–97%) and high to excellent stereoselectivities (92–97% *ee*).

Chapter 4 presented an enantioselective cascade Mannich–Intramolecular ring cyclization–tautomerization reaction of malononitrile with 2-hydroxyl N-protected-amido sulfones, which provided a novel route to the synthesis of privileged scaffold 2-amino-4H-chromene in high yields (up to 94%) and with good to high enantiomeric excesses (74–89% ee).

Chapter 5 documented a highly efficient catalytic decarboxylative [1,2]-addition strategy based on readily available isatins and α-functionalized acetic acids, using a catalytic amount of weak base. This catalytic protocol was utilized to efficiently assemble important pharmaceutical 3-hydroxyoxindole natural products, such as (±)-flustraminol B, (±)-convolutamydine A, (±)-alline, donaxaridine, (±)-convolutamydine E, (±)-convolutamydine B and (±)-CPC-1.

Chapter 6 showed a direct enantioselective decarboxylation of readily accessible α,β-unsaturated carbonyls and malonic acid half thioesters to furnish chiral saturated δ-lactones, ubiquitous bioactive *o*-heterocycles in nature, in high yields and high to excellent enantioselectivities. The synthetic utility of this strategy was demonstrated by the versatile ready modifications of the thiophenyl group and the applicability of this method to the concise synthesis of (-)-Paroxetine, marketed as Paxil/Seroxat.

List of Tables

List of Figures

List of Schemes

List of Abbreviations

Ac	Acetyl
Å	ångström
ABH	*aza*-Baylis Himman
Aq	Aqueous
Ar	Aryl
β-ICD	β-isocupreidine
br	broad
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
Bs	Brosylate
Bz	Benzoyl
Bu	Butyl
Cat.	Catalysts
Cbz	Carboxybenzyl
CD	Cinchonidine
CN	Cinchonine
Conc.	Concentrated
CPME	Cyclopentyl methyl ether

d	doublet
dd	doublet of doublet
d.r.	Diastereomeric ratio
DABCO	1,4-diazabicyclo[2.2.2]octane
DCE	1,2-Dichloroethylene
DCM	Dichloromethane
DEGEE	Diethylene glycol monoethyl ether
DHQ	Dihydroquinine
DHQD	Dihydroquinidine
DIAD	Diisopropylazodicarboxylate
DIBAL-H	Diisobutylaluminium hydride
DKR	Dynamic kinetic resolution
DMAP	4-Dimethylaminopyridine
DME	Dimethyl ether
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DPPA	Diphenylphosphoryl azide
ee	Enantiomeric excess
E^+	Electrophile
EA	Ethyl acetate
EVE	Ethyl vinyl ether

Et	Ethyl
EWG	Electron-withdrawing group
h	Hour
HRMS	High-resolution mass spectrometry
HOMO	Highest occupied molecular orbital
HPLC	High performance liquid chromatography
Hz	Hertz
i-Pr	isopropyl
IPA	*iso*-Propanol
IPDA	Isophoronediamine
LA	Lewis acid
LUMO	Lowest unoccupied molecular orbital
m	multiplet
m/z	mass-to-charge ratio
mmol	millimole
m-CPBA	*meta*-Chloroperoxybenzoic acid
MAHTs	Malonic acid half thioesters
MBH	Morita–Bayliss–Hillman
Me	Methyl
Ms	Methyl sulfonyl
M.S.	Molecular sieve

MTBE	Methyl *tert*-butyl ether
μL	microlitre
NMR	Nuclear magnetic resonance
NR	No reaction
Ns	2-nitrophenylsulfonyl
Nu	Nucleophile
ppm	parts per million
Ph	Phenyl
Piv	Pivaloyl
PG	Protecting group
Pr	Propyl
q	quartet
QD	Quinidine
QN	Quinine
r.t.	Room temperature
RDS	Rate-determining step
s	singlet
SOMO	Singly occupied molecular orbital
TBME	*tert*-Butylmethylether
TBD	Triazabicyclodecene
TBDPS	*tert*-butyldiphenylsilyl

TBS	*tert*-butyldimethylsilyl
TEA	Triethylamine
TES	Triethylsilyl
Tf	Triflyl
TFA	Trifluoromethylacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TMIPDA	N,N,N',N'-tetramethylisophoronediamine
TMS	Trimethylsilyl
TOF	Turn-Over-Frequency
Troc	2,2,2-Trichloroethoxycarbonyl
TS	Transition state
Ts (Tos)	*p*-Toluenesulfonyl

List of Publications

1. **Qiao Ren,** Jian Wang. "Recent Developments in Amine-catalyzed Non-asymmetric Transformations", *Asian J. Org. Chem.* **2013**, *2*, 542.

2. **Qiao Ren**, Jian Wang. "Enantioselective Decarboxylation of α,β-Unsaturated Carbonyls and Malonic Half-thioesters: Rapid Access to Chiral δ-lactones", **Manuscript in preparation**.

3. **Qiao Ren,** Jiayao Huang, Lei Wang, Wenjun Li, Hui Liu, Xuefeng Jiang, Jian Wang. "Highly Efficient Assembly of 3-Hydroxy Oxindole Scaffold *via* a Catalytic Decarboxylative [1,2]-Addition Strategy", *ACS Catal.* **2012**, *2*, 2622.

4. **Qiao Ren,** Woon-Yew Siau, Zhiyun Du, Kun Zhang, Jian Wang. "Expeditious Assembly of a 2-Amino-4*H*-chromene Skeleton by Using an Enantioselective Mannich–Intramolecular Ring Cyclization–Tautomerization Cascade Sequence", *Chem. –Eur. J.* **2011**, *17*, 7781.

5. **Qiao Ren,** Yaojun Gao, Jian Wang. "Chiral Indane Skeleton Based Thiourea Catalyzed Highly Stereoselective Cascade Michael–Enolation–Cyclization Reaction", *Org. Biomol. Chem.* **2011**, *9*, 5297.

6. **Qiao Ren,** Yaojun Gao, Jian Wang. "Enantioselective Synthesis of Densely Functionalized Pyranochromenes *via* an Unpredictable Cascade Michael–*oxa*-Michael–Tautomerization Sequence", *Chem. –Eur. J.* **2010**, *16*, 13594.

7. **Qiao Ren**, Jian Wang. "Enantioselective N-Heterocyclic Carbene-Catalyzed Reaction of Ynals with 1,2-Diketone: Facile Synthesis of Chiral Bicyclic δ-lactones", **Manuscript in preparation**.

8. Xuefeng Jiang, Jian Wang, **Qiao Ren**, Hui Liu. *Faming Zhuanli Shenqing* 201210086826.5.

9. Woon-Yew Siau, Wenjun Li, Fei Xue, **Qiao Ren,** Minghu Wu, Shaofa Sun, Haibing Guo, Xuefeng Jiang, Jian Wang. "Catalytic and Enantioselective

α-Functionalization of Oxindoles Through Oxidative Reactions with Naphthoquinones", *Chem. –Eur. J.* **2012**, *18*, 9491.

10. Zhiyun Du, Chenggang Zhou, Yaojun Gao, **Qiao Ren**, Kun Zhang, Hansong Cheng, Wei Wang, Jian Wang. "Expeditious Diastereoselective Construction of a Thiochroman Skeleton *via* a Cinchona Alkaloid-derived Catalyst", *Org. Biomol. Chem.*, **2012**, *10*, 36.

11. Yaojun Gao, **Qiao Ren,** Woon-Yew Siau, Jian Wang. "Asymmetric Organocatalytic Cascade Michael/hemiketalization/retro-Henry Reaction of β,γ-Unsaturated Ketoesters with α-Nitroketones", *Chem. Commun.* **2011,** *47*, 5819.

12. Yaojun Gao, **Qiao Ren,** Swee-Meng Ang, Jian Wang. "Enantioselective Organocatalytic Michael-Hemiketalization Catalyzed by a *trans*-bifunctional Indane Thiourea Catalyst", *Org. Biomol. Chem.* **2011**, *9*, 3691.

13. Yaojun Gao, **Qiao Ren,** Hao Wu, Maoguo Li, Jian Wang. "Enantioselective Heterocyclic Synthesis of Spiro Chromanone-Thiochroman Complexes Catalyzed by a Bifunctional Indane Catalyst", *Chem. Commun.* **2010**, *46*, 9232.

14. Yaojun Gao, **Qiao Ren,** Lei Wang, Jian Wang. "Enantioselective Synthesis of Coumarins Catalyzed by a Bifunctional Amine-Thiourea Catalyst", *Chem. –Eur. J.* **2010**, *16*, 13068.

Chapter 1 Enantioselective Hydrogen Bonding Catalysis Mediated by Urea and Thiourea Derivatives

1.1 Introduction of Hydrogen Bonding Catalysis

Organocatalysis refers to the utilization of precisely designed catalysts consisting of carbon, hydrogen, nitrogen and other nonmetal elements to enormously accelerate reaction rates and effectively control various organic transformations.[1,2] Because of its relative stability, environment friendliness, relative nontoxicity, high functional group tolerance, operational simplicity and ready availability, as compared with conventional transition metal catalysis,[1,2] it has emerged as a practical and powerful synthetic methodology to synthesize divergent attractive biologically active building blocks in the past few decades. A number of novel and unprecedented organic transformations have been discovered in this explosively growing field of enantioselective organocatalysis.[1,2,3] In the synthesis of natural and pharmaceutical products, organocatalysis can be categorized into several activation modes: amino catalysis, phase transfer catalysis, hydrogen-bonding catalysis, and so on.

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[1] For selected books on organocatalysis, see: a) Berkessel, A.; Groger, H. in *Asymmetric Organocatalysis*, Wiley, Weinheim **2005**; b) Dalko, P. I. in *Enantioselective Organocatalysis*, Wiley, Weinheim, **2007**; c) Reetz, M. T.; List, B.; Jaroch, S.; Weinmann, H. in *Organocatalysis*, Springer, **2007**; d) List, B. in *Asymmetric Organocatalysis*, Springer, **2009**.

[2] For selected reviews of asymmetric organocatalysis, see: a) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2001**, *40*, 3726; b) Dalko, P. I.; Maison, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138; c) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 1570; d) List, B. *Chem. Rev.* **2007**, *107*, 5413; e) Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo, N. T. *Drug Discovery Today* **2007**, *12*, 8; f) Walji, A. M.; MacMillan, D. W. C. *Synlett.* **2007**, 1477; g) Dondoni, A.; Massi, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 4638; h) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178; i) Hegedus, L. S. *J. Am. Chem. Soc.* **2009**, *131*, 17995; j) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167; k) Albrecht, Ł.; Jiang, H.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2011**, *50*, 8492.

[3] For selected examples of asymmetric organocatalysis, see: a) Dudding, T.; Hafez, A. M.; Taggi, A. E.; Wagerle, T. R.; Lectka, T. *Org. Lett.* **2002**, *4*, 387; b) Yamamoto, Y.; Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 5962; c) Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051; d) Yang, J. W.; Fonseca, M. T. H.; List, B. *J. Am. Chem. Soc.* **2005**, *127*, 15036; e) Marigo, M.; Schulte, T.; Franzen, J.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 15710; f) Enders, D.; Hüttl, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861; g) Wang, Y.; Liu, X. F.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 3928; h) Wang, W.; Li, H.; Wang, J.; Zu, L. *J. Am. Chem. Soc.* **2006**, *128*, 10354; i) Sunden, H.; Ibrahem, I.; Zhao, G. L.; Eriksson, L.; Córdova, A. *Chem. –Eur. J.* **2007**, *12*, 574; j) Li, H.; Zu, L.; Xie, H.; Wang, J.; Jiang, W.; Wang, W. *Angew. Chem. Int. Ed.* **2007**, *46*, 3732; k) Hayashi, Y.; Okano, T.; Aratake, S.; Hazelard, D. *Angew. Chem. Int. Ed.* **2007**, *46*, 4922.

Remarkably, amino catalysis has received immeasurable attention in the synthetic community for the past few years.[4,11] The origin of amino catalysis was ascribable to the research studies of Emil Knoevenagel, who utilized primary and secondary amines to promote the aldol condensation.[5] However, after the discovery of the important Knoevenagel reaction, the amino catalysis was not fully explored in the following decades. The significance of amino catalysis was not discovered until List and Barbas published the seminal investigations of intermolecular enamine catalysis in the presence of the fairly general and efficient L-proline (Scheme 1.1a).[6] The formation of nucleophilic reactive enamine, *in situ* generated from carbonyl compounds, elevated the overall energy of the highest occupied molecular orbital (HOMO). Almost simultaneously, MacMillan *et al.* reported the first enantioselective example of iminium catalysis strategy.[7] The activated iminium ion from enal and imidazolidinone reacted with suitable coupling partners (nucleophiles), by lowering the energy of the lowest unoccupied molecular orbital (LUMO) (Scheme 1.1b). Subsequently, MacMillan's research group described a novel enantioselective α-functionalization of aldehydes via singly occupied molecular orbital (SOMO) acitivation mode (Scheme 1.1c).[8] The first organocatalytic enantioselective γ-functionalization of α, β-unsaturated aldehydes was directly conducted through the formation of the dienamine intermediate (Scheme 1.1d).[9a] Since then, a rapid growth in asymmetric synthesis was witnessed based on the dienamine[9] and similar

[4] a) List, B. *Acc. Chem. Res.* **2004**, *37*, 548; b) List, B. *Chem. Commun.* **2006**, 819; c) see *Ref.* 2e; d) List, B. *Angew. Chem. Int. Ed.* **2010**, *49*, 1730; e) Renzi, P.; Bella, M. *Chem. Commun.* **2012**, *48*, 6881.

[5] a) Knoevenagel, E. *Ber. Dtsch. Chem. Ges.* **1896**, *29*, 172; b) Knoevenagel, E. *Ber. Dtsch. Chem. Ges.* **1898**, *31*, 738; c) Knoevenagel, E. *Ber. Dtsch. Chem. Ges.* **1898**, *31*, 2585; d) Knoevenagel, E. *Ber. Dtsch. Chem. Ges.* **1898**, *31*, 2596.

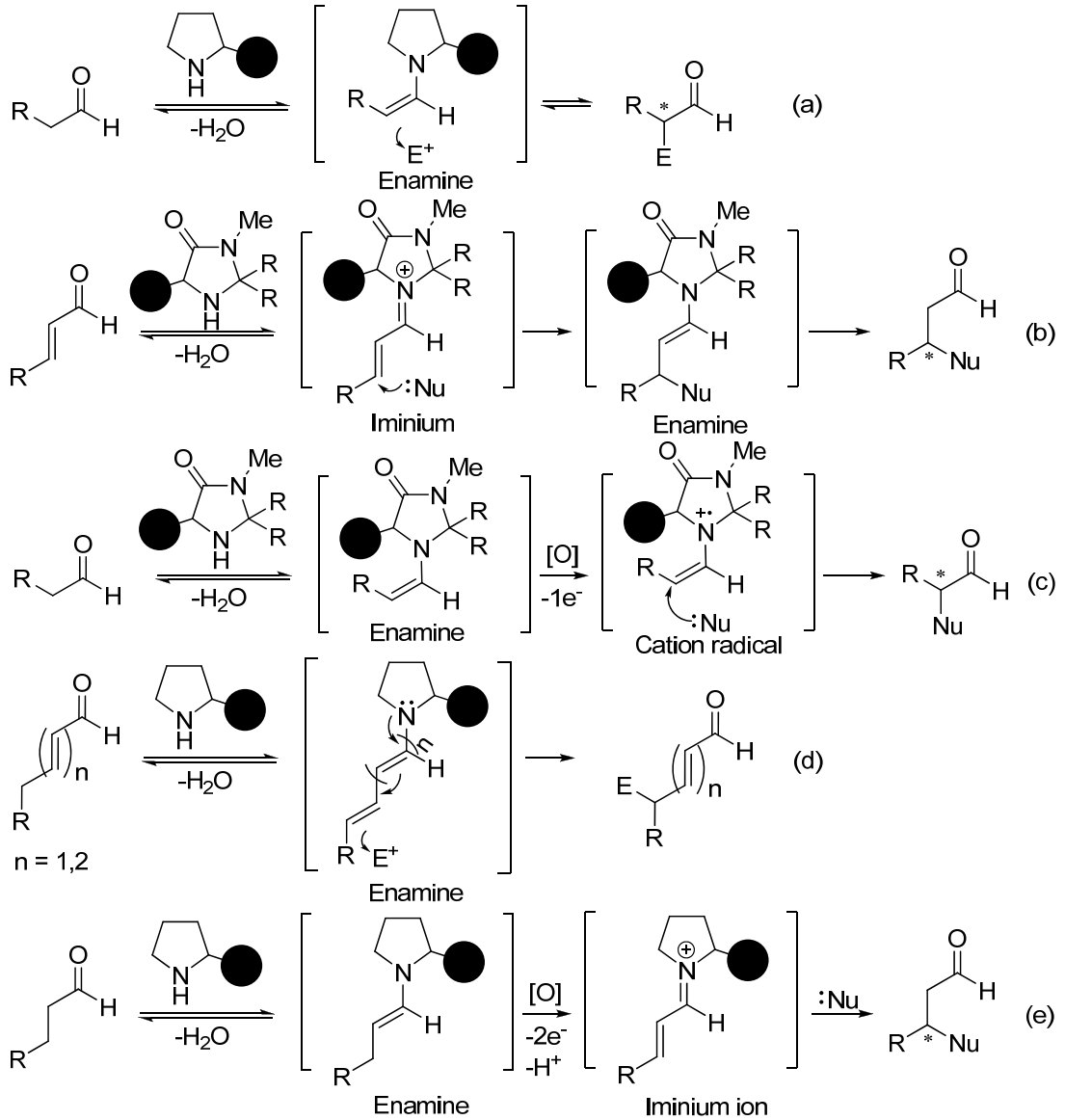
[6] a) List, B.; Lerner, R. A.; Barbas, C. F., III *J. Am. Chem. Soc.* **2000**, *122*, 2395. Also see: b) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386; c) List, B.; Pojarliev, P.; Castello, C. *Org. Lett.* **2001**, *3*, 573; d) Notz, W.; Tanaka, F.; Barbas, C. F., III *Acc. Chem. Res.* **2004**, *37*, 580; e) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471.

[7] a) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243. Also see: b) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458; c) Wilson, R. M.; Jenand, W. S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 11616; d) Lelais, G.; MacMillan, D. W. C. *Aldrichim. Acta.* **2006**, *39*, 79; e) Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416.

[8] Beeson, T. D.; Mastracchio, A.; Hong, J.; Ashton, K.; MacMillan, D. W. C. *Science* **2007**, *316*, 582.

[9] a) Bertelsen, S.; Marigo, M.; Brandes, S.; Dinér, P.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 12973; b) Han, B.; He, Z. Q.; Li, J. L.; Li, R.; Jiang, K.; Liu, T. Y.; Chen, Y. C. *Angew. Chem. Int. Ed.* **2009**, *48*, 5474; c) Han, B.; Xiao, Y. C.; He, Z. Q.; Chen, Y. C. *Org. Lett.* **2009**, *11*, 4660; d) Bencivenni, G.; Galzerano, P.; Mazzanti, A.; Bartoli, G.; Melchiorre, P. *PNAS*, **2010**, *107*, 20642; e) Li, J. L.; Kang, T. R.; Zhou, S. L.; Li, R.; Wu, L.; Chen, Y.

trienamine[10] organocatalysis. Recently, a facile and efficient oxidative enamine catalysis was developed independently by Wang[11] and Hayashi[12] (Scheme 1.1e).



Scheme 1.1 Amino catalysis:[11] a) enamine catalysis; b) iminium catalysis; c) SOMO catalysis ; d) di- and tri-enamine catalysis; e)oxidative enamine catalysis.

C. *Angew. Chem. Int. Ed.* **2010**, *49*, 6418; f) Ramachary, D. B.; Ramakumar, K. *Eur. J. Org. Chem.* **2011**, *14*, 2599; g) Parra, A.; Reboredo, S.; Alemán, José *Angew. Chem. Int. Ed.* **2012**, *51*, 9734; h) Ramachary, D. B.; Reddy, Y. V. *Eur. J. Org. Chem.* **2012**, 865; i) Albrecht, Ł.; Dickmeiss, G., Acosta, F. C., Rodríguez-Escrich, C.; Davis, R. L.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2012**, *134*, 2543; j) Li, J. L.; Zhou, S. L.; Chen, P. Q.; Dong, L.; Liu, T. Y.; Chen, Y. C. *Chem. Sci.* **2012**, *3*, 1879; k) Albrecht, Ł.; Dickmeiss, G.; Weise, C. F.; Rodríguez-Escrich, C.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2012**, *51*, 1.

[10] a) Jia, Z. J.; Jiang, H.; Li, J. L.; Gschwend, B.; Li, Q. Z.; Yin, X.; Grouleff, J.; Chen, Y. C.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2011**, *133*, 5053; b) Jia, Z. J.; Zhou, Q.; Zhou, Q. Q.; Chen, P. Q.; Chen, Y. C. *Angew. Chem. Int. Ed.* **2011**, *50*, 8638; c) Jiang, H.; Gschwend, B.; Albrecht, Ł.; Hansen, A. G.; Jørgensen, K. A. *Chem. Eur. J.* **2011**, *17*, 9032; d) Xiong, X. F.; Zhou, Q.; Gu, J.; Dong, L.; Liu, T. Y.; Chen, Y. C. *Angew. Chem. Int. Ed.* **2012**, *51*, 4401; e) Albrecht, Ł.; Acosta, F. C.; Fraile, A.; Albrecht, A.; Christensen, J.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2012**, *51*, 9088; f) Halskov, K. S.; Johansen, T. K.; Davis, R. L.; Steurer, M.; Jensen, F.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2012**, *134*, 12943.

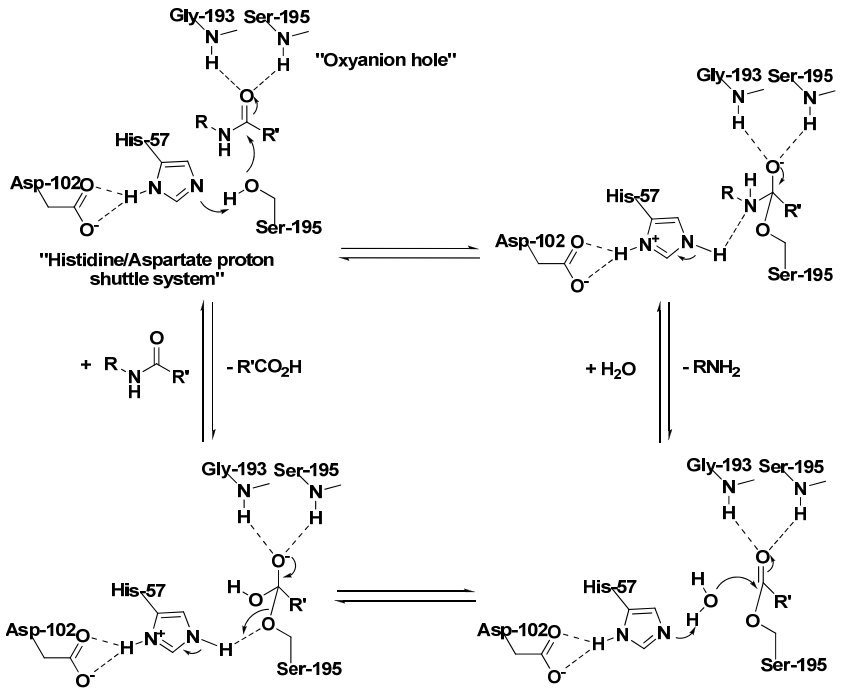
[11] Zhang, S. L.; Xie, H. X.; Zhu, J.; Li, H; Zhang, X. S; Li, J.; Wang, W. *Nat. Commun.* **2011**, *2*, 211.

[12] Hayashi, Y.; Itoh, T.; Ishikawa, H. *Angew. Chem. Int. Ed.* **2011**, *50*, 3920.

In contrast to typical covalent organocatalysis (amino catalysis) which requires high catalyst loading, non-covalent organocatalysis just needs low catalyst loading to promote C–C and C–heteroatom bond formation reactions. Remarkably, hydrogen bond organocatalysis is considered as a broadly applicable type of non-covalent organocatalysis that relies on the function of explicit hydrogen bonding interactions to accelerate and control a wide range of chemical processes. In a hydrogen bond -mediated chemical reaction, weakly acidic small organic molecule incorporating distinct hydrogen bond motif could decrease the electron density of electrophile to decrease the energy of LUMO and stabilize the transition state (TS) of reaction intermediate resulting in lowering the energy barrier of the reaction and formation of a well-defined chiral environment.

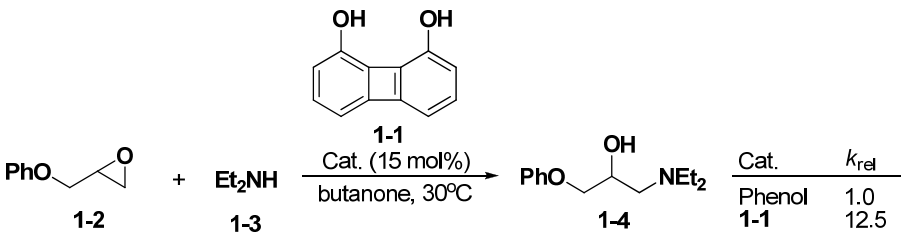
Actually, the design of small hydrogen bond donors as organocatalysts originates from the biological catalytic systems, such as enzymes, antibodies and ribonucleases.[13] It is widely known that hydrogen bond donors of enzyme's active sites could selectively coordinate and activate the embedded electrophiles in the wide range of biochemical transformations. The most notable example of electrophile activation by hydrogen bonding in biological processes is the serine protease that is responsible for the enzymatic hydrolysis of amide bonds.[14] The mechanistic study of action of this class of enzymes has shed light on the key feature of highly active-site nucleophilic serine residue, which activates the amide carbonyl group by the serine protease "oxyanion hole" composed of double hydrogen bonding. Simultaneously, the serine hydroxyl group was effectively activated by a general basic histidine/aspartate proton shuttle system.

[13] Schramm, V. L. *Chem. Rev.* **2006**, *106*, 3029.
[14] Wharton, C. W. In *Comprehensive Biological Catalysis, vol. 1* (Ed. M. L. Sinnott), Academic Press, London, **1998**.



Scheme 1.2 Serine protease: Biological amide hydrolysis with the assistance of double H-bonding, multiple non-covalent catalyst-substrate interactions and bifunctional catalysis.[14]

Inspired by the crucial role of hydrogen bonding in biochemical electrophilic activation, small well-defined H-bond donors have been developed as organocatalysts to accelerate reaction rates and stereocontrol the organic transformations since the seminal studies were performed by Hine and co-workers.[15] They proposed that the reaction between phenyl glycidyl ether **1-2** with diethylamine **1-3** was enormously enhanced by 1,8-biphenylenediol **1-1** capable of synergetic donation of two identical strong hydrogen bonds to the oxygen atom of the electrophile compared with phenol (Scheme 1.3).



Scheme 1.3 Epoxide opening reaction promoted by 1,8-biphenylenediol **1-1**

[15] a) Hine, J.; Ahn, K.; Gallucci, J. C.; Linden, S. M. *J. Am. Chem. Soc.* **1984**, *106*, 7980; b) Hine, J.; Linden, S. M.; Kanagasabapathy, V. M. *J. Am. Chem. Soc.* **1985**, *107*, 1082; c) Hine, J.; Hahn, S.; Miles, D. E.; Ahn, K. *J. Org. Chem.* **1985**, *50*, 5092; d) Hine, J.; Linden, S. M.; Kanagasabapathy, V. M. *J. Org. Chem.* **1985**, *50*, 5096; e) Hine, J.; Hahn, S.; Miles, D. E. *J. Org. Chem.* **1986**, *51*, 577; f) Hine, J.; Ahn, K. *J. Org. Chem.* **1987**, *52*, 2083; g) Hine, J.; Ahn, K. *J. Org. Chem.* **1987**, *52*, 2089.

In the recent few decades, significant advances have been made in hydrogen-bond-mediated asymmetric catalysis. Many small H-bond donor catalysts have been reported which consist of various structural and functional frameworks and differ widely in acidities of the hydrogen donor motif spanning over 20 pK_a units (Figure 1.1).[16] According to the distinction of activation mode in the transition state, these catalysts could be categorized into two classes: single H-bond donors and double H-bond donors.[16] Single H-bond donors providing only a single hydrogen bond, such as diols, biphenols, hydroxyl acids and phosphoric acids, are engaged to assemble the well-defined multidimensional catalyst-substrate complexes. However, compared with single H-bond donors, dual H-bond donors capable of simultaneous donation of two hydrogen bonds to the electrophiles, such as ureas/thioureas, guanidinium and amidinium ions, induce increased strength and directionality.[16] They have emerged as a class of widely applicable and privileged organocatalysts in many important and diverse transformations.

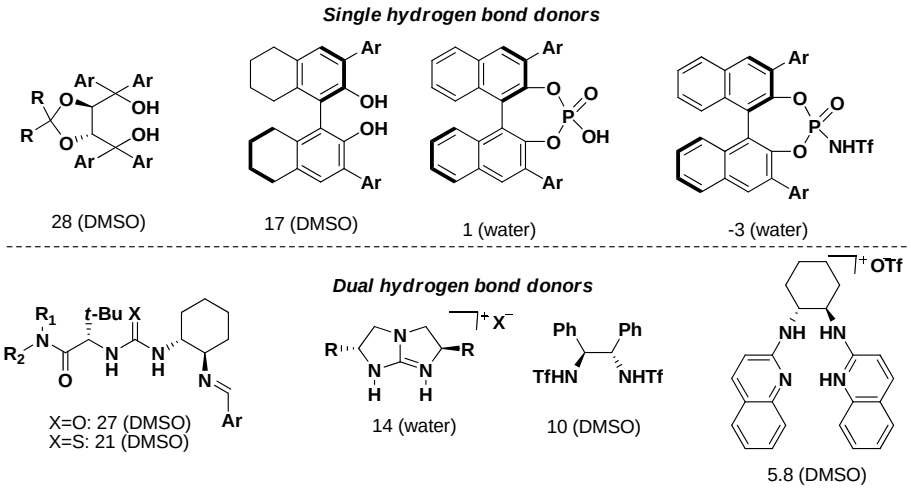


Figure 1.1 Approximate pK_as of H-bond donor motifs in small-molecule catalysis[16]

Among these double H-bond donors, urea and thiourea derivatives have been

[16] a) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713; Thiourea and urea: b) Bordwell, F. G.; Algrim, D. J.; Harrelson, J. A. *J. Am. Chem. Soc.* **1988**, *110*, 5903; Guanidinium: c) Angyal, S. J.; Warburton, W. K. *J. Chem. Soc*. **1951**, 2492; Triflamide: d) Zhuang, W.; Poulsen, T. B.; Jørgensen, K. A. *Org. Biomol. Chem*. **2005**, *3*, 3284; Amidinium: e) Hess, A. S.; Yoder, R. A.; Johnston, J. N. *Synlett* **2006**, 147; Alcohols: f) Olmstead, W. N.; Margolin, Z.; Bordwell, F. G. *J. Org. Chem.* **1980**, *45*, 3295; g) Bordwell, F. G.; McCallum, R. J.; Olmstead, W. N. *J. Org. Chem.* **1984**, *49*, 1424; Phosphoric acid: h) Quin, L. D. *A Guide to Organophosphorus Chemistry*; John Wiley & Sons: New York, **2000**; Chapter 5, p 133. i) Nakashima, D.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 9626; j) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2006**, *45*, 1520.

intensively investigated in the area of biological molecular recognition through binding to carboxylic acids, sulfonic acids, nitrates and other hydrogen-bonding acceptors.[17] Furthermore, urea and thiourea organocatalysts play a crucial role in various catalytic transformations through stabilization of the electrophiles, tetrahedral intermediates and anionic fragments by explicit double H-bond interactions, owing to their advantages, no product inhibition, high Turn-Over-Frequency (TOF), low catalyst loading, relative stability, acid-labile substrate tolerance, operational simplicity and ready availability.[18] So many groups have paid huge attention to the utilization of properly developed urea and thiourea derivatives in many non-asymmetric and enantioselective reactions. Among these studies, seminal investigations by Kelly and Etter inspired the impressive development of achiral urea catalysts. Kelly and co-workers reported that acidic bisphenol **1-5** could accelerate Diels-Alder reactions.[19] Subsequently, Etter and co-workers recognized the ability of electron-deficient diaryl ureas **1-6** to form cocrystals with a variety of proton acceptors such as carbonyl compouds.[20] In 1994, the first example of achiral urea catalyst was reported by Curran and Kuo that a Lewis acid, diarylurea **1-7** could alter the rate and stereochemical outcome of the allylation reactions of cyclic sulfinyl radicals with allyltributylstannane.[21] Since then, Many groups have reported the utilization of various effective chiral scaffolds based urea and thiourea catalysts in diverse enantioselective transformations.

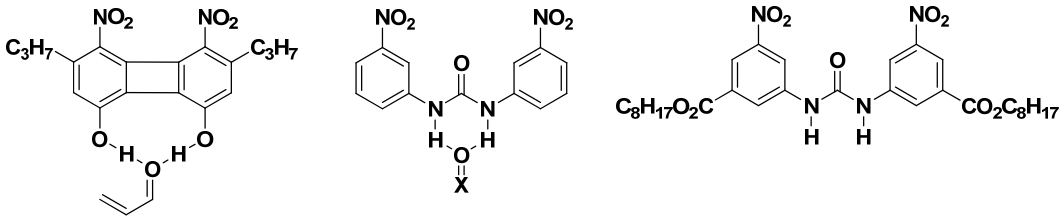


Figure 1.2 Seminal investigations of urea derivatives[19,20,21]

[17] Takemoto, Y. *Org. Biomol. Chem*. **2005**, *3*, 4299.

[18] Kotke, M.; Schreiner, P. R. *Synthesis* **2007**, *5*, 779.

[19] Kelly, T. R.; Meehani, P.; Ekkundi, V. S. *Tetrahedron Lett.* **1990**, *31*, 3381.

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

[21] Curran, D. P.; Kuo, L. H. *J. Org. Chem.* **1994**, *59*, 3259.

The following sections of this chapter will reveal the applications of different chiral scaffold-based urea and thiourea catalysts in diverse fantastic enantioselective transformations to afford densely functionalized and synthetically useful chiral building blocks. Focus will be given to various classic well-known reactions, such as Strecker reaction, Michael reaction, Mannich reaction, Morita-Baylis-Hillman (MBH) reaction, Friedel-Craft alkylation, Henry reaction, as well as dynamic kinetic resolution. Furthermore, some novel cascade reactions will also be depicted under the catalysis of bifunctional urea/thiourea derivatives, incorporating Lewis base functionalities on chiral scaffolds, which are responsible for creating a well-defined chiral environment for both the acceptors and donors. Non-stereoselective urea/thiourea catalysis is beyond the scope of this thesis owing to the absence of optical activity of the final products.

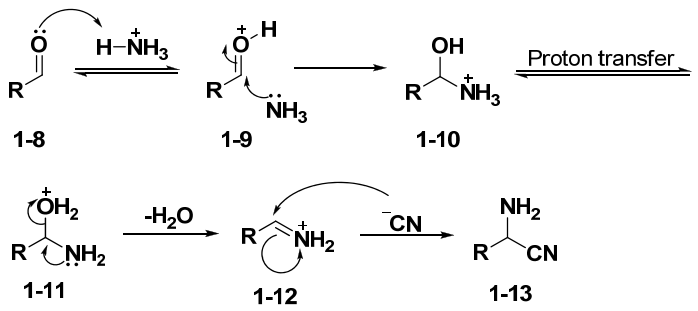
1.2 Enantioselective Reactions Catalyzed by (Thio)Urea Derivatives

1.2.1 The Strecker Reaction

The Strecker reaction, firstly documented by the German chemist Adolph Strecker in 1850, is a series of well-known economical chemical reactions which combine an aldehyde, ammonium chloride and potassium cyanide to form an α-aminonitrile.[22] Subsequently, α-aminonitriles could be hydrolyzed to obtain the privileged α-amino acids. Although the arguments for the mechanism of the Strecker reaction arose between the cyanohydrin pathway and the imine pathway around early 20th century,[23] control experiments and kinetic studies proved the rate-determining step (RDS) is imine formation.[24] Firstly, protonation of the carbonyl oxygen is followed by a nucleophilic attack of ammonia to afford the ammonium salt **1-10**. Subsequently, proton transfer and dehydration could synthesize the iminium ion

[22] a) Strecker, A. *Ann. Chem. Pharm.* **1850**, *75*, 27; b) Strecker, A. *Ann. Chem. Pharm.* **1854**, *91*, 349.
[23] a) Stadnikoff, G. *Ber.* **1907**, *40*, 1014; b) Stadnikoff, G. *J. Russ. Phys. Chem. Soc.* **1914**, *46*, 1201; c) Snyesarev, A. P. *J. Russ. Phys. Chem. Soc.* **1914**, *46*, 217.
[24] a) Ogata, Y.; Kawasaki, A. *J. Chem. Soc. B* **1971**, 325; b) Taillade, J.; Commeyras, A. *Tetrahedron* **1974**, *30*, 2493.

intermediate **1-12**, which acts as a reactive electrophile to react with the cyanide anion yielding the α-aminonitrile **1-13** (Scheme 1.4). Since the pioneering studies, the Strecker reaction gradually captured much attention of many research groups in both organic and biological chemistry, because it could afford a facile, robust and powerful method to synthesize various natural and non-natural α-amino acids from easily available simple starting materials.[25] Besides, α-aminonitriles also could be functionalized as valuable iminium ion equivalents after elimination of a cyanide anion to afford a series of natural pharmaceutical products.[26]



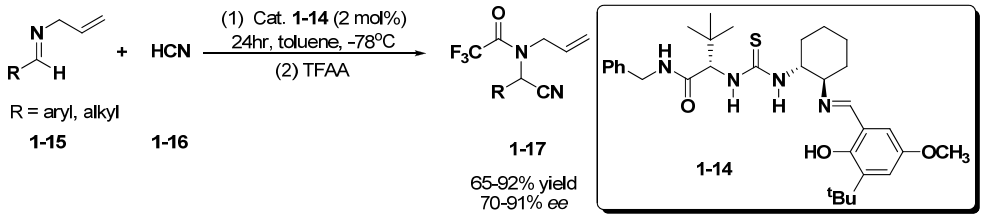
Scheme 1.4 Mechanism of the typical Strecker reaction.

Inspired by the initial nonasymmetric methodologies, in recent decades, considerable progress has been achieved in the development of asymmetric versions of the Strecker reaction to obtain enantiomerically pure α-aminonitriles assisted by stoichiometric amounts of chiral auxiliaries or chiral catalysts.[27] Among these various methodologies, urea and thiourea derivatives provide a concise and powerful approach which serves as an essential complement to other chiral transition-metal complex catalysts and organocatalysts.[27]

In 1998, the Jacobsen group demonstrated the first Schiff-base thiourea catalyst promoted enantioselective Strecker reaction.[28] Actually, this landmark work paved the way for the rapid development of organocatalysis mediated by urea/thiourea derivatives in a wide range of biological enantioselective transformations. In the

[25] a) Najera, C.; Sansano, J. M. *Chem. Rev.* **2007**, *107*, 4584; b) Soloshonok, V. A.; Izawa, K.; Eds. *Asymmetric Synthesis and Application of R-Amino Acids*; American Chemical Society: Washington, DC, **2009**.
[26] a) Enders, D.; Shilvock, J. P. *Chem. Soc. Rev.* **2000**, *29*, 359; b) Opatz, T. *Synthesis* **2009**, 1941.
[27] a) Merino, P.; Marques-Lopez, E.; Tejero, T.; Herrera, R. P. *Tetrahedron* **2009**, *65*, 1219; b) Wang, J.; Liu, X. H.; Feng, X. M. *Chem. Rev.* **2011**, *111*, 6947.
[28] Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901.

presence of Schiff base thiourea catalyst **1-14**, *N*-allyl aldimines **1-15**, derived from both aromatic and aliphatic aldehydes, reacted with HCN **1-16** in toluene to construct the respective trifluoroacetylated Strecker adducts **1-17** in good yields (65-92 %) and enantioselectivities (70-91 %) (Scheme 1.5).



Scheme 1.5 Thiourea-catalyzed asymmetric Strecker reaction (First-Generation Catalyst)

The concept of the catalyst design originated from the initial research object to develop a potential tridentate chiral ligand for organometallic catalysis.[28,29] Based on the results of parallel screening and conventional linear optimization, polystyrene-bound **1-18** was identified as the optimal catalyst in terms of best enantioselectivity which was higher than metal-containing alternatives evaluated under otherwise identical conditions. On the basis of the core structural features of polystyrene-bound **1-18**, the Jacobsen group incorporated three important components into this practical Schiff base thiourea derivative **1-14**, (1*R*, 2*R*)-diaminocyclohexane unit as a chiral backbone, α-amino acid unit (*L*-tert-Leucin) as a chiral diverse function, salicylaldimine unit as a sterically demanding function. Experimental results conceived these components as crucial elements for the formation of precise chiral environment in the transition state.

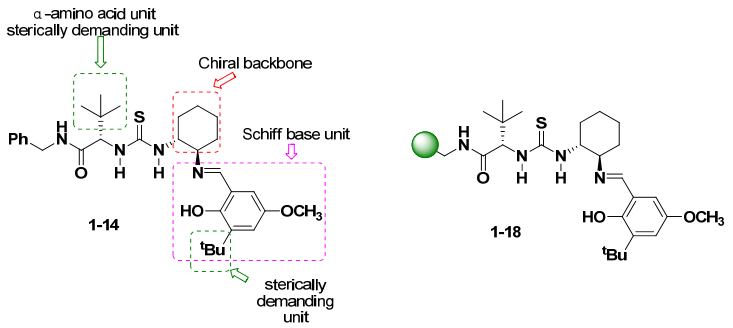


Figure 1.3 The key features of Schiff base thiourea catalyst **1-14** and polystyrene-bound **1-18**.

[29] Yu, X. H.; Wang, W. *Chem. Asian J.* **2008**, *3*, 516.

Four years later, this assumption was proved by a mechanistic study based on NMR, structure-activity, kinetic and theoretical analysis. This study revealed that high catalytic activity could be ascribed to the thiourea group which coordinated and activated the imine (*Z*)-isomer *via* an explicit dual H-bond interaction with the lone pair of imine nitrogen. This well-defined chiral environment could largely minimize the steric interactions between the large imine substitute and the thiourea moiety (Figure 1.4).[30]

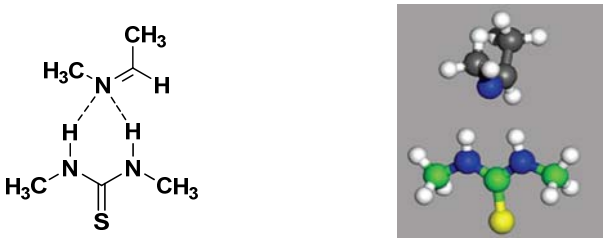
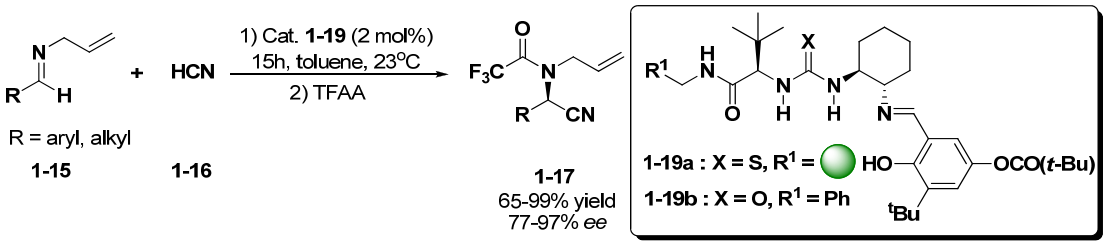


Figure 1.4 Dual H-bond interaction in the thiourea-catalyzed enantioselective Strecker reaction

In view of the vital structure of catalyst **1-18**, further optimization of a new parallel library revealed that both the polymer-bound catalyst **1-19a** and non-immobilized urea analogue **1-19b** could be employed for the direct construction of diverse unnatural aromatic and aliphatic substituted α-aminonitriles **1-17** in high yields and enantiomeric excesses (Scheme 1.6). Remarkably, the utilization of resin-bound catalyst **1-19a** could simplify the purification process by simple filtration and solvent removal. Moreover, the catalytic activity and enantio induction of **1-19a** still remained even after over ten times recycles.[31]

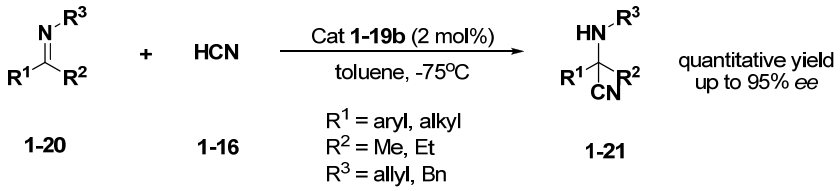


Scheme 1.6 Asymmetric Strecker reaction catalyzed by Schiff base thiourea catalysts **1-19**

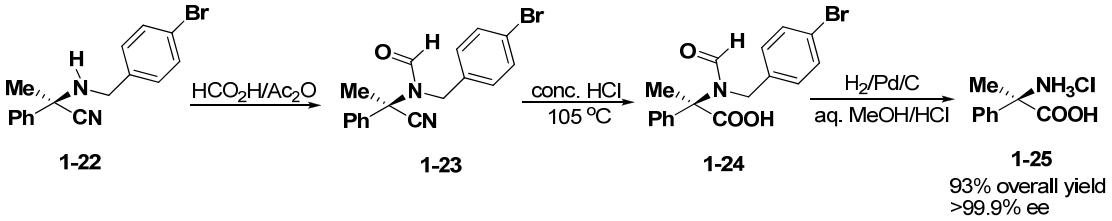
In addition to the successful applications of Schiff base thiourea catalysts in the

[30] Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012.
[31] Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2000**, *39*,1279.

Strecker reaction of *N*-aldimines, Jacobsen and co-workers also expanded this reaction substrate scope to ketoimines. The first highly enantioselective Strecker reaction of HCN to ketoimines **1-20** was described to construct α-quaternary α-amino acid precusors **1-21** in the presence of readily available and recyclable Schiff base catalyst **1-19b** in quantitative isolated yields and up to 95% enantioselectivities (Scheme 1.7).[31] Furthermore, the authors documented a concise and effective formylation/hydrolysis sequence to convert the α-quaternary α-aminonitrile adducts **1-21** to the respective α-quaternary α-amino acids in high yields (for example, α-methyl phenylglycine **1-25**, Scheme 1.8).[32]



Scheme 1.7 Asymmetric Strecker reaction of HCN to ketoimines **1-20.**

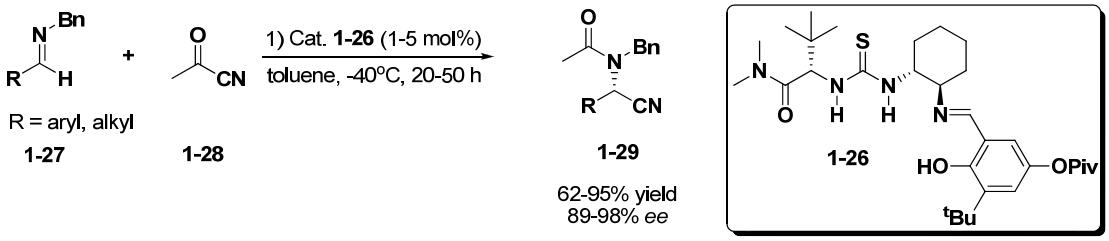


Scheme 1.8 The synthesis of α-methyl phenylglycine **1-25.**

Due to the extremely high toxicity and volatility of the problematic HCN, List and coworkers replaced it with commercially available liquid reagent acetyl cyanide **1-28** as the cyanide source in the highly enantioselective acyl-Strecker reaction.[33] The Jacobsen catalyst **1-26** turned out to be an efficient and practical organocatalyst to promote the acetylcyanation of diverse *N*-benzyl aliphatic and aromatic aldimines **1-27** in moderate to high yields and excellent enantioselectivities (Scheme 1.9). Furthermore, the desired *N*-protected α-aminonitriles **1-29** could be readily converted into the corresponding α-amino acid salts without erosion of enantioselectivities through acid-mediated hydrolysis and hydrogenolysis. Subsequently, the List group

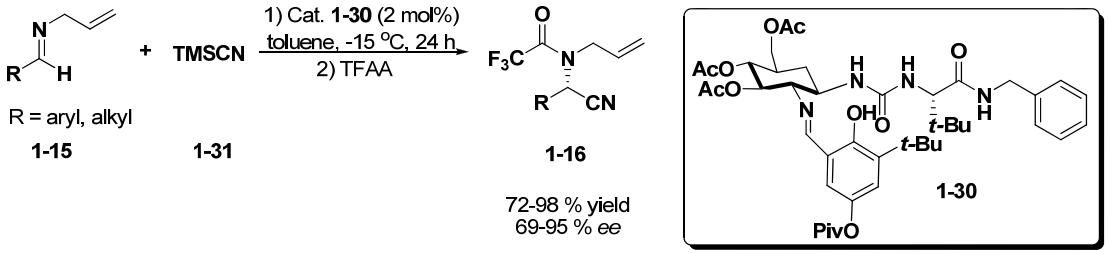
[32] Vachal, P.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 867.
[33] Pan, S. C.; Zhou, J.; List, B. *Angew. Chem. Int. Ed.* **2007**, *46*, 612.

further developed this methodology to the first asymmetric variant of three-component Strecker reaction in the presence of the same Jacobsen thiourea catalyst **1-26**. This one-pot highly economic reaction of aldehydes, amines, and acyl cyanides actually provided an attractive approach to construct different α-amino acid precusors.[34]



Scheme 1.9 Catalytic asymmetric acylcyanation of aldimines **1-27**.

In the same year, Kunz *et al.* designed and synthesized an efficient organic thiourea catalyst **1-30** incorporating a readily accessible chiral monosaccharidic backbone for the efficient asymmetric Strecker and Mannich reactions (Scheme 1.10).[35] In the presence of this catalyst, the Strecker reactions of a variety of aromatic *N*-allyl aldimines **1-15** and TMSCN **1-31** as cyanide source were accomplished in good to excellent yields (72-98%) and moderate to excellent enantioselectivities (69-95%). The powerful enantioinduction of catalyst **1-30** was considered to be ascribed to the restriction on the conformational flexibility of the common monosaccharidic backbone.

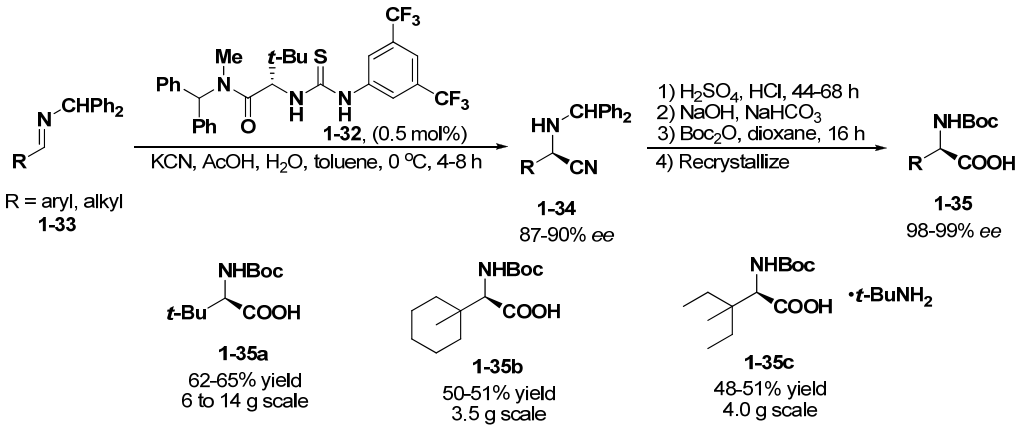


Scheme 1.10 Catalytic asymmetric acylcyanation of aldimines **1-15**.

Another significant progress in the urea/thiourea derivatives catalyzed Strecker

[34] Pan, S. C.; List, B. *Org. Lett.* **2007**, *9*, 1149.
[35] Becker, C.; Hoben, C.; Kunz, H. *Adv. Synth. Catal.* **2007**, *349*, 417.

reactions was reported by the Jacobsen group in 2009.[36] The authors designed and synthesized a simple and robust chiral amido-thiourea catalyst **1-32** without sensitive functional groups, which was compatible with safer and cheaper aqueous KCN salts compared with other hazardous cyanide sources. This catalyst was proved to be effective in the hydrocyanation of *N*-protected imines **1-33** derived from aryl, heteroaryl, alkyl and alkenyl aldehydes affording excellent enantioselectivities in the presence of 0.5 mol% catalyst loading under mild reaction conditions. The particularly attractive point of this methodology was its adaptability to large-scale synthesis of highly enantiomerically enriched natural and non-natural α-amino acids in one or two steps. The *tert*-butoxycarbonyl protected α-amino acids **1-35** were afforded from corresponding α-aminonitriles **1-34** through a two-step sequence involving H_2SO_4/HCl mediated hydrolysis and treatment with di-*tert*-butyl dicarbonate (Boc_2O).

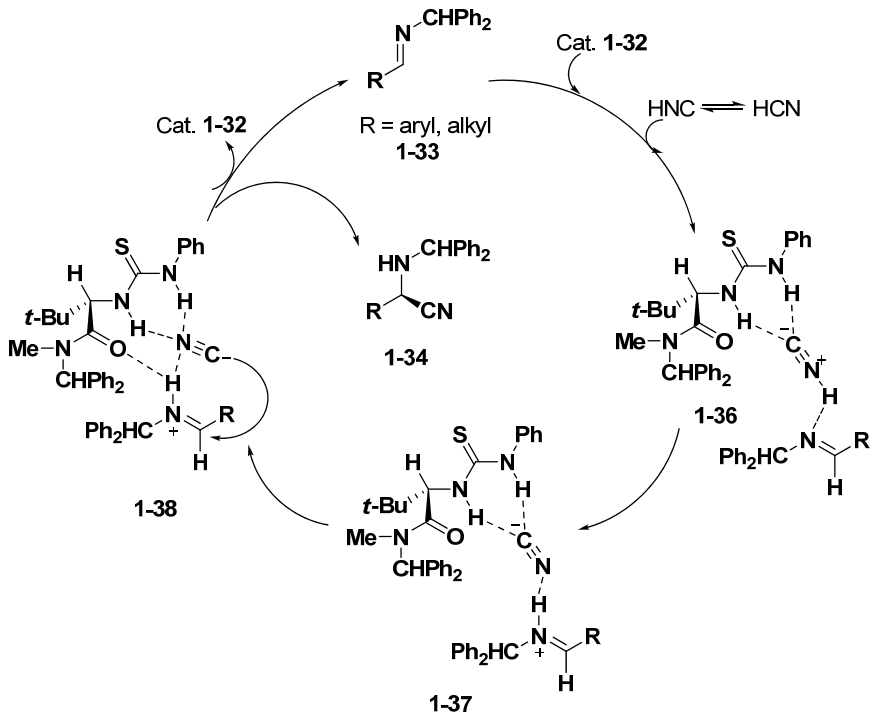


Scheme 1.11 Potassium cyanide-mediated Strecker synthesis catalyzed by chiral amido-thiourea catalyst **1-32.**

Authors also studied the detailed mechanism of this Strecker reaction through spectroscopic, labeling, kinetic and computational experiments.[37] The study of these experiments had shed light on a novel and unexpected mechanism involving formation of an iminium/cyanide ion pair that coordinated the catalyst through multiple non-covalent interactions rather than direct activation of the aldimine's

[36] Zuend, S. J.; Coughlin, M. P.; Lalonde, M. P.; Jacobsen, E. N. *Nature* **2009**, *461*, 968.
[37] Zuend, S. J.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2009**, *131*, 15358.

nitrogen through explicit double hydrogen bonding interactions. The proposed mechanism began with the coordinating of HNC, existing in equilibrium with HCN, to the thiourea moiety of the catalyst, followed by protonation of aldimine to form the key iminium-cyanide ion pair. In this catalyst-iminium-cyanide complex **1-37**, the amide carbonyl also provided one H-bond interaction to stabilize the iminium component. Subsequently, rotated cyanide anion attacked the iminium to yield the final α-aminonitrile **1-34** with concurrent release of the elegant organocatalyst **1-32** (Scheme 1.12).



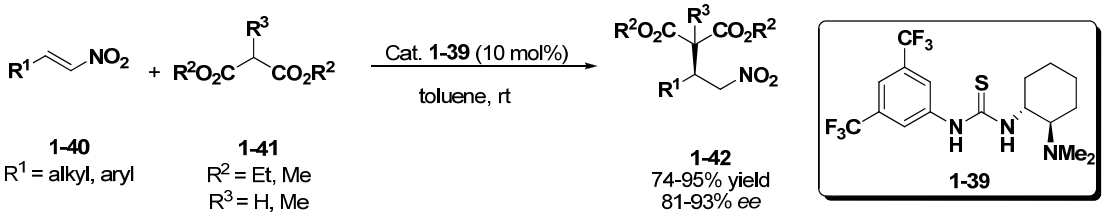
Scheme 1.12 Proposed mechanism of the Strecker reaction catalyzed by amino-thiourea catalyst **1-32**.

1.2.2 The Michael Reaction

As a powerful and efficient catalytic C–C or C–X bond formation reaction, the Michael reaction represents one of the most interesting and challenging fields in organic synthesis. It represents an important and atom-economic nucleophilic addition of enolate equivalents to Michael acceptors resulting in increasing complexity and structural diversity of the final products' carbon skeletons. A number of asymmetric

Michael additions to α,β-unsaturated carbonyl compounds have been reported in the presence of chiral organocatalysts.[38] It is noteworthy that a variety of compounds could operate as Michael donors, such as 1,3-diketones, β-ketoesters, malonates, malononitrile, α-nitro esters. These active methylenes are usually adjacent to electron-withdrawing groups which could increase the methylenes' acidity and stabilize the carbanion derived from the deprotonation of methylenes by base. Moreover, many activated alkenes constantly act as acceptors in typical Michael reactions, such as nitroalkenes, enones, enals, unsaturated imides, ynones, chalcones, maleimides, quinones and so on.

The first asymmetric Michael addition catalyzed by thiourea derivatives was documented by Takemoto group in 2003.[39] By the catalysis of the bifunctional amine thiourea organocatalyst **1-39**, a range of aromatic and aliphatic nitroalkenes **1-40** reacted with diethyl malonate **1-41** to afford the addition product nitroalkanes **1-42**, which possessed the versatility in further synthetic manipulation to other important organic functional groups, in yields ranging from 74-95% and with 81-93% *ee* values (Scheme 1.13).



Scheme 1.13 First enantioselective Michael addition catalyzed by Takemoto's bifunctional thiourea catalyst **1-39**.

Remarkably, it was the pioneering report about the design and synthesis of the bifunctional organocatalyst **1-39**, which bore a tertiary amine group, a thiourea moiety and a 1,2-*trans* diamine chiral scaffold. Actually, the concept of bifunctionality principle originated from highly catalytic natural enzymic systems, for example, serine protease. Furthermore, inspired by the catalyst design principles in the seminal work of Curran, Jacobsen and Schreiner, the Takemoto group utilized the key features

[38] a) see *Ref.* 1a; b) see *Ref.* 1b.
[39] Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672.

of biological H-bonding organocatalysis to develop a novel bifunctional thiourea catalyst. Through mimicking the "oxyanion hole" and histidine/aspartate proton shuttle system, the bifunctional organocatalyst respectively incorporated the corresponding thiourea moiety and base functionality into the chiral scaffold (1*R*, 2*R*)-diaminocyclohexane (Figure 1.5). The thiourea moiety donated explicit double H-bond to coordinate and activate the electrophile component, whereas the Brønsted basic functionality simultaneously activated the nucleophile resulting in higher rate enhancement and stereoinduction, in contrast with comparable monofunctional thiourea organocatalyst.[39, 40] The synthesis of this excellent Takemoto catalyst (bifunctional amine thiourea derivative **1-39**) triggered the rapid development of organocatalytic enantioselective transformations to afford natural and pharmaceutical products.

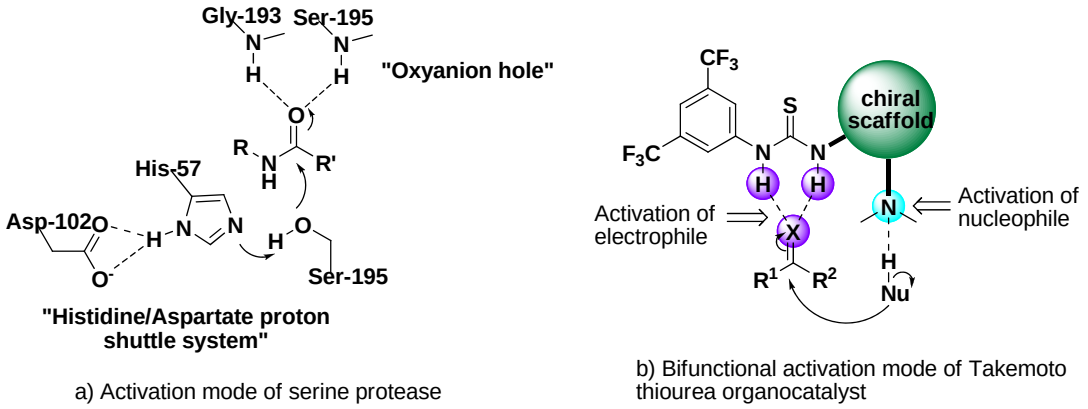
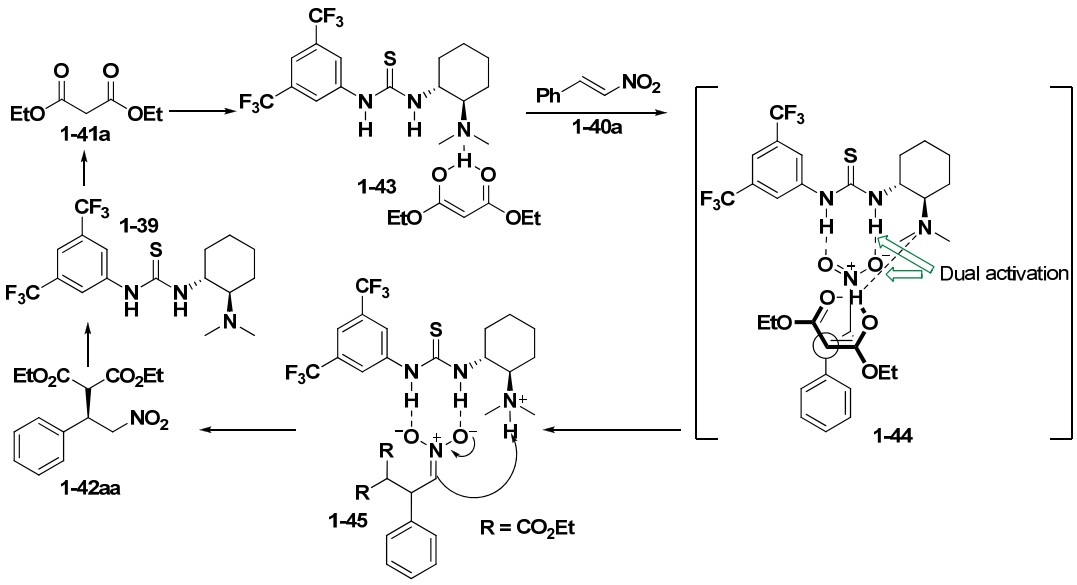


Figure 1.5 Comparison of activation modes between H-bond biocatalysis and bifunctional organocatalysis.

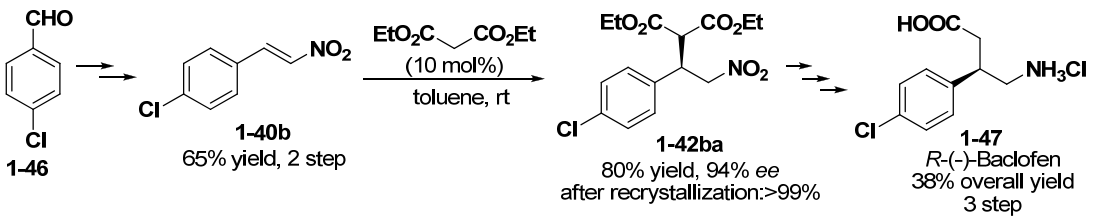
Subsequently, in 2005, the Takemoto group elucidated the plausible reaction mechanism according to the results of kinetic and catalyst modification studies (Scheme 1.14).[41] The six-membered enol form of diethyl malonate **1-41a** was firstly stabilized through H-bond interaction with the amino moiety of Takemoto catalyst **1-39**. Subsequently, the Michael acceptor *trans*-β-nitrostyrene **1-40a** reacted with the thiourea moiety of complex **1-43** through explicit double H-bond interactions resulting in the formation of a new ternary complex **1-44.** On the basis of the elegant

[40] Siau, W.-Y.; Wang, J. *Catal. Sci. Technol.* **2011**, *1*, 1298.
[41] Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119.

steric organization and proper relative organization of the reaction components, diethyl malonate **1-41a** attacked the β position of *trans*-β-nitrostyrene **1-40a** in a (*R*)-favored mode to form the nitronate complex **1-44**. This nitronate complex **1-44** was effectively stabilized through explicit dual H-bonds between the two amide protons and the two negatively charged oxygens of the nitro group. Finally, proton transfer from the ammonium group of the catalyst to the nitronate afforded the final Michael adduct. This study also demonstrated that various β-ketoesters and α-substituted β-ketoesters were compatible with this methodology with good to excellent diastereoselectivities and enantioselectivities. Furthermore, the synthetic utility of this protocol was shown by the vital step of the total synthesis of (*R*)-(–)-baclofen (Scheme 1.15), a widely acceptable antispastic agent.



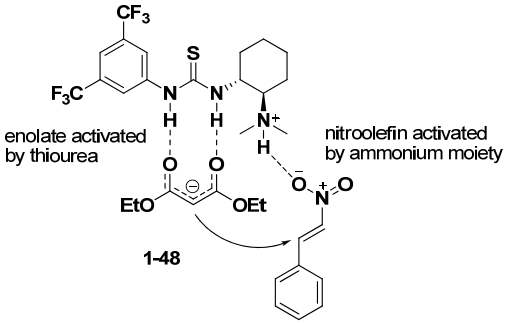
Scheme 1.14 Proposed mechanism of the first enantioselective Michael addition catalyzed by Takemoto's bifunctional amine thiourea organocatalyst **1-39**.



Scheme 1.15 Total synthesis of (*R*)-(–)-baclofen.

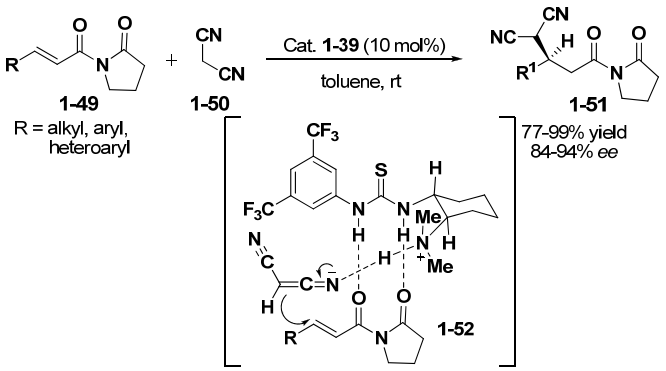
Compared with the Takemoto proposed dual activation mode, Papai *et al.* elucidated an alternative mechanistic insight of this reaction by using the *in silico*

study.[42] In their proposed dual activation mode **1-48** (Scheme 1.16), the Michael acceptor *trans*-β-nitrostyrene **1-40a** preferred to coordinate the generated ammonium group through single H-bonding interaction, while the enolate was H-bonded to the thiourea moiety of the catalyst. Although the activation mode was distinct from the above mentioned activation mechanism, both of them predicted the same stereochemistry.



Scheme 1.16 DFT-calculated dual activation mode **1-48**.

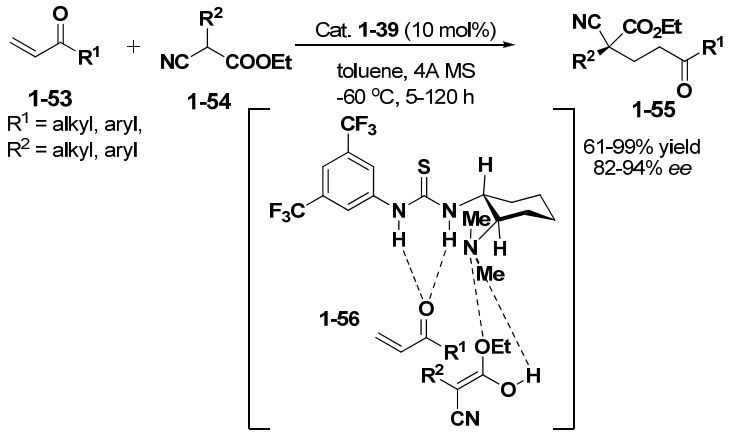
In order to expand the synthetic utility of the Takemoto amine thiourea catalyst **1-39**, the Takemoto group further demonstrated the first enantioselective Michael addition of the highly acidic malonitrile **1-50** to α,β-unsaturated imides **1-49**.[43] As depicted in Scheme 1.17, the pyrrolidinone moiety of α,β-unsaturated imides **1-49** played a crucial role in the formation of explicit dual H-bond interaction in the ternary complex **1-52**. In addition, the lability of pyrrolidinone moiety revealed the feasibility of the general transformation of Michael adducts **1-51** to esters, aldehydes and carboxylic acids.



Scheme 1.17 Asymmetric Michael reaction of malononitrile to α,β-unsaturated imides **1-49**.

[42] Hamza, A.; Schubert, G.; Soós, T.; Papai, I. *J. Am. Chem. Soc.* **2006**, *128*, 13151.
[43] Hoashi, Y.; Okino, T.; Takemoto, Y. *Angew. Chem. Int. Ed.* **2005**, *44*, 4032.

Apart from malonates and malonitrile, α-substituted cyanoacetates **1-54** incapable of providing two strong H-bond binding sites were still demonstrated by the Chen group to be applied in the Takemoto bifunctional amine thiourea catalyzed enantioselective Michael addition.[44] A wide range of α-aryl or alkyl cyanoacetates **1-54** reacted with vinyl ketones **1-53** resulting in constructing multifunctional compounds α,α-disubstituted cyanoacetates **1-55** with a configurationally stable quaternary stereocenter in moderate to excellent yields (61-99%) and enantioselectivities (82-97% *ee*). The enantiopure α,α-disubstituted cyanoacetates **1-55** could be smoothly converted to various optical pure $\beta^{2,2}$-amino acids, which were important unique pharmacological entities in natural products. Based on the experimental and computational studies, the authors proposed an interesting reaction model **1-56** that tertiary amine thiourea catalyst **1-39** synergistically activated the nucleophile and electrophile through multiple hydrogen-bonding interactions.

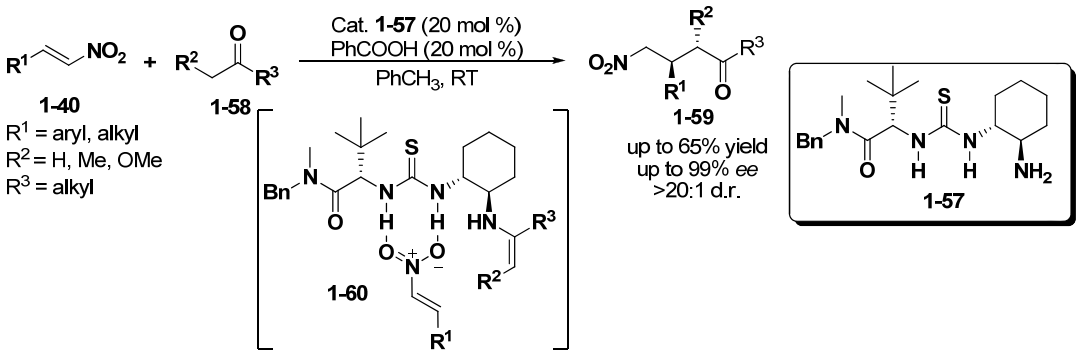


Scheme 1.18 Asymmetric Michael reaction of α-substituted cyanoacetates **1-54** to vinyl ketones **1-53**.

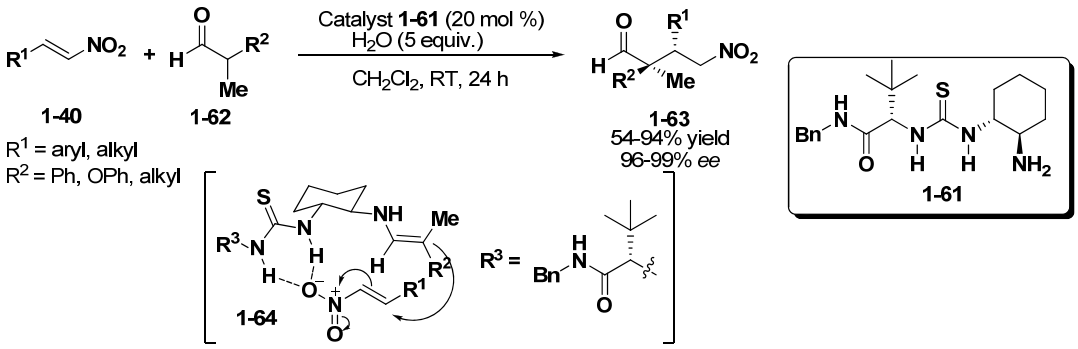
To expand the scope of Michael donors, Huang and Jacobsen further modified the monofunctional Jacobsen thiourea catalyst to develop a novel bifunctional primary amine thiourea catalyst **1-57**, which incorporated a primary amine moiety to replace the Schiff base unit. This highly enantioselective catalyst was particularly efficient for the conjugate addition of various aromatic or aliphatic nitroalkenes **1-40** to a wide variety of ketones **1-58** with up to 99% *ee* values and good-to-excellent

[44] Liu, T. Y.; Li, R.; Chai, Q.; Long, J.; Li, B. J.; Wu, Y.; Ding, L. S.; Chen, Y. C. *Chem. Eur. J.* **2007**, *13*, 319.

diastereoselectivities. In this reaction, the bifunctional organocatalyst synergetically activated both the electrophile, by H-bonding interaction between thiourea moiety and nitro group, and the nucleophile by forming a *Z*-enamine intermediate (Scheme 1.19).[45]



Scheme 1.19 Direct Michael addition of ketones **1-58** to nitroalkenes **1-40** catalyzed by primary amine thiourea catalyst **1-57**.



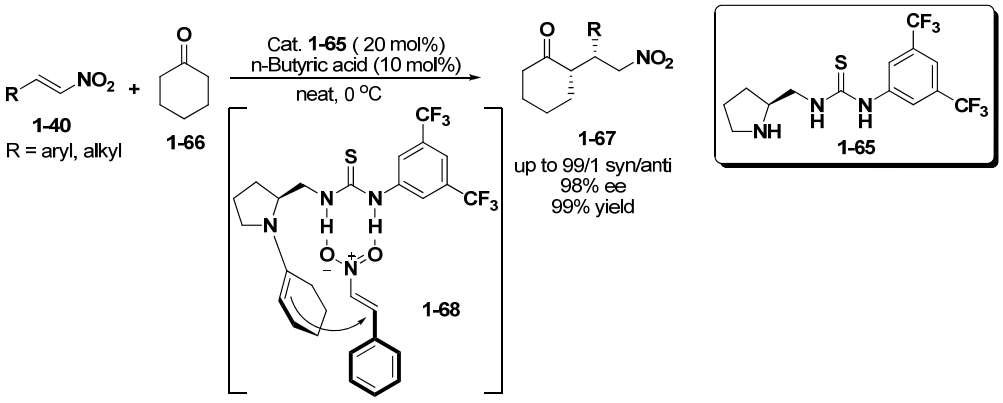
Scheme 1.20 Direct Michael addition of α,α-disubstituted aldehydes **1-62** to nitroalkenes **1-40** catalyzed by primary amine thiourea **1-61**.

In addition to the above mentioned ketones, α,α-disubstituted aldehydes **1-62** were also compatible with direct and most appealing approach to afford versatile multifunctional nitroalkanes **1-63** in high yields, excellent enantioselectivities and *syn*-favored diastereoselectivities in the presence of the primary amine thiourea catalyst **1-61**.[46] In the author's proposed mechanism, the thermodynamically favored (*E*)-enamine was responsible for *syn*-favored diastereoselectivity. The explicit double H-bonding interaction between thiourea motif and only a single oxygen atom of nitroalkenes facilitated the close proximity of the enamine to a variety of aromatic and aliphatic nitroalkenes **1-40**. The addition of 5 equiv. water accelerated the final imine

[45] Huang, H. B.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2006**, *128*, 7170.
[46] Lalonde, M. P.; Chen, Y. G.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2006**, *45*, 6366.

hydrolysis and effected the initial imine formation.

Since impressive progress has been made by tertiary amine and primary amine thiourea organocatalysts, the Tang group paid attention to develop a novel bifunctional secondary amine thiourea organocatalyst **1-65**, combining the pyrrolidine and thiourea functionalities in the well-designed chiral skeleton.[47] In the presence of 20 mol % of catalyst **1-65** and 10 mol % of *n*-butyric acid, cyclohexanone **1-66** reacted with both aryl and alkyl nitroolefins **1-40** to furnish Michael adducts **1-67** with high enantio- and diastereoselectivities (Scheme 1.21). As shown in the proposed stereochemical model **1-68**, the pyrrolidine moiety firstly reacted with the carbonyl group of cyclohexanone **1-66** to form an enamine, while the thiourea motif of the catalyst donated the explicit double H-bond to activate the nitroolefin. The generated enamine attacked the activated nitroolefin from the *re*-face in a rigid chiral environment, which accounted for the stereochemistry of the final adduct **1-67**, as well as high enantioselectivity and high diastereoselectivity.



Scheme 1.21 Asymmetric Michael reaction promoted by chiral pyrrolidine thiourea **1-65** and the stereochemical model **1-68**.

Cinchona alkaloids isolated from the bark of trees in the cinchona genus could act as especially useful pharmaceutical agents in the treatment of various diseases. They combine a secondary hydroxyl group at C-9 position and a basic quinuclidine moiety in a well-defined chiral environment. On the basis of their structural tunability and ready availability, a series of natural cinchona alkaloids (Figure 1.6) and their

[47] Cao, C. L.; Ye, M. C.; Sun, X. L.; Tang, Y. *Org. Lett.* **2006**, *8*, 2901.

analogues have been applied in a broad range of organic transformations as chiral auxiliaries, as chiral ligands in transition metal mediated processes, and as phase transfer catalysts and organocatalysts.[48]

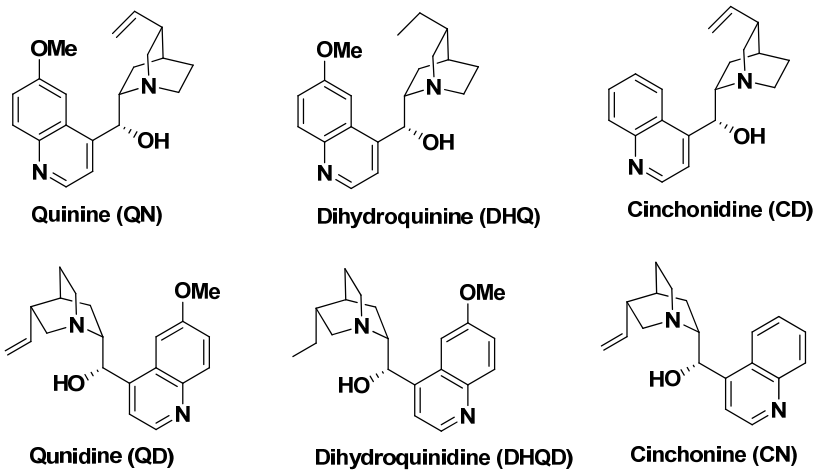


Figure 1.6 Various natural cinchona alkaloids.

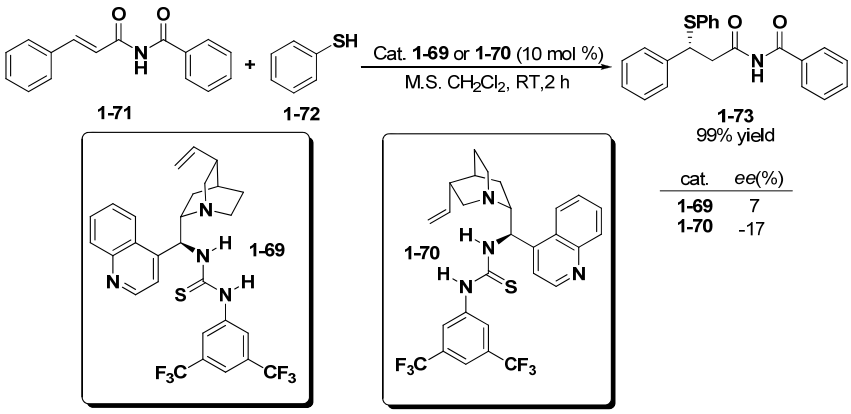
The pioneering work of cinchona alkaloids' asymmetric induction, reported by Wynberg and coworkers in 1981, demonstrated that the *sulfa*-Michael addition reactions of aromatic thiols to cycloalkenones could be promoted by catalytic amount of unmodified natural QN, QD, CD, CN.[49] The rate enhancements and enantioselectivities conducted by natural cinchona alkaloids were higher than those of C9-OH acylated cinchona alkaloid derivatives, which implied the potential application of cinchona alkaloids as bifunctional catalysts. They provided a plausible dual activation mode through H-bonding from the C-9 OH group and deprotonation from the basic quinuclidine motif.

In view of the dual activation mode of natural cinchona alkaloids, four groups independently modified and developed these catalysts by incorporating privileged urea/thiourea moieties, better H-bond donors, to substitute the C-9 hydroxy group with or without inversion of C9 configuration. In addition, the C'-6 position could also be modified by combining a rigid 3,5-bis(trifluoromethyl)phenyl-thiourea component,

[48] a) Kacprzak, K.; Gawronski, J. *Synthesis* **2001**, 961; b) Tian, S. K.; Chen, Y.; Hang, J.; Tang, L.; McDaid, P.; Deng, L. *Acc. Chem. Res.* **2004**, *37*, 621.
[49] a) Helder, R.; Arends, R.; Bolt, W.; Hiemstra, H.; Wynberg, H. *Tetrahedron Lett.* **1977**, *18*, 2181; b) Hiemstra, H.; Wynberg, H. *J. Am. Chem. Soc.* **1981**, *103*, 417.

while the C9-OH group was revised to an ether or ester. These variable modifications enhanced the catalytic activity and influenced the relative stereochemistry between Brønsted acidic and Brønsted basic groups. On account of these advantages benefited from modifications on chiral scaffolds, (thio)urea-substituted cinchona alkaloid derivatives have emerged in the last eight years as elegant, robust and tunable bifunctional organocatalysts in extensive synthetically useful transformations.[50]

The first synthesis and application of thiourea-substituted cinchona alkaloids were reported by Chen and co-workers. They revealed that the thiourea substituted cinchonidine and cinchonine-derived bifunctional catalysts **1-69** and **1-70** respectively catalyzed the *sulfa*-Michael addition of thiophenol **1-72** to α,β-unsaturated imide **1-71** with high efficiency (99% yield/2h), but low enantioselectivity (7% or -17% *ee*) (Scheme 1.22).[51]

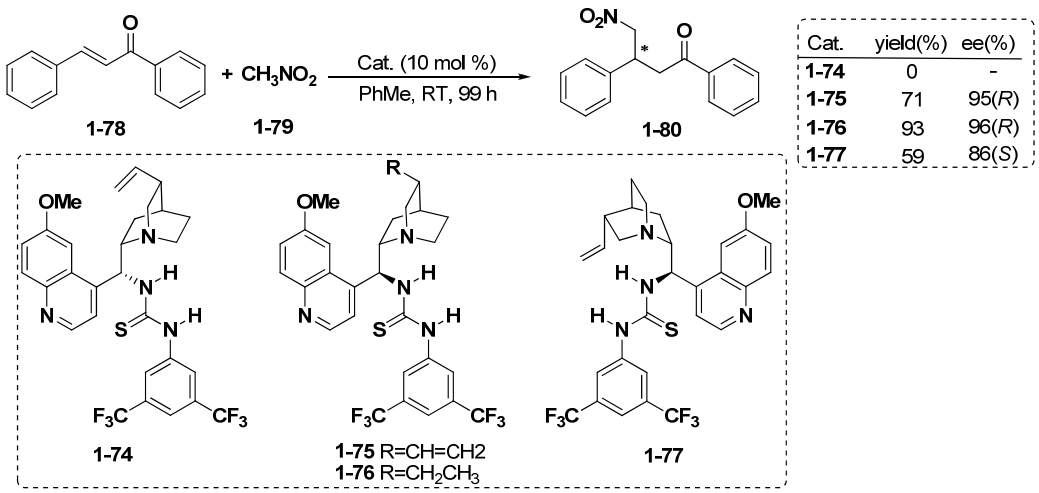


Scheme 1.22 The first report of thiourea-substituted cinchona alkaloid catalyzed *sulfa*-Michael addition.

Subsequently, a significant breakthrough in this field was made by Soós and co-workers in the same year.[52] They developed a suite of thiourea-substituted quinine/quinidine-derived cinchona alkaloid catalysts **1-74** – **1-77** (Scheme 1.23) in the *nitro*-Michael addition of nitromethane **1-79** to chalcone **1-78**. Surprisingly, the bifunctional thiourea derivative with natural stereochemistry at C-9 (i.e. **1-74**) showed no catalytic activity, while its epimers (**1-75**) exhibited high activity (71% yield) and

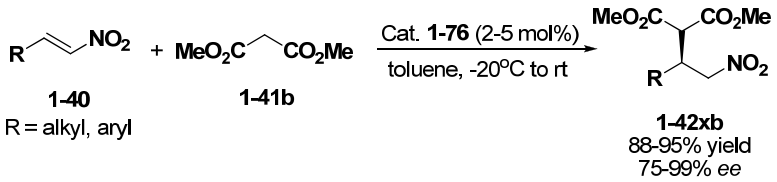
[50] Connon, S. J. *Chem. Commum.* **2008**, 2499.
[51] Li, B. J.; Jiang, L.; Liu, M.; Chen, Y. C.; Ding, L. S.; Wu, Y. *Synlett* **2005**, 603.
[52] Vakulya, B.; Varga, S.; Csampai, A.; Soós, T. *Org. Lett.* **2005**, *44*, 6367.

excellent enantioselectivity (95% *ee*). So the relative orientation of thiourea and quinuclidine moiety played a crucial role in the catalysis. It was notable that the system operated *via* a bifunctional synergistic activation mechanism.

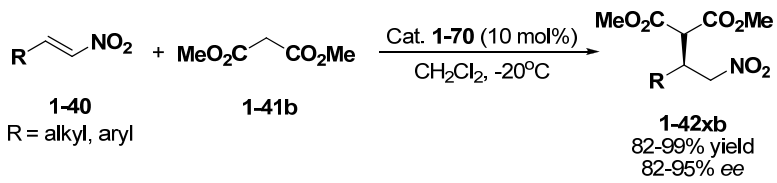


Scheme 1.23 Organocatalysis of the *nitro*-Michael addition of nitromethane to chalcone.

Subsequently, the Connon group[53] and Dixon group[54] demonstrated that the typical asymmetric Michael reaction of dimethyl malonate **1-41b** to nitroalkenes **1-40** could be promoted by their independently developed similar (thio)urea organocatalysts derived from by the corresponding **DHQ/DHQD** (Scheme 1.24) or **CN** (Scheme 1.25) backbones with excellent catalytic activities and enantioselectivities.



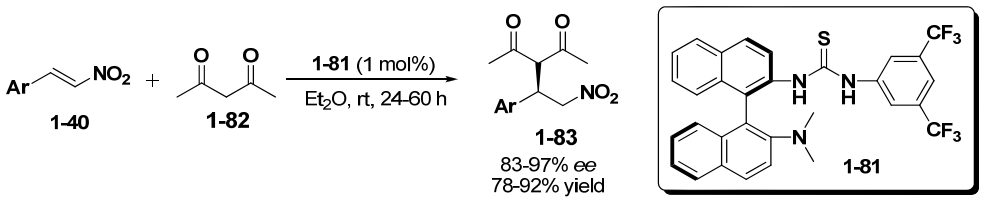
Scheme 1.24 The typical Michael addition catalyzed by thiourea-substituted **DHQ 1-76.**



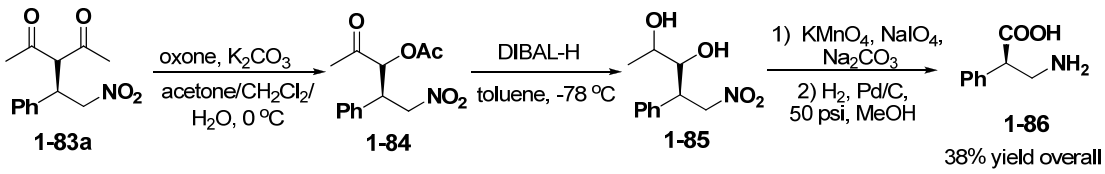
Scheme 1.25 The typical Michael addition catalyzed by cinchonine-derived thiourea **1-70.**

[53] McCooey, S. H.; Connon, S. J. *Angew. Chem. Int. Ed.* **2005**, *44*, 6367.
[54] Ye, J.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481.

Based on the catalytically privileged axially chiral binaphthyl scaffold[55], Wang *et al.* designed a new class of bifunctional tertiary amine thiourea catalysts prepared from commercially available (*R*)-binaphthyl amine.[56] In the presence of binaphthyl thiourea catalyst **1-81**, the asymmetric typical Michael reactions between 1,3-diketone **1-82** and nitroolefins **1-40** bearing electron-donating and electron-withdrawing substituents on aryl group were carried out at room temperature to furnish the desired Michael adducts **1-83** (Scheme 1.26). It was worth noting that a synthetically useful protocol was developed with the Michael adducts **1-83** as starting materials to form valuable α-substituted-β-amino acids **1-86**. Similar with Takemoto catalyst's activation mode, binaphthyl thiourea catalyst was expected to simultaneously coordinate and stabilize both the enolized 2,4-pentandione and nitroolefins through the basic amine moiety and thiourea motif.



Scheme 1.26 The typical Michael reactions catalyzed by binaphthyl-derived thiourea **1-81**.

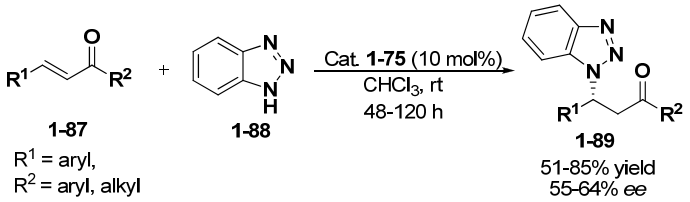


Scheme 1.27 The synthetic utility of **1-81** catalyzed Michael reaction.

Apart from the typical Michael addition for C–C bond formation, *aza*-, *sulfa*- and *oxa*- Michael addition for new C–N, C–S and C–O bond formation also captured much attention of many research groups to construct particularly useful heteroatom compounds. Particularly, the *aza*-Michael addition was considered as the most direct and atom-economic approach to access valuable nitrogen-containing compounds with

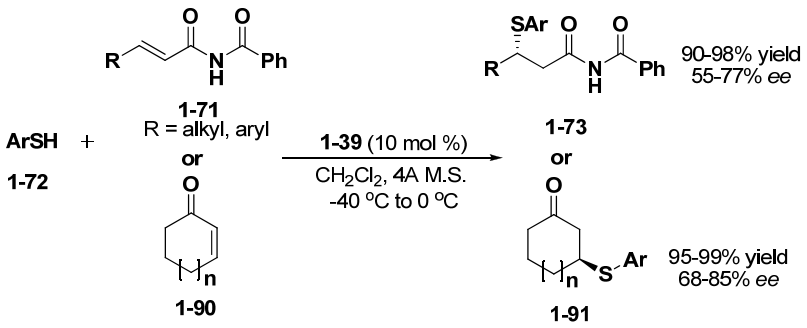
[55] Yoon, T. P.; Jacobsen, E. N. *Science* **2003**, *299*, 1691.
[56] Wang, J.; Li, H., Duan, W. H.; Zu, L.; Wang, W. *Org. Lett.* **2005**, *7*, 4713.

broad synthetic utility and application in organic and medicinal chemistry. In the presence of catalytic amount of quinine-derived thiourea **1-75**, enantioselective *aza*-Michael reaction of 1*H*-benzotriazole **1-88** as a nitrogen source was accomplished (Scheme 1.28).[57] A variety of α,β-unsaturated ketones **1-87** were well tolerated in this protocol to form the desired products in moderate to good yields (51-85%) and moderate enantioselectivities (55-64%). The quinine-derived thiourea **1-75** simultaneously activated the enones **1-87** through double hydrogen-bonding and 1*H*-benzotriazoles **1-88** by amine-group mediated deprotonation.



Scheme 1.28 The *aza*-Michael addition catalyzed by quinine-derived thiourea **1-75**.

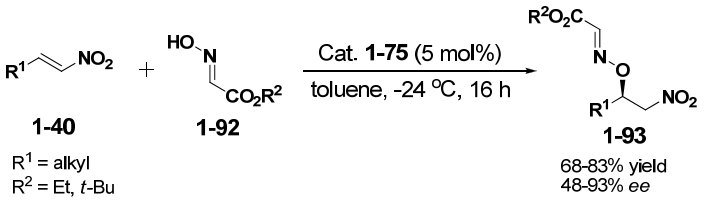
Although the *sulfa*-Michael addition reaction catalyzed by the cinchonidine/ cinchonine thiourea derivatives failed to demonstrate good catalytic activities and enantioselectivities, Chen and co-workers reported that the Takemoto catalyst **1-39** based on a more rigid skeleton of chiral 1,2-cyclohexanediamine could efficiently promote the asymmetric *sulfa*-Michael addition of arenethiols **1-72** to 2-cycloalkenones **1-90** and α,β-unsaturated *N*-benzoyl imides **1-71** with up to 85% *ee* value.[58]



Scheme 1.29 The *sulfa*-Michael addition catalyzed by Takemoto catalyst **1-39**.

[57] Wang, J.; Zu, L.; Li, H.; Xie, H.; Wang, W. *Synthesis,* **2007**, 2576.
[58] Li, B. J.; Jiang, L.; Liu, M.; Chen, Y. C.; Ding, Li. S.; Wu, Y. *Synlett* **2005**, *4*, 603.

The enantioselective *oxa*-Michael reaction [59] of functionalized aliphatic nitroalkenes **1-40** with ethyl glyoxylate oxime **1-92** as oxygen source was conducted as well in the presence of 5 mol% quinine-derived thiourea catalyst **1-75** to obtain the final optically active aliphatic nitro- or aminoalcohols **1-93** (Scheme 1.30).[60] In the plausible transition model, the oxime was activated by single hydrogen-bonding with basic quinuclidine nitrogen atom, while the Michael acceptor was coordinated and activated by double hydrogen-bonding with the C9-thiourea motif. The synthetic utility of this approach was demonstrated by selective cleavage of O-N bond to furnish the corresponding enantiopure *N*-Boc protected amino alcohol (1. H_2/Pd/C; 2. $(Boc)_2O$) or (*R*)-configured β-hydroxy nitroalcohol ($ZrCl_4$/$NaBH_4$/THF).

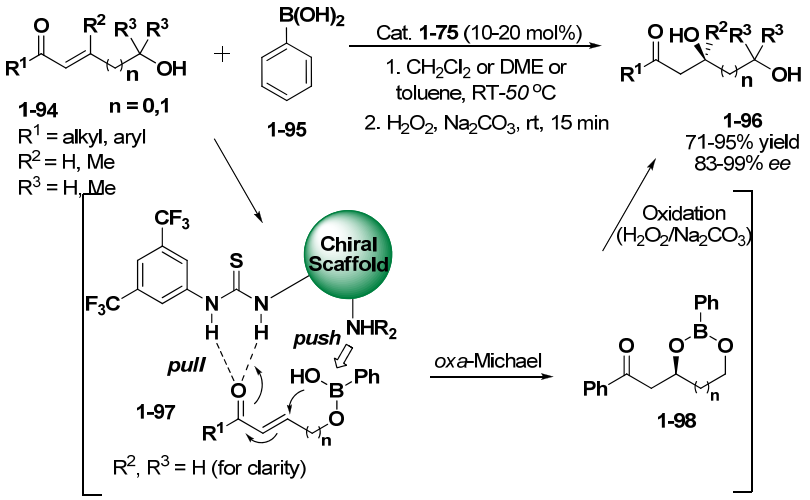


Scheme 1.30 The *oxa*-Michael addition catalyzed by quinine-derived thiourea **1-75**.

Furthermore, an unprecedented intramolecular *oxa*-Michael addition reaction was described by the Flack group to accomplish the β-hydroxylation of hydroxyl-enone substrates **1-94**.[61] Under the catalysis of a push/pull bifunctional quinine-derived thiourea **1-75**, a variety of γ-hydroxy-α,β-enones and δ-hydroxy-α,β-enones **1-94** reacted with phenylboronic acid **1-95** to generate boronic acid hemiesters **1-97** in situ, which attacked the β-position of enones to furnish the chiral target diols **1-96** after mild oxidative work-up with high yields and excellent enantioselectivities. As depicted in Scheme 1.31, the complexation between the tertiary nitrogen with boron atom (push effect) and the hydrogen-bonding coordination between the carbonyl group with the thiourea motif (pull effect) synergistically increased the nucleophilicity of the boronate oxygen and created a

[59] Recent reviews on *oxa*-Michael reactions: a) Nising, C. F.; Bräse, S. *Chem. Soc. Rev.* **2008**, *37*, 1218; b) Nising, C. F.; Bräse, S. *Chem. Soc. Rev.* **2012**, *41*, 988.
[60] Dinér, P.; Nielsen, M.; Bertelsen, S.; Niess, B.; Jørgensen, K. A. *Chem. Commun.* **2007**, 3646.
[61] Li, D. R.; Murugan, A.; Flack, J. R.; *J. Am. Chem. Soc.* **2008**, *130*, 46.

well-defined chiral environment, which accounted for the excellent enantioselectivity of this intramolecular *oxa*-Michael reaction.



Scheme 1.31 The intramolecular *oxa*-Michael addition of hydroxyl-enone substrates **1-94**.

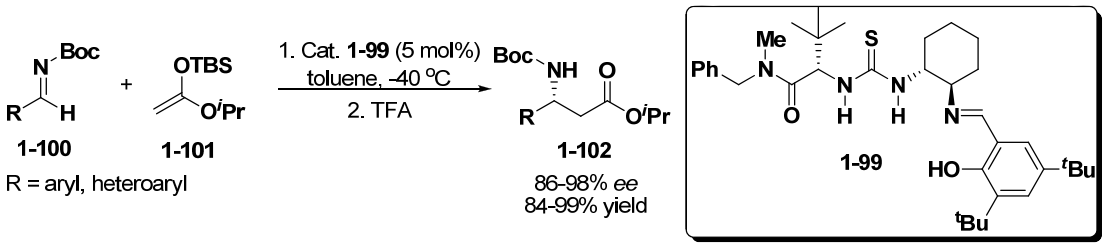
1.2.3 The Mannich Reaction

The Mannich reaction, named after chemist Carl Mannich[62], has presented as a classic and particularly powerful carbon–carbon bond-forming reaction in organic chemistry. This reaction consists of an amino alkylation of α-proton adjacent to a carbonyl functional group with aldehydes/ketones and amines with the generation of β-amino carbonyl compounds. In addition to α-CH-acidic compounds, activated phenyl substitutes and several electron-rich heterocycles, such as furan, pyrrole, thiophene and indole could be compatible with this protocol. Due to functional and structural diversity of final products, the mannich reaction has always emerged as a key step in medicinal chemistry. Up to now, significant advances have been made in the development of catalytic enantioselective Mannich reactions.[63]

In 2002, Wenzel and Jacobsen utilized a Schiff base thiourea derivative **1-99** to

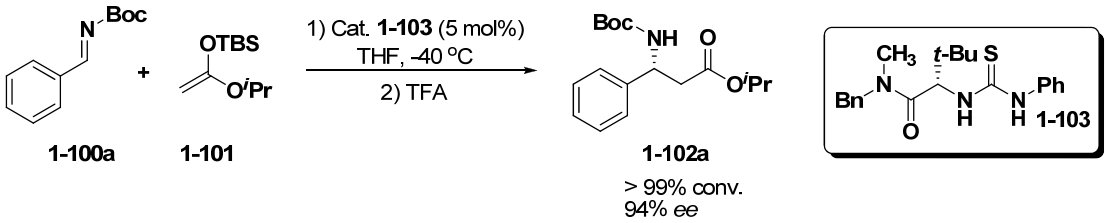
[62] Mannich, C.; Krösche, W. *Archiv der Pharmazie* **1912**, *250*, 647.
[63] For reviews on the asymmetric Mannich reaction, see: (a) Benaglia, M.; Cinquini, M.; Cozzi, F. *Eur. J. Org. Chem.* **2000**, *4*, 563; b) Denmark, S.; Nicaise, J. C. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, **1999**; Vol. 2, pp 954; c) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069.

induce the asymmetric Mannich addition of *N*-Boc protected aldimines **1-100** with silyl ketene acetal **1-101**. [64] Both aryl and heteroaryl derivatives were consistent with this methodology to afford β-amino ester products **1-102** with nearly quantitative yields and up to 98% enantioselectivities (Scheme 1.32).



Scheme 1.32 The Mannich reaction of *N*-Boc-protected aldimines **1-100** and silyl ketene acetal **1-101**.

Subsequently, Jacobsen group revealed that in the above-mentioned Mannich reaction the diaminocyclohexane-derived Schiff base portion of the typical Jacobsen monofunctional thiourea catalyst was not crucial for the catalytic activity and enantioinduction. The remarkably simpler catalyst **1-103** incorporating a phenyl group instead of diaminocyclohexane-derived Schiff base moiety exhibited improved activity (> 99% conv.) and high enantioselectivity (94% *ee*) (Scheme 1.33).[65]

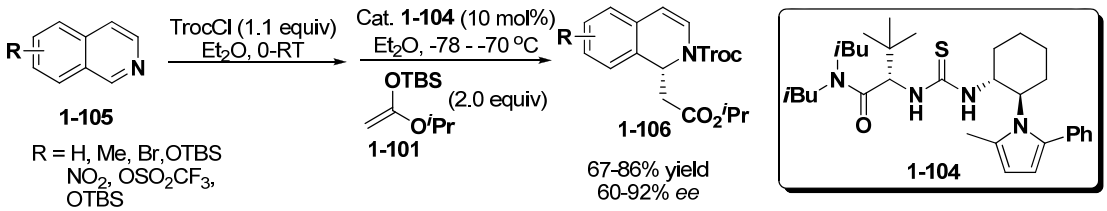


Scheme 1.33 The Mannich reaction catalyzed by simple amino acid derived organocatalyst **1-103**.

Although attractive progress has been made by classic Jacobsen Schiff base thiourea catalysis in many enantioselective transformations, it is necessary to further develop some novel thiourea catalysts in catalytic enantioselective methodologies engaging aromatic π systems as starting materials. In 2005, Taylor and Jacobsen reported asymmetric acyl-Mannich reactions of substituted isoquinoline substrates **1-105** and silyl ketene acetal **1-101** to furnish a number of dihydroisoquinolines **1-106**

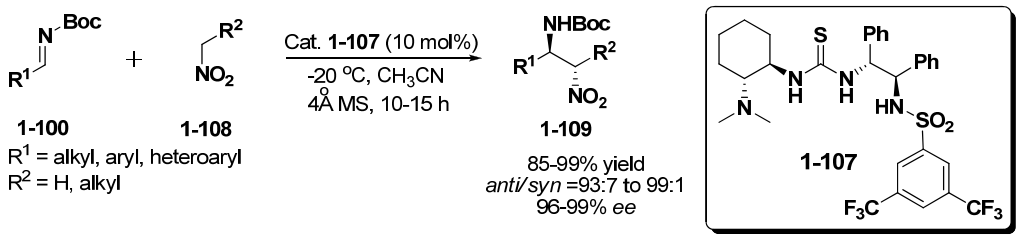
[64] Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964.
[65] Wenzel, A. G.; Lalonde, M. P.; Jacobsen, E. N. *Synlett* **2003**, *12*, 1919.

in good yields and excellent enantioselectivities in the presence of a pyrrole-derived thiourea catalyst **1-104**.[66] Moreover, the synthetic utility of this methodology was demonstrated by the conversion of acyl-Mannich adduct dihydroisoquinolines **1-106** to the corresponding enantioenriched 1-substituted tetrahydroisoquinoline derivatives through hydrogenation of the enamide moiety (Et_3SiH/TFA) and reductive cleavage of the trichloroethyl carbamate group (Zn/AcOH).



Scheme 1.34 Acyl-Mannich reaction of substituted isoquinolines **1-105**.

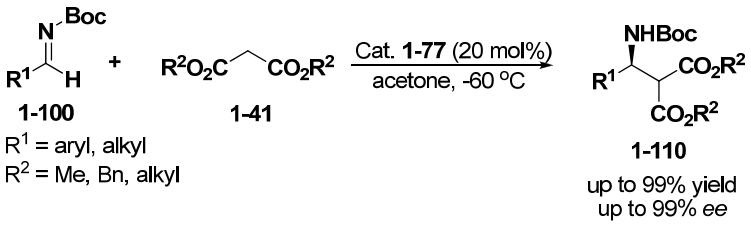
Although several organocatalytic asymmetric nitro-Mannich reactions have been reported to afford excellent enantioselectivity and high antiselectivity,[67] it was not until 2008 that Wang *et al.* described the best result for enantioselective organocatalytic nitro-Mannich reaction in the presence of a new class of bifunctional amine-thiourea catalyst **1-107**.[68] This bifunctional catalyst bearing multiple hydrogen bonding donors (an extra hydrogen bonding donor in sulphonamide moiety) showed enormously enhanced reaction rates, good to excellent yields (85-99%), high *anti*-selectivities (93:7-99:1) and excellent enantioselectivities (96-99%) (Scheme 1.35).



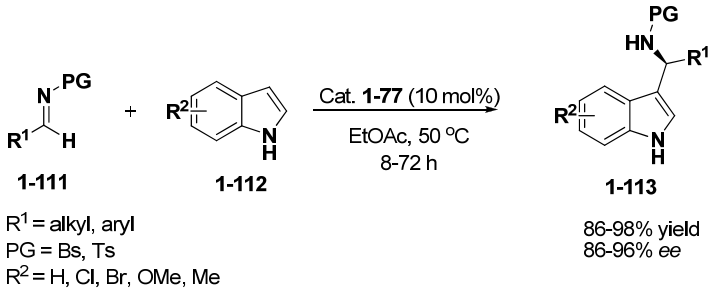
Scheme 1.35 Nitro-Mannich (*aza*-Henry) reactions catalyzed by multiple hydrogen bonding donors **1-107**.

[66] Taylor, M. S.; Tokunaga, T.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2005**, *44*, 6700.
[67] a) Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 625; b) Xu, X.; Furukawa, T.; Okino,T.; Miyabe, H.; Takemoto, Y. *Chem. –Eur. J.* **2006**, *12*, 466.
[68] Wang, C. J.; Dong, X. Q.; Zhang, Z. H.; Xue, Z. Y.; Teng, H. L. *J. Am. Chem. Soc.* **2008**, *130*, 8606.

In order to further expand the applications of cinchona alkaloids derived amine thiourea catalysts, Deng's group described the first direct efficient enantioselective Mannich reactions of malonates **1-41** and *N*-Boc aryl and alkyl imines **1-100** in the presence of quinidine-derived amine thiourea organocatalyst **1-77** under mild, moisture and air-compatible conditions (Scheme 1.36). [69] Furthermore, this highly attractive and convergent approach was also applicable to β-keto esters. The synthetic utility of this methodology was demonstrated by providing a wide variety of biological interesting β-amino acids.



Scheme 1.36 Enantioselective Mannich reaction of malonates **1-41** to *N*-Boc-imines **1-100** catalyzed by quinidine-derived thiourea catalyst **1-77**.



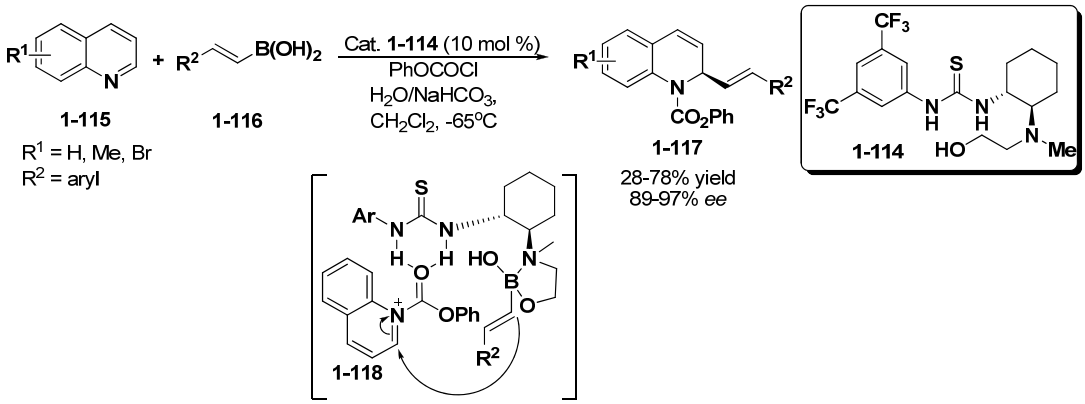
Scheme 1.37 Quinidine-derived thiourea **1-77** catalyzed Friedel-Crafts reactions of indoles **1-112** with aldimines **1-111**.

Subsequently, the same group further employed the quinidine derived thiourea catalyst **1-77** to catalyze the first highly enantioselective Friedel-Crafts reaction of indoles **1-112** with imines **1-111** to construct the 3-indolyl methanamine structural motif **1-113**,[70] which displayed the potential application in the synthesis of numerous indole alkaloids (Scheme 1.37).[71] This direct, versatile and unprecedented protocol was sustainable for a wide range of indoles and aldimines bearing aromatic and aliphatic substituents. It was also found that the high enantioselectivities were

[69] Song, J.; Wang, Y.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 6048.
[70] Wang, Y. Q.; Song, J.; Hong, R.; Li, H. M.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 8156.
[71] a) Atta-ur-Rahman; Basha, A. *Indole Alkaloids*; Harwood Academic: Chichester, U.K., **1998**; b) Amat, M.; Llor, N.; Bosch, J.; Solans, X. *Tetrahedron* **1997**, *53*, 719; c) Faulkner, D. J. *Nat. Prod. Rep.* **2002**, 1.

independent of the electronic properties of indole rings and the *N*-protected groups of aldimines.

As a modern variation of the Mannich reaction[72], the Petasis reaction was firstly developed by Petasis and co-workers.[73] The Petasis reaction involves an amine, an aldehyde and a vinyl or aryl boronic acid to furnish a highly substituted amine. In 2007, Takemoto and co-works developed an enantioselective Petasis reaction of various quinolines **1-115**, phenylvinyl boronic acids **1-116** and phenyl chloroformate in the presence of a novel bifunctional aminol thiourea catalyst **1-114**. [74] This new catalyst was modified from the classic Takemoto thiourea catalyst through mono-hydroxy alkylation of the ternary amine motif. In the proposed mechanism, the hydroxyl group moiety activated vinylboronic acids **1-116** with formation of a five-membered ring. Subsequently, the activated alkyl vinyl unit attacked the hydrogen-bonded *N*-acetylated quinolinium ions **1-118** in this well-defined chiral environment to effectively afford useful 1,2-dihydroquinoline adducts **1-117** in relatively low to high yields (28-78%) and high to excellent enantioselectivities (89-97%) (Scheme 1.38). $H_2O/NaHCO_3$ as the additive system regenerated the active catalyst structure by removal of the final boronic acid side product and the proton source to facilitate product formation.

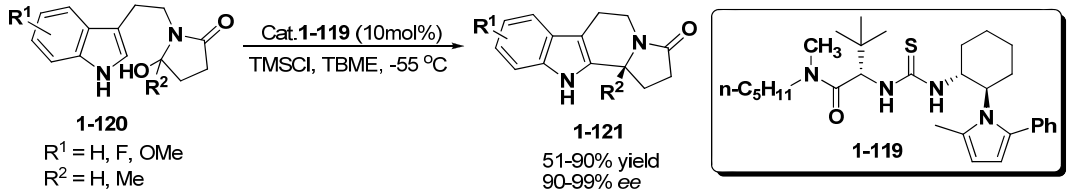


Scheme 1.38 Asymmetric Petasis reaction catalyzed by aminol thiourea organocatalyst **1-114**.

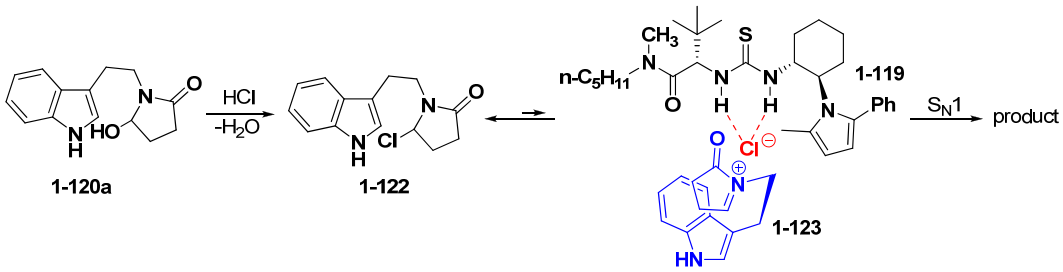
The Pictet-Spengler reaction, discovered in 1911 by Amé Pictet and Theodor

[72] Arend, M.; Westermann, B.; Risch, N. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 1045.
[73] a) Petasis, N. A.; Akritopoulou, I. *Tetrahedron Lett.* **1993**, *34*, 583; b) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1997**, *119*, 445; c) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 11798.
[74] Yamaoka, Y.; Miyabe, H.; Takemoto, Y. *J. Am. Chem. Soc.* **2007**, *129*, 6686.

Spengler, is considered as a special class of the Mannich reaction in which β-arylethylamine undergoes ring closure after the formation of an imine or iminium ion from an aldehyde or ketone.[75] Usually, indole or pyrrole nucleophilic aromatic rings could afford better results under mild conditions compared with less nucleophilic phenyl rings. Since the seminal work, the development of asymmetric Pictect-Spenger reaction has attracted much attention because of its particular importance in the fields of alkaloid and pharmaceutical synthesis. In 2007, Jacobsen group utilized a novel bifunctional thiourea pyrrole derivative **1-119** to induce the enantioselective *N*-acyl-Pictet-Spengler cyclization of β-indolyl ethyl hydroxylactams **1-120** to furnish highly enantioenriched cyclization products **1-121** with excellent *ee* values ranging from 90% to 99% (Scheme 1.39)[76]. On the basis of the results of various NMR studies, the mechanism of this reaction was considered as anion-binding catalysis. Firstly, β-indolyl ethyl hydroxylactams **1-120** reacted with TMSCl as a dehydrating agent resulting in rapid and irreversible formation of chlorolactams **1-122**. Subsequently, the catalyst abstracted a chloride counterion and then closely bounded to the activated iminium ion as a result of a chiral *N*-acyliminium–chloride–thiourea complex **1-123**, which underwent the final intramolecular cyclization step in this well-defined chiral environment.



Scheme 1.39 Pyrrole thiourea-catalyzed *N*-acyl-Pictet-Spengler cyclization.

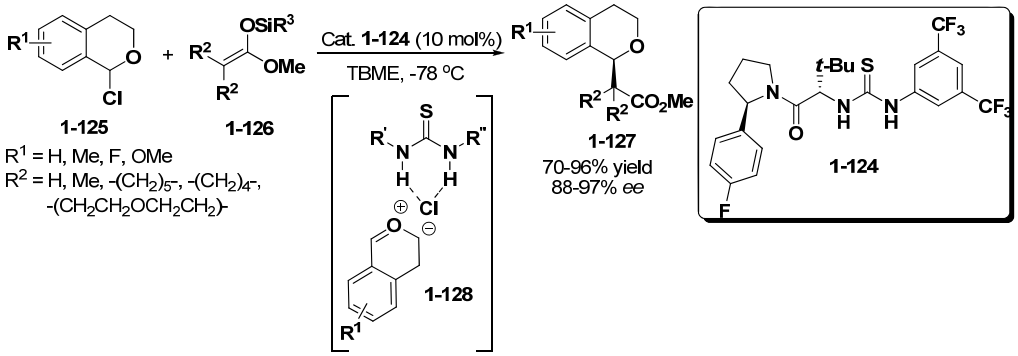


Scheme 1.40 Proposed mechanism for pyrrole thiourea-catalyzed *N*-acyl-Pictet-Spengler

[75] Pictet, A.; Spengler, T. *Berichte der deutschen chemischen Gesellschaft* **1911**, *44*, 2030.
[76] a) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558; b) Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 13404.

cyclization.

Inspired by the previously described *N*-acyl-Pictet-Spengler reaction, the Jacobsen group further applied this thiourea organocatalysis by anion binding to the intermolecular enantioselective additions to oxocarbenium ions.[77] A new thiourea derivative **1-124** bearing a tertiary benzylic amide group was developed to catalyze the substitution of silyl ketene acetals **1-126** onto oxocarbenium ions, which act as important reaction components in the synthesis of complex natural products and carbohydrates. It was shown that the starting chloroethers **1-125** could epimerize under the optimal reaction conditions and the thiourea firstly abstracted the chloride to afford a closely associated ion pair in the form of the oxocarbenium–thiourea–chloride complex **1-128**. Finally, the enol silane nucleophile attacked the asymmetric ion pair to generate the final alkylated isochromans **1-127** with excellent enatioselectivities.



Scheme 1.41 Enantioselective addition of silyl ketene acetals **1-126** to oxocarbenium ions.

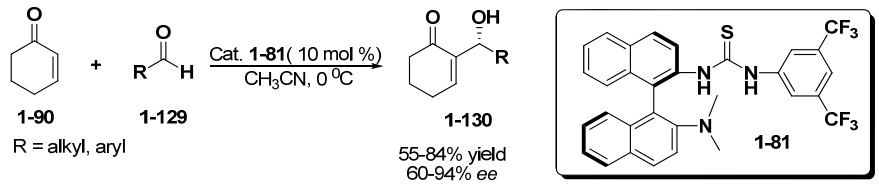
1.2.4 The Morita-Baylis-Hillman (MBH) reaction

As one of the most important and superior atom-enocomic carbon-carbon bond formation reactions, the Morita-Baylis-Hillman (MBH) reaction, firstly reported by Morita[78] in tertiary phosphine catalysis and Baylis-Hillman[79] in tertiary amine catalysis, has gradually attracted huge attention in modern catalytic synthesis.[80] The

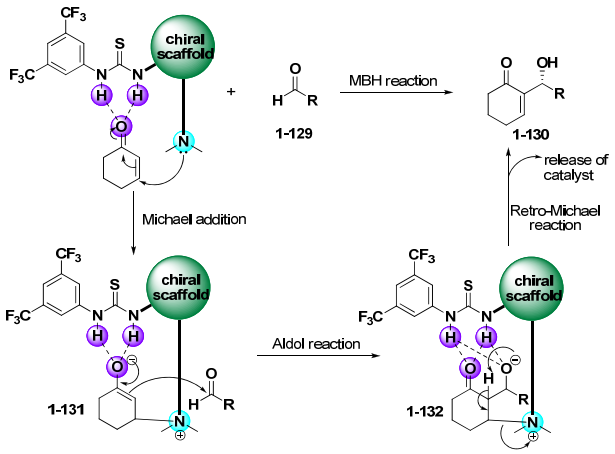
[77] Reisman, S. E.; Doyle, A. G.; Jacosen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 7198.
[78] a) Morita, K. *Japan Patent 6803364*, **1968**; *Chem. Abstr.* **1968**, *69*, 58828; b) Morita, K.; Suzuki, Z.; Hirose, H. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2815.
[79] Baylis, A. B.; Hillman, M. E. D. German Patent **2155113**, **1972**.
[80] a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811; b) Masson, G.; Housseman, C.; Zhu,

MBH reaction represents as a condensation of electron-deficient alkenes and sp^2 hybridized carbon electrophiles, such as aldehydes, ketones and aldimines, to construct allylic alcohols or allylic amines in the presence of Lewis bases (amine or phosphine).

In 2005, the Wang group demonstrated the first bifunctional amine thiourea catalyzed Morita-Baylis-Hillman reaction.[81] The newly developed binaphthyl derived amine thiourea **1-81** conducted the reaction of cyclic enones **1-90** and a broad range of aromatic and linear aliphatic aldehydes **1-129** to furnish allylic alcohols **1-130** in yields ranging from 55% to 84% and with *ee* values ranging from 60% to 94%. In the proposed catalytic cycle, the explicit double hydrogen bonding interaction between thiourea moiety and cyclic enone could facilitate the initial Michael reaction of the tertiary amine motif to the β-position of enone. The subsequent aldol reaction formed the bifunctional catalyst-zwitterionic ion complex **1-132**, which was converted to the final allylic alcohols **1-130** by the rate-determing deprotonation of the α-hydrogen.



Scheme 1.42 Asymmetric MBH reaction catalyzed by bifunctional organocatalyst **1-81**.



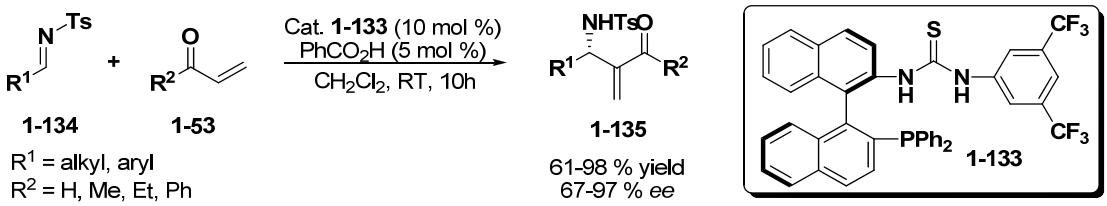
Scheme 1.43 Proposed catalytic cycle for the binaphthyl amine thiourea **1-81** promoted MBH

J. P. *Angew. Chem. Int. Ed.* **2007**, *46*, 4614; c) Basavaiah, D.; Reddy, B. S.; Badsara, S. S. *Chem. Rev.* **2010**, *110*, 5447; d) Basavaiah, D.; Veeraraghavaiah, G. *Chem. Soc. Rev.* **2012**, *41*, 68.

[81] Wang, J.; Li, H.; Yu, X. H.; Zu, L. S.; Wang, W. *Org. Lett.* **2005**, *7*, 4293.

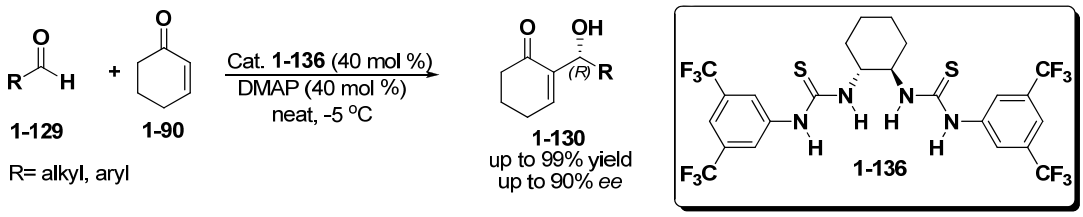
reaction.

However, it is well known that aromatic tertiary amines are much weaker nucleophiles than phosphines. Modification of the binaphthyl derived amine thiourea catalyst **1-81** with replacement of the amine motif with stronger phosphine nucleophiles resulted in a novel bifunctional phosphine thiourea catalyst **1-133.** The *aza*-MBH reaction of *N*-Tos aldimines **1-134** and methyl vinyl ketones **1-53** under the catalysis of **1-133** furnished the *N*-protected allylic amines **1-135** in high yields and excellent enantioselectivities (Scheme 1.44).[82]



Scheme 1.44 Asymmetric MBH reaction catalyzed by binaphthyl derived phosphine thiourea catalyst **1-133**.

In addition to binaphthyl derived thiourea catalysts, C_2-symmetric chiral 1,2-diaminocyclohexane-derived bisthiourea **1-136**, prepared by Nagasawa and co-workers,[83] was employed in the Morita-Baylis-Hillman (MBH) reaction to simultaneously activate the aldehydes **1-129** and cyclohexenone **1-90** in a spatially restricted chiral environment. With the aid of Lewis base DMAP, this method provided access to various allylic alcohols **1-130** bearing both aromatic and aliphatic groups with high catalytic activities and up to 90% *ee* in the case of cyclohexanecarboxaldehyde.

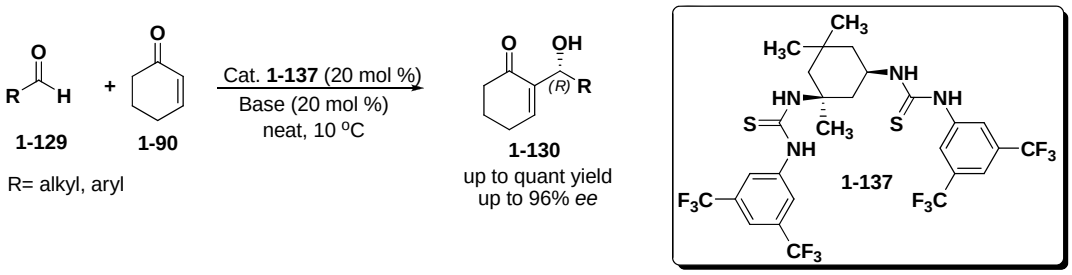


Scheme 1.45 Asymmetric MBH reactions promoted by C_2-symmetric bisthiourea **1-136**.

Another important development in enantioselective MBH reaction was disclosed

[82] Shi, Y. L.; Shi, M. *Adv. Synth. Catal.* **2007**, *349*, 2129.
[83] Sohtome, Y.; Tanatani, A.; Hashimoto, Y.; Nagasawa, K. *Tetrahedron Lett.* **2004**, *45*, 5589.

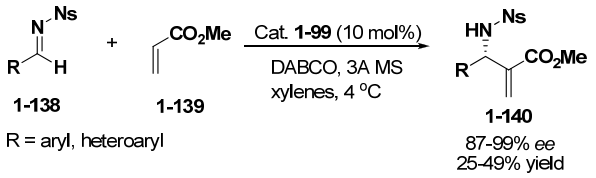
by Berkessel *et al.*[84] A new and efficient bisthiourea catalyst **1-137** was designed and synthesized from readily available isophoronediamine (IPDA) in one step. In combination with a nucleophilic base (N,N,N',N'-tetramethylisophoronediamine TMIPDA or DABCO) the bisthiourea catalyst **1-137** controlled the relative orientation of enone **1-90** and a series of aldehydes **1-129** to obtain good to excellent yields and up to 96% *ee* values.



Scheme 1.46 Asymmetric MBH reactions promoted by bisthiourea **1-137**.

Despite the important advance has been made in asymmetric aza-Baylis-Hillman (ABH) reaction with enone substrates as pre-nucleophiles[85], Raheem and Jacobsen further expanded the substrate scope of the ABH reaction to simple acrylate devivatives.[86] In the presence of catalytic amount of Jacobsen catalyst **1-99** and 1.0 equiv. of 1,4-diazabicyclo[2.2.2]octane (DABCO), this unprecedented protocol was well applicable to a wide range of aromatic imines **1-138** to construct highly functionalized nosyl-protected amines **1-140** with high to excellent enantioselectivities (87-99% *ee*), albeit in low to moderate yields (25-49%). The vital synthetic utility of this methodology was well revealed through some representative synthetic transformations, such as dihydroxylation, hydrogenation, alkalation, epoxidation, [3+2] cycloaddition and so on. Besides, this report also depicted the first isolation or characterization of zwitterionic ion and its dihydrochloride salt in MBH or ABH reactions.

[84] Berkessel, A.; Roland, K.; Neudörfl, J. M. *Org. Lett.* **2006**, *8*, 4195.
[85] a) Shi, M.; Xu, Y. M. *Eur. J. Org. Chem.* **2002**, *4*, 696; b) Shi, M.; Zhao, G. L. *Adv. Synth. Catal.* **2004**, *346*, 1205; c) Shi, M. Chen, L. H.; Li, C. Q. *Tetrahedron: Asymmetry* **2005**, *16*, 1385; d) Shi, M.; Chen, L. H.; Li, C. Q. *J. Am. Chem. Soc.* **2005**, *127*, 3790; e) Matsui, K.; Takizawa, S.; Sasai, H. *J. Am. Chem. Soc.* **2005**, *127*, 3680.
[86] Raheem, I. T.; Jacobsen, E. N. *Adv. Synth. Catal.* **2005**, *347*, 1701.



Scheme 1.47 Jacobsen thiourea catalyst **1-99** promoted *aza*-Baylis-Hillman reactions.

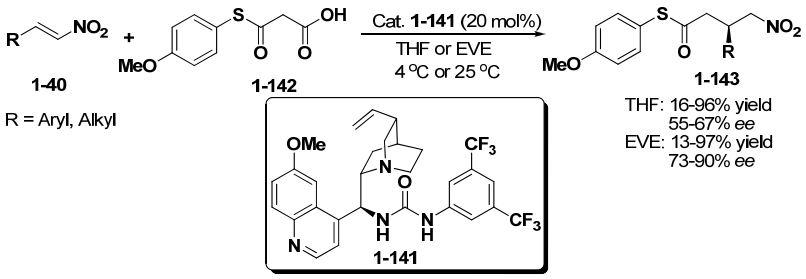
1.2.5 Decarboxylative Reactions

As one of the oldest organic reactions, decarboxylation commonly plays a particularly vital role in biological and synthetic chemistry. It is a chemical process that removes a carbonyl group (COOH) with concurrent release of CO_2. The first decarboxylative Claisen condensation was conducted by Kobuke under enzyme-free conditions with magnesium acetate as catalyst in 1978.[87] Subsequently, the Shair[88] and Cozzi [89] group independently developed Cu(II)-catalyzed enantioselective decarboxylative Aldol reactions of malonic acid half-thioesters (MAHTs) to aldehydes under mild reaction conditions. Since then, organocatalytic decarboxylation has gradually attracted a great deal of interest.

In 2007, the Wennemers[90] group made a major breakthrough in asymmetric organocatalytic decarboxylative synthesis. By mimicking the active site of polyketide synthases, a quinine derivative **1-141** incorporating both a basic quinuclidine site and a urea moiety was utilized to conduct the enantioselective decarboxylative reaction of various aromatic and aliphatic nitroolefins **1-40** and malonic acid half-thioesters (MAHTs) **1-142** served as thioester enolate equivalents. The final high yields and good enantioselectivities were ascribed to the simultaneous activation of substrates through explicit double hydrogen-bond interactions and deprotonation. Furthermore, the resulting γ-nitrothioesters **1-143** were readily converted to versatile building blocks by reduction of the nitro group and intramolecular cyclization, such as

[87] Kobuke, Y.; Yoshida, J. I. *Tetrahedron Lett.* **1978**, *19*, 367.
[88] *a*) Lalic, G.; Aloise, A. D.; Shair, M. D. *J. Am. Chem. Soc.* **2003**, *125*, 2852; *b*) Magdziak, D.; Lalic, G.; Lee, H. M.; Fortner, K. C.; Aloise, A. D.; Shair, M. D. *J. Am. Chem. Soc.* **2005**, *127*, 7284; *c*) Fortner, K. C.; Shair, M. D. *J. Am. Chem. Soc.* **2007**, *129*, 1032.
[89] Orlandi, S.; Benaglia, M.; Cozzi, F. *Tetrahedron Lett.* **2004**, *45*, 1747.
[90] Lubkoll, J.; Wennemers, H. *Angew. Chem. Int. Ed.* **2007**, *46*, 6841.

antidepressant rolipram. Subsequently, another considerable achievement was made by the Ricci[91] group. They employed the quinidine-derived alkaloid β-isocupreidine (β-ICD) in asymmetric organocatalytic decarboxylative Mannich reactions *via* hydrogen bonding catalysis.

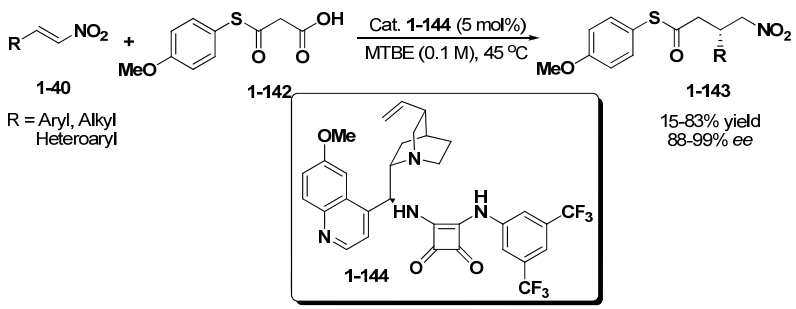


Scheme 1.48 Quinine derived urea catalyst **1-141** promoted decarboxylative addition of MAHT to nitroolefins.

However, the previous pioneering works' catalytic activity and enantioselectivity were insufficient for further synthetic utility. In order to address this problem, the Song group employed a superior quinine-based ternary amine squaramide **1-144** to promote the biomimetic decarboxylative Michael addition of MATHs **1-142** to a variety of nitroolefins **1-40**, resulting in the formation of the optically active γ-amino acid precursors **1-143**. [92] In comparison to thiourea motifs, chiral squaramides[93] could serve as more efficient hydrogen bond donors in many enantioselective organic transformations due to the higher Brønsted acidity of the NH protons of the squaramides[94] and spatial fixed anti/anti-orientation of the NH protons relative to the carbonyl groups [95]. Remarkably, it was shown that this protocol proceeded enantioconvergently to provide high catalytic activity and excellent enantioselectivity. The authors also presented the synthetic utility of this methodology of the conversion

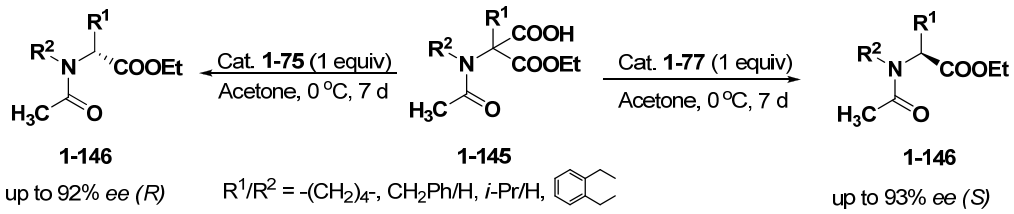
[91] Ricci, A.; Pettersen, D.; Bernardi, L.; Fini, F.; Fochi, M.; Herrera, R. P.; Sgarzani, V. *Adv. Synth. Catal.* **2007**, *349*, 1037.
[92] Bae, H. Y.; Some, S.; Lee, J. H.; Kim, J. Y.; Song, M. J.; Lee, S.; Zhang, Y. J.; Song, C. E. *Adv. Synth. Catal.* **2011**, *353*, 3196.
[93] a) Malerich, J. P.; Hagihara, K.; Rawal, V. H. *J. Am. Chem. Soc.* **2008**, *130*, 14416; b) Lee, J. W.; Ryu, T. H.; Oh, J. S.; Bae, H. Y.; Jang, H. B.; Song, C. E. *Chem. Commun.* **2009**, 7224; c) Konishi, H.; Lam,T. Y.; Malerich, J. P.; Rawal, V. H. *Org. Lett.* **2010**, *12*, 2028; d) Zhu, Y.; Malerich, J. P.; Rawal, V. H. *Angew. Chem. Int. Ed.* **2010**, *49*, 153.
[94] Xu, D. Q.; Wang, Y. F.; Zhang, W.; Luo, S. P.; Zhong, A. G.; Xia, A. B.; Xu, Z. Y. *Chem. Eur. J.* **2010**, *16*, 4177.
[95] a) Muthyala, R. S.; Subramaniam. G.; Todaro, L. *Org. Lett.* **2004**, *6*, 4663; b) Fu, N.; Allen, A. D.; Kobayashi, S.; Tidwell, T. T.; Vukovic, S.; Arumugam, S.; Popik, V. V.; Mishima, M. *J. Org. Chem.* **2007**, *72*, 1951; c) Ramalingam, V.; Domaradzki, M. E.; Jang, S.; Muthyala, R. S. *Org. Lett.* **2008**, *10*, 3315.

to pharmaceutically important γ-amino acids through simple reduction and intramolecular cyclization steps.



Scheme 1.49 Quinine derived squaramide catalyst **1-144** promoted decarboxylative addition of MAHT to nitroolefins.

In recent reports, enantioselective organocatalytic decarboxylation was proved as a particularly powerful and effective process in many reactions, such as protonations[96], Aldol reactions[97] and Mannich reactions[98]. All of these decarboxylative processes were promoted by *cinchona*-based tertiary amines or chiral guanidines.



Scheme 1.50 Enantioselective decarboxylative protonation mediated by pseudoenantiomers **1-75** and **1-77**.

The Rouden group firstly applied the cinchona alkaloids based thiourea derivatives to the asymmetric decarboxylative protonation of acyclic, cyclic or bicyclic α-aminomalonate hemiesters **1-145**, affording optically active aminoesters **1-146** in high yields and up to 93% enantiomeric excess under mild conditions (Scheme 1.50).[96d] Both the quinidine-based thiourea derivative **1-77** and its

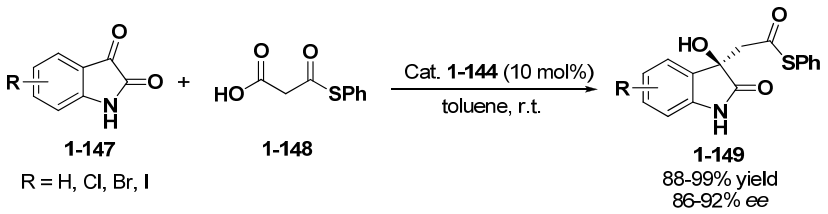
[96] a) Brunner, H.; Schmidt, P. *Eur. J. Org. Chem.* **2000,** 2119; b) Brunner, H.; Baur, M. A. *Eur. J. Org. Chem.* **2003**, 2854; c) Seitz, T.; Baudoux, J.; Bekolo, H.; Cahard, D.; Plaquevent, J. C.; Lasne, M. C.; Rouden, J. *Tetrahedron* **2006**, *62*, 6155; d) Amere, M.; Lasne, M. C.; Rouden, J. *Org. Lett.* **2007**, *9*, 2621.

[97] *a*) Hara, N.; Nakamura, S.; Funahashi, Y.; Shibata, N. *Adv. Synth. Catal.* **2011**, *353*, 2976; *b*) Zhong, F.; Yao, W.; Dou, X.; Lu, Y. *Org. Lett.* **2012**, *14*, 4018; *c*) Zheng, Y.; Xiong, H.; Nie, J.; Hua, M.; Ma, J. *Chem. Commun.*, **2012**, *48*, 4308.

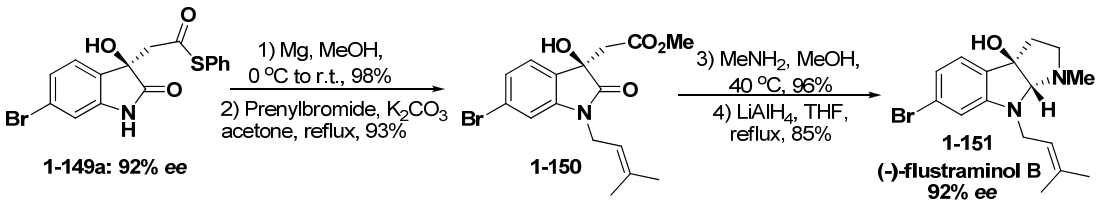
[98] *a*) Pan, Y.; Kee, C. W.; Jiang, Z.; Ma, T.; Zhao, Y.; Yang, Y.; Xue, H.; Tan, C. H. *Chem. –Eur. J.* **2011**, *17*, 8363; *b*) Hara, N.; Nakamura, S.; Sano, M.; Tamura, R.; Funahashi, Y.; Shibata, N. *Chem. –Eur. J.,* **2012**, *18*, 9276; *c*) Jiang, C. Zhong, F.; Lu, Y. *Beilstein J. Org. Chem.* **2012**, *8*, 1279.

pseudoenantiomer **1-75** could afford the conformational rigidity to anchor the chiral protonating agent and the prochiral enolate in a well-defined chiral environment.

The Shibata group firstly demonstrated the organocatalytic decarboxylative aldol addition of malonic acids half thioesters to ketones in the presence of quinine-derived squaramide catalyst.[97a] Under optimal conditions, a series of isatins **1-147** reacted with MAHTs **1-148** to afford chiral 3-substituted 3-hydroxy-2-oxindole derivatives **1-149** in excellent yields (88-99%) and good enantiomeric excesses (86-92%) (Scheme 1.51). The final products could act as key intermediates in the synthesis of various biologically active compounds, such as convolutamydines, CPC-1, (-)-flustraminol B. Remarkably, this work showed the first report on the enantioselective synthesis of optically active (-)-flustraminol B **1-151** (Scheme 1.52). Based on the results of preliminary experiments, the authors also elucidated the mechanism of this reaction. The activation of MAHT by squaramide functionality's double hydrogen bonding and deprotonation of carboxylic acid would facilitate the decarboxylation of MAHT to generate a thioester enolate. Simultaneously, the protonated catalyst coordinated the two carbonyl oxygen from isatin through hydrogen bonding. Finally, the *in situ* generated thioester enolate attacked the carbonyl group of the isatins **1-147** from the *Si*-face as a result of the preferable formation of (*R*)-isomer.

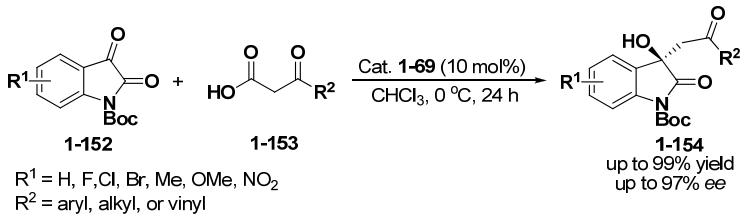


Scheme 1.51 Enantioselective decarboxylative aldol reactions of isatins **1-147** with MAHT.



Scheme 1.52 Synthesis of optically active (-)-flustraminol B.

Subsequently, the Lu group also demonstrated a facile and important protocol for the synthesis of biologically crucial 3-substituted 3-hydroxy oxindole derivatives through decarboxylative additions.[97b] As synthetic equivalents of aryl/alkyl methyl ketone enolates, a wide range of β-ketoacids **1-153** reacted with isatins **1-152** bearing different substituents on the aromatic ring to afford good yields and excellent enantioselectivities. On the basis of the results of experimental study in the mechanism, the authors proposed a decarboxylation–nucleophilic addition pathway in this reaction. However, some other catalytic systems fully support the alternative nucleophilic addition–decarboxylation reaction sequence. Further investigations toward the deep understanding of the mechanism in the decarboxylation are still highly desirable.



Scheme 1.53 Enantioselective decarboxylative aldol reactions of isatins **1-152** with β-ketoacids **1-153**.

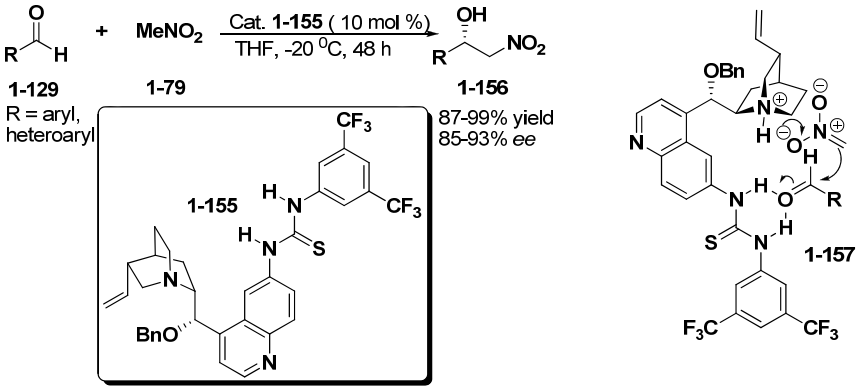
1.2.6 Miscellaneous Reactions

In the following section, some elegant and crucial transformations are described. These particularly efficient reactions have emerged as powerful and promising strategies for the synthesis of some natural and pharmacologically important structural motifs.

The Henry reaction (nitro-aldol reaction), discovered in 1895 by L. Henry,[99] is an efficient and classic C–C bond formation reaction in organic chemistry. It involves the base-catalyzed condensation of a nitroalkane bearing an α-hydrogen atom and a carbonyl compound (aldehyde or ketone) resulting in the formation of β-nitroalcohol.

[99] Henry, L. *Compt. Rend.* **1895**, *120*, 1265.

The synthetic utility of this well-known reaction is demonstrated by the conversions of the final β-nitroalcohol products to other particularly useful synthetic intermediates, such as nitroalkenes by dehydration, α-nitro ketones by oxidation of the secondary alcohol and β-amino alcohols by reduction of the nitro group. Although many efficient catalytic asymmetric Henry reactions have been described, it is not until 2006 that Hiemstra *et al.* reported a highly enantioselective organic reaction between activated aromatic aldehydes **1-129** and nitromethane **1-79** in the presence of cinchona derivatives. On the cinchona alkaloid backbone, the C9 position was not the sole position where thiourea functionality could be installed.[100] So they modified the chiral cinchona scaffold through replacement of the 6'-OMe group with a thiourea moiety to furnish a novel and powerful bifunctional catalyst **1-155**. [101] As illustrated in Scheme **1-54**, this catalyst activated the aldehyde by the thiourea unit and simultaneously deprotonated the nitromethane by the basic quinuclidine ring. A variety of aldehydes **1-129** bearing aryl and heteroaryl substituents were compatible with this protocol to afford high yields (87-99%) and excellent enantiomeric excesses (85-93%).

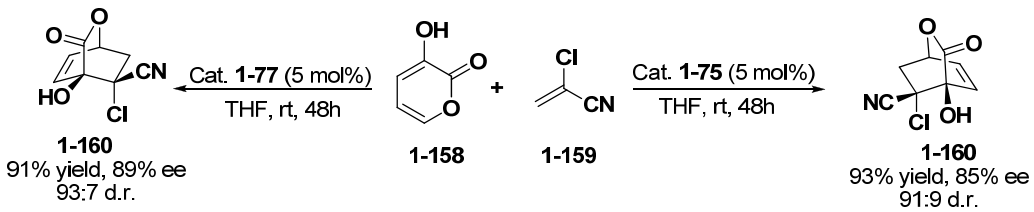


Scheme 1.54 Asymmetric Henry reactions catalyzed by **1-155** and proposed activation mode.

The Diels-Alder reaction has attained a preeminent position in organic chemistry for the convenient construction of synthetically valuable six-membered cyclohexene rings due to requirement of very little energy.[102] So far, many strategies have been

[100] See *Ref.* 50.
[101] Marcelli, T.; van der Haas, R. N. S.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem. Int. Ed.* **2006**, *45*, 929.
[102] a) Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007; b) Evans, D. A.; Johnson, J. S. in *Comprehensive Asymmetric Catalysis*, Springer, **1999**.

reported to realize this reaction.[102] In 2007, Deng *et al*. demonstrated the first example of cinchona alkaloid based thiourea derivative as an efficient bifunctional catalyst for a highly diastereoselective and enantioselective Diels-Alder reaction with 2-pyrones **1-158**. [103] The amine and thiourea moiety of catalyst not only activated the HOMO-LUMO, but also controlled the rearrangement of the dienes and dienophiles in a spatial conformational rigid environment. Remarkably, many dienophiles including fumaronitrile, maleonitrile, acrylonitrile as well as α-acrylonitrile **1-159** were compatible with this protocol to afford excellent yields and enantioselectivities, especially with high endo/exo selectivities (Scheme 1.55).

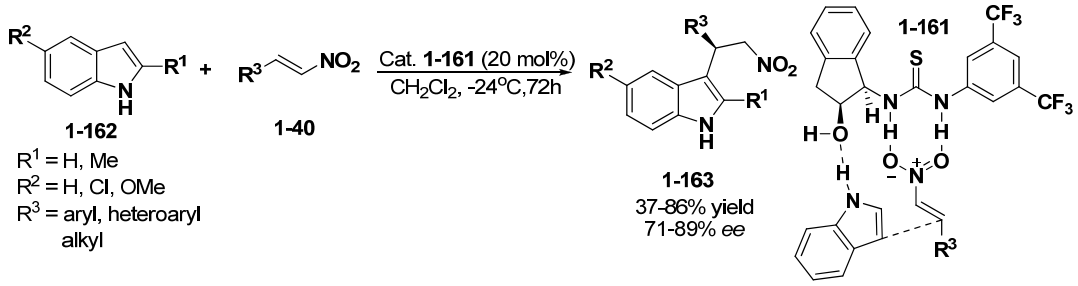


Scheme 1.55 Exo-selective cinchona-based thiourea deviratives **1-75** or **1-77** promoted Diels-Alder reaction.

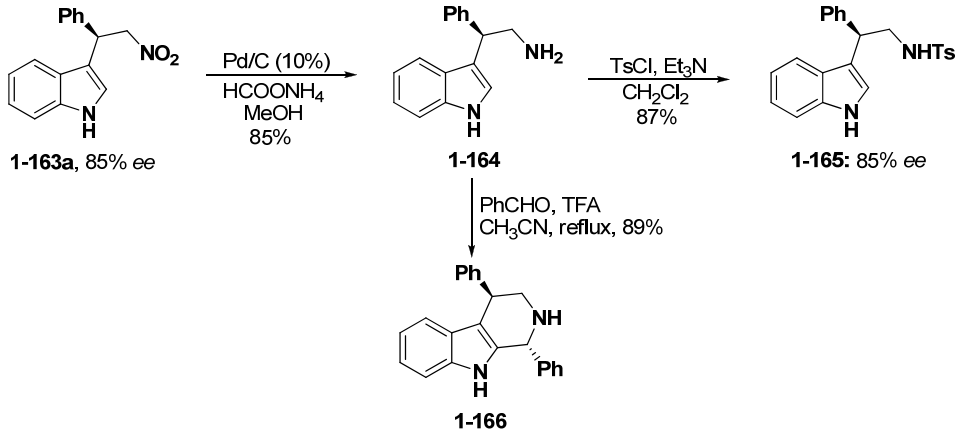
The Friedel-Crafts reaction, developed by Charles Friedel and James Crafts in 1877[104], has emerged as a key reaction in synthetic organic chemistry resulting in the formation of new C-C bonds.[105] It could be generally classified into two main types, alkylation reaction and acylation reaction. The nucleophilic addition of aromatic substrates to electron-deficient alkenes is usually considered as a Friedel-Crafts type alkylation. The first catalytic enantioselective Friedel-Crafts alkylation of indoles with nitroalkenes was developed by Ricci and coworkers in the presence of a novel chiral indane-based hydroxyl thiourea catalyst **1-161**.[106] This methodology was consistent with various indoles **1-162** and a wide range of nitroalkenes **1-40** bearing aryl and alkyl substituents with fairly good yields and excellent enantioselectivities (Scheme 1.56). This asymmetric Friedel-Crafts alkylation facilely provided the enantioenriched 2-indolyl-1-nitro derivatives **1-163**, which could be easily converted into particularly

[103] Wang, Y.; Li, H.; Wang, Y. O.; Liu, Y.; Foxman, B.M.; Deng, L. *J. Am. Chem. Soc.* **2007**, *129*, 6364.
[104] Friedel, C.; Crafts, J. M. *Compt. Rend.* **1877**, *84*, 1392.
[105] Olah, G. A. *Friedel–Crafts and Related Reactions, Vol. II*, part 1, Wiley-Interscience, New York, **1964.**
[106] Herrera, R. P.; Sgarzani, V.; Bernardi, L.; Ricci, A. *Angew. Chem. Int. Ed*. **2005**, *44*, 6576.

valuable biological compounds, such as tryptamines or 1,2,3,4-tetrahydro-β-carbolines (Scheme 1.57). In the proposed mechanism mode, the nitroalkene was activated by two thiourea hydrogen atoms, whereas the free alcoholic function of catalyst interacted with the indolic proton by a simple hydrogen bond. The activated indole nucleophile attacked the *Si* face of the nitroolefin.



Scheme 1.56 Asymmetric Friedel-Crafts alkylations catalyzed by chiral hydroxyl-thiourea **1-161**.

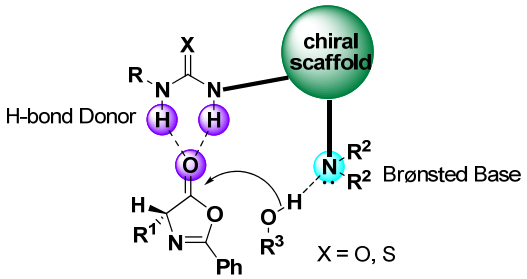


Scheme 1.57 The synthetic utility of the optically active 2-indolyl-1-nitro derivatives **1-163**.

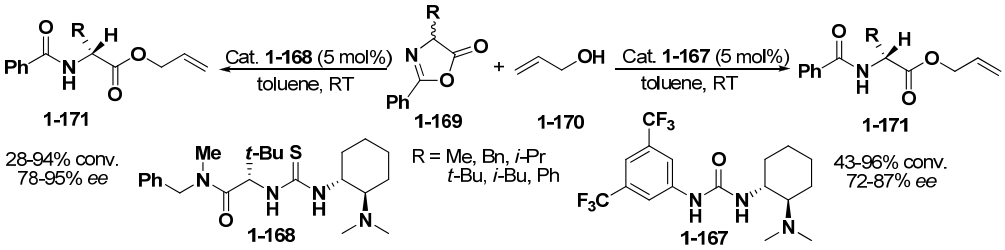
To date, only few catalysts based on chiral indane scaffold have been developed in organic chemistry. The above mentioned work revealed that the particularly privileged indane scaffold could induce a well-defined chiral environment for the reaction substrates. On the basis of these initial results, our group firstly designed and synthesized a series of indane amine-thiourea catalysts that have been confirmed to be especially effective in many asymmetric cascade transformations.

In comparison with standard kinetic resolution in the maximum yield of 50%, dynamic kinetic resolution has emerged as a particularly practical methodology to access the highly enantiomerically pure compounds in theoretically quantitative yield

from cheap and easily available racemic precursors. In order to increase the enantioselectivity of organocatalyzed DKRs of azlactone, Berkessel and co-workers employed bifunctional amine urea/thiourea organocatalysts in this strategy.[107] Based on the NMR spectroscopic studies, the authors proposed a plausible mechanism that the thiourea motif activated the azlactone by explicit hydrogen bonding (Scheme 1.58). The Brønsted basic tertiary amine activated the alcohol nucleophile through deprotonation. Besides, the H^1 and C^{13} spectra of the catalyst-azlatone complex indicated that one of two possible diastereomers of this complex was preferentially formed as a result of rapid interconversion of the azlactone enantiomers.[107a] Under optimized conditions, both Takemoto catalyst analogue **1-167** and Jacobsen catalyst analogue **1-168** could promote the alcoholytic ring opening of various racemic azlactones **1-169** to generate the desired optically active N,C-doubly protected α-amino acid derivatives **1-171** with high conversions and excellent enantioselectivities. It was noteworthy that the products could be readily transformed to enantiopure natural and non-natural α-amino acids which possessed a huge application in the synthesis of many valuable pharmaceuticals and catalysts.[107]



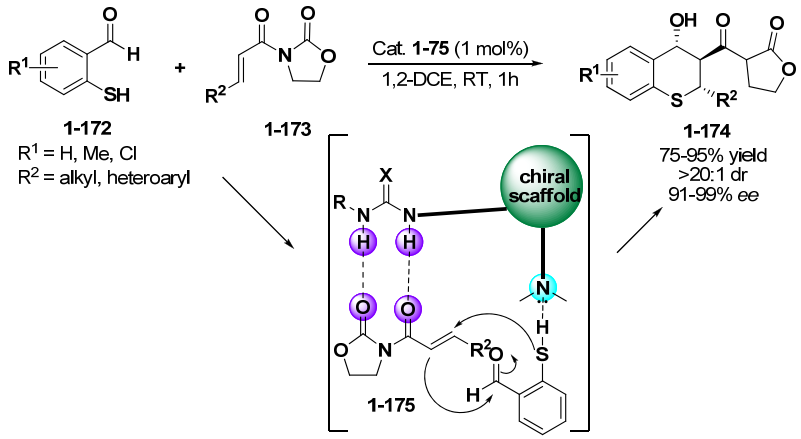
Scheme 1.58 The mechanism of alcoholytic dynamic kinetic resolution.



Scheme 1.59 Asymmetric alcoholytic dynamic kinetic resolution of azlactones **1-169**.

[107] a) Berkessel, A.; Cleemann, F.; Mukherjee, S.; Müller T. N.; Lex, J. *Angew. Chem. Int. Ed.* **2005**, *44*, 807; b) Berkessel, A.; Mukherjee, S.; Cleemann, F.; Müller T. N.; Lex, J. *Chem. Commun.* **2005**, 1898.

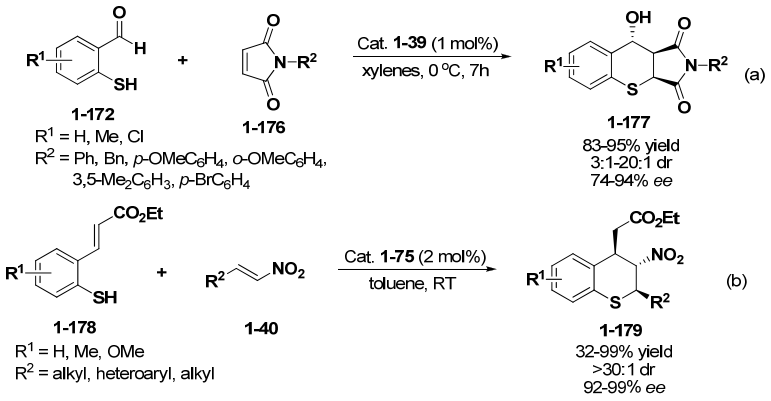
Cascade synthetic strategy is of considerable significance in both academic and industrial chemistry, because it provides an elegant and efficient protocol to construct complex molecular architectures in atom and step economic processes. So the development in the asymmetric versions of cascade reactions caught enormous interest of chemists in recent years. In 2007, Wang *et al.* disclosed a highly effective, enantio- and diastereoselective cascade Michael-aldol reaction in the presence of a quinine based thiourea organocatalyst **1-75**.[108] The synergistic non-covalent H-bonding activation of 2-mercaptobenzaldehydes **1-172** and various α,β-unsaturated oxazolidinones **1-173** facilitated the construction of versatile synthetically useful and medicinally important chiral thiochromanes **1-174** with three stereogenic centers in good to excellent yields (75-95%), excellent enantiomeric excesses (91-99%) as well as excellent distereoselectivities (>20:1) (Scheme 1.60).



Scheme 1.60 Asymmetric cascade Michael-aldol reaction catalyzed by quinine-based thiourea organocatalyst **1-75**.

To expand the scope of the electrophiles and nucleophiles in cascade synthetic strategies, the Wang group also described highly enantio- and diastereoselective hydrogen-bond-mediated tandem Michael-Aldol and Michael-Michael reactions, respectively, utilizing maleimides **1-176** or *trans*-3-(2-mercaptophenyl)-2-propenoic acid ethyl esters **1-178** as substrates, to incorporate three adjacent stereogenic centers in the particularly privileged biological scaffolds.[109]

[108] Zu, L. S.; Wang, J.; Li, H.; Xie, H. X.; Jiang, W.; Wang, W. *J. Am. Chem. Soc.* **2007**, *129*, 1036.
[109] a) Zu, L. S.; Xie, H. X.; Li, H.; Wang, J.; Jiang, W.; Wang, W. *Adv. Synth. Catal.* **2007**, *349*, 1882; b) Wang, J.; Xie, H. X.; Li, H. Zu, L. S.; Wang, W. *Angew. Chem. Int. Ed.* **2008**, *47*, 4177.



Scheme 1.61 Hydrogen-bond mediated asymmetric cascade reactions: a) domino Michael-Aldol sequence; b) domino Michael-Michael sequence.

1.3 Project Objectives

As shown in previous sections, hydrogen-bond-mediated catalysis has emerged as a powerful and practical tool in organic synthesis. It is noteworthy that the discovery of a variety of mono- and bifunctional urea/thiourea catalysts has triggered the rapid development of the application of urea/thiourea activation mode in asymmetric organocatalysis. In the past few decades, these elegant powerful urea/thiourea catalysts based on various crucial scaffolds have proven to be specifically efficient implements to afford biologically and pharmaceutically important molecules in many novel and interesting enantioselective reactions, such as Strecker reaction, Michael reaction, Mannich reaction, Henry reaction, acyl-Pictet-Spengler reaction, Morita-Baylis-Hillman (MBH) reaction, Petasis-type reaction and so on.

Although great advances have been made in urea/thiourea catalyzed organic transformations, it is still highly desired to develop novel and versatile urea/thiourea catalysts due to limited chiral structural scaffolds. Moreover, the previously mentioned urea/thiourea catalysts would lose or decrease their catalytic activities and chiral inductions in some specific reactions. Therefore, how to enlarge the reaction scope still remains one challenge in urea/thiourea-mediated catalysis.

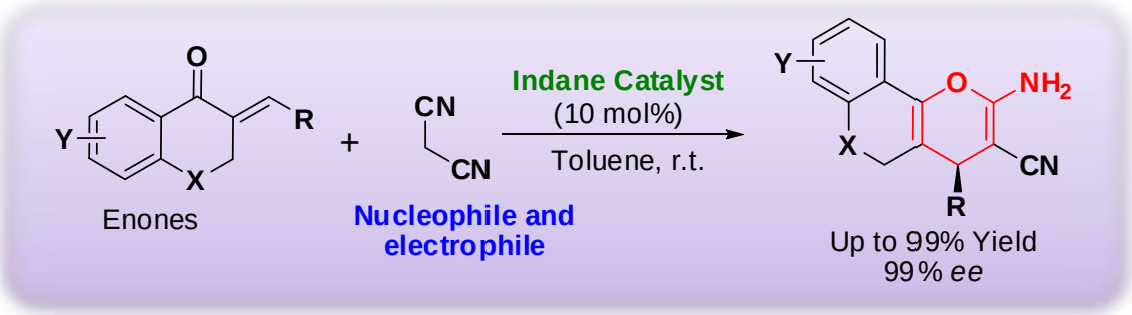
The main objective of this project is to:

- design and develop a small library of novel and easily synthesized bifunctional indane amine-thiourea catalysts.
- apply these powerful catalysts to many unique enantioselective cascade reactions.
- expeditiously assemble versatile synthetically useful and densely functionalized privileged medicinal scaffolds in both organic and biological chemistry.

The study of this project could provide a facile and concise strategy to synthesize a series of bifunctional indane amine-thiourea catalysts from various readily available and cheap starting materials. These powerful catalysts could serve as an essential complement to other chiral scaffold-based urea/thiourea catalysts to catalyze many useful enantioselective cascade transformations.

Furthermore, this project will mainly focus on some unanticipated cascade sequences because of their advantages, such as simple operation, environmental friendliness, and rapid one-pot entries to molecular complexity. These cascade synthetic protocols would construct some interesting, potential biological and pharmaceutical molecules in the presence of the bifunctional indane amine-thiourea catalysts. Many typical and important named reactions are outside the scope of this project because excellent enantioselectivities have been achieved in these reactions catalyzed by previously mentioned classic scaffold-based (thio)urea catalysts. In Chapter 2, a Michael–*Oxa*-Michael–tautomerization reaction will be described. Chapter 3 will demonstrate the highly stereoselective cascade Michael–enolation–cyclization reaction catalyzed by chiral indane-based thiourea. Furthermore**,** Chapter 4 will depict these catalysts' practical application in enantioselective Mannich–intramolecular ring cyclization–tautomeriztion cascade sequence. Subsequently, a highly efficient catalytic decarboxylative [1,2]-addition strategy to quickly assemble 3-hydroxy-2-oxindole scaffolds would be demonstrated in Chapter 5. Finally, Chapter 6 will disclose a direct enantioselective decarboxylation of α,β-unsaturated carbonyls and malonic half-thioesters to construct ubiquitous bioactive δ-lactones.

Chapter 2 Enantioselective Synthesis of Densely Functionalized Pyrano–chromenes *via* an Unanticipated Cascade Michael–*Oxa*-Michael–Tautomerization Sequence



A surprising example of enantioselective cascade Michael–oxa-Michael–tautomerization reactions of malononitrile and benzylidenechromanones has been developed. In this case, malononitrile worked as both the nucleophile and the electrophile. Meanwhile, a simple bifunctional indane amine-thiourea catyalyst has been discovered to promote this process to afford high yields (up to 99%) and high to excellent enantiomeric excesses (81–99% ee).

2.1 Introduction

Cascade synthetic strategy has been developed as a uniquely powerful tool for forging synthetic connections and plays a pivotal role in modern organic synthesis.[110] Given its widespread use, the development of new synthetic cascade reactions for the construction of complex molecules is an important goal of research carried in both academic and industrial laboratories.[111] In particular, asymmetric organocatalytic cascade processes[112] are even more appealing because of their advantages, such as operational simplicity, environment friendliness, and rapid one-pot entries to molecular complexity via atom, step and redox economic or protecting-group-free protocols.

The catalytic asymmetric C–C bond formation represents one of the most interesting and challenging fields in organic chemistry. A number of asymmetric Michael additions to α,β-unsaturated carbonyl acceptors catalyzed by chiral organocatalysts have been reported.[113] However, the nucleophiles employed in the asymmetric Michael addition reactions are restricted to malonate esters,[114] diketones,[115] ketoesters[116] and nitroalkanes[117]. Extending the scope of either the

[110] For selected reviews, see: a) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem. Int. Ed.* **2006**, *45*, 7134; b) Nicolaou, K. C.; Montagnon, T. *Molecules that Changed the World: A Brief History of the Art and Science of Synthesis and its Impact on Society*, Wiley-VCH, **2008**; c) Nicolaou, K. C.; Chen, J. S. *Chem. Soc. Rev.* **2009**, *38*, 2993.

[111] For book reviews, see: a) Nicolaou, K. C.; Sorensen, E. J. Wiley-VCH, **1995**; b) Nicolaou, K. C.; Snyder, S. A. Wiley-VCH, **2003**.

[112] For selected reviews of organocatalytic cascade reactions, see: a) see *Ref.* 3a; b) see *Ref.* 3b; c) Yang, J. W.; Hechavarria Fonseca, M. T.; List, B. *J Am Chem Soc* **2005**, *127*, 15036; d) Marigo, M.; Schulte, T.; Franzen, J.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *125*, 15710; e) see *Ref.* 3f; f) see *Ref.* 3g; g) Sunden, H.; Ibrahem, I.; Zhao, G. L.; Eriksson, L. *Chem. –Eur. J.* **2007**, *13*, 574; h) Wang, W.; Li, H.; Wang, J.; Zu, L. *J. Am. Chem. Soc.* **2006**, *128*, 10345; i) Galzerano, P.; Pesciaioli, F.; Mazzanti, A.; Bartoli, G.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2009**, *48*, 7892.

[113] For book reviews, see: a) see *Ref.* 1a; b) see *Ref.* 1b.

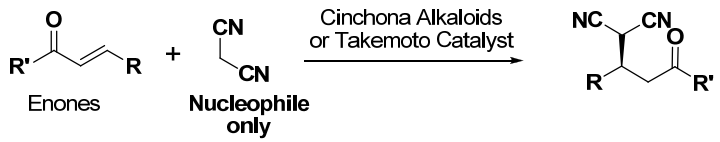
[114] For selected examples of organocatalytic conjugation addition of malonlate esters, see: a) Halland, N.; Aburel, P. S.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2003**, *42*, 661; b) Ye, J. X.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, *35*, 4481; c) Li, H. M.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2004**, *126*, 9906; d) see *Ref.* 41; e) see *Ref.* 53; f) Terada, M.; Ube, H.; Yaguchi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 1454; g) Wang, J.; Li, H.; Zu, L. S.; Jiang, W.; Xie, H. X.; Duan, W. H.; Wang, W. *J. Am. Chem. Soc.* **2006**, *128*, 12652.

[115] For selected examples of asymmetric conjugate additions of diketones, see: a) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356; b) Tillman, A. L.; Ye, J. X.; Dixon, D. J. *Chem. Commun.* **2006**, 1191; c) Hatano, M.; Maki, T.; Moriyama, K.; Arinobe, M.; Ishihara, K. *J. Am. Chem. Soc.* **2008**, *130*, 16858; d) Jiang, X. X.; Zhang, Y. F.; Liu, X.; Zhang, G.; Lai, L. H.; Wu, L. P.; Zhang, J. N.; Wang, R. *J. Org. Chem.* **2009**, *74*, 5562; e) see *Ref.* 93a; f) see *Ref.* 56.

[116] For the conjugate addition of ketoesters, see: a) Wu, F.; Li, H.; Hong, R.; Deng, L. *Angew. Chem. Int. Ed.* **2006**, *45*, 947; b) Elsner, P.; Bernardi, L.; Dela, S. G.; Overgaard, J.; Jørgensen, K. A. *J. Am. Chem. Soc* **2008**, *130*, 4897; c) Li, H.; Zhang, S. L.; Yu, C. G.; Song, X. X.; Wang, W. *Chem. Commun.* **2009**, 2136; d) Murai, K.; Fukushima,

acceptors or the donors employable in the asymmetric Michael addition is an important advance in order to have access to diversely functionalized and synthetically useful chiral building blocks. The utilization of malononitrile as nucleophile in Michael additions has received much less attention, although the nitrile group can undergo further transformations to 1,3-dicarbonyl derivatives, or imines. Quite recently, the Jacobsen and Kanemasa groups independently reported the enantioselective Michael additions of malononitrile to α,β-unsaturated imides catalyzed by metal catalysts.[118] Later on, the Takemoto group reported the first example of enantioselective Michael reactions of malonontrile to α,β-unsaturated imides in the presence of a chiral organocatalyst (Scheme 2.1).[119] More recently, the Deng,[120] and Lattanzi[121] groups also independently reported a cinchona alkaloid catalyzed enantioselective Michael addition of malononitrile to enones (Scheme 2.1). Furthermore, the Zhao group also successfully incorporated malononitrile into a three-component reaction for the synthesis of pyranopyrazoles.[122] However, all above-mentioned cases demonstrated that malononitrile was only utilized as the nucleophile.

Takemoto (*2005*), Deng (*2008*), Lattanzi (*2009*)



S.; Hayashi, S.; Takahara, Y.; Fujioka, H. *Org. Lett.* **2010**, *12*, 964.

[117] For selected examples of asymmetric conjugate addition of nitroalkanes, see: a) Halland, N.; Hazell, G.; Jørgensen, K. A. *J. Org. Chem.* **2002**, *67*, 8331; b) Mitchell, C. E. T.; Brenner, S. E.; Ley, S. V. *Chem. Commun.* **2005**, 5346; c) Hojabri, L.; Hartikka, A.; Moghaddam, F. M.; Arvidsson, P. I. *Adv. Synth. Catal.* **2007**, *349*, 740; d) Vakulya, B.; Varga, S.; Soós, T. *J. Org. Chem.* **2008**, *73*, 3475; e) Bernardi, L.; Fini, F.; Fochi, M.; Ricci, A. *Synlett.* **2008**, 1857.

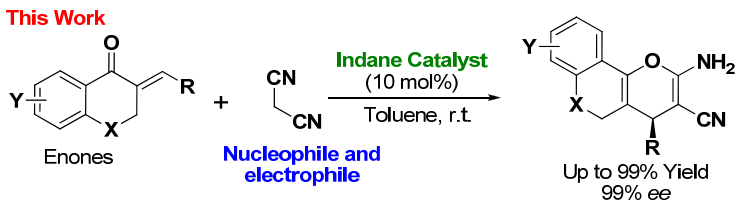
[118] a) Itoh, K.; Kanemasa, S. *J. Am. Chem. Soc* **2002**, *202*, 13394; b) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc* **2003**, *125*, 11204; c) Kanemasa, S.; Itoh, K. *Eur. J. Org. Chem.* **2004**, 4741; d) Raheen, I. T.; Goodman, S. N.; Jaconsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 706.

[119] See *Ref.* 43.

[120] Li, X. F.; Cun, L. F.; Lian, C. X.; Zhong, L.; Chen, Y. C.; Liao, J.; Zhu, J.; Deng, J. G. *Org. Biomol. Chem.* **2008**, *6*, 349.

[121] Russo, A.; Perfetto, A.; Lattanzi, A. *Adv. Synth. Catal.* **2009**, *351*, 3067.

[122] Gogoi, S.; Zhao, C. G. *Tetrahedron Lett.* **2009**, *50*, 2252.



Scheme 2.1 Organocatalyst promoted cascade reactions of malononitrile with α,β-unsaturated ketones.

To extend the synthetic utility of malononitrile as electrophile or both electrophile and nucleophile in asymmetric catalysis, we wish to undertake an investigation of new protocols. We hypothesized that the novel Michael reaction based process might facilitate a new synthetic pathway to construct a complex molecule instead of a simple Michael adduct. Surprisingly, the results of our novel reaction exploration envisioned that the change of common enones to benzylidenechromanones efficiently drove the reaction to interact with malononitrile to generate novel chiral pyrano–chromene complexes (Scheme 2.1). Herein, malononitrile worked as both electrophile and nucleophile. Notably, these pyrano–chromene complexes might possess a broad application in medicinal chemistry.[123] Herein, we disclose a new enantioselective organocatalytic cascade reaction with a Michael–*Oxa*-Michael–Tautomerization sequence that generates highly functionalized chiral pyrano–chromene complexes in a concise manner. Notably, the features of the strategy include (1) the cascade process efficiently catalyzed by a new indane amine-thiourea catalyst *via* hydrogen-bonding catalysis in good to excellent yields (up to 99%); (2) the first utilization of malononitrile as both nucleophile and electrophile in asymmetric organocatalytic Michael addition; (3) the efficient assembly of highly functionalized pyrano–chromene complexes with high to excellent enantioselectivities (up to 99% ee) in a one-pot reaction.

2.2 Results and Discussion

2.2.1 Catalyst Screening

[123] For book review, see: Ellis, G. P.; Lockhart, I. M.; Meeder-Nycz, D.; Schweizer, E. E. *Chromenes, Chromanones and Chromones*, Viley, New York, **1977**.

To explore the feasibility of the proposed catalytic cascade Michael–*Oxa*-Michael–Tautomerization process, reactions of (*E*)-3-benzylidenechroman-4-one (**2-5a**) with malononitrile (**2-6**) were performed in CH_2Cl_2 at room temperature in the presence of a cinchona alkaloid amine-thiourea catalyst **2-1**, independently developed by Connon[53] and Soós[124] groups (Figure 2.1). As shown in Table 2.1, the major Michael adduct **2-7a** was afforded by catalyst **2-1** with 65% yield and 0.7:1 d.r. (Table 2.1, entry 1). Interestingly, a small amount of unpredicted complex **2-8a** was also formed by a 21% yield and a moderate 65% *ee*. The ^{1}H and ^{13}C NMR results of complex **2-8a** demonstrated that it has an absolutely different structure in comparison with Michael adduct **2-7a**. This phenomenon envisioned that malononitrile could be utilized both as nucleophile and electrophile, especially in asymmetric organocatalysis. Inspired by this discovery, we then devoted to discover a proportionate powerful chiral organocatalyst which could efficiently promote the reaction to selectively synthesize **2-8a** and also highly control the stereochemistry of **2-8a**.

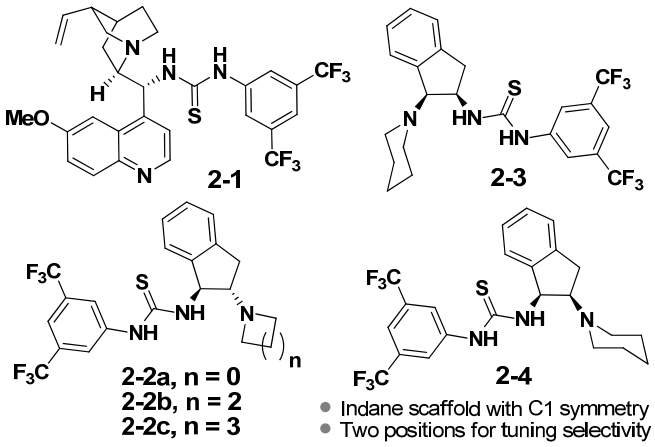
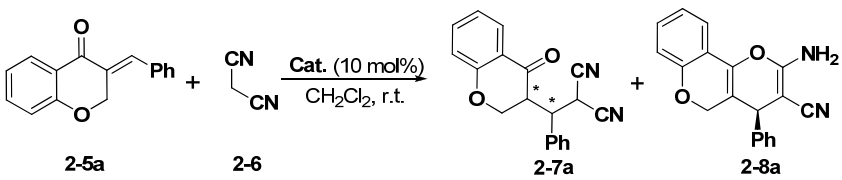


Figure 2.1 Evaluated bifunctional chiral organocatalysts.

Table 2.1 Evaluation of the bifunctional organocatalyst.[a]



[124] Vakulya, B.; Varga, S.; Csampai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967.

Entry	Catalyst	**2-7a**		**2-8a**	
		Yield [%][b]	d.r.[%][c]	Yield [%][b]	*ee* [%][d]
1	**2-1**	**65**	**0.7:1**	**21**	**65**
2	**2-2a**	41	1.5:1	12	65
3	**2-2b**	78	1.3:1	16	45
4	**2-2c**	72	1.9:1	18	67
5	**2-3**	72	1.5:1	26	–72
6	**2-4**	**21**	**0.4:1**	**72**	**79**

[a] Reaction was conducted on 0.1 mmol scale in DCM (0.1 mL) at r.t. for 3 d, and the ratio of **2-5a/2-6** was 1:1.5. [b] Yield of isolated product. [c] Determined by ^{1}H NMR analysis of the crude product. [d] Enantiomeric excess (*ee*) was determined by HPLC analysis.

Recently, our group developed a series of novel bifunctional indane amine-thiourea catalysts which were approved to be efficient chiral catalysts for Michael-type reactions.[125] Based on these results, we discovered indane catalysts exhibited a number of amazing properties, such as high reactivity and excellent stereo-control in many cases. Thereby, a test of our indane catalysts' superiority in this reaction was investigated. To this end, a small library of indane catalysts synthesized by our group **2-2**–**2-4** (Figure 2.1) was applied to this reaction. The library includes (1) catalyst **2-2a**, **2-2b** and **2-2c** with modifications on the conformation of the amine functional group; (2) catalyst **2-3** with a specific alternation on the relative orientation of the amine and thiourea functional groups in comparison with catalyst **2-2c**; (3) catalyst **2-4** with an adjustment of the relative positions of the amine and thiourea functional groups in contrast with catalyst **2-3**. To the best of our knowledge, we believe the dihedral angle between two functional groups is one of the key issues for stereo-control. We envision that the change of dihedral angel between the functional groups of the amine and thiourea might introduce an ideal and stable transition state to assist excellent stereocontrol. Eventually, the novel catalyst **2-4** was discovered as a relatively ideal promoter to catalyze this cascade process under the same condition we stated above (Table 2.1, entry 6, 72% and 79% *ee* for **2-8a**). In catalyst screening, we

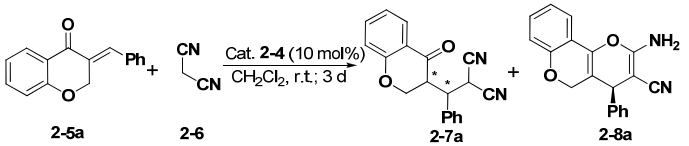
[125] Gao, Y. J.; Ren, Q.; Wang, L.; Wang, J. *Chem. –Eur. J.* **2010**, *16*, 13068.

observed that the geometry and the relative positions of the amine and thiourea functional groups played a critical role in promoting reaction and controlling the enantioselectivity. If there was *anti*-geometry between the amine and thiourea functional groups, the reactivity of catalysts (**2-2a-c**) was relative weak and the major product was Michael adduct **2-7a** (entries, 2–4, 41%, 78% and 72%, respectively). Nevertheless, catalyst **2-4** manifested a relatively higher level of catalyst efficiency and stereo-control with a formation of desired product **2-8a**. In terms of catalyst **2-4**'s structure, we found that a *syn*-geometry between the amine and thiourea functional groups in catalyst **2-4** was a significant factor. Surprisingly, a slight interchange of the relative positions of the amine and thiourea functional groups (from **2-4** to **2-3**) definitely caused the loss of desired compound **2-8a** (entry 5, 72% yield for major Michael adduct **2-7a** and only 26% yield for **2-8a**). In contrast to other catalysts, we envisioned that catalyst **2-4** could further reduce the activation energy of the *oxa*-Michael step for promoting this cascade sequence.

2.2.2 Reaction Optimization

In view of high enantioselectivity, further optimization efforts were performed by examining other parameters, such as solvents, temperatures and reaction concentrations (Table 2.2). In contrast to other solvents, toluene was revealed as the best media (Table 2.2, entry 9, 95% and 87% *ee,* 3 d). In the hope of higher enantioselectivity, we decreased the reaction concentration from 1.0 M to 0.5 M. As a result, an excellent enantiomeric excess was achieved (entry 13, 95%, 92% *ee*) without much time penalty (entry 13, reaction completed in 4 d). If concentration was down to 0.2 M, 95% *ee* was achieved, but with a consumption of 9 d (entry 14).

Table 2.2 Influence of solvent and concentration on the enantioselective reaction.[a]



Entry	Solvent	**2-7a**		**2-8a**	
		Yield [%][b]	d.r.[%][c]	Yield [%][b]	*ee* [%][d]
1	CH_2Cl_2	21	0.4:1	72	79
2	$CHCl_3$	13	0.8:1	83	75
3	DCE	9	0.7:1	86	77
4	Et_2O	10	0.9:1	81	67
5	THF	23	2.6:1	56	62
6	Dioxane	35	3.0:1	61	67
7	MeOH	25	1.8:1	73	6
8	*i*-PrOH	25	2.2:1	68	34
9	Toluene	<5	n.d.	95	87
10	Xylenes	<5	n.d.	92	88
11	DMF	59	1.9:1	33	7
12	Cyclohexane	10	1.1:1	34	85
13[e]	**Toluene**	**<5**	**n.d.**	**95**	**92**
14[f]	Toluene	<5	n.d.	90	95

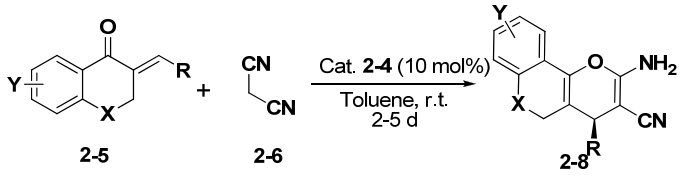
[a] Unless specified, see the Experimental section for reaction conditions. [b] Yield of isolated product. [c] Determined by ^{1}H NMR analysis of the crude mixture. [d] Enantiomeric excess (*ee*) was determined by HPLC analysis. [e] 0.5 M, 4 d. [f] 0.2 M, 9 d.

2.2.3 Substrate Scope

Having established the optimal reaction conditions, we next examined the generality of this catalytic process. Remarkably, this enantioselective cascade reaction served as a reliable synthetic process for the preparation of densely functionalized pyrano–chromenes (Table 2.3). Significantly, the new stereogenetic center was efficiently created in good to excellent enantioselectivities in a one-pot manner. Moreover, the process not only afforded a pyrano–chromene complex, and also bore a diversely structural variation of (*E*)-3-benzylidenechroman-4-ones **2-5** (Table 2.3, entries 1–17, when R = aryl; entries 18 and 19, when R = alkyl). The process also bore the replacement of "O" by "S" and "CH_2" to introduce different heterocycles

(entries 16 and 17). For example, the catalyst **2-4**-promoted cascade process smoothly afforded moderate to excellent yields (60–99%) and high to excellent enantioselectivities (80–99% *ee*). The efficiency of catalyst **2-4** allowed the reaction to bear a diverse structure of benzylidenechroman-4-one substrates which possess neutral functional groups (entries 1, 14–17, 60–95%, 80–94% *ee*), electron-donating groups (entries 2–7, 72–99%, 82–93% *ee*) and electron-withdrawing groups (entries 8–12, 85–91%, 87–99% *ee*) in the backbone. Noticeably, the bulky alkyl group involved in benzylidenechroman-4-ones also worked to afford the desired product with good yields (86% and 75% respectively, entries 18 and 19) and high enantioselectivities (86% and 87% *ee*, entries 18 and 19). When a heterocyclic thiophene was introduced to benzylidenechroman-4-one backbone, the reaction still provided a good enantioselectivity (entry 13, 86%, 81% *ee*). The absolute configuration of the pyrano–chromene **2-8f** was unequivocally determined by single-crystal X-ray diffraction analysis (Figure 2.2).[126]

Table 2.3 Substrate scope of the reaction.[a]



Entry	X	Y	R	Yield [%][b]	ee [%][c]
1[f]	O	H	Ph(**2-8a**)	95	92
2[e]	O	H	3-ClC_6H_4(**2-8b**)	93	88
3[e]	O	H	4-ClC_6H_4(**2-8c**)	92	90
4[e]	O	H	3,4-$Cl_2C_6H_3$(**2-8d**)	88	92
5[e]	O	H	2-F-4-ClC_6H_3(**2-8e**)	83	87
6[e]	O	H	2-BrC_6H_4(**2-8f**)	99	86

[126] CCDC 790340 (**2-8f**) contains the supplementary crystallographic data for this paper. These data can be ontained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

7[d]	O	H	4-$NO_2C_6H_4$(**2-8g**)	72	93
8[g]	O	H	4-$MeOC_6H_4$(**2-8h**)	90	99
9[g]	O	H	4-allyloxyC_6H_4(**2-8i**)	85	90
10[e]	O	H	2-allyloxyC_6H_4(**2-8j**)	91	92
11[e]	O	H	3-$PhOC_6H_4$(**2-8k**)	90	87
12[f]	O	H	4-*i*-PrC_6H_4(**2-8l**)	88	88
13[g]	O	H	2-thiophenyl(**2-8m**)	86	81
14[e]	O	6-Cl	Ph(**2-8n**)	88	92
15[e]	O	6-Me	Ph(**2-8o**)	91	94
16[g]	CH_2	H	Ph(**2-8p**)	60	80
17[g]	S	H	Ph(**2-8q**)	85	81
18[g]	O	H	Cyclohexyl(**2-8r**)	86	86
19[g]	O	H	*i*-Pr(**2-8s**)	75	87

[a] Unless specified, see the Experimental section for reaction conditions. [b] yield of isolated product. [c] Enantiomeric excess (*ee*) was determined by HPLC analysis. [d] Reaction time: 2 d. [e] 3 d. [f] 4 d. [g] 5 d.

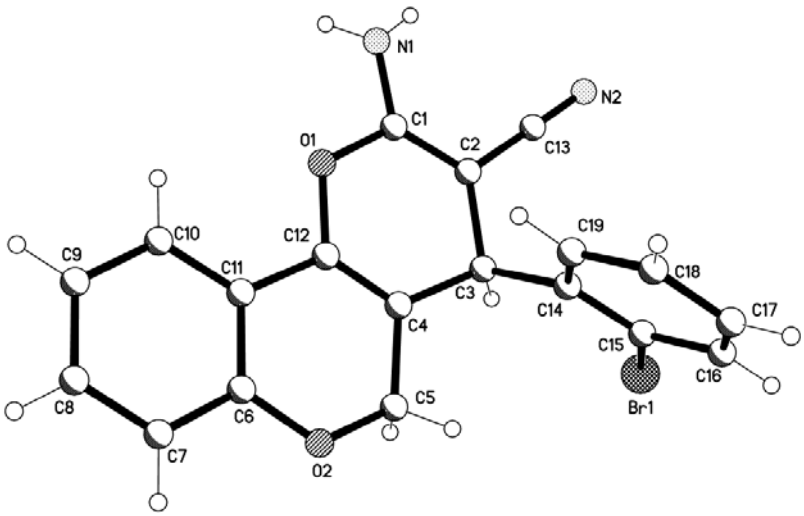


Figure 2.2 X-ray crystal structure of compound **2-8f**.

2.3 Conclusions

In conclusion, this study has developed a small library of novel and easily accessible chiral bifunctional indane amine-thiourea catalysts and applied them to a cascade Michael–*Oxa*-Michael–Tautomerization reaction of malononitrile to enones. The densely functionalized chiral pyrano–chromenes were obtained in a one-pot manner in good to high yields (up to 99%) and high to excellent enantioselectivities (up to 99% *ee*). Moreover, this catalytic system also tolerated many synthetically useful functional groups, such as nitrile, nitro, amino groups which might be manipulated for accessing more sophisticated heterocyclic compounds. This study is of considerable importance since it provides a facile and concise way to synthesize a series of bifunctional indane amine-thiourea catalysts from different available starting materials. These powerful catalysts serve as essential complements to other chiral scaffolds based urea/thiourea catalysts to catalyze this interesting Michael–*Oxa*-Michael–Tautomerization reaction. Further application of the catalytic system to other new reactions is under investigation.

2.4 Experimental Section

2.4.1 General Information

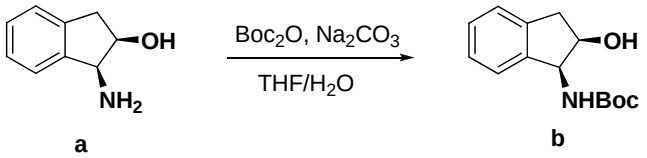
Chemicals and solvents were purchased from commercial suppliers and used as received. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ACF300 (300 MHz) or AMX500 (500 MHz) spectrometer. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (chloroform δ 7.26), carbon (chloroform δ 77.0) or tetramethylsilane (TMS δ 0.00) was used as a reference. Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), bs (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 ninhydrin followed by heating using a heat gun. Flash chromatography 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. Optical rotations were recorded on Jasco DIP-1000 polarimeter.

2.4.2 Preparation of Catalysts

Preparation of indane catalysts 2-2a/2b/2c

tert-Butyl (1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-ylcarbamate **b**[127]

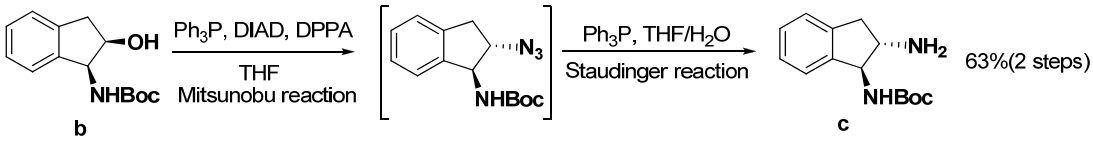


A solution of $(Boc)_2O$ (2.4 g, 11 mmol) in THF (5 ml) was added to the mixture of the amino alcohol **a** (1.5 g, 10 mmol) and sodium carbonate (2.12 g, 20 mmol) in THF/H_2O (1:1, 60 ml) at 0°C. The mixture was stirred at 0°C for 1h and then at room temperature for another two 2h (TLC was used to monitor the reaction). Water (30 ml) was added to the mixture upon completion. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 x 50 ml). The combined organic layers was washed with brine (60 ml) and dried with anhydrous $MgSO_4$ for 1h. It was then filtered and the solvent was removed under vacuum to give the product (2.5 g) with quantitative yield. It was sufficiently pure for the next step. The pure product was obtained by purification with silica gel chromatography. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.3-7.29 (m, 1H), 7.24-7.22 (m, 3H), 5.11 (d, *J* = 28.7 Hz, 2H), 4.60 (s,

[127] Abdur-Rashid, K.; Guo, R.; Chen, X.; Jia, W. Application: **WO 2008148202 A1**.

1H), 3.13 (dd, *J* = 16.6, 5.2 Hz, 1H), 2.93 (dd, *J* = 16.6, 1.7 Hz, 1H), 1.96 (s, 1H), 1.51 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.30, 140.82, 139.82, 128.18, 127.12, 125.33, 124.47, 79.88, 73.65, 58.89, 39.41, 28.39; HRMS (ESI) calcd for $C_{14}H_{19}NO_3$ (M + H^+) 249.1365, found 249.1367.

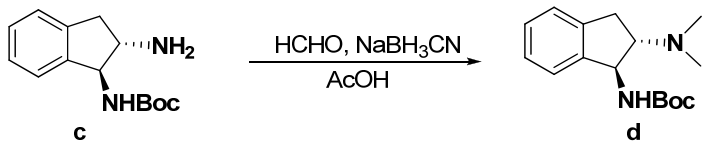
tert-Butyl (1*S*,2*S*)-2-amino-2,3-dihydro-1*H*-inden-1-ylcarbamate **c**[128]



Diisopropyl azodicarboxylate (3.0 g, 15 mmol) was added to a stirred solution of compound **b** (2.5 g, 10 mmol) and triphenylphosphane (3.15 g, 12 mmol) in THF (50 mL) at 0 °C *via* syringe under nitrogen atmosphere. After 10 min, diphenylphosphoryl azide (DPPA) (4.1 g, 15 mmol) was added dropwise by syringe. The solution was stirred overnight at room temperature. After that, triphenylphosphane (5.3 g, 20 mmol) was added in one portion, and the solution was stirred at room temperature for 2 hours. Water (5 mL) was then added and the solution was heated at 50°C for 6 h. The reaction mixture was concentrated and the residue was purified by silica gel chromatography (eluting with 1:1 EtOAc-DCM then 1:10 methanol-DCM) to obtain the white solid product (1.57 g, 63% yield, two steps). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.20-7.19 (d, *J* = 5.9 Hz, 4H), 4.85-4.63 (m, 2H), 3.42 (dd, *J* = 14.8, 7.5 Hz, 1H), 3.19 (dd, *J* = 15.6, 7.4 Hz, 1H), 2.63 (dd, *J* = 15.6, 8.2 Hz, 1H), 1.75 (s, 2H), 1.49 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.29, 141.55, 140.60, 128.07, 126.94, 124.78, 123.80, 79.65, 64.52, 62.39, 39.25, 28.37; HRMS (ESI) calcd for $C_{14}H_{21}N_2O_2$ (M + H^+) 249.1603, found 249.1601.

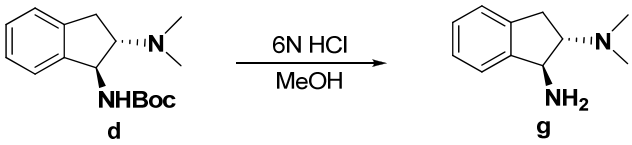
tert-Butyl (1*S*,2*S*)-2-(dimethylamino)-2,3-dihydro-1*H*-inden-1-ylcarbamate **d**[129]

[128] See *Ref.* 124.
[129] Mitchell, J. M.; Finney, N. S. *Tetrahedron Lett.* **2000**, *41*, 8431.



To a solution of compound **c** (0.75 g, 3 mmol) in 15 mL CH_3CN was added aqueous formaldehyde (37% w/w, 1.2 mL, 15 mmol), the solution was stirred at room temperature for 15 minutes. After that, $NaBH_3CN$ (0.38 g, 6 mmol) was added, followed 15 minutes stirring later by AcOH (1 mL). After 1 hour, the reaction mixture was dilute with 2% methanol-DCM (40 mL), washed with 1.0 M NaOH (3 x 30), dried by $MgSO_4$, and concentrated. The resulting residue was purified by silica gel chromatography (eluting with 1: 20 methanol-DCM) to afford the pure product (0.79 g, 95% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.26-7.15 (m, 4H), 5.20 (t, *J* = 8.4 Hz, 1H), 4.77 (d, *J* = 8.8 Hz, 1H), 3.03 (m, 2H), 2.87 (dd, *J* = 14.0, 7.4 Hz, 1H), 2.40 (s, 6H), 1.49 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.49, 142.61, 139.71, 127.90, 126.96, 124.59, 124.13, 79.49, 74.59, 57.25, 42.94, 33.68, 28.43; HRMS (ESI) calcd for $C_{16}H_{25}N_2O_2$ (M + H^+) 277.1916, found 277.1918.

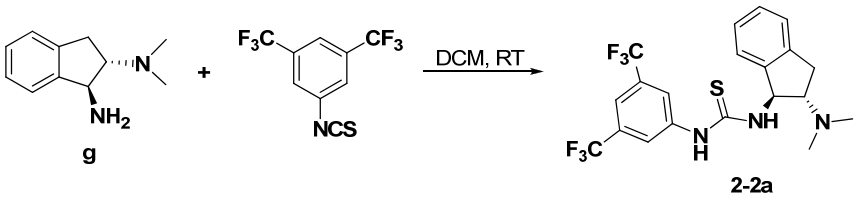
(1*S*,2*S*)-*N*^{2},*N*^{2}-Dimethyl-2,3-dihydro-1*H*-indene-1,2-diamine **g**



To a solution of compound **d** (0.7 g, 2.5 mmol) in 3 mL methanol was added 3 mL concentrated HCl solution. The mixture was stirred at room temperature for 5 hrs, then 40% NaOH solution was added until pH of mixture was 14. After extraction by DCM (5 x 10 mL), the organic layer was combined and dried by $MgSO_4$, then concentrated. The pure product (0.41 g, 93% yield) was obtained by silica gel chromatography (very short column, eluting with 1:10 to 1:5 methanol-DCM). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.30 (d, *J* = 7.3 Hz, 1H), 7.23-7.16 (m, 3H), 4.23 (d, *J* = 7.3 Hz, 1H), 2.95 (dd, *J* = 13.4, 6.1 Hz, 1H), 2.89-2.80 (m, 2H), 2.40 (s, 6H), 1.81 (s,

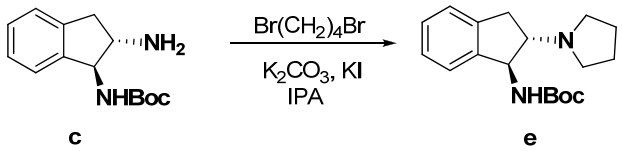
2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 145.30, 139.71, 127.30, 126.68, 124.59, 123.42, 77.76, 59.07, 43.02, 31.17; HRMS (ESI) calcd for $C_{11}H_{17}N_2$ (M + H^+) 177.1392, found 177.1391.

1-(3,5-Bis(trifluoromethyl)phenyl)-3-((1*S*,2*S*)-2-(dimethylamino)-2,3-dihydro-1*H*-indeen-1-yl)thiourea **2-2a**



To a solution of compound **g** (0.4 g, 2.27 mmol) in 10 mL DCM was added 1-isothiocyanato-3,5-bis(trifluoromethyl)benzene (0.59 g, 2.16 mmol) dropwise. The mixture was stirred at room temperature for 30 min, reaction completed. The solvent was removed by rotary evaporation and pure product **2-2a** (1.0 g, 98% yield) was obtained by silica gel chromatography (eluting with 1:5 EtOAc-hexane then 1: 10 methanol-DCM). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 12.84 (s, 1H), 8.10 (s, 2H), 7.61 (s, 1H), 7.42-7.28 (m, 4H), 6.86 (d, *J* = 3.2 Hz, 1H), 5.22 (m, 1H), 3.75 (q, *J* = 8.5 Hz, 1H), 3.08 (ddd, *J* = 44.1, 15.9, 9.0 Hz, 2H), 2.52 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 182.25, 141.95, 139.83, 137.38, 133.15, 132.06, 131.80, 131.53, 131.26, 129.35, 127.86, 125.57, 124.18, 123.46, 122.73, 122.01, 117.60, 74.45, 62.57, 40.75, 25.39; HRMS (ESI) calcd for $C_{20}H_{20}F_6N_3S$ (M + H^+) 448.1282, found 448.1277.

tert-Butyl (1*S*,2*S*)-2-(pyrrolidin-1-yl)-2,3-dihydro-1*H*-inden-1-ylcarbamate **e**[130]

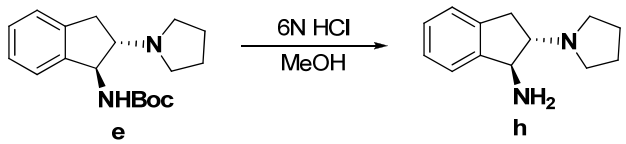


Compound **c** (0.75 g, 3 mmol), 1,4-dibromobutane (0.78 g, 3.6 mmol), potassium

[130] Soh, J. Y.-T.; Tan, C.-H. *J. Am. Chem. Soc.* **2009**, *131*, 6904.

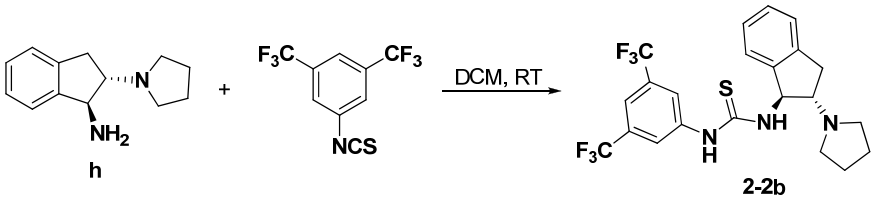
carbonate (1.08 g, 7.8 mmol), potassium iodide (0.1 g, 0.6 mmol) and 10 mL iso-propanol were added into a sealed tube. The mixture was heated at 80 °C for 48 hrs and then allowed to cool to room temperature. The mixture was filtered and washed with DCM, the filtrate was concentrated and the resulting residue was purified by silica gel chromatography (eluting with 1:5 EtOAc-hexane then 1:10 methanol-DCM) to obtain the product **e** (0.64 g, 70% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.26-7.16 (m, 4H), 5.25-5.22 (m, 1H), 4.81 (d, *J* = 9.1 Hz, 1H), 3.17 (dd, *J* = 18.9, 11.0 Hz, 1H), 3.01-2.98 (m, 2H), 2.80-2.75 (m, 4H), 1.85 (s, 4H), 1.49 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.44, 142.25, 139.68, 128.06, 127.05, 124.56, 124.08, 79.61, 72.61, 59.61, 52.34, 36.24, 28.41, 23.36; HRMS (ESI) calcd for $C_{18}H_{27}N_2O_2$ (M + H$^+$) 303.2073, found 303.2062.

(1*S*,2*S*)-2-(Pyrrolidin-1-yl)-2,3-dihydro-1*H*-inden-1-amine **h**



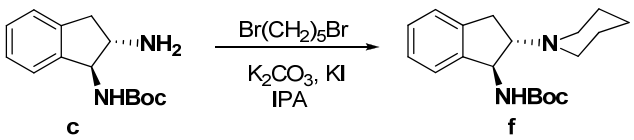
To a solution of compound **e** (0.6 g, 2.0 mmol) in 3 mL methanol was added 3 mL concentrated HCl solution. The mixture was stirred at room temperature for 5 hrs, then 40% NaOH solution was added until pH of mixture was 14. After extraction by DCM (5 x 10 mL), the organic layer was combined and dried by $MgSO_4$, then concentrated. The pure product (0.36 g, 90% yield) was obtained by silica gel chromatography (very short column, eluting with 1:10 to 1:5 methanol-DCM). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.31-7.16 (m, 4H), 4.35 (d, *J* = 7.3 Hz, 1H), 3.10 (dd, *J* = 15.3, 7.7 Hz, 1H), 2.94 (dd, *J* = 15.3, 9.0 Hz, 1H), 2.86-2.81 (m, 5H), 2.41 (s, 2H), 1.86 (dd, *J* = 9.0, 3.9 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.37, 139.57, 127.40, 126.78, 124.37, 123.45, 75.99, 61.21, 52.62, 35.34, 23.23; HRMS (ESI) calcd for $C_{13}H_{19}N_2$ (M + H$^+$) 203.1548, found 203.1543.

1-(3,5-Bis(trifluoromethyl)phenyl)-3-((1*S*,2*S*)-2-(pyrrolidin-1-yl)-2,3-dihydro-1*H*-inden-1-yl)thiourea **2-2b**



To a solution of compound **h** (0.36 g, 1.78 mmol) in 10 mL DCM was added 1-isothiocyanato-3,5-bis(trifluoromethyl)benzene (0.51 g, 1.87 mmol) dropwise. The mixture was stirred at room temperature for 30 min, reaction completed. The solvent was removed by rotary evaporation and pure product **2-2b** (0.84 g, 95% yield) was obtained by silica gel chromatography (eluting with 1:5 EtOAc-hexane then 1: 10 methanol-DCM). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 12.82 (s, 1H), 8.05 (s, 2H), 7.63 (s, 1H), 7.34 (ddd, *J* = 37.5, 21.3, 6.6 Hz, 4H), 6.68 (s, 1H), 5.25-5.23 (m, 1H), 4.03 (q, *J* = 8.2 Hz, 1H), 3.11 (dd, *J* = 8.7, 3.6 Hz, 2H), 2.94-2.84 (m, 4H), 1.90 (s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 182.77, 141.97, 140.04, 137.91, 132.10, 131.83, 131.31, 129.36, 127.95, 125.62, 124.29, 123.49, 123.42, 122.12, 117.94, 77.25, 77.00, 76.75, 70.55, 63.20, 48.55, 26.86, 23.93; HRMS (ESI) calcd for $C_{22}H_{22}F_6N_3S$ (M + H^+) 474.1439, found 474.1443.

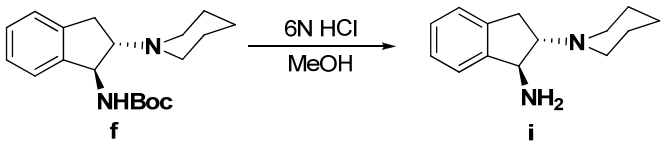
tert-Butyl (1*S*,2*S*)-2-(piperidin-1-yl)-2,3-dihydro-1*H*-inden-1-ylcarbamate **f**[130]



Compound **c** (0.75 g, 3 mmol), 1,5-dibromopentane(0.83 g, 3.6 mmol), potassium carbonate (1.08 g, 7.8 mmol), potassium iodide (0.1 g, 0.6 mmol) and 10 mL *iso*-propanol were added into a sealed tube. The mixture was heated at 80 °C for 48hrs and then allowed to cool to room temperature. The mixture was filtered and washed with DCM, the filtrate was concentrated and the resulting residue was

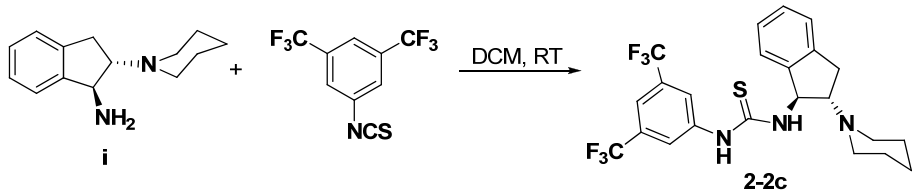
purified by silica gel chromatography (eluting with 1:10 EtOAc-hexane then 1:10 methanol-DCM) to obtain the product **f** (0.71 g, 75% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.28-7.12(m, 4H), 5.24 (dd, *J* = 13.7, 5.2 Hz, 1H), 4.89-4.87 (m, 1H), 3.05 (s, 2H), 2.87 (dd, *J* = 18.6, 11.7 Hz, 1H), 2.60 (dd, *J* = 23.2, 4.9 Hz, 4H), 1.61-1.59 (m, 4H), 1.48 (s, 11H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.41, 142.52, 139.97, 127.85, 126.88, 124.50, 124.14, 79.44, 74.64, 56.53, 51.60, 33.81, 28.41, 26.13, 24.45; HRMS (ESI) calcd for $C_{19}H_{29}N_2O_2$ (M + H^+) 317.2229, found 317.2227.

(1*S*,2*S*)-2-(Piperidin-1-yl)-2,3-dihydro-1*H*-inden-1-amine **i**



To a solution of compound **f** (0.7 g, 2.2 mmol) in 3 mL methanol was added 3 mL concentrated HCl solution. The mixture was stirred at room temperature for 5 hrs, then 40% NaOH solution was added until pH of mixture was 14. After extraction by DCM (5 x 10 mL), the organic layer was combined and dried by $MgSO_4$, then concentrated. The pure product (0.43 g, 90% yield) was obtained by silica gel chromatography (very short column, eluting with 1:10 to 1:5 methanol-DCM). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 7.3 Hz, 1H), 7.14-7.07 (m, 3H), 4.25 (d, *J* = 6.9 Hz, 1H), 2.92 (dd, *J* = 13.9, 6.6 Hz, 1H), 2.81 (ddd, *J* = 21.8, 14.7, 8.2 Hz, 2H), 2.53 (s, 4H), 2.15 (s, 2H), 1.58-1.53 (m, 4H), 1.40 (dt, *J* = 11.3, 5.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 145.16, 139.87, 127.20, 126.56, 124.42, 123.38, 77.71, 58.33, 51.96, 31.95, 25.96, 24.40; HRMS (ESI) calcd for $C_{14}H_{21}N_2$ (M + H^+) 217.1705, found 217.1708.

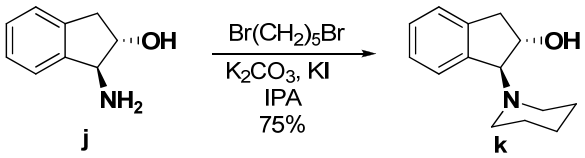
1-(3,5-Bis(trifluoromethyl)phenyl)-3-((1*S*,2*S*)-2-(piperidin-1-yl)-2,3-dihydro-1*H*-inden-1-yl)thiourea **2-2c**



To a solution of compound **i** (0.4 g, 1.85 mmol) in 10 mL DCM was added 1-isothiocyanato-3,5-bis(trifluoromethyl)benzene (0.53 g, 1.95 mmol) dropwise. The mixture was stirred at room temperature for 30 min, reaction completed. The solvent was removed by rotary evaporation and pure product **2-2c** (0.87 g, 97% yield) was obtained by silica gel chromatography (eluting with 1:10 EtOAc-hexane then 1: 10 methanol-DCM). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 12.20 (s, 1H), 8.06 (s, 2H), 7.70 (s, 1H), 7.43-7.26 (m, 4H), 6.72 (s, 1H), 5.31 (m, 1H), 3.72 (q, *J* = 8.2 Hz, 1H), 3.21 (dd, *J* = 16.1, 8.5 Hz, 1H), 3.01 (dd, *J* = 16.1, 8.8 Hz, 1H), 2.77-2.67 (m, 4H), 1.56 (dd, *J* = 44.8, 22.4 Hz, 7H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 183.44, 141.53, 140.37, 137.76, 132.13, 131.85, 131.58, 131.31, 129.41, 127.85, 125.78, 125.58, 124.25, 123.61, 122.07, 118.82, 75.27, 62.04, 50.65, 26.33, 25.94, 23.84; HRMS (ESI) calcd for $C_{23}H_{24}F_6N_3S$ (M + H$^+$) 488.1595, found 488.1598.

Preparation of indane catalysts 2-3

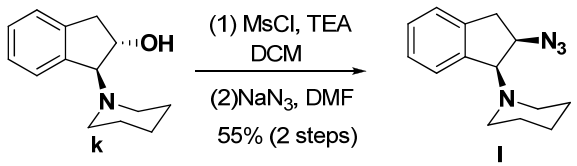
(1*S*,2*S*)-1-(Piperidin-1-yl)-2,3-dihydro-1*H*-inden-2-ol **k**[130]



Compound **j** (0.75 g, 5 mmol), 1,5-dibromopentane (1.38 g, 6.0 mmol), potassium carbonate (1.80 g, 13 mmol), potassium iodide (0.17 g, 1.0 mmol) and 10 mL iso-propanol were added into a sealed tube. The mixture was heated at 80 °C for 48 hrs and then allowed to cool to room temperature. The mixture was filtered and washed with DCM, the filtrate was concentrated and the resulting residue was purified by silica gel chromatography (eluting with 1:5 EtOAc-hexane then 1:10

methanol-DCM) to obtain the product **k** (0.82 g, 75% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36-7.33 (m, 1H), 7.12-7.16 (m, 3H), 4.66 (dd, *J* = 12.3, 5.3 Hz, 1H), 4.08 (d, *J* = 4.8 Hz, 1H), 3.25 (dd, *J* = 16.2, 7.1 Hz, 1H), 2.80 (dd, *J* = 16.2, 5.5 Hz, 1H), 2.62-2.61 (m, 4H), 1.58-1.54 (m, 4H), 1.46 (d, *J* = 5.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.62, 140.33, 127.66, 126.41, 125.82, 124.90, 78.49, 73.54, 50.79, 40.06, 26.51, 24.66; HRMS (ESI) calcd for $C_{14}H_{20}NO$ (M + H^+) 218.1545, found 218.1545.

1-((1S,2R)-2-Azido-2,3-dihydro-1H-inden-1-yl)piperidine **l**[131]

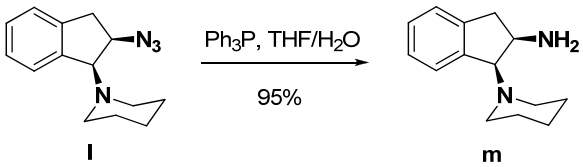


To a stirred solution of compound **k** (0.78 g, 3.6 mmol) and triethylamine (1.1 g, 10.8 mmol) in dry DCM (10 mL) at 0°C under nitrogen was added dropwise methanesulfonyl chloride (0.62 g, 5.4 mmol). The mixture was stirred for another 20 min at room temperature, and the solvent was evaporated under reduced pressure. The residue was extracted with DCM, washed successively with water, and brine, and dried over $MgSO_4$. The organic layer was concentrated to afford crude mesylate intermediate. Then the crude mesylate intermediate was redissolve d in DMF (10 mL), followed by adding NaN_3 (1.87 g, 28.8 mmol). The mixture was heated under nitrogen at 70°C for 6 hrs. After the mixture was cooled, the solvent was evaporated under reduced pressure and the residue was extracted with EtOAc (25 mL x 3) and dried over $MgSO_4$. The organic layer was removed under reduced pressure, and the crude product was purified by silica gel chromatography (eluting with 1:10 EtOAc-hexane) to afford product **l** (0.48 g, 55% yield, two step). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.26-7.10 (m, 4H), 4.63 (d, *J* = 6.9 Hz, 1H), 3.17 (td, *J* = 8.0 Hz, 6.8, 1H), 3.03 (dd, *J* = 15.8, 7.9 Hz, 1H), 2.81 (dd, *J* = 15.8, 7.9 Hz, 1H), 2.48 (ddt, *J* = 38.5,

[131] Govindaraju, T.; Kumar, V. A.; Ganesh, K. N. *J. Org. Chem.* **2004**, *69*, 5725.

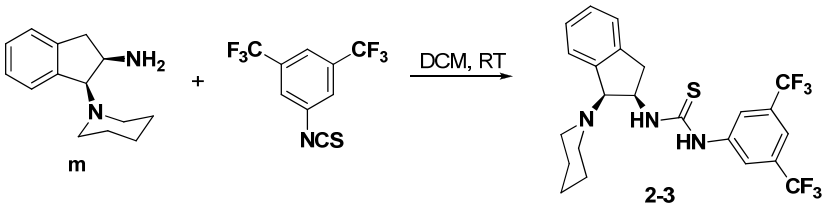
10.7, 5.2 Hz, 4H), 1.53 (dt, J = 11.3, 5.7 Hz, 4H), 1.39 (dd, J = 11.7, 6.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 140.43, 139.14, 128.56, 126.94, 124.71, 124.15, 72.82, 66.85, 51.91, 33.83, 25.94, 24.30; HRMS (ESI) calcd for $C_{14}H_{19}N_4$ (M + H^+) 243.1610, found 243.1612.

(1*S*,2*R*)-1-(Piperidin-1-yl)-2,3-dihydro-1*H*-inden-2-amine **m**[131]



To a solution of compound **l** (0.46 g, 1.9 mmol) in 10 mL THF was added triphenylphosphane (1.5 g, 5.7 mmol). The mixture was stirred at room temperature for 3 h, then added 3 mL water, heated at 60 ^{o}C for 4 hrs. The solvent was removed by reduced pressure, and the resulting residue was purified by a very short silica gel column (eluting with 1:10 to 1: 5 methanol-DCM) to afford compound **m** (0.39 g, 95% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.27 (t, J = 5.8 Hz, 1H), 7.19-7.11 (m, 3H), 4.31 (d, J = 6.9 Hz, 1H), 2.99-2.83 (m, 3H), 2.60-2.58(m, 4H), 2.45 (s, 2H), 1.64-1.59 (m, 4H), 1.45 (dt, J = 11.7, 5.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 144.92, 139.73, 127.18, 126.54, 124.36, 123.34, 77.45, 58.16, 51.84, 31.67, 25.82, 24.29; HRMS (ESI) calcd for $C_{14}H_{21}N_2$ (M + H^+) 217.1705, found 217.1708.

1-(3,5-Bis(trifluoromethyl)phenyl)-3-((1*S*,2*R*)-1-(piperidin-1-yl)-2,3-dihydro-1*H*-indeн-2-yl)thiourea **2-3**

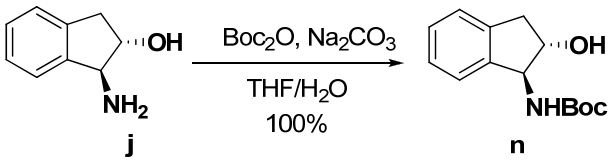


To a solution of compound **m** (0.39 g, 1.81 mmol) in 10 mL DCM was added

1-isothiocyanato-3,5-bis(trifluoromethyl)benzene (0.52 g, 1.90 mmol) dropwise. The mixture was stirred at room temperature for 30min, reaction completed. The solvent was removed by rotary evaporation and pure product **2-3** (0.90 g, 97% yield) was obtained by silica gel chromatography (eluting with 1:10 EtOAc-hexane then 1: 10 methanol-DCM). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 12.14 (s, 1H), 7.98 (s, 2H), 7.61 (s, 1H), 7.27 (ddd, *J* = 20.9, 12.6, 4.3 Hz, 4H), 6.68 (s, 1H), 5.22 (m, 1H), 3.63 (dd, *J* = 6.2, 8.3 Hz, 1H), 3.13 (dd, *J* = 16.1, 8.6 Hz, 1H), 2.92 (dd, *J* = 16.2, 8.9 Hz, 1H), 2.68-2.60 (m, 4H), 1.56-1.44 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 183.34, 141.50, 140.33, 137.67, 132.31, 131.87, 131.42, 130.98, 129.36, 127.78, 125.76, 125.53, 124.93, 123.58, 121.31, 118.75, 75.21, 62.01, 50.56, 26.29, 25.90, 23.78; HRMS (ESI) calcd for $C_{23}H_{24}F_6N_3S$ (M + H^+) 488.1595, found 488.1587.

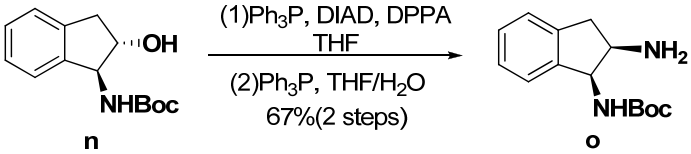
Preparation of indane catalysts 2-4

tert-Butyl (1*S*,2*S*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-ylcarbamate **n**[127]



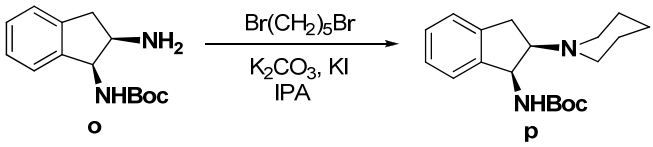
It was prepared by using the same procedure for the synthesis of compound **b**. Quantitative yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.18-7.11 (m, 4H), 5.00 (s, 1H), 4.82 (t, *J* = 5.9 Hz, 1H), 4.35-4.28 (m, 1H), 3.19 (dd, *J* = 15.8, 7.7 Hz, 1H), 2.81 (dd, *J* = 15.8, 8.1 Hz, 1H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.35, 140.12, 139.34, 128.40, 127.09, 125.09, 123.05, 81.82, 80.40, 63.98, 38.31, 28.31; HRMS (ESI) calcd for $C_{14}H_{19}NO_3$ (M + H^+) 249.1365, found 249.1366.

tert-Butyl (1*S*,2*R*)-2-amino-2,3-dihydro-1*H*-inden-1-ylcarbamate **o**[128]



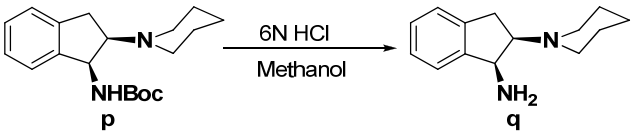
It was prepared by using the same procedure for the synthesis of compound **c**. (67% yield, two steps) ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.29 (m, 1H), 7.21 (d, *J* = 2.2 Hz, 3H), 5.23 (s, 1H), 5.03 (s, 1H), 3.82 (s, 1H), 3.12 (dd, *J* = 15.9, 6.1 Hz, 1H), 2.69 (dd, *J* = 15.9, 3.3 Hz, 1H), 1.73 (s, 2H), 1.49 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.05, 141.43, 140.60, 128.00, 126.94, 125.20, 124.71, 79.53, 58.56, 54.70, 39.70, 28.38; HRMS (ESI) calcd for $C_{14}H_{21}N_2O_2$ (M + H^+) 249.1603, found 249.1606.

tert-Butyl (1*S*,2*R*)-2-(piperidin-1-yl)-2,3-dihydro-1*H*-inden-1-ylcarbamate **p**[130]



It was prepared by using the same procedure for the synthesis of compound **f**. (75% yield) ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.58 (s, 1H), 7.21-7.14 (m, 3H), 5.81 (d, *J* = 5.3 Hz, 1H), 4.90 (s, 1H), 3.02 (p, *J* = 7.4 Hz, 1H), 2.92-2.89 (m, 2H), 2.42 (dd, *J* = 11.7, 6.2 Hz, 4H), 1.58 (dt, *J* = 12.0, 6.1 Hz, 6H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.03, 143.35, 140.42, 127.83, 126.62, 125.95, 124.17, 78.75, 67.58, 54.81, 52.40, 34.51, 28.34, 25.76, 24.26; HRMS (ESI) calcd for $C_{19}H_{29}N_2O_2$ (M + H^+) 317.2229, found 317.2225.

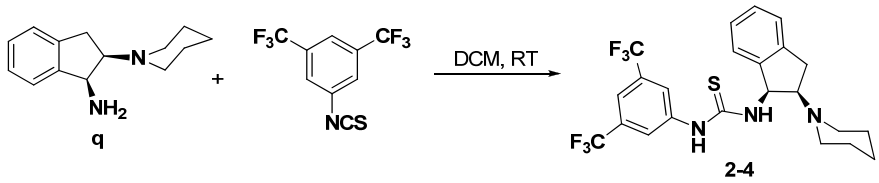
(1*S*,2*R*)-2-(Piperidin-1-yl)-2,3-dihydro-1*H*-inden-1-amine **q**



It was prepared by using the same procedure for the synthesis of compound **i**. (90% yield) ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.30 (d, *J* = 6.3 Hz, 1H), 7.14-7.08 (m, 3H), 4.15 (d, *J* = 5.4 Hz, 1H), 2.80 (qd, *J* = 14.8, 8.5 Hz, 2H), 2.72-2.68 (m, 1H), 2.48 (s, 2H), 2.38 (d, *J* = 3.8 Hz, 2H), 2.30 (s, 2H), 1.56 (dt, *J* = 11.0, 5.7 Hz, 4H), 1.42-1.40 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 144.85, 140.48, 127.51, 126.39, 124.44,

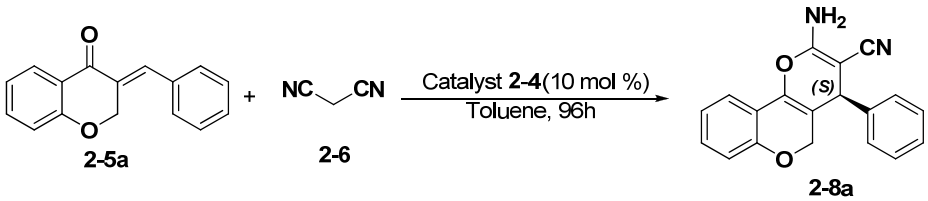
124.35, 69.87, 55.40, 52.58, 33.51, 25.53, 24.04; HRMS (ESI) calcd for $C_{14}H_{21}N_2$ (M + H^+) 217.1705, found 217.17010.

1-(3,5-Bis(trifluoromethyl)phenyl)-3-((1*S*,2*R*)-2-(piperidin-1-yl)-2,3-dihydro-1H-indeen-1-yl)thiourea **2-4**



It was prepared by using the same procedure for the synthesis of catalyst **2-2c**. (97% yield) ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.38 (s, 1H), 7.78 (d, *J* = 51.1 Hz, 3H), 7.60 (s, 1H), 7.15-7.05 (m, 3H), 5.53 (s, 1H), 3.06 (d, *J* = 6.6 Hz, 1H), 2.89 (dd, *J* = 15.4, 6.9 Hz, 1H), 2.79-2.74 (m, 1H), 2.31 (s, 4H), 1.25 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 180.13, 141.42, 140.74, 139.08, 133.36, 133.08, 132.81, 132.55, 128.71, 126.97, 126.83, 126.05, 124.47, 123.88, 123.71, 121.71, 119.54, 118.85, 68.02, 58.90, 52.26, 34.34, 25.63, 23.88; HRMS (ESI) calcd for $C_{23}H_{24}F_6N_3S$ (M + H^+) 488.1595, found 488.1590.

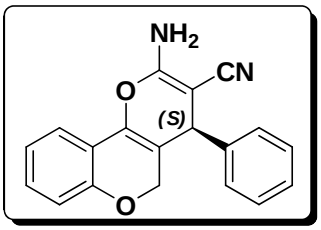
2.4.3 Representative Procedure for Michael–*Oxa*-Michael–Tautomerization Reaction



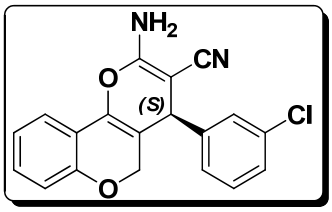
To a solution of malononitrile **2-6** (10 mg, 0.15mmol) in 0.2mL toluene was added (*E*)-3-benzylidenechroman-4-one **2-5a** (24 mg, 0.1 mmol) at room temperature, followed by adding catalyst **2-4** (4.9 mg, 0.01 mmol). The mixture was stirred at room temperature for 4 d. The crude product was purified by column chromatography on

silica gel, eluted by hexane/EtOAc=8:1 then 4:1 to afford 28.7 mg (95% yield) of the desired product **2-8a** as yellow solid.

2.4.4 Analytical Data of Michael–*Oxa*-Michael–Tautomerization Products

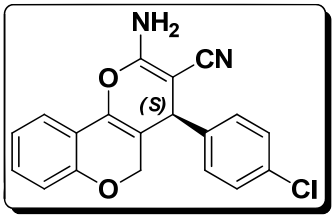


(*S*)-2-Amino-4-phenyl-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (2-8a) (Table 2.3 , entry 1). 95% yield, 92% *ee*; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.39–7.32 (m, 3H), 7.27 (q, *J* = 6.0 Hz, 3H), 7.23–7.15 (m, 1H), 6.95 (t, *J* = 7.5 Hz, 1H), 6.79 (d, *J* = 8.1 Hz, 1H), 4.64 (s, 2H), 4.63 (d, *J* = 13.2 Hz, 1H), 4.43 (d, *J* = 13.8 Hz, 1H), 4.03 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.77, 154.12, 140.87, 138.01, 130.30, 129.02, 127.92, 127.88, 121.26, 121.04, 119.26, 116.66, 115.94, 105.05, 66.48, 61.16, 39.71; HRMS (EI) calcd for $C_{19}H_{14}O_2N_2$ 302.1055, found 302.1048; HPLC (Chiralpak IC, *i*-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 27.5 min, t_R (minor) = 15.9 min, *ee* = 92%; $[\alpha]^{30}_{D}$ = -64.1 (*c* = 0.98 in $CHCl_3$).

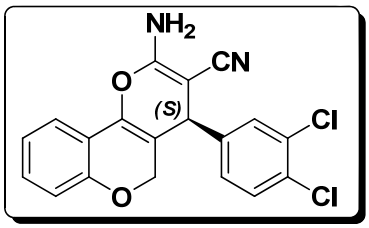


(*S*)-2-Amino-4-(3-chlorophenyl)-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (2-8b) (Table 2.3 , entry 2). 93% yield, 88% *ee*; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35 (d, *J* = 7.7Hz, 1H), 7.30–7.26 (m, 3H), 7.21 (t, *J* = 7.9Hz, 1H), 7.17 (d, *J* = 6.8Hz, 1H), 6.97 (t, *J* = 7.6Hz, 1H), 6.81 (d, *J* = 8.2Hz, 1H), 4.66 (s, 2H), 4.64 (d, *J* = 14.5Hz, 1H), 4.43 (d, *J* = 14.5Hz, 1H), 4.02 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.99,

154.13, 143.10, 138.35, 135.03, 130.52, 130.28, 128.25, 127.94, 126.19, 121.35, 121.14, 119.04, 116.45, 116.00, 104.28, 66.30, 60.42, 39.53; HRMS (EI) calcd for $C_{19}H_{13}O_2N_2Cl$ 336.0666, found 336.0649; HPLC (Chiralpak IC, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 12.1 min, t_R (minor) = 7.1 min, *ee* = 88%; $[\alpha]^{30}_D$ = -53.6 (*c* = 0.85 in $CHCl_3$).

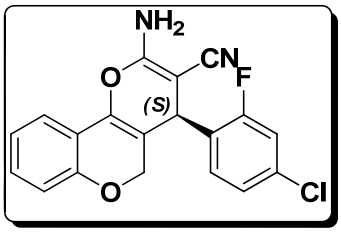


(*S*)-2-Amino-4-(4-chlorophenyl)-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (2-8c) (Table 2.3 , entry 3). 92% yield, 90% *ee*; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.29 (m, 3H), 7.24–7.16 (m, 3H), 6.96 (t, *J* = 7.6Hz, 1H), 6.80(d, *J* = 7.6Hz, 1H), 4.67 (s, 2H), 4.62 (d, *J* = 13.7Hz, 1H), 4.41 (d, *J* = 13.8Hz, 1H), 4.02 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.82, 154.15, 139.49, 138.34, 133.82, 130.51, 129.25, 129.24, 121.36, 121.12, 119.03, 116.49, 116.03, 104.44, 66.31, 60.78, 39.21; HRMS (EI) calcd for $C_{19}H_{13}O_2N_2Cl$ 336.0666, found 336.0653; HPLC (Chiralpak IC, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 12.5 min, t_R (minor) = 7.3 min, *ee* = 90%; $[\alpha]^{30}_D$ = -62.3 (*c* = 0.90 in $CHCl_3$).

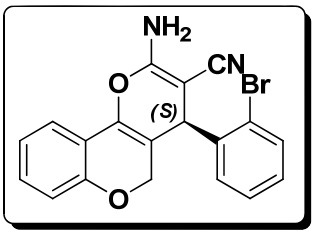


(*S*)-2-Amino-4-(3,4-dichlorophenyl)-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (2-8d) (Table 2.3 , entry 4). 88% yield, 92% *ee*; ^{1}H NMR (500 MHz,DMSO-d_6): δ = 7.64 (d, *J* = 8.3Hz, 1H), 7.53 (d, *J* = 2.0Hz, 1H), 7.37 (dd, *J* = 7.6, 1.3Hz, 1H), 7.29 (dd, *J* = 8.3, 2.0Hz, 1H), 7.27–7.21 (m, 1H), 7.08 (s, 2H), 7.01 (t, *J* = 7.2Hz, 1H),

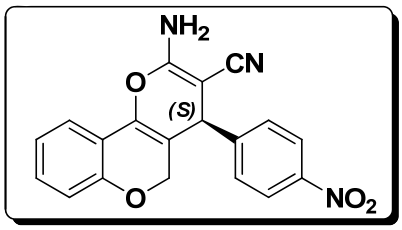
6.82 (d, J = 8.0Hz, 1H), 4.75 (d, J = 14.6Hz, 1H), 4.33 (d, J = 14.0Hz, 1H), 4.21 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 159.80, 153.63, 143.54, 137.26, 131.31, 131.13, 130.43, 130.04, 129.67, 128.16, 121.29, 121.02, 119.82, 116.49, 115.70, 104.34, 65.58, 55.44, 38.03; HRMS (EI) calcd for $C_{19}H_{12}O_2N_2Cl_2$ 370.0276, found 370.0179; HPLC (Chiralpak IC, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 12.4 min, t_R (minor) = 6.4 min, *ee* = 92%; $[\alpha]^{30}_D$ = -67.7 (c = 1.05 in $CHCl_3$).



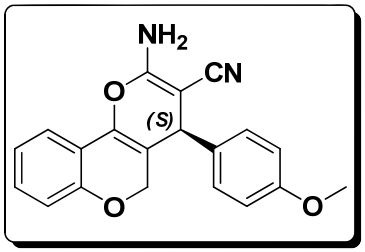
(*S*)-2-Amino-4-(4-chloro-2-fluorophenyl)-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (2-8e) (Table 2.3 , entry 5). 83% yield, 87% *ee*; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33 (dd, J = 7.7, 1.5Hz, 1H), 7.26 (t, J = 8.2Hz, 1H), 7.20 (td, J = 7.9, 1.5Hz, 1H), 7.16 (dd, J = 8.3, 1.9Hz, 1H), 7.11 (dd, J = 9.8, 2.0Hz, 1H), 6.96 (dd, J = 11.0, 4.1Hz, 1H), 6.80 (d, J = 8.0Hz, 1H), 4.73–4.68 (m, 3H), 4.45–4.43 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.45, 159.63, 159.45, 154.18, 138.70, 134.58, 134.50, 130.69, 130.66, 130.57, 126.55, 126.45, 125.50, 125.47, 121.37, 121.10, 118.77, 116.73, 116.53, 116.43, 116.04, 103.67, 66.10, 59.08, 32.21; HRMS (EI) calcd for $C_{19}H_{12}O_2N_2ClF$ 354.0571, found 354.0558; HPLC (Chiralpak IC, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 10.6 min, t_R (minor) = 6.4 min, *ee* = 87%; $[\alpha]^{30}_D$ = -38.0 (c = 1.03 in $CHCl_3$).



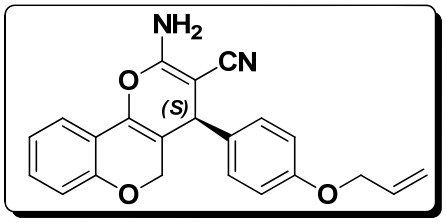
(*S*)-2-Amino-4-(2-bromophenyl)-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (2-8f) (Table 2.3 , entry 6). 99% yield, 86% *ee*; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.56 (dd, *J* = 8.0, 1.1Hz, 1H), 7.39–7.30 (m, 3H), 7.20 (td, *J* = 7.9, 1.6Hz, 1H), 7.14 (ddd, *J* = 8.0, 7.1, 1.9Hz, 1H), 6.96 (td, *J* = 7.6, 1.0Hz, 1H), 6.79 (dd, *J* = 8.1, 0.9Hz, 1H), 4.73 (m, 4H), 4.40 (dd, *J* = 13.8, 0.9Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.35, 154.18, 139.89, 138.16, 133.21, 130.56, 130.40, 129.43, 128.49, 123.78, 121.29, 121.05, 118.90, 116.52, 115.97, 104.95, 66.07, 60.05, 38.36; HRMS (EI) calcd for $C_{19}H_{13}O_2N_2Br$ 380.0160, found 380.0143; HPLC (Chiralpak IC, *i*-propanol/hexane = 15/85, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 14.7 min, t_R (minor) = 10.8 min, *ee* = 86%; $[\alpha]^{30}_D$ = -18.1 (*c* = 0.58 in $CHCl_3$).



(*S*)-2-Amino-4-(4-nitrophenyl)-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (2-8g) (Table 2.3 , entry 7). 72% yield, 93% *ee*; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.30–8.21 (m, 2H), 7.53–7.44 (m, 2H), 7.36 (dd, *J* = 7.7, 1.5Hz, 1H), 7.23 (td, *J* = 7.9, 1.6Hz, 1H), 6.98 (td, *J* = 7.6, 0.8Hz, 1H), 6.82 (d, *J* = 8.1Hz, 1H), 4.78 (s, 2H), 4.66 (dd, *J* = 13.7, 0.9Hz, 1H), 4.38 (d, *J* = 13.7Hz, 1H), 4.18 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.09, 154.20, 148.23, 147.72, 139.07, 130.87, 128.86, 124.41, 121.53, 121.26, 118.65, 116.22, 116.15, 103.37, 66.11, 59.90, 39.63; HRMS (EI) calcd for $C_{19}H_{13}O_4N_3$ 347.0906, found 347.0917; HPLC (Chiralpak IC, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 32.3 min, t_R (minor) = 21.0 min, *ee* = 93%; $[\alpha]^{30}_D$ = -106.5 (*c* = 0.23 in $CHCl_3$).

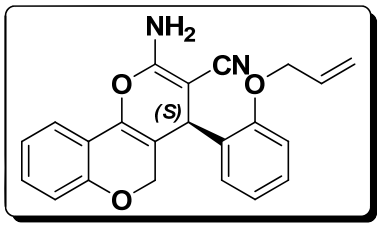


(*S*)-2-Amino-4-(4-methoxyphenyl)-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (2-8h) (Table 2.3 , entry 8). 90% yield, 99% *ee*; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34 (dd, *J* = 7.7, 1.4Hz, 1H), 7.23–7.14 (m, 3H), 6.95 (td, *J* = 7.6, 0.8Hz, 1H), 6.90–6.84 (m, 2H), 6.79 (d, *J* = 8.1Hz, 1H), 4.62 (d, *J* = 13.9Hz, 1H), 4.60 (s, 2H), 4.44 (d, *J* = 13.9Hz, 1H), 4.00 (s, 1H), 3.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.28, 158.58, 154.14, 137.86, 133.00, 130.26, 128.96, 121.26, 121.02, 119.30, 116.74, 115.95, 114.43, 105.31, 66.53, 61.62, 55.30, 38.94; HRMS (EI) calcd for $C_{20}H_{16}O_3N_2$ 332.1161, found 332.1158; HPLC (Chiralpak IA, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 10.4 min, t_R (minor) = 8.2 min, *ee* = 99%; $[\alpha]^{30}_{D}$ = -45.5 (*c* = 0.97 in $CHCl_3$).

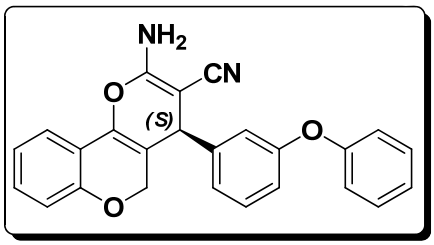


(*S*)-4-(4-(Allyloxy)phenyl)-2-amino-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (2-8i) (Table 2.3 , entry 9). 85% yield, 90% *ee*; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34 (dd, *J* = 7.6, 1.5Hz, 1H), 7.22–7.14 (m, 3H), 6.95 (td, *J* = 7.6, 0.9Hz, 1H), 6.91–6.85 (m, 2H), 6.79 (dd, *J* = 8.1, 0.8Hz, 1H), 6.05 (ddt, *J* = 17.1, 10.5, 5.3Hz, 1H), 5.41 (ddd, *J* = 17.2, 3.1, 1.5Hz, 1H), 5.32–5.26 (m, 1H), 4.65–4.56 (m, 3H), 4.52 (dt, *J* = 5.3, 1.4Hz, 2H), 4.44 (dd, *J* = 13.7, 0.9Hz, 1H), 3.99 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.62, 158.29, 154.10, 137.81, 133.17, 133.15, 130.24, 128.93, 121.25, 121.01, 119.35, 117.75, 116.72, 115.93, 115.19, 105.28, 68.85, 66.51, 61.45, 38.92; HRMS (EI) calcd for $C_{22}H_{18}O_3N_2$ 358.1317, found 358.1317; HPLC (Chiralpak IC,

i-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 15.3 min, t_R (minor) = 10.1 min, *ee* = 90%; $[\alpha]^{30}_D$ = -52.9 (*c* = 1.05 in $CHCl_3$).

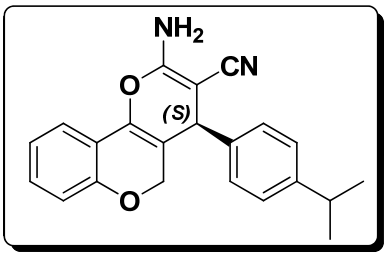


(*S*)-4-(2-(Allyloxy)phenyl)-2-amino-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (2-8j) (Table 2.3 , entry 10). 91% yield, 92% *ee*,; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.31 (dd, *J* = 7.7, 1.5Hz, 1H), 7.26 (dd, *J* = 7.7, 1.4Hz, 1H), 7.24–7.19 (m, 1H), 7.17 (td, *J* = 7.8, 1.6Hz, 1H), 6.94 (ddd, *J* = 10.9, 8.4, 4.2Hz, 2H), 6.87 (d, *J* = 8.2Hz, 1H), 6.77 (dd, *J* = 8.1, 0.6Hz, 1H), 6.06 (ddt, *J* = 17.1, 10.5, 5.3Hz, 1H), 5.46–5.36 (m, 1H), 5.33–5.21 (m, 1H), 4.72 (dd, *J* = 13.9, 1.1Hz, 1H), 4.65 (s, 1H), 4.62 (s, 2H), 4.56 (d, *J* = 5.3Hz, 2H), 4.48 (dd, *J* = 13.9, 0.7Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.56, 156.18, 154.10, 137.81, 133.16, 129.98, 129.32, 129.20, 128.80, 121.50, 121.14, 120.83, 119.50, 117.65, 116.92, 115.80, 112.17, 105.82, 69.23, 66.50, 60.32, 32.16; HRMS (EI) calcd for $C_{22}H_{18}O_3N_2$ 358.1317, found 358.1311; HPLC (Chiralpak IC, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 11.3 min, t_R (minor) = 8.0 min, *ee* = 92%; $[\alpha]^{30}_D$ = -11.6 (*c* = 0.6 in $CHCl_3$).

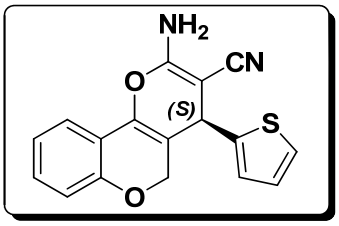


(*S*)-2-Amino-4-(3-phenoxyphenyl)-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (2-8k) (Table 2.3 , entry 11). 90% yield, 87% *ee*; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.27 (m, 4H), 7.22–7.16 (m, 1H), 7.09 (t, *J* = 7.4Hz, 1H), 7.05–6.99 (m, 3H), 6.97 (t, *J* = 1.9Hz, 1H), 6.94 (t, *J* = 7.5Hz, 1H), 6.88 (dd, *J* = 8.1, 2.3Hz, 1H), 6.80 (d,

J = 8.1Hz, 1H), 4.65(s, 2H), 4.63 (d, *J* = 13.5Hz, 1H), 4.47 (d, *J* = 13.7Hz, 1H), 4.00 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.89, 157.82, 156.90, 154.17, 143.07, 138.13, 130.38, 130.32, 129.78, 123.40, 122.69, 121.29, 121.09, 119.07, 118.91, 118.47, 118.00, 116.60, 115.95, 104.72, 66.45, 60.93, 39.66; HRMS (EI) calcd for $C_{25}H_{18}O_3N_2$ 394.1317, found 394.1307; HPLC (Chiralpak IC, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 11.9 min, t_R (minor) = 7.5 min, *ee* = 87%; $[\alpha]^{30}_D$ = -25.6 (*c* = 1.12 in $CHCl_3$).

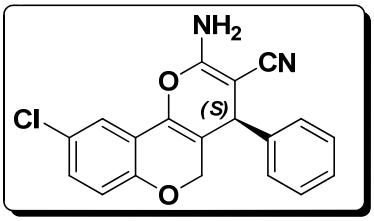


(*S*)-2-Amino-4-(4-isopropylphenyl)-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (2-8l) (Table 2.3 , entry 12). 88% yield, 88% *ee*; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34 (dd, *J* = 7.7, 1.5Hz, 1H), 7.22–7.14 (m, 5H), 6.95 (td, *J* = 7.6, 1.0Hz, 1H), 6.83–6.76 (m, 1H), 4.68–4.56 (m, 3H), 4.46 (dd, *J* = 3.8, 0.7Hz, 1H), 3.99 (s, 1H), 2.88 (m, 1H), 1.23 (d, *J* = 6.9Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.75, 154.10, 148.45, 138.17, 137.83, 130.20, 127.73, 127.04, 121.22, 120.99, 119.42, 116.73, 115.90, 105.34, 66.55, 61.29, 39.25, 33.72, 23.91, 23.88; HRMS (EI) calcd for $C_{22}H_{20}O_2N_2$ 344.1525, found 344.1526; HPLC (Chiralpak IC, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 12.4 min, t_R (minor) = 7.1 min, *ee* = 88%; $[\alpha]^{30}_D$ = -36.0 (*c* = 1.25 in $CHCl_3$).

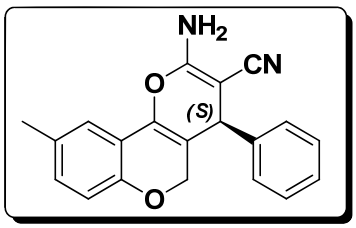


(*S*)-2-Amino-4-(thiophen-2-yl)-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile

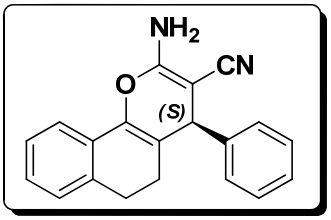
(2-8m) (Table 2.3 , entry 13). 86% yield, 81% *ee*; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34 (dd, *J* = 7.7, 1.5Hz, 1H), 7.28–7.24 (m, 1H), 7.21 (td, *J* = 7.9, 1.6Hz, 1H), 7.00–6.96 (m, 1H), 6.97–6.92 (m, 2H), 6.81 (d, *J* = 8.1Hz, 1H), 4.69 (m, 3H), 4.64–4.58 (m, 1H), 4.40 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.76, 154.25, 145.68, 137.90, 130.49, 126.97, 125.83, 125.65, 121.32, 121.23, 119.01, 116.60, 116.04, 104.61, 66.45, 61.45, 34.86; HRMS (EI) calcd for $C_{17}H_{12}O_2N_2S$ 308.0619, found 308.0612; HPLC (Chiralpak IC, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 13.5 min, t_R (minor) = 10.0 min, *ee* = 81%; $[\alpha]^{30}_D$ = -57.9 (*c* = 0.96 in $CHCl_3$).



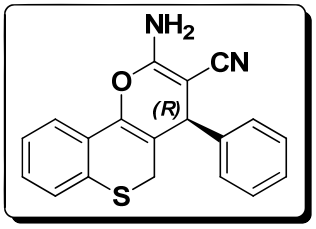
(*S*)-2-Amino-9-chloro-4-phenyl-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (2-8n) (Table 2.3 , entry 14). 88% yield, 92% *ee*; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36 (dd, *J* = 10.1, 4.6Hz, 2H), 7.33–7.23 (m, 4H), 7.14 (dd, *J* = 8.6, 2.6Hz, 1H), 6.72 (d, *J* = 8.6Hz, 1H), 4.70–4.60 (m, 3H), 4.43 (dd, *J* = 14.0, 0.8Hz, 1H), 4.03 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.54, 152.61, 140.54, 137.15, 129.93, 129.13, 128.08, 127.88, 126.40, 121.05, 118.94, 117.92, 117.27, 106.29, 66.68, 61.26, 39.72; HRMS (EI) calcd for $C_{19}H_{13}O_2N_2Cl$ 336.0666, found 336.0653; HPLC (Chiralpak IC, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 9.2 min, t_R (minor) = 8.0 min, *ee* = 92%; $[\alpha]^{30}_D$ = -12.2 (*c* = 0.88 in $CHCl_3$).



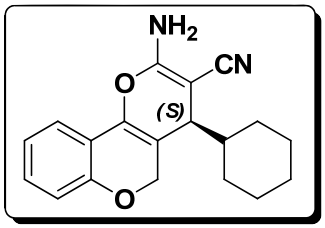
(*S*)-2-Amino-9-methyl-4-phenyl-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (2-8o) (Table 2.3 , entry 15). 91% yield, 94% *ee*; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.33 (m, 2H), 7.29–7.26 (m, 3H), 7.16 (d, *J* = 1.9Hz, 1H), 7.00 (dd, *J* = 8.2, 1.9Hz, 1H), 6.70 (d, *J* = 8.2Hz, 1H), 4.60(s, 2H), 4.59 (dd, *J* = 13.7, 1.0Hz, 1H), 4.39 (dd, *J* = 13.7, 0.8Hz, 1H), 4.03 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.76, 152.00, 140.96, 138.22, 130.76, 130.66, 129.02, 127.89, 121.42, 119.22, 116.44, 115.71, 105.13, 66.47, 61.37, 39.78, 20.68; HRMS (EI) calcd for $C_{20}H_{16}O_2N_2$ 316.1212, found 316.1214; HPLC (Chiralpak IC, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 11.3 min, t_R (minor) = 8.0 min, *ee* = 94%; $[\alpha]^{30}_D$ = -68.7 (*c* = 0.64 in $CHCl_3$).



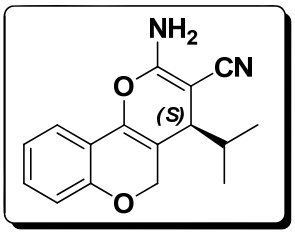
(*S*)-2-Amino-4-phenyl-5,6-dihydro-4H-benzo[*h*]chromene-3-carbonitrile (2-8p) (Table 2.3 ,entry 16). 60% yield, 80% *ee*; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.46 (d, *J* = 7.3Hz, 1H), 7.35–7.19 (m, 7H), 7.11 (d, *J* = 7.1Hz, 1H), 4.55 (s, 2H), 4.08 (s, 1H), 2.84–2.65 (m, 2H), 2.23–2.00 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.99, 142.67, 140.86, 135.55, 128.76, 128.42, 128.19, 128.04, 127.47, 126.47, 120.76, 119.77, 111.77, 61.18, 42.82, 27.47, 25.00; HRMS (EI) calcd for $C_{20}H_{16}ON_2$ 300.1263, found 300.1249; HPLC (Chiralpak IC, *i*-propanol/hexane = 15/85, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 10.6 min, t_R (minor) = 12.3 min, *ee* = 80%; $[\alpha]^{30}_D$ = -39.5 (*c* = 0.45 in $CHCl_3$).



(*R*)-2-Amino-4-phenyl-4,5-dihydrothiochromeno[4,3-*b*]pyran-3-carbonitrile (2-8q) (Table 2.3 , entry 17). 85% yield, 81% *ee*; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.54–7.52 (m, 1H), 7.37–7.31 (m, 4H), 7.31–7.26 (m, 1H), 7.23 (dd, *J* = 6.4, 2.7Hz, 1H), 7.21–7.14 (m, 2H), 4.59 (s, 2H), 4.14 (s, 1H), 3.28 (d, *J* = 15.2Hz, 1H), 3.13 (d, *J* = 15.1Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.62, 142.03, 141.61, 132.75, 128.98, 128.12, 127.90, 127.30, 127.09, 125.50, 123.20, 119.28, 108.04, 61.18, 43.08, 27.06; HRMS (EI) calcd for $C_{19}H_{14}ON_2S$ 318.0827, found 316.0816; HPLC (Chiralpak IA, *i*-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 9.9 min, t_R (minor) = 6.7 min, *ee* = 81%; $[\alpha]^{30}_D$ = -68.5 (*c* = 0.88 in $CHCl_3$).



(*S*)-2-Amino-4-cyclohexyl-5,6-dihydro-4*H*-benzo[*h*]chromene-3-carbonitrile (2-8r) (Table 2.3 , entry 18). 86% yield, 86% *ee*; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.28 (dd, *J* = 7.6, 1.5Hz, 1H), 7.21 (td, *J* = 7.8, 1.5Hz, 1H), 6.97 (t, *J* = 7.4Hz, 1H), 6.84 (d, *J* = 7.7, 1H), 6.83 (s, 2H), 4.85 (d, *J* = 13.9Hz, 1H), 4.75 (d, *J* = 14.0Hz, 1H), 2.83 (d, *J* = 2.5Hz, 1H), 1.76–0.90 (m, 11H); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 162.05, 153.60, 138.38, 129.81, 121.52, 121.19, 120.56, 117.11, 115.57, 106.71, 66.50, 52.08, 42.73, 29.76, 29.31, 27.78, 26.15, 25.96, 25.78; HRMS (EI) calcd for $C_{19}H_{20}O_2N_2$ 308.1525, found 308.1520; HPLC (Chiralpak IC, *i*-propanol/hexane = 15/85, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 20.8 min, t_R (minor) = 7.8 min, *ee* = 86%; $[\alpha]^{30}_D$ = -60.1 (*c* = 0.70 in $CHCl_3$).



(*S*)-2-Amino-4-isopropyl-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (2-8s) (Table 2.3 , entry 19). 75% yield, 87% *ee*; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.27 (dd, *J* = 7.7, 1.5Hz, 1H), 7.19 (td, *J* = 8.1, 1.6Hz, 1H), 6.94 (td, *J* = 7.6, 0.9Hz, 1H), 6.84 (d, *J* = 8.1Hz, 1H), 4.83 (d, *J* = 13.6Hz, 1H), 4.68 (d, *J* = 13.6Hz, 1H), 4.60 (s, 2H), 2.93 (d, *J* = 2.7Hz, 1H), 1.89 (m, 1H), 1.07 (d, *J* = 7.0Hz, 3H), 0.90 (d, *J* = 6.9Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.27, 154.09, 139.46, 130.01, 121.35, 120.89, 120.66, 117.18, 115.89, 106.14, 67.22, 56.72, 40.17, 32.77, 19.43, 17.88; HRMS (EI) calcd for $C_{16}H_{16}O_2N_2$ 268.1212, found 268.1205; HPLC (Chiralpak IC, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 12.2 min, t_R (minor) = 6.6 min, *ee* = 87%; $[\alpha]^{30}_D$ = -83.2 (*c* = 0.61 in $CHCl_3$).

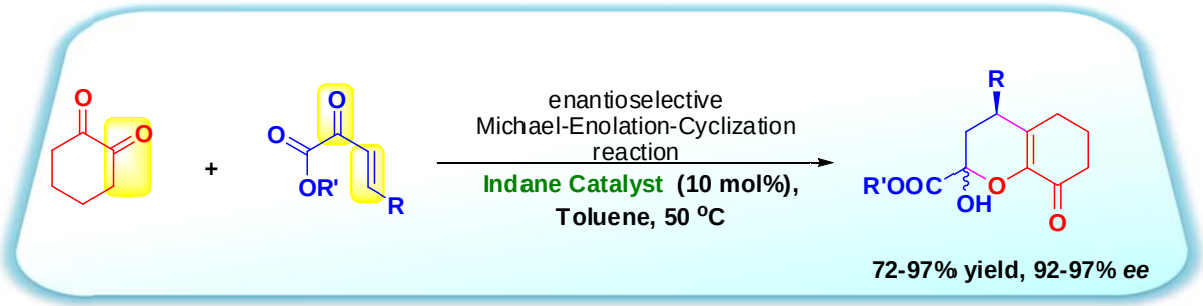
2.4.5 X-ray Crystallographic Analysis

Table 2.4 Crystal data and structure refinement for **2-8f**.

Empirical formula	C19 H13 Br N2 O2	
Formula weight	381.22	
Temperature	223(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 6.6093(4) Å	a= 90°.
	b = 10.9299(7) Å	b= 90°.
	c = 22.8035(15) Å	g = 90°.
Volume	1647.30(18) Å^3	
Z	4	
Density (calculated)	1.537 Mg/m^3	
Absorption coefficient	2.509 mm^{-1}	
F(000)	768	
Crystal size	0.54 x 0.50 x 0.08 mm^3	
Theta range for data collection	1.79 to 27.48°	

Index ranges	-8<=h<=8, -14<=k<=9, -29<=l<=29
Reflections collected	11623
Independent reflections	3778 [R(int) = 0.0629]
Completeness to theta = 27.48°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.8245 and 0.3444
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3778 / 0 / 225
Goodness-of-fit on F^2	1.006
Final R indices [I>2sigma(I)]	R1 = 0.0517, wR2 = 0.1142
R indices (all data)	R1 = 0.0730, wR2 = 0.1234
Absolute structure parameter	0.005(13)
Largest diff. peak and hole	0.773 and -0.816 e.$Å^{-3}$

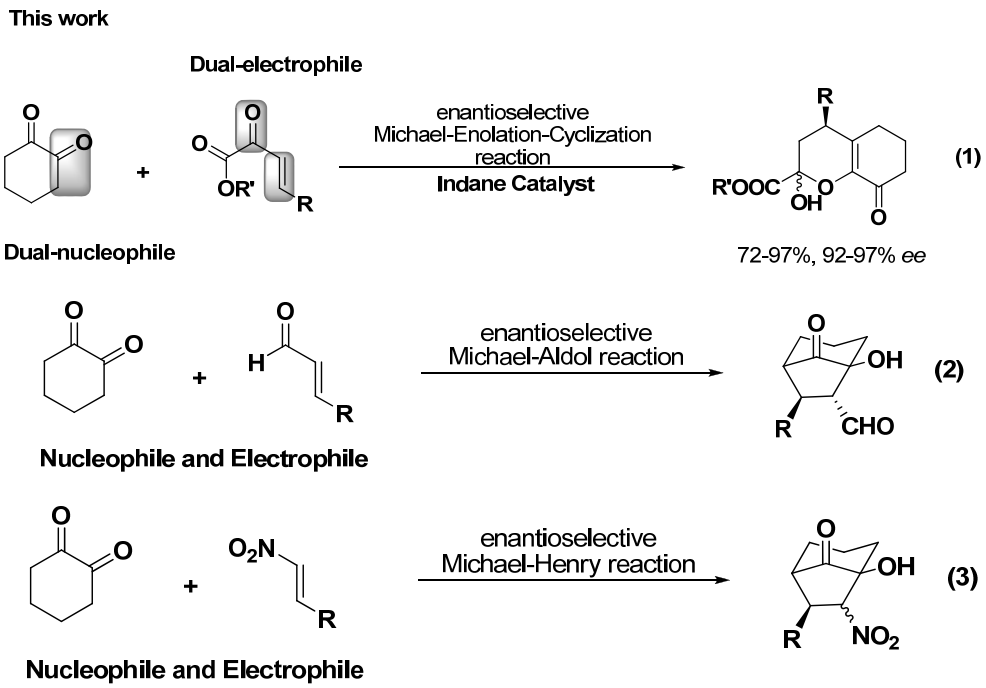
Chapter 3 Chiral Indane Skeleton Based Thiourea Catalyzed Highly Stereoselective Cascade Michael–Enolation–Cyclization Reaction



An efficient asymmetric cascade reaction catalyzed by a chiral bifunctional indane amine-thiourea catalyst has been developed. A broad substrate scope of chiral dihydro-2H-pyran complexes that contained two stereogenic centers were obtained in a one-pot manner in good to excellent yields (72–97%) and high to excellent stereoselectivities (92–97% ee).

3.1 Introduction

The scope of metal-free organocatalysts to promote asymmetric cascade reactions has expanded in the last few years.[132] Recently, a number of useful cascade reactions have been reported.[133] Undoubtedly, the utilization of cascade reactions provides a useful synthetic tool for organic synthesis. It offers a possibility to form multiple chemical bonds in a one-pot process without isolating intermediates, changing reaction conditions, or adding reagents. Finally, this strategy reduces the synthetic costs and simplifies synthetic steps and processes. Inspired by the advantages and significances of this cascade strategy, we have become interested in exploring a new enantioselective cascade reaction.



In contrast, the utilization of 1,2-diones is still rare.[134] However, their

[132] For reviews of organocatalytic cascade reactions, see: a) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem. Int. Ed.* **2007**, *119*, 1570; b) see *Ref.* 2f; c) see *Ref.* 2j.

[133] For recent selected examples of cascade reactions, see: a) see *Ref.* 3b; b) see *Ref.* 3c; c) see *Ref.* 3d; d) see *Ref.* 3e; e) see *Ref.* 3f; f) see *Ref.* 3h; g) Rios, R.; Sunden, H.; Ibrahem, I.; Zhao, G. L.; Eriksson, L.; Córdova, A. *Tetrahedron Lett.* **2006**, *47*, 8547; h) see *Ref.* 3i; i) see *Ref.* 3j; j) see *Ref.* 3k; k) Vicario, J. L.; Reboredo, S.; BadNa, D.; Carrillo, L. *Angew. Chem. Int. Ed.* **2007**, *119*, 5260.

[134] For selected examples of the application of 1,2-diones in organic synthesis, see: a) Parsons, A. F.; Williams, D. *Tetrahedron Lett.* **2000**, *56*, 7217; b) Wolf, C.; Liu, S. *J. Am. Chem. Soc.* **2006**, *128*, 10996; c) Li, X.; Vince, R. *Bioorg. Med. Chem. Lett.* **2006**, *14*, 2942; d) Maruoka, H.; Kashige, N.; Miake, F.; Yamaguchi, T. *Chem. Pharm. Bull.* **2005**, *53*, 1359; e) Zhao, Z.; Wisnoski, D. D.; Wolkenberg, S. E.; Leister, W. H.; Wang, Y.; Lindsley, C. W. *Tetrahedron Lett.* **2004**, *45*, 4873; f) Curiel, D.; Cowley, A.; Beer, P. D. *Chem. Commun.* **2005**, *2*, 236; g) Ding, Y.;

functionality offers a good starting point for additional transformations. Therefore, we wish to use them as a group of interesting synthetic blocks for further asymmetric transformations. Herein, we report a new enantioselective organocatalytic cascade reaction with a formation of functionalized 3,4-dihydro-2*H*-pyran complexes [Eq. (1)]. Notably, the features of the strategy include 1) a novel indane amine-thiourea catalyst; 2) good to excellent yields (72–97%) and high to excellent enantioselectivities (92–97% *ee*); 3) a first trial of 1,2-diones to β,γ–unsaturated α–keto esters.

Rueping et al. have reported a stereoselective Lewis base catalyzed domino Michael/aldol reaction for the formation of chiral bicycle[3.2.1]octane-6-carbaldehydes [Eq. (2)].[135] Several α,β–unsaturated aldehydes have been applied to this system to access the target compounds. Furthermore, nitroolefins have also been utilized as the replacement of α,β–unsaturated aldehydes to afford a similar bicycle[3.2.1]octane structure discovered by the Rueping and Zhao groups independently [Eq. (3)].[136] As a significant complement, we document an interesting reaction which tolerated 1,2-diones as dual-nucleophiles to react with β,γ–unsaturated α–keto esters which were firstly utilized as dual-electrophiles. A privileged 4-dihydro-2*H*-pyran structure (Eq. (1)) was finally constructed.

3.2 Results and Discussion

3.2.1 Catalyst Screening

To probe the feasibility of the proposed cascade reaction, (*E*)-ethyl 2-*oxo*-4-phenylbut-3-enoate (**3-2a**) was treated with 1,2-cyclohexadione **3-1** in the presence of catalyst **3-I**, developed by the Soós[137], Dixon[138] and Connon[139] groups

Girardet, J.; Smith, K. L.; Larson, G.; Prigaro, B.; Lai, V. C. H.; Zhong, W.; Wu, J. Z. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 675; h) Wu, S.; Fluxe, A.; Janusz, J. M.; Sheffer, J. B.; Browning, G.; Cobum, B. B. K.; Hedges, R.; Murawsky, M.; Fang, B.; Fadayel, G. M.; Hare, M.; Djandjighian, L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5859; i) Held, I.; Xu, S.; Zipse, H. *Synthesis* **2007**, 1185; j) Liu, S.; Wolf, C. *Org. Lett.* **2007**, *9*, 2965.

[135] Rueping, M.; Kuenkel, A.; Tato, F.; Bats, J. W. *Angew. Chem. Int. Ed.* **2009**, *48*, 3699.

[136] a) Rueping, M.; Kuenkel, A.; Fröhlich, R. *Chem. –Eur. J.* **2010**, *16*, 4173; b) Ding, D.; Zhao, C. G.; Guo, Q. S.; Arman, H. *Tetrahedron* **2010**, *66*, 4424.

[137] See *Ref.* 124.

[138] See *Ref.* 54.

[139] See *Ref.* 53.

respectively, in CH_2Cl_2 at room temperature (Table 3.1). As shown in Table 3.1, unfortunately, catalyst **3-I** exhibited a poor catalytic activity so that a very trace amount of desired product was generated after 96 h (Table 3.1, entry 1). Therefore, we wish to discover an active chiral catalyst which could promote the reaction and result in high efficiency and excellent stereo-control. In planning our catalyst investigation, we were evoked by our group reported indane bifuncationl amine-thiourea catalysts. This type of catalysts demonstrated some interesting aspects, such as high activity, good stereo-control, and flexible chiral structure.[140] On the basis of these experiences we decided to examine the catalytic activity and stereoselectivity of our indane catalysts in this type of reaction. Unfortunately, catalyst **3-II** showed a similar performance as well as catalyst **3-I** (Table 3.1, entries 2–4). In view of catalyst **3-II**'s structure (Figure 3.1), we found that two functional groups, amine and thiourea, are in the anti-position. We then suspected if the relative position of the two functional groups would affect the catalyst's activity. However, the results showed that our inference was wrong (Table 3.1, entry 5, < 5%). A switch of these important functional groups would not enhance the catalytic performance. Then the next exploration was the change of the chiral center's orientation. As demonstrated in Figure 3.1, catalyst **3-V** was synthesized and investigated. It is noteworthy that catalyst **3-V** was firstly discovered by our research group and already verified as an active catalyst in some catalytic transformations.[140] Surprisingly, it still could not efficiently promote this reaction (Table 3.1, entry 7). It appeared that indane amine–thiourea catalysts have no enough power to complete such a task. However, we did not cease our exploration before we reached our target. By chance, we finally disclosed a novel indane bifuncational catalyst **3-IV** which demonstrated a superior performance in both activity and stereoselectivity (Table 3.1, entry 6, 53%, 96% *ee*). It was obvious that catalyst **3-IV** was derived from catalyst **3-V** *via* a switch of two functional groups. These results again emphasized the unique of our indane C-1

[140] For some examples of our group developed bifunctional indane thiourea catalyzed reactions, see: a) Gao, Y. J.; Ren, Q.; Wu, H.; Li, M. G.; Wang, J. *Chem. Commun.* **2010**, *46*, 9232; b) Ren, Q.; Gao, Y. J.; Wang, J. *Chem. –Eur. J.* **2010**, *16*, 13594; c) Gao,Y. J.; Ren, Q.; Siau, W.-Y.; Wang, J. *Chem. Commun.* **2011**, *47*, 5819; d) Gao, Y. J.; Ren, Q.; Siau, W.-Y.; Wang, J. *Org. Biomol. Chem.* **2011**, *9*, 3691.

symmetric catalytic system. Based on NMR data, we found compound **3-3a** coexisted with its anomer **3-3a'**. In this reaction, the compound **3-3a** was kinetically favored based on the ratio (> 10:1) between **3-3a** and it's anomer (See Supporting Information).

Figure 3.1 Evaluated bifunctional amine-thiourea organocatalysts.

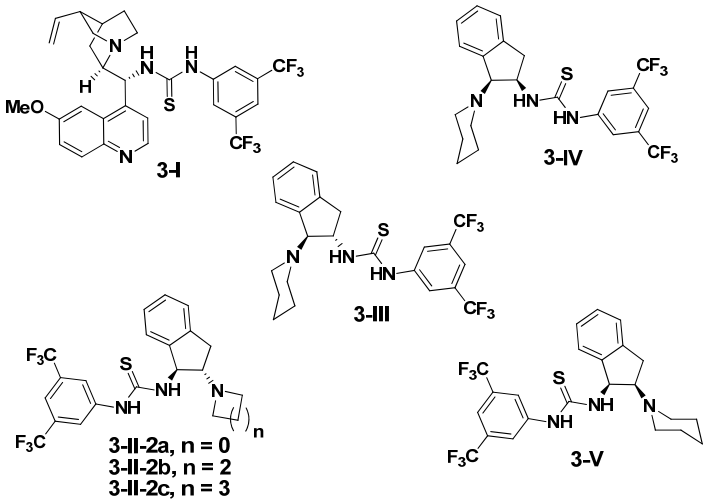
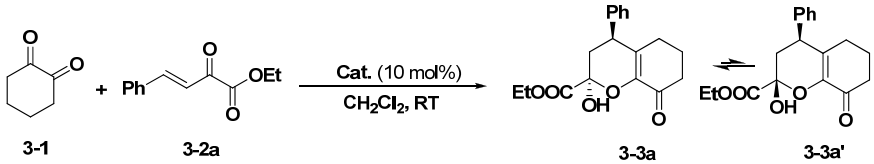


Table 3.1 Evaluation of bifunctional chiral organocatalysts.[a]

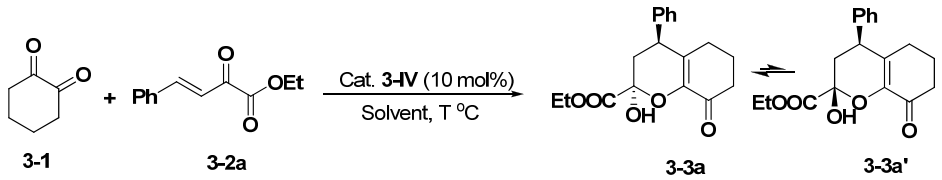


Entry	Cat.	t(h)	Yield(%)[b]
1	**3-I**	96	<5
2	**3-II-a**	96	<5
3	**3-II-b**	96	<5
4	**3-II-c**	96	<5
5	**3-III**	96	<5
6	**3-IV**	**48**	**53**
7	**3-V**	96	<5

[a] Reaction was conducted on 0.1 mmol scale in CH_2Cl_2 (0.5 mL) at r.t. for 48–96 h, and the ratio of **3-1**/**3-2a** is 1.5:1. [b] Yield of isolated productafter column chromatography.

3.2.2 Reaction Optimization

Table 3.2 Optimization of the reaction conditions.[a]



Entry	Solvent	T(°C)	t(h)	Yield(%)[b]	*ee*(%)[c]
1	CH_2Cl_2	23	48	53	96
2	CH_2Cl_2	40	16	66	92
3	Et_2O	40	16	88	94
4	$Cl(CH_2)_2Cl$	50	14	73	96
5	Anisole	50	12	75	94
6	Toluene	50	8	94	95
7	Xylenes	50	8	84	95
8	$PhCF_3$	50	8	78	93
9	*i*-PrOH	50	12	44	85
10	DMSO	50	14	50	37

[a] Unless specified, see the Experimental section for reaction conditions. [b] Yield of isolated product after column chromatography. [c] Enantiomeric excess (*ee*) was determined by HPLC.

For further optimization, solvent, as well as reaction temperature, was varied (Table 3.2). These experiments revealed that the best results with regard to reactivity and stereoselectivity were obtained with toluene at 50°C (Table 3.2, entry 6). The process was completed within 8 h and afforded 3,4-dihydro-2*H*-pyran complex **3-3a** in 94% yield and with an excellent enantioselectivity (95% *ee*). In varying reaction temperature, the catalytic activity can be dramatically enhanced by a slight addition on temperature. Most importantly, no significant drop in the stereoselectivity was found in the process (Table 3.2, entries 1 and 2, 48 to 16 h, 53% to 66% yield, 96% to 92% *ee*). Furthermore, less polar solvents were fundamental for obtaining high enantioselectivities (Table 3.2, entries 1–8, 92–95% *ee*). For high polar solvents, relatively lower enantioselectivities were aroused by a potential destruction of

H-bonding interaction (Table 3.2, entries 9 and 10, 85% and 37% *ee*).

3.2.3 Reaction Scope

Under the optimized reaction conditions, the generality of our cascade process was examined by using various β,γ–unsaturated α–keto esters **3-2** (Table 3.3). Aromatic β,γ–unsaturated α–keto esters **3-2** having both electron-withdrawing (Table 3.3, entries 2–7) and electron-donating substituents (Table 3.3, entries 8–13) can effectively be applied to this transformation; the substitution pattern of the arene had limited influence on the enantioselectivity of the reaction (Table 3.3, entries 2–13). In addition, it was possible to use both heteroaromatic (Table 3.3, entry 14) and aliphatic β,γ–unsaturated α–keto esters (Table 3.3, entry 16) in this reaction. Meanwhile, the ester modification also had no obvious effect on the enantioselectivity (Table 3.3, entry 17). The ability to control the formation of two new stereogenic centers permitted the assembly of a variety of functionalized 3,4-dihydro-2*H*-pyran complexes **3-3** in good to high yields (72–97%) and with high to excellent enantioselectivities (92–97% *ee*). The absolute configuration of the products was determined by single-crystal X-ray analysis of **3-3i** (Figure 3.2).[141]

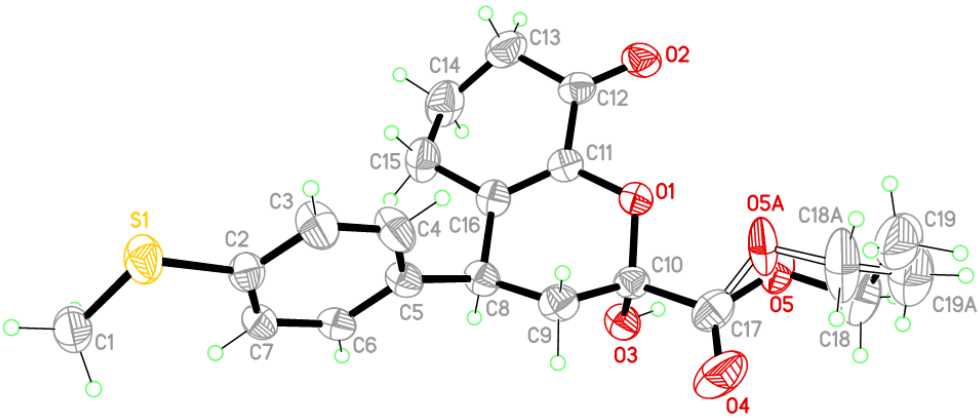
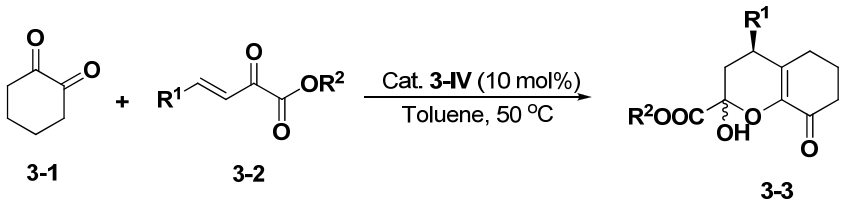


Figure 3.2 X-ray crystal structure of **3-3i**.

[141] CCDC 800064 (**3-3i**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/ data_request/cif.

Table 3.3 Substrate scope.[a]



Entry	R^1	R^2	t(h)	Yield(%)[b]	ee(%)[c]
1	Ph(**3-3a**)	Et	8	94	95
2	2-ClC_6H_4(**3-3b**)	Et	6	92	96
3	3-ClC_6H_4(**3-3c**)	Et	6	95	92
4	4-ClC_6H_4(**3-3d**)	Et	6	90	96
5	4-FC_6H_4(**3-3e**)	Et	6	91	95
6	2-BrC_6H_4(**3-3f**)	Et	6	95	97
7	4-$NO_2C_6H_4$(**3-3g**)	Et	4	84	93
8	4-$MeOC_6H_4$(**3-3h**)	Et	24	82	95
9	4-$MeSC_6H_4$(**3-3i**)	Et	24	82	95
10	4-allyloxyC_6H_4(**3-3j**)	Et	24	87	94
11	4-$PhOC_6H_4$(**3-3k**)	Et	12	94	96
12	4-$BnOC_6H_4$(**3-3l**)	Et	24	86	93
13	4-*i*PrC_6H_4(**3-3m**)	Et	12	91	95
14	2-thiophenyl(**3-3n**)	Et	24	84	93
15	1-naphthyl(**3-3o**)	Et	24	91	95
16	Et(**3-3p**)	Et	24	72	96
17	Ph(**3-3q**)	Me	6	97	96

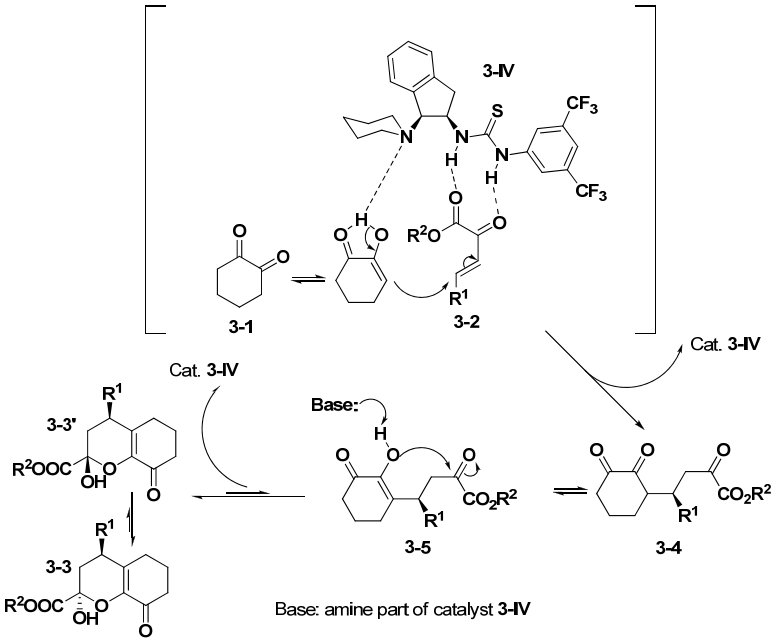
[a] Unless specified, see the Experimental section for reaction conditions. [b] Yield of isolated product after column chromatography. [c] Enantiomeric excess (ee) was determined by HPLC.

3.2.4 Reaction Mechanism

With regard to the reaction mechanism, an enantioselective cascade Michael–enolation–cyclization process was proposed for the formation of highly

stereo-controlled products **3-3** (Scheme 3.1). Catalyst **3-IV** activated 1,2-cyclohexadione **3-1** and β,γ–unsaturated α–keto esters **3-2** *via* amine and thiourea functional groups (Scheme 3.1). After formation of Michael adducts **3-4**, an enolation automatically occurred to generate a tautomeric structure, intermediate **3-5**, an active enol which subsequently underwent an *oxa*-nucleophilic attack to trigger the completion of cyclization step. Finally, complex **3-3** involving two possible anomers were in equilibrium with the Michael product **3-4**.

Scheme 3.1 Bifunctional activation mode: a proposed catalytic cycle for the asymmetric cascade reaction.



3.3 Conclusion

In summary, this project has disclosed a novel and highly stereoselective Michael–enolation–cyclization cascade reaction catalyzed by an elegant chiral indane amine-thiourea catalyst. A broad substrate scope of chiral dihydro-2*H*-pyran complexes that contained two stereogenic centers were obtained in a one-pot manner

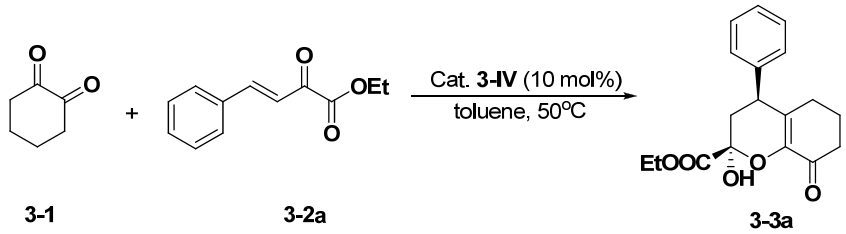
in good to excellent yields (72–97%) and high to excellent stereoselectivities (92–97% *ee*). Our investigation, with a new reaction mode, expands the scope of asymmetric organocatalytic reactions. It's anticipated to find further applications of this activation mode in other organic transformations together with detailed mechanistic aspects.

3.4 Experimental Section

3.4.1 General Information

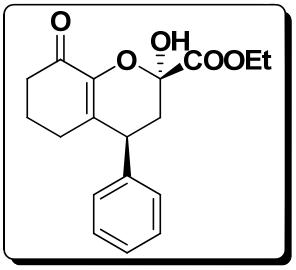
Chemicals and solvents were purchased from commercial suppliers and used as received. ^{1}H and ^{13}C NMR spectra were recorded on a AMX500 (500 MHz) spectrometer. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (chloroform δ 7.26), carbon (chloroform δ 77.0) or tetramethylsilane (TMS δ 0.00) was used as a reference. Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), bs (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 ninhydrin followed by heating using a heat gun. Flash chromatography 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. Optical rotations were recorded on Jasco DIP-1000 polarimeter.

3.4.2 Representative Procedure for Michael–Enolation–Cyclization Reaction

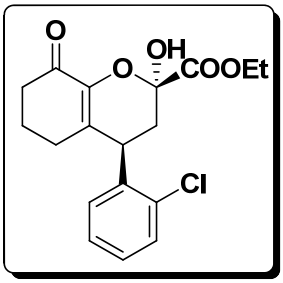


To a solution of (*E*)-ethyl 2-oxo-4-phenylbut-3-enoate **3-2a** (20.4 mg, 0.1 mmol) and cyclohexane-1,2-dione **3-1** (16.8 mg, 0.15 mmol) in 0.2 mL toluene, catalyst **3-IV** (4.9 mg, 0.01 mmol) was added. The reaction mixture was stirred at 50°C for 8 h. The crude product was purified by column chromatography on silica gel, eluted by hexane/EtOAc=5:1 then 3:1 to afford 30.0 mg (94% yield) of the desired product **3-3a** as colorless oil.

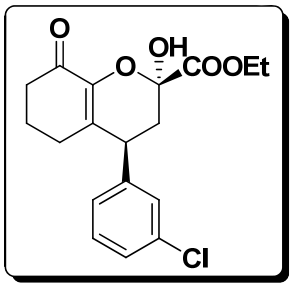
3.4.3 Analytical Data of Michael–Enolation–Cyclization Products



(2*R*,4*S*)-Ethyl 2-hydroxy-8-oxo-4-phenyl-3,4,5,6,7,8-hexahydro-2*H*-chromene-2-carboxylate (3-3a) (Table 3.3 , entry 1). 94% yield, 95% *ee*; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36 (t, *J* = 7.4 Hz, 2H), 7.29 (t, *J* = 7.3 Hz, 1H), 7.24 (d, *J* = 7.2 Hz, 2H), 4.50 (br, 1H), 4.38–4.23 (m, 2H), 3.81 (dd, *J* = 12.5, 6.5 Hz, 1H), 2.55–2.41 (m, 2H), 2.34 (t, *J* = 13.1 Hz, 1H), 2.23 (dd, *J* = 13.6, 6.5 Hz, 1H), 2.09–2.01 (m, 2H), 1.96–1.84 (m, 2H), 1.32 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.83, 169.13, 142.88, 140.83, 134.12, 128.94, 128.53, 127.31, 93.67, 63.01, 40.09, 38.29, 36.86, 27.81, 22.11, 13.93; HRMS (EI) calcd for $C_{18}H_{20}O_5$ 316.1311, found 316.1307; HPLC (Chiralpak IA, *i*-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 9.6 min, t_R (minor) = 11.9 min, *ee* = 95%; $[\alpha]^{25}_{D}$ = +113.0 (*c* = 1.11 in $CHCl_3$).

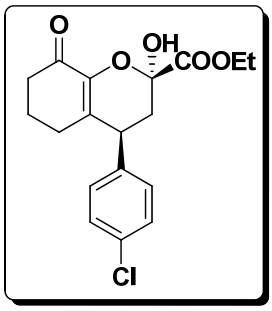


(2*R*,4*R*)-Ethyl 4-(2-chlorophenyl)-2-hydroxy-8-oxo-3,4,5,6,7,8-hexahydro-2*H*-chromene-2-carboxylate (3-3b) (Table 3.3, entry 2). 92% yield, 96% *ee*; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.39 (dd, *J* = 11.8, 4.7 Hz, 1H), 7.32–7.17 (m, 3H), 4.54 (br, 1H), 4.38–4.23 (m, 2H), 2.59–2.43 (m, 2H), 2.35–2.03 (m, 4H), 2.00–1.93 (m, 2H), 1.32 (td, *J* = 7.1, 3.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.77, 168.96, 144.26, 138.11, 134.14, 133.59, 131.86, 129.83, 129.72, 128.50, 128.35, 127.49, 126.86, 94.51, 93.66, 63.04, 62.79, 38.41, 38.26, 35.55, 34.09, 34.04, 28.06, 27.59, 22.25, 22.10, 13.96, 13.92; HRMS (EI) calcd for $C_{18}H_{19}O_5Cl$ 350.0921, found 350.0916; HPLC (Chiralpak IA, *i*-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 9.8 min, t_R (minor) = 11.9 min, *ee* = 96%; $[\alpha]^{25}_D$ = +75.3 (*c* = 0.98 in $CHCl_3$).

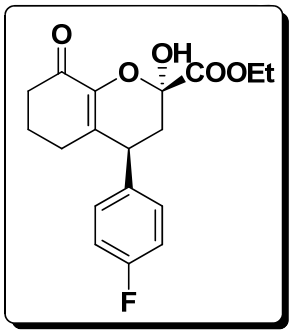


(2*R*,4*S*)-Ethyl 4-(3-chlorophenyl)-2-hydroxy-8-oxo-3,4,5,6,7,8-hexahydro-2*H*-chromene-2- carboxylate (3-3c) (Table 3.3, entry 3). 95% yield, 92% *ee*; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.32–7.22 (m, 3H), 7.13 (dt, *J* = 7.0, 1.5 Hz, 1H), 4.71 (br, 1H), 4.38–4.24 (m, 2H), 3.81 (dd, *J* = 12.3, 6.7 Hz, 1H), 2.57–2.41 (m, 2H), 2.34–2.26 (m, 1H), 2.23 (dd, *J* = 13.6, 6.7 Hz, 1H), 2.14–1.99 (m, 2H), 1.94–1.89 (m, 2H), 1.33 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.80, 168.93, 142.95, 142.90, 134.75, 132.98, 130.21, 128.59, 127.57, 126.72, 93.57, 63.04, 39.86, 38.18, 36.66, 27.69, 22.05, 13.90; HRMS (EI) calcd for $C_{18}H_{19}O_5Cl$ 350.0921, found

350.0918; HPLC (Chiralpak IA, *i*-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 9.0 min, t_R (minor) = 11.4 min, *ee* = 92%; $[\alpha]^{25}_D$ = +104.2 (*c* = 0.96 in $CHCl_3$).

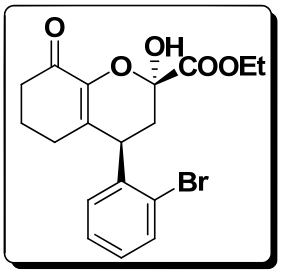


(2*R*,4*S*)-Ethyl 4-(4-chlorophenyl)-2-hydroxy-8-oxo-3,4,5,6,7,8-hexahydro-2*H*-chromene-2- carboxylate (3-3d) (Table 3.3, entry 4). 90% yield, 96% *ee*; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34 (d, *J* = 8.3 Hz, 2H), 7.18 (d, *J* = 8.2 Hz, 2H), 4.54 (br, 1H), 4.38–4.21 (m, 2H), 3.80 (dd, *J* = 12.4, 6.6 Hz, 1H), 2.56–2.41 (m, 2H), 2.29 (t, *J* = 13.0 Hz, 1H), 2.21 (dd, *J* = 13.6, 6.6 Hz, 1H), 2.09–1.98 (m, 2H), 1.96–1.85 (m, 2H), 1.32 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.70, 168.96, 153.86, 142.97, 139.32, 133.19, 129.85, 129.16, 93.58, 63.08, 39.53, 38.24, 36.77, 27.75, 22.08, 13.92; HRMS (EI) calcd for $C_{18}H_{19}O_5Cl$ 350.0921, found 350.0910; HPLC (Chiralpak IA, *i*-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 11.1 min, t_R (minor) = 14.0 min, *ee* = 96%; $[\alpha]^{25}_D$ = +120.9 (*c* = 1.09 in $CHCl_3$).

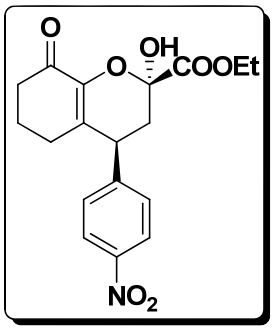


(2*R*,4*S*)-Ethyl 4-(4-fluorophenyl)-2-hydroxy-8-oxo-3,4,5,6,7,8-hexahydro-2*H*-chromene-2- carboxylate (3-3e) (Table 3.3, entry 5). 91% yield, 95% *ee*; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.20 (dd, *J* = 8.6, 5.3 Hz, 2H), 7.05 (t, *J* = 8.6 Hz, 2H), 4.50 (br,

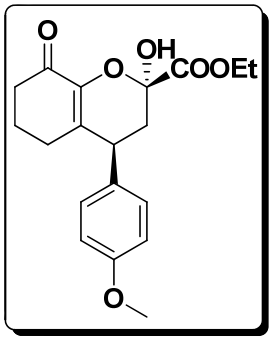
1H), 4.36–4.27 (m, 2H), 3.81 (dd, J = 12.5, 6.6 Hz, 1H), 2.54–2.46 (m, 2H), 2.30 (t, J = 13.1 Hz, 1H), 2.21 (dd, J = 13.6, 6.6 Hz, 1H), 2.08–2.02 (m, 2H), 1.93–1.88 (m, 2H), 1.33 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.83, 169.01, 162.96, 161.00, 142.88, 136.45, 136.42, 133.68, 130.03, 129.96, 115.94, 115.78, 93.62, 63.10, 39.34, 38.24, 36.88, 27.77, 22.08, 13.93; HRMS (EI) calcd for $C_{18}H_{19}O_5F$ 334.1217, found 334.1216; HPLC (Chiralpak IA, *i*-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 10.7 min, t_R (minor) = 13.5 min, *ee* = 95%; $[\alpha]^{25}_D$ = +102.4 (c = 1.15 in $CHCl_3$).



(2*R*,4*R*)-Ethyl 4-(2-bromophenyl)-2-hydroxy-8-oxo-3,4,5,6,7,8-hexahydro-2*H*-chromene-2- carboxylate (3-3f) (Table 3.3, entry 6). 95% yield, 97% *ee*; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.58 (dd, J = 12.7, 4.6 Hz, 1H), 7.34 (t, J = 7.4 Hz, 1H), 7.21–7.13 (m, 2H), 4.63 (br, 1H), 4.51 (dd, J = 11.2, 6.3 Hz, 1H), 4.38–4.22 (m, 2H), 2.59–2.43 (m, 2H), 2.32 (dd, J = 13.2, 6.5 Hz, 1H), 2.24–2.02 (m, 3H), 2.01–1.88 (m, 2H), 1.32 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.75, 168.89, 143.36, 140.17, 133.57, 133.07, 132.94, 129.12, 128.70, 128.61, 128.14, 127.50, 125.24, 93.63, 62.98, 62.72, 38.98, 38.34, 38.24, 35.73, 34.40, 27.61, 22.21, 22.07, 13.95, 13.88; HRMS (EI) calcd for $C_{18}H_{19}O_5Br$ 394.0416, found 394.0400; HPLC (Chiralpak IA, *i*-propanol/hexane = 5/95, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 17.8 min, t_R (minor) = 21.6 min, *ee* = 97%; $[\alpha]^{25}_D$ = +63.3 (c = 0.98 in $CHCl_3$).

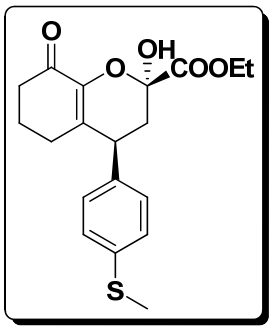


(2*R*,4*S*)-Ethyl 2-hydroxy-4-(4-nitrophenyl)-8-oxo-3,4,5,6,7,8-hexahydro-2*H*-chromene-2- carboxylate (3-3g) (Table 3.3, entry 7). 84% yield, 93% *ee*; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.24 (d, *J* = 8.7 Hz, 2H), 7.44 (d, *J* = 8.7 Hz, 2H), 4.50 (br, 1H), 4.37–4.28 (m, 2H), 3.97 (dd, *J* = 12.4, 6.6 Hz, 1H), 2.61–2.43 (m, 2H), 2.31 (dd, *J* = 20.1, 7.7 Hz, 1H), 2.24 (dd, *J* = 13.5, 6.6 Hz, 1H), 2.07–1.87 (m, 4H), 1.33 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.48, 168.68, 148.57, 147.38, 143.28, 131.47, 129.46, 124.29, 93.40, 63.29, 40.09, 38.25, 36.63, 27.80, 22.11, 13.94; HRMS (EI) calcd for $C_{18}H_{19}O_7N$ 361.1162, found 361.1160; HPLC (Chiralcel OD-H, *i*-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 17.8 min, t_R (minor) = 29.3 min, *ee* = 93%; $[\alpha]^{25}_{D}$ = +127.2 (*c* = 1.00 in $CHCl_3$).

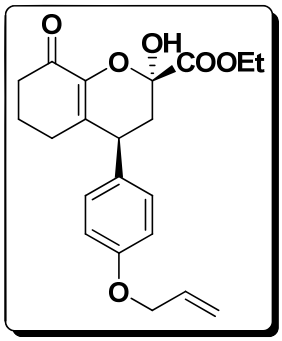


(2*R*,4*S*)-Ethyl 2-hydroxy-4-(4-methoxyphenyl)-8-oxo-3,4,5,6,7,8-hexahydro-2*H*-chromene-2- carboxylate (3-3h) (Table 3.3, entry 8). 82% yield, 95% *ee*; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.15 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 4.52 (br, 1H), 4.39–4.22 (m, 2H), 3.81 (s, 3H), 3.77 (dd, *J* = 13.6, 7.6 Hz, 1H), 2.55–2.41 (m, 2H), 2.31 (t, *J* = 13.1 Hz, 1H), 2.20 (dd, *J* = 13.6, 6.5 Hz, 1H), 2.12–2.01 (m, 2H), 1.95–1.83 (m, 2H), 1.32 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 192.76, 169.16,

158.88, 142.77, 134.53, 132.69, 129.48, 114.39, 93.74, 62.94, 55.28, 39.22, 38.28, 36.90, 27.80, 22.11, 13.91; HRMS (EI) calcd for $C_{19}H_{22}O_6$ 346.1416, found 346.1413; HPLC (Chiralpak IA, *i*-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 12.8 min, t_R (minor) = 16.9 min, *ee* = 95%; $[\alpha]^{25}_D$ = +142.6 (*c* = 0.95 in $CHCl_3$).

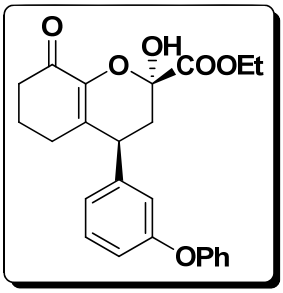


(2*R*,4*S*)-Ethyl 2-hydroxy-4-(4-(methylthio)phenyl)-8-oxo-3,4,5,6,7,8-hexahydro-2*H*-chromene-2-carboxylate (3-3i) (Table 3.3, entry 9). 82% yield, 95% *ee*; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.2 Hz, 2H), 7.16 (d, *J* = 8.2 Hz, 2H), 4.50 (br, 1H), 4.39–4.22 (m, 2H), 3.77 (dd, *J* = 12.5, 6.5 Hz, 1H), 2.56–2.41 (m, 5H), 2.31 (t, *J* = 13.0 Hz, 1H), 2.20 (dd, *J* = 13.6, 6.5 Hz, 1H), 2.13–2.01 (m, 2H), 1.97–1.83 (m, 2H), 1.32 (t, *J* =7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.85, 169.07, 142.86, 137.57, 137.51, 133.98, 128.98, 127.07, 93.62, 63.05, 39.53, 38.26, 36.74, 27.79, 22.08, 15.80, 13.92; HRMS (EI) calcd for $C_{19}H_{22}O_5S$ 362.1188, found 362.1180; HPLC (Chiralpak IA, *i*-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 12.6 min, t_R (minor) = 17.2 min, *ee* = 95%; $[\alpha]^{25}_D$ = +140.8 (*c* = 0.97 in $CHCl_3$).

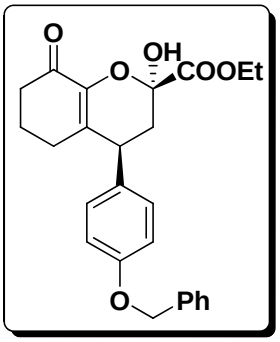


(2*R*,4*S*)-Ethyl 4-(4-(allyloxy)phenyl)-2-hydroxy-8-oxo-3,4,5,6,7,8-hexahydro

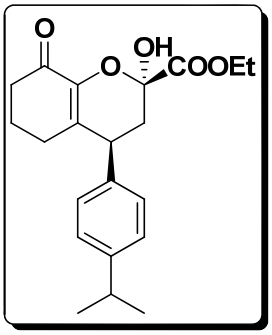
-2*H*-chromene-2- carboxylate (3-3j) (Table 3.3, entry 10). 87% yield, 94% *ee*; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.16– 7.11(m, 2H), 6.93–6.88 (m, 2H), 6.12–5.98 (m, 1H), 5.42 (ddd, *J* = 17.3, 3.1, 1.6 Hz, 1H), 5.30 (ddd, *J* = 10.5, 2.7, 1.3 Hz, 1H), 4.55–4.53 (m, 3H), 4.39–4.22 (m, 2H), 3.76 (dd, *J* = 12.5, 6.6 Hz, 1H), 2.56–2.41 (m, 2H), 2.36–2.27 (m, 1H), 2.20 (dd, *J* = 13.6, 6.6 Hz, 1H), 2.13–1.98 (m, 2H), 1.97–1.83 (m, 2H), 1.32 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 193.02, 169.19, 157.85, 142.71, 134.73, 133.18, 132.77, 129.48, 117.71, 115.14, 93.71, 68.87, 63.01, 39.20, 38.25, 36.84, 27.80, 22.08, 13.93; HRMS (EI) calcd for $C_{21}H_{24}O_6$ 372.1573, found 372.1561; HPLC (Chiralpak IA, *i*-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 11.7 min, t_R (minor) = 15.0 min, *ee* = 94%; $[\alpha]^{25}_D$ = +144.6 (*c* = 0.83 in $CHCl_3$).



(2*R*,4*S*)-ethyl 2-hydroxy-8-oxo-4-(3-phenoxyphenyl)-3,4,5,6,7,8-hexahydro-2*H*-chromene-2- carboxylate (3-3k) (Table 3.3, entry 11). 94% yield, 96% *ee*; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37-7.29 (m, 3H), 7.13 (t, *J* = 7.4 Hz, 1H), 7.05–6.99 (m, 2H), 6.97 (d, *J* = 7.7 Hz, 1H), 6.94–6.88 (m, 2H), 4.52 (br, 1H), 4.38–4.23 (m, 2H), 3.78 (dd, *J* = 12.4, 6.6 Hz, 1H), 2.56–2.40 (m, 2H), 2.31 (t, *J* = 13.0 Hz, 1H), 2.23 (dd, *J* = 13.6, 6.6 Hz, 1H), 2.18–2.02 (m, 2H), 1.98–1.85 (m, 2H), 1.32 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.82, 169.02, 157.82, 156.82, 142.85, 142.83, 133.60, 130.19, 129.80, 123.56, 123.21, 118.95, 118.85, 117.44, 93.58, 63.04, 39.94, 38.24, 36.64, 27.71, 22.08, 13.92; HRMS (EI) calcd for $C_{24}H_{24}O_6$ 408.1573, found 408.1559; HPLC (Chiralpak IA, *i*-propanol/hexane = 5/95, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 17.5 min, t_R (minor) = 21.9 min, *ee* = 96%; $[\alpha]^{25}_D$ = +95.0 (*c* = 1.05 in $CHCl_3$).

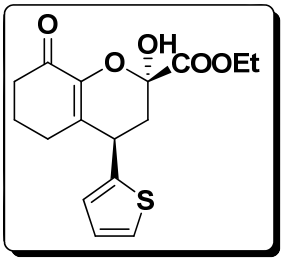


(2*R*,4*S*)-Ethyl 4-(4-(benzyloxy)phenyl)-2-hydroxy-8-oxo-3,4,5,6,7,8-hexahydro-2*H*-chromene-2-carboxylate (3-3l) (Table 3.3, entry 12). 86% yield, 93% *ee*; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.46–7.30 (m, 5H), 7.17–7.12 (m, 2H), 6.99–6.94 (m, 2H), 5.06 (s, 2H), 4.51 (br, 1H), 4.37–4.23 (m, 2H), 3.76 (dd, *J* = 12.5, 6.5 Hz, 1H), 2.56–2.40 (m, 2H), 2.35–2.27 (m, 1H), 2.20 (dd, *J* = 13.6, 6.5 Hz, 1H), 2.12–1.97 (m, 2H), 1.96–1.83 (m, 2H), 1.32 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.91, 169.17, 158.08, 142.75, 136.89, 134.60, 132.94, 129.53, 128.59, 128.00, 127.43, 115.28, 93.71, 70.12, 63.00, 39.22, 38.26, 36.87, 27.82, 22.09, 13.92; HRMS (EI) calcd for $C_{25}H_{26}O_6$ 422.1729, found 422.1709; HPLC (Chiralpak IA, *i*-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 17.5 min, t_R (minor) = 22.4 min, *ee* = 93%; $[\alpha]^{25}_{D}$ = +104.5 (*c* = 1.11 in $CHCl_3$).

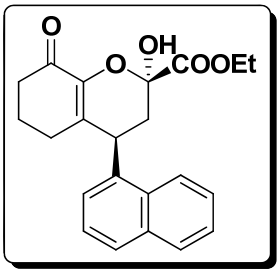


(2*R*,4*S*)-Ethyl 2-hydroxy-4-(4-isopropylphenyl)-8-oxo-3,4,5,6,7,8-hexahydro-2*H*-chromene-2- carboxylate (3-3m) (Table 3.3, entry 13). 91% yield, 95% ee; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.21 (d, *J* = 8.1 Hz, 2H), 7.16–7.12 (m, 2H), 4.53 (br, 1H), 4.38–4.22 (m, 2H), 3.78 (dd, *J* = 12.5, 6.5 Hz, 1H), 2.91 (dt, *J* = 13.9, 6.9 Hz, 1H), 2.56–2.41 (m, 2H), 2.33 (t, *J* = 13.1 Hz, 1H), 2.21 (dd, *J* = 13.6, 6.6 Hz, 1H), 2.15–1.99

(m, 2H), 1.96–1.83 (m, 2H), 1.31 (t, J = 7.3 Hz, 3H), 1.26 (d, J = 6.9 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 193.01, 169.21, 147.95, 142.76, 137.97, 134.69, 128.41, 126.93, 93.69, 62.99, 39.65, 38.27, 36.89, 33.70, 27.85, 23.92, 22.07, 13.92; HRMS (EI) calcd for $C_{21}H_{26}O_5$ 358.1780, found 358.1764; HPLC (Chiralpak IA, *i*-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 7.0 min, t_R (minor) = 9.8 min, *ee* = 95%; $[\alpha]^{25}_D$ = +121.1 (c = 0.95 in $CHCl_3$).

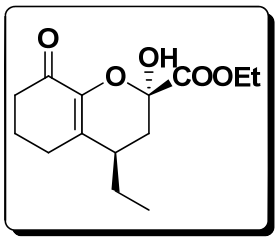


(2*R*,4*R*)-Ethyl 2-hydroxy-8-oxo-4-(thiophen-2-yl)-3,4,5,6,7,8-hexahydro-2*H*-chromene-2-carboxylate (3-3n) (Table 3.3, entry 14). 84% yield, 93% *ee*; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.25 (dd, J = 5.0, 0.6 Hz, 1H), 7.00–6.94 (m, 2H), 4.60 (br, 1H), 4.41–4.24 (m, 2H), 4.19 (dd, J = 12.5, 6.3 Hz, 1H), 2.51–2.40 (m, 3H), 2.33 (dd, J = 13.5, 6.4 Hz, 1H), 2.21–2.11 (m, 2H), 1.91 (dd, J = 10.2, 4.2 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125MHz, $CDCl_3$): δ = 193.04, 168.90, 143.29, 142.01, 133.44, 126.84, 126.43, 124.65, 93.60, 63.10, 38.12, 37.04, 35.00, 27.24, 21.98, 13.91; HRMS (EI) calcd for $C_{16}H_{18}O_5S$ 322.0875, found 322.0870; HPLC (Chiralpak IA, *i*-propanol/hexane = 5/95, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 17.4 min, t_R (minor) = 20.8 min, *ee* = 93%; $[\alpha]^{25}_D$ = +82.9 (c = 1.02 in $CHCl_3$).

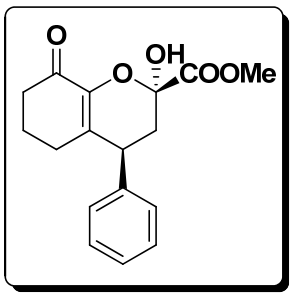


(2*R*,4*S*)-Ethyl 2-hydroxy-4-(naphthalen-1-yl)-8-oxo-3,4,5,6,7,8-hexahydro-2*H*-chromene-2-carboxylate (3-3o) (Table 3.3, entry 15). 91% yield, 95% *ee*; ^{1}H NMR

(500 MHz, $CDCl_3$): δ = 8.24–7.98 (m, 1H), 7.94–7.87 (m, 1H), 7.86–7.75 (m, 1H), 7.61–7.32 (m, 4H), 4.86–4.63 (m, 1H), 4.38–4.21 (m, 2H), 2.89 (t, *J* = 13.3 Hz, 0.4H), 2.65–2.45 (m, 2H), 2.39 (d, *J* = 8.5, 1H), 2.29 (dd, *J* = 14.9, 7.9 Hz, 0.8H), 2.20 (dd, *J* = 13.8, 6.5 Hz, 1H), 2.05–1.79 (m, 4H), 1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.93, 169.13, 143.80, 141.98, 137.31, 136.05, 135.50, 134.95, 134.50, 133.95, 132.03, 131.04, 129.45, 129.33, 129.13, 128.70, 127.61, 126.60, 126.42, 125.91, 125.75, 125.66, 125.60, 125.48, 125.42, 123.57, 122.32, 93.93, 93.83, 63.02, 41.71, 38.38, 38.21, 37.12, 34.30, 34.08, 29.65, 27.74, 27.25, 22.23, 22.05, 14.01, 13.90; HRMS (EI) calcd for $C_{22}H_{22}O_5$ 366.1467, found 366.1481; HPLC (Chiralpak IA, *i*-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 9.2 min, t_R (minor) = 11.1 min, *ee* = 95%; $[\alpha]^{25}_D$ = +84.8 (*c* = 1.01 in $CHCl_3$).



(2*R*,4*R*)-Ethyl 4-ethyl-2-hydroxy-8-oxo-3,4,5,6,7,8-hexahydro-2*H*-chromene-2-carboxylate (3-3p) (Table 3.3, entry 16). 72% yield, 96% *ee*; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.40–4.19 (m, 2H), 2.63–2.22 (m, 4H), 2.11–1.78 (m, 4H), 1.45–1.16 (m, 6H), 0.96 (t, *J* = 7.5, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.96, 169.51, 142.24, 135.43, 93.72, 62.97, 37.98, 33.10, 32.36, 29.69, 26.78, 23.74, 22.02, 13.96, 10.71; HRMS (EI) calcd for $C_{14}H_{20}O_5$ 268.1311, found 268.1310; HPLC (Chiralpak AD-H, *i*-propanol/hexane = 2/98, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 34.5 min, t_R (minor) = 37.3 min, *ee* = 96%; $[\alpha]^{25}_D$ = +13.3 (*c* = 0.15 in $CHCl_3$).



(2*R*,4*S*)-Methyl 2-hydroxy-8-oxo-4-phenyl-3,4,5,6,7,8-hexahydro-2*H*-chromene -2-carboxylate (3-3q) (Table 3.3, entry 17). 97% yield, 96% *ee*; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35 (t, *J* = 7.4 Hz, 2H), 7.31–7.27 (m, 1H), 7.23 (dd, *J* = 5.2, 3.1 Hz, 2H), 4.48 (br, 1H), 3.85 (s, 3H), 3.81 (dd, *J* = 12.6, 6.6 Hz, 1H), 2.56–2.41 (m, 2H), 2.39–2.30 (m, 1H), 2.24 (dd, *J* = 13.6, 6.6 Hz, 1H), 2.13–2.00 (m, 2H), 1.96–1.84 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 192.90, 169.56, 142.74, 140.67, 134.26, 128.94, 128.49, 127.33, 93.74, 53.54, 39.97, 38.22, 36.82, 27.78, 22.06; HRMS (EI) calcd for $C_{17}H_{18}O_5$ 302.1154, found 302.1151; HPLC (Chiralpak IA, *i*-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 10.4 min, t_R (minor) = 13.1 min, *ee* = 96%; $[\alpha]^{25}_{D}$ = +124.0 (*c* = 1.05 in $CHCl_3$).

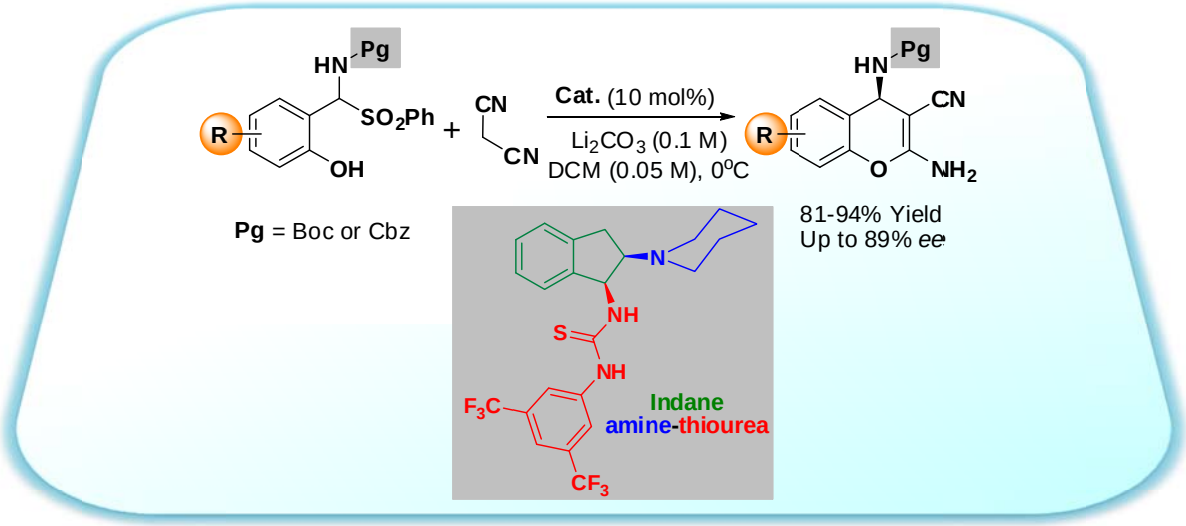
3.4.4 X-ray Crystallographic Analysis

Table 3.4 Crystal data and structure refinement for **3-3i**.

Empirical formula	C19 H22 O5 S	
Formula weight	362.43	
Temperature	223(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 7.8373(7) Å	a= 90°.
	b = 8.6462(8) Å	b= 94.152(2)°.
	c = 13.3583(12) Å	g = 90°.
Volume	902.82(14) Å^3	
Z	2	

Density (calculated)	1.333 Mg/m^3
Absorption coefficient	0.205 mm^{-1}
F(000)	384
Crystal size	0.60 x 0.44 x 0.12 mm^3
Theta range for data collection	1.53 to 27.49°
Index ranges	-10<=h<=10, -6<=k<=11, -17<=l<=17
Reflections collected	6390
Independent reflections	2899 [R(int) = 0.0246]
Completeness to theta = 27.49°	99.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9758 and 0.8867
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2899 / 31 / 256
Goodness-of-fit on F^2	1.076
Final R indices [I>2sigma(I)]	R1 = 0.0428, wR2 = 0.1088
R indices (all data)	R1 = 0.0447, wR2 = 0.1102
Absolute structure parameter	0.06(9)
Largest diff. peak and hole	0.345 and -0.175 e.$Å^{-3}$

Chapter 4 Expeditious Assembly of 2-Amino-4*H*-chromene Skeleton *via* an Enantioselective Mannich–Intramolecular Ring Cyclization–Tautomerization Cascade Sequence

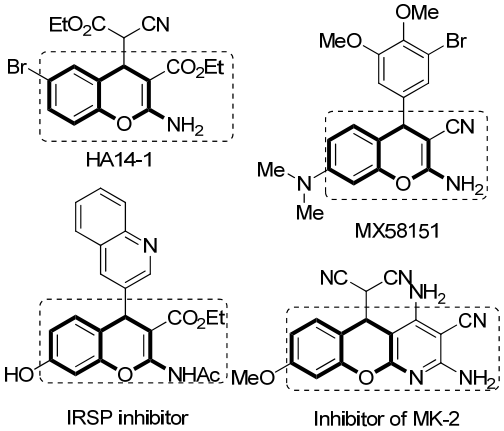


An enantioselective cascade Mannich–intramolecular ring cyclization–tautomerization reaction of malononitrile with 2-hydroxyl N-protected α-amido sulfone is described, which provides a novel route to the synthesis of privileged scaffold 2-amino-4H-chromene in high yields (up to 94%) and with good to high enantiomeric excesses (74–89% ee).

4.1 Introduction

The concept of "privileged medicinal scaffold" has emerged as one of the guiding principles in the process of drug discovery.[142] The privileged scaffold commonly consists of a rigid hetero-ring system that assigns a well-defined orientation of appended functionalities for target recognition.[143] In the light of this, the accessibility of convenient methods for the diversification of privileged scaffold functionalities impacts on the success in seeking potential drugs. Undoubtedly, the discovery of novel synthetic methodologies to facilitate the preparation of compound libraries is a pivotal focal point in modern medicinal chemistry.[144]

Figure 4.1 Examples of 2-amino-4*H*-chromene derivatives as pharmaceutical drugs.



Chromene, as one of the privileged scaffolds, often appears as an important structural component in both biologically active and natural compounds. It appears in natural alkaloids, tocopherols, flavonoids, and anthocyanins.[145] Moreover, in recent

[142] a) Evans, B. E.; Rittle, K. E.; Bock, M. G.; DiPardo, R. M.; Freidinger, R. M.; Whitter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S.; Chang, R. S. L.; Lotti, V. G.; Cerino, D. J.; Chen, T. B.; Kling, P. J.; Kunkel, K. A.; Springer, J. P.; Hirshfield, J. *J. Med. Chem.* **1988**, *31*, 2235; b) Patchett, A. A.; Nargund, R. P. *Ann. Rep. Med. Chem*. **2000**, *35*, 28; c) Triggle, D. J. *Cell. Mol. Neurobiol*. **2003**, *23*, 293; d) Poupaert, J.; Carato, P.; Colacino, E. *Curr. Med. Chem.* **2005**, *12*, 87.

[143] Bemis, G. W.; Murcko, M. A. *J. Med. Chem.* **1996**, *39*, 2887.

[144] For selected reviews, see: a) Nefzi, A.; Ostresh, J. M.; Houghten, R. A. *Chem. Rev.* **1997**, *97*, 44; b) Thompson, L. A. *Curr. Opin. Chem. Biol.* **2000**, *4*, 32.

[145] For selected examples of natural molecules containing the chromene scaffold, see: a) Iacobucci, G. A.; Sweeny, J. G. *Tetrahedron* **1983**, *39*, 3005; b) Harborne, J. B. (Ed.), *The Flavanoids – Advances in Research*, Chapman & Hall, London, **1988**; c) Bohm, B. A.; Choy, J. B.; Lee, A. Y.-M. *Phytochemistry* **1989**, *28*, 501; d) Parmar, V. S.; Jain, S. C.; Bisht, K. S.; Jain, R.; Taneja, P.; Jha, A.; Tyagi, O. D.; Prasad, A. K.; Wengel, J.; Olsen, C. E.; Boll, P. M. *Phytochemistry* **1997**, *46*, 597.

years functionalized chromenes have played an ever-increasing role in the field of synthetic and medicinal chemistry.[146] Among the diverse chromene systems, 2-amino-4*H*-chromenes are particular privileged medicinal scaffolds serving for the generation of small-molecule based ligands with highly pronounced spasmolytic, diuretic, anticoagulant, and antianaphylactic activities.[147] In particular, the current interest in 2-amino-4*H*-chromene derivatives bearing a nitrile functionality arises from their potential applications in the treatment of human inflammatory TNFa-mediated diseases, such as rheumatoid and psoriatic arthritis (Figure 4.1).[148]

The corresponding cyano-functionalized benzopyranopyridine (Figure 4.1, inhibitor of MK-2) originating from the 2-amino-4*H*-chromene scaffold was found to inhibit mitogen-activated protein kinase (MAPK)-activated protein kinase 2 (MK-2) and suppress the expression of TNF-a in U937 cells.[148] In the case of cancer therapy, the tumor antagonist HA14-1 (Figure 4.1) and a family of related alkyl (4*H*-chromen-4-yl)cyanoacetates are a new class of small molecules that exhibit a binding activity for the surface pocket of the cancer-implicated Bcl-2 protein and induce apoptosis or programmed cell death in follicular lymphoma B cells and leukemia HL-60 cells.[148] The 2-amino-3-cyano-4*H*-chromene MX58151 (Figure 4.1) bearing a 3-bromo-4,5-dimethoxyphenyl substituent at the 4-position represents a

[146] For recent selected examples, see: a) Garino, C.; Bihel, F.; Pietrancosta, N.; Laras, Y.; QuSlSver, G.; Woo, I.; Klein, P.; Bain, J.; Boucher, J.-L.; Kraus, J.-L. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 135; b) Sun, W.; Cama, L. J.; Birzin, E. T.; Warrier, S.; Locco, L.; Mosley, R.; Hammond, M. L.; Rohrer, S. P. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1468; c) Stachulski, A. V.; Berry, N. G.; Low, A. C. L.; Moores, S.; Row, E.; Warhurst, D. C.; Adagu, I. S.; Rossignol, J.-F. *J. Med. Chem*. **2006**, *49*, 1450.

[147] a) Andreani, L. L.; Lapi, E. *Boll. Chim. Farm.* **1960**, *99*, 583; b) Witte, E. C.; Neubert, P.; Roesch, A. German Patent **DE 3,427,985**, **1986**; c) Foye, W. O. *Prinicipi di Chemico Farmaceutica*, Piccin, Padova, **1991**, p 416; d) Bonsignore, L.; Loy, G.; Secci, D.; Calignano, A. *Eur. J. Med. Chem.* **1993**, *28*, 517; e) DeSimone, R. W.; Currie, K. S.; Mitchell, S. A.; Darrow, J. W.; Pippin, D. A. *Comb. Chem. High Throughput Screening* **2004**, *7*, 473.

[148] a) Wang, J. L.; Liu, D.; Zhang, Z.; Shan, S.; Han, X.; Srinvasula, S. M.; Croce, C. M.; Alnemeri, E. S.; Huang, Z. *Proc. Natl. Acad. Sci.* **2000**, *97*, 7124; b) Kasibhatla, S.; Gourdeau, H.; Meerovitch, K.; Drewe, J.; Reddy, S.; Qiu, L.; Zhang, H.; Bergeron, F.; Bouffard, D.; Yang, Q.; Herich, J.; Lamothe, S.; Cai, S. X.; Tseng, B. *Mol. Cancer Ther.* **2004**, *3*, 1365; c) Gourdeau, H.; Leblond, L.; Hamelin, B.; Desputeau, C.; Dong, K.; Kianicka, I.; Custeau, D.; Bourdeau, C.; Geerts, L.; Cai, S. X.; Drewe, J.; Labrecque, D.; Kasibhatla, S.; Tseng, B. *Mol. Cancer Ther.* **2004**, *3*, 1375; d) Kemnitzer, W.; Drewe, J.; Jiang, S.; Zhang, H.; Wang, Y.; Zhao, J.; Jia, S.; Herich, J.; Labreque, D.; Storer, R.; Meerovitch, K.; Bouffard, D.; Rej, R.; Denis, R.; Blais, C.; Lamothe, S.; Attardo, G.; Gourdeau, H.; Tseng, B.; Kasibhatla, S.; Cai, S. X. *J. Med. Chem.* **2004**, *47*, 6299; e) Anderson, D. R.; Hegde, S.; Reinhard, E.; Gomez, L.; Vernier, W. F.; Lee, L.; Liu, S.; Sambandam, A.; Snider, P. A.; Masih, L. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1587; f) Kemnitzer, W.; Kasibhatla, S.; Jiang, S.; Zhang, H.; Zhao, J.; Jia, S.; Xu, L.; Crogan-Grundy, C.; Denis, R.; Barriault, N.; Vaillancourt, L.; Charron, S.; Dodd, J.; Attardo, G.; Labrecque, D.; Lamothe, S.; Gourdeau, H.; Tseng, B.; Drewe, J.; Cai, S. X. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4745; g) Yeatman, H.; Frederick, F. A. O.; Chai, S. Y.; Albiston, A. L.; Ye, S. Y.; Watson, K. G.; Parker, M. W.; Ng, H. L. *Aust. Pat. Appl*. **2009**, 55.

promising class of proapoptotic small-molecule agents with multiple action modes against the breast cancer cell line T47D, the lung cancer cell line H1299, and the colorectal cancer cell line DLD-1.[148] It induces caspase-mediated apoptosis in tumor cells, and is about as potent as or slightly more potent than the commonly prescribed anticancer alkaloids vinblastine and paclitaxel in the caspase activation assay.[148] Furthermore, compound MX58151 might have an advantage for the treatment of drug-resistant cancers as it retains activity in tumor cells resistant towards current antimitotic agents, taxanes (including Taxol and Taxotere), and Vinca alkaloids.[148] The inhibition of tubuline polymerization and disruption of preformed endothelial cell capillary tubules constitute other significant activities of 2-amino-3-cyano-4-aryl-4*H*-chromenes of type 3 that can place them in the row of effective anticancer therapeutics with an analogous mode of action.[148] Most recently, another 2-amino-4-aryl-4*H*-chromene compound (Figure 4.1, IRSP inhibitor) has been discovered as an insulin-refulated aminopeptidase inhibitor. In particular, this inhibitor is maybe useful in therapeutic application including enhancing memory and learning functions.[148]

In view of the significance of this framework, efficient syntheses of 2-amino-4*H*-chromenes are of great interest. Despite the fact that asymmetric organocatalysis has evolved as a powerful tool for the preparation of enantiomerically enriched compound,[149] organocatalytic method to generate optically pure 2-amino-4*H*-chromenes is still absent. Recently, H-bonding mediated catalysis for C–C bond formation has been discovered as a new powerful tool and powerful synthetic method for the efficient construction of molecular architectures.[150] In particular, there was a remarkable development and application on chiral bifunctional thiourea catalysis.[151] The utilization of inexpensive and readily synthesized chiral thiourea

[149] For selected books of organocatalysis, see: a) see *Ref.* 1a; b) see *Ref.* 1b; c) see *Ref.* 1c; d) see *Ref.* 1d.

[150] For selected reviews on hydrogen bonding, see: a) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289; b) see *Ref.* 16a; c) see *Ref.* 29; d) Miyabe, H.; Takemoto, Y. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 785; e) Connon, S. J. *Chem. Commun.* **2008**, 2499.

[151] For selected examples of chiral bifunctional thiourea catalysis, see: a) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 5315; b) Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2000**, *39*, 1279; c) see *Ref.* 30; d) see *Ref.* 39; e) see *Ref.* 41; f) see *Ref.* 150a; g) Pihko, P. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2062;

catalysts attracted considerable interests and proved to be effective in several asymmetric transformations. Herein, we document a novel strategy for the preparation of chiral 2-amino-4*H*-chromenes through a H-bonding mediated enantioselective cascade process. To date, such a progress has not been described. Significantly, this strategy allows a quick construction of diversely functionalized 2-amino-4*H*-chromenes under mild reaction conditions with good to high enantioselectivities (74–89% *ee*) and high to excellent yields (81–94%) could be achieved. In this context, we sought to extend the usage of the indane catalytic system for the construction of novel and useful complexes based on the several successful examples disclosed by our research group.

4.2 Results and Discussion

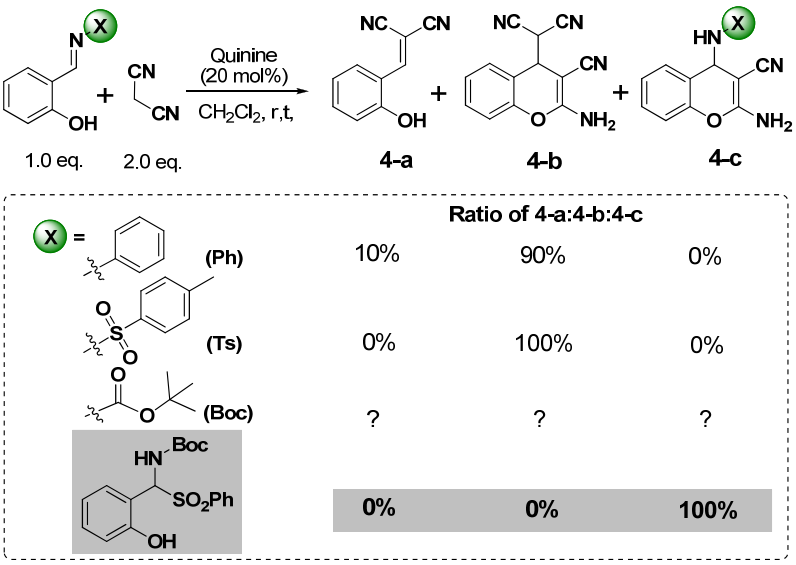
4.2.1 Catalyst Screening

We began our investigation by examining the organic base catalyzed reaction of 2-hydroxy imine with malononitrile. The initial experiment results showed that the use of a catalytic amount of quinine enabled a reaction between 2-hydroxy imine and malononitrile. Surprisingly, if a phenyl group was introduced to 2-hydroxy imine, a mixture of undesired compound **4-a** and **4-b** were generated in 10 mins (Scheme 4.1, **4-a**:**4-b** = 10:90). Then we tried a stronger electron-withdrawing group involved 2-hydroxy *N*-Tos imine (Scheme 4.1, X = Tos). However, only compound **4-b** was finally resembled (Scheme 4.1, **4-a**:**4-b** = 0:100). Based on above experimental results, we deduced that both strong electron withdrawing groups and good leaving groups supported 2-hydroxyl imine might assist the Knoevenagel-type reaction to form intermediate **4-a**. Then it triggered the sequential reactions to generate undesired compound **4-b**. In order to avoid these side reactions, we were tentative to introduce a poor leaving group (X = Boc) with a less electron-withdrawing character to the imine

h) see *Ref.* 17; i) Connon, S. J. *Chem. –Eur. J.* **2006**, *12*, 5419; j) see *Ref.* 16a; k) see *Ref.* 36; l) Peschiulli, A.; Procuranti, B.; O'Connor, C. J.; Connon, S. J. *Nat. Chem.* **2010**, *2*, 380; m) see *Ref.* 53.

structure. To our knowledge, *N*-Boc protected imine is an ideal choice. Unfortunately, we failed to seek a successful method to synthesize 2-hydroxyl *N*-Boc imine (Scheme 4.1). Instead, an *N*-Boc α-amido sulfone,[152] one of the precursors of *N*-Boc imine, was used to react with malononitrile. Gratifyingly, the investigation showed only desired compound **4-c** was afforded (Scheme 4.1, **4-a**:**4-b**:**4-c** = 0:0:100).

Scheme 4.1 Investigation of 2-hydroxy imines.



Having this finding in hands, we then wish to probe the asymmetric catalytic feasibility of this reaction. *tert*-Butyl (2-hydroxyphenyl)(phenylsulfonyl) methylcarbamate **4-1a** was treated with malononitrile **4-2** in the presence of catalyst **4-VII** (quinine-thiourea) which was developed by the Soós, Dixon and Connon groups respectively (Figure 4.2).[153] As shown in Table 4.1, catalyst **4-VII** gave a 43% yield in 10 min with a 16% *ee* value (Table 4.1, entry 7). Takemoto thiourea catalyst

[152] For selected examples of the application of *N*-Boc α-amido sulfones, see: a) Fini, F.; Sgarzani, V.; Pettersen, D.; Herrera, R. P.; Bernardi, L.; Ricci, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 7975; b) Marianacci, O.; Micheletti, G.; Bernardi, L.; Fini, F.; Fochi, M.; Pettersen, D.; Sgarzani, V.; Ricci, A. *Chem. –Eur. J.* **2007**, *13*, 8338; c) Mizuta, S.; Shibata, N.; Goto, Y.; Furukawa, T.; Nakamura, S.; Toru, T. *J. Am. Chem. Soc.* **2007**, *129*, 6394; d) Niess, B.; Jørgensen, K. A. *Chem. Commun.* **2007**, 1620; e) Gianelli, C.; Sambri, L.; Carlone, A.; Bartoli, G.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2008**, *47*, 8700; f) Jiang, X.; Zhang, Y. F.; Wu, L. P.; Zhang, G.; Liu, X.; Zhang, H. L.; Fu, D.; Wang, R. *Adv. Synth. Catal.* **2009**, *351*, 2096; g) Momo, R. D.; Fini, F.; Bernardi, L.; Riccia, A. *Adv. Synth. Catal.* **2009**, *351*, 2283; h) Cassani, C.; Bernardi, L.; Fini, F.; Ricci, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 5694; i) Zhang, H. L.; Syed, S.; Barbas, C. F., III *Org. Lett.* **2010**, *12*, 708.

[153] a) see *Ref.* 124; b) see *Ref.* 54; c) see *Ref.* 53.

4-VI also only offered a 46% yield and a 42% *ee* (Table 4.1, entry 6). Consequently, the discovery of a novel and active chiral catalyst which can promote this reaction with both high efficiency and excellent stereo-control became our main focus. In this context, we sought to extent the usage of the indane amine-thiourea catalytic system based on several successful examples disclosed by our research group.[154] Undoubtedly, bifunctional indane amine-thiourea organocatalysts demonstrated some unique aspects, such as higher activity, excellent stereo-control, and flexible skeleton. Catalyst **4-I**, **4-II** and **4-IV** (Figure 4.2) exhibited high stereoselectivity in several Michael addition reaction triggered cascade processes. Unfortunately, catalyst **4-I** supported a poor result in this catalytic process (Table 4.1, 38% yield, 29% *ee*). Catalyst **4-III**, the similar analogue of catalyst **4-I** with a switch of amine and thiourea functional groups, showed a good enantioselectivity (Table 4.1, 50% yield, 77% *ee*). Further improvement went on, and we have noticed the critical factor played by the dihedral angle between the two functional groups on the catalyst in the stereochemistry control. Consequently, catalysts **4-II** and **4-IV** (Figure 4.2) were synthesized with the amine and thiourea group are *anti* to each other. In contrast to catalysts **4-I** and **4-III**'s structure, catalysts **4-II** and **4-IV** just have a chiral inversion on the amine part respectively while maintaining all the other features. Result showed that catalysts **4-II** and **4-IV** were not the best catalysts (Table 4.1, entries 2 and 4, 9% *ee* and 30% *ee*, respectively). Meanwhile, we examined catalyst **4-V**, L-*tert*-leucine derivative. However, only a moderate result was generated (Table 4.1, entry 5, 61% yield, 44% *ee*). Having failed to find a catalyst more promising than **4-III**, a base screening was then performed.

[154] For some examples of our group developed bifunctional indane thiourea catalyzed reactions, see: a) see *Ref.* 140a; b) see *Ref.* 140b; c) see *Ref.* 140c; d) see *Ref.* 140d.

Figure 4.2 Bifunctional chiral organocatalysts.

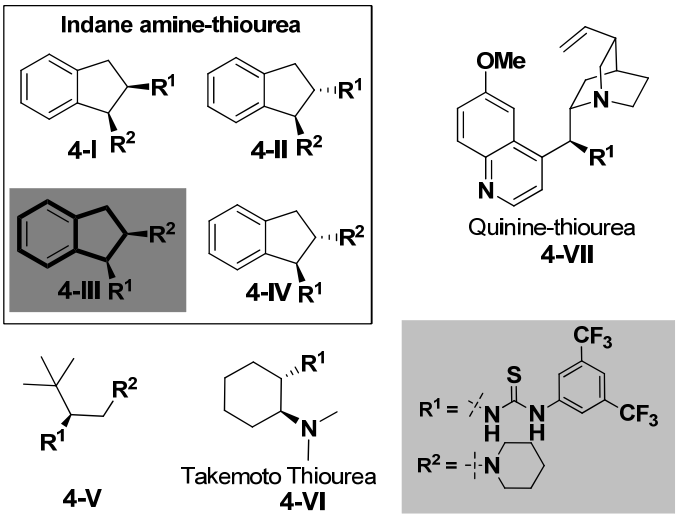
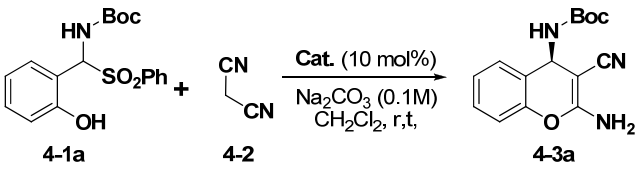


Table 4.1 Evaluation of different bifunctional chiral organocatalysts.[a]



Entry	Catalyst	Yield [%][b]	ee [%][c]
1	**4-I**	38	-29
2	**4-II**	43	9
3	**4-III**	50	77
4	**4-IV**	48	30
5	**4-V**	61	44
6	**4-VI**	46	42
7	**4-VII**	43	16

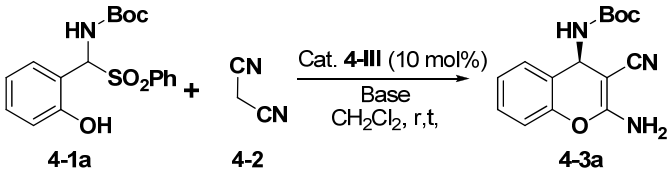
[a] Reaction conditions: DCM (0.2 mL), *tert*-butyl (2-hydroxyphenyl)(phenylsulfonyl) methylcarbamate **4-1a** (0.1 mmol, 1.0 equiv.), malononitrile **4-2** (0.11 mmol, 1.1 equiv.), Na_2CO_3 (0.1 M, 0.12 mmol, 1.2 equiv.) solution, 10 mol% catalyst at room temperature. [b] Yield of isolated product after column chromatography. [c] Enantiomeric excess (*ee*) was determined by HPLC.

4.2.2 Reaction Optimization

Optimization studies highlighted the ability of a range of bases, either a solid or an aqueous solution (Table 4.2), to generate the *N*-Boc imine *in situ*. Stronger aqueous

bases K_2CO_3, Cs_2CO_3, LiOH or KOH, did increase the conversion to the desired product, but did not increase the *ee* value (Table 4.2, entries 4, 5, 7, and 8). Use of solid Na_2CO_3 (no water) decreased the reaction rate and *ee* value (entry 2, 720 min, 52% *ee*). A slightly weaker base Li_2CO_3 improved the reaction conversion and remained the *ee* value (entry 3, 88% yield, 77% *ee*). Slow conversion was observed when $NaHCO_3$ was used (Table 8, entry 9). These evidences promoted us to select aqueous Li_2CO_3 as the base media of choice and further optimization of the standard reaction parameters was carried out.

Table 4.2 Base effect.[a]



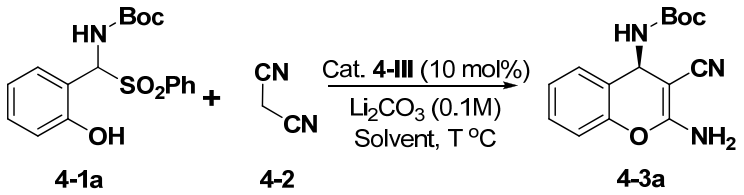
Entry	Base	t [min]	Yield[%][b]	*ee* [%][c]
1	Na_2CO_3	10	50	77
2[d]	Na_2CO_3	720	74	52
3	Li_2CO_3	10	88	77
4	K_2CO_3	10	70	76
5	Cs_2CO_3	10	77	74
6	$(NH_4)_2CO_3$	30	86	74
7	LiOH	2	71	73
8	NaOH	2	82	71
9	$NaHCO_3$	180	85	68

[a] Reaction conditions: *tert*-butyl (2-hydroxyphenyl)(phenylsulfonyl) methylcarbamate **4-1a** (0.1 mmol, 1.0 equiv.), malononitrile **4-2** (0.11 mmol, 1.1 equiv.), base (0.1 M, 0.12 mmol, 1.2 equiv.), 10 mol% catalyst **4-III**, DCM (0.2 mL) and room temperature. [b] Yield of isolated product after column chromatography. [c] Enantiomeric excess (*ee*) was determined by HPLC. [d] 0.12 mmol of dry Na_2CO_3 was used.

For further optimization, solvent, as well as reaction temperature, was examined (Table 4.3). The initial solvent screen was performed at room temperature. In general, less polar solvents were crucial for obtaining good enantioselectivities at room

temperature (Table 4.3, entries 1–5, 71–78% *ee*). For high polar solvents, relatively lower enantioselectivities were obtained due to potential destruction of H-bonding interaction between substrates and the catalyst (Table 4.3, entries 6 and 7, 27% and 3% *ee*, respectively). Finally, CH_2Cl_2 gave the best results with respect to reaction rate, yield and *ee* (Table 4.3, entry 1). In order to further optimize the reaction, we varied the reaction temperatures and the concentrations of Li_2CO_3. The results showed that the enantioselectivity can be enhanced by an appropriate temperature and base concentration (entry 10, 30 min, 94% yield, 88% *ee*).

Table 4.3 Evaluation of other parameters.[a]



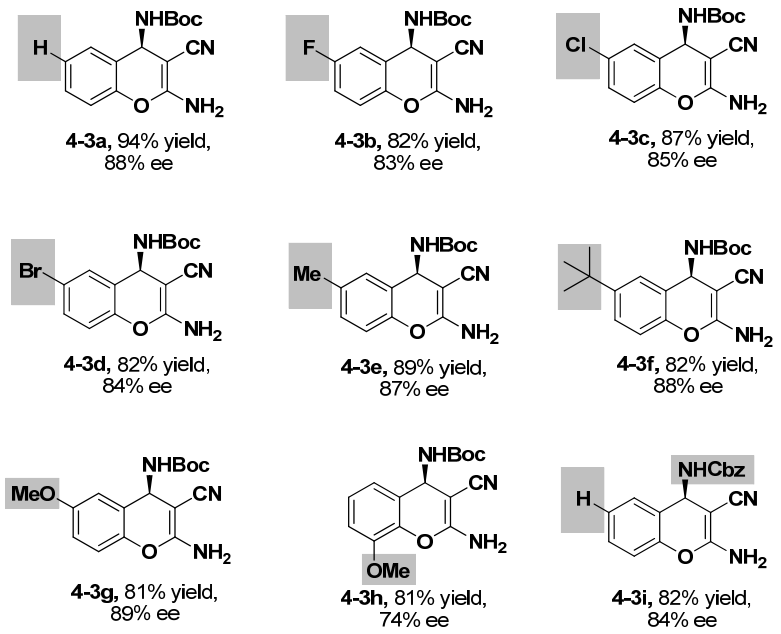
Entry	Solvent	T [°C]	[C][b]	t [min]	Yield [%][c]	ee [%][d]
1	CH_2Cl_2	r.t.	0.5	10	88	77
2	DCE	r.t.	0.5	10	78	71
3	Toluene	r.t.	0.5	60	72	76
4	$PhCF_3$	r.t.	0.5	60	80	72
5	Anisole	r.t.	0.5	60	67	78
6	*i*-PrOH	r.t.	0.5	60	67	27
7	DMSO	r.t.	0.5	60	77	3
8	CH_2Cl_2	0	0.5	10	89	79
9	CH_2Cl_2	0	0.1	10	90	83
10	CH_2Cl_2	0	0.05	30	94	88
11	CH_2Cl_2	0	0.025	120	94	83
12	CH_2Cl_2	-10	0.05	180	92	83

[a] Reaction conditions: *tert*-butyl (2-hydroxyphenyl)(phenylsulfonyl) methylcarbamate **4-1a** (0. 1 mmol, 1.0 equiv.), malononitrile **4-2** (0.11 mmol, 1.1 equiv.), Li_2CO_3 (0.1 M, 0.12 mmol, 1.2 equiv.), 10 mol% catalyst **4-III**. [b] Concentration. [c] Yield of isolated product after column chromatography. [d] Enantiomeric excess (*ee*) was determined by HPLC.

4.2.3 Reaction Scope

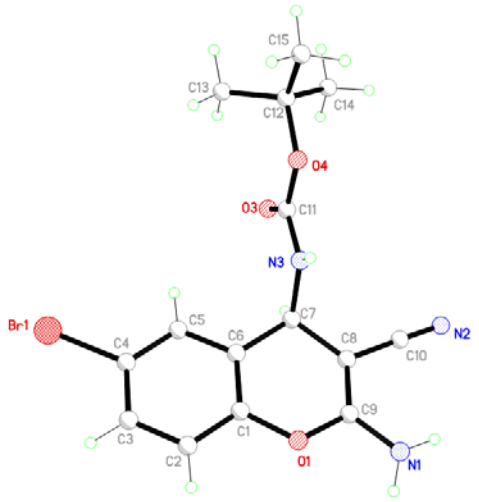
Under the optimized reaction conditions, the generality of our cascade process was examined by using various *in situ* generated aromatic *N*-carbamoyl α-imino ethyl glyoxylates (Table 4.4). Aromatic *N*-carbamoyl α-imino ethyl glyoxylates **4-1** having both electron-withdrawing (Table 4.4, entries 2–4, 82–87% yield, 83–85% *ee*) and electron-donating substituents (Table 4.4, entries 5–8, 81–89% yield, 74–89% *ee*) could be applied to this transformation; the substitution pattern of the arene had limited influence on the enantioselectivity of the reaction. In addition, it was possible to use Cbz as protecting group in this reaction (Table 4.4, entry 9, 82% yield, 84% *ee*). The absolute configuration of the products was determined by single-crystal X-ray analysis of **4-3d** (Figure 4.3).[155]

Table 4.4 Substrate scope.



[155] CCDC 818689 (compound **4-3d**) contains the supplementary crystallographic data for this paper. These data can be ontained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

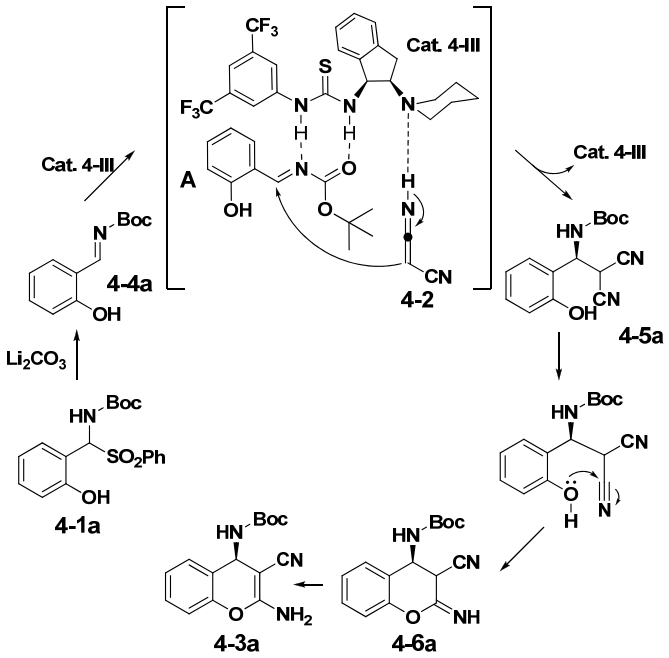
Figure 4.3 X-ray crystal structure of **4-3d**.



4.2.4 Proposed Mechanism

Our postulated reaction pathways were summarized in Scheme 4.2. In the initial step, elimination of compound **4-1a** caused the formation of the intermediate imine **4-4a** in the presence of Li_2CO_3. The subsequent Mannich reaction of intermediate **4-4a** with malononitrile **4-2** formed the intermediate **4-5a** catalyzed by indane amine-thiourea **4-III**. Then, the intramolecular *oxa*-nucleophilic addition to nitrile group led to the intermediate **4-6a**. Finally, intermediate **4-6a** underwent tautomerization to offer the desired compound **4-3a**.

Scheme 4.2 Proposed catalytic cycle.



4.3 Conclusion

In summary, we have developed an efficient and convenient cascade process for the synthesis of 2-amino-4*H*-chromenes in high to excellent yields (81–94%) and with good to high enantioselectivities (74–89% *ee*). This protocol proceeded through a Mannich-cyclization-tautomerization cascade sequence of malononitrile with 2-hydroxyl *N*-protected α-amido sulfone. This finding is significant because it provides a novel and powerful route to the synthesis of privileged scaffold 2-amino-4*H*-chromene bearing a nitrile functionality, which reveals potential application in the treatment of human inflammatory TNFa-mediated diseases. However, it is still highly desirable to apply this catalytic system and strategy to other asymmetric transformations to efficiently assemble chiral materials with complex structures. Further elaboration of the products to other types of biologically active compounds and potential applications of the catalytic system will draw much attention in the further.

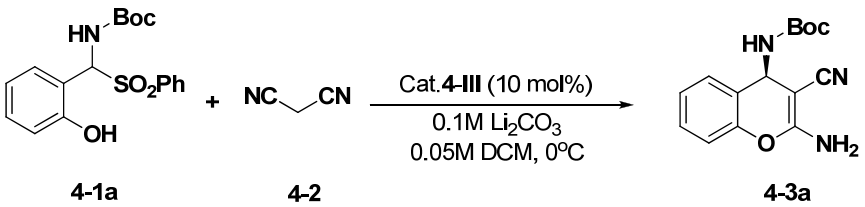
4.4 Experimental Section

4.4.1 General Information

Chemicals and solvents were purchased from commercial suppliers and used as received. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ACF300 (300 MHz) 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) or tetramethylsilane (TMS δ 0.00) was used as a reference. Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), bs (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

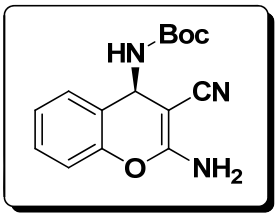
obtained on a Finnigan/MAT 95XL-T spectrometer. For thin layer chromatography (TLC), Merck pre-coated TLC plates (Merck 60 F254) were used, and compounds were visualized with a UV light at 254 nm. Further visualization was achieved by staining with iodine, or ninhydrin followed by heating using a heat gun. Flash chromatography 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. Optical rotations were recorded on Jasco DIP-1000 polarimeter.

4.4.2 Representative Procedure for Mannich–Intramolecular Ring Cyclization–Tautomerization Reaction

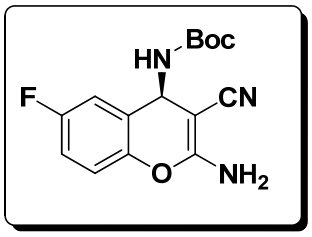


To a solution of *tert*-butyl (2-hydroxyphenyl)(phenylsulfonyl)methylcarbamate **4-1a** (36 mg, 0.1 mmol,), malononitrile **4-2** (7.3 mg, 0.11 mmol) and catalyst **4-III** (4.9 mg, 0.01 mmol) in DCM (2.0 mL) at 0 °C, was added chilled lithium carbonate aqueous solution (0.10 M, 1.2 mL) in one portion. The resulting biphasic reaction mixture was kept stirring at 0°C for 0.5 h. Then the reaction mixture was diluted with water (2 mL) and extracted with ethyl acetate (5 mL, three times). Organic layers were combined, washed with brine (6 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. Crude product was purified by silica gel flash chromatography, eluted by hexane/EtOAc=3:1 to afford the desired product **4-3a** as white solid (27.0 mg, 94% yield).

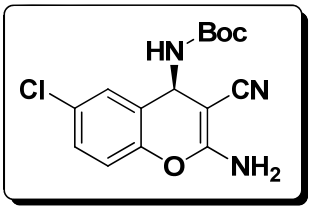
4.4.3 Analytical Data of Mannich–Intramolecular Ring Cyclization–Tautomerization products



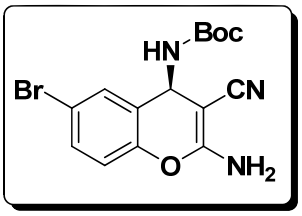
(*R*)-*tert*-butyl 2-amino-3-cyano-4*H*-chromen-4-ylcarbamate (4-3a). 94% yield, 88% *ee*; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.49 (s, 1H), 7.33 – 7.22 (m, 1H), 7.16 (t, *J* = 7.5 Hz, 1H), 6.97 (d, *J* = 8.2 Hz, 1H), 5.64 (d, *J* = 7.9 Hz, 1H), 4.94 (d, *J* = 7.9 Hz, 1H), 4.87 (m, 2H), 1.46 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.57, 155.07, 148.38, 129.18, 129.11, 125.35, 121.35, 118.96, 116.13, 80.00, 58.56, 43.90, 28.30; HRMS (ESI) calcd for $C_{15}H_{17}N_3O_3Na$ (M + Na^+) 310.1162, found 310.1169; HPLC (Chiralpak IA, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 7.7 min, t_R (minor) = 14.7 min, *ee* = 88%; $[\alpha]^{25}_D$ = -63.2 (*c* = 0.79 in Acetone).



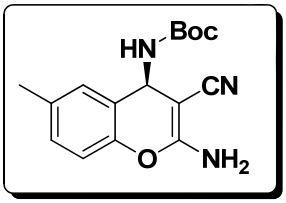
(*R*)-*tert*-butyl 2-amino-3-cyano-6-fluoro-4*H*-chromen-4-ylcarbamate (4-3b). 82% yield, 83% *ee*; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.60 (d, *J* = 8.6 Hz, 1H), 7.17 (td, *J* = 8.5, 3.0 Hz, 1H), 7.07 (dt, *J* = 7.4, 3.5 Hz, 2H), 7.02 (m, 2H), 5.33 (d, *J* = 8.6 Hz, 1H), 1.39 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 161.16, 159.13, 157.21, 155.06, 144.82, 119.93, 118.05, 117.69, 117.63, 115.97, 115.77, 113.97, 113.78, 78.14, 53.83, 43.98, 28.12; HRMS (ESI) calcd for $C_{15}H_{16}FN_3O_3Na$ (M + Na^+) 328.1068, found 328.1073; HPLC (Chiralpak IA, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 7.2 min, t_R (minor) = 15.8 min, *ee* = 83%; $[\alpha]^{25}_D$ = -78.1 (*c* = 1.00 in Acetone).



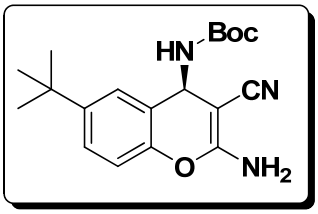
(*R*)-*tert*-butyl 2-amino-6-chloro-3-cyano-4*H*-chromen-4-ylcarbamate (4-3c). 87% yield, 85% *ee*; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.50 (s, 1H), 7.23 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.93 (d, *J* = 8.8 Hz, 1H), 5.59 (d, *J* = 8.3 Hz, 1H), 4.94 (s, 1H), 4.83 (m, 2H), 1.47 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.28, 155.00, 146.93, 130.39, 129.39, 128.80, 122.90, 118.49, 117.61, 80.40, 58.47, 43.79, 28.29; HRMS (ESI) calcd for $C_{15}H_{16}ClN_3O_3Na$ (M + Na^+) 344.0772, found 344.0776; HPLC (Chiralpak IA, *i*-propanol/hexane = 40/60, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 4.7 min, t_R (minor) = 8.6 min, *ee* = 85%; $[\alpha]^{25}_D$ = -21.9 (*c* = 0.88 in Acetone).



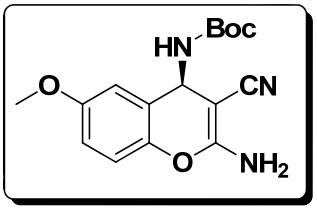
(*R*)-*tert*-butyl 2-amino-6-bromo-3-cyano-4*H*-chromen-4-ylcarbamate (4-3d). 82% yield, 84% *ee*; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.64 (s, 1H), 7.38 (dd, *J* = 8.7, 2.1 Hz, 1H), 6.87 (d, *J* = 8.7 Hz, 1H), 5.59 (d, *J* = 7.4 Hz, 1H), 4.94 (s, 1H), 4.83 (m, 2H), 1.47 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.22, 155.00, 147.47, 132.29, 131.79, 123.28, 118.48, 117.96, 117.77, 80.41, 58.56, 43.69, 28.29; HRMS (ESI) calcd for $C_{15}H_{16}BrN_3O_3Na$ (M + Na^+) 388.0267, found 388.0274; HPLC (Chiralpak IA, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 8.1 min, t_R (minor) = 22.6 min, *ee* = 84%; $[\alpha]^{25}_D$ = -1.9 (*c* = 0.97 in Acetone).



(*R*)-*tert*-butyl 2-amino-3-cyano-6-methyl-4*H*-chromen-4-ylcarbamate (4-3e). 89% yield, 87% *ee*; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.48 (d, *J* = 8.8 Hz, 1H), 7.10 (d, *J* = 5.8 Hz, 1H), 6.95 – 6.86 (m, 3H), 5.32 (d, *J* = 8.9 Hz, 1H), 2.26 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 161.13, 155.03, 146.44, 133.48, 129.27, 128.25, 121.64, 120.08, 115.46, 77.85, 54.79, 43.79, 28.12, 20.20; HRMS (ESI) calcd for $C_{16}H_{19}N_3O_3Na$ (M + Na^+) 324.1319, found 324.1323; HPLC (Chiralpak IA, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 7.4 min, t_R (minor) = 17.6 min, *ee* = 87%; $[\alpha]^{25}_D$ = -3.9 (*c* = 0.79 in Acetone).

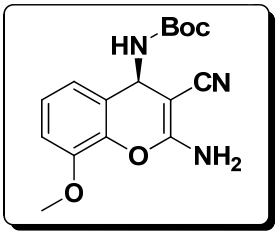


(*R*)-*tert*-butyl 2-amino-6-*tert*-butyl-3-cyano-4*H*-chromen-4-ylcarbamate (4-3f). 82% yield, 88% *ee*; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.50 (d, *J* = 9.0 Hz, 1H), 7.41 (s, 1H), 7.33 (dd, *J* = 8.6, 2.0 Hz, 1H), 6.93 (d, *J* = 9.1 Hz, 3H), 5.36 (d, *J* = 9.0 Hz, 1H), 1.40 (s, 9H), 1.24 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 161.22, 155.25, 146.88, 146.12, 125.80, 124.45, 121.66, 120.20, 115.19, 77.89, 54.13, 44.01, 33.95, 31.00, 28.09; HRMS (ESI) calcd for $C_{19}H_{25}N_3O_3Na$ (M + Na^+) 366.1788, found 366.1795; HPLC (Chiralpak IA, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 5.9 min, t_R (minor) = 10.7 min, *ee* = 88%; $[\alpha]^{25}_D$ = -18.9 (*c* = 1.02 in Acetone).

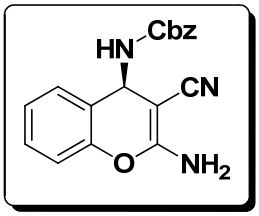


(*R*)-*tert*-butyl 2-amino-3-cyano-6-methoxy-4*H*-chromen-4-ylcarbamate (4-3g). 81% yield, 89% *ee*; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.02 (s, 1H), 6.90 (d, *J* = 9.0 Hz, 1H), 6.81 (dd, *J* = 8.9, 2.9 Hz, 1H), 5.62 (d, *J* = 8.7 Hz, 1H), 4.93 (d, *J* = 7.8 Hz, 1H), 4.78

(m, 2H), 3.77 (s, 3H), 1.47 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.72, 156.83, 155.20, 142.37, 122.08, 119.05, 117.14, 116.30, 111.88, 80.03, 58.06, 55.71, 44.35, 28.31; HRMS (ESI) calcd for $C_{16}H_{19}N_3O_4Na$ (M + Na^+) 340.1268, found 340.1274; HPLC (Chiralpak IA, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 8.7 min, t_R (minor) = 19.1 min, *ee* = 89%; $[\alpha]^{25}_D$ = -31.6 (*c* = 0.84 in Acetone).



(*R*)-*tert*-butyl 2-amino-3-cyano-8-methoxy-4*H*-chromen-4-ylcarbamate (4-3h). 81% yield, 74% *ee*; ^{1}H NMR (500 MHz, DMSO-d_6) δ = 7.49 (d, *J* = 8.9 Hz, 1H), 7.09 (t, *J* = 7.9 Hz, 1H), 6.99 (dd, *J* = 14.8, 7.2 Hz, 3H), 6.87 (d, *J* = 7.7 Hz, 1H), 5.34 (d, *J* = 8.9 Hz, 1H), 3.81 (s, 3H), 1.38 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ = 161.05, 154.98, 146.74, 138.08, 124.22, 122.85, 120.06, 119.31, 111.22, 77.85, 59.67, 55.71, 43.92, 28.15; HRMS (ESI) calcd for $C_{16}H_{19}N_3O_4Na$ (M + Na^+) 340.1268, found 340.1273; HPLC (Chiralpak IA, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 12.9 min, t_R (minor) = 11.5 min, *ee* = 74%; $[\alpha]^{25}_D$ = -18.3 (*c* = 1.17 in Acetone).



(*R*)-benzyl 2-amino-3-cyano-4*H*-chromen-4-ylcarbamate (4-3i). 82% yield, 84% *ee*; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.99 (d, J = 8.7 Hz, 1H), 7.39 – 7.25 (m, 7H), 7.18 (d, J = 7.4 Hz, 1H), 7.02 (d, J = 7.1 Hz, 3H), 5.42 (d, J = 8.7 Hz, 1H), 5.06 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ = 161.25, 155.54, 148.50, 137.01, 128.95, 128.41, 128.26, 127.68, 127.53, 124.63, 121.72, 120.03, 115.77, 65.20, 54.29, 44.55;

HRMS (ESI) calcd for $C_{18}H_{15}N_3O_3Na$ (M + Na^+) 344.1006, found 344.1010; HPLC (Chiralpak IB, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 15.8 min, t_R (minor) = 35.7 min, *ee* = 84%; $[\alpha]^{25}_D$ = -51.4 (*c* = 1.17 in Acetone).

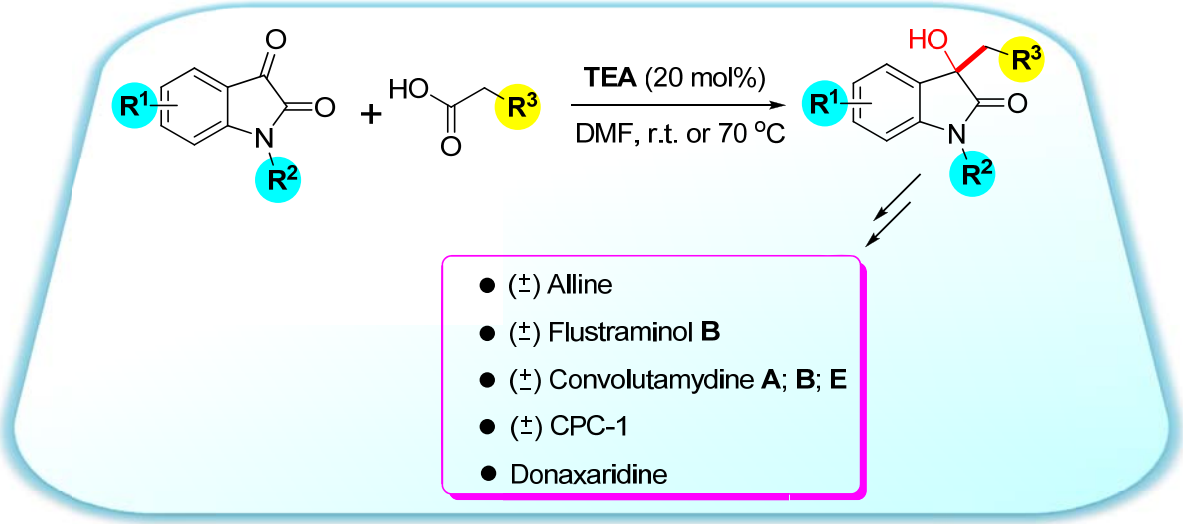
4.4.4 X-ray Crystallographic Analysis

Table 4.5 Crystal data and structure refinement for **4-3d**.

Empirical formula	C15 H16 Br N3 O3	
Formula weight	366.22	
Temperature	223(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 5.3714(4) Å	a= 90°.
	b = 16.8874(11) Å	b= 90°.
	c = 17.4864(12) Å	g = 90°.
Volume	1586.17(19) $Å^3$	
Z	4	
Density (calculated)	1.534 Mg/m^3	
Absorption coefficient	2.607 mm^{-1}	
F(000)	744	
Crystal size	0.70 x 0.08 x 0.06 mm^3	
Theta range for data collection	1.68 to 27.48°	
Index ranges	-6<=h<=6, -20<=k<=21, -21<=l<=22	
Reflections collected	11171	
Independent reflections	3592 [R(int) = 0.0573]	
Completeness to theta = 27.48°	99.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.8621 and 0.6334	
Refinement method	Full-matrix least-squares on F^2	

Data / restraints / parameters	3592 / 3 / 211
Goodness-of-fit on F^2	1.016
Final R indices [I>2sigma(I)]	R1 = 0.0467, wR2 = 0.0954
R indices (all data)	R1 = 0.0600, wR2 = 0.1003
Absolute structure parameter	0.010(12)
Largest diff. peak and hole	0.852 and -0.357 e.$Å^{-3}$

Chapter 5 Highly Efficient Assembly of 3-Hydroxy Oxindole Scaffold *via* a Catalytic Decarboxylative [1,2]-Addition Strategy



The 3-hydroxy-2-oxindole scaffold is being continuously discovered to be at the core of a diverse set of natural products. Herein, we document a highly efficient catalytic decarboxylative [1,2]-addition strategy to quickly assemble this scaffold, using a catalytic amount of weak base.

5.1 Introduction

Over the past few decades, natural products have proven to be useful small molecule probes in the medicinal community.[156] Since they have coevolved with their putative biological targets, natural products intersect biological space effectively and perturb its function in a highly controlled manner. It is not surprising that natural products have endured as promising leads for drug discovery. A rapid access to small molecules that are guided by natural products appears to be quintessential for the success of chemical genetics/genomics-based program. The design and synthesis of novel scaffolds as chiral core structures for the library generation of natural product-like derivatives is an essential step in accessing a wide range of structural complexes in an efficient manner.[157]

Herein, we wish to disclose a concise decarboxylative[158] [1,2]-addition process of readily accessible α-functionalized carboxylic acids with isatins under mild reaction conditions to assemble the valuable 3-functionalized 3-hydroxy-2-oxindoles (Figure 5.1).[159]

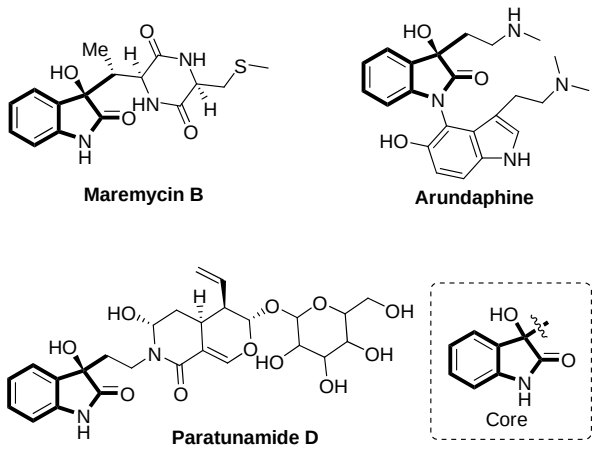
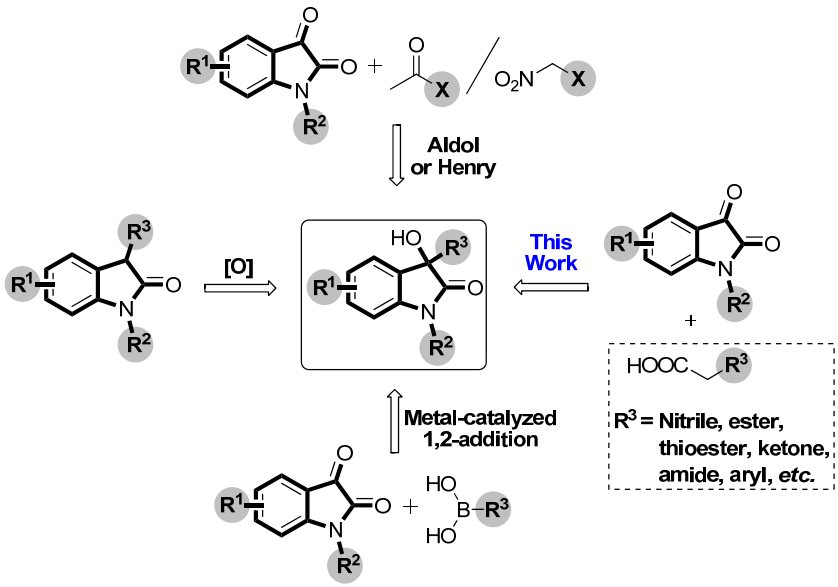


Figure 5.1 Representative bioactive natural products built on a 3-hydroxy-2-oxindole core scaffold.

[156] a) see *Ref.* 110b; b) Dewick, P. M. *Medicinal Natural Products*, Wiley, West Sussex, **2009**.
[157] a) Schreiber, S. L. *Bioorg. Med. Chem.* **1998**, *6*, 1127; b) Schreiber, S. L. *Science* **2000**, *287*, 1964; c) Crew, C. M. *Curr. Opin. Chem. Biol.* **2000**, *4*, 47; d) Weber, L. *Curr. Opin. Chem. Biol.* **2000**, *4*, 295; e)Wendeborn, S.; De Mesmaeker, A.; Brill, W. K.-D.; Berteina, S. *Acc. Chem. Res.* **2000**, *33*, 215.
[158] a) see *Ref.* 90; b) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991; c) see *Ref.* 91; d) Jiang, Z.; Pan, Y.; Zhao, Y.; Ma, T.; Lee, R.; Yang, Y.; Huang, K.-W.; Wong, M. W.; Tan, C.-H. *Angew. Chem. Int. Ed.* **2009**, *48*, 3627.
[159] a) Galliford, C. V.; Scheidt, K. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 8748; b) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209.

Good to excellent yields have been obtained at a suitable condition. These features render this synthetic protocol particularly attractive for practical application in drug discovery. It is noteworthy that the synthetic value has been broadly demonstrated in the formal and total synthesis of bioactive natural products,[159, 160] such as (±)-flustraminol B, (±)-convolutamydine A, (±)-alline, donaxaridine, (±)-convolutamydine E, (±)-convolutamydine B, and (±)-CPC-1.



Scheme 5.1 Routes for the preparation of 3-functionalized-3-hydroxy-2-oxindole framework.

Some elegant works have been reported to directly construct the 3-functionalized-3-hydroxy-2-oxindole framework (Scheme 5.1). One of the most straightforward strategies is the catalytic aldol reactions of ketones and aldehydes with isatins.[161] In line with the nucleophilic addition to the 3-carbonyl of isatins as a strategy for the synthesis of 3-substituted-3-hydroxy oxindoles, metal-mediated additions of carbon nucleophiles/equivalents, such as boronic acids, have been

[160] a) Goehring, R. R.; Sachdeva, Y. P.; Pisipati, J. S.; Sleevi, M. C.; Wolfe, J. F. *J. Am. Chem. Soc.* **1985**, *107*, 435; b) Rasmussen, H. B.; MacLeod, J. K. *J. Nat. Prod.* **1997**, *60*, 1152; c) Jiménez, J. I.; Huber, U.; Moore, R. E.; Patterson, G. M. L. *J. Nat. Prod.* **1999**, *62*, 569; d) Kohno, J.; Koguchi, Y.; Nishio, M.; Nakao, K.; Juroda, M.; Shimizu, R.; Ohnuki, T.; Komatsubara, S. *J. Org. Chem.* **2000**, *65*, 990; e) Suchy, M.; Kutschy, P.; Monde, K.; Goto, H.; Harada, N.; Takasugi, M.; Dzurilla, M.; Balentova, E. *J. Org. Chem.* **2001**, *66*, 3940; f) Komakine, N.; Takaishi, Y.; Honda, G.; Ito, M.; Takeda, Y.; Kodzhimatov, O. K.; Ahurmetov, O. *Natural Medicines* **2005**, *59*, 45; g) Kagata, T.; Saito, S.; Shigemori, H.; Ohsaki, A.; Ishiyama, H.; Kubota, T.; Kobayashi, J. *J. Nat. Prod.* **2006**, *69*, 1517.

[161] a) Braude, F.; Lindwall, H. G. *J. Am.Chem. Soc*. **1933**, *55*, 325; b) Luppi, G.; Cozzi, P. G.; Monari, M.; Kaptein, B.; Broxterman, Q. B.; Tomasini, C. *J. Org. Chem*. **2005**, *70*, 7418; c) Guo, Q.; Bhanushali, M.; Zhao, C. G. *Angew. Chem. Int. Ed.* **2010**, *49*, 9460.

explored.[162] Recently, a catalytic Henry reaction of isatins with alkanes has also been reported to make this core structure.[163] In addition, the oxidation of 3-substituted oxindoles is showing itself to be a useful method for the construction of this medicinal scaffold. [164] Notably, a dimeric quinidine-catalyzed enantioselective aminooxygenation of oxindoles has been reported to generate chiral 3-substituted oxindoles.[165] However, all the above methods are limited to special substrates.[166] To our knowledge, there has been no powerful method that can construct a 3-hydroxy oxindole scaffold and bear a wide spectrum of functional groups at the C3 position (Scheme 5.1). As part of a program geared toward the design and development of novel organocatalytic strategies for the efficient and mild synthesis of 3-functionalized-3-hydroxy-2-oxindole framework, we proposed a decarboxylative [1,2]-addition of various α-functionalized acetic acids to isatins catalyzed by a weak base.

5.2 Results and Discussion

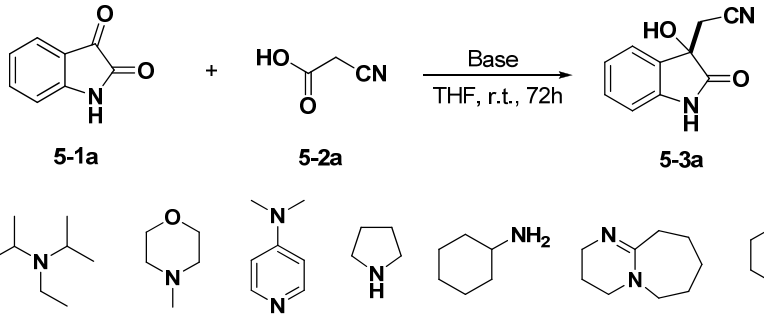
5.2.1 Catalyst Screening

We began our investigation by examining base-promoted reaction of isatin **5-1a** and cyanoacetic acid **5-2a** (Table 5.1). The initial experiment results showed that the use of a stoichiometric amount of triethylamine **5-I** (1.0 equiv.) enabled a reaction between isatin **5-1a** and cyanoacetic acid **5-2a** to afford a 82% yield at room temperature (Table 5.1, entry 1, 72 h). To seek more efficient catalysts, we then examined some other tertiary amines, second and primary amines, but the reaction

[162] a) Marshall, J. A. *Chem. Rev.* **2000**, *100*, 3163; b) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763; c) Shintani, R.; Inoue, M.; Hayashi, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 3353.
[163] Liu, L.; Zhang, S.; Xue, F.; Lou, G.; Zhang, H.; Ma, S.; Duan, W.; Wang, W. *Chem. –Eur. J.* **2011**, *17*, 7791.
[164] a) Miah, S.; Moody, C. J.; Richards, I. C.; Slawin, A. M. Z. *J. Chem. Soc., Perkin Trans. 1,* **1997**, 2405; b) Ishimaru, T.; Shibata, N.; Nagai, J.; Nakamura, S.; Toru, T.; Kanemasa, S. *J. Am. Chem. Soc.*, **2006**, *128*, 16488; c) Sano, D.; Nagata, K.; Itoh, T. *Org. Lett.* **2008**, *10*, 1593.
[165] Bui, T.; Candeias, N. R.; Barbas, C. F., III *J. Am. Chem. Soc.* **2010**, *132*, 5574.
[166] a) Qian, Z. Q.; Zhou, F.; Du, T. P.; Wang, B. L.; Ding, M.; Zhao, X. L.; Zhou, J. *Chem. Commun*. **2009**, 6753; b) Hara, N.; Nakamura, S.; Shibata, N.; Toru, T. *Chem.–Eur. J.* **2009**, *15*, 6790; c) Zhou, F.; Liu, Y. L.; Zhou, J. *Adv. Synth. Catal.* **2010**, *352*, 1381; d) Liu, Y. L.; Wang, B. L.; Cao, J. J.; Chen, L.; Zhang, Y. X.; Wang, C.; Zhou, J. *J. Am. Chem. Soc.* **2010**, *132*, 15176; e) Liu, Y. L.; Zhou, J. *Chem. Commun*. **2012**, *48*, 1919.

yields were lower (Table 5.1, entries 2-6, < 69%). Surprisingly, super organic bases, **5-VII** and **5-VIII** did not show a higher activity as expected (entries 7 and 8). In addition, several inorganic bases were also investigated, but the results demonstrated these inorganic bases were not efficient promoters in this reaction.

Table 5.1 Base effect[a]



Entry	Base	Yield (%)[b]	Entry	Base	Yield (%)[b]
1	**5-I**	82	7	**5-VII**	80
2	**5-II**	69	8	**5-VIII**	43
3	**5-III**	18	9	Li_2CO_3	<5
4	**5-IV**	48	10	Cs_2CO_3	<5
5	**5-V**	42	11	NaOAc	27[d]
6	**5-VI**	*c*	12	NaOH	48

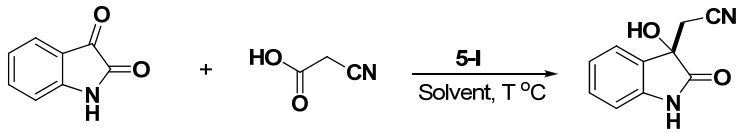
[a] Reaction conditions: THF (1.0 mL), **5-1a** (0.2 mmol, 1.0 equiv), **5-2a** (0.4 mmol, 2.0 equiv), base (1.0 equiv), 72 h, room temperature. [b] Yield of isolated product after column chromatography. [c] No reaction. [d] NaOAc was dissolved in H_2O (0.1 mL), 72 h.

5.2.2 Reaction Optimization

Having this finding in hands, we started to probe other parameters. A high yield was obtained if the reaction was carried out in polar solvent DMF (Table 5.2, entry 10, 90%, 72 h, room temperature). Other polar solvents, such as water and isopropanol however were proved to be poor media in this reaction (Table 5.2, entries 8 and 9, no reaction and 49%, respectively). To reduce the reaction time, we tried to increase the

reaction temperature. The results showed that a higher reaction temperature can largely improve the reaction rate (entry 12, 70 °C, 95%, 1 h). As shown in Table 5.2, a 20 mol% catalyst **5-I** also efficiently promoted the reaction (entry 13, 95%, 3 h). However, a high reaction concentration (1.0 mol/L) caused a loss of reaction yield because of some unknown side reactions (entry 14, 75%). In addition, the low catalyst loading also supported a good reaction yield in a suitable time (entry 16, 5 mol% **5-I**, 81%, 8 h).

Table 5.2 Optimization of other parameters[a]



5-1a 5-2a 5-3a

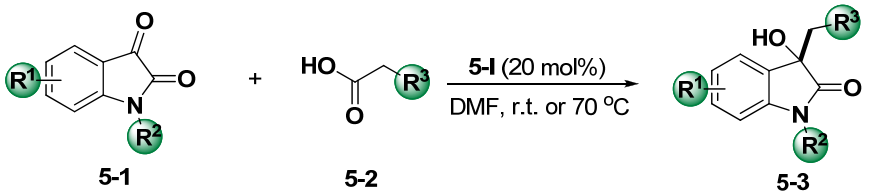
Entry	Solvent	t(h)	**5-I** (mol%)	T(°C)	Yield (%)[b]
1	CH_2Cl_2	72	100	r.t.	38
2	toluene	72	100	r.t.	*f*
3	THF	72	100	r.t.	82
4	Et_2O	72	100	r.t.	*f*
5	MeCN	72	100	r.t.	72
6	acetone	72	100	r.t.	65
7	EtOAc	72	100	r.t.	33
8	H_2O	72	100	r.t.	*f*
9	IPA[e]	72	100	r.t.	49
10	DMF	72	100	r.t.	90
11	DMF	18	100	50	98
12	DMF	1	100	70	95
13[c]	DMF	3	20	70	95
14[d]	DMF	3	20	70	75
15	DMF	6	10	70	88
16	DMF	8	5	70	81

[a] Reaction conditions: **5-1a** (0.2 mmol, 1.0 equiv), **5-2a** (0.4 mmol, 2.0 equiv), concentration (0.2 mol/L). [b] Yield of isolated product after column chromatography. [c] **5-2a** (0.22 mmol, 1.1 equiv). [d] Concentration (1.0 mol/L). [e] Isopropyl alcohol. [f] No reaction.

5.2.3 Reaction Scope

Having established a standard reaction protocol, we then probed a diverse set of isatins **5-1** and α-functionalized acetic acids **5-2**. As revealed in Table 5.3, the process proved to be a general strategy to construct 3-functionalized 3-hydroxyoxindoles **5-3**. Impressively, all reactions proceeded quickly (3–24 h), in good to excellent yields (up to 96%). The substitution pattern of R^1 was observed to possess limited effect on reaction rate, regardless of the neutral, electron-donating, or electron-withdrawing properties of substituents (Table 5.3, entries 1–16). We also found that the introduction of R^2 did not obviously affect this reaction (entries 17–20, 80–95%, 3 h). More importantly, a variety of α-functionalized groups, such as nitriles, esters, thioesters, amides, ketones, and aryls were successfully introduced to the core scaffold and desired products **5-3u – 5-3z** were achieved in moderate to high yields (entries 21–26, 61–95%, 3–24 h).

Table 5.3 Substrate scope[a]



Entry	R^1	R^2	R^3	T(h)	Yield (%)[b]
1	H	H	CN(**5-3a**)	3	95
2	5-F	H	CN(**5-3b**)	3	95
3	5-Cl	H	CN(**5-3c**)	3	96
4	5-Br	H	CN(**5-3d**)	3	92

5	5-NO_2	H	CN(**5-3e**)	3	85
6	5-MeO	H	CN(**5-3f**)	3	91
7	5-Me	H	CN(**5-3g**)	3	92
8	5-*i*-Pr	H	CN(**5-3h**)	3	88
9	5-*n*-C_7H_{15}	H	CN(**5-3i**)	3	73
10	4-Cl	H	CN(**5-3j**)	3	96
11	4-Br	H	CN(**5-3k**)	3	90
12	6-Cl	H	CN(**5-3l**)	3	93
13	6-Br	H	CN(**5-3m**)	3	91
14[c]	4,6-Me_2	H	CN(**5-3n**)	24	90
15	4,6-Br_2	H	CN(**5-3o**)	3	87
16	5,7-Br_2	H	CN(**5-3p**)	3	85
17	H	Bz	CN(**5-3q**)	3	81
18	H	Ac	CN(**5-3r**)	3	80
19	H	Bn	CN(**5-3s**)	3	95
20	H	Me	CN(**5-3t**)	3	91
21	H	H	CO_2Me(**5-3u**)	3	90
22[d]	H	H	CO_2Ph(**5-3v**)	24	92
23[d]	H	H	COSPh(**5-3w**)	24	61
24	H	H	CONHPh(**5-3x**)	18	81
25	H	H	COPh(**5-3y**)	3	86
26	H	H	4-NO_2Ph(**5-3z**)	3	95

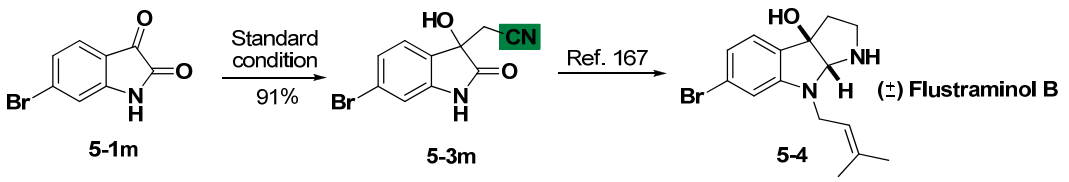
[a] Reaction Conditions: DMF (1.0 mL), **5-1** (0.2 mmol, 1.0 equiv), **5-2** (0.22 mmol, 1.1 equiv), **5-I** (20 mol%), 70 ^{o}C. [b] Yield of isolated product after column chromatography. [c] **5-I** (1.0 equiv). [d] Room temperature.

5.2.4. Methodology Application: Synthesis of Natural Products

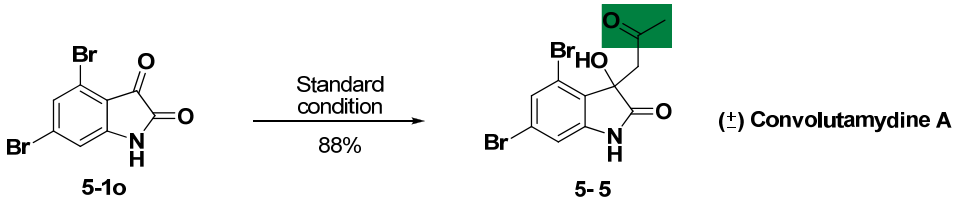
To illustrate the broad synthetic utility of this methodology, we undertook the

formal synthesis of several natural products, such as (±)-flustraminol B (eq 1)[167], (±)-convolutamydine A (eq 2), (±)-alline (eq 3)[168], (±)-convolutamydine E (eq 4), (±)-convolutamydine B (eq 4)[169] and donaxaridine (eq 5)[170]. As shown in eqs 1-5, we efficiently synthesized a series of important intermediates **5-3a**, **5-3m**, **5-3w** and **5-7** which could be efficiently converted to targeted natural products (±)-alline **5-6**, (±)-flustraminol B **5-4**, donaxaridine **5-11**, (±)-convolutamydine E **5-8** and (±)-convolutamydine B **5-9** *via* known methods respectively. Moreover, (±)-convolutamydine A **5-5** was directly synthesized by our one-pot decarboxylative [1,2]-addition strategy in 88% yield.

In addition, this method was applied to efficiently synthesize (±)-CPC-1. The synthesis commenced with an initial step, the bis-methylation of **5-3a**, to afford the *N*,*O*-dimethylated intermediate which was then converted to the Boc-protected amine in the presence of $NiCl_2$ and reducing agent $NaBH_4$. Followed that, the Boc protecting group was transferred into a methyl group using Red-Al. This intermediate then cyclized with the oxindole functionality to afford the desired alkaloid (±)-CPC-1 (Scheme 5.2). Meanwhile, the large scale synthesis by using 1.47 g of **5-1a** to react with 0.94 g of **5-2a** demonstrated that the process is practicable (eq 6, 91%).

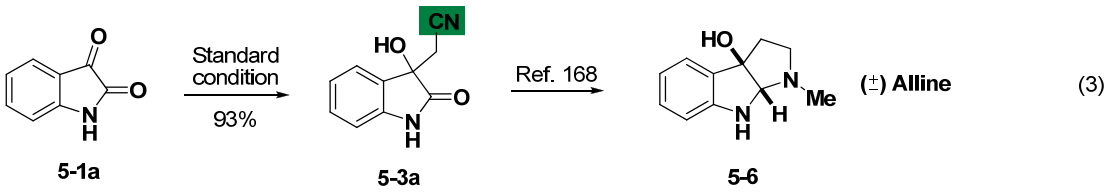


(1)

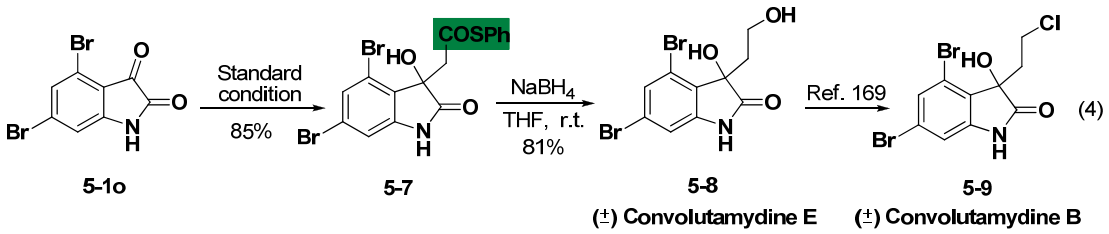


(2)

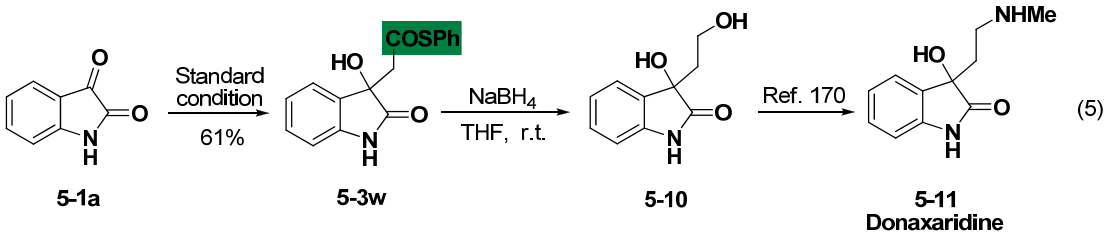
[167] Singh, A.; Poth, G. P. *Tetrahedron Lett.* **2012**, *53*, 4889.
[168] Singh, A.; Poth, G. P. *Org. Lett.* **2011**, *13*, 2118.
[169] Hara, N.; Nakamura, S.; Shibata, N.; Toru, T. *Chem. –Eur. J.* **2009**, *15*, 6790.
[170] See *Ref.* 160b.



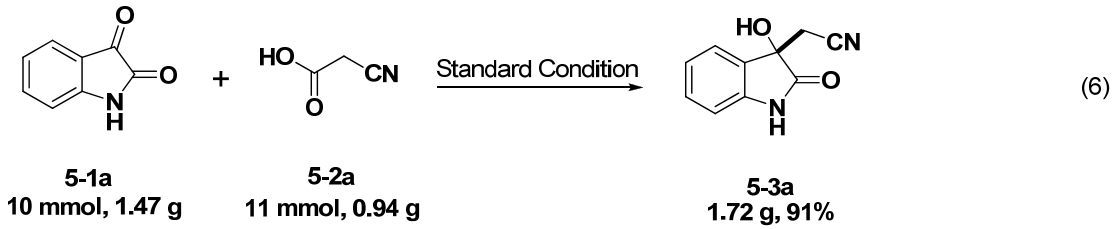
(3)



(4)

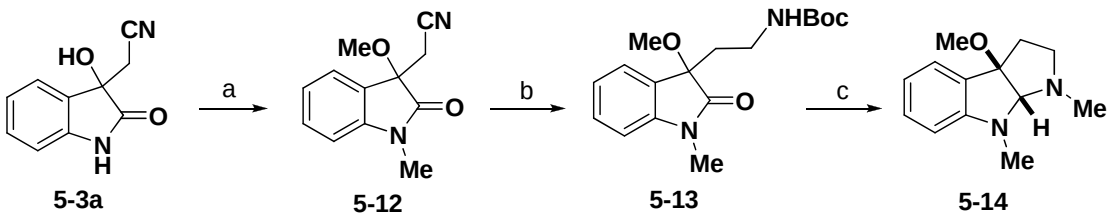


(5)



(6)

Scheme 5.2 Synthesis of (±)-CPC-1 **5-14**[a]



[a] Reagents: a) Cs_2CO_3, Me_2SO_4, CH_3CN/DMF, 71%; b) $NiCl_2$/$NaBH_4$, $(Boc)_2O$, MeOH, r.t., 77%; c) Red-Al, toluene, 0 to 80 °C.

5.3 Conclusion

In conclusion, inspired by the "medicinal" scaffold of 3-functionalized 3-hydroxyoxindoles, we have documented a concise decarboxylative [1,2]-addition strategy based on readily available isatins and α-functionalized acetic acids, using a catalytic amount of weak base. We have demonstrated the broad synthetic utility of our catalytic protocol in the efficient and quick assembly of pharmaceutical important 3-hydroxyoxindole natural products. This protocol extends previous work on the highly efficient assembly of 3-hydroxy oxindole scaffold *via* a catalytic decarboxylative strategy. The formal and total synthesis of bioactive natural products demonstrates the synthetic value of this protocol for practical application in drug discovery. However, the synthesis of chiral pharmaceutical 3-hydroxyoxindole natural products was not taken into account due to lack of suitable powerful organocatalysts. Therefore, further research is necessary to apply this catalytic strategy to various crucial applications and to develop an enantioselective methodology to construct "medicinal" 3-hydroxyoxindole scaffolds.

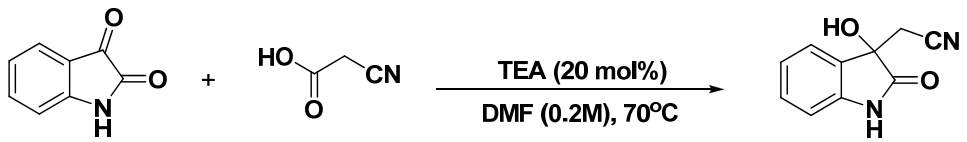
5.4 Experimental Section

5.4.1 General Information

Chemicals and solvents were purchased from commercial suppliers and used as received. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ACF300 (300 MHz) 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, DMSO δ 2.50), carbon (chloroform δ 77.0, DMSO δ 39.5) or tetramethylsilane (TMS δ 0.00) was used as a reference. Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), bs (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. Melting points were checked on Gallenkamp melting point apparatus. 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. Flash chromatography separations were performed on Merck 60 (0.040-0.063 mm) mesh silica gel.

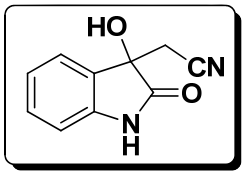
5.4.2 Representative Procedure for Organocatalytic Decarboxylative Addition



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

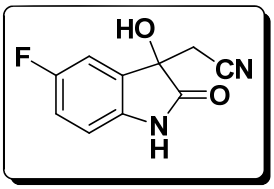
To a solution of isatin **5-1a** (29.4 mg, 0.20 mmol) in 1.0 mL DMF was added cyanoacetic acid **5-2a** (18.7 mg, 0.22 mmol) at room temperature, followed by adding catalyst **5-I** TEA (5.6 μL, 0.04 mmol). The mixture was stirred at 70 ^{o}C for 3 hours. The crude product was purified by column chromatography on silica gel, eluted by hexane/EtOAc = 2:1 to afford 35.8 mg (95% yield) of the desired product **5-3a** as white solid.

5.4.3 Analytical Data of Organocatalytic Decarboxylative Addition Products

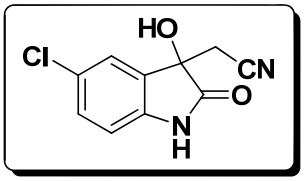


2-(3-hydroxy-2-oxoindolin-3-yl)acetonitrile (5-3a). White solid, 3h, 95% yield; mp 164 – 166 ^{o}C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.52 (s, 1H), 7.46 (d, J = 7.2 Hz, 1H), 7.29 (td, J = 7.7, 1.2 Hz, 1H), 7.04 (td, J = 7.6, 0.8 Hz, 1H), 6.87 (d, J = 7.8 Hz,

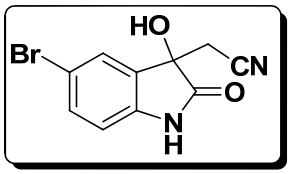
1H), 6.59 (s, 1H), 3.04 (d, J = 16.4 Hz, 1H), 2.95 (d, J = 16.4 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 176.7, 141.6, 123.0, 129.8, 124.18, 122.0, 117.02, 110.0, 72.0, 26.1; MS (ESI) *m/z*: 211 ([M + Na]$^+$); HRMS (ESI): Exact mass calculated for $C_{10}H_8N_2O_2$ [M + Na]$^+$ 211.0483, found 211.0481.



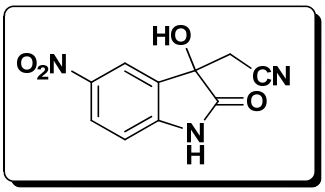
2-(5-fluoro-3-hydroxy-2-oxoindolin-3-yl)acetonitrile (5-3b). White solid, 3h, 95% yield; mp 186 – 188 ^{o}C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.56 (s, 1H), 7.30 (dd, J = 8.1, 2.7 Hz, 1H), 7.17 – 7.10 (m, 1H), 6.87 (dd, J = 8.5, 4.3 Hz, 1H), 6.73 (s, 1H), 3.09 (d, J = 16.4 Hz, 1H), 3.01 (d, J = 16.4 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 176.57, 158.95, 157.07, 137.76, 137.74, 131.39, 131.33, 116.80, 116.36, 116.17, 111.99, 111.80, 111.00, 110.94, 72.29, 25.83; MS (ESI) *m/z*: 229 ([M + Na]$^+$); HRMS (ESI): Exact mass calculated for $C_{10}H_7FN_2O_2$ [M + Na]$^+$ 229.0389, found 229.0383.



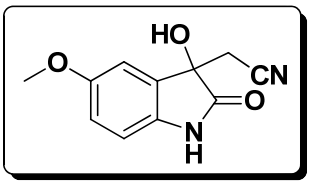
2-(5-chloro-3-hydroxy-2-oxoindolin-3-yl)acetonitrile (5-3c). White solid, 3h, 96% yield; mp 217 – 219 ^{o}C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.67 (s, 1H), 7.48 (d, J = 2.2 Hz, 1H), 7.35 (dd, J = 8.3, 2.2 Hz, 1H), 6.89 (d, J = 8.3 Hz, 1H), 6.74 (s, 1H), 3.11 (d, J = 16.4 Hz, 1H), 3.02 (d, J = 17.1 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 176.29, 140.52, 131.70, 129.80, 125.93, 124.31, 116.83, 111.57, 72.07, 25.74; MS (ESI) *m/z*: 245 ([M + Na]$^+$); HRMS (ESI): Exact mass calculated for $C_{10}H_7ClN_2O_2$ [M + Na]$^+$ 245.0094, found 245.0097.



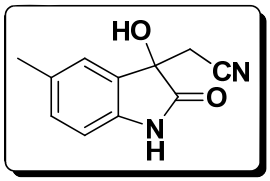
2-(5-bromo-3-hydroxy-2-oxoindolin-3-yl)acetonitrile (5-3d). White solid, 3h, 92% yield; mp 238 – 240 ^{o}C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.68 (s, 1H), 7.60 (d, *J* = 2.0 Hz, 1H), 7.48 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.84 (d, *J* = 8.3 Hz, 1H), 6.74 (s, 1H), 3.11 (d, *J* = 16.4 Hz, 1H), 3.02 (d, *J* = 16.4 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 176.17, 140.94, 132.65, 132.09, 127.05, 116.85, 113.57, 112.10, 72.03, 25.75; MS (ESI) *m/z*: 289 ([M + Na]$^{+}$); HRMS (ESI): Exact mass calculated for $C_{10}H_7BrN_2O_2$ [M + Na]$^{+}$ 288.9589, found 288.9589.



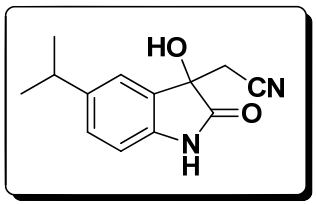
2-(3-hydroxy-5-nitro-2-oxoindolin-3-yl)acetonitrile (5-3e). White solid, 3h, 85% yield; mp 221 – 223 ^{o}C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.26 (s, 1H), 8.34 (d, *J* = 2.3 Hz, 1H), 8.27 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.09 (d, *J* = 8.6 Hz, 1H), 6.93 (s, 1H), 3.22 (d, *J* = 16.4 Hz, 1H), 3.14 (d, *J* = 17.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 176.91, 148.13, 142.34, 130.64, 127.20, 119.90, 116.71, 110.39, 71.64, 25.45; MS (ESI) *m/z*: 232 ([M – H]$^{-}$); HRMS (ESI): Exact mass calculated for $C_{10}H_7N_3O_4$ [M – H]$^{-}$ 232,0358, found 232.0354.



2-(3-hydroxy-5-methoxy-2-oxoindolin-3-yl)acetonitrile (5-3f). White solid, 3h, 91% yield; mp 177 – 179 ^{o}C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.35 (s, 1H), 7.10 (d, *J* = 2.5 Hz, 1H), 6.86 (dd, *J* = 8.4, 2.6 Hz, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 6.60 (s, 1H), 3.73 (s, 3H), 3.05 (d, *J* = 17.0 Hz, 1H), 2.95 (d, *J* = 17.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 176.52, 155.03, 134.63, 130.88, 116.96, 114.50, 111.15, 110.45, 72.37, 55.50, 26.06; MS (ESI) *m/z*: 241 ([M + Na]$^{+}$); HRMS (ESI): Exact mass calculated for $C_{11}H_{10}N_2O_3$ [M + Na]$^{+}$ 241.0589, found 241.0590.

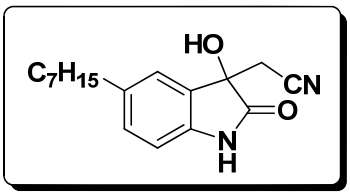


2-(3-hydroxy-5-methyl-2-oxoindolin-3-yl)acetonitrile (5-3g). White solid, 3h, 92% yield; mp 196 – 198 ^{o}C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.42 (s, 1H), 7.27 (s, 1H), 7.09 (dd, *J* = 7.9, 0.7 Hz, 1H), 6.76 (d, *J* = 7.9 Hz, 1H), 6.53 (s, 1H), 3.02 (d, *J* = 17.1 Hz, 1H), 2.92 (d, *J* = 16.4 Hz, 1H), 2.28 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 176.61, 139.05, 130.79, 130.09, 129.78, 124.67, 116.99, 109.74, 72.05, 26.08, 20.63; MS (ESI) *m/z*: 225 ([M + Na]$^{+}$); HRMS (ESI): Exact mass calculated for $C_{11}H_{10}N_2O_2$ [M + Na]$^{+}$ 225.0640, found 225.0645.

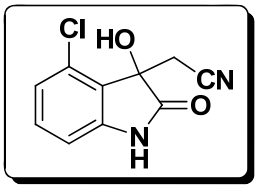


2-(3-hydroxy-5-isopropyl-2-oxoindolin-3-yl)acetonitrile (5-3h). White solid, 3h, 88% yield; mp 170 – 172 ^{o}C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.42 (s, 1H), 7.37 (d, *J* = 1.3 Hz, 1H), 7.16 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.79 (d, *J* = 7.9 Hz, 1H), 6.54 (s, 1H), 3.02 (d, *J* = 16.4 Hz, 1H), 2.94 (d, *J* = 16.4 Hz, 1H), 2.87 (dt, *J* = 13.8, 6.9 Hz, 1H),

1.20 (s, 3H), 1.19 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 176.72, 142.14, 139.36, 129.76, 127.60, 122.10, 117.07, 109.71, 72.06, 33.10, 26.14, 24.07, 24.06; MS (ESI) *m/z*: 253 ([M + Na]$^+$); HRMS (ESI): Exact mass calculated for $C_{13}H_{14}N_2O_2$ [M + Na]$^+$ 253.0953, found 253.0950.

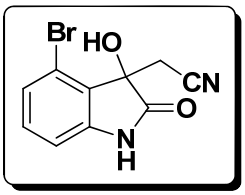


2-(5-heptyl-3-hydroxy-2-oxoindolin-3-yl)acetonitrile (5-3i). White solid, 6h, 73% yield; mp 188 – 190 ^{o}C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.44 (s, 1H), 7.29 (d, *J* = 1.2 Hz, 1H), 7.09 (dd, *J* = 7.9, 1.6 Hz, 1H), 6.76 (d, *J* = 7.9 Hz, 1H), 6.55 (s, 1H), 3.02 (d, *J* = 16.4 Hz, 1H), 2.93 (d, *J* = 17.1 Hz, 1H), 2.53 (t, *J* = 7.6 Hz, 2H), 1.53 (br, 2H), 1.34 – 1.21 (m, 8H), 0.85 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 176.70, 139.26, 136.01, 129.76, 129.56, 124.04, 117.08, 109.74, 72.06, 34.82, 31.29, 31.25, 28.54, 26.13, 22.08, 13.95; MS (ESI) *m/z*: 309 ([M + Na]$^+$); HRMS (ESI): Exact mass calculated for $C_{17}H_{22}N_2O_2$ [M + Na]$^+$ 309.1579, found 309.1574.

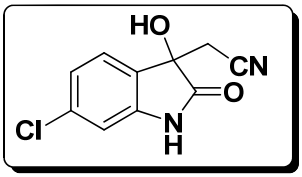


2-(4-chloro-3-hydroxy-2-oxoindolin-3-yl)acetonitrile (5-3j). White solid, 3h, 96% yield; mp 201 – 203 ^{o}C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.81 (s, 1H), 7.31 (t, *J* = 8.0 Hz, 1H), 7.03 (dd, *J* = 8.2, 0.5 Hz, 1H), 6.85 (dd, *J* = 7.8, 0.6 Hz, 1H), 6.75 (s, 1H), 3.30 (d, *J* = 16.4 Hz, 1H), 3.15 (d, *J* = 16.4 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 175.75, 143.92, 131.86, 130.48, 125.38, 122.82, 115.97, 109.11, 73.43, 23.53; MS (ESI) *m/z*: 245 ([M + Na]$^+$); HRMS (ESI): Exact mass calculated

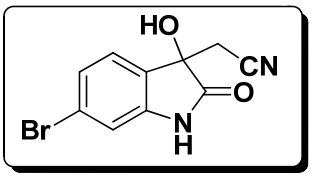
for $C_{10}H_7ClN_2O_2$ $[M + Na]^+$ 245.0094, found 245.0090.



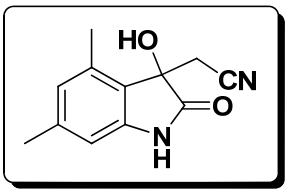
2-(4-bromo-3-hydroxy-2-oxoindolin-3-yl)acetonitrile (5-3k). White solid, 3h, 90% yield; mp 227 – 229 ^oC; ^1H NMR (500 MHz, DMSO-d_6): δ = 10.80 (s, 1H), 7.26 – 7.21 (m, 1H), 7.18 (dd, J = 8.1, 0.8 Hz, 1H), 6.89 (dd, J = 7.6, 0.8 Hz, 1H), 6.72 (s, 1H), 3.34 (d, J = 17.1 Hz, 1H), 3.13 (d, J = 17.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 175.80, 144.14, 132.04, 126.96, 125.88, 118.80, 115.88, 109.58, 74.03, 23.39; MS (ESI) *m/z*: 289 ($[M + Na]^+$); HRMS (ESI): Exact mass calculated for $C_{10}H_7BrN_2O_2$ $[M + Na]^+$ 288.9589, found 288.9582.



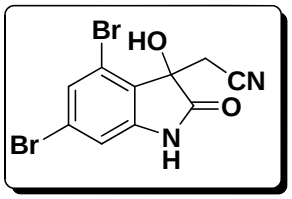
2-(6-chloro-3-hydroxy-2-oxoindolin-3-yl)acetonitrile (5-3l). White solid, 3h, 93% yield; mp 203 – 205 ^oC; ^1H NMR (500 MHz, DMSO-d_6): δ = 10.71 (s, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.11 (dd, J = 8.0, 1.9 Hz, 1H), 6.89 (d, J = 1.8 Hz, 1H), 6.69 (s, 1H), 3.07 (d, J = 16.4 Hz, 1H), 2.99 (d, J = 17.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 176.59, 143.16, 134.25, 128.66, 125.67, 121.75, 116.94, 110.13, 71.66, 25.84; MS (ESI) *m/z*: 245 ($[M + Na]^+$); HRMS (ESI): Exact mass calculated for $C_{10}H_7ClN_2O_2$ $[M + Na]^+$ 245.0094, found 245.0095.



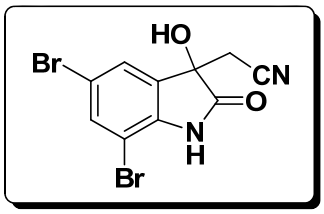
2-(6-bromo-3-hydroxy-2-oxoindolin-3-yl)acetonitrile (5-3m). White solid, 3h, 91% yield; mp 229 – 231 ^{o}C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.68 (s, 1H), 7.40 (d, J = 7.9 Hz, 1H), 7.25 (dd, J = 7.9, 1.7 Hz, 1H), 7.02 (d, J = 1.7 Hz, 1H), 6.68 (s, 1H), 3.06 (d, J = 16.4 Hz, 1H), 2.98 (d, J = 17.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 176.44, 143.26, 129.04, 125.96, 124.62, 122.61, 116.83, 112.86, 71.71, 25.77; MS (ESI) *m/z*: 289 ([M + Na]$^{+}$); HRMS (ESI): Exact mass calculated for $C_{10}H_7BrN_2O_2$ [M + Na]$^{+}$ 288.9589, found 288.9586.



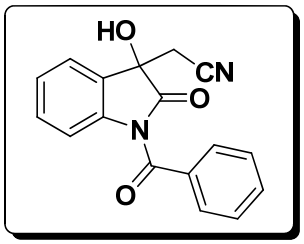
2-(3-hydroxy-4,6-dimethyl-2-oxoindolin-3-yl)acetonitrile (5-3n). White solid, 24h, 90% yield; mp 261 – 263 ^{o}C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.46 (s, 1H), 6.60 (s, 1H), 6.50 (s, 1H), 6.45 (s, 1H), 3.16 (d, J = 17.1 Hz, 1H), 3.03 (d, J = 16.4 Hz, 1H) 2.32 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 177.02, 141.99, 139.45, 135.41, 124.78, 123.76, 116.62, 108.35, 73.49, 24.83, 21.17, 16.90; MS (ESI) *m/z*: 239 ([M + Na]$^{+}$); HRMS (ESI): Exact mass calculated for $C_{12}H_{12}N_2O_2$ [M + Na]$^{+}$ 239.0796, found 239.0800.



2-(4,6-dibromo-3-hydroxy-2-oxoindolin-3-yl)acetonitrile (5-3o). White solid, 3h, 87% yield; mp 239 – 241 ^{o}C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.97 (s, 1H), 7.45 (d, J = 1.5 Hz, 1H), 7.05 (d, J = 1.5 Hz, 1H), 6.81 (s, 1H), 3.33 (d, J = 16.7 Hz, 1H), 3.14 (d, J = 16.7 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 175.77, 145.31, 127.65, 126.52, 123.69, 119.70, 115.81, 112.52, 73.81, 23.31; MS (ESI) *m/z*: 343 ([M – H]$^-$); HRMS (ESI): Exact mass calculated for $C_{10}H_6Br_2N_2O_2$ [M – H]$^-$ 342.8718, found 342.8716.

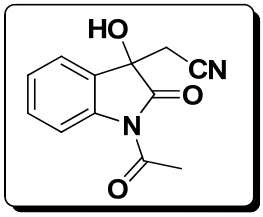


2-(5,7-dibromo-3-hydroxy-2-oxoindolin-3-yl)acetonitrile (5-3p). White solid, 3h, 85% yield; mp 246 – 248 ^{o}C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.04 (s, 1H), 7.76 (d, J = 1.8 Hz, 1H), 7.62 (d, J = 1.8 Hz, 1H), 6.87 (s, 1H), 3.18 – 3.04 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ = 176.07, 140.66, 134.49, 133.29, 126.20, 116.66, 114.06, 103.29, 72.76, 25.60; MS (ESI) *m/z*: 343 ([M – H]$^-$); HRMS (ESI): Exact mass calculated for $C_{10}H_6Br_2N_2O_2$ [M – H]$^-$ 342.8718, found 342.8713.

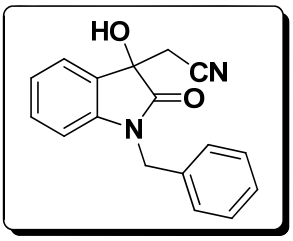


2-(1-benzoyl-3-hydroxy-2-oxoindolin-3-yl)acetonitrile (5-3q). White solid, 3h, 81% yield; mp 140 – 142 ^{o}C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.79 (dd, J = 11.7, 4.5 Hz, 3H), 7.68 (ddd, J = 9.5, 5.4, 1.0 Hz, 2H), 7.56 – 7.48 (m, 3H), 7.36 (t, J = 7.5 Hz,

1H), 7.02 (s, 1H), 3.33 (d, J = 16.4 Hz, 1H), 3.23 (d, J = 16.4 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 175.03, 168.59, 139.29, 133.77, 133.09, 130.31, 129.35, 129.23, 128.31, 125.27, 124.28, 116.82, 114.57, 71.89, 26.10; MS (ESI) *m/z*: 315 ([M + Na]$^+$); HRMS (ESI): Exact mass calculated for $C_{17}H_{12}N_2O_3$ [M + Na]$^+$ 315.0746, found 315.0742.

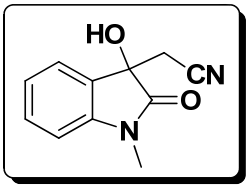


2-(1-acetyl-3-hydroxy-2-oxoindolin-3-yl)acetonitrile (5-3r). White solid, 3h, 80% yield; mp 131 – 133 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.23 (d, J = 8.2 Hz, 1H), 7.68 (dd, J = 7.6, 1.0 Hz, 1H), 7.48 (td, J = 8.1, 1.4 Hz, 1H), 7.33 (td, J = 7.6, 0.9 Hz, 1H), 3.49 (s, 1H), 3.06 (d, J = 16.4 Hz, 1H), 2.84 (d, J = 17.1 Hz, 1H), 2.63 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.72, 170.38, 139.42, 131.63, 126.44, 126.35, 123.87, 117.20, 114.61, 72.46, 27.82, 26.42; MS (ESI) *m/z*: 253 ([M + Na]$^+$); HRMS (ESI): Exact mass calculated for $C_{12}H_{10}N_2O_3$ [M + Na]$^+$ 253.0589, found 253.0580.

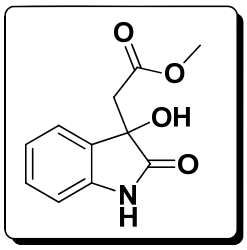


2-(1-benzyl-3-hydroxy-2-oxoindolin-3-yl)acetonitrile (5-3s). White solid, 3h, 95% yield; mp 152 – 154 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.65 (dd, J = 7.4, 0.7 Hz, 1H), 7.35 – 7.27 (m, 6H), 7.14 (td, J = 7.6, 0.8 Hz, 1H), 6.78 (d, J = 7.9 Hz, 1H), 4.96 (d, J = 15.1 Hz, 1H), 4.82 (d, J = 15.8 Hz, 1H), 4.00 (s, 1H), 3.12 (d, J = 17.1 Hz, 1H),

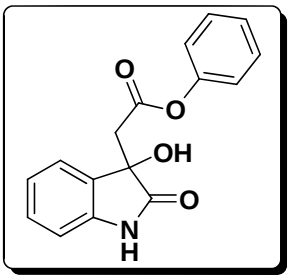
2.79 (d, J = 16.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.54, 142.00, 134.61, 130.92, 128.96, 127.99, 127.44, 127.21, 124.33, 123.99, 115.27, 110.20, 72.67, 44.17, 27.48; MS (ESI) *m/z*: 301 ([M + Na]$^+$); HRMS (ESI): Exact mass calculated for $C_{17}H_{14}N_2O_2$ [M + Na]$^+$ 301.0953, found 301.0955.



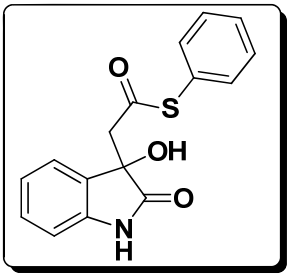
2-(3-hydroxy-1-methyl-2-oxoindolin-3-yl)acetonitrile (5-3t). White solid, 3h, 91% yield; mp 130 – 132 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.65 (d, J = 7.4 Hz, 1H), 7.42 (td, J = 7.8, 1.1 Hz, 1H), 7.21 – 7.15 (m, 1H), 6.91 (d, J = 7.8 Hz, 1H), 4.32 (s, 1H), 3.21 (s, 3H), 3.03 (d, J = 16.4 Hz, 1H), 2.70 (d, J = 17.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.52, 142.76, 130.93, 127.57, 124.25, 123.97, 115.37, 109.14, 72.60, 27.35, 26.55; MS (ESI) *m/z*: 225 ([M + Na]$^+$); HRMS (ESI): Exact mass calculated for $C_{11}H_{10}N_2O_2$ [M + Na]$^+$ 225.0640, found 225.0639.



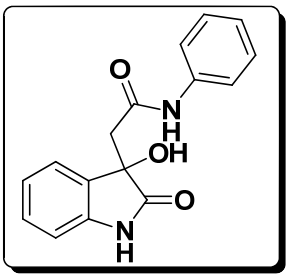
Methyl 2-(3-hydroxy-2-oxoindolin-3-yl)acetate (5-3u). White solid, 3h, 90% yield; mp 127 – 129 ^{o}C; ^{1}H NMR (500 MHz, DMSO-d_6) δ = 10.26 (s, 1H), 7.31 (d, J = 7.3 Hz, 1H), 7.22 – 7.16 (m, 1H), 6.93 (t, J = 7.5 Hz, 1H), 6.79 (d, J = 7.7 Hz, 1H), 6.10 (s, 1H), 3.39 (s, 3H), 3.01 (d, J = 15.8 Hz, 1H), 2.94 (d, J = 15.2 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 177.79, 169.10, 142.49, 130.84, 129.20, 124.00, 121.32, 109.46, 72.58, 51.12, 41.32; MS (ESI) *m/z*: 244 ([M + Na]$^+$); HRMS (ESI): Exact mass calculated for $C_{11}H_{11}NO_4$ [M + Na]$^+$ 244.0586, found 244.0586.



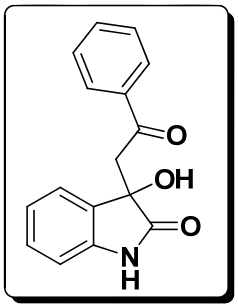
Phenyl 2-(3-hydroxy-2-oxoindolin-3-yl)acetate (5-3v). White solid, 24h, 92% yield; mp 133 – 135 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.61 (s, 1H), 7.38 (d, *J* = 7.3 Hz, 1H), 7.27 – 7.06 (m, 4H), 6.99 (td, *J* = 7.6, 0.9 Hz, 1H), 6.84 – 6.72 (m, 3H), 4.48 (s, 1H), 3.23 – 3.09 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 178.58, 168.54, 150.02, 140.81, 130.33, 129.40, 129.23, 126.12, 124.37, 123.24, 121.34, 110.80, 74.02, 41.61; MS (ESI) *m/z*: 306 ([M + Na]$^{+}$); HRMS (ESI): Exact mass calculated for $C_{16}H_{13}NO_4$ [M + Na]$^{+}$ 306.0742, found 306.0747.



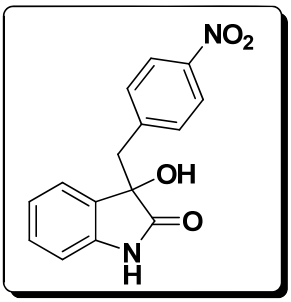
***S*-phenyl 2-(3-hydroxy-2-oxoindolin-3-yl)ethanethioate (5-3w).** White solid, 24h, 61% yield; mp 136 – 138 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.62 (s, 1H), 7.41 – 7.33 (m, 4H), 7.23 (td, *J* = 7.7, 1.2 Hz, 1H), 7.06 (td, *J* = 7.6, 0.8 Hz, 1H), 6.80 (d, *J* = 7.8 Hz, 1H), 4.47 (s, 1H), 3.35 (d, *J* = 15.8 Hz, 1H), 3.27 (d, *J* = 15.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 195.05, 178.18, 140.63, 134.38, 130.21, 129.74, 129.27, 128.99, 126.71, 124.49, 123.09, 110.78, 74.77, 49.32; MS (ESI) *m/z*: 322 ([M + Na]$^{+}$); HRMS (ESI): Exact mass calculated for $C_{16}H_{13}NO_3S$ [M + Na]$^{+}$ 322.0514, found 322.0509.



2-(3-hydroxy-2-oxoindolin-3-yl)-N-phenylacetamide (5-3x). White solid, 18h, 81% yield; mp 169 – 171 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.92 (s, 1H), 8.68 (s, 1H), 7.32 (d, *J* = 7.9 Hz, 2H), 7.24 (d, *J* = 7.3 Hz, 1H), 7.15 (t, *J* = 7.8 Hz, 2H), 7.04 – 6.98 (m, 2H), 6.86 (t, *J* = 7.5 Hz, 1H), 5.83 (br, 1H), 2.84 (d, *J* = 15.2 Hz, 1H), 2.68 (d, *J* = 15.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 179.09, 168.43, 140.23, 137.29, 129.98, 129.94, 128.86, 124.62, 124.19, 123.21, 120.50, 110.99, 74.81, 43.26; MS (ESI) *m/z*: 305 ([M + Na]$^{+}$); HRMS (ESI): Exact mass calculated for $C_{16}H_{14}N_2O_3$ [M + Na]$^{+}$ 305.0902, found 305.0903.



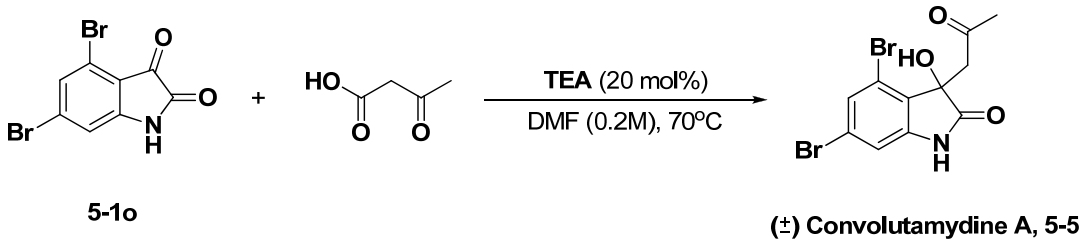
3-hydroxy-3-(2-oxo-2-phenylethyl)indolin-2-one (5-3y). White solid, 3h, 86% yield; mp 174 – 176 ^{o}C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.28 (s, 1H), 7.92 – 7.86 (m, 2H), 7.61 (d, *J* = 7.3 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 2H), 7.28 (d, *J* = 7.3 Hz, 1H), 7.16 (t, *J* = 7.6 Hz, 1H), 6.91 – 6.76 (m, 2H), 6.08 (s, 1H), 4.07 (d, *J* = 17.6 Hz, 1H), 3.59 (d, *J* = 17.6 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 196.51, 178.38, 142.98, 136.15, 133.45, 131.78, 128.95, 128.75, 127.92, 123.61, 121.16, 109.44, 73.02, 45.77; MS (ESI) *m/z*: 290 ([M + Na]$^{+}$); HRMS (ESI): Exact mass calculated for $C_{16}H_{13}NO_3$ [M + Na]$^{+}$ 290.0793, found 290.0797.



3-hydroxy-3-(4-nitrobenzyl)indolin-2-one (3z). White solid, 3h, 95% yield; mp 226 – 228 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.15 (s, 1H), 8.00 (d, J = 8.5 Hz, 2H), 7.22 (d, J = 8.5 Hz, 2H), 7.13 (t, J = 7.6 Hz, 1H), 7.05 (d, J = 7.3 Hz, 1H), 6.91 (t, J = 7.5 Hz, 1H), 6.65 (d, J = 7.7 Hz, 1H), 6.27 (s, 1H), 3.30 (d, J = 12.6 Hz, 1H), 3.11 (d, J = 12.7 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 178.35, 146.23, 143.56, 141.42, 131.46, 130.42, 129.10, 124.55, 122.47, 121.37, 109.47, 76.13, 42.98; MS (ESI) *m/z*: 283 ([M – H]$^-$); HRMS (ESI): Exact mass calculated for $C_{15}H_{12}N_2O_4$ [M – H]$^-$ 283.0719, found 283.0719.

5.4.4 Methodology Application: Synthesis of Natural Products

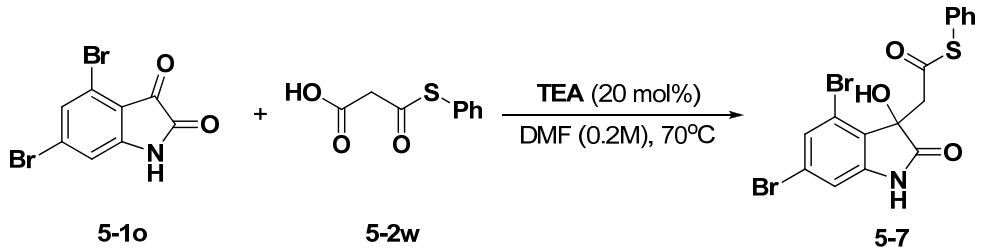
Synthesis of (±) Convolutamydine **A**



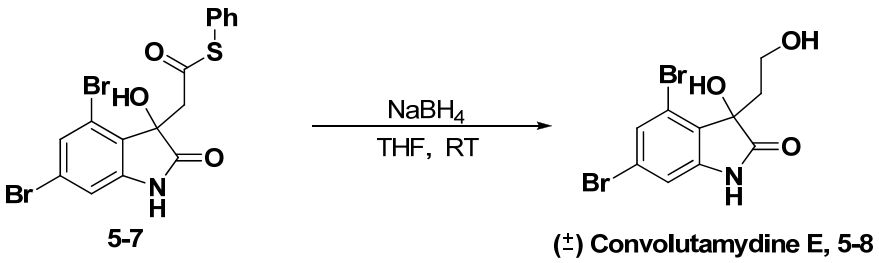
To a solution of 4,6-dibromoisatin **5-1o** (30.5 mg, 0.10 mmol) in 0.5 mL DMF was added acetoacetic acid (11.2 mg, 0.11 mmol) at room temperature, followed by adding catalyst **5-I** TEA (2.8 µl, 0.02 mmol). The mixture was stirred at 70 °C for 3 hours. The crude product was purified by column chromatography on silica gel, eluted by hexane/EtOAc = 2:1 to afford 32.1 mg (88% yield) of the desired product (±) Convolutamydine **A 5-5** as white solid. mp 212 – 214 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.60 (s, 1H), 7.27 (d, J = 1.6 Hz, 1H), 6.95 (d, J = 1.6 Hz, 1H), 6.20

(s, 1H), 3.73 (d, J = 17.6 Hz, 1H), 3.16 (d, J = 17.6 Hz, 1H), 2.03 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 205.16, 177.23, 146.35, 128.70, 126.69, 122.32, 118.93, 111.77, 73.68, 48.27, 29.93; MS (ESI) *m/z*: 384 ([M + Na]$^+$); HRMS (ESI): Exact mass calculated for $C_{11}H_9Br_2NO_3$ [M + Na]$^+$ 383.8847, found 383.8838.

Synthesis of (±) Convolutamydine **E**



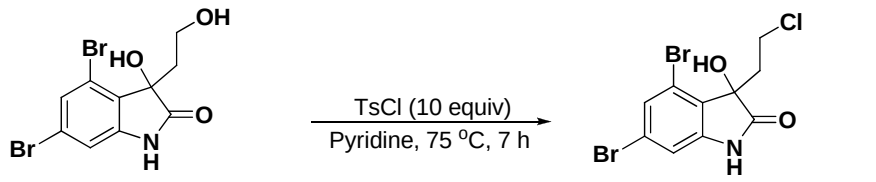
To a solution of 4,6-dibromoisatin **5-1o** (100.6 mg, 0.33 mmol) in 1.65 mL DMF was added malonic acid half thioester **5-2w** (71.2 mg, 0.36 mmol) at room temperature, followed by adding catalyst **5-I** TEA (9.2 µl, 0.066 mmol). The mixture was stirred at 70 °C for 3 hours. The crude product was purified by column chromatography on silica gel, eluted by hexane/EtOAc = 2:1 to afford 130.7 mg (85% yield) of the desired product **5-7** as white solid. mp 226 – 228 °C; ^{1}H NMR (300 MHz, Acetone-d_6): δ = 9.69 (s, 1H), 7.42 – 7.36 (m, 3H), 7.34 (d, J = 1.6 Hz, 1H), 7.29 – 7.23 (m, 2H), 7.07 (d, J = 1.6 Hz, 1H), 5.54 (s, 1H), 4.06 (d, J = 15.8 Hz, 1H), 3.49 (d, J = 15.8 Hz, 1H); ^{13}C NMR (75 MHz, Acetone-d_6): δ = 194.00, 177.73, 147.54, 135.89, 131.06, 130.73, 129.18, 128.92, 128.71, 124.82, 121.49, 113.92, 76.17, 49.62; MS (ESI) *m/z*: 454 ([M – H]$^-$); HRMS (ESI): Exact mass calculated for $C_{16}H_{11}Br_2NO_3S$ [M – H]$^-$ 453.8748, found 453.8749.



To a solution of **5-7** (45.7 mg, 0.1 mmol) in THF (0.5 ml) was added $NaBH_4$

(18.9 mg, 0.5 mmol) at 0 ℃. The reaction mixture was stirred for additional 30 min at RT, before it was quenched with aqueous HCl solution. The mixture was extracted with ethyl acetate. The combined organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (50% ethyl acetate in hexane) on silica gel to afford 28.3 mg (81% yield) (±) Convolutamydine **E 5-8** as white solid. mp 211 – 213 °C; ^{1}H NMR (500 MHz, Acetone-d_6) δ = 9.54 (s, 1H), 7.32 (d, J = 1.6 Hz, 1H), 7.06 (d, J = 1.6 Hz, 1H), 5.22 (s, 1H), 3.67 (s, 1H), 3.51 – 3.49 (m, 2H), 2.45 (t, J = 6.7 Hz, 2H); ^{13}C NMR (75 MHz, Acetone-d_6) δ = 179.53, 146.96, 130.31, 129.24, 124.18, 121.51, 113.77, 77.98, 58.80, 39.10; MS (ESI) *m/z*: 348 ([M – H]$^-$); HRMS (ESI): Exact mass calculated for $C_{10}H_9Br_2NO_3$ [M – H]$^-$ 347.8871, found 347.8868.

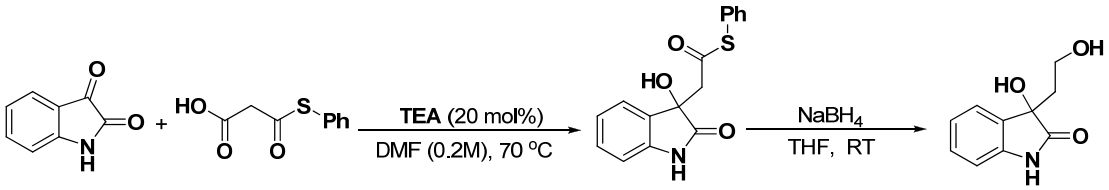
Synthesis of (±) Convolutamydine **B**[169]



(±) Convolutamydine E, 5-8 **(±) Convolutamydine B, 5-9**

Chem. Eur. J. **2009**, *15*, 6790

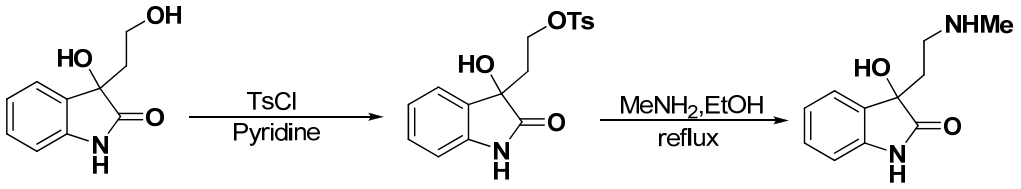
Synthesis of Donaxaridine[170]



5-1a **5-2w** **5-3w** **5-10**

To a solution of **5-3w** (59.5 mg, 0.2 mmol) in THF (1.0 mL) was added $NaBH_4$ (37.8 mg, 1.0 mmol) at 0 ℃. The reaction mixture was stirred for additional 30 min at RT, before it was quenched with aqueous HCl solution. The mixture was extracted

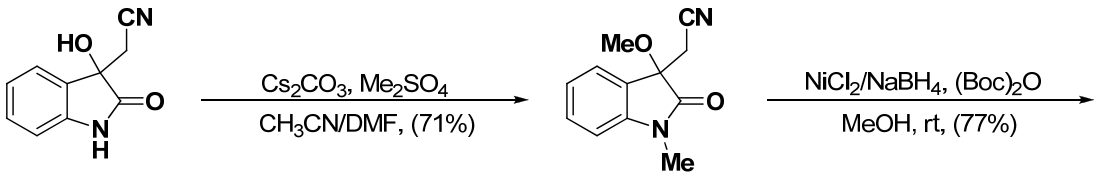
with ethyl acetate. The combined organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (60% ethyl acetate in hexane) on silica gel to afford 25.2 mg of **5-10** (65% yield) as white solid. mp 146 – 148 ^oC; ^1H NMR (500 MHz, Acetone-d_6): δ = 9.16 (s, 1H), 7.24 (d, J = 7.4 Hz, 1H), 7.11 (td, J = 7.7, 1.2 Hz, 1H), 6.90 (td, J = 7.5, 0.9 Hz, 1H), 6.77 (d, J = 7.7 Hz, 1H), 5.00 (s, 1H), 3.68 (s, 1H), 3.58 (s, 2H), 2.00 – 1.89 (m, 2H); ^{13}C NMR (125 MHz, Acetone-d_6): δ = 180.73, 143.07, 133.67, 130.60, 125.61, 123.46, 111.22, 76.76, 58.94, 41.79; MS (ESI) *m/z*: 192 ([M – H]$^-$); HRMS (ESI): Exact mass calculated for $C_{10}H_{11}NO_3$ [M – H]$^-$ 192.0661, found 192.0664.



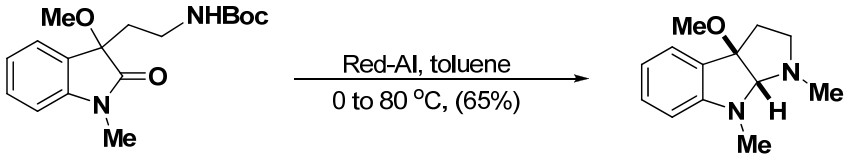
5-10 **Donaxaridine 5-11**

J. Nat. Prod. **1997**, *60*, 1152

Synthesis of (±) CPC-1 **5-14**[168]



5-3a **5-12**



5-13 **(±) CPC-1 5-14**

A solution of **5-3a** (0.752 g, 4.0 mmol) in CH_3CN/DMF (2:1, 30.0 mL) was

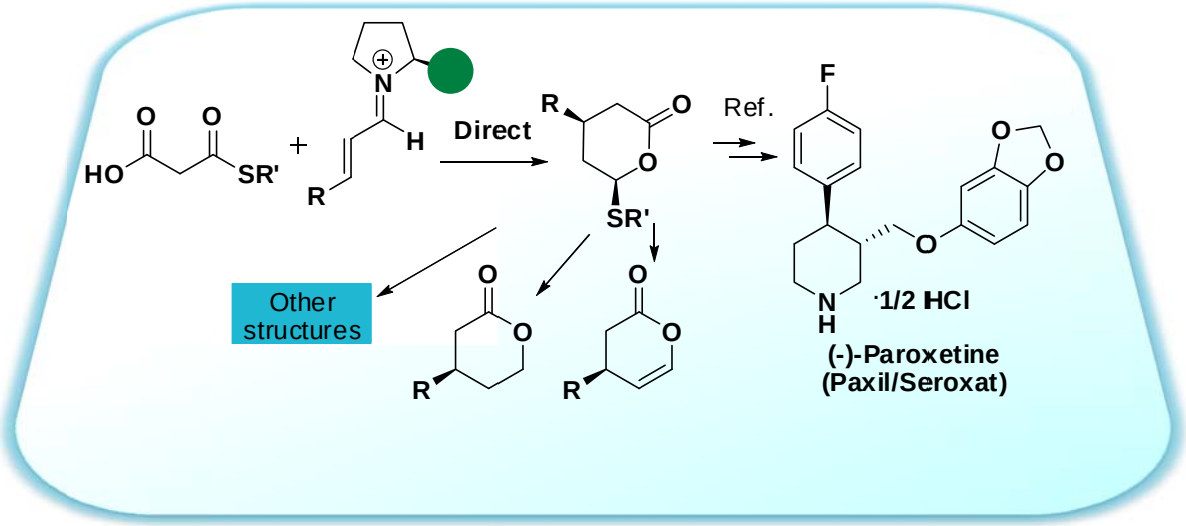
cooled to 0 °C and Cs_2CO_3 (4.56 g, 14.0 mmol) was added followed by Me_2SO_4 (1.33 ml, 14.0 mmol). The reaction was stirred for 1.5 h at 0 °C (monitored by TLC) before filtering over celite (washings by EtOAc). The crude product was purified by column chromatography (40% ethyl acetate in hexane) to provide **5-12** as a yellow oil (617 mg, 71%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.59 (d, *J* = 7.5 Hz, 1H), 7.44 (td, *J* = 7.8, 1.2 Hz, 1H), 7.23 – 7.18 (m, 1H), 6.92 (d, *J* = 7.9 Hz, 1H), 3.25 (s, 3H), 3.10 – 3.04 (m, 4H), 2.67 (d, *J* = 16.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.14, 143.75, 131.20, 124.81, 124.11, 123.78, 115.30, 108.96, 78.17, 53.39, 26.64, 26.42; MS (ESI) *m/z*: 239 ([M + Na]$^+$); HRMS (ESI): Exact mass calculated for $C_{12}H_{12}N_2O_2$ [M + Na]$^+$ 239.0796, found 239.0796.

A solution of **5-12** (0.216 g, 1.0 mmol), $(Boc)_2O$ (0.436 g, 2.0 mmol), and $NiCl_2$ (25 mg, 0.2 mmol) in MeOH (25 mL) was cooled to 0 °C and $NaBH_4$ (257 mg, 7.0 mmol) was added in portions. The reaction was stirred for 4 hours at room temperature and then quenched with water and filtered over celite (washings with EtOAc). The crude product was purified by column chromatography (40% ethyl acetate in hexanes) to provide **5-13** as a white solid (245 mg, 77%). mp 100 – 102 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35 (t, *J* = 7.7 Hz, 1H), 7.31 (d, *J* = 7.3 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 6.85 (d, *J* = 7.8 Hz, 1H), 4.91 (s, 1H), 3.25 (m, 2H), 3.21 (s, 3H), 3.00 (s, 3H), 2.07 (t, *J* = 6.8 Hz, 2H), 1.41 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 175.80, 155.76, 143.69, 130.00, 126.80, 124.37, 123.17, 108.50, 81.87, 79.00, 52.92, 37.33, 35.45, 28.40, 26.13; MS (ESI) *m/z*: 343 ([M + Na]$^+$); HRMS (ESI): Exact mass calculated for $C_{17}H_{24}N_2O_4$ [M + Na]$^+$ 343.1634, found 343.1615.

A solution of **5-13** (32.0 mg, 0.1 mmol) was cooled to 0 °C and Red-Al® (289 uL, 70 w% in toluene, 1.0 mmol) was added. The reaction was stirred at room temperature for 30 minutes and then heated at 80 °C overnight. Reaction was then cooled, quenched with water, and the suspension obtained was filtered through celite (washings with EtOAc). The crude product obtained was purified by column chromatography to provide **5-14** as a colorless oil (11.2 mg, 51%). ^{1}H NMR (500

MHz, $CDCl_3$): δ = 7.20 (t, *J* = 7.7 Hz, 1H), 7.15 (d, *J* = 7.3 Hz, 1H), 6.75 (t, *J* = 7.3 Hz, 1H), 6.51 (d, *J* = 8.0 Hz, 1H), 4.36 (s, 1H), 3.04 (s, 3H), 2.97 (s, 3H), 2.82 – 2.78 (m, 1H), 2.64 – 2.59 (m, 1H), 2.58 (s, 3H), 2.38 – 2.32 (m, 1H), 2.16 – 2.11 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 153.15, 129.74, 128.04, 124.08, 117.92, 107.80, 94.06, 91.73, 52.49, 52.43, 39.37, 38.67, 36.27; MS (ESI) *m/z*: 219 ($[M + H]^+$); HRMS (ESI): Exact mass calculated for $C_{13}H_{19}N_2O$ $[M + H]^+$ 219.1497, found 219.1496.

Chapter 6 Enantioselective Decarboxylation of α,β-Unsaturated Carbonyls and Malonic Half-thioesters: Rapid Access to Chiral δ-Lactones



Chiral saturated δ-lactones, ubiquitous bioactive o-heterocycles in nature, are readily prepared via a direct enantioselective decarboxylation of α,β-unsaturated carbonyls and malonic half-thioesters.

6.1 Introduction

The assembly of *O*-heterocycles is an important field of research due to their prevalence in natural products and drugs.[171] Of the *O*-heterocycles, δ-lactones are well-known six-membered oxygen-containing heterocycles that form the structural scaffolds of many biologically active molecules,[172] hence, they are broadly used in medicinal chemistry as important structural elements. Notably, a large number of δ-lactones involved biologically active important molecules exist as a single enantiomer.[172,173] As exemplified in Figure 6.1, Lovastatin[174] **6-a** marketed by Merck under the trade name Mevacor, is a member of the drug class of statins, used in the treatment of dyslipidemia and the prevention of cardiovascular disease. Artemisitene[175] **6-b**, isolated from *Artemisia annua* L., has been shown to possess antimalarial activity. Crassin acetate[176] **6-c**, a lactonic cembrane diterpene, has been shown to be the principal antineoplastic agent present in the marine invertebrates. Leiodermatolide[177] **6-d** is a structurally unique macrolide isolated from the deep-water marine sponge *Leiodermatium* sp. which exhibits potent antiproliferative activity against a range of human cancer cell lines and drastic effects on spindle formation in mitotic cells.

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[171] For selected books, see: a) Collett, L. A.; Davis-Coleman, M. T.; Rivett, D. E. A. In *Progress in the Chemistry of Organic Natural Products*, Springer-Verlag, New York, **1998**; b) Francke, W.; Schultz, S. *Comprehensive Natural Products Chemistry*, Elsevier, Amsterdam, **1999**; c) see *Ref.* 110b; d) Dewick, P. M. *Medicinal Natural Products*, Wiley-VCH, Weinheim, **2009**.

[172] For reviews, see: a) Collins, I. *J. Chem. Soc. Perkin Trans. 1* **1999**, 1377; b) Mondon, M.; Gesson, J. P. *Curr. Org. Synth.* **2006**, *3*, 41; c) Boucard, V.; Broustal, G.; Campagne, J. M. *Eur. J. Org. Chem.* **2007**, 225; d) Florence, G. J.; Gardner, N. M.; Paterson, I. *Nat. Prod. Rep.* **2008**, *25*, 342; e) Chiu, P.; Leung, L. T.; Ko, C. B. B. *Nat. Prod. Rep.* **2010**, *27*, 1066.

[173] For selected recent reports, see: a) Connolly, J. D.; Hill, R. A. *Dictionary of Terpenoids, Vol. 1,* Chapman and Hall, London, **1991**; b) Istvan, E. S.; Deisenhofer, J. *Science*, **2001**, *292*, 1160; c) Shaw, S. J.; Sundermann, K. F.; Burlingame, M. A.; Myles, D. C.; Freeze, B. S.; Xian, M.; Brouard, I.; Smith, A. B., III *J. Am. Chem. Soc.* **2005**, *127*, 6532; d) You, Z. W.; Jiang, Z. X.; Wang, B. L.; Qing, F. L. *J. Org. Chem.* **2006**, *71*, 7261; e) Bonazzi, S.; Güttinger, S.; Zemp, I.; Kutay, U.; Gardemann, K. *Angew. Chem. Int. Ed.* **2007**, *46*, 8707; f) Giaralli, L.; Bassetti, M.; Pasquini, C. *J. Org. Chem.* **2007**, *72*, 6067; g) Esteban, J.; Costa, A. M.; Gómez, A.; Vilarrasa, J. *Org. Lett.* **2008**, *10*, 65; h) Fukui, H.; Shiina, I. *Org. Lett.* **2008**, *10*, 3153; i) Prasad, K. R.; Gholap, S. L. *J. Org. Chem.* **2008**, *73*, 2; j) Maauer, T.; Martin, H. J.; Mulzer, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 6032; k) Exner, C. J.; Laclef, S.; Poli, F.; Turks, M.; Vogel, P. *J. Org. Chem.* **2011**, *76*, 8707.

[174] Gunde-Cimerman, N.; Cimerman, A. *Exp Mycol.* **1995**, *19*, 1.

[175] a) Ekthawathchai, S.; Kamchonwongpaisan, S.; Kongsaeree, P.; Tarnchompoo, B.; Thebtaranonth, Y.; Yuthavong, Y. *J. Med. Chem.* **2001**, *44*, 4688; b) Avery, M. A.; Alvim-Gaston, M.; Vroman, J. A.; Wu, B.; Ager, A.; Peters, W.; Robinson, B. L.; Charman, W. *J. Med. Chem.* **2002**, *45*, 4321.

[176] a) Weinheimer, A. J.; Chang, C. W. J.; Matson, J. A. *Fortschr. Chem. Org. Naturst.* **1979**, *36*, 285; b) McMurry, J. E.; Dushin, R. G. *J. Am. Chem. Soc.* **1990**, *112*, 6942.

[177] Paterson, I.; Dalby, S. M.; Roberts, J. C.; Naylor, G. J.; Guzmán, E. A.; Isbrucker, R.; Pitts, T. P.; Linley, P.; Divlianska, D.; Reed, J. K.; Wright, A. E. *Angew. Chem. Int. Ed.* **2011**, *50*, 3219.

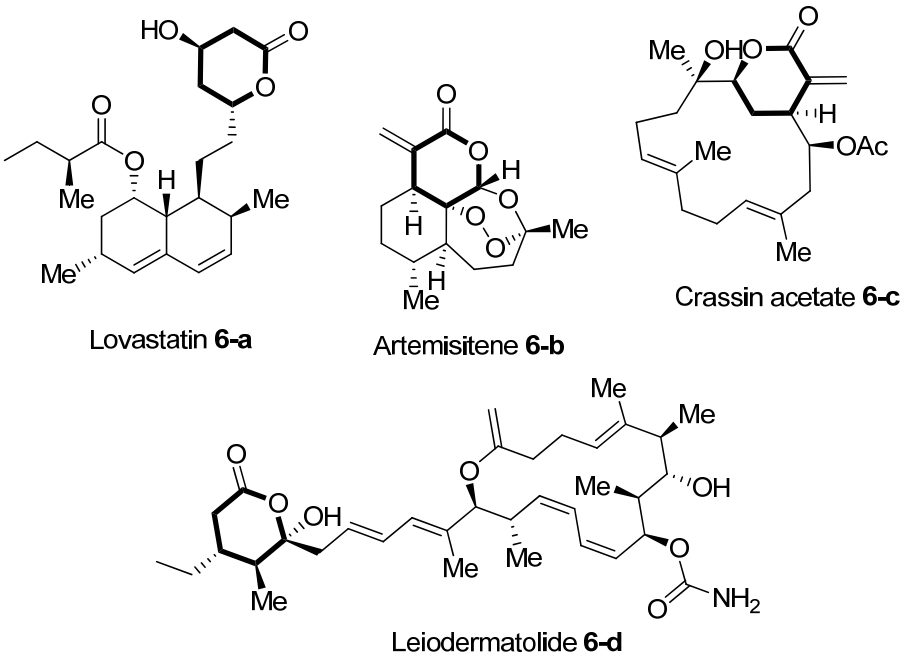

Figure 6.1 Examples of natural products or drugs containing δ-lactone moiety.

Especially, pharmaceuticals are figuring large in human health due to their chirality. Most beneficial drugs are sold as a single enantiomeric form because of the higher efficiency than its mirror image enantiomer and displaying better fit to its receptor. In addition, the other enantiomer may even cause harmful results.[178] Given the fact that within a chiral surrounding two enantiomers often show distinct biological activity, the development of effective protocols to access optical pure δ-lactones would be extremely desirable for further studies of the correlation between the chirality of these compounds and their propensities for biological activities to seek more potent and/or appropriate pharmaceutical candidates. Building enantiopure complex molecules simply, in a minimum number of operations, and in environmentally benign approach is one of the greatest challenges for synthetic chemistry, and particularly, for the industrial application of an laboratory-scale

[178] a) O'Reilly, R. A. *N. Engl. J. Med.* **1976**, *295*, 354; b) Wingard, L. B.; O'Reilly, R. A.; Levy, G. *Clic. Pharmacol. Ther.* **1978**, *23*, 212; c) Rang, H. P.; Dale, M. M.; Ritter, J. M.; Gardner, P. *Pharmacology, 4th ed. Churchill Livingston. Philadephia.* **2001**.

reaction (functional group/H_2O tolerance, simple procedures, no extreme temperatures),[179] cascade organocatalysis has recently appeared as a method of choice to fulfil this ideal goal of reaction efficiency.[179] In our continuing efforts toward the development of new approaches for the stereoselective construction of enantiopure synthetically useful building blocks,[180] we thought about expanding the scope of organocatalytic decarboxylative reactions[181, 182] to α,β-unsaturated aldehydes[183]. Although many methods have been reported on chiral δ-lactone synthesis, most of them were prepared for the assembly of α,β- or γ,δ-unsaturated δ-lactones.[184,185] Herein, we disclose a direct and efficient enantioselective strategy for functionalized and saturated δ-lactone synthesis (Scheme 6.1).

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[179] For recent reviews and selected examples on organocatalysis, see: a) List, B.; Yang, J.-W. *Science* **2006**, *313,* 1584; b) see *Ref.* 2e; c) see *Ref.* 2d *(special issue on organocatalysis)*; d) MacMillan, D. W. C. *Nature* **2008**, *455,* 304; e) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem. Int. Ed.* **2008**, *47,* 6138; f) see *Ref.* 2h; g) see *Ref.* 2j; h) Moyano, A.; Rios, R. *Chem. Rev.* **2011**, *111,* 4703; i) Vaxelaire, C.; Winter, P.; Christmann, M. *Angew. Chem. Int. Ed.* **2011**, *50,* 3605; j) see *Ref.* 2k; k) Jensen, K. L.; Dickmeiss, G.; Jiang, H.; Albrecht, Ł.; Jørgensen, K. A. *Acc. Chem. Res.* **2012**, *45,* 248; For an interesting recent highlight on the necessary factors for the application of an academic reaction to industry, see: l) Cooper, T. W. J.; Campbell, I. B.; MacDonald, S. J. F. *Angew. Chem. Int. Ed.* **2010**, *49,* 8082.

[180] a) see *Ref.* 140a; b) see *Ref.* 140b; c) see *Ref.* 125; d) Ren, Q.; Siau, W.-Y.; Du, Z.; Zhang, K.; Wang, J. *Chem. –Eur. J.* **2011**, *17*, 7781; e) see *Ref.* 40; f) see *Ref.* 140c; g) Tan, H. R.; Ng, H. F.; Chang, J.; Wang, J. *Chem. –Eur. J.* **2012**, *18*, 3865; h) Siau, W.-Y.; Li, W.-J.; Xue, F.; Ren, Q.; Wu, M.-H.; Sun, S.-F.; Guo, H.-B.; Jiang, X.-F.; Wang, J. *Chem. –Eur. J.* **2012**, *18*, 9491; i) Li, W.-J.; Liu, H.; Jiang, X. F.; Wang, J. *ACS Catal.* **2012**, *2*, 1535.

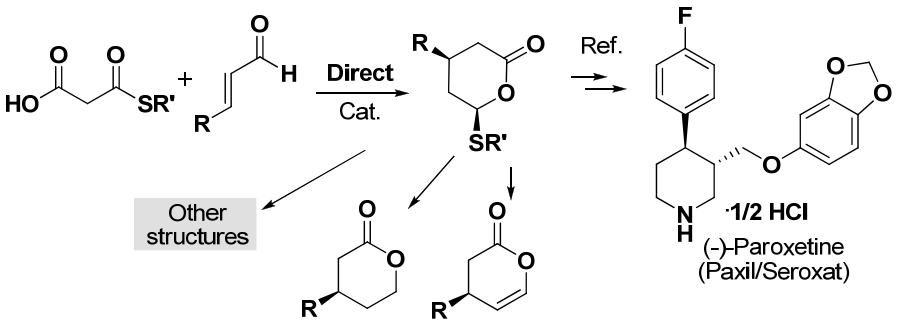
[181] For examples of decarboxylative reactions, see: a) see *Ref.* 87; b) see *Ref.* 88a; c) see *Ref.* 89; d) see *Ref.* 88b; e) see *Ref.* 88c.

[182] For selected examples of enantioselective decarboxylative reactions, see: a) see *Ref.* 90; b) see *Ref.* 96d; c) see *Ref.* 91; d) see *Ref.* 92; e) see *Ref.* 97a; f) see *Ref.* 98a; g) see *Ref.* 97b; h) Zheng, Y.; Xiong, H.; Nie, J.; Hua, M.; Ma, J. *Chem. Commun.* **2012**, *48*, 4308; i) Hara, N.; Nakamura, S.; Sano, M.; Tamura, R.; Funahashi, Y.; Shibata, N. *Chem. –Eur. J.* **2012**, *18*, 9276; j) see *Ref.* 98c;. k) Yuan, H. A.; Wang, S.; Nie, J.; Meng, W.; Yao, Q. W.; Ma, J. A. *Angew. Chem. Int. Ed.* **2013**, *52,* 3869.

[183] To the best of our knowledge, there is no enantioselective decarboxylative reaction of α,β-unsaturated carbonyls and half-thioesters catalyzed by second amine.

[184] For selected examples of α,β- or γ,δ-unsaturated δ-lactone synthesis, see: a) Du, H.; Zhao, D.; Ding, K. *Chem. –Eur. J.* **2004**, *10*, 5964; b) Oisaki, K.; Zhao, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 7439; c) Tiseni, P. S.; Peters, R. *Angew. Chem. Int. Ed.* **2007**, *46*, 5325; d) Tozawa, T.; Nagao, H.; Yamane, Y.; Mukaiyama, T. *Chem. Asian. J.* **2007**, *2*, 123; e) Tiseni, P. S.; Peters, R. *Org. Lett.* **2008**, *10*, 2019; f) Lin, L.; Chen, Z.; Yang, X.; Liu, X.; Feng, X. *Org. Lett.* **2008**, *10*, 1311; g) Ryan, S. J.; Candish, L.; Lupton, D. W. *J. Am. Chem. Soc.* **2009**, *131*, 14176; h) You, G. Q; Dai, L.-X.; You, S.-L. *Org. Lett.* **2009**, *11*, 1623; i) Tiseni, P. S.; Peters, R. *Chem. –Eur. J.* **2010**, *16*, 2503; j) Belmessieri, D.; Morrill, L. C.; Simal, C.; Slawin, A. M. Z.; Smith, A. D. *J. Am. Chem. Soc.* **2011**, *133*, 2714; k) Lin, L.; Kuang, Y. L.; Liu, X. H.; Feng, X. M. *Org. Lett.* **2011**, *15*, 3868; l) Mo, J. M.; Chen, X. K.; Chi, Y. G. *J. Am. Chem. Soc.* **2012**, *134*, 8810; m) Mahatthananchai, J.; Kaeobamrung, J.; Bode, J. W. *ACS Catal.* **2012**, *2*, 494.

[185] For examples of enantioselective synthesis of saturated δ-lactones, see: a) Brandau, S.; Landa, A.; Franzén, J.; Marigo, M.; Jøgensen, K. A. *Angew. Chem.* **2006**, *118*, 4411; *Angew. Chem., Int. Ed.* **2006**, *45*, 4305; b) Moran, J.; Smith, A. G.; Carris, R. M.; Johnson, J. S.; Krische, M. J. *J. Am. Chem. Soc.* **2011**, *131*, 18618; c) Peed, J.; Domínguez, I. P.; Davis, I. R.; Cheeseman, M.; Taylor, J. E.; Kociok-Köhn, G.; Bull, S. D. *Org. Lett.* **2011**, *13*, 3592; d) Albrecht, A.; Morana, F.; Fraile, A.; Jøgensen, K. A. *Chem. –Eur. J.* **2012**, *18*, 10348; e) Murai, K.; Nakamura, A.; Matsushita, T.; Shimura, M.; Fujioka, H. *Chem. –Eur. J.* **2012**, *18*, 8448; f) Jiang, X. J.; Tan, C. K.; Zhou, L.; Yeung, Y. Y. *Angew. Chem. Int. Ed.* **2012**, *51*, 7771; g) Dobish, M. C.; Johnston, J. N. *J. Am. Chem. Soc.* **2012**, *134*, 6068.



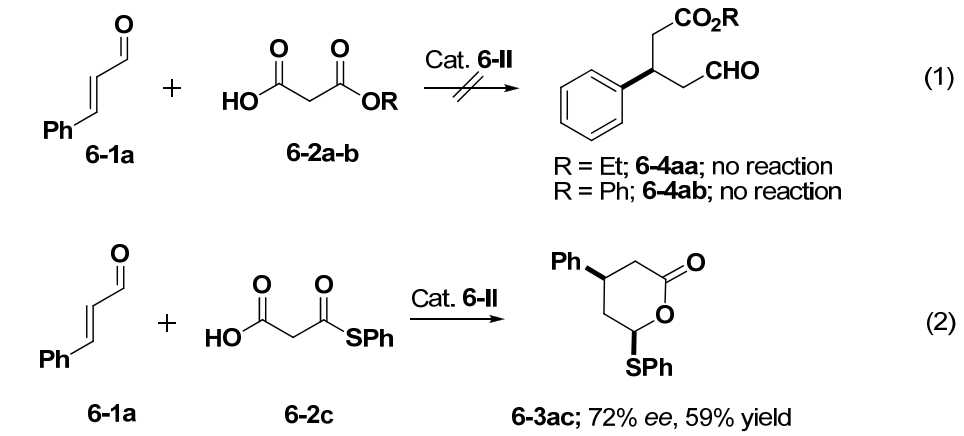
Scheme 6.1 Efficient synthesis of chiral δ-lactones.

6.2 Results and Discussion

6.2.1 Reaction Optimization for Decarboxylation of MAHTs and Enals

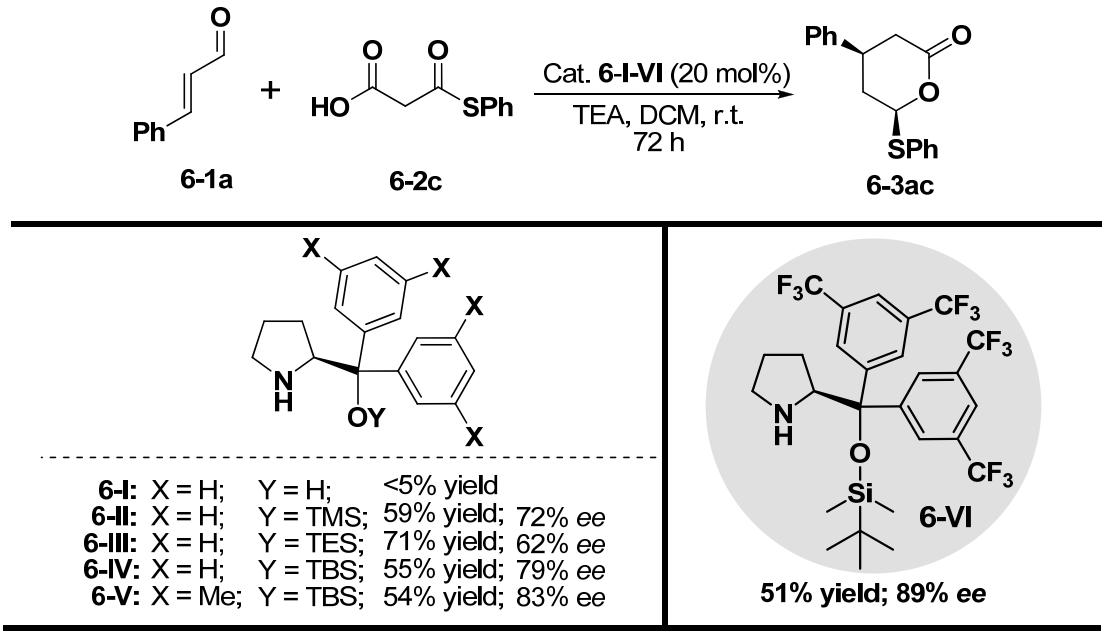
During our initial studies on the use of malonic acid mono-protected esters (**6-2a–c**, Scheme 6.2) in amino-catalyzed intermolecular reactions with cinnamaldehyde **6-1a** we have observed no reaction for malonic monoesters (**6-2a–b)**. However, in the context of exploring an efficient and enantioselective catalytic process we observed that when a malonic half-thioester (**6-2c)** and a TMS-protected prolinol catalyst **6-II** (Table 6.1) were employed for the combination of cinnamaldehyde (**6-1a)** and malonic half-thioester (**6-2c)**, the product δ-lactone (**6-3ac**) was obtained (72% *ee*, 59% yield). Further screening of catalysts revealed that increasing the bulk of the silyl ether moiety of catalysts (Cat. **6-I-VI**) led to improved enantiocontrol of the reaction. As shown in Table 6.1, *tert*-butyldimethylsilane ether **6-VI** (TBDMS) gave the best result (89% *ee*, 51% yield).

Scheme 6.2 Initial experiments.[a]



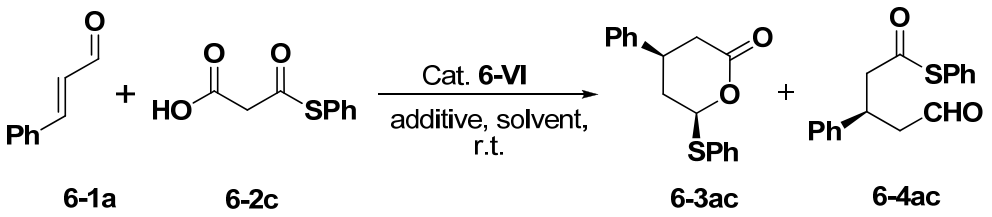
[a] Reaction conditions: **6-1a** (0.20 mmol), **6-2** (0.24 mmol), TEA (0.20 mmol), DCM (1.0 mL), 72 h, room temperature.

Table 6.1 Screened catalysts.[a]



[a] Reaction condition: **6-1a** (0.20 mmol), **6-2c** (0.24 mmol), TEA (1.0 equiv.), Cat. **6-I-VI** (20 mol%), DCM (1.0 mL), 72 h, room temperature.

Table 6.2 Optimization of other reaction parameters.[a]



Entry	Additive	Solvent	**6-3ac** [%][b]	**6-3ac** *ee* [%][c]
1	TEA	DCM	51	89
2	Na_2CO_3	DCM	22(**6-4ac**)	18
3	TBD[g]	DCM	37	78
4	TEA	Toluene	53	81
5	TEA	THF	47	84
6	TEA	IPA[f]	47	89
7[d]	TEA	DCM	57	89
8[d,e]	TEA	DCM	82	92

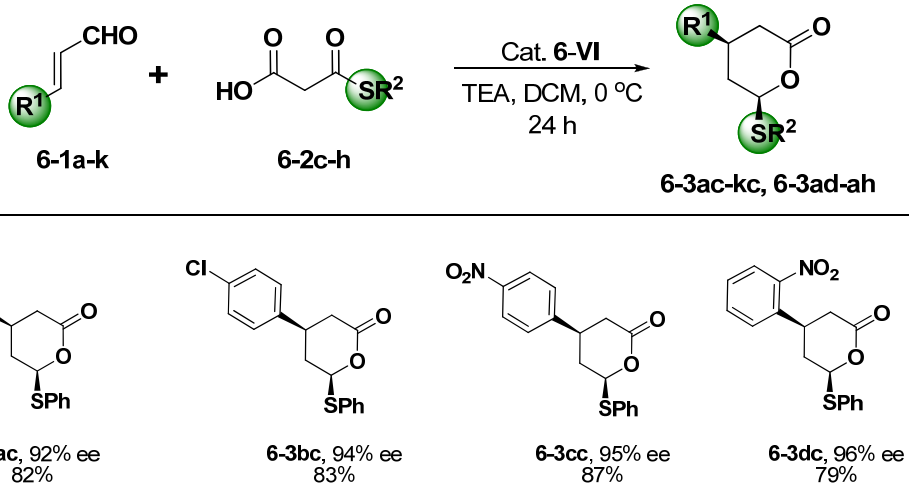
[a] Reactions were performed with **6-1a** (0.20 mmol), **6-2c** (0.24 mmol), additive (0.20 mmol) in the solvent (1.0 mL). [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] **6-2c** (0.50 mmol), TEA (0.50 mmol). [e] TEA dissolved in 0.50 mL of DCM was added dropwise in 10 min, 0 °C. [f] Isopropanol. [g] 1,5,7-Triazabicyclo[4.4.0]dec-5-ene.

Subsequent solvent survey (Table 6.2, entries 1 and 4–6) indicated that the use of DCM resulted in pronounced increase in enantioselectivity (81–89% *ee*). Further screening other additives applied (*e.g.* bases) did not lead to an improvement of the results (Table 6.2, entries 2–3). It was noteworthy that Na_2CO_3 caused the major formation of acyclic 3-phenyl 1-aldehyde 5-thioester **6-4ac**. Occasionally, we disclosed that dropwise addition of additive TEA in a limited amount of solvent can further improve the enantiocontrol and chemical yield (92% *ee*, 82% yield). Controlled experiment indicated that one-pot addition of TEA caused a rapid decomposition of malonic half-thioester **6-2c**.

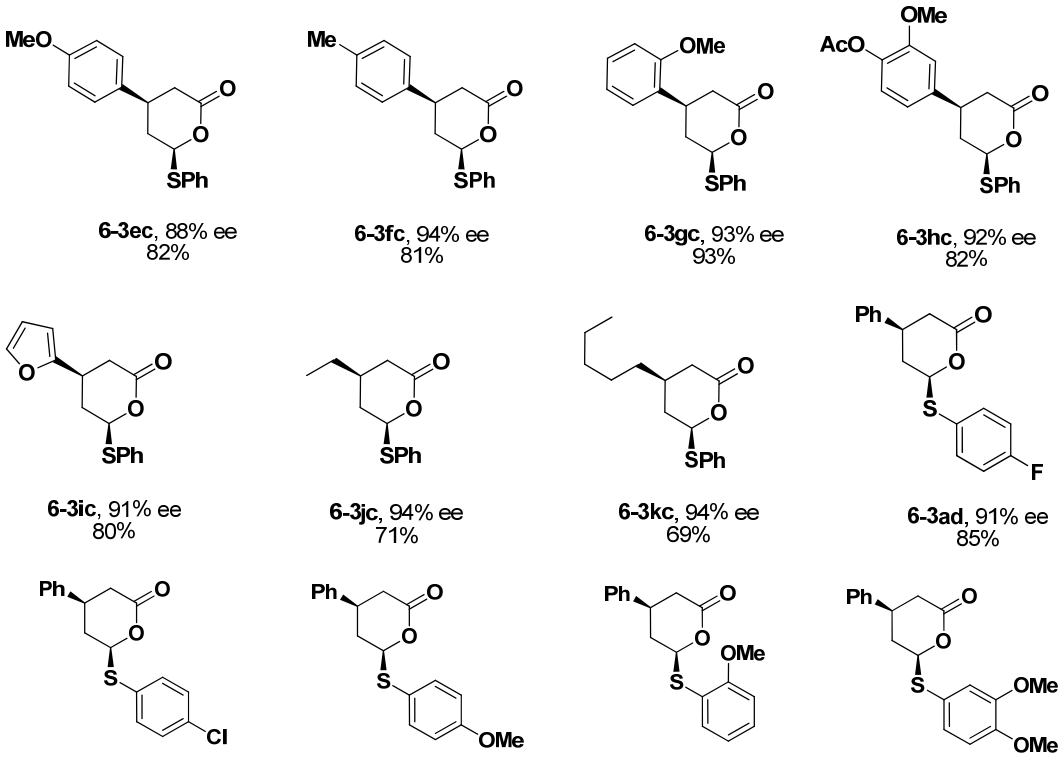
6.2.2 Reaction Scope for Decarboxylation of MAHTs and Enals

After having optimized the conditions for the cascade reaction, the scope of the methodology was evaluated. Initially, various α,β-unsaturated aldehydes **6-1** with different substitution patterns and electronic properties were examined (Table 6.3). The substitution patterns of malonic half-thioesters had limited impact on the yields or enantioselectivities, thereby providing the only regioisomer with *ee* values ranging from 91 to 94% (Table 6.3, **6-3ac–ah**, all dr > 20:1). Pleasingly, α,β-unsaturated aldehydes **6-1a–h** bearing different electron-withdrawing and electron-donating substituents on the aromic ring were easily reacted under the established reaction conditions (**6-3ac–hc**). In most of the cases, good yields and high steroselectivities were obtained. Additionally, α,β-unsaturated aldehydes **6-1i–k** bearing heterocyclic rings and alkyl groups could be utilized as well in good yields with rigorous stereoselectivities (**6-3ic–kc**).[186] Additionally, α,β,γ,δ-unsaturated aldehyde **6-1l** could react with **6-2c** to afford 3-alkenyl δ-lactone **3lc** in 74% yield and with 80% *ee* (Eq. [3]).

Table 6.3 Substrate scope of α,β-unsaturated aldehydes.[a-d]

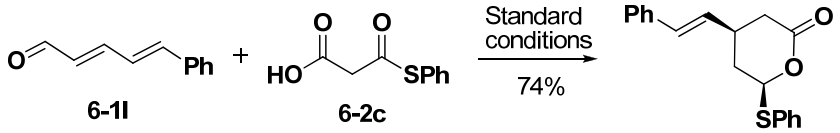


[186] CCDC 856259 (**6-3ac**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/ data_request/cif.



6-3ec, 88% ee 82%
6-3fc, 94% ee 81%
6-3gc, 93% ee 93%
6-3hc, 92% ee 82%
6-3ic, 91% ee 80%
6-3jc, 94% ee 71%
6-3kc, 94% ee 69%
6-3ad, 91% ee 85%
6-3ae, 92% ee 79%
6-3af, 92% ee 85%
6-3ag, 94% ee 84%
6-3ah, 92% ee 80%

[a] Reaction conditions: **6-1a-k** (0.20 mmol), **6-2c-h** (0.50 mmol), TEA (0.50 mmol) and catalyst **6-VI** (0.04 mmol), DCM (1.0 mL), 0 °C for 24 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] all dr > 20:1.



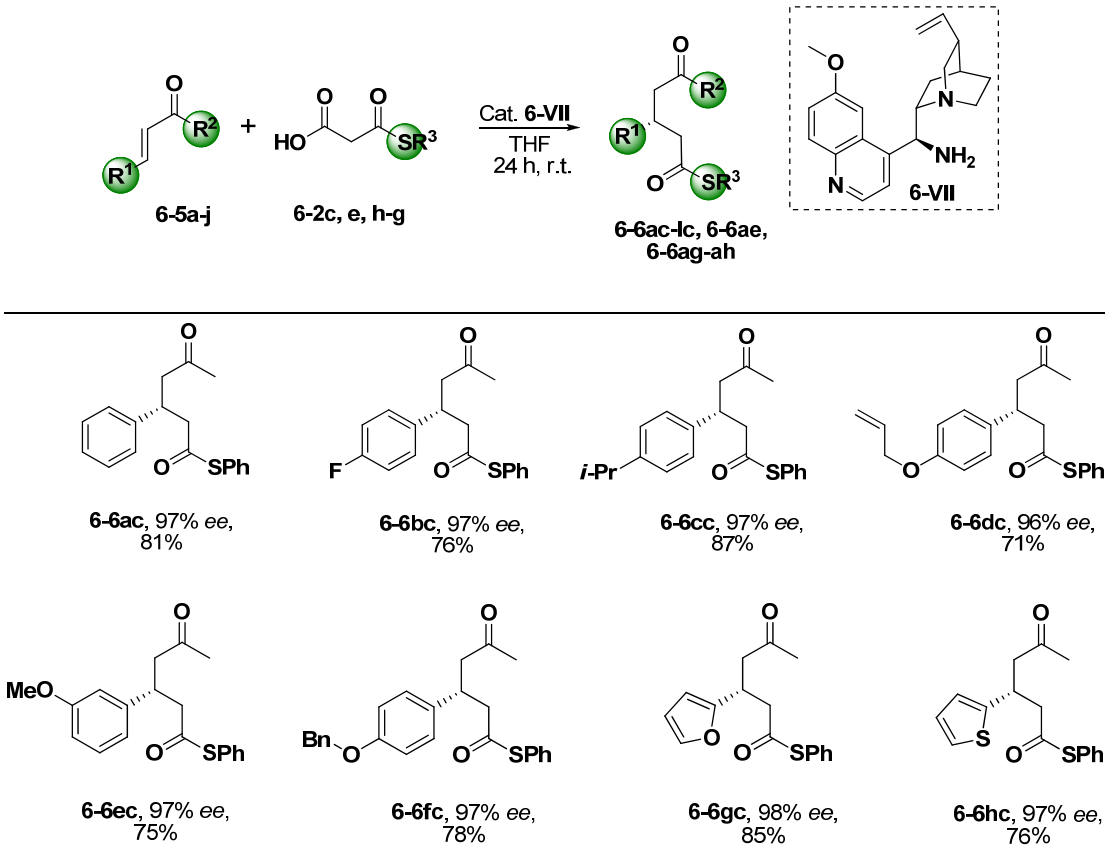
6-1l **6-2c** **6-3lc**, 80% *ee* (3)

6.2.3 Reaction Scope for Decarboxylation of MAHTs and Enones

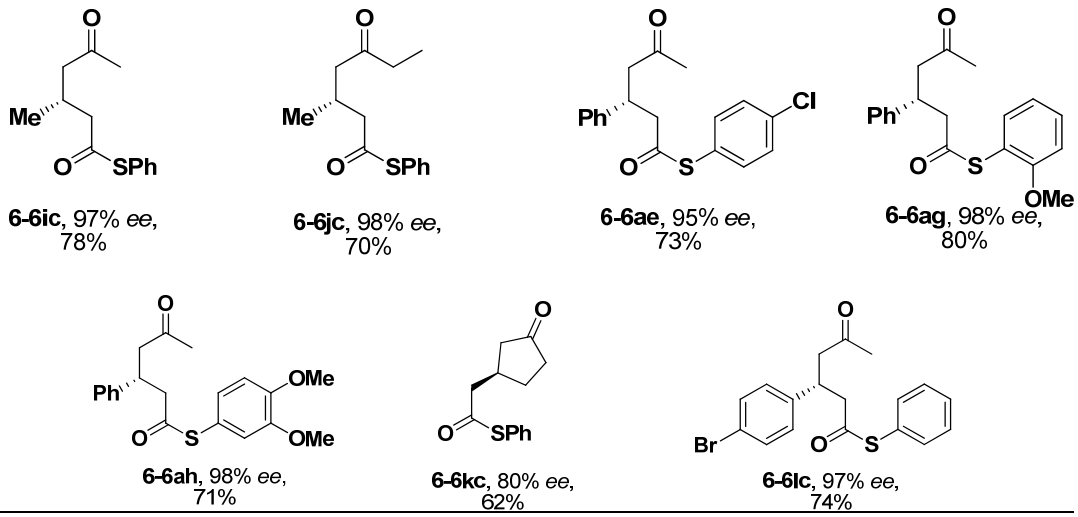
With the successful implementation of highly enantioselective annulations of α,β-unsaturated aldehydes and malonic half-thioesters, we moved our focus to the use of a different type of α,β-unsaturated carbonyls. α,β-unsaturated ketones are a class of α,β-unsaturated substrates prepared from simple condensation of aldehydes and ketones. Taking into account their similar properties relative to the parent α,β-unsaturated aldehydes, we envisaged that their use as electrophiles in the enantioselective annulation developed herein would provide a logical and

distinguished way to give the corresponding products. Unfortunately, no reaction was found in the presence of previous standard condition, which was used in the annulations of α,β-unsaturated aldehydes and malonic half-thioesters. This result showed that secondary amine catalyst (**6-VI**) was not suitable for the reaction of α,β-unsaturated ketones. A further catalyst screening indicated that catalyst **6-VII** (a cinchona alkaloid structure based primary amine) proved to be an efficient catalyst and gave 3-substituted 1,5-dicarbonyls instead. α,β-Unsaturated ketones bearing a variety of substituent patterns and electron-withdrawing and electron-donating groups were all tolerated, giving the corresponding acyclic 1,5-dicarbonyls in moderate to high yields (Table 6.4, 62–87%) and good to excellent stereocontrol (80–98% *ee*).[187] Notably, the 3-substituted 1,5-dicarbonyl is also a potential precursor of chiral δ-lactone.

Table 6.4 Substrate scope of α,β-unsaturated ketones.[a-c]



[187] CCDC 903996 (**6-6lc**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/ data_request/cif.

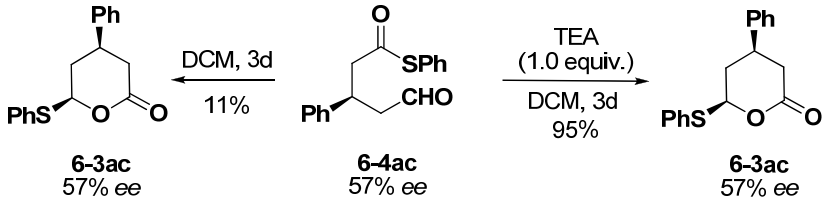


[a] Reaction conditions: **6-5a-l** (0.20 mmol), **6-2c-h** (0.50 mmol), catalyst **6-VII** (0.04 mmol), THF (1.0 mL), 24 h, room temperature. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

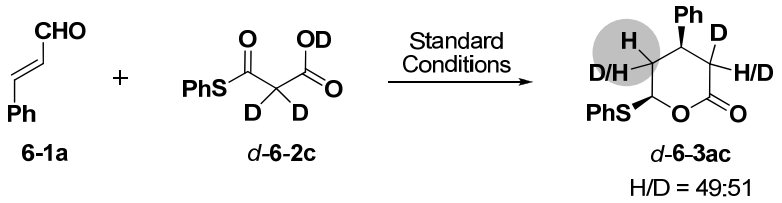
6.2.4 Mechanistic Investigations

We speculate that the mechanism of this cascade reaction may involve the following sequence (Scheme 6.3). Initially, malonic half-thioester **6-2c** reacts with triethyl amine to form the intermediate **6-8** followed by nucleophilic attack on the iminium intermediate **6-7**. A subsequent decarboxylation triggers the formation of the Michael addition intermediate **6-9**. Hydrolysis of intermediate **6-9** would lead to a recycle of cat.**6-VI** and generates the intermediate **6-10**. The intermediate **6-10** undergoes a sequence of tautomerization, cyclization and nucleophilic addition to afford the product **6-3ac**. As proof of this mechanism, we set out to investigate the key intermediate. For example, the potential intermediate **6-4ac** was synthesized and applied to synthesize the product **6-3ac** in the absence of cat. **6-VI** (Eq. [4]). The result exhibited that the lactone cyclization step could be promoted by a weak base or even in a base-free condition (spontaneous reaction) and did not loss any *ee* value. We suspect that the formation of **6-9** may be the rate-determining step. To deeply understand the proton transfer in this transformation, we conducted an isotopic experiment using deuterated half-thioester *d*-**6-2c** to react with cinnamaldehyde **6-1a** under standard conditions. ^{1}H NMR analysis of *d*-**6-3ac** demonstrated the isotope labelling of two protons located at α-position of carbonyl group is ab. 49:51 (Eq.

[5]). [188] This suggests that the water (generated from the condensation of cinnamaldehyde **6-1a** and cat. **6-VI**), functionalized as a potential proton source, is not involved in the Michael addition step.

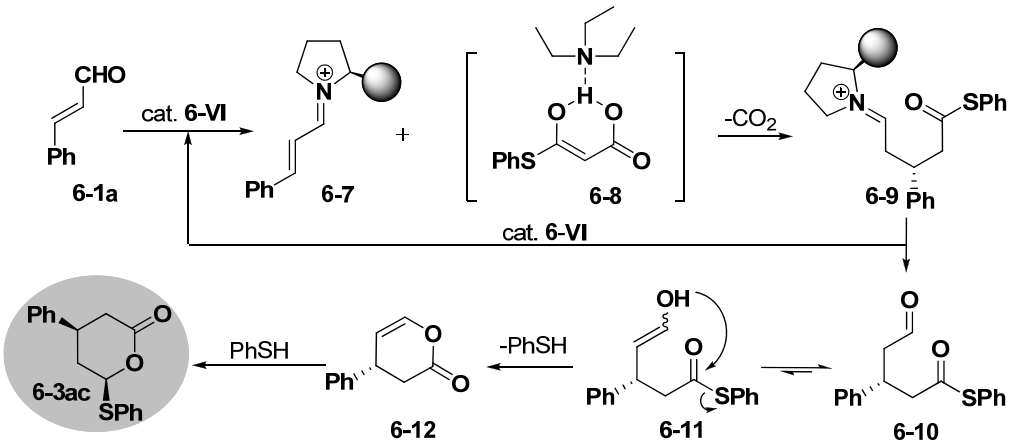


(4)



(5)

Scheme 6.3 Postulated mechanism.



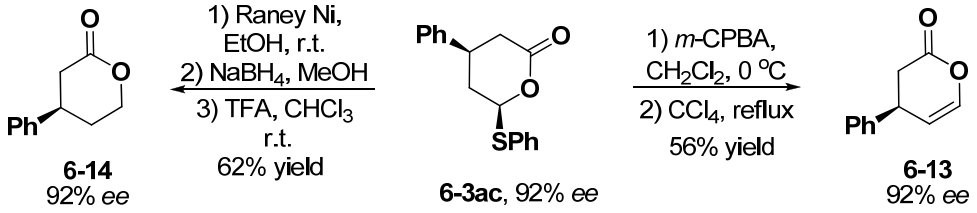
6.2.5. Methodology Application

The thiophenyl moiety in lactone **6-3ac** is a synthetically versatile functional group that can be readily converted into several valuable functionalities. Oxidation of **6-3ac** with *m*-CPBA and a subsequent elimination gave 3,4-dihydro δ-lactone **6-13** without racemization (Scheme 6.4, 56% yield). Removal of thiophenyl group

[188] See the details of isotope experiments in Experimental Section.

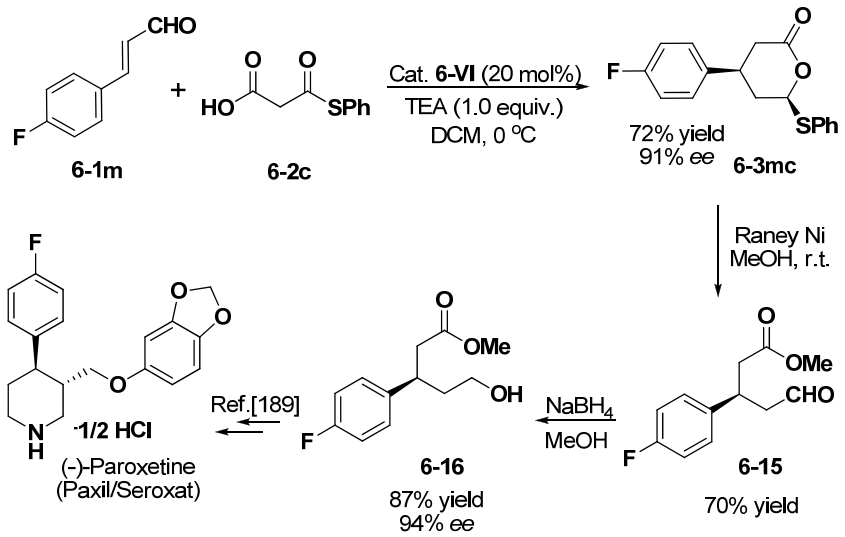
(replaced by H) was achieved using Raney Ni and $NaBH_4$. Performing the reduction in MeOH and the subsequent cyclization in the presence of TFA at room temperature afforded **6-14** in 62% yield.

Scheme 6.4 Synthetic modification of the thiophenyl group



Further application study was embarked on examining the applicability of our method to the concise synthesis of (-)-Paroxetine, marketed as Paxil/Seroxat (Scheme 6.5). The reaction of **6-1m** with **6-2c** catalyzed by **6-VI** and TEA gave the corresponding **6-3mc** in 72% yield and 91% *ee* (Scheme 6.5). Next, Lewis acid Ni-catalyzed ring opening reaction gave the corresponding 3-substituted 1,5-dicarbonyl **6-15**, and subsequent reduction of **6-15** afforded the key intermediate **6-16**. According to reported procedure,[189] the intermediate **6-16** can be converted to target (-)-Paroxetine, an antidepressant drug.

Scheme 6.5 Formal total synthesis of (-)-Paroxetine (Paxil/Seroxat).



[189] Yu, M. S.; Lantos, I.; Peng, Z. Q.; Yu, J.; Cacchio, T. *Tetrahedron Lett*. **2000**, *41*, 5647.

6.3 Conclusion

In summary, we have established a new method for the direct enantioselective synthesis of α,β-unsaturated carbonyls and malonic half-thioesters using chiral prolinol derivatives or cinchona alkaloid amines as organocatalysts. Our methodology provided a straightforward way to generate valuable chiral δ-lactone scaffold, which may have ubiquitous biological significance in the field of medicinal chemistry, in high yields and high to excellent enantioselectivities. The ready accessibility of the starting materials makes the current methodology particularly attractive in organic synthesis. The synthetic utility of this strategy was demonstrated by the versatile ready modifications of the thiophenyl group and the applicability of this method to the concise synthesis of (-)-Paroxetine, marketed as Paxil/Seroxat. Studies towards further expanding the synthetic utility of this strategy are currently underway.

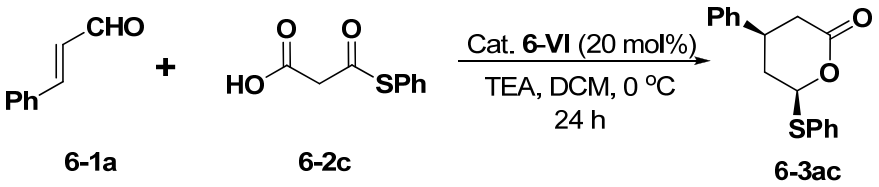
6.4 Experimental Section

6.4.1 General Information

Chemicals and solvents were purchased from commercial suppliers and used as received. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ACF300 (300 MHz) 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) or tetramethylsilane (TMS δ 0.00) was used as a reference. Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), bs (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

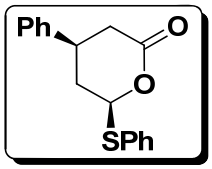
were visualized with a UV light at 254 nm. Flash chromatography separations were performed on Merck 60 (0.040-0.063 mm) mesh silica gel. The enantiomeric excesses of products were determined by chiral phase HPLC analysis. Optical rotations were recorded on Jasco DIP-1000 polarimeter.

6.4.2 Pepresentative Procedure for Decarboxylation of MAHTs and Enals



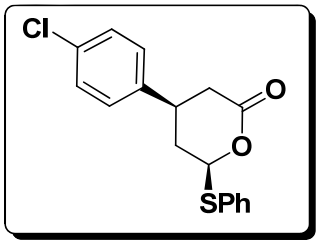
To a solution of cinnamaldehyde **6-1a** (26.4 mg, 25.2 uL, 0.2 mmol,) in DCM (0.5 mL) was added catalyst **6-VI** (25.6 mg, 0.04 mmol) at 0 °C. After 40 min, malonic acid half thioester **6-2c** (98.1 mg, 0.5 mmol) was added in one portion. Then, TEA (50.5 mg, 69.6 uL, 0.5 mmol) in 0.5 mL DCM was added dropwise *via* syringe in 10 min at 0 °C. The resulting reaction mixture was kept stirring at 0°C for 24 h. The crude product was purified by silica gel flash chromatography, eluted by hexane/EtOAc = 10:1 to afford the desired product **6-3ac** as white solid (46.7 mg, 82% yield).

6.4.3 Analytical Data for Decarboxylation of MAHTs and Enals

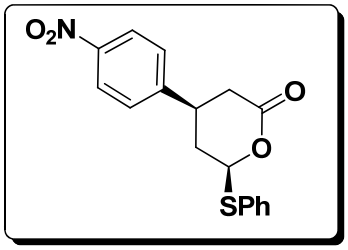


(4*S*,6*S*)-4-phenyl-6-(phenylthio)tetrahydro-2*H*-pyran-2-one (6-3ac) (46.7 mg, 82% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.61 – 7.59 (m, 2H), 7.36 (ddd, *J* = 7.7, 4.0, 1.7 Hz, 5H), 7.30 – 7.26 (m, 1H), 7.17 – 7.16 (m, 2H), 5.74 (dd, *J* = 11.3, 4.1 Hz,

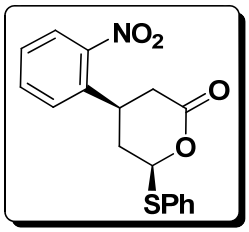
1H), 3.19 (tt, J = 12.3, 4.4 Hz, 1H), 2.88 (ddd, J = 17.7, 5.1, 2.3 Hz, 1H), 2.58 – 2.51 (m, 2H), 2.04 – 1.97 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 169.43, 141.54, 133.27, 131.78, 129.16, 129.05, 128.59, 127.47, 126.38, 86.32, 37.44, 37.20, 36.30; HRMS (EI) calcd for $C_{17}H_{16}O_2S$ 284.0871, found 284.0876; HPLC (Chiralpak IC, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 28.2 min, t_R (minor) = 23.0 min, *ee* = 92%; $[\alpha]^{25}_D$ = -96.6 (c = 1.08 in DCM).



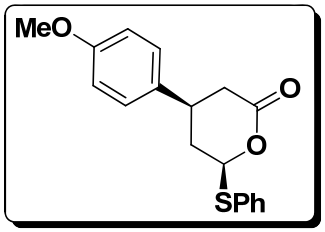
(4*S*,6*S*)-4-(4-chlorophenyl)-6-(phenylthio)tetrahydro-2*H*-pyran-2-one (6-3bc) (52.9 mg, 83% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.60 – 7.58 (m, 2H), 7.38 – 7.34 (m, 3H), 7.34 – 7.31 (m, 2H), 7.11 – 7.09 (m, 2H), 5.72 (dd, J = 11.3, 4.1 Hz, 1H), 3.17 (tt, J = 12.2, 4.5 Hz, 1H), 2.86 (ddd, J = 17.6, 5.1, 2.2 Hz, 1H), 2.56 – 2.46 (m, 2H), 2.00 – 1.93 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 169.10, 139.97, 133.34, 133.30, 131.57, 129.21, 129.19, 128.70, 127.75, 86.19, 37.10, 36.88, 36.14; HRMS (EI) calcd for $C_{17}H_{15}O_2ClS$ 318.0481, found 318.0486; HPLC (Chiralpak IC, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 28.4 min, t_R (minor) = 24.7 min, *ee* = 94%; $[\alpha]^{25}_D$ = -52.7 (c = 1.05 in DCM).



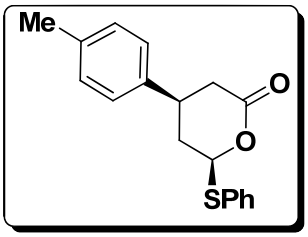
(4*S*,6*S*)-4-(4-nitrophenyl)-6-(phenylthio)tetrahydro-2*H*-pyran-2-one (6-3cc) (57.3 mg, 87% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.21 (d, *J* = 8.7 Hz, 2H), 7.60 – 7.58 (m, 2H), 7.37 – 7.34 (m, 5H), 5.74 (dd, *J* = 11.1, 4.1 Hz, 1H), 3.35 (tt, *J* =12.1, 4.5 Hz, 1H), 2.90 (ddd, *J* = 17.5, 5.2, 2.2 Hz, 1H), 2.61 – 2.51 (m, 2H), 2.02 (dt, *J* = 13.8, 11.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 168.45, 148.66, 147.26, 133.41, 131.25, 129.24, 128.84, 127.46, 124.32, 85.97, 37.27, 36.61, 35.69; HRMS (EI) calcd for $C_{17}H_{15}O_4NS$ 329.0722, found 329.0723; HPLC (Chiralpak IA, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 36.5 min, t_R (minor) = 26.9 min, *ee* = 95%; $[\alpha]^{25}_D$ = -68.8 (*c* = 0.97 in DCM).



(4*S*,6*S*)-4-(2-nitrophenyl)-6-(phenylthio)tetrahydro-2*H*-pyran-2-one (3dc) (52.0 mg, 79% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.87 (d, *J* = 8.1 Hz, 1H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.59 (dd, *J* = 6.4, 2.8 Hz, 2H), 7.44 (t, *J* = 7.7 Hz, 1H), 7.37 – 7.35 (m, 4H), 5.74 (dd, *J* = 11.3, 3.8 Hz, 1H), 3.79 (td, *J* = 11.6, 5.8 Hz, 1H), 2.99 (ddd, *J* = 17.5, 5.3, 1.8 Hz, 1H), 2.64 – 2.54 (m, 2H), 2.03 (dd, *J* = 25.3, 11.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 168.74, 149.33, 135.98, 133.65, 133.32, 131.40, 129.20, 128.73, 128.31, 127.36, 124.90, 85.99, 36.49, 35.84, 32.18; HRMS (EI) calcd for $C_{17}H_{15}O_4NS$ 329.0722, found 329.0734; HPLC (Chiralpak IA, *i*-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 30.4 min, t_R (minor) = 34.1 min, *ee* = 96%; $[\alpha]^{25}_D$ = -57.2 (*c* = 1.00 in DCM).

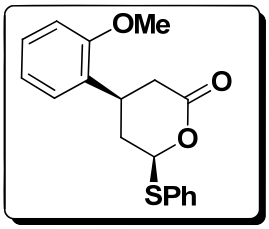


(4*S*,6*S*)-4-(4-methoxyphenyl)-6-(phenylthio)tetrahydro-2*H*-pyran-2-one (6-3ec) (51.7 mg, 82% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.59 (dd, *J* = 6.4, 3.2 Hz, 2H), 7.35 (dd, *J* = 4.9, 1.9 Hz, 3H), 7.10 – 7.04 (m, 2H), 6.90 – 6.87 (m, 2H), 5.72 (dd, *J* = 11.3, 4.1 Hz, 1H), 3.80 (s, 3H), 3.13 (tt, *J* = 12.6, 3.8 Hz, 1H), 2.86 (ddd, *J* = 17.7, 5.1, 2.3 Hz, 1H), 2.55 – 2.46 (m, 2H), 2.00 – 1.92 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 169.61, 158.82, 133.62, 133.23, 131.80, 129.15, 128.57, 127.36, 114.38, 86.36, 55.30, 37.45, 36.66, 36.53; HRMS (EI) calcd for $C_{18}H_{18}O_3S$ 314.0977, found 314.0987; HPLC (Chiralpak IC, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 42.9 min, t_R (minor) = 38.0 min, *ee* = 88%; $[\alpha]^{25}_{D}$ = -74.7 (*c* = 0.91 in DCM).

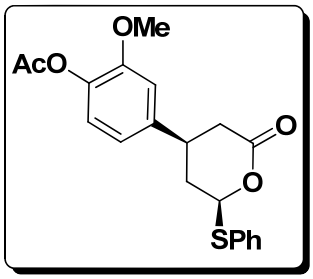


(4*S*,6*S*)-6-(phenylthio)-4-p-tolyltetrahydro-2*H*-pyran-2-one (6-3fc) (48.6 mg, 81% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.60 (dd, *J* = 6.4, 3.1 Hz, 2H), 7.38 – 7.33 (m, 3H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.05 (d, *J* = 8.0 Hz, 2H), 5.73 (dd, *J* = 11.3, 4.1 Hz, 1H), 3.15 (tt, *J* = 12.0, 4.4 Hz, 1H), 2.86 (ddd, *J* = 17.7, 5.1, 2.3 Hz, 1H), 2.55 – 2.48 (m, 2H), 2.34 (s, 3H), 2.02 – 1.94 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 169.56, 138.57, 137.16, 133.24, 131.82, 129.67, 129.14, 128.56, 126.23, 86.35, 37.30, 37.05, 36.42, 20.96; HRMS (EI) calcd for $C_{18}H_{18}O_2S$ 298.1028, found 298.1028; HPLC (Chiralpak IC, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm):

t_R (major) = 25.8 min, t_R (minor) = 22.5 min, *ee* = 93%; $[\alpha]^{25}_D$ = -35.2 (*c* = 1.05 in DCM).

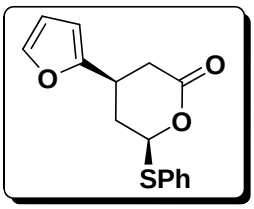


(4*S*,6*S*)-4-(2-methoxyphenyl)-6-(phenylthio)tetrahydro-2*H*-pyran-2-one (6-3gc) (58.3 mg, 93% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.63 – 7.59 (m, 2H), 7.36 – 7.33 (m, 3H), 7.26 (td, *J* = 8.0, 1.7 Hz, 1H), 7.06 (dd, *J* = 7.5, 1.6 Hz, 1H), 6.94 (td, *J* = 7.5, 0.9 Hz, 1H), 6.88 (d, *J* = 8.2 Hz, 1H), 5.74 (dd, *J* = 11.4, 3.9 Hz, 1H), 3.81 (s, 3H), 3.53 (tt, *J* = 12.0, 4.7, 1H), 2.87 (ddd, *J* = 17.6, 5.4, 2.1 Hz, 1H), 2.57 (dd, *J* = 17.6, 11.7 Hz, 1H), 2.49 (dtd, *J* = 13.8, 3.9, 2.1 Hz, 1H), 2.11 – 2.03 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 170.22, 156.83, 133.11, 132.06, 129.59, 129.08, 128.41, 128.37, 126.52, 120.83, 110.69, 86.44, 55.15, 35.53, 34.51, 31.94; HRMS (EI) calcd for $C_{18}H_{18}O_3S$ 314.0977, found 314.0977; HPLC (Chiralpak IC, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 20.6 min, t_R (minor) = 24.6 min, *ee* = 94%; $[\alpha]^{25}_D$ = -25.3 (*c* = 1.37 in DCM).

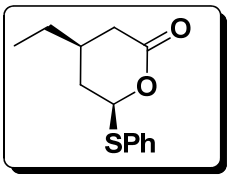


2-methoxy-4-((4*S*,6*S*)-2-*oxo*-6-(phenylthio)tetrahydro-2*H*-pyran-4-yl)phenyl acetate (6-3hc) (60.8 mg, 82% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.61 – 7.58 (m, 2H), 7.37 – 7.34 (m, 3H), 7.02 – 6.99 (m, 1H), 6.73 (dd, *J* = 6.7, 1.9 Hz, 2H), 5.72 (dd, *J* = 11.3, 4.1 Hz, 1H), 3.82 (s, 3H), 3.18 (tt, *J* = 12.2, 4.4 Hz, 1H), 2.88 (ddd,

J = 17.6, 5.1, 2.2 Hz, 1H), 2.60 – 2.47 (m, 2H), 2.31 (s, 3H), 2.04 – 1.91 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 169.30, 169.02, 151.37, 140.42, 138.91, 133.30, 131.63, 129.16, 128.65, 123.22, 118.33, 110.65, 86.22, 55.87, 37.32, 37.15, 36.30, 20.60; HRMS (EI) calcd for $C_{20}H_{20}O_5S$ 372.1031, found 372.1024; HPLC (Chiralpak IA, *i*-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 36.7 min, t_R (minor) = 40.9 min, *ee* = 92%; $[\alpha]^{25}_D$ = -31.6 (*c* = 1.34 in DCM).

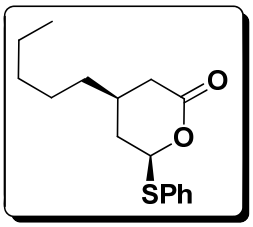


(4*S*,6*S*)-4-(furan-2-yl)-6-(phenylthio)tetrahydro-2*H*-pyran-2-one (6-3ic) (43.8 mg, 80% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.59 – 7.58 (m, 2H), 7.35 – 7.33 (m, 4H), 6.31 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.06 (d, *J* = 3.2 Hz, 1H), 5.70 (dd, *J* = 11.3, 4.0 Hz, 1H), 3.32 (tt, *J* = 11.8, 4.6 Hz, 1H), 2.94 (ddd, *J* = 17.7, 5.3, 2.1 Hz, 1H), 2.66 (dtd, *J* = 14.1, 4.0, 2.2 Hz, 1H), 2.57 (dd, *J* = 17.7, 11.9 Hz, 1H), 1.95 (dt, *J* = 14.1, 11.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 168.80, 154.38, 142.06, 133.35, 131.58, 129.16, 128.66, 110.25, 104.95, 86.03, 34.22, 33.91, 31.21; HRMS (EI) calcd for $C_{15}H_{14}O_3S$ 274.0664, found 274.0667; HPLC (Chiralpak IC, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 23.3 min, t_R (minor) = 19.0 min, *ee* = 91%; $[\alpha]^{25}_D$ = -67.7 (*c* = 0.96 in DCM).

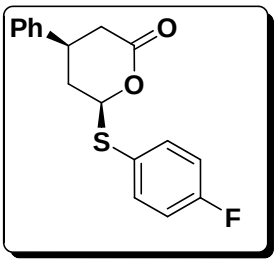


(4*S*,6*S*)-4-ethyl-6-(phenylthio)tetrahydro-2*H*-pyran-2-one (6-3jc) (33.4 mg, 71% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.58 – 7.56 (m, 2H), 7.35 – 7.32 (m, 3H),

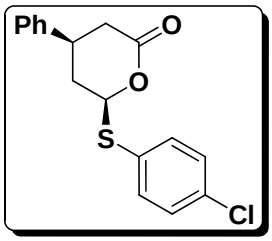
5.59 (dd, J = 11.2, 4.0 Hz, 1H), 2.68 (ddd, J = 17.5, 5.2, 2.0 Hz, 1H), 2.36 (dtd, J = 13.9, 4.0, 2.2 Hz, 1H), 2.05 (dd, J = 17.5, 11.6 Hz, 1H), 1.91 – 1.82 (m, 1H), 1.48 (dt, J = 13.9, 11.4 Hz, 1H), 1.37 (p, J = 7.3, 2H), 0.93 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 170.08, 133.03, 132.12, 129.09, 128.41, 86.39, 35.88, 34.82, 33.30, 28.67, 10.73; HRMS (EI) calcd for $C_{13}H_{16}O_2S$ 236.0871, found 236.0870; HPLC (Chiralpak IC, *i*-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 35.2 min, t_R (minor) = 40.4 min, *ee* = 94%; $[\alpha]^{25}_D$ = -11.9 (c = 0.86 in DCM).



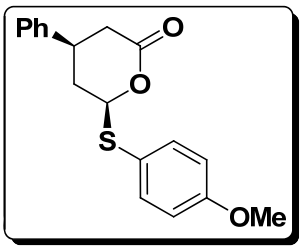
(4*S*,6*S*)-4-pentyl-6-(phenylthio)tetrahydro-2*H*-pyran-2-one (6-3kc) (38.2 mg, 69% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.57 – 7.55 (m, 2H), 7.34 – 7.32 (m, 3H), 5.59 (dd, J = 11.3, 4.0 Hz, 1H), 2.67 (ddd, J = 17.4, 5.0, 2.0 Hz, 1H), 2.37 – 2.32 (m, 2H), 2.05 (dd, J = 17.4, 11.6 Hz, 1H), 1.95 – 1.91 (m, 1H), 1.48 (dt, J = 13.8, 11.4 Hz, 1H), 1.37 – 1.26 (m, 8H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 170.11, 133.01, 132.11, 129.09, 128.41, 86.41, 36.21, 35.83, 35.18, 31.69, 31.62, 25.88, 22.48, 13.96; HRMS (EI) calcd for $C_{16}H_{22}O_2S$ 278.1341, found 278.1341; HPLC (Chiralpak IC, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 18.1 min, t_R (minor) = 20.7 min, *ee* = 94%; $[\alpha]^{25}_D$ = -20.6 (c = 0.89 in DCM).



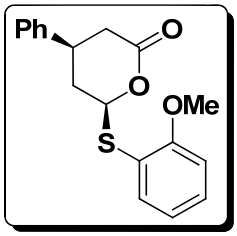
(4*S*,6*S*)-6-(4-fluorophenylthio)-4-phenyltetrahydro-2*H*-pyran-2-one (6-3ad) (51.6 mg, 85% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.62 – 7.59 (m, 2H), 7.36 (dd, *J* = 10.3, 4.7 Hz, 2H), 7.30 – 7.27 (m, 1H), 7.17 – 7.15 (m, 2H), 7.08 – 7.04 (m, 2H), 5.65 (dd, *J* = 11.3, 4.1 Hz, 1H), 3.19 (tt, *J* = 12.0, 4.4 Hz, 1H), 2.88 (ddd, *J* = 17.7, 5.1, 2.3 Hz, 1H), 2.56 – 2.50 (m, 2H), 1.96 (ddd, *J* = 13.9, 12.2, 11.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 169.42, 164.32, 162.34, 141.42, 136.22, 136.15, 129.08, 127.54, 126.50, 126.37, 116.42, 116.24, 86.44, 37.40, 37.18, 36.23; HRMS (EI) calcd for $C_{17}H_{15}O_2FS$ 302.0777, found 302.0777; HPLC (Chiralpak IC, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 22.7 min, t_R (minor) = 16.6 min, *ee* = 91%; $[\alpha]^{25}_D$ = -76.2 (*c* = 1.01 in DCM).



(4*S*,6*S*)-6-(4-chlorophenylthio)-4-phenyltetrahydro-2*H*-pyran-2-one (6-3ae) (50.6 mg, 79% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.54 – 7.52 (m, 2H), 7.38 – 7.31 (m, 4H), 7.29 (d, *J* = 7.5 Hz, 1H), 7.17 (d, *J* = 7.5 Hz, 2H), 5.69 (dd, *J* = 11.3, 4.1 Hz, 1H), 3.19 (tt, *J* = 12.3, 4.4 Hz, 1H), 2.89 (ddd, *J* = 17.7, 5.1, 2.2 Hz, 1H), 2.58 – 2.52 (m, 2H), 1.98 (dt, *J* = 13.8, 11.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 169.25, 141.38, 135.09, 134.65, 130.18, 129.36, 129.10, 127.56, 126.37, 86.12, 37.43, 37.18, 36.26; HRMS (EI) calcd for $C_{17}H_{15}O_2ClS$ 318.0481, found 318.0485; HPLC (Chiralpak IC, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 23.8 min, t_R (minor) = 18.0 min, *ee* = 92%; $[\alpha]^{25}_D$ = -90.1 (*c* = 1.05 in DCM).

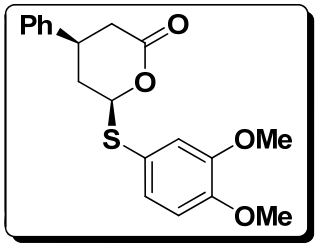


(4*S*,6*S*)-6-(4-methoxyphenylthio)-4-phenyltetrahydro-2*H*-pyran-2-one (6-3af) (53.6 mg, 85% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.56 – 7.53 (m, 2H), 7.35 (dd, *J* = 10.3, 4.7 Hz, 2H), 7.28 (dt, *J* = 3.9, 1.6 Hz, 1H), 7.15 (d, *J* = 7.2 Hz, 2H), 6.90 – 6.88 (m, 2H), 5.59 (dd, *J* = 11.2, 4.1 Hz, 1H), 3.82 (s, 3H), 3.16 (tt, J = 12.0, 4.5 Hz, 1H), 2.85 (ddd, *J* = 17.7, 5.1, 2.3 Hz, 1H), 2.53 – 2.45 (m, 2H), 1.94 (ddd, *J* = 13.9, 12.3, 11.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 169.64, 160.55, 141.65, 136.44, 129.02, 127.43, 126.39, 121.47, 114.70, 86.71, 55.35, 37.38, 37.20, 36.26; HRMS (EI) calcd for $C_{18}H_{18}O_3S$ 314.0977, found 314.0978; HPLC (Chiralpak IC, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 43.3 min, t_R (minor) = 28.1 min, *ee* = 92%; $[\alpha]^{25}_{D}$ = -60.3 (*c* = 1.08 in DCM).

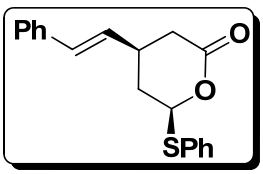


(4*S*,6*S*)-6-(2-methoxyphenylthio)-4-phenyltetrahydro-2*H*-pyran-2-one (6-3ag) (52.7 mg, 84% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.61 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.37 – 7.27 (m, 4H), 7.21 – 7.18 (m, 2H), 6.97 (td, *J* = 7.5, 1.1 Hz, 1H), 6.91 (d, *J* = 8.2 Hz, 1H), 5.87 (dd, *J* = 10.9, 4.3 Hz, 1H), 3.89 (s, 3H), 3.20 (tt, *J* = 12.6, 4.4 Hz, 1H), 2.88 (ddd, *J* = 17.5, 5.0, 2.3 Hz, 1H), 2.63 – 2.56 (m, 2H), 2.05 (ddd, *J* = 14.0, 12.2, 11.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 169.60, 158.41, 141.70, 134.40, 129.99, 129.02, 127.40, 126.39, 121.38, 119.91, 111.06, 84.53, 55.89, 37.39, 37.33, 36.00; HRMS (EI) calcd for $C_{18}H_{18}O_3S$ 314.0977, found 314.0979;

HPLC (Chiralpak IA, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 11.1 min, t_R (minor) = 13.1 min, *ee* = 94%; $[\alpha]^{25}_D$ = -67.5 (*c* = 0.96 in DCM).

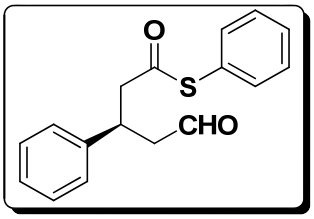


(4*S*,6*S*)-6-(3,4-dimethoxyphenylthio)-4-phenyltetrahydro-2*H*-pyran-2-one (6-3ah) (54.8 mg, 80% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.35 (dd, *J* = 10.2, 4.7 Hz, 2H), 7.30 – 7.25 (m, 2H), 7.19 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.16 – 7.13 (m, 3H), 6.85 (d, *J* = 8.3 Hz, 1H), 5.63 (dd, *J* = 11.2, 4.2 Hz, 1H), 3.89 (s, 6H), 3.20 – 3.13 (m, 1H), 2.85 (ddd, *J* = 17.7, 5.1, 2.3 Hz, 1H), 2.55 – 2.43 (m, 2H), 1.94 (ddd, *J* = 13.9, 12.3, 11.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 169.58, 150.14, 149.05, 141.59, 129.03, 127.93, 127.44, 126.38, 121.66, 117.65, 111.44, 86.55, 56.08, 55.93, 37.33, 37.21, 36.27; HRMS (EI) calcd for $C_{19}H_{20}O_4S$ 344.1082, found 344.1081; HPLC (Chiralpak IA, *i*-propanol/hexane = 5/95, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 46.4 min, t_R (minor) = 52.4 min, *ee* = 92%; $[\alpha]^{25}_D$ = -61.1 (*c* = 0.99 in DCM).



(4*S*,6*S*)-6-(phenylthio)-4-styryltetrahydro-2*H*-pyran-2-one (6-3lc) (46.2 mg, 74% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.55 (dd, *J* = 6.5, 2.9 Hz, 2H), 7.31 – 7.21 (m, 8H), 6.39 (d, *J* = 15.9 Hz, 1H), 5.97 (dd, *J* = 15.9, 7.0 Hz, 1H), 5.63 (dd, *J* =

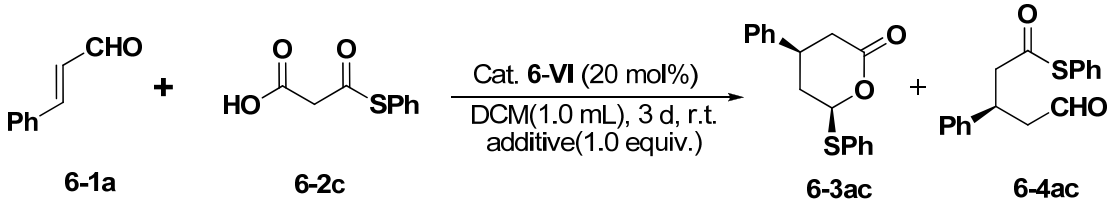
11.2, 4.0 Hz, 1H), 2.82 – 2.72 (m, 2H), 2.42 (ddd, J = 13.9, 6.1, 3.8 Hz, 1H), 2.29 (dd, J = 17.2, 11.4 Hz, 1H), 1.72 (dt, J = 13.8, 11.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 169.21, 136.28, 133.30, 131.71, 130.80, 129.86, 129.15, 128.65, 128.60, 127.87, 126.23, 86.09, 35.71, 35.11, 35.08; HRMS (EI) calcd for $C_{19}H_{18}O_2S$ 310.1028, found 310.1035; HPLC (Chiralpak IC, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 36.6 min, t_R (minor) = 29.6 min, *ee* = 80%; $[\alpha]^{25}_D$ = -48.2 (c = 0.78 in DCM).



(*R*)-S-phenyl 5-*oxo*-3-phenylpentanethioate (6-4ac). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 9.74 (s, 1H), 7.47 – 7.45 (m, 3H), 7.42 – 7.38 (m, 4H), 7.34 – 7.31 (m, 3H), 3.95 – 3.86 (m, 1H), 3.09 (d, J = 7.2 Hz, 2H), 3.00 – 2.89 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 200.35, 195.64, 141.83, 134.36, 129.47, 129.16, 128.83, 127.35, 127.32, 127.20, 49.48, 48.96, 36.66; HRMS (EI) calcd for $C_{17}H_{16}O_2S$ 284.0871, found 284.0878.

6.4.4 Condition Optimization for Decarboxylation of MAHTs and Enals

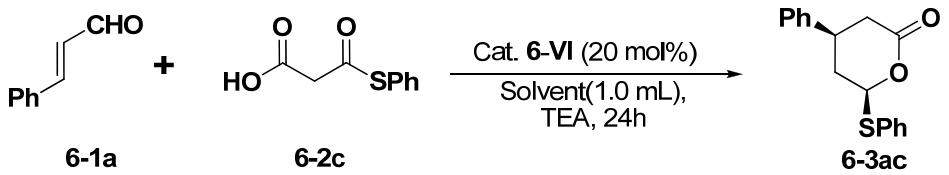
Table 6.5 Screening of additives[a]



Entry	Additive	Yield(%)[b]	ee(%)[c]	Entry	Additive	Yield(%)[b]	ee(%)[c]
1	LiOH	<20	-	8	PhCOOH	-	-
2	NH_4OAc	<20	-	9	2,6-lutidine	55(**6-4ac**)	49
3	NaOAc	<20	-	10	Et_3N	51(**6-3ac**)	89
4	$NaHCO_3$	<20	-	11	TBD	37(**6-3ac**)	78
5	Li_2CO_3	<20	-	12	DABCO	54(**6-3ac**)	89
6	Na_2CO_3	22(**6-4ac**)	18	13	Quinine	63(**6-3ac**)	88
7	Cs_2CO_3	46(**6-4ac**+**6-3ac**)	81/82				

[a] Reactions were performed with cinnamaldehyde **6-1a** (0.20 mmol), MAHT **6-2c** (0.24 mmol), additive (0.20 mmol) and catalyst **6-VI** (0.04 mmol) in the DCM (1.0 mL) at RT. [b] Isolated yield after column chromatography. [c] Determined by HPLC analysis.

Table 6.6 Optimization of the reaction conditions[a]

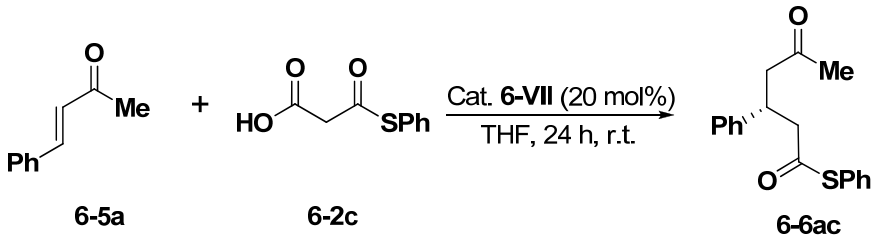


Entry	Solvent	T/°C	TEA(equiv.)	**6-1a**:**6-2c**	Yield(%)[b]	ee(%)[c]
1	DCM	RT	1.0	1.0:1.2	51	89
2	DCE	RT	1.0	1.0:1.2	53	78
3	$CHCl_3$	RT	1.0	1.0:1.2	55	52
4	Toluene	RT	1.0	1.0:1.2	53	81
5	Xylenes	RT	1.0	1.0:1.2	50	82
6	Anisole	RT	1.0	1.0:1.2	52	80
7	THF	RT	1.0	1.0:1.2	47	84
8	IPA	RT	1.0	1.0:1.2	47	89
9	EA	RT	1.0	1.0:1.2	52	81
10	DMF	RT	1.0	1.0:1.2	<10	-
11	DEGEE	RT	1.0	1.0:1.2	-	-
12	Acetone	RT	1.0	1.0:1.2	54	83
13	DCM	40	1.0	1.0:1.2	46(**6-4ac**)	84

14	DCM	RT	1.0	2.0:1.0	45	44
15	DCM	RT	1.0	1.0:2.5	-	55
16	DCM	RT	2.5	1.0:2.5	57	89
17	DCM	RT	4.0	1.0:2.5	-	-
18	DCM	RT	0.2	1.0:2.5	-	-
19[d]	DCM	RT	2.5	1.0:2.5	82	71
20[e]	DCM	RT	2.5	1.0:2.5	81	86
21[f]	DCM	RT	2.5	1.0:2.5	76	86
22[e]	DCM	0	2.5	1.0:2.5	82	92
23[e]	DCM	-20	2.5	1.0:2.5	<10	-
24[e,g]	DCM	0	2.5	1.0:2.5	<10	-

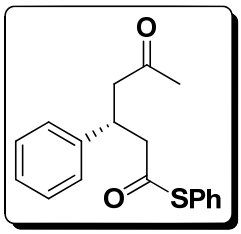
[a] Reactions were performed with cinnamaldehyde **6-1a** (0.20 mmol), MAHT **6-2c**, TEA and catalyst **6-VI** (0.04 mmol) in the solvent (1.0 mL). [b] Isolated yield after column chromatography. [c] Determined by HPLC analysis. [d] TEA (69.6 uL) in 0.50 mL DCM was added dropwise in 1 hour. [e] TEA (69.6 uL) in 0.50 mL DCM was added dropwise in 10 min.[f] TEA (69.6 uL) in 0.50 mL DCM was added dropwise in 5 min. [g] 60.0 mg MS was added into the reaction mixture.

6.4.5 Representative Procedure for Decarboxylation of MAHTs and Enones

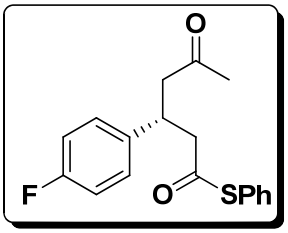


To a solution of *trans*-4-Phenyl-3-buten-2-one **6-5a** (29.2 mg, 0.2 mmol,) and catalyst **6-VII** (12.9 mg, 0.04 mmol) in THF (1.0 mL) at room temperature, was added malonic acid half thioester **6-2c** (98.1 mg, 0.5 mmol) in one portion. The reaction mixture was kept stirring at room temperature for 24 h. The crude product was purified by silica gel flash chromatography, eluted by hexane/EtOAc = 10:1 to afford the desired product **6-6ac** as colorless oil (48.3 mg, 81% yield).

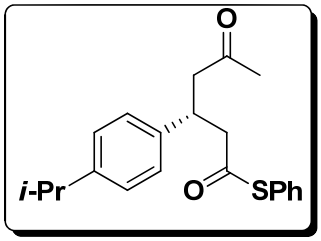
6.4.6 Analytical Data for Decarboxylation of MAHTs and Enones



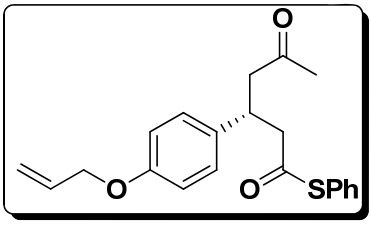
(*R*)-*S*-phenyl 5-oxo-3-phenylhexanethioate (6-6ac) (48.3 mg, 81% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.40 – 7.36 (m, 3H), 7.33 – 7.29 (m, 4H), 7.24 – 7.21 (m, 3H), 3.77 (p, J = 7.2 Hz, 1H), 3.04 – 2.81 (m, 4H), 2.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 206.53, 195.84, 142.40, 134.37, 129.37, 129.12, 128.65, 127.49, 127.36, 126.96, 49.36, 48.90, 37.81, 30.34; HRMS (ESI) calcd for $C_{18}H_{18}O_2SNa^+$ [M + Na^+] 321.0920, found 321.0929; HPLC (Chiralpak IC, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 15.6 min, t_R (minor) = 20.5 min, *ee* = 97%; $[\alpha]^{25}_D$ = -74.2 (c = 1.01 in DCM).



(*R*)-*S*-phenyl 3-(4-fluorophenyl)-5-oxohexanethioate (6-6bc) (48.1 mg, 76% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.42 – 7.36 (m, 3H), 7.33 – 7.27 (m, 2H), 7.23 – 7.17 (m, 2H), 6.99 (t, J = 8.6 Hz, 2H), 3.76 (p, J = 7.2 Hz, 1H), 3.02 – 2.78 (m, 4H), 2.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 206.25, 195.70, 162.66, 160.72, 138.12, 138.10, 134.34, 129.45, 129.17, 128.96, 128.90, 127.36, 115.54, 115.38, 49.34, 48.96, 37.04, 30.35; HRMS (ESI) calcd for $C_{18}H_{17}O_2FSNa^+$ [M + Na^+] 339.0825, found 339.0831; HPLC (Chiralpak IC, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 9.9 min, t_R (minor) = 14.5 min, *ee* = 97%; $[\alpha]^{25}_D$ = -77.1 (c = 0.90 in DCM).

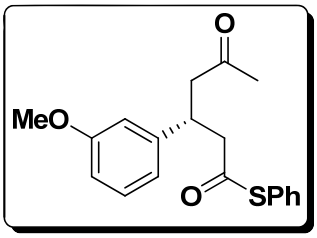


(*R*)-*S*-phenyl 3-(4-isopropylphenyl)-5-oxohexanethioate (6-6cc) (59.2 mg, 87% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.38 – 7.36 (m, 3H), 7.30 (dd, *J* = 6.6, 3.0 Hz, 2H), 7.17 – 7.13 (m, 4H), 3.74 (p, *J* = 7.2 Hz, 1H), 3.02 – 2.80 (m, 5H), 2.06 (s, 3H), 1.24 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 206.73, 195.99, 147.45, 139.72, 134.39, 129.35, 129.12, 127.60, 127.23, 126.66, 49.49, 49.02, 37.44, 33.65, 30.31, 23.94, 23.91; HRMS (ESI) calcd for $C_{21}H_{24}O_2SNa^+$ [M + Na^+] 363.1389, found 363.1407; HPLC (Chiralpak IC, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 11.3 min, t_R (minor) = 16.9 min, *ee* = 97%; $[\alpha]^{25}_D$ = -64.2 (*c* = 1.23 in DCM).

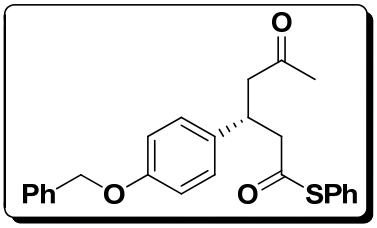


(*R*)-*S*-phenyl 3-(4-(allyloxy)phenyl)-5-oxohexanethioate (6-6dc) (50.4 mg, 71% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.41 – 7.34 (m, 2H), 7.33 – 7.27 (m, 2H), 7.17 – 7.11 (m, 2H), 6.89 – 6.83 (m, 2H), 6.05 (ddt, *J* = 17.2, 10.5, 5.3 Hz, 1H), 5.40 (ddd, *J* = 17.2, 3.1, 1.5 Hz, 1H), 5.28 (ddd, *J* = 10.5, 2.6, 1.3 Hz, 1H), 4.51 (dt, *J* = 5.3, 1.4 Hz, 2H), 3.71 (p, *J* = 7.2 Hz, 1H), 3.00 – 2.77 (m, 4H), 2.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 206.70, 195.90, 157.48, 134.59, 134.37, 133.28, 129.35, 129.11, 128.34, 127.55, 117.58, 114.84, 68.79, 49.60, 49.12, 37.15, 30.35; HRMS (ESI) calcd for $C_{21}H_{22}O_3SNa^+$ [M + Na^+] 377.1182, found 377.1191; HPLC (Chiralpak IC, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_R

(major) = 15.7 min, t_R (minor) = 24.6 min, *ee* = 96%; $[\alpha]^{25}_D$ = -79.8 (*c* = 1.16 in DCM).

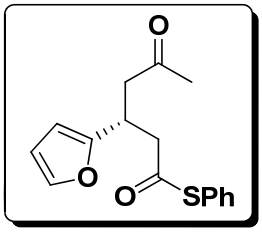


(*R*)-*S*-phenyl 3-(3-methoxyphenyl)-5-oxohexanethioate (6-6ec) (49.2 mg, 75% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.39 – 7.37 (m, 3H), 7.32 – 7.30 (m, 2H), 7.23 (dd, *J* = 8.8, 7.7 Hz, 1H), 6.82 (d, *J* = 7.8 Hz, 1H), 6.77 (dd, *J* = 3.8, 1.5 Hz, 2H), 3.80 (s, 3H), 3.74 (p, *J* = 7.2 Hz, 1H), 3.01 – 2.80 (m, 4H), 2.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 206.51, 195.84, 159.78, 144.13, 134.40, 129.69, 129.40, 129.15, 127.55, 119.62, 113.38, 112.18, 55.19, 49.32, 48.87, 37.84, 30.36; HRMS (ESI) calcd for $C_{19}H_{20}O_3SNa^+$ [M + Na^+] 351.1025, found 351.1009; HPLC (Chiralpak IC, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 25.2 min, t_R (minor) = 27.1 min, *ee* = 97%; $[\alpha]^{25}_D$ = -69.5 (*c* = 0.96 in DCM).

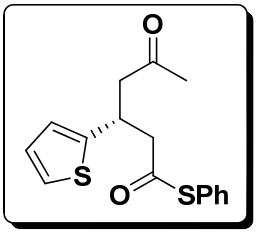


(*R*)-*S*-phenyl 3-(4-(benzyloxy)phenyl)-5-oxohexanethioate (6-6fc) (63.1mg, 78% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.44 – 7.42 (m, 2H), 7.39 – 7.37 (m, 5H), 7.34 – 7.29 (m, 3H), 7.15 (d, *J* = 8.6 Hz, 2H), 6.93 (d, *J* = 8.6 Hz, 2H), 5.04 (s, 2H), 3.72 (p, *J* = 7.2 Hz, 1H), 3.00 – 2.78 (m, 4H), 2.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 206.68, 195.90, 157.69, 136.99, 134.72, 134.37, 129.36, 129.13, 128.54, 128.39, 127.92, 127.55, 127.45, 114.97, 70.00, 49.60, 49.12, 37.15, 30.36;

HRMS (ESI) calcd for $C_{25}H_{24}O_3SNa^+$ [M + Na^+] 427.1338, found 427.1324; HPLC (Chiralpak IC, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 18.4 min, t_R (minor) = 28.4 min, *ee* = 97%; $[\alpha]^{25}_D$ = -71.0 (*c* = 1.29 in DCM).

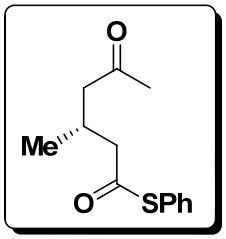


(*R*)-*S*-phenyl 3-(furan-2-yl)-5-oxohexanethioate (6-6gc) (49.0mg, 85% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.40 – 7.38 (m, 3H), 7.37 – 7.34 (m, 2H), 7.32 (dd, *J* = 1.8, 0.8 Hz, 1H), 6.28 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.07 (d, *J* = 3.2 Hz, 1H), 3.86 (p, *J* = 6.9 Hz, 1H), 3.06 – 2.97 (m, 2H), 2.92 – 2.83 (m, 2H), 2.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 206.21, 195.64, 155.15, 141.47, 134.41, 129.45, 129.18, 127.46, 110.23, 105.73, 46.54, 46.20, 31.38, 30.16; HRMS (ESI) calcd for $C_{16}H_{16}O_3SNa^+$ [M + Na^+] 311.0712, found 311.0716; HPLC (Chiralpak IC, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 16.2 min, t_R (minor) = 39.8 min, *ee* = 98%; $[\alpha]^{25}_D$ = -43.7 (*c* = 1.13 in DCM).

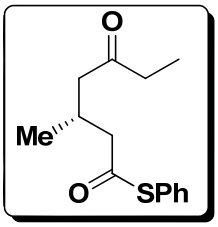


(*R*)-*S*-phenyl 5-oxo-3-(thiophen-2-yl)hexanethioate (6-6hc) (46.3 mg, 76% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.40 – 7.38 (m, 3H), 7.35 – 7.33 (m, 2H), 7.16 (d, *J* = 5.0 Hz, 1H), 6.92 (dd, *J* = 5.0, 3.5 Hz, 1H), 6.88 (d, *J* = 3.2 Hz, 2H), 4.09 (p, *J* = 6.9 Hz, 1H), 3.08 – 2.99 (m, 2H), 2.98 – 2.86 (m, 2H), 2.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 206.07, 195.59, 145.90, 134.41, 129.46, 129.18, 127.41,

126.76, 124.54, 123.66, 49.87, 49.58, 33.14, 30.35; HRMS (ESI) calcd for $C_{16}H_{16}O_2S_2Na^+$ [M + Na^+] 327.0484, found 327.0488; HPLC (Chiralpak IC, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 14.6 min, t_R (minor) = 23.0 min, *ee* = 97%; $[\alpha]^{25}_D$ = -56.5 (*c* = 1.05 in DCM).

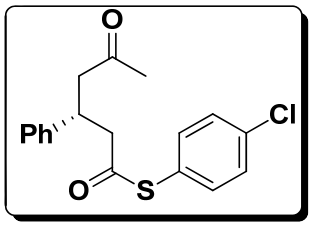


(*R*)-*S*-phenyl 3-methyl-5-oxohexanethioate (6-6ic) (36.9 mg, 78% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.40 (br, 5H), 2.68 (ddd, *J* = 8.5, 6.3, 2.7 Hz, 1H), 2.58 (ddd, *J* = 12.4, 11.4, 5.9 Hz, 3H), 2.40 – 2.34 (m, 1H), 2.13 (s, 3H), 1.03 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 207.50, 196.46, 134.38, 129.37, 129.16, 127.73, 49.55, 30.30, 29.65, 27.01, 19.79; HRMS (ESI) calcd for $C_{13}H_{16}O_2SNa^+$ [M + Na^+] 259.0763, found 259.0761; HPLC (Chiralpak ID, *i*-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 10.4 min, t_R (minor) = 9.5 min, *ee* = 97%; $[\alpha]^{25}_D$ = -5.7 (*c* = 0.90 in DCM).

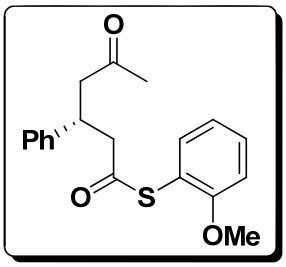


(*R*)-*S*-phenyl 3-methyl-5-oxoheptanethioate (6-6jc) (35.1 mg, 70% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.40 (br, 5H), 2.71 – 2.66 (m, 1H), 2.63 – 2.52 (m, 3H), 2.45 – 2.33 (m, 3H), 1.04 (dd, *J* = 12.8, 6.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 210.22, 196.53, 134.42, 129.38, 129.18, 127.81, 49.68, 48.28, 36.37, 27.15, 19.90, 7.71; HRMS (ESI) calcd for $C_{14}H_{18}O_2SNa^+$ [M + Na^+] 273.0920, found

273.0920; HPLC (Chiralpak IC, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 8.2 min, t_R (minor) = 9.2 min, *ee* = 98%; $[\alpha]^{25}_D$ = -6.5 (*c* = 1.20 in DCM).

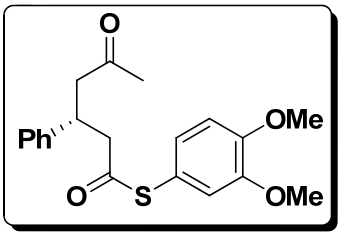


(*R*)-*S*-4-chlorophenyl 5-oxo-3-phenylhexanethioate (6-6ae) (48.6 mg, 73% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.35 – 7.30 (m, 4H), 7.24 – 7.20 (m, 5H), 3.76 (p, *J* = 7.2 Hz, 1H), 2.98 (qd, *J* = 15.1, 7.2 Hz, 2H), 2.87 (qd, *J* = 16.9, 7.1 Hz, 2H), 2.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 206.46, 195.34, 142.30, 135.81, 135.60, 129.38, 128.70, 127.36, 127.04, 125.95, 49.40, 48.92, 37.80, 30.37; HRMS (ESI) calcd for $C_{18}H_{17}O_2ClSNa^+$ [M + Na^+] 355.0530, found 355.0547; HPLC (Chiralpak IC, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 12.4 min, t_R (minor) = 16.1 min, *ee* = 95%; $[\alpha]^{25}_D$ = -79.7 (*c* = 0.98 in DCM).

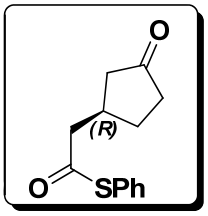


(*R*)-*S*-2-methoxyphenyl 5-oxo-3-phenylhexanethioate (6-6ag) (52.6 mg, 80% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.30 (td, *J* = 8.4, 1.6 Hz, 1H), 7.26 – 7.11 (m, 6H), 6.86 (dd, *J* = 14.6, 7.9 Hz, 2H), 3.73 – 3.65 (m, 4H), 2.94 – 2.73 (m, 4H), 1.95 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 206.59, 195.06, 159.08, 142.54, 136.53,

131.61, 128.56, 127.36, 126.82, 121.00, 115.74, 111.51, 55.84, 49.12, 48.83, 37.87, 30.29; HRMS (ESI) calcd for $C_{19}H_{20}O_3SNa^+$ [M + Na^+] 351.1025, found 351.1035; HPLC (Chiralpak ID, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 15.4 min, t_R (minor) = 17.3 min, *ee* = 98%; $[\alpha]^{25}_D$ = -66.4 (*c* = 1.15 in DCM).

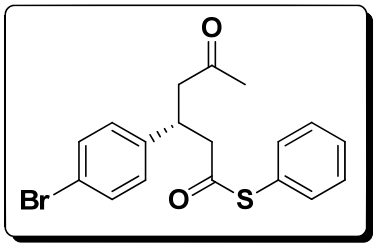


(*R*)-*S*-3,4-dimethoxyphenyl 5-oxo-3-phenylhexanethioate (6-6ah) (50.9 mg, 71% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.31 – 7.28 (m, 2H), 7.21 (dd, *J* = 10.9, 4.4 Hz, 3H), 6.86 (d, *J* = 2.5 Hz, 2H), 6.76 (s, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.76 (p, *J* = 7.1 Hz, 1H), 3.00 – 2.80 (m, 4H), 2.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 206.53, 196.85, 150.22, 149.15, 142.46, 128.60, 127.60, 127.38, 126.90, 118.37, 117.23, 111.49, 55.92, 55.84, 49.11, 48.92, 37.82, 30.32; HRMS (ESI) calcd for $C_{20}H_{22}O_4SNa^+$ [M + Na^+] 381.1131, found 381.1140; HPLC (Chiralpak IA, *i*-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 20.0 min, t_R (minor) = 22.2 min, *ee* = 96%; $[\alpha]^{25}_D$ = -70.3 (*c* = 0.95 in DCM).



(*R*)-*S*-phenyl 2-(3-oxocyclopentyl)ethanethioate (6-6kc) (29.1 mg, 62% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.43 – 7.40 (m, 5H), 2.85 – 2.75 (m, 2H), 2.75 – 2.65 (m, 1H), 2.51 (dd, *J* = 18.3, 7.7 Hz, 1H), 2.36 – 2.15 (m, 3H), 1.94 (dd, *J* = 18.4, 9.8 Hz, 1H), 1.70 – 1.61 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 217.75, 195.86, 134.40, 129.56, 129.27, 127.36, 48.58, 44.37, 38.16, 33.97, 29.12; HRMS

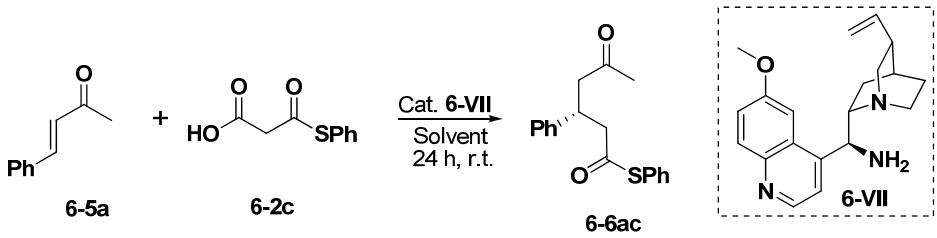
(ESI) calcd for $C_{13}H_{14}O_2SNa^+$ [M + Na^+] 257.0607, found 257.0609; HPLC (Chiralpak IC, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 27.0 min, t_R (minor) = 32.6 min, *ee* = 80%; $[\alpha]^{25}_D$ = -73.0 (*c* = 0.86 in DCM).



(*R*)-*S*-phenyl 3-(4-bromophenyl)-5-oxohexanethioate (6-6lc). (55.5 mg, 74% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.44 – 7.38 (m, 5H), 7.31 – 7.29 (m, 2H), 7.11 (d, *J* = 8.2 Hz, 2H), 3.73 (p, *J* = 7.2 Hz, 1H), 3.01 – 2.77 (m, 4H), 2.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 206.05, 195.59, 141.49, 134.36, 131.74, 129.49, 129.19, 127.30, 120.75, 48.99, 48.69, 37.12, 30.35; HRMS (ESI) calcd for $C_{18}H_{17}O_2BrSNa^+$ [M + Na^+] 399.0025, found 399.0036; HPLC (Chiralpak IC, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 9.8 min, t_R (minor) = 14.7 min, *ee* = 97%; $[\alpha]^{25}_D$ = -87.3 (*c* = 0.93 in DCM)

6.4.7 Condition Optimization for Decarboxylation of MAHTs and Enones

Table 6.7 Optimization of the reaction conditions[a]

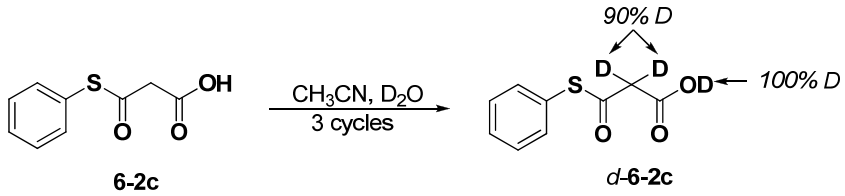


Entry	Solvent	Yield (%)[b]	ee(%)[c]	Entry	Solvent	Yield (%)[b]	ee(%)[c]
1	DCM	65	90	10	IPA	44	84

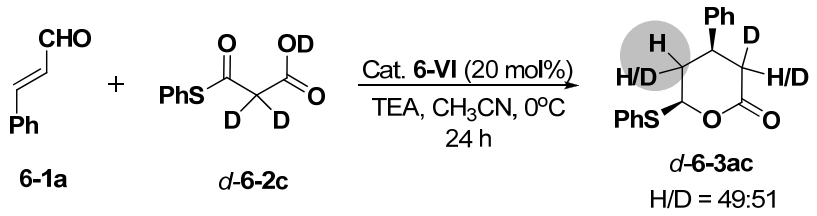
2	DCE	56	88	11	CH_3CN	52	57
3	Toluene	54	92	12	DMF	<10	-
4	Xylenes	52	90	13	1,4-Dioxane	53	98
5	CF_3Ph	52	84	14	THF	76	97
6	Anisole	63	95	15	CPME	76	96
7	Anisole	<10	-	16	Et_2O	76	93
8	EA	68	95	17[e]	THF	81	97
9	EA[d]	<10	-				

[a] Reactions were conducted with *trans*-4-Phenyl-3-buten-2-one **6-5a** (0.2 mmol), MAHT **6-2c** (0.24 mmol), catalyst **6-VII** (0.04 mmol) in the solvent (1.0 mL) at RT for 24 h. [b] Isolated yield. [c] Determined by HPLC analysis. [d] 0°C. [e] MAHT **6-2c** (0.5 mmol).

6.4.8 Mechanistic Investigations



490.6 mg (2.5 mmol) of malonic acid half thioester (MAHT) **6-2c** was placed into a 50 mL flask and 5.0 mL of acetonitrile was added. When the MAHT **6-2c** has dissolved, 6.0 mL D_2O was added and the solution was stirred for 6 hours under nitrogen. The solvent was removed under vaccum and the process was repeated two more times to yield 473.2 mg (95% yield) of the product *d*-**6-2c**.[190] ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.46 – 7.42 (m, 5H), 3.70 (s, 0.2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 189.87, 170.48, 134.44, 129.99, 129.40, 126.43, 48.00 (t, 1C, J = 20.5 Hz).

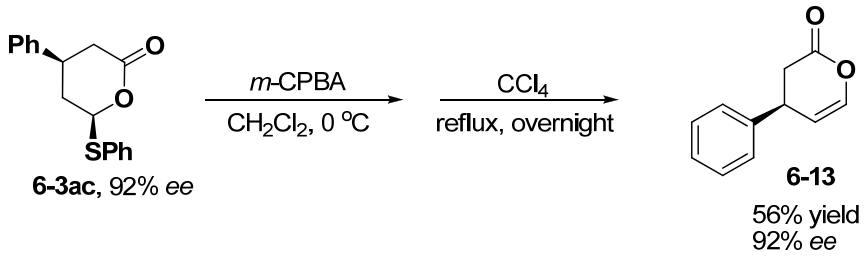


[190] See *Ref.* 88c.

To a solution of cinnamaldehyde **6-1a** (66.1 mg, 62.9 uL, 0.5 mmol) in CH_3CN (2.5 mL) was added catalyst **6-VI** (64.0 mg, 0.1 mmol) at 0 °C. After 40 min, *d*-**6-2c** (249.0 mg, 1.25 mmol) was added in one portion. Then, TEA (126.2 mg, 173.9 uL, 1.25 mmol) was added dropwise at 0 °C. The resulting reaction mixture was kept stirring at 0°C for 24 h. The crude product was purified by silica gel flash chromatography, eluted by hexane/EtOAc = 10:1 to afford the desired product *d*-**6-3ac** as white solid (89.1 mg, 62% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ(ppm): 7.60 (dd, *J* = 6.4, 3.2 Hz, 2H), 7.40 – 7.32 (m, 5H), 7.28 (t, *J* = 7.4 Hz, 1H), 7.16 (d, *J* = 7.6 Hz, 2H), 5.74 (dd, *J* = 11.2, 4.0 Hz, 1H), 3.23 – 3.14 (m, 1H), 2.88 (dd, *J* = 17.7, 5.0 Hz, 0.49H), 2.59 – 2.49 (m, 1H), 2.04 – 1.97 (m, 0.49H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 169.48, 141.54, 133.27, 131.79, 129.16, 129.05, 128.61, 127.47, 126.38, 86.34, 86.30, 86.26, 86.22, 37.36, 37.27, 37.17, 36.31.

6.4.9 Methodology Application

Synthesis of 3,4-Dihydro-2*H*-pyran-2-one (enol lactone) **6-13**[191]

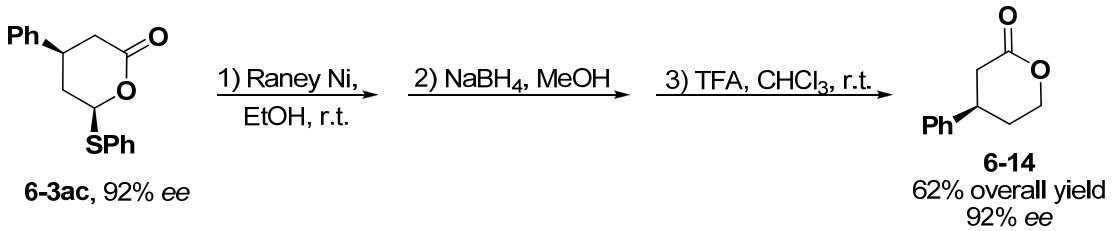


m-CPBA (28.5 mg; 0.165 mmol) was added to a solution of **6-3ac** (42.7 mg, 0.15 mmol) in CH_2Cl_2 (5.0 mL) at 0 °C with stirring. The mixture was stirred at 0 °C for 10 min and the reaction was quenched by adding saturated aq Na_2SO_3 (5 mL) and $NaHCO_3$ (30 mL). The mixture was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were dried with $MgSO_4$. Filtration and evaporation of the solvent gave a residue which was purified by silica gel column chromatography (hexane–EtOAc = 3:1) to afford a mixture of two diastereomers. Then, the mixture was added into 1.0 mL CCl_4. The reaction mixture was refluxed for overnight. The

[191] a) Ochiai, M.; Nishide, K.; Node, M.; Fujita, E. *Chem. Lett.* **1981**, 283; b) Shimizu, H.; Fukuda, S.; Sugiyama, S.; Satoh, T. *Synthesis* **2009**, *8*, 1323.

crude product was purified by silica gel column chromatography (hexane–EtOAc = 20:1) to afford the desired product **6-13** as a colourless oil (14.6 mg, 56% overall yield, 92% *ee*). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.35 (dd, *J* = 10.2, 4.6 Hz, 2H), 7.30 – 7.26 (m, 1H), 7.24 – 7.19 (m, 2H), 6.68 (dd, *J* = 6.0, 1.8 Hz, 1H), 5.44 (dd, *J* = 5.9, 4.1 Hz, 1H), 3.83 – 3.79 (m, 1H), 2.98 (dd, *J* = 16.0, 6.9 Hz, 1H), 2.74 (dd, *J* = 15.9, 8.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 167.29, 141.65, 141.16, 129.09, 127.52, 126.82, 109.39, 37.31, 36.73; HRMS (EI) calcd for $C_{11}H_{10}O_2$ 174.0681, found 174.0682; HPLC (Chiralpak AD-H, *i*-propanol/hexane = 2/98, flow rate 1.0 mL/min, λ = 254 nm): t_R (minor) = 12.7 min, t_R (major) = 14.1 min, *ee* = 92%; $[\alpha]^{25}_D$ = -20.1 (*c* = 0.51 in DCM).

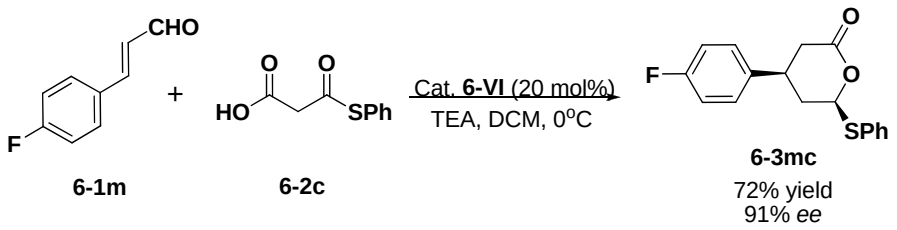
Synthesis of δ-lactone **6-14**



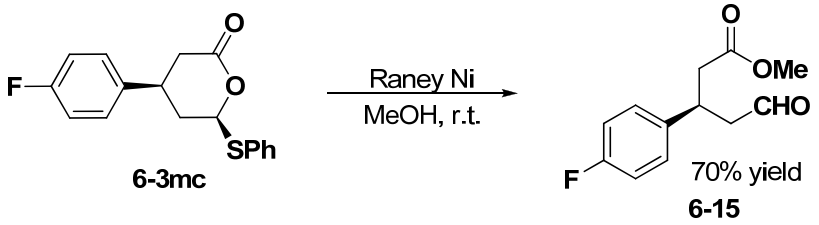
Compound **6-3ac** (227.0mg, 0.8 mmol) was added to a suspension of Raney Ni (1.0 g) in absolute EtOH (10 mL). The mixture was stirred for overnight at room temperature, before the Raney Ni was removed by filtration through a celite pad. Then the catalyst was washed with absolute EtOH (3 × 10 mL) and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane–EtOAc = 10:1) to afford the intermediate γ-ester aldehyde as a colourless oil (142.1 mg, 81% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.65 (d, *J* = 1.6 Hz, 1H), 7.32 – 7.27 (m, 2H), 7.25 – 7.18 (m, 3H), 4.06 – 4.02 (m, 2H), 3.73 (p, *J* = 7.4 Hz, 1H), 2.87 – 2.74 (m, 2H), 2.72 – 2.59 (m, 2H), 1.15 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 200.67, 171.44, 142.35, 128.67, 127.19, 126.97, 60.44, 49.32, 40.84, 36.16, 13.99; HRMS (EI) calcd for $C_{13}H_{16}O_3$ 220.1099, found 220.1108.

Sodium borohydride (5.7 mg, 0.15 mmol) was added into a solution of compound γ-ester aldehyde (22.0 mg, 0.10 mmol) in MeOH (1.0 mL) at $0^{o}C$. The reaction mixture was stirred at RT for 30 min. Then water (0.5 mL) was added to quench this reaction. The mixture was extracted with CH_2Cl_2 and the combined organic layers were dried with $MgSO_4$. Filtration and evaporation of the solvent gave a residue which was purified by silica gel column chromatography (hexane–EtOAc = 4:1) to yield a colourless oil. Then this colourless oil was directly dissolved in 5.0 mL $CHCl_3$, followed by adding trifluoroacetic acid (38.3 uL, 0.50 mmol). The reaction mixture was stirred at room temperature for 1 hour and the reaction was quenched by adding saturated $NaHCO_3$ (10 mL). The mixture was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were dried with $MgSO_4$. Filtration and evaporation of the solvent gave a residue which was purified by silica gel column chromatography (hexane–EtOAc = 4:1) to afford the product δ-lactone **6-14** as a colourless oil (13.5 mg, 77% yield, 92% *ee*). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.29 (dd, *J* = 10.3, 4.7 Hz, 2H), 7.22 – 7.18 (m, 1H), 7.17 – 7.13 (m, 2H), 4.43 (ddd, *J* = 11.4, 4.7, 4.2 Hz, 1H), 4.35 – 4.29 (m, 1H), 3.20 – 3.14 (m, 1H), 2.85 (ddd, *J* = 17.6, 6.0, 1.6 Hz, 1H), 2.57 (dd, *J* = 17.6, 10.6 Hz, 1H), 2.11 (dqd, *J* = 13.9, 4.0, 1.6 Hz, 1H), 1.97 (dtd, *J* = 14.2, 10.5, 4.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 170.61, 142.75, 128.95, 127.20, 126.42, 68.58, 37.45, 37.41, 30.28; HRMS (EI) calcd for $C_{11}H_{12}O_2$ 176.0837, found 176.0834; HPLC (Chiralpak AS-H, *i*-propanol/hexane = 30/70, flow rate 0.6 mL/min, λ = 254 nm): t_R (major) = 32.7 min, t_R (minor) = 39.5 min, *ee* = 92%; $[\alpha]^{25}_{D}$ = -10.8 (*c* = 1.00 in DCM).

Synthesis of **(-)-Paroxetine**

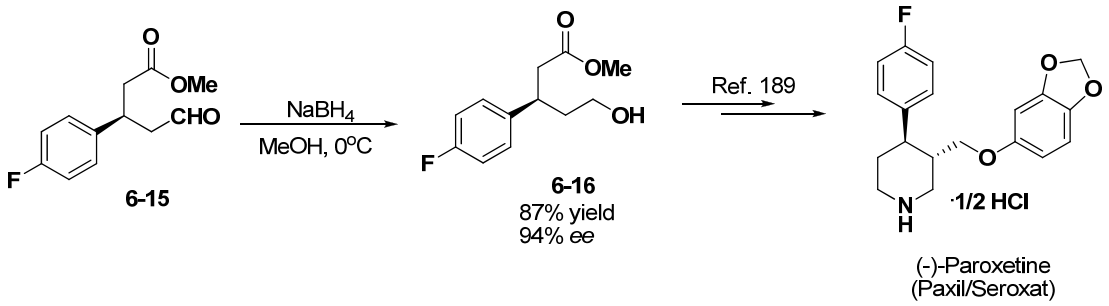


To a solution of 4-fluorocinnamaldehyde **6-1m** (300.1 mg, 2.0 mmol,) in DCM (5.0 mL) was added catalyst **6-VI** (238.8 mg, 0.4 mmol) at 0 °C. After 40 min, malonic acid half thioester **6-2c** (981.1 mg, 5.0 mmol) was added in one portion. Then, TEA (695.6 uL, 5.0 mmol) in 5.0 mL DCM was added dropwise *via* syringe at 0 °C. The resulting reaction mixture was kept stirring at 0°C for 24 h. The crude product was purified by silica gel flash chromatography, eluted by hexane/EtOAc = 10:1 to afford the desired product **6-3mc** as a white solid (436.2 mg, 72% yield, 91% *ee*).^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.59 (dd, *J* = 6.2, 2.8 Hz, 2H), 7.39 – 7.33 (m, 3H), 7.13 (dd, *J* = 8.5, 5.3 Hz, 2H), 7.04 (t, *J* = 8.6 Hz, 2H), 5.72 (dd, *J* = 11.2, 4.1 Hz, 1H), 3.18 (ddd, *J* = 12.3, 8.4, 4.5 Hz, 1H), 2.87 (ddd, *J* = 17.6, 5.0, 2.1 Hz, 1H), 2.57 – 2.46 (m, 2H), 1.97 (dd, *J* = 25.7, 11.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 169.19, 162.98, 161.02, 137.33, 137.30, 133.35, 131.68, 129.21, 128.70, 127.96, 127.90, 116.05, 115.88, 86.23, 37.38, 36.80, 36.42; HRMS (EI) calcd for $C_{17}H_{15}FO_2S$ 302.0777, found 302.0771; HPLC (Chiralpak IC, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_R (minor) = 23.4 min, t_R (major) = 25.8 min, *ee* = 91%; $[\alpha]^{25}_D$ = -78.2 (*c* = 1.51 in DCM).



Compound **6-3mc** (302.36mg, 1.0 mmol) was added to a suspension of Raney Ni (0.3 g) in absolute MeOH (5.0 mL). The mixture was stirred for 10 hours at room temperature, before the Raney Ni was removed by filtration through a celite pad. Then the catalyst was washed with absolute MeOH (3 × 10 mL) and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane–EtOAc = 6:1) to afford the compound **6-15** as a colourless oil (156.1 mg, 70% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.64 (t, *J* = 1.5 Hz, 1H), 7.23 – 7.12 (m, 2H), 7.03 – 6.94 (m, 2H), 3.78 – 3.68 (m, 1H), 3.58 (s, 3H),

2.88 – 2.71 (m, 2H), 2.71 – 2.56 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 200.26, 171.75, 163.29, 160.04, 138.10, 138.06, 128.77, 128.66, 115.68, 115.40, 51.62, 49.37, 40.62, 35.30; HRMS (EI) calcd for $C_{12}H_{13}FO_3$ 224.0849, found 224.0841.



Sodium borohydride (11.3 mg, 0.3 mmol) was added into a solution of compound **6-15** (44.8 mg, 0.20 mmol) in MeOH (2.0 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min. Then water (1 mL) was added to quench this reaction. The mixture was extracted with CH_2Cl_2 and the combined organic layers were dried with $MgSO_4$. Filtration and evaporation of the solvent gave a residue which was purified by silica gel column chromatography (hexane–EtOAc = 3:1) to afford the product **6-16** as a colourless oil (39.4 mg, 87% yield, 94% *ee*). ^{1}H NMR (500 MHz, CD_3OD) δ = 7.25 – 7.22 (m, 2H), 7.02 – 6.99 (m, 2H), 3.54 (s, 3H), 3.42 (ddd, J = 11.0, 6.9, 5.3 Hz, 1H), 3.37 – 3.32 (m, 1H), 3.31 – 3.24 (m, 1H), 2.70 (dd, J = 15.2, 6.4 Hz, 1H), 2.59 (dd, J = 15.2, 9.0 Hz, 1H), 1.94 – 1.87 (m, 1H), 1.82 – 1.76 (m, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ = 174.28, 163.98, 162.05, 140.78, 140.76, 130.34, 130.28, 116.14, 115.96, 60.47, 51.93, 42.30, 39.88, 39.27; HRMS (EI) calcd for $C_{12}H_{15}FO_3$ 226.1005, found 226.0999; HPLC (Chiralpak OB-H, *i*-propanol/hexane = 10/90, flow rate 0.8 mL/min, λ = 254 nm): t_R (major) = 11.1 min, t_R (minor) = 14.1 min, *ee* = 94%; $[\alpha]^{25}_D$ = -16.0 (c = 1.06 in DCM).

6.4.10 X-ray Crystallographic Analysis

Table 6.8 Crystal data and structure refinement for **6-3ac**.

Empirical formula	C17 H16 O2 S	
Formula weight	284.36	
Temperature	223(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 8.9700(6) Å	a= 90°.
	b = 6.0133(4) Å	b= 95.276(2)°.
	c = 28.3443(18) Å	g = 90°.
Volume	1522.39(17) $Å^3$	
Z	4	
Density (calculated)	1.241 Mg/m^3	
Absorption coefficient	0.211 mm^{-1}	
F(000)	600	
Crystal size	0.54 x 0.50 x 0.36 mm^3	
Theta range for data collection	0.72 to 27.47°	
Index ranges	-7<=h<=11, -7<=k<=7, -36<=l<=36	
Reflections collected	10737	
Independent reflections	6647 [R(int) = 0.0233]	
Completeness to theta = 27.47°	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9280 and 0.8946	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6647 / 196 / 404	
Goodness-of-fit on F^2	1.029	
Final R indices [I>2sigma(I)]	R1 = 0.0708, wR2 = 0.1707	
R indices (all data)	R1 = 0.0850, wR2 = 0.1821	
Absolute structure parameter	0.09(11)	
Largest diff. peak and hole	0.545 and -0.246 $e.Å^{-3}$	

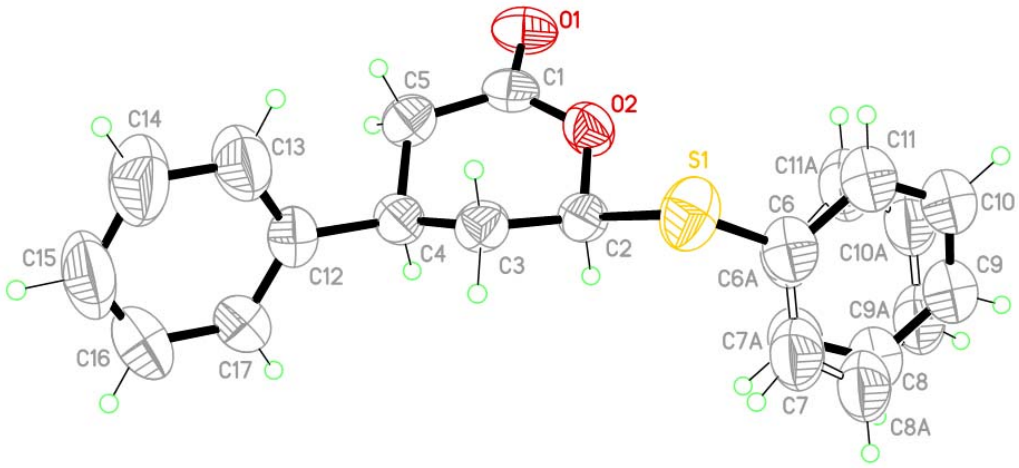


Figure 6.2 X-ray crystal structure of **6-3ac**

Table 6.9 Crystal data and structure refinement for **6-6lc**.

Empirical formula	C18 H17 Br O2 S	
Formula weight	377.29	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 5.6074(6) Å	a= 90°.
	b = 14.7841(16) Å	b= 90°.
	c = 20.027(2) Å	g = 90°.
Volume	1660.2(3) $Å^3$	
Z	4	
Density (calculated)	1.509 Mg/m^3	
Absorption coefficient	2.606 mm^{-1}	
F(000)	768	
Crystal size	0.56 x 0.24 x 0.10 mm^3	
Theta range for data collection	2.03 to 27.50°	
Index ranges	-7<=h<=7, -18<=k<=19, -26<=l<=24	
Reflections collected	11718	
Independent reflections	3802 [R(int) = 0.0359]	

Completeness to theta = 27.50°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7806 and 0.3232
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3802 / 0 / 200
Goodness-of-fit on F^2	1.016
Final R indices [I>2sigma(I)]	R1 = 0.0290, wR2 = 0.0599
R indices (all data)	R1 = 0.0320, wR2 = 0.0608
Absolute structure parameter	0.018(7)
Largest diff. peak and hole	0.613 and -0.289 e.$Å^{-3}$

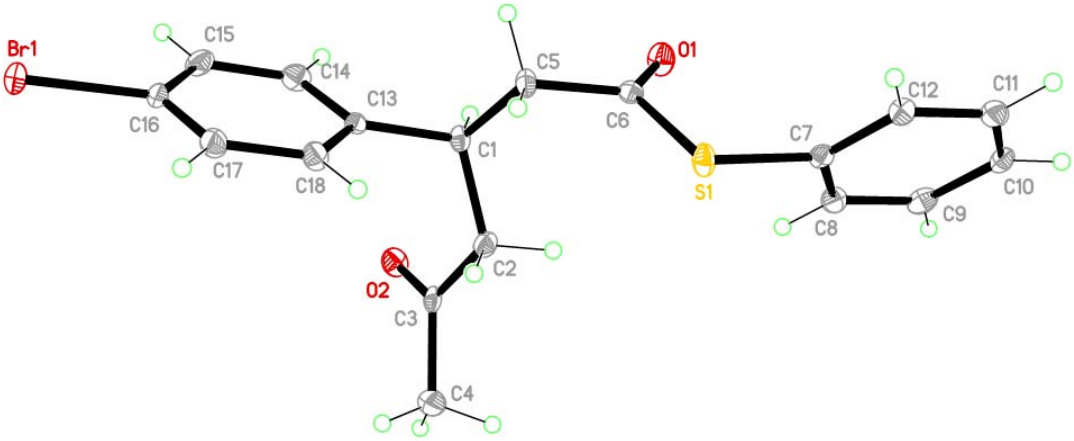


Figure 6.3 X-ray crystal structure of **6-6lc**.