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NANYANG TECHNOLOGICAL UNIVERSITY

NEW CHIRAL LIGANDS AND CATALYSTS FOR ASYMMETRIC SYNTHESIS

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XIAO JIAN

SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

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NEW CHIRAL LIGANDS AND CATALYSTS FOR ASYMMETRIC SYNTHESIS

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School of Physical and Mathematical Sciences

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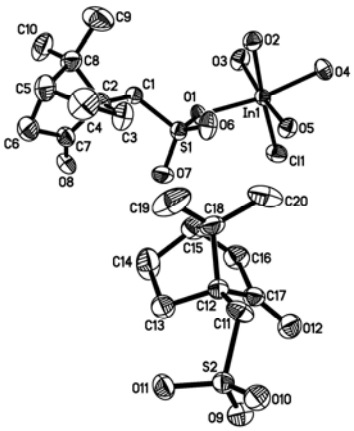
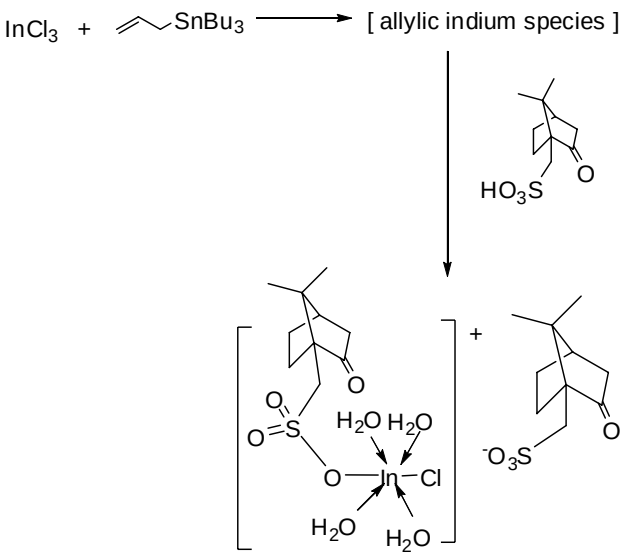
SUMMARY

This thesis describes the design and syntheses of a series of new chiral ligands and catalysts as well as their application in asymmetric synthesis and green chemistry.

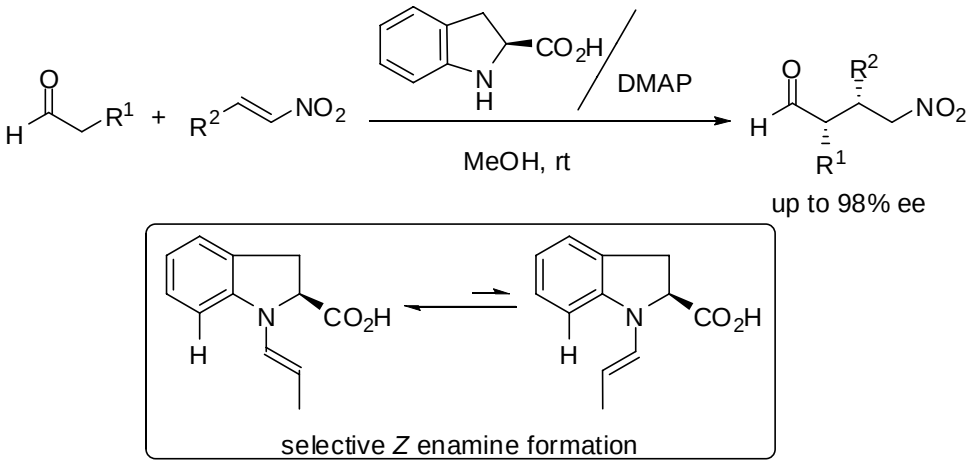
I. A NOVEL, WATER TOLERANT CHIRAL INDIUM COMPLEX

A novel chiral indium(III) camphorsulfonate complex has been developed as a water tolerant Lewis acid catalyst to afford high yields (up to 99%) in an one-pot three-component Mannich-type reaction in water. This new chiral indium complex can be prepared from reaction of (1*S*)-(+)-10-camphorsulfonic acid (CSA) with the desired allylic indium species, resulting from transmetallation of allylic stannane with indium trihalides. Although control of chirality was not observed in this aqueous reactions, this study provides useful information on designing new water tolerant chiral indium catalyst.





II. A NEW MODULARLY DESIGNED BICYCLIC ORGANOCATALYST

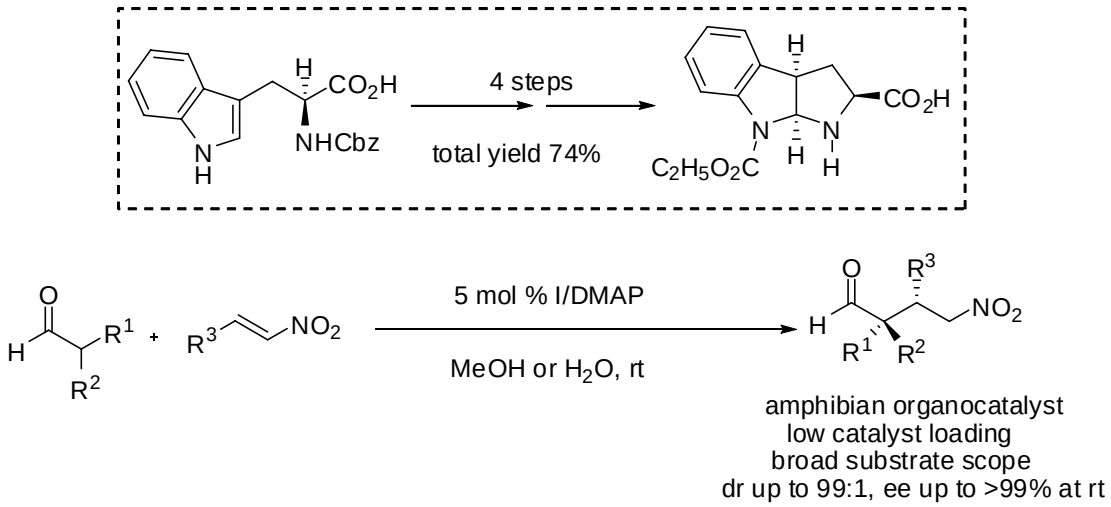


We have explored a new class of bicyclic organocatalyst by virtue of self assembly strategy. The asymmetric Michael reaction of aldehydes and nitrostyrene was selected as the model reaction to test our hypothesis. The success of this hypothesis breaks the regime of mono five-membered pyrrolindine ring dominated enamine organocatalysis and make significant contribution to enamine catalysis.

III. A NEW CLASS OF STRUCTURALLY RIGID TRICYCLIC AMPHIBIAN ORGANOCATALYST

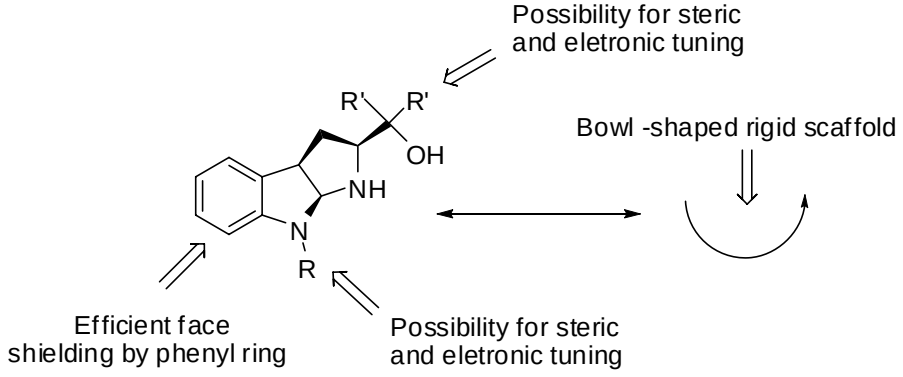
A new class of structurally rigid tricyclic amphibian chiral organocatalysts based on the hexahydropyrrolo[2,3-*b*]indole skeleton was rationally designed. The desired catalyst could be easily synthesized in 4 steps from cheap L-tryptophan derivative on a large scale with a total yield of 74 %. The efficiency of this catalyst has been demonstrated in the asymmetric Michael addition of aldehydes to nitrostyrenes. The special features of this catalyst include: (1) easily prepared in large scale; (2) **I**/DMAP

catalyst has been shown to afford the desired products in high yields and excellent enantioselectivities both in organic solvents and in water; (3) only slight excess of aldehyde is used in this system; (4) low catalyst loading and broad substrate scope. These advantages render this chiral catalyst more suitable for practical use and will certainly find application in asymmetric synthesis.

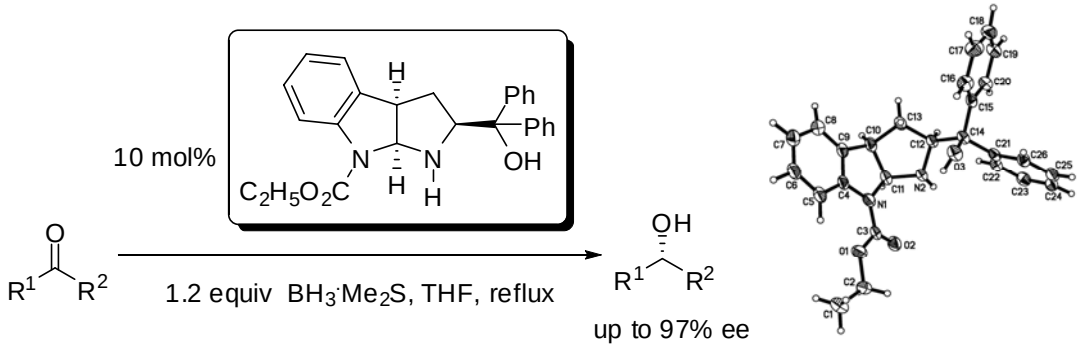


IV. A NEW CLASS OF STRUCTURALLY RIGID TRICYCLIC CHIRAL LIGANDS

A series of a new class of structurally rigid tricyclic chiral ligands based on a hexahydropyrrolo[2,3-b]indole skeleton have been rationally designed and

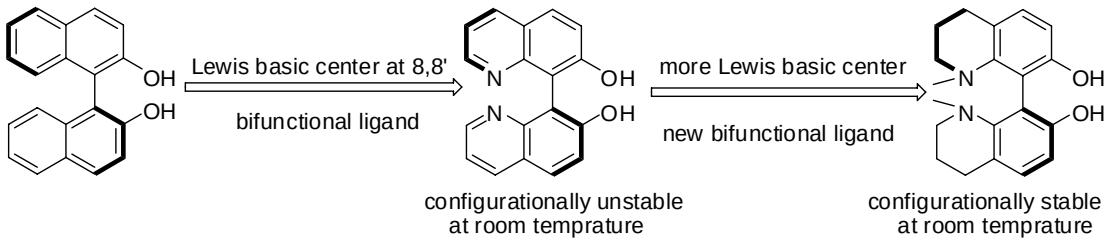


conveniently synthesized from the commercially available L-tryptophan derivative in five steps. These ligands have been shown to serve as efficient chiral ligands in the enantioselective borane reduction of prochiral ketones to afford the corresponding alcohols in excellent yield and high enantioselectivities (up to 97% *ee*). The rigid backbone and easy modification of these ligands skeleton, as well as their recoverability make them promising ligands for asymmetric catalysis. The successful natural skeleton based design will lead to a conceptually new familly of modular chiral ligands or chiral catalysts.



V. A NEW BIFUNCTIONAL LIGAND: 1,1'-DIMETHYL-OCTAHYDRO-8,8'-BIQUINOLINE-7,7'-DIOL

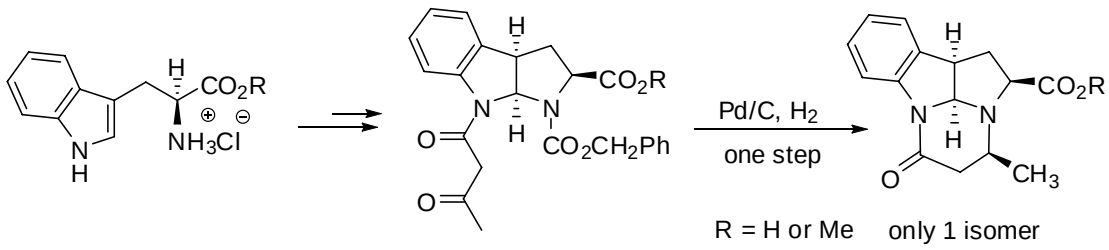
A new bifunctional ligand，1,1'-dimethyl-octahydro-8,8'-biquinoline-7,7'-diol, an aza analogue of BINOL, has been rationally designed and synthesized. Both the enantiomers of 1,1'-dimethyl-octahydro-8,8'-biquinoline-7,7'-diol have been



successfully resolved in few steps. Its application in asymmetric catalysis is highly anticipated. This new member of the aza BINOL family exhibits different properties as compared to BINOL and open up new catalyst design as well as providing synthetic material in many fields such as chiral supramolecular recognition and crystal engineering.

VI. UNEXPECTED DOMINO RING CLOSURE FOR CONSTRUCTION OF TETRACYCLIC INDOLE ALKALOID RING SYSTEM

During the course of our synthetic efforts aimed at developing the above new chiral ligands for asymmetric catalysis, we identified an unexpected domino ring closure process which provided an easy and stereoselective access to tetracyclic [6,5,5,6] indole ring system.



INDEX OF ABBREVIATIONS

δ	chemical shift
°C	degree centigrade
Ac	acetyl
AcCl	acetyl chloride
Ac_2O	acetic anhydride
aq.	aqueous
Ar	aryl
BINAP	2,2'-diphenylphosphino-l, l′-binaphthyl
BINOL	1,1′-binaphthyl-2,2′-diol
Bn	benzyl
br	broad singlet
Bu	butyl
BuLi	butyl lithium
calcd	calculated
CAN	ceric ammonium nitrate
Cbz	benzyloxycarbonyl
CH_2Cl_2	dichoromethane
$CDCl_3$	deuterated chloroform
cm^{-1}	inverse centimeter
CSA	camphorsulfonic acid
Cy	cyclohexanyl
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DBSA	dodecylbenzenesulfonic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
dd	doublet of doublets

de	diastereomeric excess
DFT	density functional theory
DIEPA	*N*,*N*-diisopropylethylamine
DMAP	4-*N*,*N*-dimethylamino pyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sufoxide
dt	doublet of triplets
ee	enantiomeric excess
EI	electron-impact ionization
equiv.	equivalent(s)
ESI	electrospray ionization
Et	ethyl
Et_3N	triethylamine
EtOAc or EA	ethyl acetate
FSG	face shielding group
FTIR	fourier transform infrared spectrometry
g	gram
h or hrs	hour(s)
HMPA	hexamethylphosphoramide
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
i-Pr	isopropyl
J	coupling constant
LDA	lithium diisopropylamide
LUMO	lowest unoccupied molecular orbital
M	molar concentration
m	multiplet

m/z	mass per charge ratio
M^+	parent ion peak (mass spectrum)
Me	methyl
MeCN	acetonitrile
MOM	methoxymethyl
MeOH	methanol
MHz	mega hertz
min	minute(s)
mL	millilitres
mmol	millimole
mol%	mole percent
MS	mass spectrometry
ms	molecular sieves
NMM	*N*-methylmorpholine
NMR	nuclear magnetic resonance
N.R.	no reaction
N.D.	not determined
Nu	nucleophile
OTf	trifluoromethane sulfonate (triflate)
p	para
Pd/C	palladium on carbon
Ph	phenyl
PMB	*p*-methoxybenzyl
ppm	parts per million
Pr	propyl
PYBOX	bis(oxazolinyl)pyridine
q	quartet
R_f	retention factor
R_t	retention time

RBF	round-bottom flask
rt	room temperature
s	singlet
sat.	saturated
SDS	sodium dodecylsulfonate
SOMO	singly occupied molecular orbital
t	triplet
TBAB	tributylammonium bromide
t-Bu	*tert*-butyl
td	triplets of doublet
tdd	triplets of doublets of doublet
TEAB	triethylammonium bromide
TFA	trifluoroacetic acid
TfOH	triflate acid
Tf_2O	triflate anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Tf	Trifluoromethanesulfonyl
Ts	*p*-toluenesulfonyl
T.S.	transition state
UV	ultraviolet
vol	volume

CHAPTER 1

A Novel, Water-tolerant Chiral Indium Complex

1.1 OVERVIEW OF MANNICH OR MANNICH-TYPE REACTIONS IN WATER

Organic reactions in aqueous media have attracted a great deal of attention in contemporary synthetic chemistry because of its cheap, safe and environmentally benign advantages over conventional reactions in organic solvents.[1] Furthermore, reactions carried out in aqueous media provide opportunity to discover new reactions and new concepts in organic synthesis since water has many unique physical and chemical properties. In this area, to perform catalytic asymmetric reactions in water is far more interesting.[2] However, unlike enantioselective reactions in organic solvents, it is usually difficult to achieve high yield and high stereoselectivity in water. This is because water can often decompose the catalyst or destroy the intermediate and the transition state, therefore compromising the stereoselectivity.

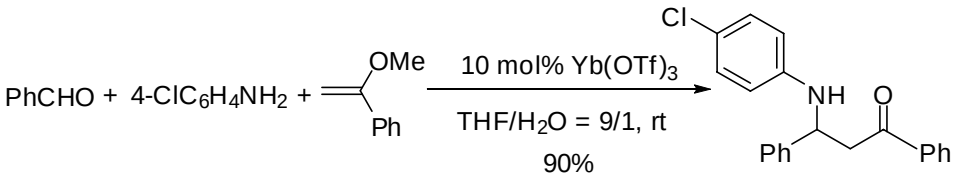
Among the most important carbon-carbon bond-forming reactions in organic synthesis, Mannich or Mannich-type reactions represent a powerful method for the synthesis of *β*-amino carbonyl compounds, which are versatile building blocks for the

[1] (a) Li, C.-J.; Chan, T. H. *Comprehensive Organic Reactions in Aqueous Media*; Wiley: Hoboken, **2007**. (b) Grieco, P. A. *Organic Synthesis in Water*; Blackie: London, **1998**. (c) Joó, F. *Aqueous Organometallic Catalysis*; Kluwer: Dordrecht, **2001**. (d) Cornils, B.; Herrmann, W. A. *Aqueous Phase Organometallic Catalysis. Concepts and Applications*; Wiley: Weinheim, **2004**. (e) Nakamura, K.; Matsuda, T. In *Organic Reactions in Water: Principles, Strategies and Applications*; Lindström, U. M., Ed.; Blackwell: Oxford, U. K. **2007**; pp 301-349. (f) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159. (g) Li, C.-J. *Chem. Rev.* **1993**, *93*, 2023. (h) Kobayashi, S.; Manabe, K. *Acc. Chem. Res.* **2002**, *35*, 209. (i) Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095. (j) Li, C.-J.; Chen, L. *Chem. Soc. Rev.* **2006**, *35*, 68. (k) Herrerias, C. I.; Yao, X.; Li, Z.; Li, C.-J. *Chem. Rev.* **2007**, *107*, 2546. (l) Dallinger, D.; Kappe, C. O. *Chem. Rev.* **2007**, *107*, 2563. (m) Minakata, S.; Komatsu, M. *Chem. Rev.* **2009**, *109*, 711. (n) Chanda, A.; Fokin, V. V. *Chem. Rev.* **2009**, *109*, 725.

[2] For reviews on stereoselective organic reactions in aqueous media, see: (a) Sinou, D. *Adv. Synth. Catal.* **2002**, *344*, 221. (b) Lindström, U. M. *Chem. Rev.* **2002**, *102*, 2751. (c) Manabe, K.; Kobayashi, S. *Chem.–Eur. J.* **2002**, *8*, 4094. (d) Gruttadauria, M; Giacalone, F; Noto, R. *Adv. Synth. Catal* **2009**, *351*, 33. (e) Dwars, T.; Oehme, G. *Adv. Synth. Catal.* **2002**, *344*, 239. (f) Pan, C.; Wang, Z. *Coord. Chem. Rev.* **2008**, *252*, 736. (g) Genêt, J.-P.; Darses, S.; Michelet, V. *Pure Appl. Chem.* **2008**, *80*, 831.

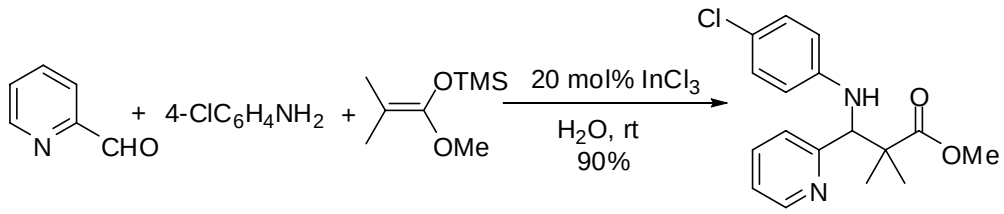
preparation of various pharmaceuticals and natural products.[3] Moreover, the asymmetric version of which could provide many optically active nitrogen-containing compounds for the synthesis of a large number of biologically important targets.

Recently, Mannich or Mannich-type reactions performed in aqueous solution have been studied extensively. Employing an aqueous medium of THF-water (9:1), Kobayashi reported the reaction of an aldehyde with an amine and a vinyl ether to give the Mannich-type product in the presence of 10 mol% of $Yb(OTf)_3$ (Scheme 1.1).[4]



Scheme 1.1 $Yb(OTf)_3$-catalyzed Mannich-type reactions in aqueous solution

Our group reported a one-pot Mannich-type reaction between aldehydes, amines and silyl enol ethers catalyzed by indium trichloride in water to give *β*-amino ketones and esters in moderate to good yields.[5] This catalyst can be recovered after the reaction had completed and can be reused for a repeat reaction without any

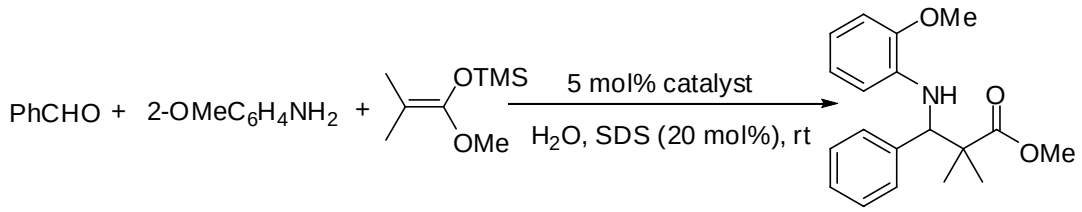


Scheme 1.2 $InCl_3$-catalyzed Mannich-type reactions in water

[3] (a) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044. (b) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069. (c) Mannich, C.; Krosche, W. *Arch. Pharm* **1912**, *250*, 674.
[4] Kobayashi, S.; Ishitani, H. *J. Chem. Soc., Chem. Commun.* **1995**, 1379.
[5] (a) Loh, T.-P.; Wei, L.-L. *Tetrahedron Lett*. **1998**, *39*, 323. (b) Loh, T.-P.; Liung, S. B. K. W.; Tan, K.-L.; Wei, L.-L. *Tetrahedron* **2000**, *56*, 3227.

significant drop in reactivity. NMR studies indicated that $InCl_3$ is essential for this Mannich-type reaction in water. Without $InCl_3$, only imines and aldol products were obtained (Scheme 1.2).

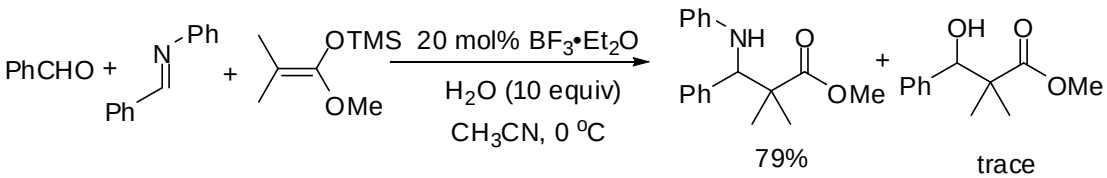
In the presence of a catalytic amount of $Ln(OTf)_3$ or $Cu(OTf)_2$, the three component Mannich-type reactions of aldehydes, amines, and silyl enolates proceeded smoothly in micellar systems to afford the corresponding *β*-amino ketones and esters in high yields (Scheme 1.3).[6]



catalyst = $Cu(OTf)_2$ (85%), $Yb(OTf)_3$ (80%), $Sc(OTf)_3$ (87%)

Scheme 1.3 $Ln(OTf)_3$ and $Cu(OTf)_2$-catalyzed Mannich-type reactions in water

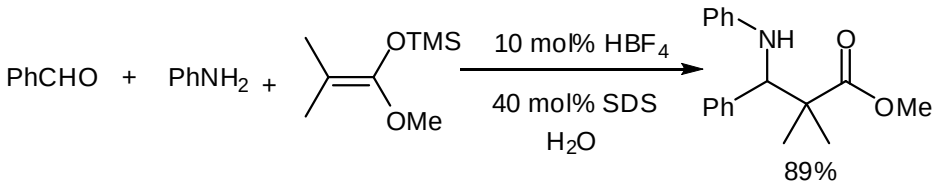
Akiyama reported that the Mannich-type reaction took place smoothly in the presence of 20 mol% $BF_3{\cdot}Et_2O$ and 10 equivalent H_2O in CH_3CN at 0 ^oC. Interestingly, aldol reaction was completely suppressed. The active species may be HBF_4 generated from $BF_3{\cdot}Et_2O$ and HF as HF is not effective itself in this reaction (Scheme 1.4).[7]



Scheme 1.4 $BF_3{\cdot}Et_2O$-catalyzed Mannich-type reactions in aqueous solution

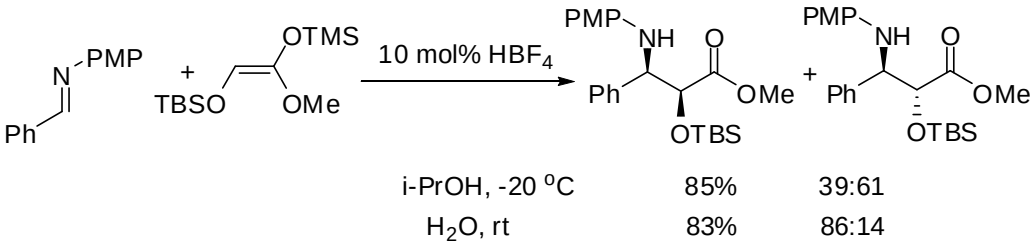
[6] Kobayashi, S.; Busujima, T.; Nagayama, S. *Synlett* **1999**, 545.
[7] Akiyama, T.; Takaya, J.; Kagoshima, H. *Chem. Lett*. **1999**, *9*, 947.

Brönsted acids have also been quite effective in catalyzing Mannich-type reactions in aqueous media. HBF_4-catalyzed Mannich-type reactions of aldehydes, amines, and silyl enolates took place smoothly in water in the presence of a surfactant to afford *β*-amino carbonyl compounds in high yields (Scheme 1.5).[8]



Scheme 1.5 HBF_4-catalyzed Mannich-type reactions in water

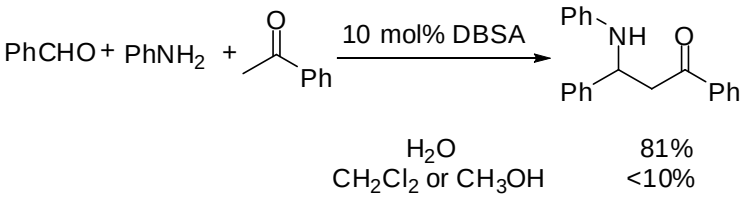
A changeover of the diastereoselectivity was found in the HBF_4-catalyzed Mannich-type reaction of ketene silyl acetal derived from *α*-siloxy ester with aldimines. The *anti* adduct was preferentially formed in aqueous 2-propanol but the *syn* adduct was the major product when the reaction was carried out in water in the presence of a water-surfactant (SDS). It was also shown that the ketene silyl acetal derived from aryl ester in aqueous 2-propanol gave *anti* product while the use of ketene silyl acetal derived from methyl ester in water gave the *syn* isomer preferentially in the presence of sodium dodecyl sulfate (Scheme 1.6).[9]



Scheme 1.6 HBF_4-catalyzed Mannich-type reactions of ketene silyl acetal with aldimines in water

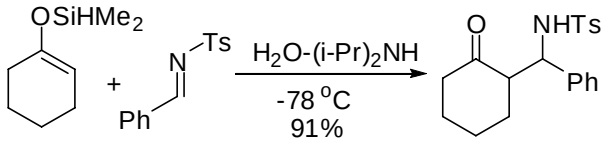
[8] (a) Akiyama, T.; Takaya, J.; Kagoshima, H. *Synlett* **1999**, 1426. (b) Akiyama, T.; Takaya, J.; Kagoshima, H. *Synlett* **1999**, 1045.
[9] Akiyama, T.; Takaya, J.; Kagoshima, H. *Tetrahedron Lett*. **2001**, *42*, 4025.

Kobayashi has developed a Brönsted acid catalyst for aqueous Mannich-type reactions. Three-component Mannich-type reactions of aldehydes, amines, and ketones were efficiently catalyzed by dodecylbenzenesulfonic acid (DBSA) at ambient temperature in water to give various *β*-amino ketones in good yields, whereas the same reaction proceeded sluggishly in organic solvents.[10] The catalyst is also effective for the reactions of aldehydes, amines, and silyl enolates in water (Scheme 1.7).[11]



Scheme 1.7 DBSA-catalyzed Mannich-type reaction in water

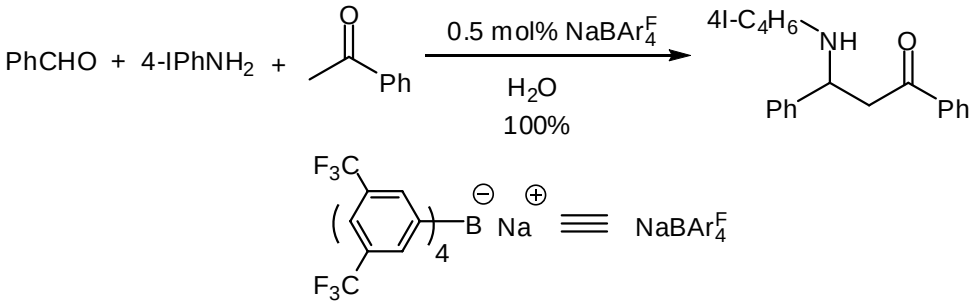
Dimethylsilyl enolates, activated by diisopropylamine and water, exhibits a high reactivity towards *N*-tosyl imines to give Mannich-type reaction product in the absence of Lewis acid or Brönsted acid. For example, the reaction of [(1-cyclohexen-1-yl)oxy]dimethylsilane) with 4-methyl-*N*-(phenylmethylene)benzene-sulfonamide gives the *anti* isomer in 91% yield stereoselectively (99:1 *anti/syn*) (Scheme 1.8).[12]



Scheme 1.8 Diisopropylamine-catalyzed Mannich-type reaction in water

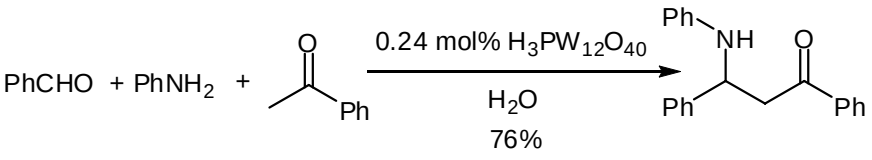
[10] Manabe, K.; Kobayashi, S. *Org. Lett*. **1999**, *1*, 1965.
[11] (a) Manabe, K.; Mori, Y.; Kobayashi, S. *Synlett* **1999**, 1401. (b) Manabe, K.; Mori, Y.; Kobayashi, S. *Tetrahedron* **2001**, *57*, 2537.
[12] Miura, K.; Tamaki, K.; Nakagawa, T.; Hosomi, A. *Angew. Chem., Int. Ed*. **2000**, *39*, 1958.

Sodium tetrakis(3,5-trifluoromethylphenyl)borate can efficiently catalyze the one-pot, three-component Mannich reaction of ketones with aromatic aldehydes and different anilines in water at room temperature to afford the corresponding *β*-amino carbonyl compounds in good to excellent yields (Scheme 1.9).[13]



Scheme 1.9 $NaBAr_4^F$ -catalyzed Mannich reaction in water

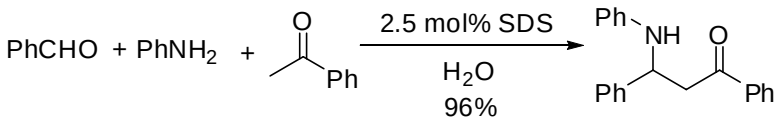
The one-pot, three-component Mannich reaction of ketones with aromatic aldehydes and amines could also be efficiently catalyzed by heteropoly acids in water to furnish the corresponding *β*-amino carbonyl compounds in good to excellent yields and with moderate diastereoselectivity. This method provides an improved modification of the three-component Mannich reaction in terms of mild reaction conditions, clean reaction profiles, low catalyst loading and simple workup procedure (Scheme 1.10).[14]



Scheme 1.10 Heteropoly acids-catalyzed Mannich reaction in water

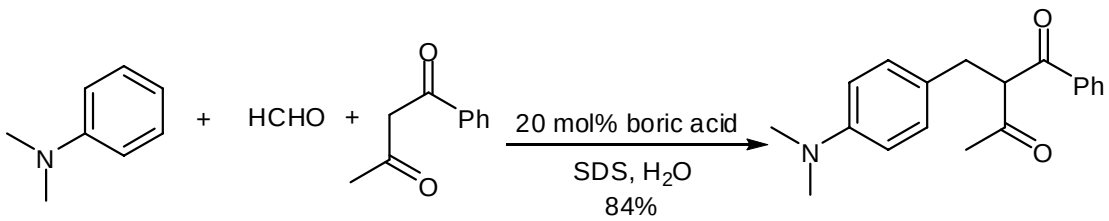
[13] Chang, C.; Liao, B.; Liu, S. *Tetrahedron Lett*. **2006**, *47*, 9257.
[14] Azizi, N.; Torkiyan, L.; Saidi, M. *Org. Lett*. **2006**, *8*, 2079.

Sodium dodecylsulfate (SDS) was also found to catalyze the reaction in neutral pure water (pH ≈ 7) and afforded the corresponding desired *β*-amino ketones precipitate in good yields, excellent regio- and diastereoselectivities with a simple workup. Interesting examples of click chemistry under neutral conditions in water were also observed (Scheme 1.11).[15]



Scheme 1.11 SDS-catalyzed Mannich reaction in water

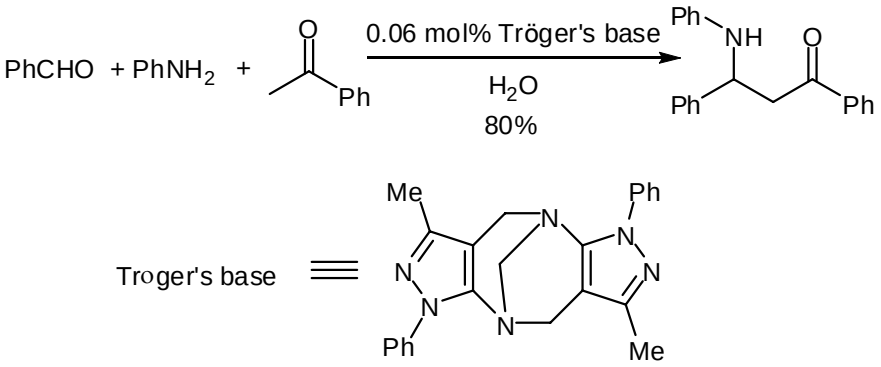
An unusual Mannich type reaction of tertiary aromatic amines, formaldehyde and 1,3-dicarbonyl compounds in aqueous micelles catalyzed by boric acid afforded dialkylaminoarylated 1,3-dicarbonyls in good yield. In this efficient Mannich type reaction, the tertiary aromatic amines first react with formaldehyde to generate an *N*-alkyl-*N*-(4-methylenecyclohexa-2,5-dienylidene)alkylaminium intermediate (aza quinone methide), which then undergoes nucleophilic addition with the 1,3-dicarbonyl compounds. The reaction is highly regioselective, providing exclusively *para* functionalized products in high yields (Scheme 1.12).[16]



Scheme 1.12 Boric acid-catalyzed Mannich reaction in water

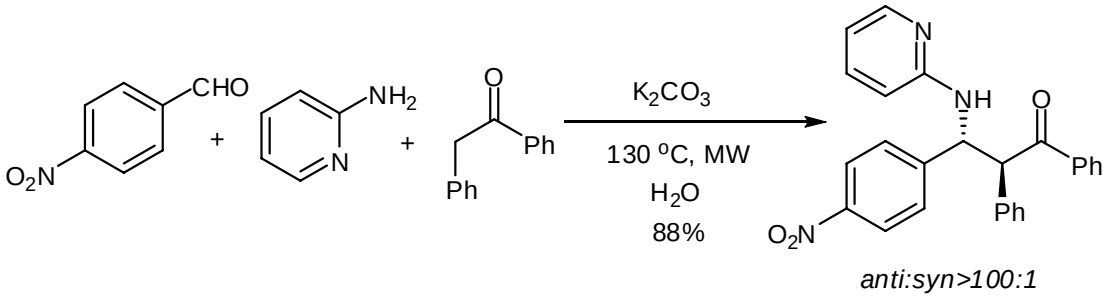
[15] Jafari, A.; Moradgholi, F.; Tamaddon, F. *Eur. J. Org. Chem.* **2009**, 1249.
[16] Kumar, A.; Maurya, R. *Tetrahedron Lett*. **2008**, *49*, 5471.

A Tröger's base derivative was reported to catalyze three-component Mannich reactions of aromatic aldehydes and aromatic amines with ketones in water at room temperature. The corresponding *β*-amino ketones were obtained in good yields and excellent stereoselectivity (Scheme 1.13).[17]



Scheme1.13 Tröger's base-catalyzed Mannich reaction in water

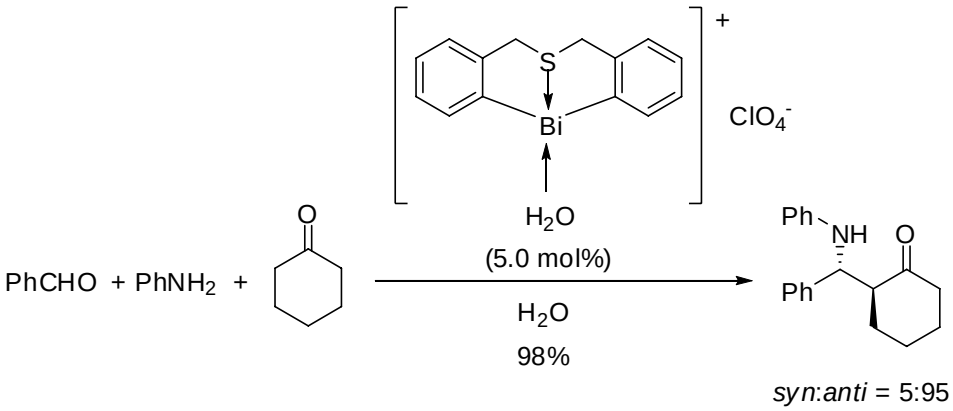
A new mild base-catalyzed Mannich reaction of aromatic aldehydes with 1,2-diphenylethanone and hetero-arylamines including pyridin-2-amine and pyrimidin-2-amine under microwave heating emerged in 2009 (Scheme 1.14).[18]



Scheme 1.14 K_2CO_3-catalyzed Mannich reaction in water

[17] Wu, H.; Chen, X.; Wan, Y.; Ye, L.; Xin, H.; Xu, H.; Yue, C.; Pang, L.; Ma, R.; Shi, D. *Tetrahedron Lett*. **2009**, *50*, 1062.
[18] Hao, W.; Jiang, B.; Tu, S.; Cao, X.; Wu, S.; Yan, S.; Zhang, X.; Han, Z.; Shi, F. *Org. Biomol. Chem.* **2009**, *7*, 1410.

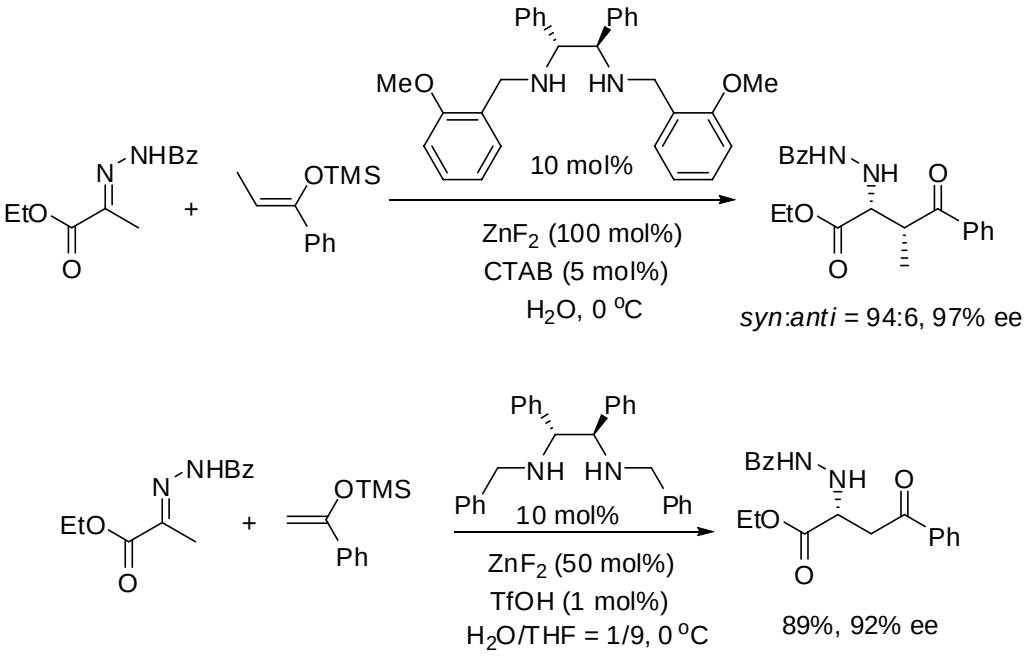
An air-stable, structurally determined cationic organobismuth complex with a perchlorate counterion has been synthesized and used to catalyze the direct Mannich reaction in water with high activity, diastereoselectivity, stability and good reusability (Scheme 1.15).[19]



Scheme 1.15 Organobismuth complex-catalyzed Mannich reaction in water

The first catalytic asymmetric Mannich-type reaction between hydrazono ester and silyl enol ether in aqueous media (THF/H_2O = 9:1) was reported by Kobayashi. The combination of chiral diamine with ZnF_2 catalyst in the presence of TfOH (1 mol%) additive generated the corresponding product in high yield and high enantioselectivity. Absence of the chiral diamine ligand or water in the system gave much less desirable results. The reaction was postulated to proceed with double activation where Zn^{2+} acts as a Lewis acid to activate the hydrozono ester and fluoride ion acts as a Lewis base to attack the silicon atom. Shortly thereafter, the conditions were further optimized to permit this reaction to proceed in pure water with similar results (Scheme 1.16).[20]

[19] Qiu, R.; Yin, S.; Zhang, X.; Xia, J.; Xu, X.; Luo, S. *Chem. Commun*, **2009**, 4759.
[20] (a) Hamada, T.; Manabe, K.; Kobayashi, S. *J. Am. Chem. Soc*. **2004**, *126*, 7768. (b) Hamada, T.; Manabe, K.; Kobayashi, S. *Chem. –Eur. J*. **2006**, *12*, 1205.



Scheme 1.16 Catalytic asymmetric Mannich-type reactions in water

1.2 DESIGN AND SYNTHESIS OF A NOVEL, WATER-TOLERANT CHIRAL INDIUM COMPLEX

1.2.1 RATIONAL DESIGN OF A NOVEL CHIRAL INDIUM COMPLEX

In the course of our investigations to develop efficient organic reactions in water, we discovered that indium complexes serve as water-tolerant Lewis acids which can be used to catalyze a wide variety of organic transformations in aqueous media.[21] Recently, two new chiral indium complexes, 1,1'-bi-2-naphthol (BINOL)–In(III) **1a–c** and 2,6-bis[4'(*S*)-isopropyloxazolin-2'-yl]pyridine (PYBOX)–In(III) complexes **2** (Figure 1.1) have been shown by our group to effect a series of reactions in high enantioselectivities.[22] However, the extension of these catalytic systems to aqueous media proved futile.[23] As such, the design of new water-tolerant chiral indium complex poses imminent challenges.

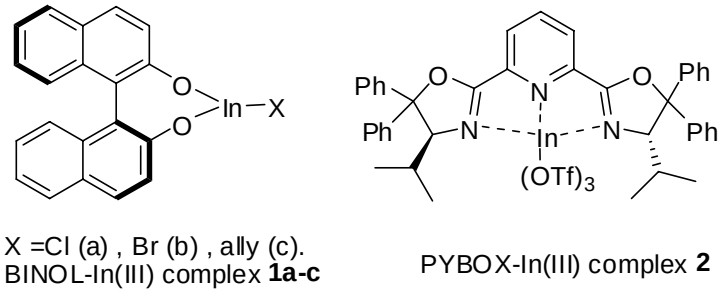
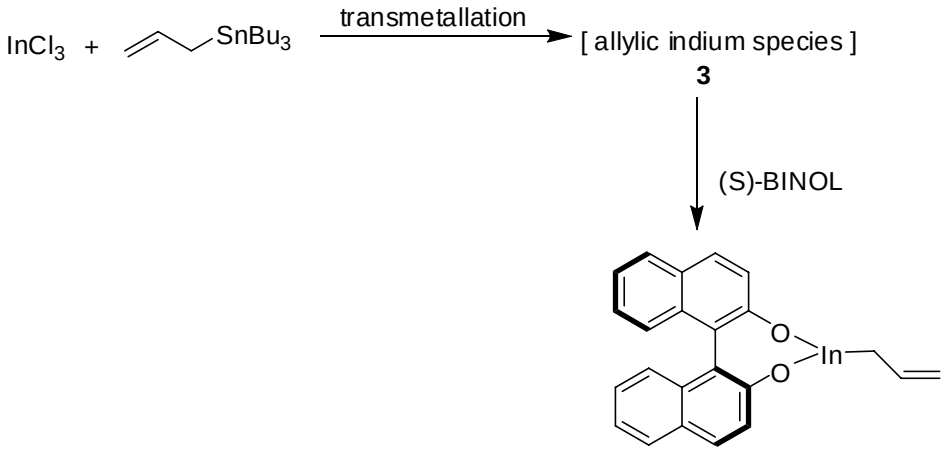


Figure 1.1 BINOL and PYBOX indium complexes

[21] (a) Loh, T. P. In *Science of Synthesis*; Yamamoto, H., Ed.; Georg Thieme Verlag: New York, **2004**; p 413. (b) Chua, G.-L.; Loh, T.-P.; In(III) Lewis acids. In *Acid Catalysis in Modern Organic Synthesis* **2008**, *1*, 377. (c) Loh, T.-P.; Chua, G.-L. *Chem. Commun,* **2006**, 2739.
[22] (a) Teo, Y.-C.; Tan, K.-T.; Loh, T.-P. *Chem.Commun.* **2005**, 1318. (b) Teo, Y.-C.; Goh, J.-D.; Loh, T.-P. *Org. Lett.* **2005**, *7*, 2743. (c) Teo, Y.-C.; Loh, T.-P. *Org. Lett.* **2005**, *7*, 2539. (d) Lu, J.; Ji, S.-J.; Teo, Y.-C.; Loh, T.-P. *Org. Lett.* **2005**, *7*, 159. (e) Lu, J.; Hong, M.-L.; Ji, S.-J.; Loh, T.-P. *Chem. Commun.* **2005**, 1010. (f) Lu, J.; Ji, S.-J.; Teo, Y.-C.; Loh, T.-P. *Tetrahedron Lett.* **2005**, *46*, 7435. (g) Zhao, J. F.; Tsui, H. Y.; Wu, P. J.; Lu, J.; Loh, T. P. *J. Am. Chem. Soc.* **2008**, *130*, 16492.
[23] Teo, Y.-C.; Goh, E.-L.; Loh, T.-P. *Tetrahedron Lett.* **2005**, *46*, 6209.

Therefore, we continue our effort towards the development of a new water-tolerant chiral indium complex which can catalyze organic transformations in aqueous media. Previous studies on the synthesis of chiral BINOL–In(III) complex revealed that allylic indium species could be obtained from transmetalation of indium trichloride with allyltributylstannane. These indium species facilitate the formation of the BINOL–In(III) complex **1c** (Scheme 1.17).

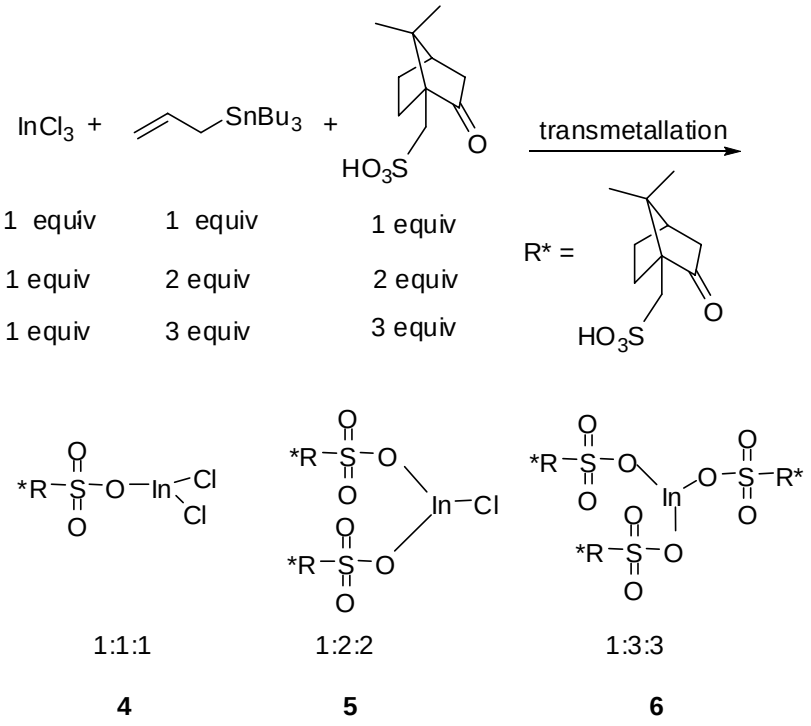


Scheme 1.17 Formation of BINOL indium complexe **1c**

In our studies on the properties of different indium complexes, we noticed that the strong Lewis acidic $In(OTf)_3$ is not stable in water, while the mild $InCl_3$ is stable. It is expected that hybrid of $In(OTf)_3$ and $InCl_3$ should exhibit water stability in the order: $InCl_3$>$InCl_2(OTf)$>$InCl(OTf)_2$>$In(OTf)_3$. However, the Lewis acidity would be of reverse order: $In(OTf)_3$>$InCl(OTf)_2$> $InCl_2(OTf)$>$InCl_3$.

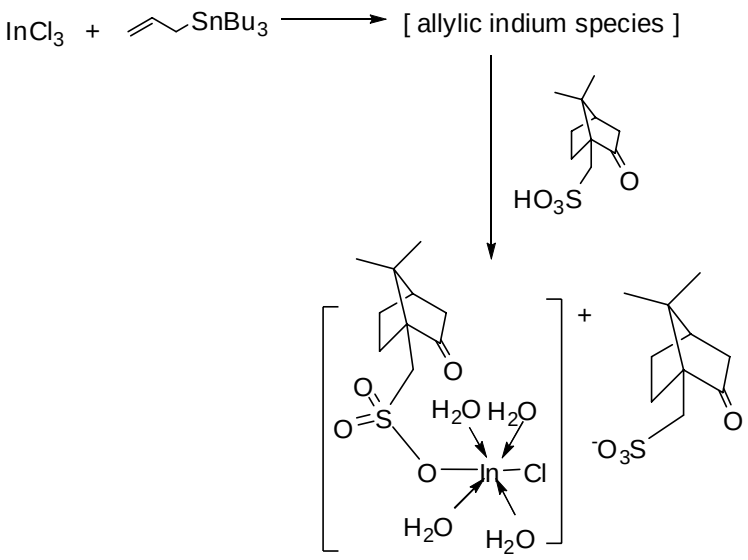
Based on these results, we envisaged that the resulting indium species **3** can also react with more acidic (1*S*)-(+)-10-camphorsulfonic acid to produce a more reactive water-tolerant chiral indium complex. Hence we could synthesize a new series of chiral water-tolerant In(III)–camphorsulfonate complexes from the transmetalation of allylic stannane with indium trihalides. We hope to synthesize chiral indium

complexes **4**, **5** and **6** with different ratio of starting material. Crystals suitable for X-ray analysis are necessary to authenticate their structures (Scheme 1.18).



Scheme 1.18 Formation of In(III)–camphorsulfonate complexes

To this end, the reaction of one equivalent of indium trichloride with two equivalents of allyltributylstannane, followed by the addition of (1*S*)-(+)-10-camphorsulfonic acid produced a new chiral indium complex **4** (Scheme 1.19). The structure of this indium complex was confirmed by X-ray crystal structure analysis (Figure 1.2). For the supposed 1:1:1 and 1:3:3 complexes, the structures obtained turn out to be identical to **4**, presumably the most stable structure**.**



4

Scheme 1.19 Formation of new chiral In(III)–camphorsulfonate complex **4**

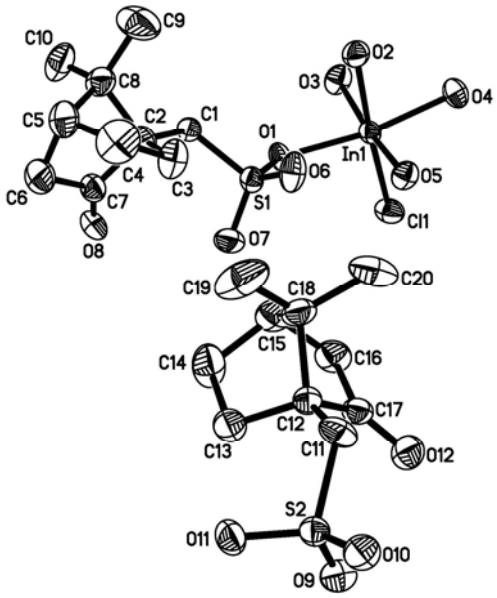
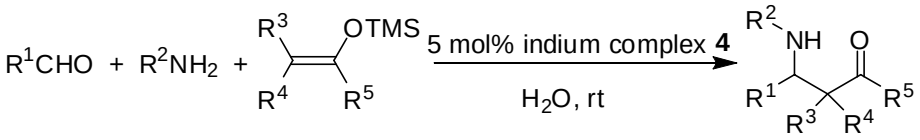


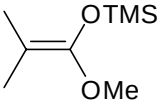
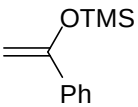
Figure 1.2 X-ray of new chiral indium complex **4**

1.2.2 APPLICATION TO ONE-POT THREE-COMPONENT MANNICH-TYPE REACTIONS IN WATER

To check the catalytic activity of this new indium complex **4** in water, preliminary studies were directed towards the application of this catalyst for the one-pot three-component Mannich-type reaction in water. The three-component reaction of benzaldehyde (0.5 mmol), aniline (0.5 mmol) and l-methoxy-2-methyl-l-trimethylsiloxypropene (1 mmol) was examined. To our delight, this indium complex

Table 1.1 Three-component Mannich-type reactions catalyzed by indium complex **4** in water [a]



Entry	Aldehyde (R^1)	Amine (R^2)	Silyl enol ether	Yield (%)[b]
1	Ph	Ph		69 (54)
2	Ph	4-ClPh		71 (23)
3	Ph	4-CH_3OPh		60 (30)
4	2-Py	Ph		99 (92)
5	2-Py	4-ClPh		99 (90)
6	H	Ph		46 (30)
7	H	4-ClPh		28 (21)
8	H	4-CH_3OPh		40 (35)
9	H	Ph		99 (91)
10	H	4-ClPh		99 (85)
11	Ph	4-ClPh		71 (60)
12	2-Py	4-CH_3OPh		99 (90)

[a] Conditions: aldehyde (1.0 equiv), amine (1.2 equiv), ketene silyl ether (2 equiv) and 5 mol% indium complex **4** in 5 mL H_2O stirred for 1 day. [b] Purified yield after column chromatography and yield in parenthesis refers to the same reaction carried out using 20 mol% of indium trichloride in water. [c] yield for mixture with tertiary Mannich product.

afforded the Mannich product in good yield even when 5 mol% of the catalyst was used (when the catalyst loading was 20%, 10%, 5%, 1%, the yield was 69%, 69%, 69%, 24% respectively). With these optimized conditions, the reactions were extended to different aldehydes, amines and the results are as shown in Table 1.1. In all cases, the reactions proceeded smoothly in water to afford the desired products in moderate to good yields. Furthermore, this new indium chiral complex **4** exhibited higher catalytic activity as compared with the reactions carried out using 20 mol% $InCl_3$ (yields are shown in parenthesis). Unfortunately, we did not observe any enantioselectivities in any of the reaction described above using this chiral indium complex. When 10 mol% indium complex was employed using the system in Entry 1 of Table 1.1, the catalyst could be recycled at least 5 times without significant loss in catalytic activity (1st: 69%, 2nd: 69%, 3rd: 60%, 4th: 50%, 5th: 50% respectively). The drop in reactivity by the 4^{th} and 5^{th} cycle may be attributed to the loss of the catalyst due to organic extraction.

1.3 CONCLUSION

In summary, we have designed and synthesized a novel chiral indium complex and found it to be an excellent water tolerant Lewis acid that can efficiently catalyze the one-pot three-component Mannich-type reactions in water using 5 mol% catalyst loading. The specificity of the reaction pathway, the high Lewis acidity as well as good recovery in this reaction, make this new catalyst very attractive for performing organic reactions in water. Although control of chirality was not achieved in this aqueous reaction, the study provided useful information on designing new water-tolerant chiral indium catalyst. The success of which will open a new area of producing chiral water-tolerant Lewis acid catalyst. Design of more rigid (bicyclic or tricyclic) indium complex is in progress.

CHAPTER 2

A New Modularly Designed Bicyclic Organocatalyst

2.1 OVERVIEW OF ASYMMETRIC ORGANOCATALYSIS

2.1.1 INTRODUCTION

Driven by the ever-increasing demand for enantioenriched compounds, asymmetric catalysis is always an important research area to both academia and industry. For a long time, the field of asymmetric catalysis was dominated by metal- and biocatalysis.[24] However, since the turn of the 21th century, the research area of asymmetric organocatalysis has grown rapidly to become one of the most exciting fields in organic chemistry, while catalytic asymmetric reactions using organocatalysts provide one of the most powerful and economical synthetic approach to a wide variety of enantiomerically enriched compounds.[25]

Organocatalysis is the acceleration of chemical reactions with a substoichiometric amount of an organic compound which does not contain a metal atom. Operational simplicity, easy availability and the non-toxicity of the organic catalysts compared to the corresponding transition metal species, as well as the high efficiencies and selectivities attainable in many organocatalytic transformations made this methodology very attractive for the formation of enantiomerically pure compounds and attracted much attention from the broad synthetic organic community.

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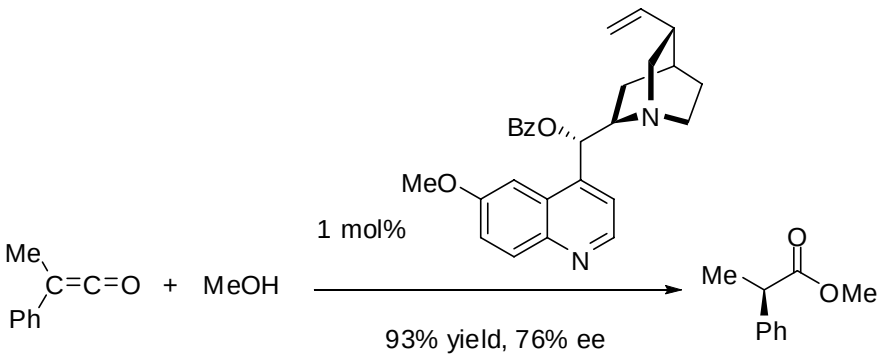
[24] Metal catalysis: (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, **1994**; (b) *Comprehensive Asymmetric Catalysis* (Ed.: Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H.), Springer, Berlin, **1999**; (c) *Catalytic Asymmetric Synthesis*, 2nd ed. (Ed.: Ojima, I.), Wiley-VCH, New York, **2000**; (d) *Transition Metals for Organic Synthesis*, 2nd ed. (Ed.: Beller, M.; Bolm, C.), Wiley-VCH, Weinheim, **2004**. Biocatalysis: (e) *Biocatalysts for Fine Chemicals Synthesis* (Ed.: Roberts, S. M.), Wiley-VCH, New York, **1999**; (f) *Enzyme Catalysis in Organic Synthesis*, 2nd ed. (Eds.: Drauz, K.; Waldmann, H.), Wiley-VCH, Weinheim, **2002**; (g) Bommarius, A. S.; Riebel, B. R. *Biocatalysis*, Wiley-VCH, Weinheim, **2004**.

[25] (a) Berkessel, A.; Groger, H. *Asymmetric Organocatalysis*; Wiley-VCH: Weinheim, **2005**. (b) Dalko, P. I., Ed. *EnantioselectiVe Organocatalysis*; Wiley-VCH: Weinheim, **2007**. (c) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (d) List, B. *Chem. Commun*. **2006**, 819. (e) Marigo, M.; Jørgensen, K. A. *Chem. Commun*. **2006**, 2001. (f) Pellissier, H. *Tetrahedron* **2007**, *63*, 9267. (g) Barbas III, C. F. *Angew. Chem., Int. Ed.* **2008**, *47*, 42. (h) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138. (i) Hayashi, Y. *J. Synth. Org. Chem. Jpn.* **2005**, *63*, 464. (j) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471.

Furthermore, with the discovery of new activation modes in this thriving area, the invention of novel chemical transformations is possible. It is also notable that combination of the concept of transition metal catalysis and organocatalysis is by itself another promising new emerging area as it allows unprecedented and previously thought impossible transformations to occur, which are not accessible by use of the transition metal complex or the organocatalyst alone.

The year 2000 has been aptly recognized as the year of conceptualization and renaissance of organocatalysis, in view that the field of asymmetric organocatalysis has a longstanding history that can be dated back to the early 20th century. In actual fact, there are some ground-breaking work which laid the foundation of organocatalysis before this new field is conceptualized. Indeed, the first case of using small organic molecules to catalyze asymmetric reactions was born in 1912.[26] In this innovative finding, the addition of hydrogen cyanide to benzaldehyde was carried out by use of enantiopure cinchona alkaloids as catalyst to provide optically active cyanohydrins with low *ee* (<10% *ee*). Nevertheless, the first notable organocatalytic transformation (up to 76% *ee*) was reported by Pracejus using *O*-benzoylquinine as an

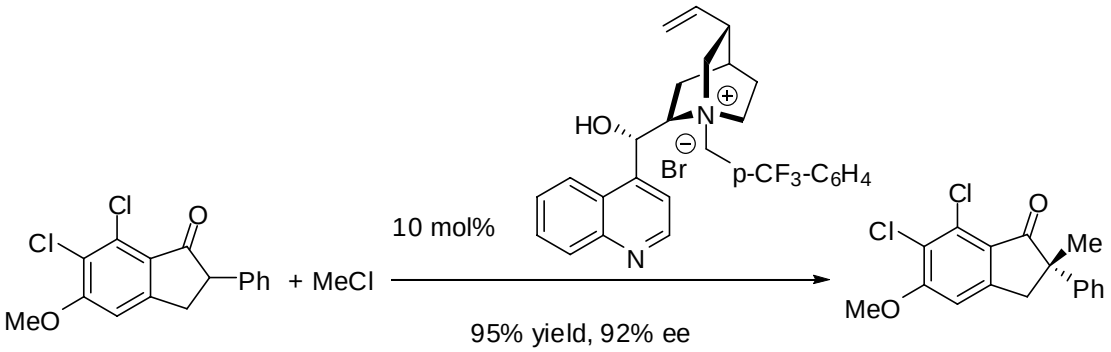


Scheme 2.1 Enantioselective methanolysis of phenylmethylketene

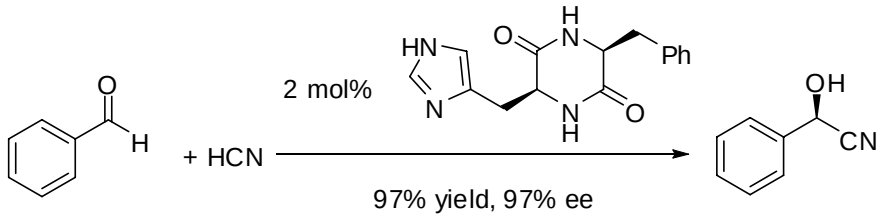
[26] (a) Bredig, G.; Fiske, P. S. *Biochem. Z.* **1912**, *46*, 7. (b) Bredig, G.; Minaeff, M. *Biochem. Z.* 1932, *249*, 241. (c) Prelog, V.; Wilhelm, M. *Helv. Chim. Acta* **1954**, *37*, 1634.

organocatalyst to catalyze the enantioselective methanolysis of phenylmethylketene (Scheme 2.1).[27]

Other pioneering work includes: the first quaternary ammonium salts-mediated asymmetric phase transfer catalysis (PTC) in 1984 developed by Merck group (Scheme 2.2),[28] cyclic histidine-containing dipeptide catalyzed addition of HCN reported by Inoue (Scheme 2.3),[29] C_2-symmetric guanidine-catalyzed enantioselective Strecker reaction developed by Corey (Scheme 2.4),[30] chiral HMPA and DMF



Scheme 2.2 The first phase-transfer methylation



Scheme 2.3 Asymmetric addition of HCN to aldehydes

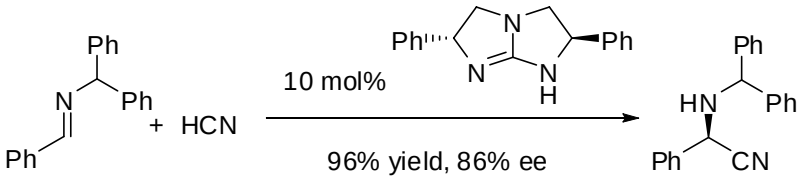
[27] (a) Pracejus, H. *Justus Liebigs Ann. Chem.* **1960**, *634*, 9. (b) Pracejus, H.; Mätje, H. *J. Prakt. Chem.* **1964**, *24*, 195.

[28] (a) Dolling, U.-H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1984**, *106*, 446. (b) Battacharya, A.; Dolling, U.-H.; Grabowski, E. J. J.; Karady, S.; Ryan, K. M.; Weinstock, L. M. *Angew. Chem. Int. Ed.* **1986**, *25*, 476. (c) Hughes, D. L.; Dolling, U.-H.; Ryan, K. M.; Schoenewaldt, E. F.; Grabowski, E. J. J. *J. Org. Chem.* **1987**, *52*, 4745.

[29] (a) Oku, J.-i.; Ito, N.; Inoue, S. *Makromol. Chem.* **1979**, *180*, 1089. (b) Oku, J.-i.; Inoue, S. J. Chem. Soc. *Chem. Commun.* **1981**, 229. (c) Oku, J.-i.; Ito, N.; Inoue, S. *Makromol. Chem.* **1982**, *183*, 579. (d) Asada, S.; Kobayashi, Y.; Inoue, S. *Makromol. Chem.* **1985**, *186*, 1755. (e) Tanaka, K.; Mori, A.; Inoue, S. *J. Org. Chem.* **1990**, *55*, 181.

[30] Corey, E. J.; Grogan, M. J. *Org. Lett.* **1999**, *1*, 157. This catalyst has been further developed, see: Leow, D.; Tan, C. H. *Chem. Asian J.* **2009**, *4*, 488.

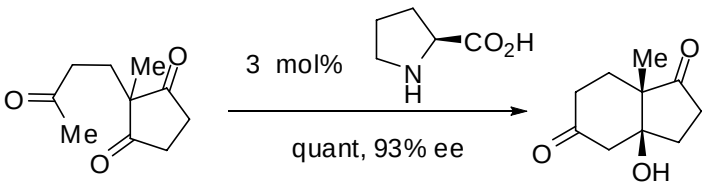
alternates[31] catalyzed enantioselective allylation and aldol reactions of aldehydes introduced by Denmark and Iseki, chiral ketone [32] mediated enantioselective epoxidation developed by Yang, Shi, and Denmark, chiral dimethylaminopyridine equivalents based on azaferrocene compounds catalyzed enantioselective acyl transfer outlined by Fu.[33]



Scheme 2.4 Ganidine-catalyzed enantioselective Strecker reaction

The famous proline-catalyzed intramolecular aldol condensation of prochiral triketones (the Hajos–Parrish reaction) came forth in the late 1960s and early 1970s. The enantioenriched bicyclic adducts could be obtained in 93% *ee*, rendering the reaction applicable in the total synthesis of natural products.[34] However, it took almost 25 years to understand the principle behind this reaction, leading to the pioneering work of Barbas *et al.* in 2000 who demonstrated the first intermolecular version of this aldol protocol.[35] Since then, a large number of chemists had been drawn into this promising field (Scheme 2.5).

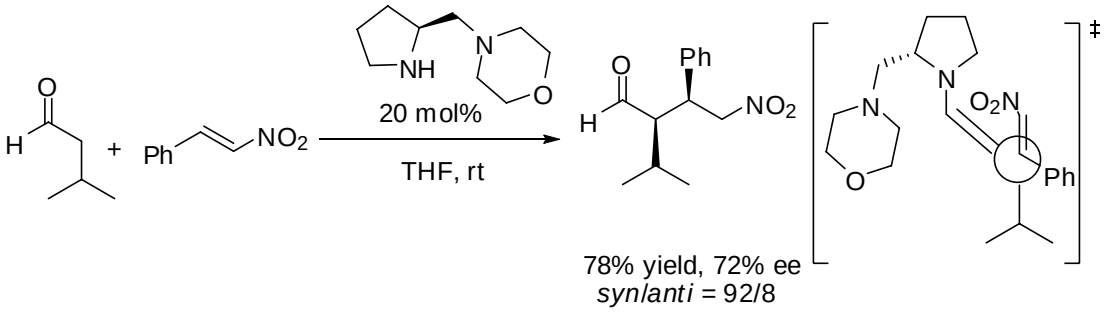
[31] (a) Denmark, S. E.; Stavenger, R. A.; Wong, K.-T. *J. Org. Chem.* **1998**, *63,* 918. (b) Iseki, K.; Mizuno, S.; Kuroki, Y.; Kobayashi, Y. *Tetrahedron Lett.* **1998**, *39*, 2767. (c) Iseki, K.; Mizuno, S.; Kuroki, Y.; Kobayashi, Y. *Tetrahedron* **1999**, *55*, 977.
[32] (a) Yang, D.; Wang, X.-C.; Wong, M.-K.; Yip, Y.-C.; Tang, M.-W. *J. Am. Chem. Soc.* **1996**, *118*, 11311. (b) Yang, D.; Yip, Y.-C.; Chen, J.; Cheung, K.-K. *J. Am. Chem. Soc.* **1998**, *120*, 7659. (c) Wang, Z.-X.; Miller, S. M.; Anderson, O. P.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 6443. (d) Wang, Z.-X.; Cao, G.-A.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 7646. (e) Warren, J. D.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 7675. (f) Shu, L.; Shi, Y. *Tetrahedron Lett.* **1999**, *40*, 8721. (f) Denmark, S. E.; Wu, Z.; Crudden, C. M.; Matsuhashi, H. *J. Org. Chem.* **1997**, *62*, 8288.
[33] Fu, G. C. *Acc. Chem. Res.* **2004**, *37*, 542.
[34] (a) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615. (b) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed.* **1971**, *10*, 496.
[35] List, B.; Lerner, R. A.; Barbas C. F. III. *J. Am. Chem. Soc.* **2000**, *122*, 2395.



Scheme 2.5 Intramolecular aldol reaction catalyzed by proline

2.1.2 DEVELOPMENT OF ASYMMETRIC CONJUGATE ADDITION OF ALDEHYDES TO NITROOLEFINS

The asymmetric Michael addition of ketones to nitroolefins has been well studied and the asymmetric Michael addition of cyclohexanone to *trans*-nitrostyrenes has become a benchmark reaction to evaluate the efficiency of newly designed organocatalysts.[36] Otherwise, the enantioselective Michael addition of aldehydes to

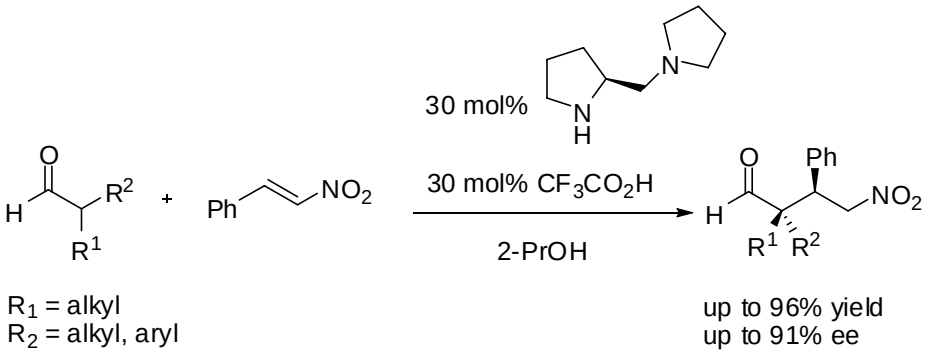


Scheme 2.6 Diamine-catalyzed conjugate addition of isovaleraldehyde to nitrostyrene

nitroalkenes remained challenging. The first example of direct catalytic enantioselective Michael addition of unmodified aldehydes to nitroalkenes was reported by Barbas's group (Scheme 2.6). A lot of pyrrolidine derivatives (20 mol%) were tested and up to 86% *ee* was obtained with (*S*)-2-(morpholinomethyl)pyrrolidine as a catalyst.[37] In terms of yield and selectivity, L-proline was a poor catalyst for this reaction. Later, the same group expanded the scope of the substrate to synthesize quaternary centers with high enantioselectivities (up to

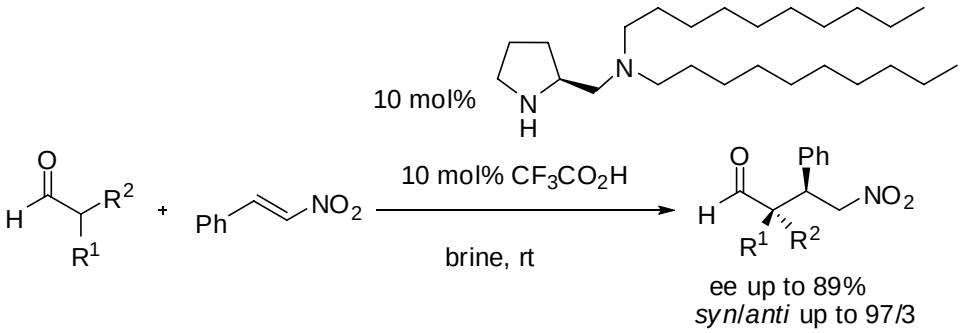
[36] Sulzer-Mossé, S.; Alexakis, A. *Chem. Commun.* **2007**, 3123.
[37] (a) Betancort, J. M.; Barbas III, C. F. *Org. Lett.* **2001**, *3*, 3737. (b) Betancort, J. M.; Sakthivel, K.; Thayumanavan, R.; Tanaka, F.; Barbas III, C. F. *Synthesis* **2004**, 1509.

91% *ee*, Scheme 2.7).[38] The nitroolefin attacked the enamine from the less hindered *Si*-face to furnish the desired product.



Scheme 2.7 Diamine catalyzed conjugate addition of α,α-disubstituted aldehydes to nitrostyrene

The reactions can also proceed in brine with a slight decrease in selectivity (Scheme 2.8).[39]

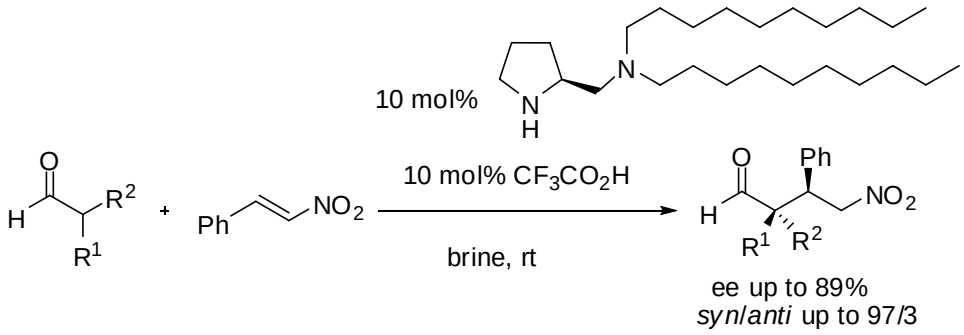


Scheme 2.8 The Michael addition of branched aldehydes to nitroalkene in brine

2,2′-bipyrrolidine derivatives (*i*PBP and *i*PBM) has also been used as catalysts to perform this reaction.[40] Higher reaction rate and selectivity were observed for linear

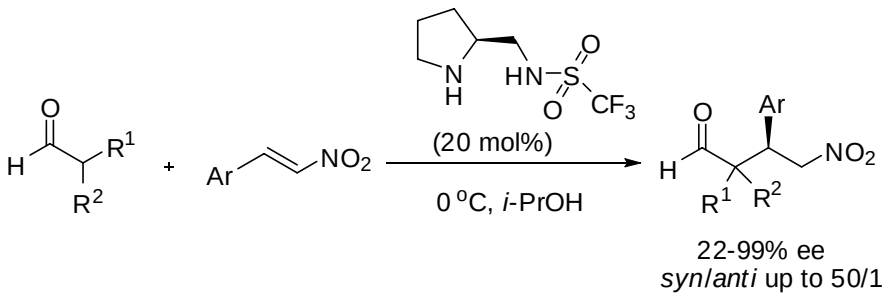
[38] Mase, N.; Thayumanavan, R.; Tanaka, F.; Barbas III, C. F. *Org. Lett*. **2004**, *6*, 2527.
[39] Mase, N.; Watanabe, K.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas III, C. F. *J. Am. Chem. Soc*. **2006**, *128*, 4966.
[40] (a) Alexakis, A.; Andrey, O. *Org. Lett*. **2002**, *4*, 3611. (b) Andrey, O.; Alexakis, A.; Tomassini, A.; Bernardinelli, G. *Adv. Synth. Catal.* **2004**, *346*, 1147.

aldehydes compared to branched aldehydes. The enantio- and diastereoselectivity were increased when the reaction temperature was decreased (Scheme 2.9).



Scheme 2.9 IPBP compared to *i*PBM for conjugate addition of aldehydes to nitrostyrenes

Wang's group has applied chiral pyrrolidine sulfonamide to catalyze the asymmetric Michael addition of aldehydes to nitroolefins to afford the products in high enantio- and diastereoselectivity in alcohol solvent.[41] However, for aliphatic nitroalkenes, this catalyst does not work well (22% *ee*) (Scheme 2.10).

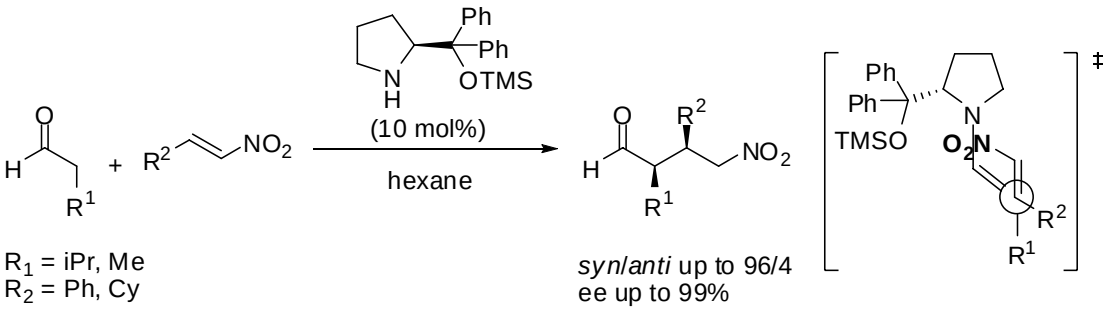


Scheme 2.10 Pyrrolidine sulfonamide-catalyzed conjugate addition of aldehydes to nitrostyrene

Hayashi's group found that diphenylprolinol silyl ether was extremely effective in catalyzing the asymmetric Michael reaction between aldehydes and nitroalkenes (Scheme 2.11).[42] In most of the examples shown in this work, perfect

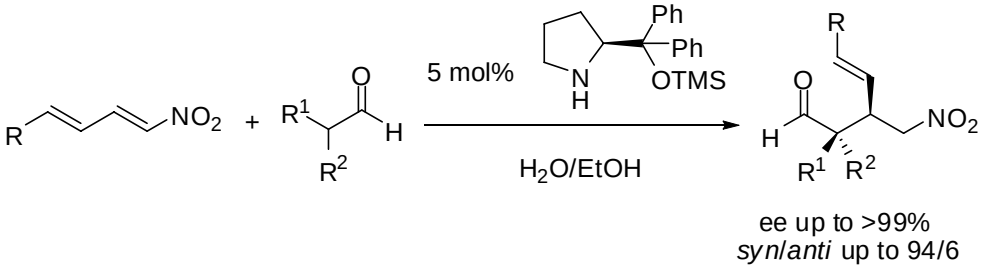
[41] Wang, W.; Wang, J.; Li, H. *Angew. Chem., Int. Ed*. **2005**, *44*, 1369.
[42] Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed*. **2005**, *44*, 4212.

enantioselectivity (99% *ee*) and excellent diastereoselectivity were achieved. Soon after that, it was shown that this catalyst exhibited higher catalytic activity when the reaction is conducted in water, requiring only 0.5–2 mol% catalyst loading.[43]



Scheme 2.11 Diphenylprolinol silyl ether-catalyzed conjugate addition of aldehydes to nitrostyrene

The asymmetric organocatalyzed Michael addition of aldehydes to α,β,γ,δ-unsaturated nitro compounds has also been accomplished using 5 mol% of (*S*)-diphenylprolinol silyl ether as catalyst and 2 equivalents of aldehyde in a mixture of ethanol and water (5% v/v). The Michael adducts were obtained in good yields, with diastereoselectivity up to 94/6 and *ee* up to 99% (Scheme 2.12).[44]

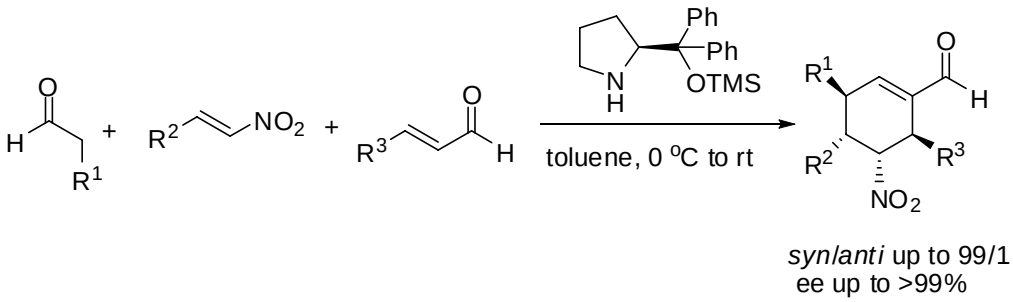


Scheme 2.12 Michael addition of aldehydes to α,β,γ,δ-unsaturated nitro compounds

In addition, Enders group applied the diphenylprolinol silyl ether as catalyst in a triple cascade organocatalytic reaction for the synthesis of tetra-substituted

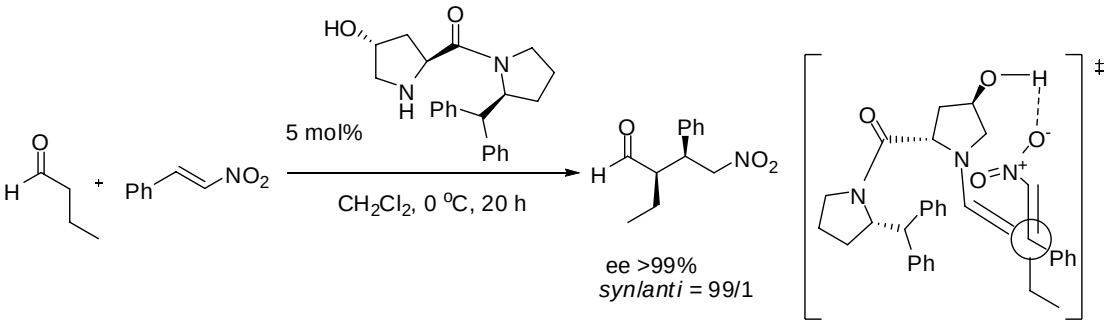
[43] Zhu, S.; Yu, S.; Ma, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 545.
[44] Belot, S.; Massaro, A.; Tenti, A.; Mordini, A.; Alexakis, A. *Org. Lett*. **2002**, *10*, 4557.

cyclohexene carbaldehydes wherein excellent diastereo- and enantioselectivities (>99% *ee*) were obtained (Scheme 2.13).[45]



Scheme 2.13 Diphenylprolinol silyl ether-catalyzed three component domino reaction

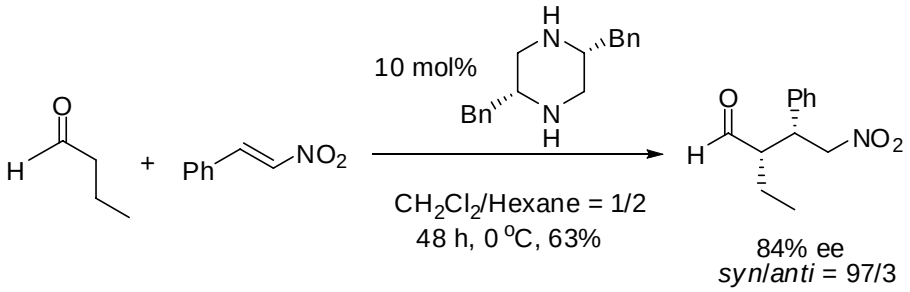
More importantly, Palomo's group has reported a new mode of organocatalyst possessing a bulky α-group and a hydrogen-bond donor directing γ-group (Scheme 2.14).[46] Only 5 mol% catalyst was needed to afford the Michael adducts with high levels of selectivity (91–99% *ee*).



Scheme 2.14 *Trans*-4-hydroxyprolylamide-catalyzed Michanel addition

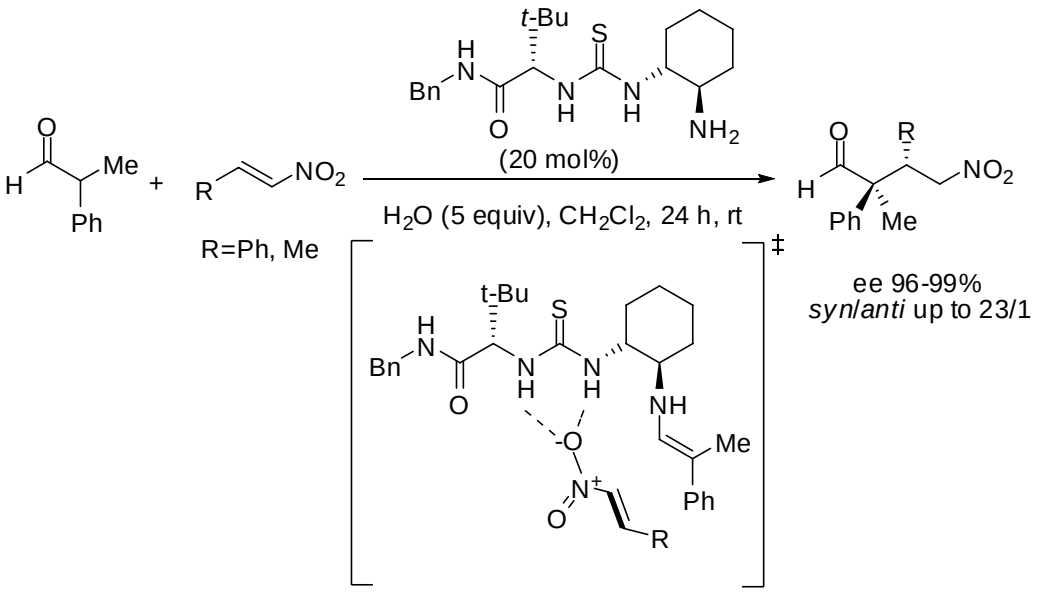
[45] Enders, D.; Hüttl, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861
[46] Palomo, C.; Vera, S.; Mielgo, A.; Gómez-Bengoa, E. *Angew. Chem., Int. Ed*. **2005**, *45*, 5948.

Chiral 2,5-disubstituted piperazines were also employed as organocatalysts to catalyze the Michael reaction between aldehydes and nitroalkenes, where only moderate enantioselectivity was achieved (Scheme 2.15).[47]



Scheme 2.15 Chiral piperazine-catalyzed Michael addition

Jacobsen's group discovered the use of primary amine-thiourea as bifunctional catalyst to simultaneously activate both the nucelophile and electrophile through covalent *E*-enamine catalysis and hydrogen-bonding (Scheme 2.16).[48] The addition of

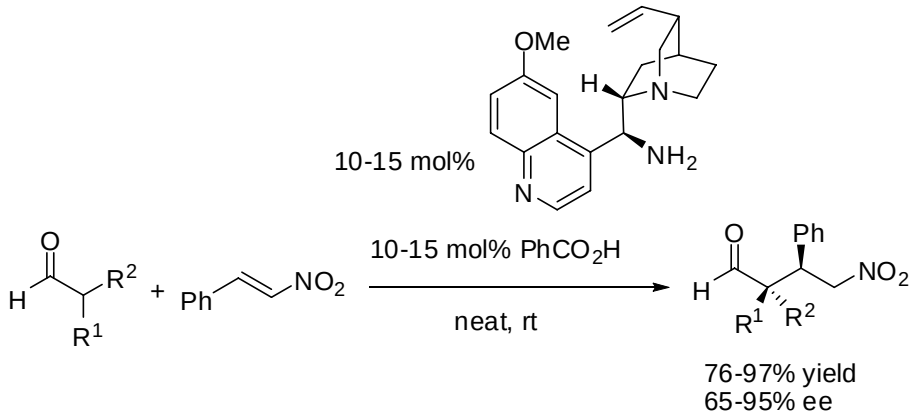


Scheme 2.16 Primary amine-thiourea derivative as catalyst

[47] Barros, M. T.; Philips, A. M. F. *Eur. J. Org. Chem*. **2007**, 178.
[48] Lalonde, M. P. ; Chen, Y. ; Jacobsen, E. N. *Angew. Chem., Int. Ed*. **2005**, *45*, 6366.

racemic α,α-disubstituted aldehydes to nitroalkenes provided synthetically-challenging contiguous quaternary and tertiary stereogenic centers in high yields and high selectivities.

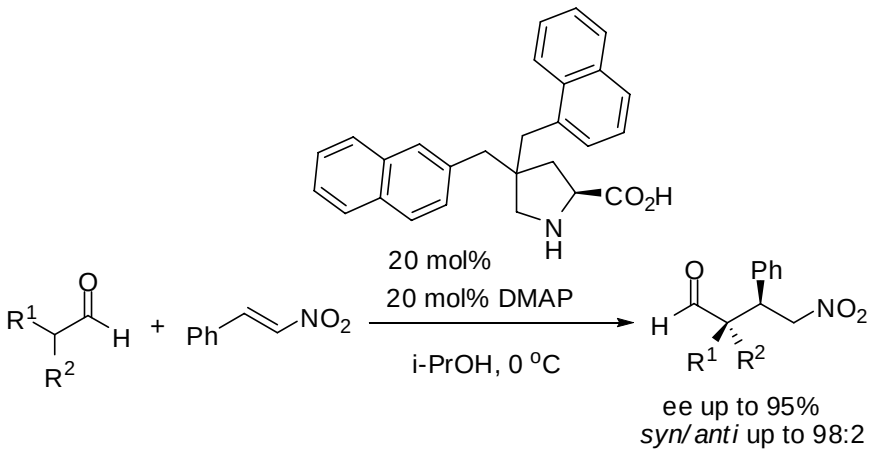
9-*epi*-DHQDA was investigated by Connon's group to catalyze the conjugate addition of aldehydes to nitroalkenes in moderate to good enantioselectivity under neat condtions (Scheme 2.17).[49]



Scheme 2.17 9-*epi*-DHQDA as catalyst

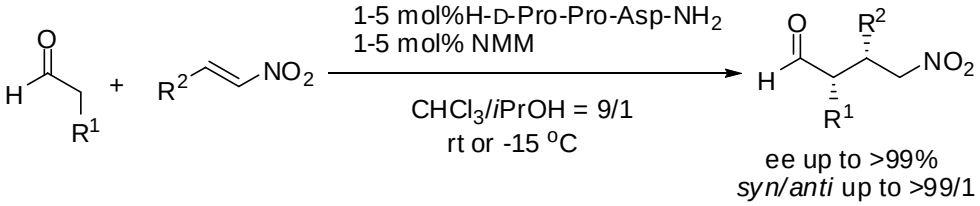
4,4′-Disubstituted-L-proline with equivalent amount of 4-dimethylaminopyridine (DMAP) were found to be an efficient catalyst for the Michael addition of aldehydes to nitrostyrenes to afford the products with high diastereo- and enantioselectivity (Scheme 2.18).[50]

[49] Connon, S. J.; McCooey, S. H. *Org. Lett*. **2007**, *9*, 599.
[50] Gua, L.; Zhao, G. *Adv. Synth. Catal.* **2007**, *349*, 1629.



Scheme 2.18 4,4′-disubstituted-L-proline/DMAP as catalyst

Tripeptides H-D-Pro-Pro-Asp-NH_2 was also a highly effective catalyst for asymmetric conjugate addition reactions between aldehydes and nitroolefins. Synthetically useful chiral γ-nitroaldehydes were obtained in excellent yields and stereoselectivities under mild conditions using only 1 mol% catalyst loadings. (Scheme 2.19).[51]

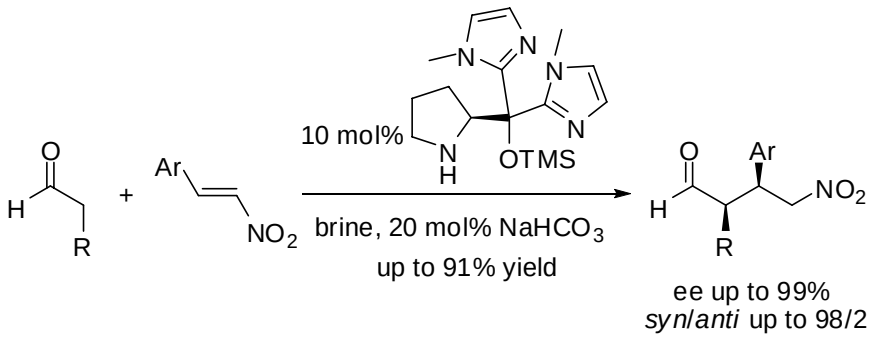


Scheme 2.19 Tripeptides as catalyst

Upon introduction of a hydrophilic bimethylimidazole group into the pyrrolidine side chain, the resulting desired water soluble di(methylimidazole)prolinol silyl ether catalyst has been shown be a very effective catalyst for the Michael reaction involving

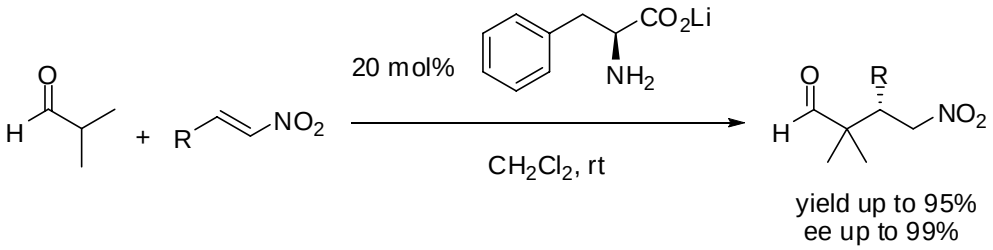
[51] Wiesner, M.; Revell, J.; Wennemers, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 1871.

various nitroolefins and aldehydes in water, when used in combination with sodium bicarbonate (Scheme 2.20).[52]



Scheme 2.20 Water soluble di(methylimidazole)prolinol silyl ether as catalyst

L-Phenylalanine lithium salt is very effective in the Michael addition of isobutyraldehyde with *trans*-*β*-nitroalkenes to form quaternary carbon-containing nitroalkanes in high yields and high enantioselectivities (Scheme 2.21).[53]

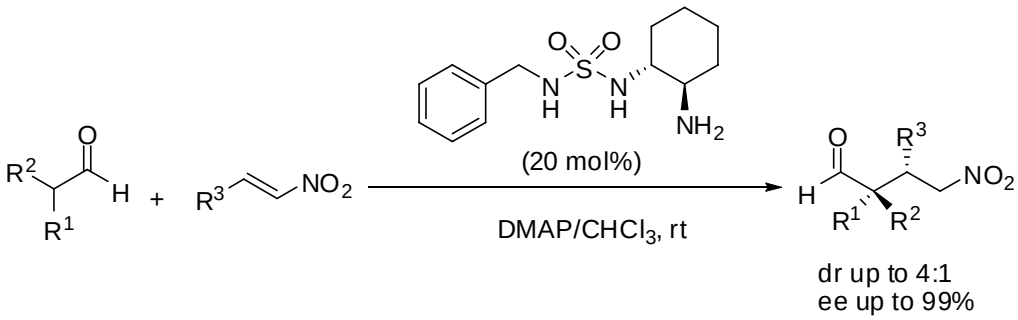


Scheme 2.21 Primary amino acid lithium salt as catalyst

Chiral bifunctional sulfamides were found to be highly efficient organocatalysts for the conjugate addition of aldehydes to nitroolefins in the presence of base additives.[54] In previous studies, Brönsted acids were found to be efficient promoters for this reaction. However, in this case, benzoic acid and acetic acid showed

[52] Wu, J.; Ni, B.; Headley, A. D. *Org. Lett.* **2009**, *11*, 3354.
[53] Sato, A.; Yoshida, M.; Hara, S. *Chem. Commun.* **2008**, 6242.
[54] Zhang, X.; Liu, S.; Li, X.; Yan, M.; Chan, A. S. C. *Chem. Commun.* **2009**, 833.

detrimental effects on reaction rate and enantioselectivity. Base additive significantly accelerated the reaction without erosion of the enantioselectivity and DMAP was identified as the best additive in view of the excellent enantioselectivity, good yield and short reaction time (Scheme 2.22).

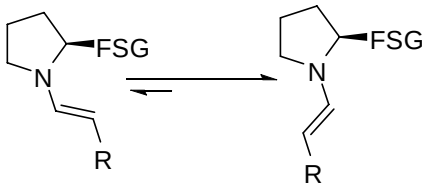


. **Scheme 2.22** Conjugate addition reactions catalyzed by chiral bifunctional sulfamides

2.2 A NEW MODULARLY DESIGNED BICYCLIC ORGANOCATALYST: APPLICATION TO ASYMMETRIC MICHAEL ADDITION OF ALDEHYDES TO NITROALKENES

2.2.1 A NEW MODULARLY DESIGNED BICYCLIC ORGANOCATALYST

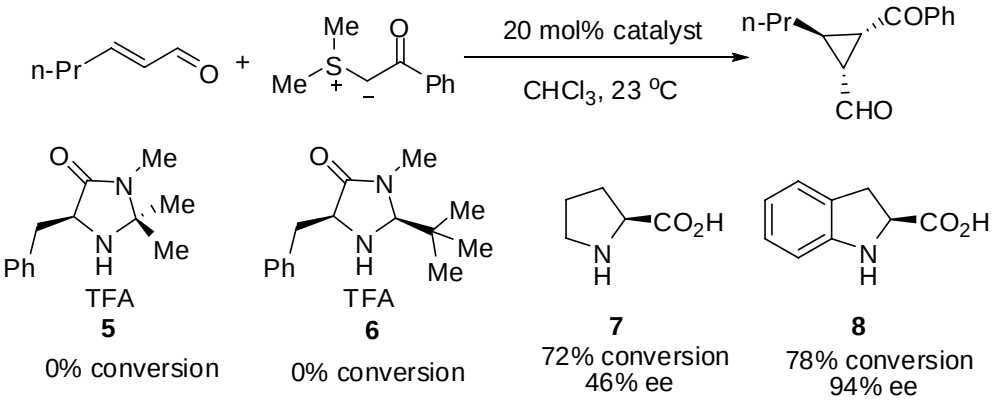
As complements to the traditional organometallic and biological approaches to asymmetric catalysis, the catalytic methods mediated by organocatalyst especially with chiral secondary amines such as L-proline and its derivatives, allowed synthetic chemists to construct chiral skeleton in an efficient, stereoselective and green manner. For five membered secondary amine organocatalyst, the bulky face shielding group (FSG) on the pyrrolidine ring plays two important roles towards the excellent enantioselectivity: promotion of the selective formation of the *anti* enamine and selective shielding of the *Re* face of the enamine double bond (Scheme 2.23). It appears that monocyclic five-membered pyrrolidine ring is crucial for the success of the organic transformation and is now regarded as one of the "privileged" skeleton for enamine catalysis.



Scheme 2.23 Five membered chiral secondary amine organocatalyst embedding FSG

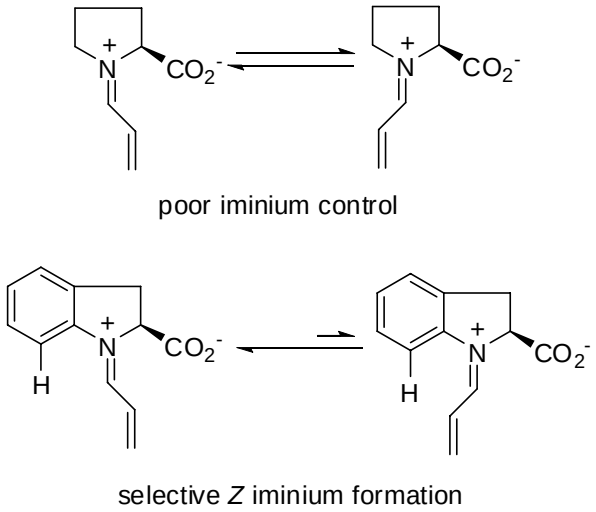
In 2005, MacMillan applied (*S*)-indoline-2-carboxylic acid **8** as a catalyst in the enantioselective cyclopropanation between α,β-unsaturated aldehydes and sulfur

ylides based upon directed electrostatic activation.[55] The cyclopropane products were obtained in good yields and high diastereo- and enantioselectivity. However, MacMillan catalyst **5** and **6** were not effective for this reaction due to inability to attain the electrostatic activation transition state (Scheme 2.24). Higher enantioselectivities observed with catalyst **8** compared to proline **7** (46% *ee*) was



Scheme 2.24 Enantioselective organocatalytic cyclopropanation

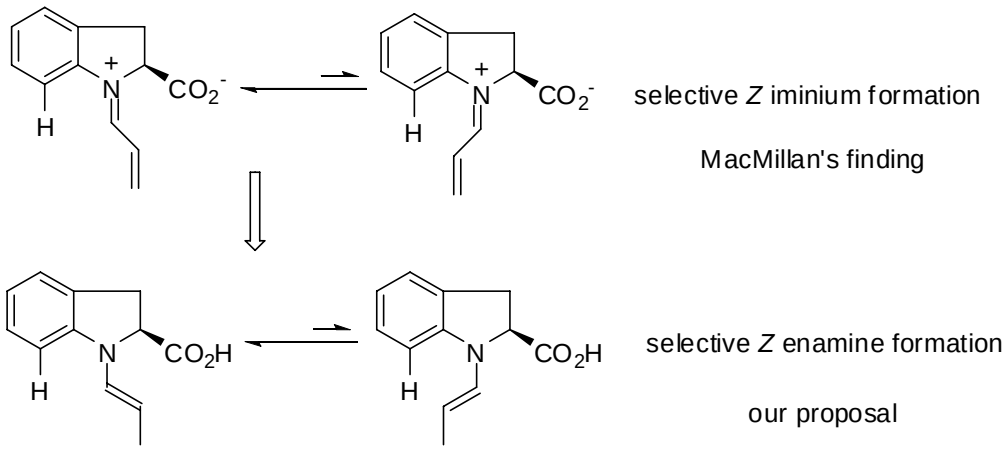
attributed to better control over the conformation of the iminium ion through steric repulsion with the hydrogen atom of the phenyl ring (Scheme 2.25).



Scheme 2.25 Efficient iminium control by catalyst **8**

[55] Kunz, R. K.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 3240.

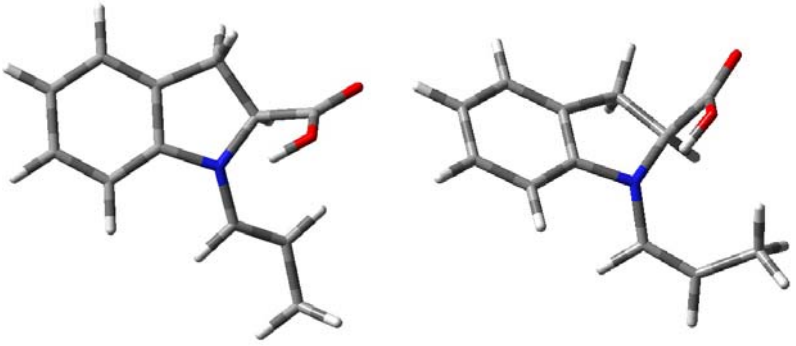
We envisage that catalyst **8** could also provide good control of the geometry of an enamine (Scheme 2.26), but previous report revealed that catalyst **8** gave low yield and low enantioselectivity in enamine catalysis.[56] The obvious disadvantage is that the activity of the amino group is attenuated by conjugation with the aromatic ring.



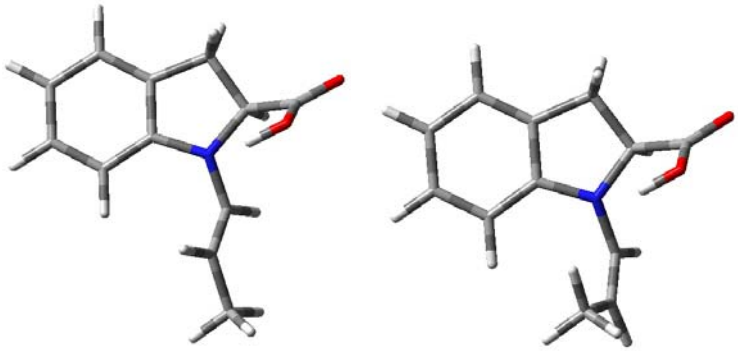
Scheme 2.26 Efficient and enamine control by catalyst **8**

To provide evidence of this hypothesis, DFT calculations were carried out to determine the most stable enamine conformation with the Gaussian 03 package. Four possible enamine conformers were investigated (Figure 2.1). The *syn* enamine **a** is the most stable conformation out of the 4 comformers. The energy of *syn* enamine **a** is 10.0 kJ/mol lower than that of *syn* enamine **b**, the second lowest energy conformer. At room temperature, *syn* enamine **a** should be the dominant intermediate in the reaction and thus the stereoselectivity is largely dictated by this conformation.

[56] Sakthivel, K.; Notz, W.; Bui, T.; Barbas III, C. F. *J. Am. Chem. Soc.* **2001**, *123*, 5260.



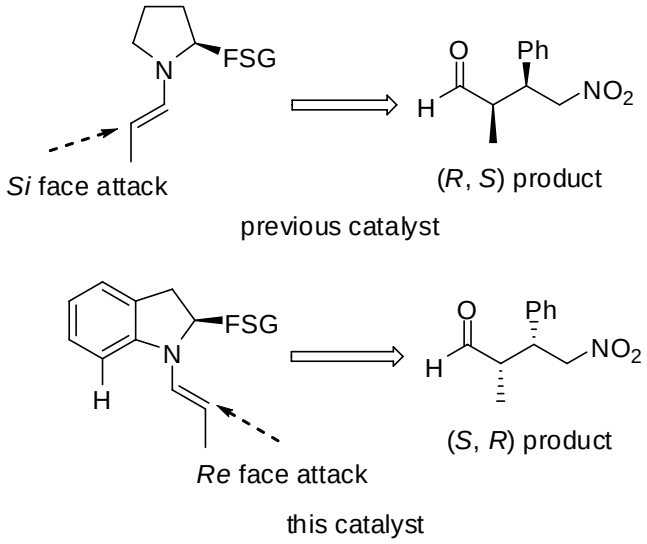
syn-enamine **a** *syn*-enamine **b**



anti-enamine **c** *anti*-enamine **d**

Figure 2.1 Different enamine conformations **a-d** by DFT calculation

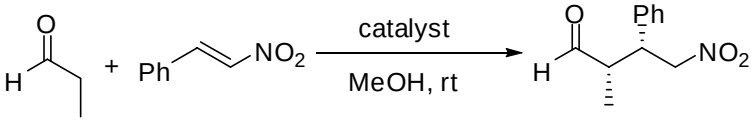
In the realm of organocatalyzed reactions, the asymmetric Michael addition of carbonyl compounds to nitroalkenes is a useful reaction for the construction of C–C bond and preparation of chiral γ-amino acids. It also served as a benchmark reaction for testing newly designed chiral catalysts. In the case of catalyst **8**, we envisioned that when a base such as DMAP is added, an acid-base interaction between the carboxyl and amino groups should lead to an ammonium salt wherein the base unit functions as the stereocontrolling module. Earlier catalysts for this reaction comprise of a "privileged" chiral pyrrolidine unit covalently adhered to a bulky face shielding group (FSG) which promotes the selective formation of the *anti* enamine to afford the (*R*,*S*) product. However, in the case of catalyst **8/DMAP**, the *syn* enamine is favored, as indicated by DFT calculation. The hydrogen bonding with DMAP play the role of FSG and nitrostryrene now attack from the *Re* face to afford the (*S*,*R*) product (Scheme 2.27).



Scbheme 2.27 Different configuration of the Michanel addition product

Initial study employed the Michael reaction of propanal and nitrostyrene. Proline and proline salt catalyst **7/DMAP** both gave low yield and low enantioselectivity of the (*R*,*S*) product (Table 1, entries 1–2). Catalyst **8** alone also provided unsatisfactory result (Table 1, entry 3). To our delight, **8/DMAP** catalyst was found to provide the

Table 2.1 The effect of DMAP in the Michael reaction of propanal and nitrostyrene



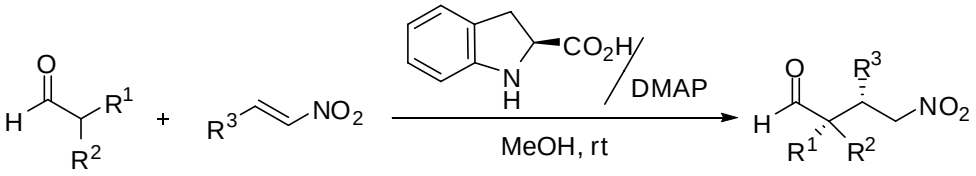
Entry	Catalyst	Catalyst loading (mol%)	Yield (%)[b]	dr[c]	ee (%)[d]
1	**7**	10	<5	N.D.[e]	N.D.
2	**7**/DMAP	10	30	85:15	–20
3	**8**	10	<10	N.D.	N.D.
4	**8**/DMAP	10	72	78:22	98
5	**8**/DMAP	5	60	78:22	98

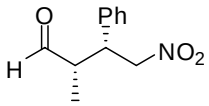
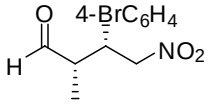
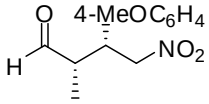
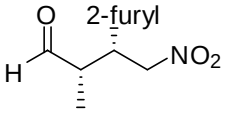
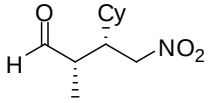
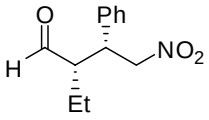
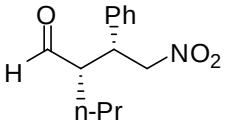
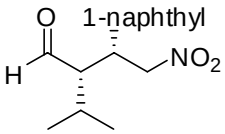
[a] Reactions were conducted with 2 equiv. of aldehyde, 1 equiv. of nitrostyene at room temperature in the presence of 1:1 (catalyst:DMAP). [b] Isolated yield. [c] Dr (*syn*/*anti*) was determined by chiral HPLC analysis. [d] Reported values refer to the *syn* isomer and were determined by chiral HPLC on a chiral stationationary phase. [e] Not determined.

(*S*,*R*) product in good yield and excellent enantioselectivity using 10 mol% catalyst loading (Table 2.1, entries 4–5). Not surprisingly, the salt was formed rapidly and quantitatively after the addition of DMAP. Although the exact function of DMAP is unclear at the moment, we believe that introduction of basic DMAP neutralizes the catalyst system, thus providing a suitable reaction environment as well as efficient face shielding which lead to a well-organized transition state, enabling this reaction to proceed efficiently.

Next, various aldehydes and nitroalkenes were also investigated to ascertain its applicability. The reaction was found to exhibit broad applicability with respect to both the Michael acceptor and the donor (Table 2.2). The adducts could be obtained in good enantioselectivity and with good *syn* diastereoselectivity in most of the cases examined. Both aryl- and alkyl-substituted nitroalkenes could serve as excellent Michael acceptors. Besides phenyl, both electron-rich and electron-deficient aryl groups, as well as heteroaromatic substituents can be present on the nitroalkene (Table 2.2, entries 1-4). Alkyl-substituted nitroalkenes, such as 2-cyclohexyl-1-nitroethene, was also good Michael acceptors (Table 2.2, entry 5). In addition to propanal, other linear aldehydes, such as *n*-butanal and *n*-pentanal (Table 2.2, entries 6 and 7) as well as bulky aldehyde (Table 2.2, entry 8) could also be employed as the Michael donors to furnish the adducts in good enantioselectivity.

Table 2.2 Catalytic asymmetric Michael addition of aldehydes to nitroalkenes[a]



Entry	Product	Catalyst (mol%)	Time (h)	Yield (%)[b]	dr[c]	ee (%)[d]
1		10	24	72	78:22	98
2		10	24	48	65:35	85
3		10	24	45	75:25	88
4		10	24	71	70:30	80
5		20	72	40	N.D.[e]	93
6		10	96	42	81:19	93
7		10	72	74	59:41	90
8		10	48	45	74:26	88

[a] Reactions were conducted with 2-4 equiv. of aldehyde, 1 equiv. of nitrostyene at room temperature in the presence of catalyst with 1:1 (catalyst **8**:DMAP). [b] Isolated yield. [c] Dr (*syn*/*anti*) was determined by chiral HPLC analysis or by ^{1}H NMR after purification. [d] Reported values refer to the *syn* isomer and were determined by chiral HPLC on a chiral stationary phase. [e] Not determined.

2.3 CONCLUSION

In summary, we have explored a new class of bicyclic organocatalyst by virtue of self assembly strategy. The asymmetric Michael reaction of aldehydes and nitrostyrene was selected as the model reaction to test our hypothesis. The success of this hypothesis breaks the regime of monocyclic five-membered pyrrolindine ring dominated enamine organocatalysis and makes significant contribution to enamine catalysis. Further application of this strategy to other asymmetric reactions are ongoing in our group.

CHAPTER 3

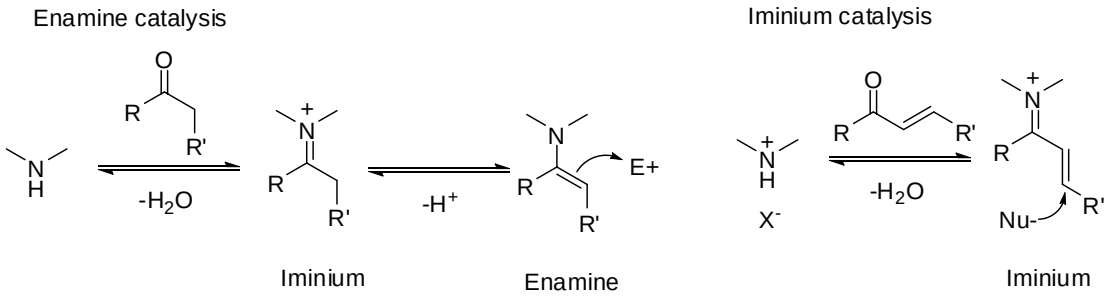
A New Class of Structurally Rigid Tricyclic Amphibian Organocatalyst

3.1 OVERVIEW OF ASYMMETRIC ENAMINE CATALYSIS

The unique activation modes which organocatalyst operates by is crucial to the success of organocatalysis in the past decade. These activation modes are: (i) enamine catalysis introduced by Barbas; (ii) iminium activation and SOMO activation established by MacMillan; [57] (iii) hydrogen-bonding and counterion catalysis demonstrated by Jacobsen.[58]

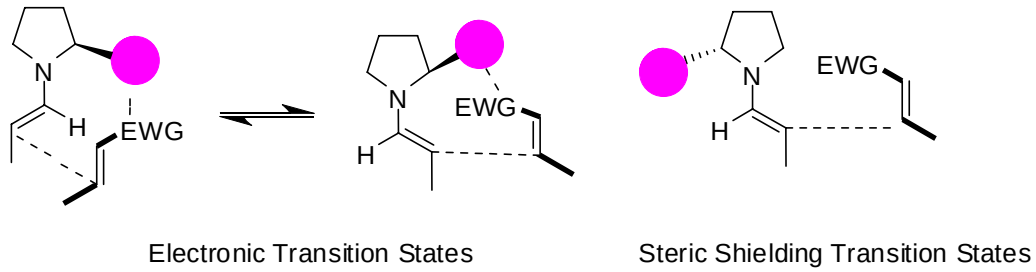
Enamine and iminium catalysis are two divergent reaction modes in organocatalysis. Secondary amine can convert the carbonyl substrate to either an enamine intermediate or an iminium intermediate (Scheme 3.1). In iminium catalysis, carbonyl compounds are activated by lowering of the LUMO energy, making it more electrophilic through the iminium intermediate. In enamine catalysis on the other hand, carbonyl compounds are converted to the more nucleophilic enamines which increase the energy of the HOMO. Enamine catalysis proceeds *via* iminium ion formation and iminium catalysis typically results in the formation of an enamine intermediate. These two opposing yet interdependent intermediates are just like the 'yin' and 'yang' in Chinese philosophy, subjugating and giving rise to each other in turn.[25d]

[57] (a) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243. (b) Beeson, T. D.; Mastracchio, A.; Hong, J., Ashton, K.; MacMillan, D. W. C. *Science*, **2007**, *316*, 582.
[58] (a) Sigman, M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901. (b) Raheem, I.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 13404. (c) Reisman, S. E.; Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc*. **2008**, *130*, 7198.



Scheme 3.1 Enamine catalysis and iminium catalysis

The cyclic five-membered secondary amine is now regarded as the "privileged" backbone for asymmetric enamine catalysis. The substituent at the α position can direct the preferential facial attack of electrophile by electronic or steric factors. Electronic interactions by means of hydrogen-bonding favour attack on the same side as the α-substituent. On the other hand, steric hindrance of bulky face shielding group will force the electrophile to attack from the opposite face (Scheme 3.2). In any case, the α-substituent on the catalyst framework will favor formation of the thermodynamic *E*-enamine, with one of the enamine rotamers predominating, which in turn also influences the facial selectivity.



Scheme 3.2 Electronic and steric shielding transition states

Proline has been ascribed as a "universal catalyst" because of its extensive applications in many enamine-catalyzed processes such as enantioselective aldol,

Mannich, amination and aminoxylation reactions.[59] However, proline is usually not an efficient catalyst in terms of yield and enantioselectivity for electrophiles that are poor hydrogen-bond acceptors, since approach of the electrophile to the enamine intermediate is controlled by hydrogen bonding to the carboxyl group. To overcome these limitations, MacMillan's imidazolidinones catalyst[60] and α,α-diarylprolinol ethers catalyst,[61] developed by Jørgensen and Hayashi independently, could induce high enantioselectivities through controlling the geometry of the enamine and efficient face shielding. In these structures, a pyrrolidine core with at least one α-substituent seems indispensable for rational catalyst design, which is found in most of

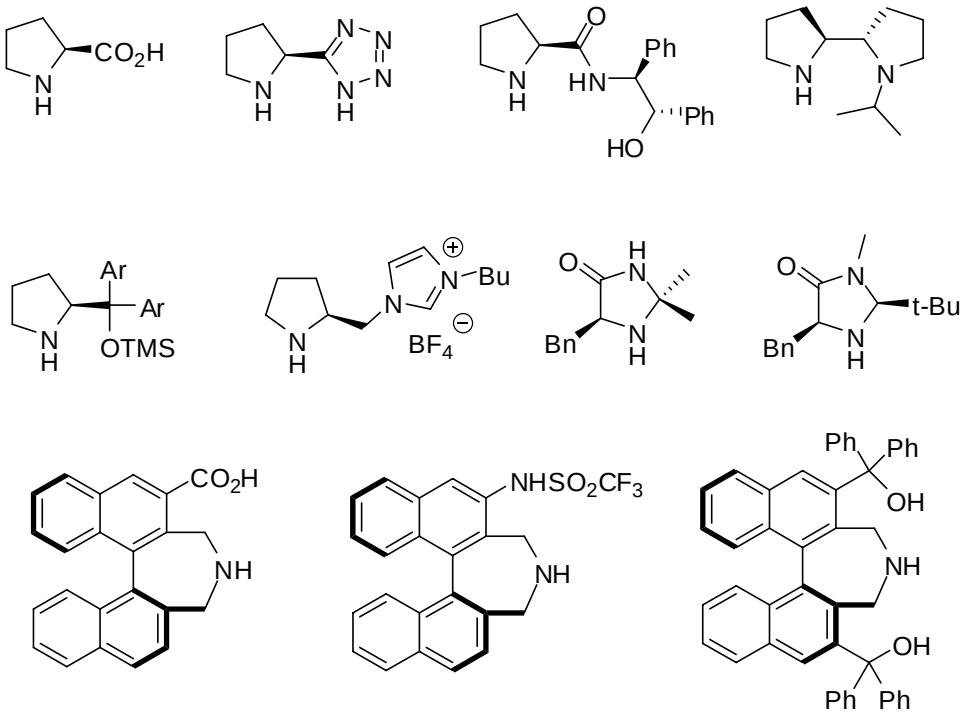


Figure 3.1 Typical organocatalysts for enamine catalysis

[59] For reviews, see: (a) List, B. *Tetrahedron* **2002**, *58*, 5573. (b) Movassaghi, M.; Jacobsen, E. N. *Science* **2002**, *298*, 1904.

[60] (a) Beeson, T. D.; Mastracchio, A.; Hong, J.-B.; Ashton, K.; MacMillan, D. W. C. *Science* **2007**, *316*, 582. (b) Jang, H.-Y.; Hong, J.-B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2007**, 129, 7004. (c) Kim, H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2008**, *130*, 398. (d) Lelais, G.; MacMillan, D. W. C. *Aldrichimica Acta* **2006**, *39*, 79.

[61] For the first reports, see: (a) Marigo, M.; Wabnitz, T. C.; Fielenbach, D. K.; Jorgensen, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 794. (b) FranzLn, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjarsgaard, A.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 18296. (c) Hayashi, Y.; Gotoh, H.; Hayasi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212. For reviews, see: (d) Palomo, C; Mielgo, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 7876; (e) Mielgo, A.; Palomo, C. *Chem. Asian J.* **2008**, *3*, 922.

the chiral secondary amine catalysts derived from proline. Professor Maruoka designed a structurally novel and robust binaphthyl-based chiral secondary amine catalyst to extend the applicability of enamine catalysis. Several secondary amine catalysts having various functional groups at the 3-position have also been developed.[62] The following are some typical catalysts for enamine catalysis (Figure 3.1).

Essentially all types of ketones and aldehydes can be used as nucleophiles with a broad range of electrophile classes. Enamine activation are finding widespread applications in a number of reactions including aldol reactions, Mannich reactions, Michael additions and Diels–Alder reactions, as well as many unprecedented processes that involve enantioselective α-carbonyl functionalization. The common electrophiles for enamine catalysis are summarized as follows (Figure 3.2).

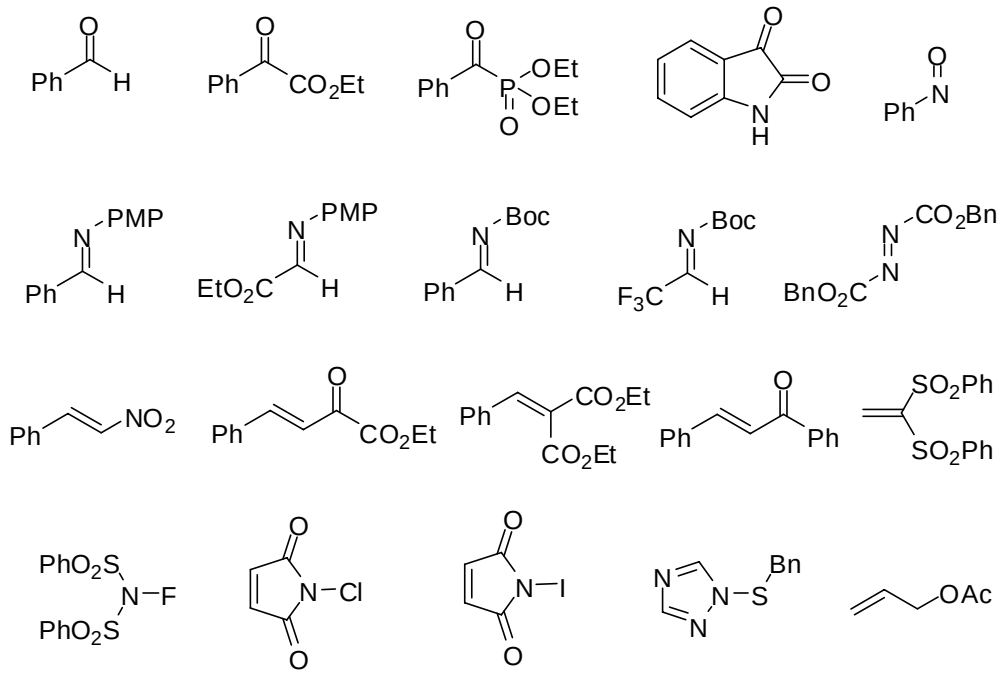


Figure 3.2 Common electrophiles for enamine catalysis

[62] Kano, T.; Maruoka, K. *Chem. Commun.* **2008**, 5465.

3.2 A NEW CLASS OF STRUCTURALLY RIGID TRICYCLIC AMPHIBIAN ORGANOCATALYST FOR ORGANOCATALYSIS

3.2.1 NEW CHIRAL ORGANOCATALYST: OUR RATIONAL DESIGN

The hexahydropyrrolo[2,3-*b*]indole skeleton is a key structural motif found in many indole alkaloids exhibiting a diverse range of biological activities (Figure 3.3).[63]

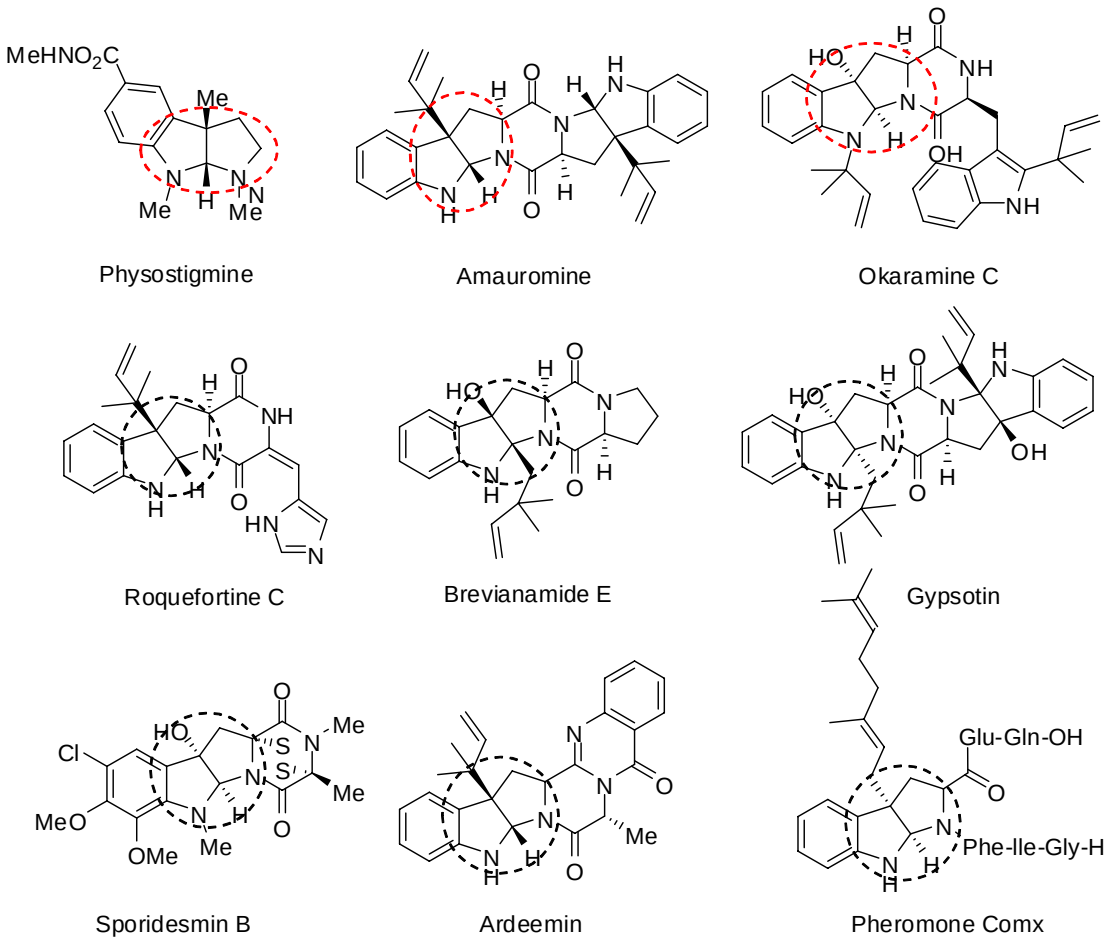
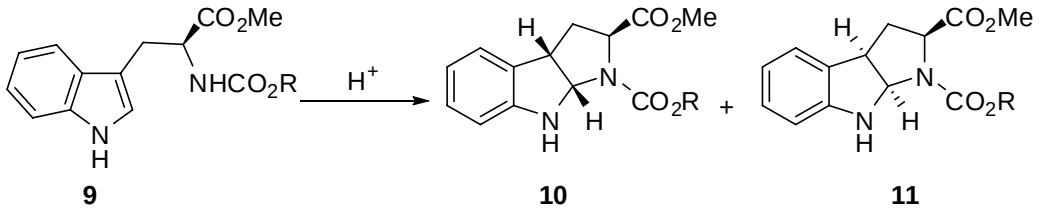


Figure 3.3 Natural products containing hexahydropyrrolo[2,3-*b*]indole skeleton

[63] (a) Hino, T.; Taniguchi, M.; Gonsho, A.; Nakagawa, M. *Heterocycles* **1979**, *12*, 1027. (b) Taniguchi, M.; Anjiki, T.; Nakagawa, M.; Hino, T. *Chem. Pharm. Bull.* **1984**, *32*, 2544. (c) Taniguchi, M.; Hino, T. *Tetrahedron* **1981**, *37*, 1487. (d) Bourne, G. T.; Crich, D.; Davies, J. W.; Horwell, D. C. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1693. (e) Crich, D.; Banerjee, A. *Acc. Chem. Res.* **2007,** *40,* 151.

As such, the chemistry of this class of heterocycles has been of interest for a long time, with the application of the hexahydropyrrolo[2,3-*b*]indole tautomers of tryptophan as key intermediates in the asymmetric synthesis of (*R*)-alkyltryptophan derivatives from tryptophan itself. Ring closure of tryptophan and tryptamine derivatives to the hexahydropyrroloindole nucleus is well documented for a variety of electrophiles, including positive halogen donors, singlet oxygen, positive oxygen donors and carbon electrophile. For example, dimethyl dioxirane (DMDO) has been utilized for the preparation of 3a-hydroxypyrroloindoles with good stereoselectivities [64] and *N*-phenylselenophthalimide effects selenocyclization to give 3a-(phenylselenyl)hexahydropyrrolo[2,3-*b*]indoles in high yields and high diastereoselectivities.[65] The most concise route to tetrahydropyrrolo[2,3-*b*]indole is based on the acid-promoted cyclization of tryptamine derivatives.[57] For instance, the cyclization of carbamate **9** yields initially the kinetically controlled compound **10**, which is quickly transformed into the thermodynamically more stable isomer **11** at room temperature (Scheme 3.3). The preferential formation of *endo* isomer **11** rather than *exo* isomer **10** under the equilibrating conditions of ring closure is crucial to our consideration of the project. Two explanations have been put forward: (i) in the *endo*



Scheme 3.3 Acid-promoted cyclization of tryptamine derivatives

[64] (a) Kameneka, T. M.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 2995. (b) Kameneka, T. M.; Danishefsky, S. J. *Chem.–Eur. J.* **2001**, *7*, 41. (c) May, J.; Fournier, P.; Pellicelli, J.; Patrick, B.; Perrin, D. *J. Org. Chem.* **2005**, *70*, 8424. (d) May, J.; Patrick, B.; Perrin, D. *Synlett* **2006**, 3403.
[65] Nicolaou, K. C.; Claremon, D. A.; Barnette, W. E.; Seitz, S. P. *J. Am. Chem. Soc.* **1979**, *101*, 3704.

isomer, the C-2 substituent is close to orthogonal to the plane of the partial N1-CO_2Me double bond, thereby minimizing ^{1,3}A strain;[66] (ii) another striking thermodynamic preference for the *endo* isomer lies in minimizing the torsional strain around the bicyclo[3.3.0]octane nucleus.[35c]

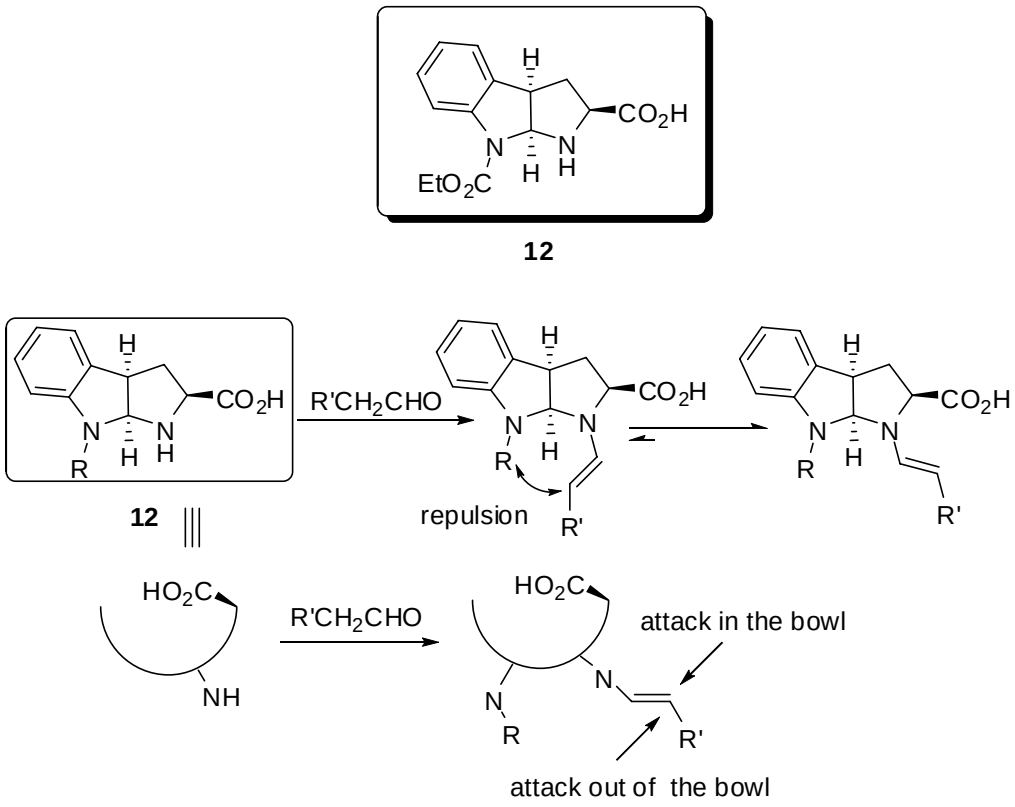
As chemists, we often turn to nature for inspiration since natural products provide chemists with a large number of stereochemically well-defined complex architectures and we can learn much from nature in regard to asymmetric synthesis: enzymatic catalysis promotes stereoselective processes with very high fidelity. Biologically active natural products often contain particularly intriguing structural features and functionalities relating to synthesis. As many chemists are engrossed in overcoming these synthetic challenges, comparatively much less attention has been given to these unique enantiopure structures themselves, which can also be used as a template or redesigned, hence providing opportunities as chiral skeleton for enantioselective catalysis.

The hexahydropyrrolo[2,3-*b*]indole skeleton is a key structural component of many indole alkaloids exhibiting a diverse range of biological activity. The tricylic rigid ring system with a stable bowl-shaped conformation attracted our attention. We envisage that this tricyclic rigid nature and its bowl-shaped conformation can act as a novel chiral skeleton for asymmetric induction. This bulky hydrophobic skeleton can also function as chiral pocket or molecular cage to repel water, enabling reaction in water. In the aldolase antibodies, the reactions occur in a hydrophobic active site, indicating that diminishing contacts between bulk water and the reaction transition states may be critical for high enantioselectivities. Thus, we hypothesize that a small

[66] Seebach, D.; Lamatsch, B.; Amstutz, R.; Beck, A. K.; Dobler, M.; Egli, M.; Fitzi, R.; Gautschi, M.; Herradon, B. *Helv. Chim. Acta* **1992**, *75*, 913.

organic catalyst with appropriate hydrophobic groups should assemble with hydrophobic reactants in water, thereby sequestering water from the transition state.

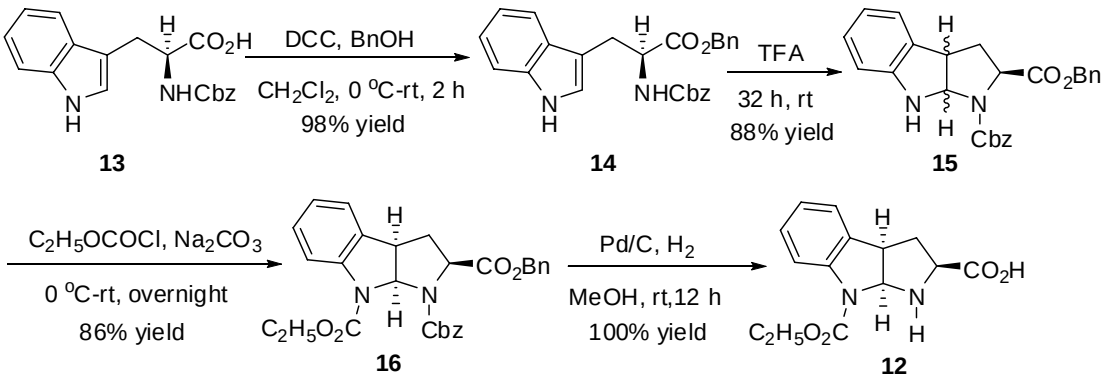
Based on the rigid tricyclic scaffold of the hexahydropyrrolo[2,3-*b*]indole framework, we designed a new type of chiral organocatalyst **12** featuring such a skeleton. Conceptually, we envisage that this new rationally designed chiral catalyst **12** could act as a novel chiral organocatalyst for asymmetric enamine catalysis. To achieve high enantioselectivity, control of the geometry of the enamine is critical. We envision that the substituted ethyl carbamate group at N-8 would favor the *E*-enamine formation, resulting from steric repulsion conferred by the ethyl carbamate group on the incipient enamine. Another important factor is efficient face shielding, which we propose the electrophile would attack the enamine from the direction either in the bowl or out of the bowl, with high enantioselectivity achievable in either case (Scheme 3.4).



Scheme 3.4 Rational design of catalyst **12** through enamine control and face shielding

3.2.2 RESULTS AND DISCUSSION

Then we start exploring the synthesis of **12.** Initially, DCC coupling of **13** with benzyl alcohol to provide **14** in 98% yield, which underwent acid-catalyzed ring closure to supply hexahydro[2,3-*b*]pyrrolo indole **15** as diastereoisomers. Protection of **15** with ethyl chloroformate in the presence sodium carbonate, exclusively gave key intermediate **16**. Ultimately, hydrogenation of **16** with the aid of Pd/C to furnish the desired catalyst **12** in quantitative yield (Scheme 3.5). The synthesis could be performed on large scale of several grams, with a total yield of 74%. The conformation of the catalyst has been confirmed by its methyl ester derivative (Figure 3.4).[67]



Scheme 3.5 Synthetic route of catalyst **12**

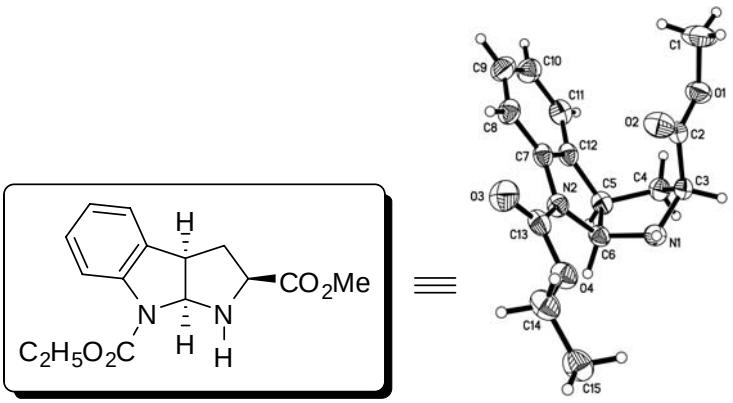
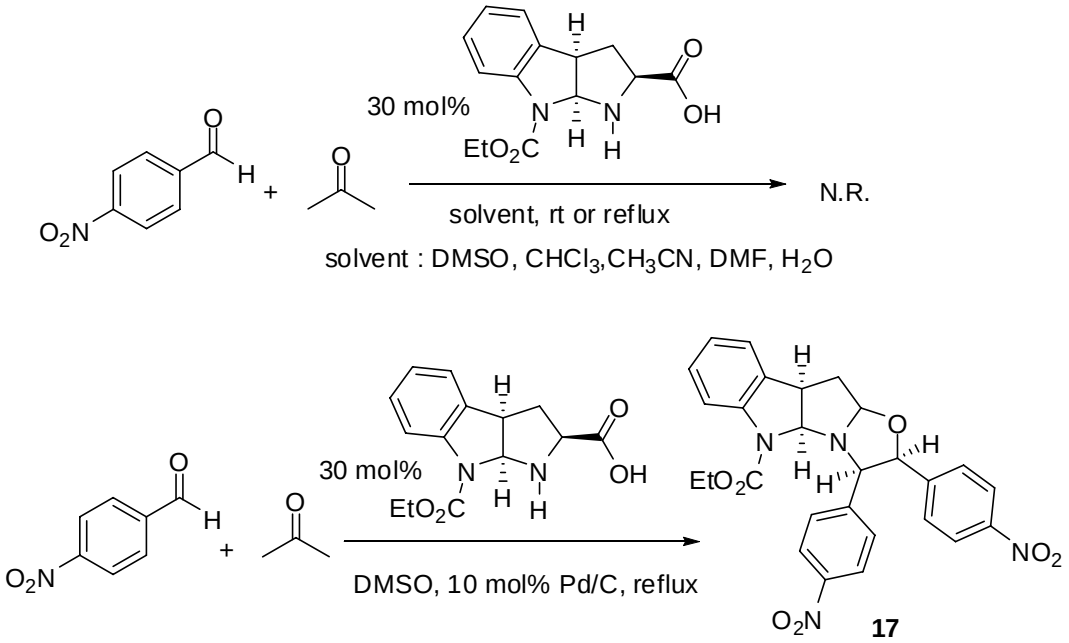


Figure 3.4 Crystal structure of methyl ester derivative of **12**

[67] Please refer to chapter 4 (Scheme 4.9) for the synthesis of methyl ester derivative of **12**.

With this catalyst in hand, we initially tried the aldol reaction between 4-nitrobenzaldehyde and acetone. No reaction was observed in all kinds of solvents at room temperature and under reflux conditions (Scheme 3.6). The failure of this reaction was possibly due to the rigidity of the catalyst skeleton and inability of the ketone substrate to form the enamine. When Pd/C was added, condensation product **17** was obtained instead, with its structure confirmed by single-crystal X-ray diffraction (Figure 3.5).



Scheme 3.6 Asymmetric aldol reaction catalyzed by **12**

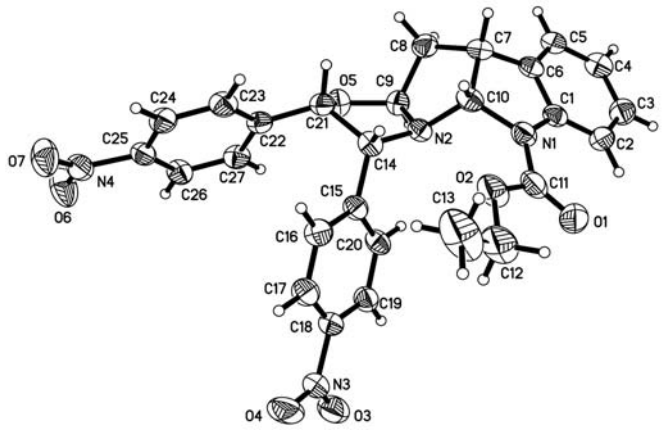
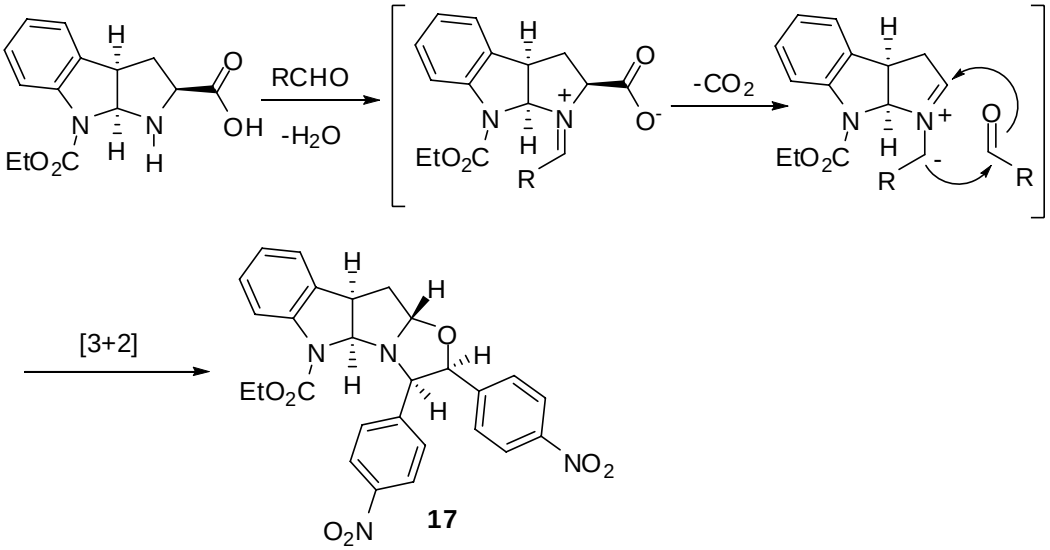


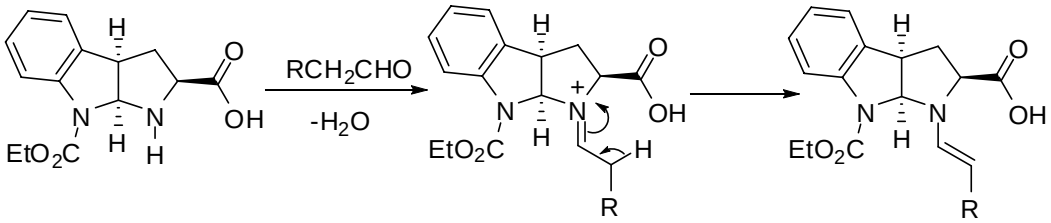
Figure 3.5 Crystal structure of compound **17**

To explain how compound **17** was formed, we postulate that the seconday amine first react with the aldehyde to form an iminium ion, followed by decarboxylation, and then [3+2] addition with another molecule of aldehyde to give the cyclized product **17** (Scheme 3.7). This phenomenon has been observed in proline-catalyzed



Scheme 3.7 Mechanism of formation of **17**

reaction previously.[68] This side-reaction indicated that the bulky amine could react with aldehyde to generate an iminium ion, and thus enamine intermediate could also be generated when linear aliphatic aldehyde is used (Scheme 3.8). Hence there is possibility for catalyst **12** to play a role in enamine catalysis still.



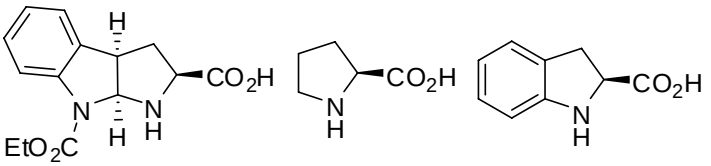
Scheme 3.8 Enamine formation

[68] Kano, T.; Takai, J.; Tokuda, O.; Maruoka, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 3055.

To demonstrate the efficiency of **12**, the enantioselective Michael addition of aldehydes to nitroalkenes was selected as the testing ground since nitroalkanes are versatile synthetic intermediates. We were delighted to find that the desired product could be obtained in 86% yield and 96% *ee* in the presence of 10 mol% catalyst **12** using 2 equivalent of propanal at room temperature in MeOH (Table 3.1, entry 1). In contrast, catalysts **7, 8, 18** and **19** gave much less desirable results in methanol (Table 3.1, entries 2–5). We envisioned that when a base such as DMAP is added, an acid-base interaction between the carboxylic acid and the amine groups should lead to an ammonium salt which renders the base as the stereocontrolling module, hence alleviating the need for tedious chemical structural modification. This is inline with the concept of the self-assembly of organocatalysts proposed recently.[69] More than 99% *ee* was achieved when DMAP was added and the catalyst loading could be decreased to as low as 2 mol% using **12**/DMAP catalyst (Table 3.1, entries 10–11). No significant difference for **7, 18 and 19** after addition of DMAP (Table 3.1, entries 6, 8–9). **8**/DMAP also showed significant improvement over **8** itself (Table 3.1, entry 7). More importantly, the **12**/DMAP catalyst was also found to catalyze the reaction in water (Table 3.1, entry 12), while no reaction was observed using either **7**/DMAP, **8**/DMAP, **18**/DMAP, **19**/DMAP or **12** itself in pure water (Table 3.1, entries 14–18). Using brine as solvent gave very low yield, albeit with high enantioselectivity (Table 3.1, entry 13).

[69] For examples of self-assembly between amines and acids, see: (a) Clarke, M. L.; Fuentes, J. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 930. (b) Mandal, T.; Zhao, C. G. *Angew. Chem., Int. Ed.* **2008**, *47*, 7714. (c) Schmuck, C.; Wienand, W. *J. Am. Chem. Soc.* **2003**, *125*, 452. (d) Gac, S. L.; Luhmer, M.; Reinaud, O.; Jabin, I. *Tetrahedron* **2007**, *63*, 10721.

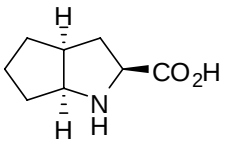
Table 3.1 Catalytic asymmetric Michael addition of propanal to nitroalkenes [a]



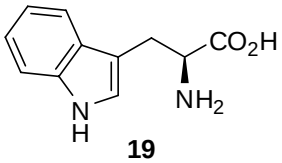
12

7

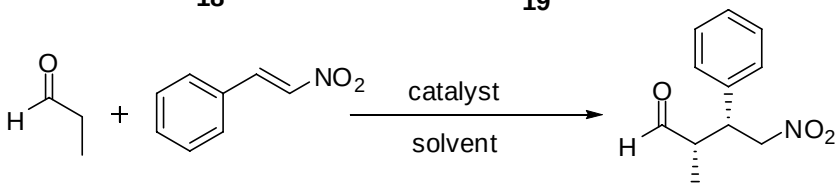
8



18



19

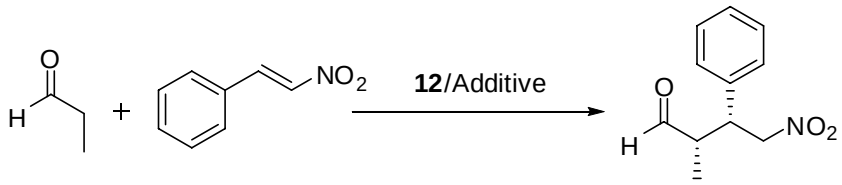


Entry	Catalyst	Solvent	Catalyst loading (mol%)	Yield (%)[b]	dr[c]	ee (%)[d]
1	**12**	MeOH	10	86	91:9	96
2	**7**	MeOH	10	30	85:15	-20
3	**8**	MeOH	10	<10	78:22	80
4	**18**	MeOH	10	<10	86:14	-20
5	**19**	MeOH	10	N.R.[e]	N.D.[f]	N.D.
6	**7**/DMAP	MeOH	10	30	85:15	-20
7	**8**/DMAP	MeOH	10	72	78:22	98
8	**18**/DMAP	MeOH	10	<10	N.D.	N.D.
9	**19**/DMAP	MeOH	10	N.R.	N.D.	N.D.
10	**12**/DMAP	MeOH	5	96	91:9	>99
11	**12**/DMAP	MeOH	2	92	75:25	>99
12	**12**/DMAP	H_2O	5	90	91:9	>99
13	**12**/DMAP	brine	10	10	86:14	96
14	**12**	H_2O	10	N.R.	N.D.	N.D.
15	**7**/DMAP	H_2O	10	N.R.	N.D.	N.D.
16	**8**/DMAP	H_2O	10	N.R.	N.D.	N.D.
17	**18**/DMAP	H_2O	10	N.R.	N.D.	N.D.
18	**19**/DMAP	H_2O	10	N.R.	N.D.	N.D.

[a] Reactions were conducted with 2 equiv. of aldehyde, 1 equiv. of nitrostyene at room temperature in the presence of catalyst with 1:1 catalyst:DMAP. [b] Isolated yield. [c] Dr (*syn*/*anti*) was determined by chiral HPLC analysis. [d] Reported values refer to the *syn* isomer and were determined by chiral HPLC on a chiral stationary phase. [e] No reaction. [f] Not determined.

Next the base effect has also been studied (Table 3.2). With pyridine, DIEPA and imidazole as base additive, the yields were lowered although the enantioselectivities were comparable (Table 3.2, entries 1–4). DIEPA was unable to catalyze the reaction in water (Table 3.2, entry 7). Not surprisingly, the strong base DBU could not catalyze this reaction both in methanol and water (Table 3.2, entries 5 and 9). With phase transfer catalyst TEAB or TBAB in place of the base, the reaction did not proceed in water at all (Table 3.2, entries 10 and 11).

Table 3.2 Catalytic asymmetric Michael addition of propanal to nitroalkenes[a]



Entry	Catalyst	Solvent	Catalyst loading (mol%)	Yield (%)[b]	dr[c]	ee (%)[d]
1	**12**/DMAP	MeOH	5	96	91:9	>99
2	**12**/Pyridine	MeOH	10	62	90:10	94
3	**12**/DIEPA	MeOH	10	60	82:18	98
4	**12**/Imidazole	MeOH	10	75	90:10	99
5	**12**/DBU	MeOH	10	N.R.[e]	N.R.	N.D.[f]
6	**12**/Pyridine	H_2O	10	60	95:5	>99
7	**12**/DIEPA	H_2O	10	N.R.	N.R.	N.R.
8	**12**/Imidazole	H_2O	10	70	98:2	>99
9	**12**/DBU	H_2O	10	N.R.	N.R.	N.D.
10	**12**/TEAB	H_2O	10	N.R.	N.R.	N.D.
11	**12**/TBAB	H_2O	10	N.R.	N.R.	N.D.

[a] Reactions were conducted with 2 equiv. of aldehyde, 1 equiv. of nitrostyene at room temperature in the presence of catalyst with 1:1 catalyst **12**:additive. [b] Isolated yield. [c] Dr (*syn*/*anti*) was determined by chiral HPLC analysis. [d] Reported values refer to the *syn* isomer and were determined by chiral HPLC on a chiral stationary phase. [e] No reaction. [f] Not determined.

^{1}H NMR revealed that the salt of **12**/DMAP was formed rapidly and quantitatively with significant chemical shift of all the protons (Figure 3.6). ^{1}H NMR monitoring experiment showed that both **12** and **12**/DMAP are stable in water. There is no significant chemical shift or peak change even after 20 days (Figure 3.7 and 3.8).

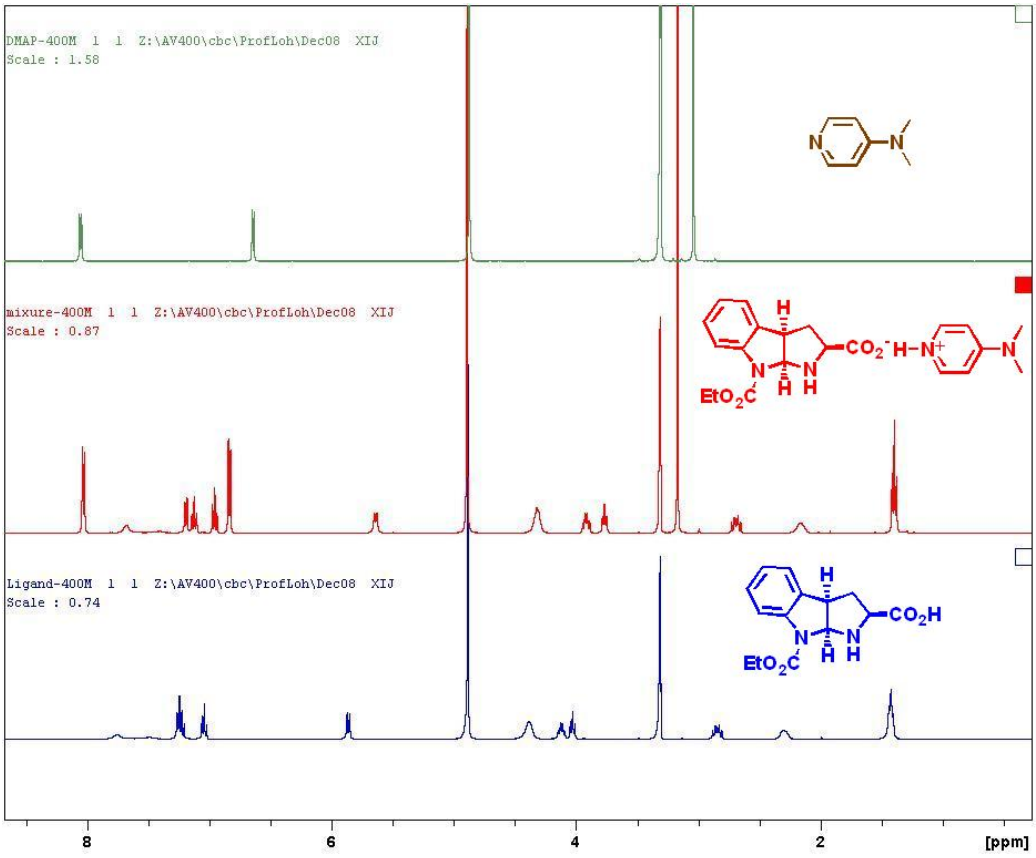


Figure 3.6 ^{1}H NMR comparison of **DMAP, 12/DMAP and 12**

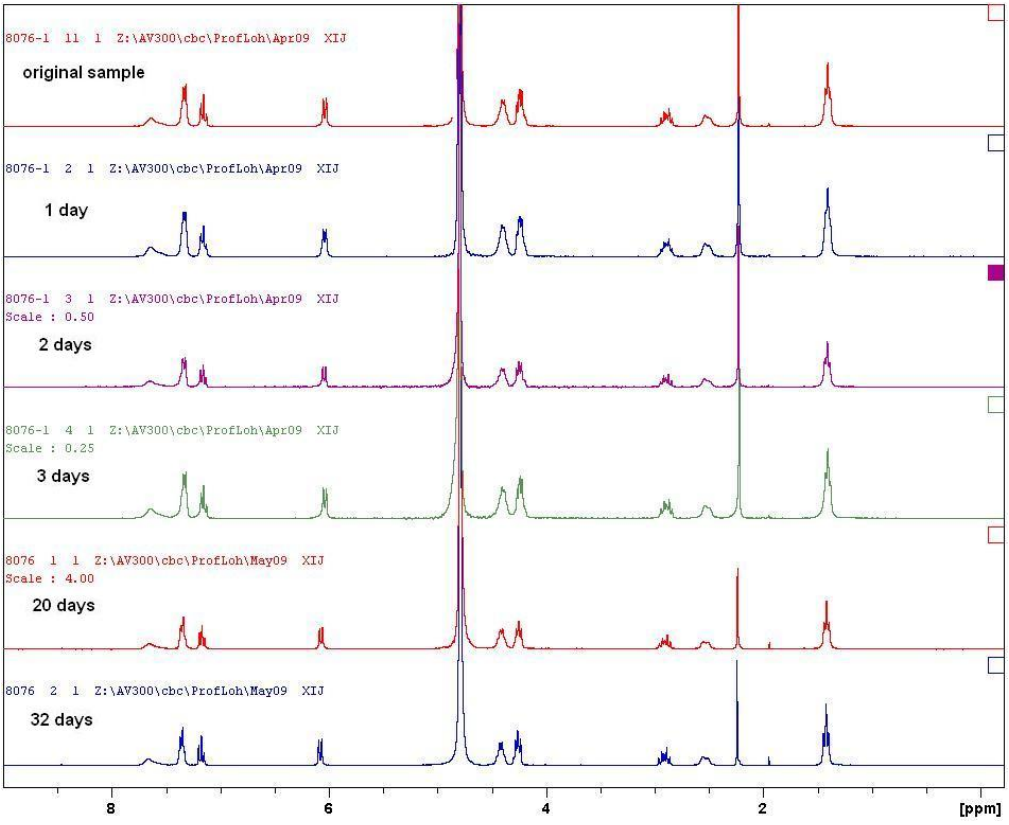


Figure 3.7 Monitoring of ^{1}H NMR of Catalyst **12** in D_2O

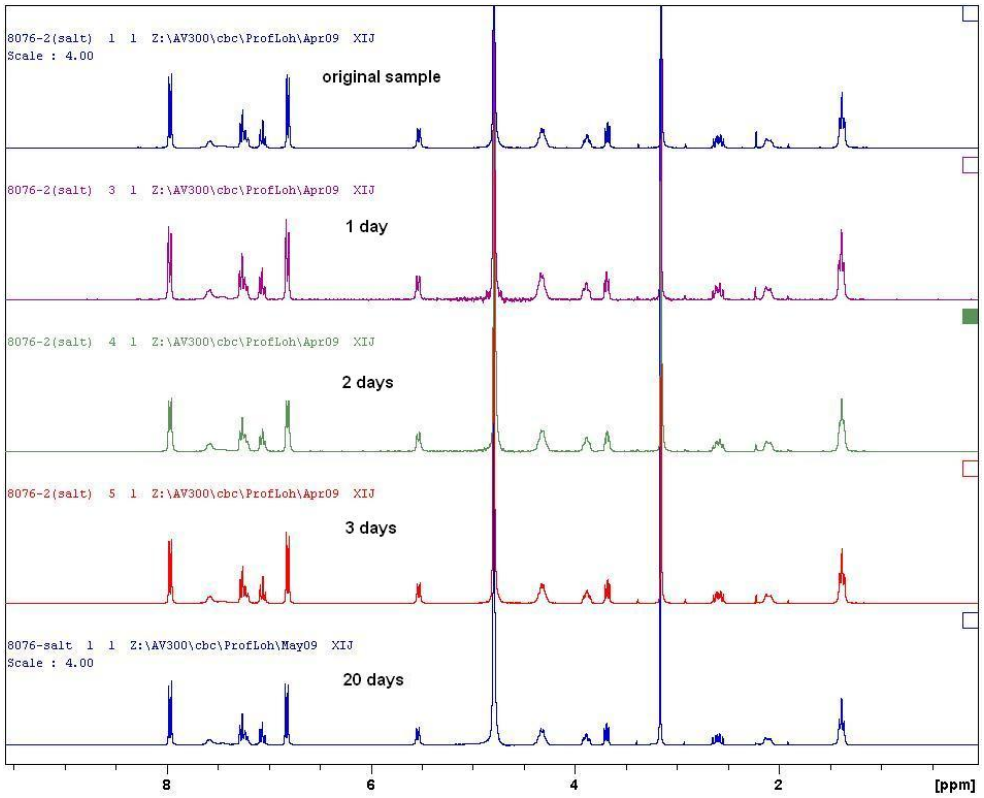


Figure 3.8 Monitoring of ^{1}H NMR of catalyst **12/DMAP** in D_2O

Next, various substrates were examined and the reaction exhibited broad applicability with respect to both the Michael acceptor and the donor. The adducts were obtained in almost optically pure form (99% *ee*) and with good *syn* diastereoselectivity. Both aromatic and alphatic aldehyes, aryl- and alkyl-substituted nitroalkenes gave the desired products in good yields and excellent enantioselectivities (Table 3.3, entries 1–11). For the more bulky isobutyraldehyde, which was found to be a poor nucleophile with only 68% *ee* using 20 mol% diaryl-prolinol ether catalyst alone, our catalyst was able to achieve 94–95% *ee* with various nitro-styrenes (Table 3.3, entries 12–14). In view of the high efficiency and high catalytic activity shown both in organic solvents and water with low catalyst loading, the catalyst **12/DMAP** can be seen as "artificial enzyme". Most of the earlier reports for this reaction were carried out at 0 ºC or even lower temperature with 10 equivalents of aldehydes. In our cases, only 2 equivalents of aldehydes was employed and excellent *ee* could be obtained at room temperature.

The stereochemistry of one of the product (Table 3.3, entry 2), (2*S*,3*R*)-3-(4-bromophenyl)-2-methyl-4-nitrobutanal (**20**), was established by X-ray crystal structure (Figure 3.9).

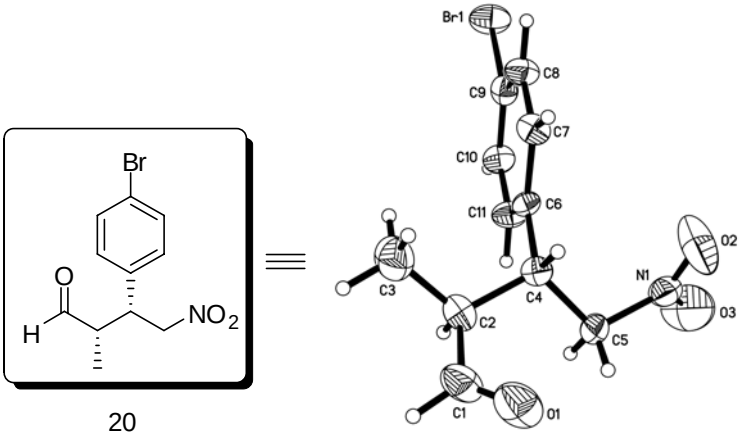
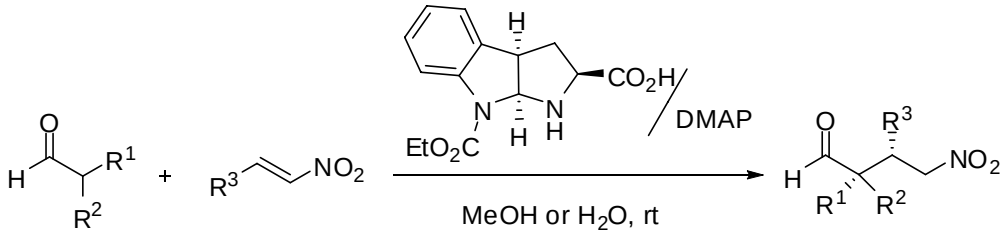


Figure 3.9 Crystal structure of product **20**

Table 3.3 Catalytic asymmetric Michael addition of aldehydes to nitroalkenes [a]



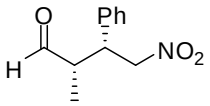
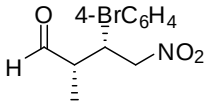
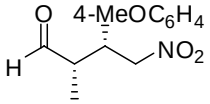
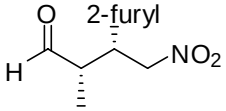
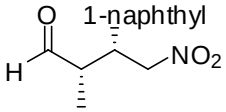
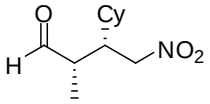
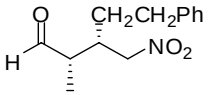
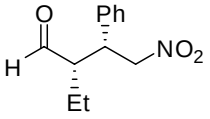
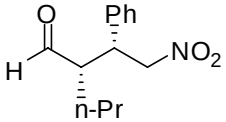
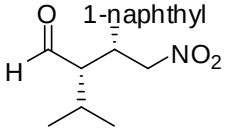
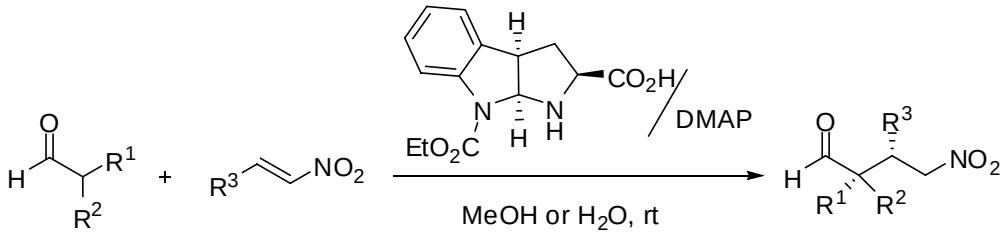
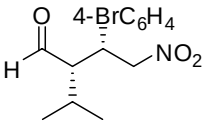
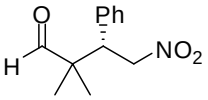
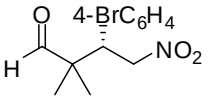
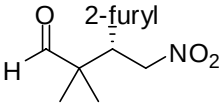
Entry	Product	Catalyst (mol%)	Solvent	Time (h)	Yield (%)[b]	dr[c]	ee(%)[d]
1		5	MeOH	8	96	91:9	>99
			H_2O	12	90	91:9	>99
2		5	MeOH	8	87	86:14	96
			H_2O	12	75	63:37	91
3		5	MeOH	8	79	72:28	93
			H_2O	12	76	63:37	92
4		5	MeOH	8	94	88:12	96
			H_2O	12	61	64:36	95
5		5	MeOH	24	92	91:9	96
			H_2O	36	87	78:22	96
6		10	MeOH	72	60	60:40	98
			H_2O	96	56	40:60	98
7		10	MeOH	72	70	80:20	96
			H_2O	96	65	76:24	96
8		5	MeOH	48	89	91:9	98
			H_2O	56	83	91:9	97
9		5	MeOH	48	81	67:33	95
			H_2O	56	80	70:30	95
10		10	MeOH	72	87	96:4	99
			H_2O	96	84	95:5	99

Table 3.3 Catalytic asymmetric Michael addition of aldehydes to nitroalkenes[a] (continued)

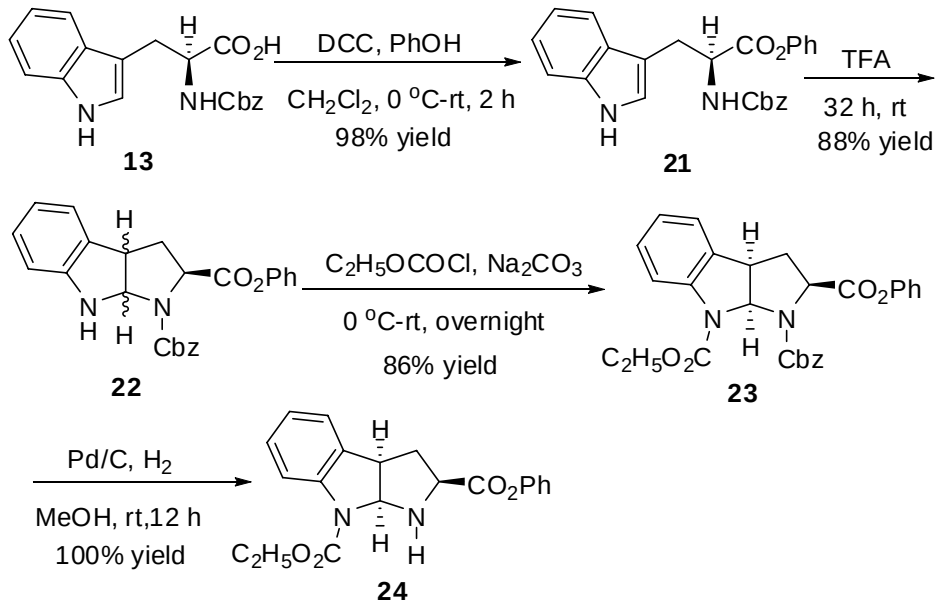


Entry	Product	Catalyst (mol%)	Solvent	Time (h)	Yield (%)[b]	dr[c]	ee(%)[d]
11		10	MeOH	72	86	99:1	>99
			H_2O	96	82	98:2	>99
12		10	MeOH	96	86	–	95
13		10	MeOH	96	82	–	94
14		10	MeOH	96	85	–	95

[a] Reactions were conducted with 1 equiv. of nitrostyene, 2 equiv. of aldehyde at room temperature or 4 equiv. aldehyde at 60 °C (for bulky aldehydes, entries 13-17) in the presence of catalyst with 1:1 (catalyst **12**:DMAP). [b] Isolated yield. [c] Dr (*syn*/*anti*) was determined by chiral HPLC analysis or by ^{1}H NMR after purification. [d] Reported values refer to the *syn* isomer and were determined by chiral HPLC on a chiral stationary phase.

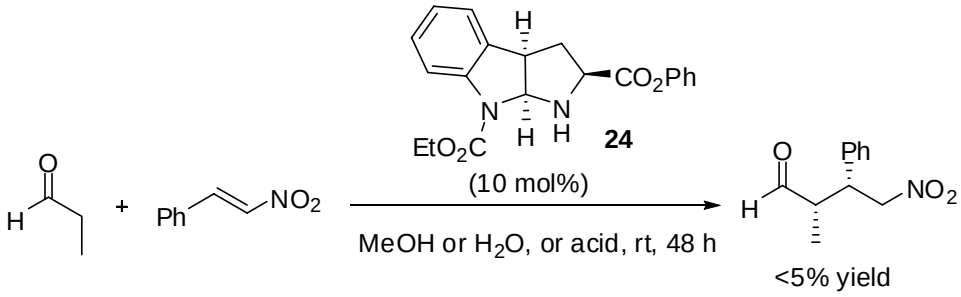
3.2.3 MECHANISTIC STUDIES

Phenyl ester derivative **24** was also synthesized as a catalyst probe in order to better understand the mechanism of this reaction. DCC coupling of **13** with phenol furnished **21**, which was treated with TFA to afford an *endo* and *exo* mixture of **22**. Reaction of **22** with ethyl chloroformate in the presence of sodium carbonate, followed by hydrogenation, gave the desired **24** in good yield (Scheme 3.9).



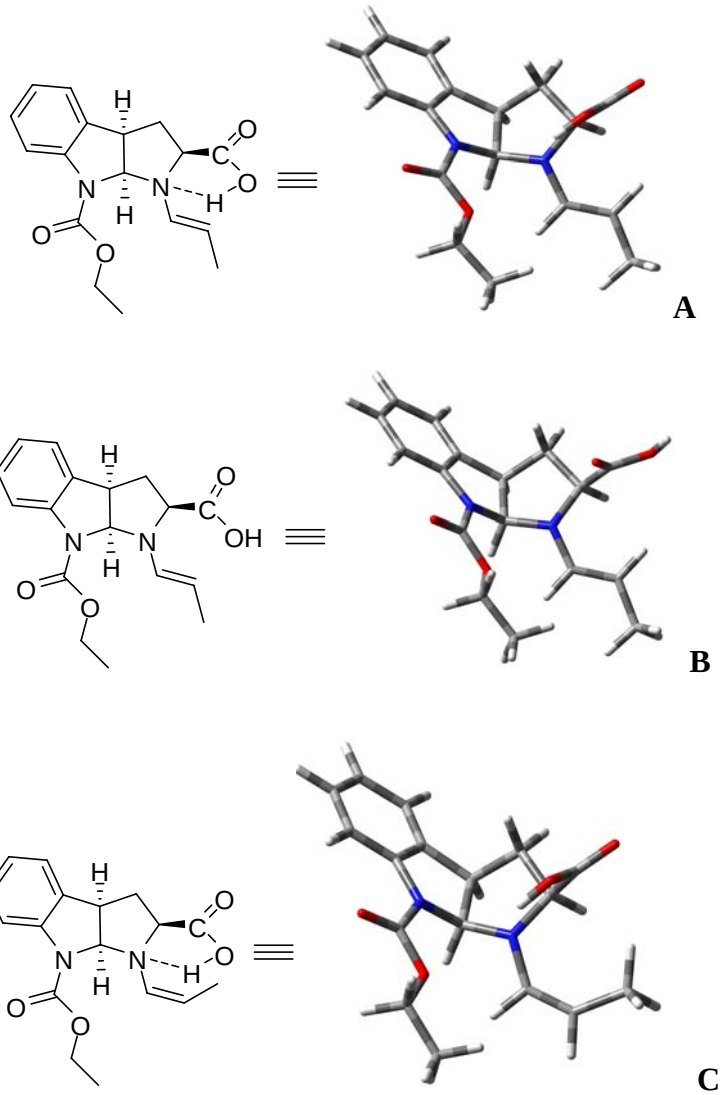
Scheme 3.9 Synthesis of phenyl ester derivative **24**

Interestingly, **24** could not catalyze this reaction both in methanol or in water, even in the presence of acid additive (Scheme 3.10).



Scheme 3.10 Phenyl ester derivative **24**–catalyzed Michael addition of propanal to nitroalkene

Next the energy of different conformers of the enamine intermediate were calculated to determine the lowest energy conformation using DFT calculation.[70] As expected, the ethyl carbamate group controls the geometry of the enamine, favouring the *syn* enamine **A** conformation (Figure 3.9). From this conformer, we can see that at the *Si* face of the enamine, there are several highly electronegative atoms such as O and N which could function.



[70] DFT calculations were carried out with the Gaussian 03 package. The structures are fully optimized by B3LYP method using 6-31G (d) basis set (Ditchfield, R.; Hehre, W. J.; Pople, J. A. *J. Chem. Phys.* **1971**, *54*, 724) and have been confirmed to be a local minima by the harmonic frequencies calculations at the same level of theory.

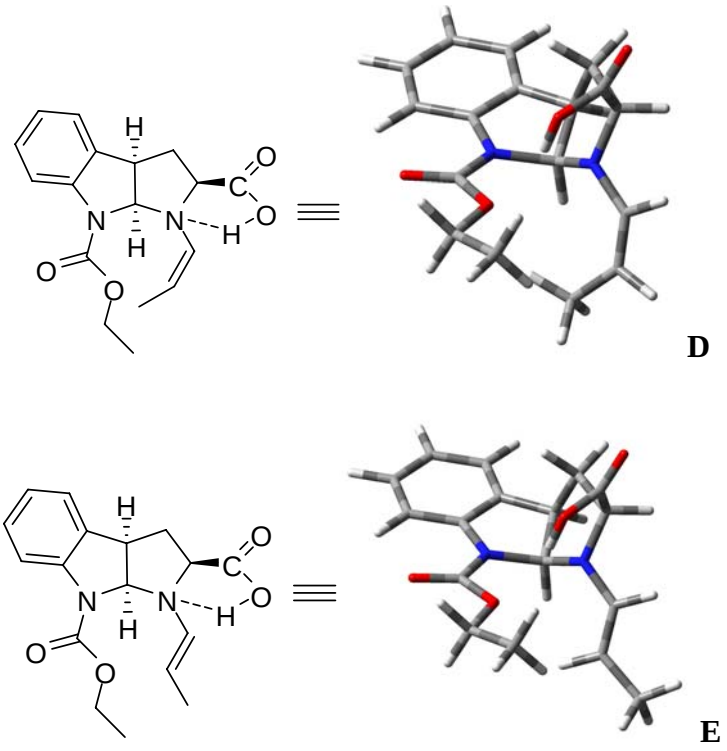


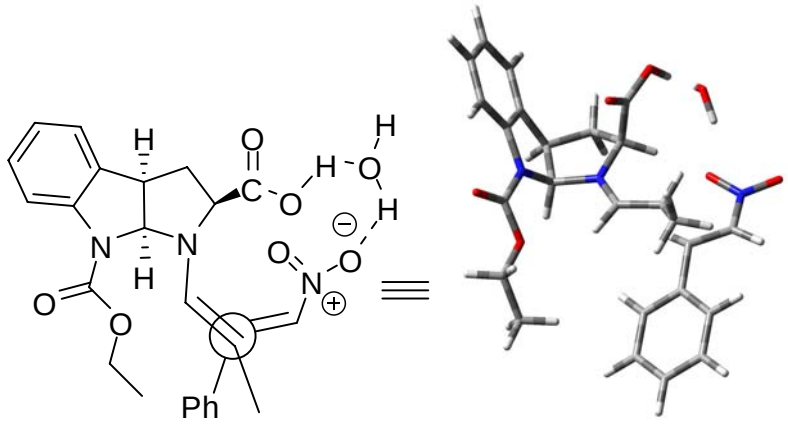
Figure 3.9 Different enamine conformations **A-E** by DFT calculation

as Hydrogen-bond acceptors. Therefore when the enamine is immersed in protic solvents such as methanol and water, the *Si* face is expected to develop strong hydrogen-bond networks which eventually block the attack of nitrostyrene from this side.[71] The whole system is stabilized by hydrogen-bonds. On this basis, nitrostyrene will attack the enamine from the *Re* face *via* transition state **A**, where a water molecule is probably involved in forming hydrogen bonds with the CO_2H and NO_2 groups, leading to the desired (*S*,*R*) product (Figure 3.10).[72] The activation energy of this transition state model **A** is 64.61 kJ/mol lower than that of transition state **B** without water molecule as hydrogen-bond bridge. The transition state **C**, which is

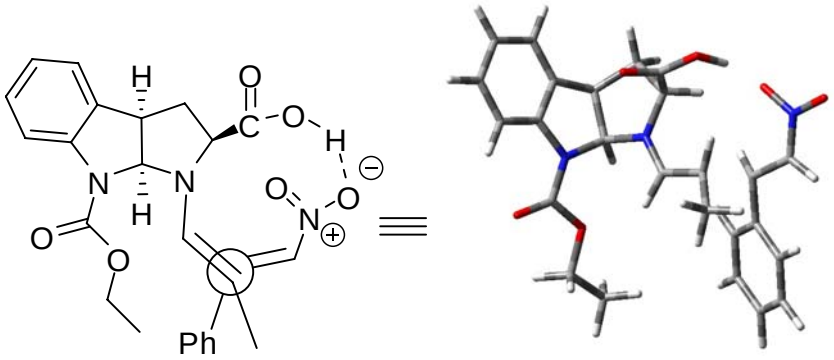
[71] Jung, Y.; Marcus, R. A. *J. Am. Chem. Soc.* **2007**, *129*, 5492.
[72] (a) Wang, J.; Li, H.; Lou, B, Zu, L.; Guo, H. Wang , W. *Chem. Eur. J.* **2006**, *12*, 4321. (b) Chen, X.-H.; Luo, S.-W.; Tang, Z.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *Chem.–Eur. J.* **2007**, *13*, 689.

consistent with Seebach's model,[73] is also calculated and the energy of **C** is 7.91 kJ/mol higher than that of transition state of **A**.

This proposal is supported by the following experimental results: (1) the phenyl ester derivative of **24** could not catalyze the reaction in MeOH or H_2O which indicates the possible activation of nitrostyrene by the carboxyl group; (2) the reaction is much slower in aprotic solvent such DMSO and DMF which implies that H_2O may be involved in the reaction through H-bonding interaction. Although the role of DMAP

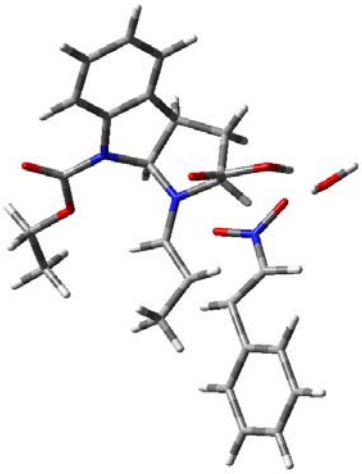


A



B

[73] (a) Seebach, D.; Golinski, J. *Helv. Chim. Acta* **1981**, *64*, 1413. (b) Seebach, D.; Beck, A. K.; Golinski, J.; Hay, J. N.; Laube, T. *Helv. Chim. Acta* **1985**, *68*, 162.



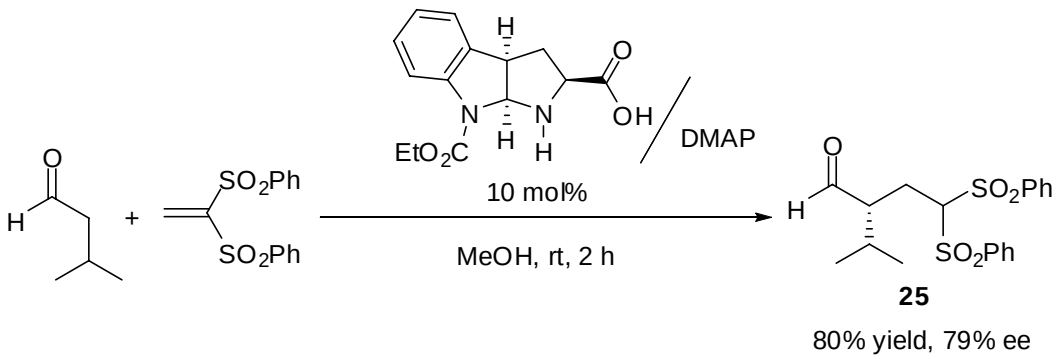
C

Figure 3.10 DFT calculated Michael addition transition state **A**, **B and C**

is not clear at this moment, the DMAP salt was found to improve the solubility of the catalyst and could also function as phase transfer catalyst when the reaction is carried out in water. This structurally rigid tricyclic skeleton provides a well-organized environment for asymmetric induction, as well as a hydrophobic pocket to enable this reaction to proceed smoothly in water. For catalyst **7, 8, 18** and **19**, they could not satisfy the above criteria.

3.2.4 APPLICATION TO OTHER ORGANOCATALYTIC ENANTIOSELECTIVE REACTIONS

To further explore the application of this new catalyst and the scope of enamine catalysis, different Michael acceptors have been tested. The reaction of propionaldehyde and alkylidene malonate did not proceed at all probably due to the lower activity of alkylidene malonate.[74] For Michael reaction of aldehydes to vinyl sulphones,[75] we found that our catalyst could catalyze this reaction efficiently. For example, in the conjugate addition of isovaleraldehyde to 1,1-bis(phenylsulfonyl)ethylene, the desired product **25** could be obtained in good yield and good enantioselectivity. However, proline catalyst **7** and **7**/DMAP give low yield and low *ee* for this reaction.



Scheme 3.11 12-catalyzed Michael addition of isovaleraldehyde to vinyl sulphone

[74] Zhao, G.-L.; Vesely, J.; Sun, J.; Christensen, K. E.; Bonneau, C.; Córdova, A. *Adv. Synth. Catal.* **2008**, *350*, 657.

[75] (a) Mossé, S.; Alexakis, A. *Org. Lett.* **2005**, *7*, 4361. (b) Mossé, S.; Alexakis, A. *Org. Lett.* **2005**, *7*, 4361. (c) Mossé, S.; Laars, M.; Kriis, K.; Kanger, T.; Alexakis, A. *Org. Lett.* **2006**, *8*, 2559. (d) Quintard, A.; Bournaud, C.; Alexakis, A. *Chem.–Eur. J.* **2008**, *14*, 7504. (e) Landa, A.; Maestro, M.; Masdeu, C.; Puente, A.; Vera, S.; Oiarbide, M.; Palomo, C. *Chem.–Eur. J.* **2009**, *15*, 1562. (f) Mossé, S.; Alexakis, A.; Mareda, J.; Bollot, G.; Bernardinelli, G.; Filinchuk, Y. *Chem.–Eur. J.* **2009**, *15*, 3204. (g) Zhu, Q.; Lu, Y. *Org. Lett.* **2008**, *10*, 4803.

3.3 CONCLUSION

In summary, a new class of structurally rigid tricyclic amphibian chiral catalysts based on the hexahydropyrrolo[2,3-*b*]indole skeleton has been developed. The special features of this catalyst include: (1) easily prepared in large scale; (2) **12**/DMAP catalyst has been shown to afford the desired products in high yields and excellent enantioselectivities in the Michael addition of aldehydes to nitroalkenes both in organic solvents and in water; (3) only slight excess of aldehyde is used in this system; (4) low catalyst loading and broad substrate scope. These advantages render this chiral catalyst more suitable for practical use and will certainly find application in asymmetric synthesis. The success of this novel catalyst design will open up new perspectives in chiral catalyst or ligand design. Further applications to other asymmetric reactions using this new catalyst or using this skeleton as chiral ligand as well as mechanistic insight are ongoing in our group.

CHAPTER 4

A New Class of Structurally Rigid Tricyclic Chiral Ligands For Asymmetric Synthesis

4.1 OVERVIEW OF BORON HYDRIDE-BASED CATALYTIC ASYMMETRIC REDUCTION OF KETONES

Optically active secondary alcohols are important chiral building blocks for the preparation of biologically active compounds. To obtain such enantiopure secondary alcohols, many enantioselective reduction methods of carbonyl compounds such as microbial process,[76] transfer hydrogenation,[77] transition metal catalyzed hydrogenations,[78] have been developed. The introduction of metal hydrides and boron hydrides as hydrogen source[79] for the reduction of carbonyl groups had a huge impact on the field of synthetic chemistry, and shoved forward the golden age of rationally designed multistep construction of complex organic molecules. For this purpose, a great number of asymmetric reducing agents, which are mostly chirally modified

[76] Selected recent examples and reviews: (a) Zhu, D.; Yang, Y.; Majkowicz, S.; Pan, T. H.-Y.; Kantardjieff, K.; Hua, L. *Org. Lett.* **2008**, *10*, 525. (b) Grau, B. T.; Devine, P. N.; DiMichele, L. N.; Kosjek, B. *Org. Lett.* **2007**, *9*, 4951. (c) de Wildeman, S. M. A.; Sonke, T.; Schoemaker, H. E.; May, O. *Acc. Chem. Res.* **2007**, *40*, 1260. (d) Ema, T.; Okita, N.; Ide, S.; Sakai, T. *Org. Biomol. Chem.* **2007**, *5*, 1175. (e) Zhang, J.; Witholt, B.; Li, Z. *Adv. Synth. Catal.* **2006**, *348*, 429. (f) Kroutil, W.; Mang, H.; Edegger, K.; Faber, K. *Curr. Opin. Chem. Biol.* **2004**, *8*, 120. (g) Zhu, D.; Hua, L. *J. Org. Chem.* **2006**, *71*, 9484. (h) Zhu, D.; Yang, Y.; Buynak J. D.; Hua, L. *Org. Biomol. Chem.* **2006**, *4*, 2690.

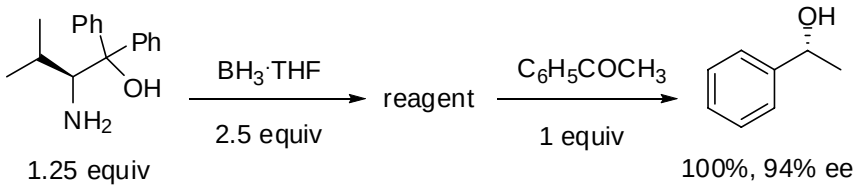
[77] For selected recent reviews, see: (a) Ikariya, T.; Blacker, A. J. *Acc. Chem. Res.* **2007**, *40*, 1300. (b) Wu, X.; Xiao, J. L. *Chem. Commun.* **2007**, 2449. (c) Gladiali, S.; Alberico, E. *Chem. Soc. Rev.* **2006**, *35*, 226. (d) Samec, J. S. M.; Bajckvall, J.-E.; Andersson, P. G.; Brandt, P. *Chem. Soc. Rev.* **2006**, *35*, 237. (e) Clapham, S. E.; Hadzovic, A.; Morris, R. H. *Coord. Chem. Rev.* **2004**, *248*, 2201. (f) Everaere, K.; Mortreux, A.; Carpentier, J.-F. *Adv. Synth. Catal.* **2003**, *345*, 67. (g) Palmer, M. J.; Wills, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2045. (h) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97.

[78] (a) Noyori, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2008. (b) Knowles, W. S. *Angew. Chem., Int. Ed.*, **2002**, *41*, 1999. (c) Noyori, R.; Takaya, H. *Acc. Chem. Res*. **1990**, *23*, 345. (d) Blaser, H. U.; Malan, C.; Pugin, B.; Spindler, F.; Steiner, H.; Studer, M. *Adv. Synth. Catal.* **2003**, *345*, 103. (e) Tang, W. J.; Zhang, X. M. *Chem. Rev*. **2003**, *103*, 3029. (f) Qiu, L. Q.; Wu, J.; Chan, S. S.; Au-Yeung, T. T. L.; Ji, J. X.; Guo, R. W.; Pai, C. C.; Zhou, Z. Y.; Li, X. S.; Fan, Q. H.; Chan,A. S. C. *Proc. Natl. Acad. Sci.* USA, **2004**, *101*, 5815. (g) Van den Berg, M.; Minnaard, A. J.; Haak, R. M.; Leeman, M.; Schudde, E. P.; Meetsma, A.; Feringa, B. L.; de Vries, A. H. M.; Maljaars, C. E. P.; Willans, C. E.; Hyett, D.; Boogers, J. A. F.; Henderickx, H. J. W.; de Vries, J. G. *Adv. Synth. Catal.* **2003**, *345*, 308.

[79] General reviews: (a) Gaylord, N. G. Reduction with Complex Metal Hydrides, Interscience, New York, **1956**. (b) Reduction Techniques and Applications in Organic Synthesis (Ed.: Augustine, R. L), Marcel Dekker, New York, **1968**. (c) Hajos, A. Complex Hydrides in Organic Synthesis, Elsevier, New York, **1979**. (d) Hudlicky, M. Reductions in Organic Chemistry, Vols. 1 and 2, Ellis Harwood, Chichester, **1984**. (e) Cho, B. T. *Chem. Soc. Rev.* **2009**, *38*, 443. (f) Nishide, K.; Node, M. Chirality, **2002**, *14*, 759. (g) Pasumansky, L.; Goralski, C. T.; Singaram, B. *Org. Process Res. Dev*. **2006**, *10*, 959.

aluminium or boron hydrides, have been reported.[80] Despite much remarkable success, the stoichiometric reagents limited their large-scale applications. Furthermore, the troublesome and costly separation and purification steps also make it less than desirable. Thus the development of catalytic processes for the reduction is highly anticipated.

The asymmetric reductions of acetophenone with optically active borane complexes was revealed by Fiaud and Kagan in 1969 using homochiral amine borane complexes derived from desoxyephedrine.[81] Insignificant enantioselectivities were obtained originally and the *ee* were increased up to 20 % when the amine and α-amino acid ester borane complexes were employed as catalysts.[82] The first effective asymmetric borane reduction of ketones using stoichiometric amounts of oxazaborolidine (OAB) was discovered by Itusno in 1981.[83] In this study, the tertiary amino alcohol derived from (*S*)-valine was reacted with two equivalents of BH_3·THF to afford (*R*)-1-phenylethanol in 94% *ee*. However, no mechanistic rationale was proposed at that point for this unexpectedly good enantioselectivity (Scheme 4.1).

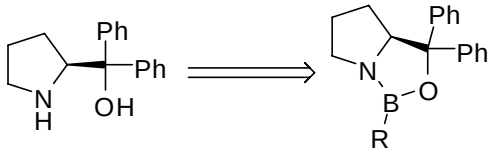


Scheme 4.1 Highly enantioselective ketone reduction reported by Itsuno

On the basis of mechanistic insights of this intriguing reaction, Corey developed a new and powerful catalytic version of oxazaborolidine catalyzed asymmetric

[80] Daverio, P.; Zanda, M. *Tetrahedron: Asymmetry* **2001**, *12*, 2225.
[81] Fiaud, J. C.; Kagan, H. B. *Bull. Sot. Chem. Fr.* **1969**, 2742.
[82] (a) Borch, R. F.; Levitan, S. R. *J. Org. Chem.* **1972**, *37* ,2347. (b) Grundon, M. F.; Cleery, D. G.; Wilson, J. W. *Tetrahedron Lett*. **1976**, *17*, 295.
[83] Hirao, A.; Itsuno, S.; Nakahama, S.; Yamazaki, N. *J. Chem. Soc., Chem. Commun.* **1981**, 315.

reduction of ketones. When (*S*)-α,α,-diphenylprolinol **26** was treated with different borane reagents, different oxazaborolidines **27a-e** (CBS catalyst) could be obtained easily (Scheme 4.2).[84] The versatility of CBS catalyst has been exploited in a variety of syntheses.



26 **27 (a-e)**

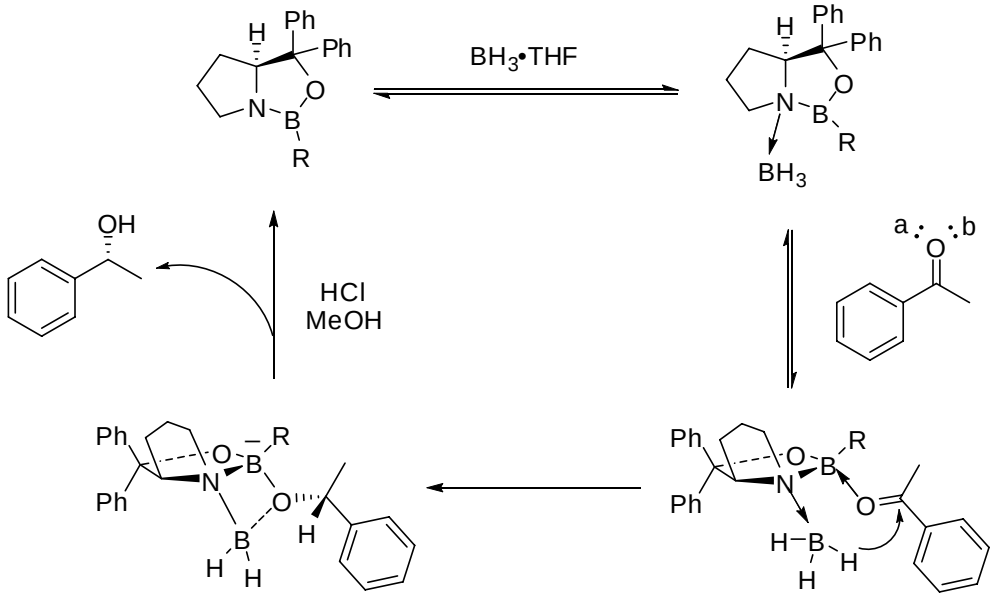
R = H(a), Me(b), n-Bu(c), Ph(d), OMe(e)

Scheme 4.2 Preparation of Corey's oxazaborolidines (OABs) **27a-e**

The mechanism for CBS-catalyzed asymmetric borane reduction of prochiral ketones is now well understood. Initially, BH_3 coordinates to the Lewis basic nitrogen atom very fast to generate the *cis*-fused oxazaborolidine-BH_3 complex. This coordination results in the activation of BH_3 as a hydride donor and enhancement of the electrophilicity of the boron atom of the oxazaborolidine ring simultaneously. Then the ketone binds to ring boron in the most easily reached manner and *cis* to the vicinal BH_3 group. The size of the phenyl group on the oxazaborolidine ring hampers rotation about the B-OCR_2 bond to facilitate intramolecular hydride transfer *via* a six-membered transition state **28** (Scheme 4.3). As a result, the CBS catalyst serves as Lewis acid-Lewis base bifunctional catalyst by activating both borane and ketone to facilitate the reduction much faster than borane itself. The CBS catalyst is also a typical representative of Lewis acid assisted Lewis acid catalyst termed by

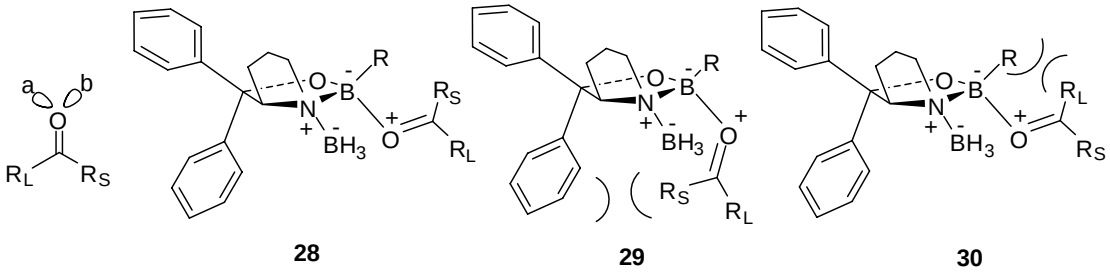
[84] (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925. (c) Corey, E. J.; Shibata, S.; Bakshi, R. K. *J. Org. Chem.* **1988**, *53*, 2861. (d) Corey, E. J. *Pure Appl. Chem.* **1990**, *62*, 1209. (e) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986.

Yamamoto. [85] Due to this bifunctional role and enzyme-like behaviour, the oxazaborolidines have been named "molecular robots" or "chemzymes".



Scheme 4.3 Catalytic cycle for CBS reduction

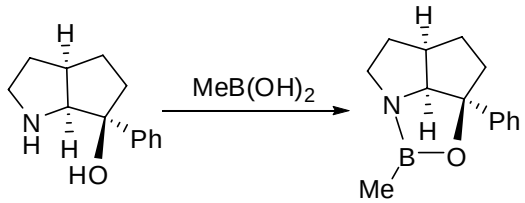
The success of CBS catalyst is mainly attributed to the excellent control for the formation of transition state **28** instead of **29** and **30** (Scheme 4.4). To minimize unfavorable steric interactions between the R group in borane and the ketone R_L group, coordination to lone pair b leads to transition state **28** and **29** in preference to **30**. However, a second steric repulsion between the *exo* phenyl ring and the ketone group



Scheme 4.4 Possible transition states for CBS reduction

[85] Yamamoto, H.; Futatsugi, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 1924.

R_S or R_L disfavor the transition state **29** which would give the antipode of the product. This effect was proven by the fact that only 44% *ee* was achieved when the *exo* phenyl ring was replaced by hydrogen (Scheme 4.5). To further demonstrate this hypothesis, the more conformationally rigid bicyclic ligand **31** has been synthesized and oxazaborolidine catalyst **32** further improved the selectivity compared to CBS catalyst without the *exo* phenyl ring, which indicates that the *endo* phenyl ring plays little role in catalyst selectivity and importance of the *exo* phenyl ring as blocking group (Scheme 4.4).[86]



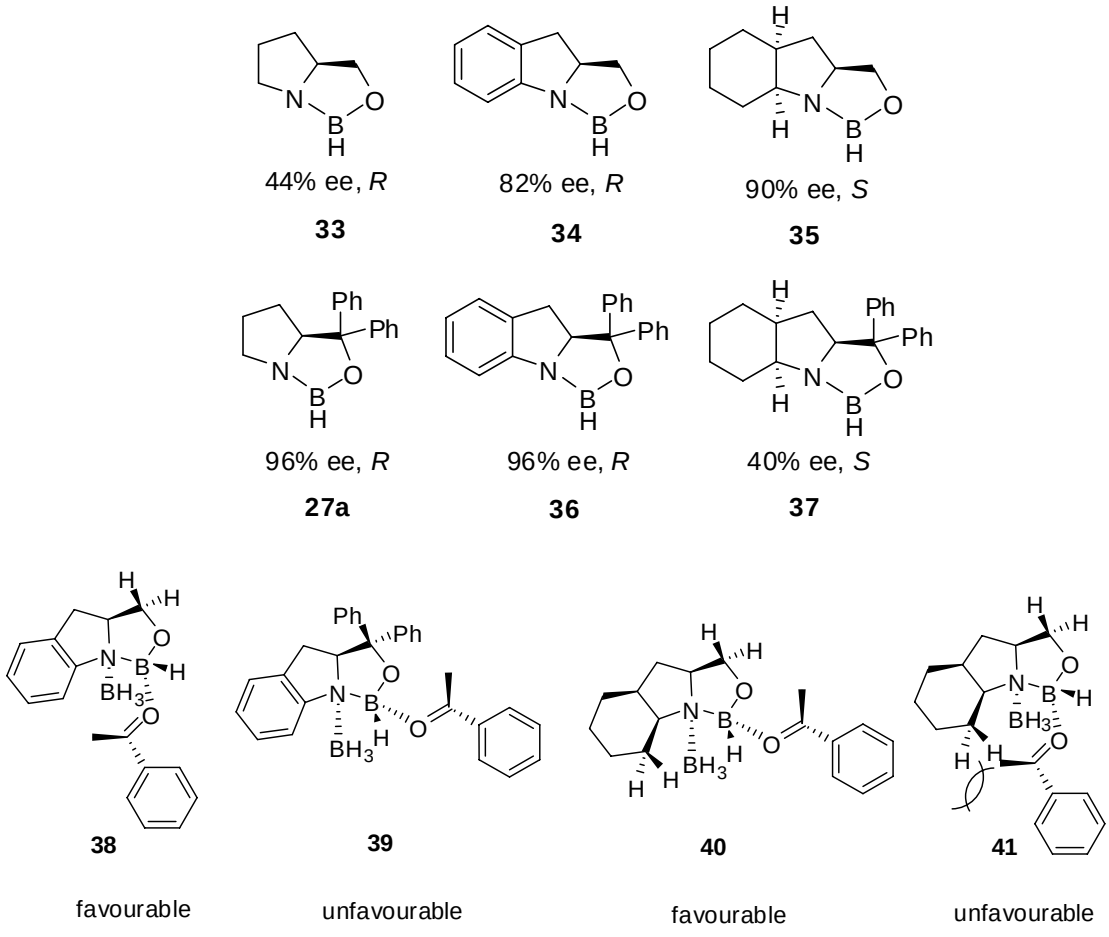
31 **32**

Scheme 4.5 Conformationally rigid tricyclic catalyst **32**

To fully understand the CBS reduction mechanism, several studies have been conducted aimed to elucidate the detailed effect of different structures of the oxazaborolidine catalyst such as the oxazaborolidine ring system and the group on the endocyclic boron atom.[86d] This detailed mechanistic study provides an impetus for exploring the different catalysts for asymmetric reduction. Various types of chiral *β*-amino alcohols have been synthesized and tested as chiral ligands for the enantioselective reduction of ketones. Although several efficient catalysts have been developed, most of the oxazaborolidines derived from L-amino acids grant access to alcohols with the (*R)*-configuration. For instance, the transition states of oxazaborolidine **34** and **36** derived from amino alcohols of (*S*)-indoline-2-carboxylic

[86] Corey, E. J.; Chen, C. P.; Reichard, G. A. *Tetrahedron Lett.* **1989,** *30*, 5547.

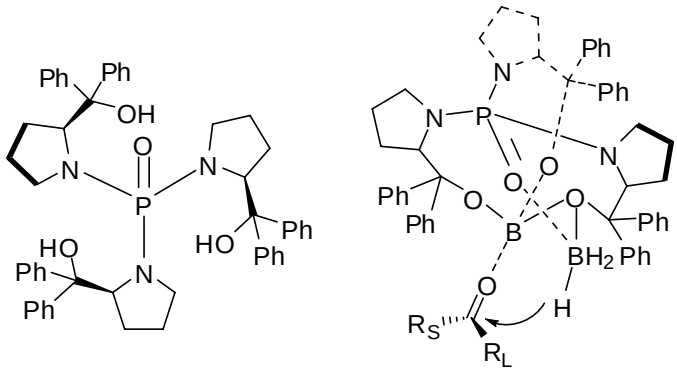
acid with acetophenone are similar to that of the CBS catalyst, as transition state **38** is more favourable than **39**. However, in the case of **35** and **37**, steric repulsion between the cyclohexane ring and the methyl group of the substrate direct approach of the *Si* face of acetophenone for the formation of transition state **40** instead of **41**, affording the (*S*)-product, with **35** giving better *ee* than **37** (Scheme 4.6)**.**



Scheme 4.6 Inversion of configuration of the product by different oxazaborolidines

Many bifunctional ligands were also synthesized and applied to the asymmetric reduction of ketones. For example, a number of bifunctional organophosphorus compounds including a N–P=O unit as a different type of chiral catalysts for the reduction have been developed. These compounds include chiral phosphoramides,

phosphonamides, phosphinamides and oxazaphospholidine oxides derived from chiral 1,2-aminoalcohols and diamines. Of all these ligands, C_3-symmetric tripodal *β*-hydroxyphosphoramide ligand **42** afforded high enantioselectivity (93–98% *ee*) with 5 mol% catalyst loading for the borane reduction of most of aryl methyl ketones.[87] However, the reduction for isobutyrophenone under the same conditions gave low enantioselectivity (43% *ee*). This new catalytic system is different from the CBS



42 **43**

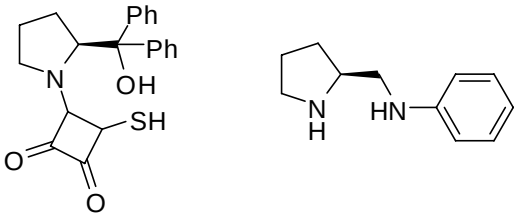
Figure 4.1 C_3-symmetric ligand **42** and transition state **43**

system in view of the absence of an active N–H group. It is assumed that in the transition state **43**, one of the boron atom is coordinated with the three hydroxyl oxygen atoms, while coordination of the phosphoramide oxygen atom with the second borane will facilitate approach of the borane to the carbonyl group from the *Re*-face of the prochiral ketone and provide the secondary alcohol in the *R* configuration (Figure 4.1).

Squaric acid has a unique rigid cyclobutenedione structure possessing acidic hydroxyl groups as well as two Lewis basic oxygen atoms. These unique structures are expected to give rise to a more rigid transition state by intramolecular coordination of catalysts with substrates. For example, a prolinol-based thiosquaryl

[87] Du, D.-M.; Fang, T.; Xu, J.; Zhang, S.-W. *Org. Lett.* **2006**, *8*, 1327.

amino alcohol **44** provided 87–95% *ee* with 10 mol% of the catalysts for the reduction of aryl methyl ketones.[88] It is interesting to note that bifunctional chiral ligand **45** without a hydroxy group could also give 82–93% *ee* for aryl methyl ketones (Figure 4.2).[89]



44 **45**

Figure4.2 Bifunctional chiral ligands **44** and **45**

[88] Zhang, J.; Zhou, H.; Lü , S.-M.; Luo, M.; Xie, R.; Choi, M.; Zhou, Z.; Chan, A. S. C.; Yang, T. *Tetrahedron: Asymmetry* **2001**, *12*, 1907.
[89] (a) Hosoda, N.; Iogawa, Y.; Shimada, Y.; Asami, M. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 274. (b) Basavaiah, D.; Rao, K. V.; Reddy, B. S. *Tetrahedron: Asymmetry* **2006**, *17*, 1041.

4.2 DESIGN AND SYNTHESES OF A NEW CLASS OF STRUCTURALLY RIGID TRICYCLIC CHIRAL LIGANDS AND THEIR APPLICATION FOR ASYMMETRIC SYNTHESIS

4.2.1 NEW PRIVILEGED CHIRAL SKELETON: HEXAHYDROPYRROLO[2,3-B]INDOLE

Catalytic asymmetric reactions provide the most powerful way to synthesize a variety of optically active compounds.[90] Chemists and biologists concentrate much effort on the development of efficient, highly selective catalysts for the synthesis of enantiomerically enriched complex molecules. Leafing through reference works on stereoselective syntheses, some chiral skeletons occur frequently. Such widely applicable chiral ligands or catalysts have been termed as "privileged structures" which create effective asymmetric induction environments for enantioselective reactions. They could be divided two categories based on their origin, namely, from natural resource or from wisdom of mankind. The former category from natural resource includes: (1) diols derived from tartaric acid (including the TADDOLs); (2) amino acid and amino alcohol that easily accessible through natural amino acids; (3) cinchona alkaloids and its derivatives (Figure 4.3). For example, TADDOL derived from tartaric acid which is the cheapest chiral starting material with C_2 symmetry available from natural sources. The latter category from wisdom of mankind includes binaphthyl and biphenyl systems. For instance, BINAP and BINOL are entirely

[90] (a) Catalytic Asymmetric Synthesis, 2 nd ed. (Ed.: Ojima, I.), Wiley-VCH, Weinheim, **2000**. (b) Comprehensive Asymmetric Catalysis, Vol. I – III (Eds.: Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H.), Springer, Berlin, **1999**; (c) Lewis Acids in Organic Synthesis (Ed.: Yamamoto, H.), Wiley-VCH, Weinheim, **2001.**

synthetic molecules developed to explore the axial chirality for asymmetric catalysis. It is interesting to see which systems will be most successful in the future, especially regarding industrial applications as well as green chemistry.

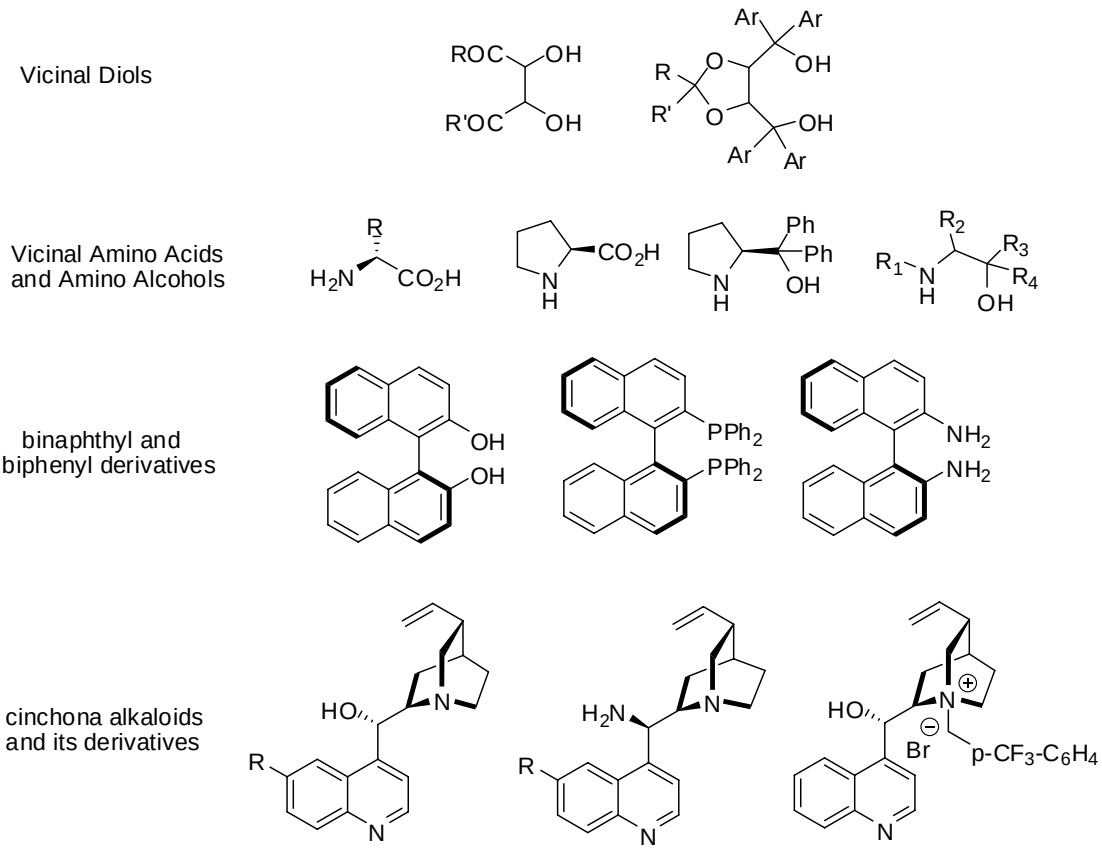


Figure 4.3 Privileged chiral ligand and catalysts

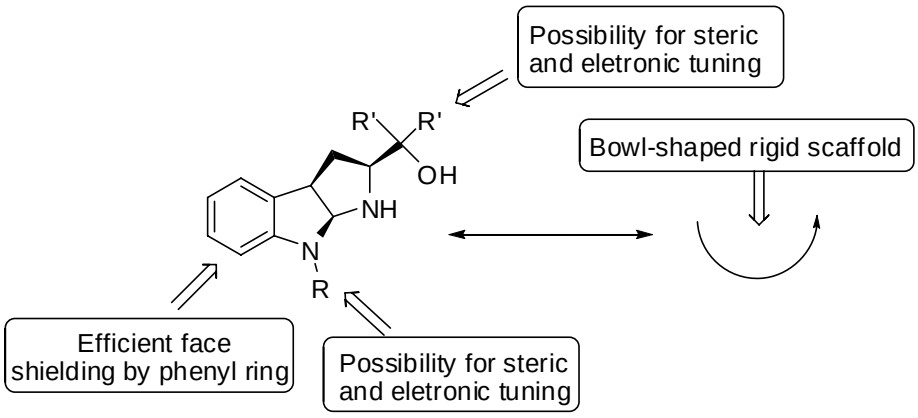
The development of new privileged chiral ligands and catalysts that exhibit high reactivity and enantioselectivity is always a challenging endeavour for organic chemists. State-of-the-art chiral ligands generally come from the profound understanding of the catalytic process, the creativity of organic chemists and sometimes, a degree of serendipity. One of the important feature of privileged chiral catalysts is the highly rigid structures, with multiple oxygen-, nitrogen-, or

phosphorous-containing functional groups to bind strongly to reactive metal centers.[91] Another important point is that it should be easily prepared and modified, thus fit well to a combinatorial approach for identifying the most suitable ligand for a particular catalytic asymmetric transformation.[92]

It is noted that the hexahydropyrrolo[2,3-*b*]indole skeleton is a key structural motif in many indole alkaloids exhibiting a diverse range of biological activities. It is well known that famous bis(oxazoline) ligands were inspired by the ligand framework of vitamin B12. Similarly, we designed a series of a new class of chiral ligands based on the tricyclic rigid scaffold of the hexahydropyrrolo[2,3-*b*]indole skeleton and promising applicability (Scheme 4.7). This diversified ligand scaffold offers remarkably high tunability in both steric and electronic properties by judicious selection of the substituted R group at the amine N atom and R' group on tertiary alcohol. Furthermore, two more stereogenic centers are incorporated as structural analogues in addition to the proline feature which would open up new perspectives in ligands design. Their unique rigidity and fine-tuning capability are expected to play a crucial role in catalytic asymmetric reactions.

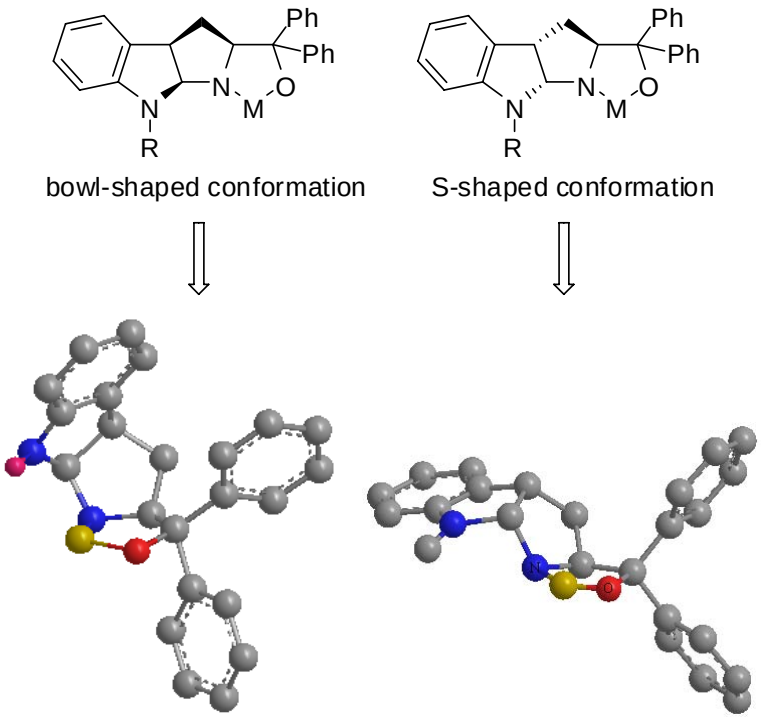
[91] (a) Yoon, T. P.; Jacobsen, E. N. *Science* **2003**, *299*, 1691. (b) Jacobsen, E. N.; Pfaltz,, A.; Yamamoto, H.; Eds. *Comprehensive Asymmetric Catalysis*, Volumes I to III (Springer, New York, 1999). (c) Pfaltz, A. and Drury III, W. J. *Proc. Nat. Acad. Sci. U.S.A.* **2004**, *101*, 5723.

[92] For examples of ligand discovery through ligand library, see: (a) Sigman, M. S.;Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901. (b) Krueger, C. A.; Kuntz, K. W.; Dzierba, C. D.; Wirschun, W. G.; Gleason, J. D.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 4284. (c) Cole, M. B.; Shimizu, K. D.; Krueger, C. A.; Harrity, J. P. A.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **1996**, *35*, 1668.



Scheme 4.7 Design of new class of structurally rigid chiral ligands

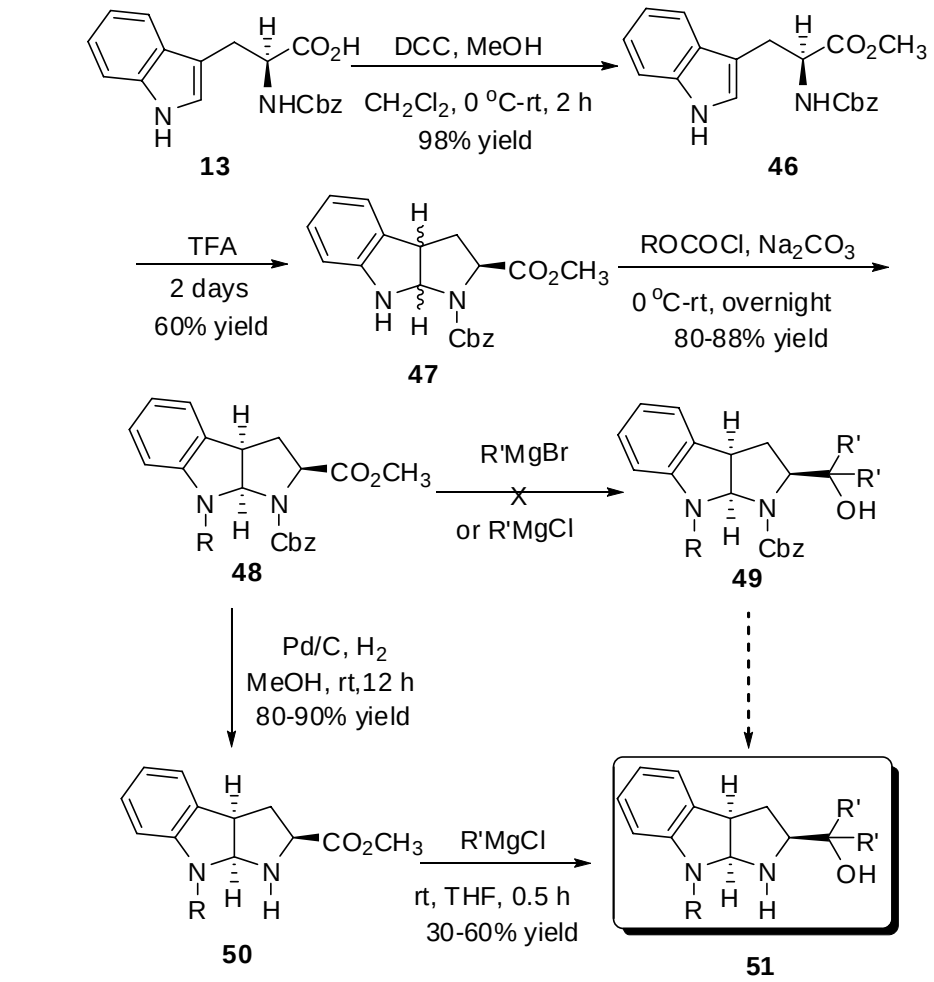
Two possible isomers, *endo* or *exo*, could be generated in the ring closure of tryptophan. These two isomers upon complexation with metal will result in a rigid bowl or *S*-shaped conformation (Scheme 4.8).



Scheme 4.8 Two different isomers of metal complexes

Starting from the commercially available *N*α-carbobenzyloxy-L-tryptophan **13**, initial DCC coupling with methanol followed by acid-catalyzed ring closure provided the hexahydro[2,3-*b*]pyrrolo indole **47** as diastereoisomeric cyclic tautomers. In agreement with literature precedent,[93] after sodium carbonate-mediated protection, the thermodynamically stable *endo* isomer **48** was obtained and the less stable diastereoisomer reverted back to starting material**.** Initial attempt to direct Grignard addition to **49** was unsuccessful, with no reaction observed. This was probably due to the highly crowded nature of the structure. To remove the steric effect, we decided to remove the protecting group to obtain **50** prior to Grignard addition. This strategy proved successful and a series of chiral ligands **51a-h** were obtained in good yields (Scheme 4.9). Crystal structures of **50a** (Figure 3.4) and **51a** further demonstrated the fascinating tricyclic rigid ring system (Figure 4.4).

[93] (a) Taniguchi, M.; Hino, T. *Tetrahedron* **1981**, *37*, 1487. (b) Bourne, G. T., Crich, D.; Davies, J. W.; Horwell, D. C. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1693. (c) Hino, T.; Nakagawa, M. Chemistry and Reactions of Cyclic Tautomers of Tryptamines and Tryptophans. *Alkaloids* **1988**, *34*, 1. (d) Crich D.; Banerjee, A. *Acc. Chem. Res.* **2007**, *40*, 151. (e) Xiao, J.; Loh, T. P. *Tetrahedron Lett.* **2008**, *49*, 7184.



(a) R = $CO_2C_2H_5$, R' = Ph; (b) R = $CO_2C_2H_5$, R' = H; (c) R = CO_2CH_3, R' = Ph;
(d) R = $COCH_3$, R' = Ph; (e) R = $CO_2CH(CH_3)_2$, R' = Ph; (f) R = $CO_2C_6H_5$, R' = Ph

Scheme 4.9 Syntheses of Chiral Ligands **51a-f**

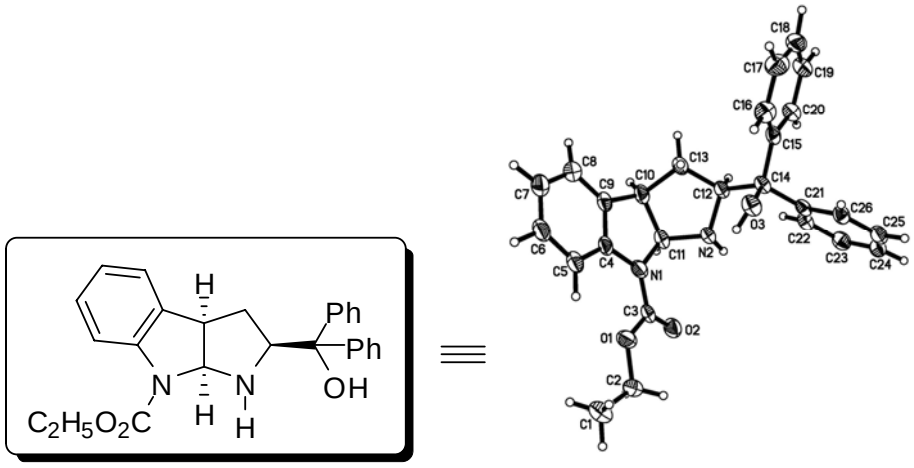
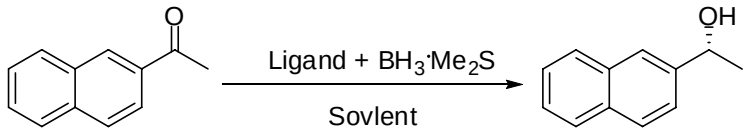


Figure 4.4 Crystal structures **51a**

4.2.2 APPLICATON OF NEW CHIRAL LIGANDS TO ASYMMETRIC REDUCTION OF KETONES

With these chiral ligands in hand, we proceeded to investigate its application for asymmetric catalysis. Inspired by the impressive discovery by Corey on the catalytic asymmetric reduction by chiral oxazaborolidine from proline-derived amino alcohol (CBS reduction), we decided to use these ligands for the asymmetric reduction of ketones. Initial study was conducted using chiral ligand **51a** with $B(OMe)_3$ to generate borane complex *in situ* for the asymmetric reduction of 2-acetonaphthone at room temperature. Unfortunately, the desired product was obtained in only 37% *ee* (Table 4.1, entry 1). Under reflux conditions, good enantioselectivity could be obtained (Table 4.1, entry 2). Direct reflux with borane gave better enantioselectivity with 89% *ee* (Table 4.1, entry 3). Screening the different substituting groups showed that ethyl carbamate protected ligand **51a** is the best ligand for this reaction. It is notable that good enantioselectivity could be obtained by varying the ligand structure (Table 4.1, entries 3–8). For example, ligand **51b** without phenyl substituent still furnished 85% *ee* in the reduction of 2-acetonaphthone (Table 4.1, entry 4). However, in the case of prolinol ligand**,** only 44% *ee* was obtained in the reduction of acetophenone (Scheme 4.6), which indicated importance of the rigid skeleton. Notably, chiral ligand **51a** could be salvaged with 90% recovery and reused for 3 times without loss of activity and enantioselectivity for the asymmetric reduction of 2-acetonaphthone (Table 4.1**,** entries 11–13).

Table 4.1 Optimizations for the enantioselective borane reduction of acetonaphthone[a]

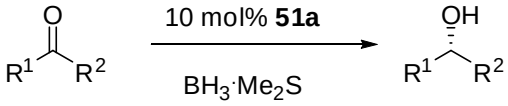


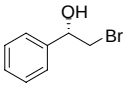
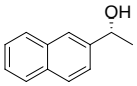
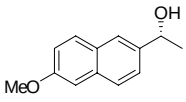
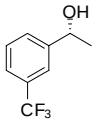
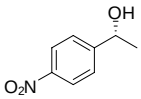
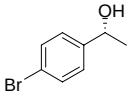
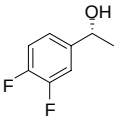
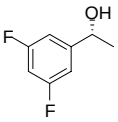
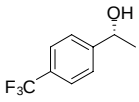
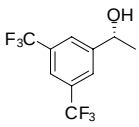
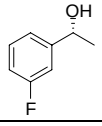
Entry	Ligand	Sovlent	Yield (%)[b]	ee (%)[c]
1[d]	**51a**	THF	96	37
2[e]	**51a**	THF	99	85
3	**51a**	**THF**	**99**	**89**
4	**51b**	THF	96	85
5	**51c**	THF	98	85
6	**51d**	THF	97	81
7	**51e**	THF	96	60
8	**51f**	THF	96	75
9	**51a**	Dioxane	95	36
10	**51a**	CH_2Cl_2	92	59
11	**51a**[f]	THF	98	89
12	**51a**[g]	THF	98	89
13	**51a**[h]	THF	98	86

[a] Reaction were performed with 0.5 mmol acetonaphthone 0.6 mmol borane, 10 mol% ligand in 2 mL of solvent at reflux temperature. [b] Isolated yield by column chromatography. [c] ee was determined by HPLC analysis using a Daicel Chiralcel AS-H column. [d] Catalyst prepared by 0.1 equiv. of ligand with 0.12 equiv. of $B(OMe)_3$ at rt and reduction was performed at rt. [e] Catalyst prepared by 0.1 equiv ligand with 0.12 equiv $B(OMe)_3$ at reflux condition and reduction was performed at refulx condition. [f] Ligand was recycled once. [g] Ligand was recycled twice. [h] Ligand was recycled third time.

Under the optimized reaction conditions, ligand **51a** was employed in the asymmetric borane reduction of a variety of aromatic ketones. As summarized in Table 4.2, high yields and enantioselectivities were obtained for prochiral ketones containing electron-withdrawing or electron-donating groups. Especially noteworthy was that (*R*)-3,5-bistrifluoromethyl phenyl ethanol (BTMP), which is an interesting chiral building block for a number of pharmaceutically interesting targets such as an

Table 4.2 Asymmetric reduction of ketones[a]



Entry	Product	Yield (%)[b]	ee[c]
1		98	81
2		95	92
3		99	89
4		92	70
5		93	86
6		96	92
7		94	76
8		99	95
9		99	95
10		99	97
11		98	93
12		97	86

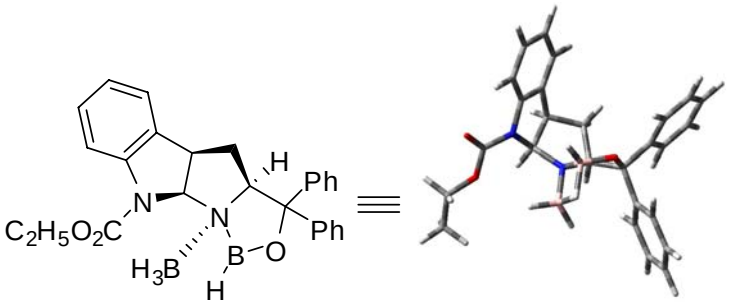
[a] Reaction were performed with 0.5 mmol ketone, 0.6 mmol borane, 10 mol% ligand in 2 mL THF at reflux temperature. [b] Isolated yield by column chromatography. [c] Determined by HPLC analysis using Daicel Chiralcel column.

NK-1 receptor antagonist,[94] could be obtained in 99% yield and 93% *ee* (Table 4.2**,** entry 10). For aliphatic ketone, only moderate enantioselectivity was obtained.[95] However, in terms of *ortho* substituted group, such as 2-fluroacetophenone, low *ee* was observed.[96]

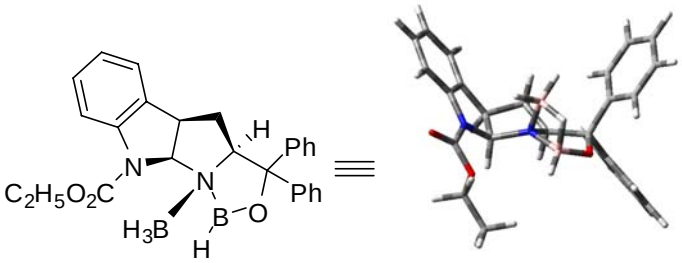
4.2.3 MECHANISTIC STUDIES

To fully understand this new finding, DFT calculations were carried out with the Gaussian 03 package. Initially, we investigated the two possible catalyst-borane complexes: the *trans* catalyst-BH_3 complex and *cis* catalyst-BH_3 complex according to the coordination manner of BH_3 relative to the hydrogen on the carbon of the ring fusion (Figure 4.5). In both cases, N–B–H–B ring is closed. The *cis* conformer is more stable as its energy is 35.3 KJ/mol lower than that of *trans* conformer. As *trans* coordination will lead to the opposite enantiomer and the tetrahydropyrrolo[2,3-*b*]indole ring will adopt a high energy twisted conformation, the presence of a rigid, fused ring system is thus important for high enantioselectivity. Next, several possible catalyst-borane-acetophenone complexes were investigated: (1) *exo/anti*; (2) *skew/anti*; (3) *endo/anti*; (4) *exo/syn* (5) *skew/syn* (Figure 3.6).[97] The calculation result shows that the *endo/anti* conformer is the most stable conformation as it has the

[94] (a) Naud, F.; Spindler, F.; Rueggeberg, C. J.; Schmidt, A. T.; Blaser, H.-U. *Org. Process Res. Dev.* **2007**, *11*, 519. (b) Pollard, D.; Truppo, M.; Pollard, J.; Cheng-Yi, C.; Moore, J. *Tetrahedron*: *Asymmetry* **2006**, *17*, 554.
[95] For example, for 4-phenyl-2-butanone, 50% *ee* was obtained.
[96] For 2′-(trifluoromethyl)acetophenone and 2′-nitroacetophenone, only 18% *ee* and 15% *ee* were obtained respectively.
[97] Alagona, G.; Ghio, C.; Persico, M.; Tomasi, S. *J. Am. Chem. Soc.* **2003**, *125*, 10027.



cis catalyst-BH_3 complex



trans catalyst-BH_3 complex

Figure 4.5 The *trans* catalyst-BH_3 complex and *cis* catalyst-BH_3 complex

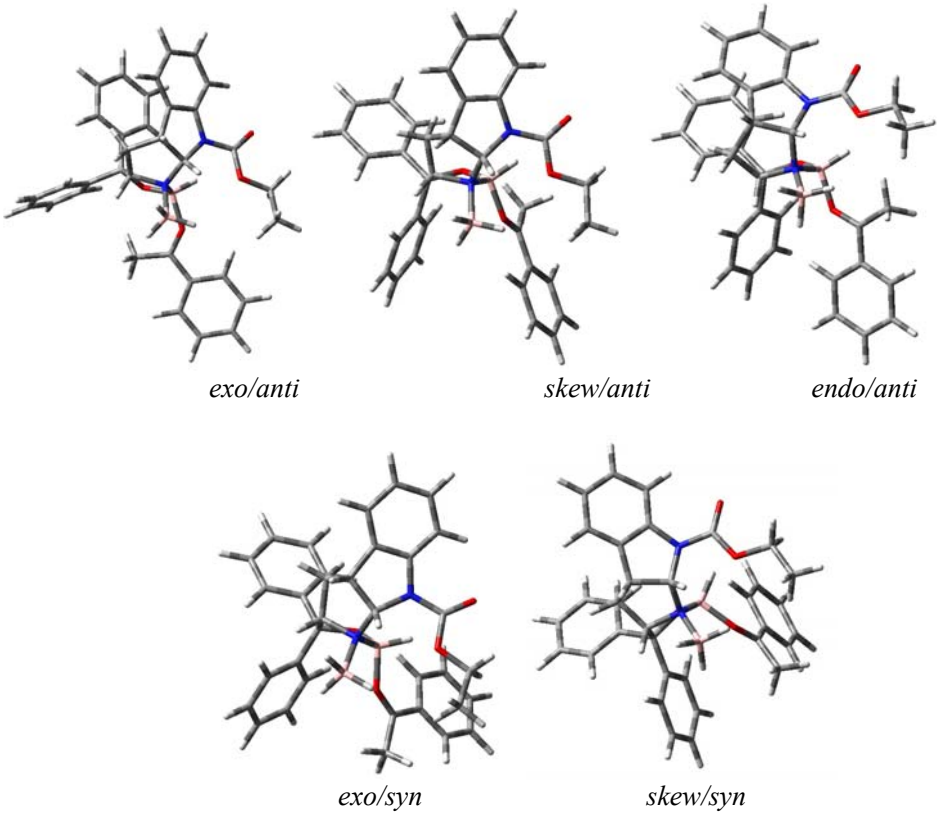


Figure 4.6 Possible catalyst-borane-acetophenone complexes

lowest energy as compared to the others (see appendix). The corresponding transition state **52** was proposed after DFT calculation (Figure 4.7). In this transition state, the *Si* face is exposed for hydride attack which leads to the *R* product that is preferentially formed in the experiment. The phenyl ring of the ketone substrate is nearly orthogonal and closer to the *exo* phenyl ring of the catalyst as compared to the CBS transition

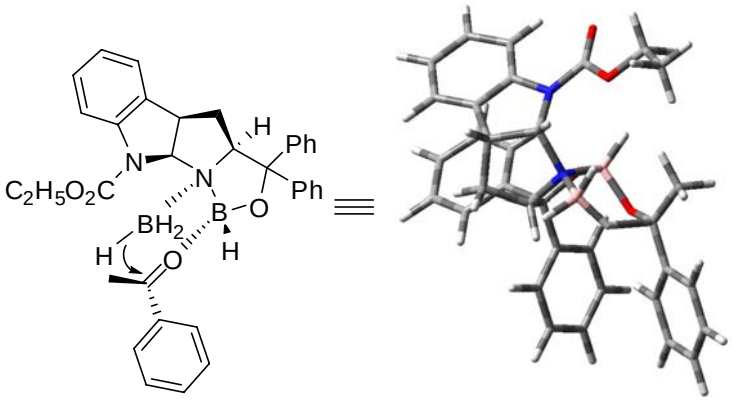


Figure 4.7 DFT calculated transition state **52**

state. In this transition state, we can conclude that the *ortho* substitute group destabilized this transition state due to steric repulsion (Figure 4.8). This is inline with the the experiments results which showed that ketone substrate with *ortho*-substituted group gave low *ee*.

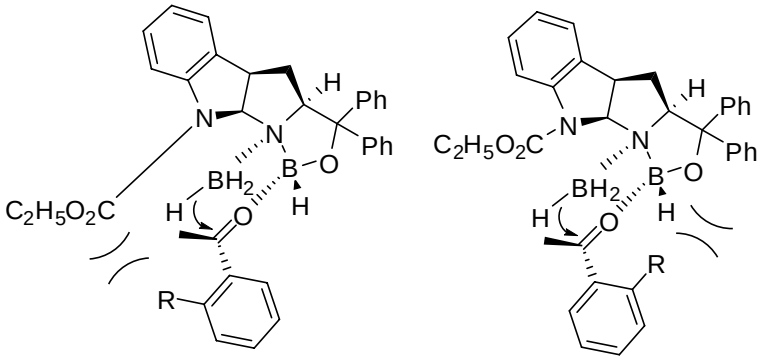
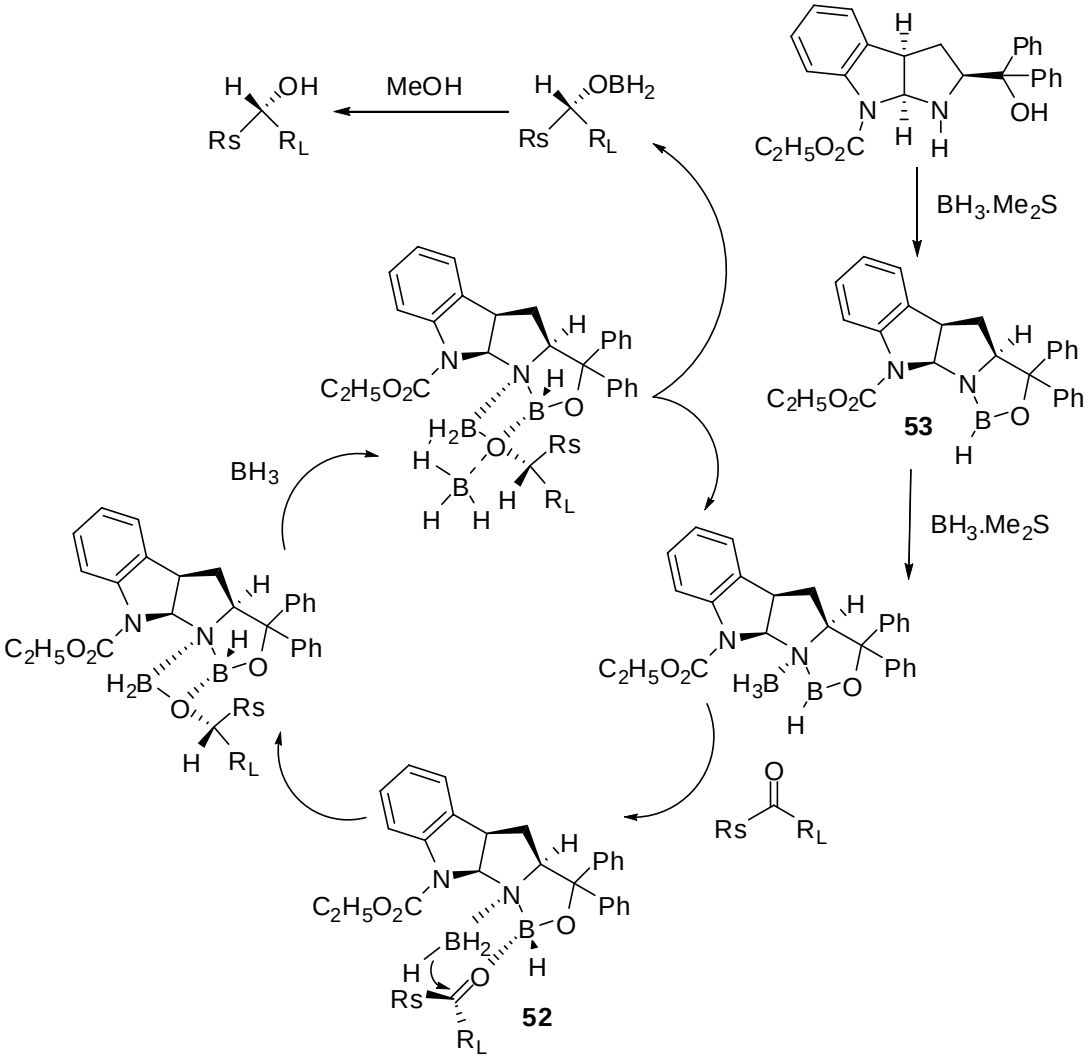


Figure 4.8 Destabilization effect by ortho substitute group

Similar to the CBS catalytic cycle, we proposed the following catalytic cycle (Scheme 4.10). Initially, ligand **51a** react with borane to form a borane complex **53**, which was subsequently coordinated by another molecule of BH_3 on the Lewis basic nitrogen to create the *cis*-fused oxazaborolidine-BH_3 complex as demonstrated by DFT calculation. Then the more easily accessible electron lone pair of ketone binds the boron atom of the oxazaborolidine ring *cis* to the vicinal BH_3 group. The bulkiness of the phenyl group and the ethyl carbamate group confer preference for the transition state **52** to facilitate intramolecular hydride transfer *via* a six-membered transition state with high facial selectivity. After hydrolysis, the product is released in the *R*-configuration.



Scheme 4.10 Catalytic cycle of the borane reduction of ketones

4.3 CONCLUSION

In summary, we have introduced a new class of structurally rigid tricyclic chiral skeleton for asymmetric synthesis. A new series of structurally rigid tricyclic chiral ligands based on the hexahydropyrrolo[2,3-b]indole skeleton have been rationally designed and conveniently synthesized from commercially available l-tryptophan derivative in five steps. Their catalytic abilities have been shown in the enantioselective borane reduction of prochiral ketones to afford the desired product in excellent yield and high enantioselectivities (up to 97% ee). The fused tricyclic rigid ring system behaves in a significantly different fashion as compared to the CBS ligand skeleton derived from the pyrrolidine ring of proline in view of the following reasons: (1) the bowl-shaped hexahydropyrrolo[2,3-b]indole skeleton provides a well-organized chiral induction environment, allowing achievement of good enantioselectivity by varying the ligand substituent, whereas for the CBS ligand, the phenyl substituent is critical for good enantioselectivity; (2) The more rigid ring system make this new ligand less reactive than CBS ligand since the catalyst preparation and reduction procedure were carried out under reflux conditions; (3) In the model reaction, while the enantioselectivity is comparable to the CBS catalyst, this skeleton could be further modified to provide diversity-oriented ligands library for other asymmetric reactions while the CBS ligand offers little room for modification. The rigid backbone and easy modification of these ligands skeleton, as well as their recoverability render them promising ligands for asymmetric catalysis. The successful natural skeleton based design will lead to a conceptually new familly of modular chiral ligands or chiral catalysts.

CHAPTER 5

A New Bifunctional Ligand: 1,1'-Dimethyl-octahydro-8,8'-Biquinoline-7,7'-diol

5.1 OVERVIEW OF BINOL AND MODIFIED BINOL LIGANDS

5.1.1 INTRODUCTION

Development of new effective chiral ligands continues to be an important endeavor in the field of organic chemistry. This is because new classes of chiral ligands not only present more synthetic opportunities but also provide new insights into fundamental chemical processes and new applications. Over the last few decades C_2-symmetric bidentate ligands have proven to be very efficient chiral sources in homogeneous or heterogeneous asymmetric catalysis.[98] Of all the widely employed chiral ligands, 1,1′-binaphthyl-2,2′-diol (BINOL) has emerged as one of the most powerful ligands in asymmetric catalysis (Figure 5.1).[99] BINOL is also an important starting material for the synthesis of enantiopure phosphine ligands such as 2,2'-diphenylphosphino-l,l′-binaphthyl, known as BINAP. Furthermore, BINOL-based synthons are also attractive molecular modules for applications in many fields such as

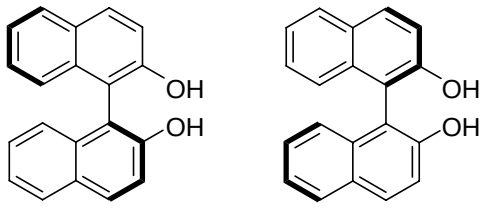
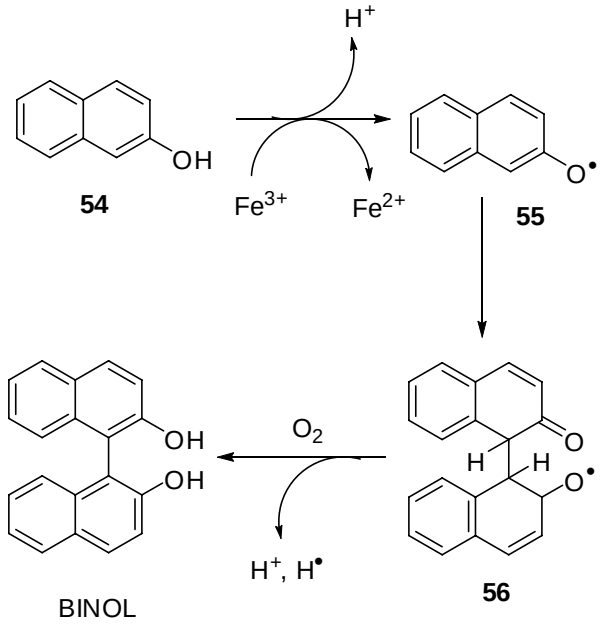


Figure 5.1 (*R*)-BINOL and (*S*)-BINOL

[98] (a) Kočovský, P.; Vyskočil, S.; Smrčina, M. *Chem. Rev.* **2003,** *103,* 3213. (b) McCarthy, M.; Guiry, P. J. *Tetrahedron* **2001**, *57*, 3809.
[99] (a) Pu, L. *Chem. Rev.* **1998**, *98*, 2405. (b) Brunel, J. M. *Chem. Rev.* **2007**, *107*, 1. (c) Chen, Y.; Yekta, S.; Yudin, A. K. *Chem. Rev.* **2003**, *103*, 3155.

chiral supramolecular recognition, crystal engineering and electronic materials.[100]

BINOL was first prepared as a racemate in 1873 by von Richter.[101] Since then, the preparation of racemic BINOL has been widely studied and a well-established method is the oxidative coupling of 2-naphthol (**54**) by use of $FeCl_3$, $K_3Fe(CN)_6$, $Mn(acac)_3$, Cu-amine complexes, $TiCl_4$ and $Ru(OH)_x/Al_2O_3$ as coupling agents.[102b] This coupling mechanism involves an one-electron oxidation of **54** with Fe^{3+} to give the radical species **55**, which traps another molecule of **54** to generate carbinyl radical **56** with formation of a new C–C bond, followed by elimination of H and oxidation by O_2 in the air, releasing H^+ to form BINOL (Scheme 5.1).



Scheme 5.1 The oxidative coupling of 2-naphthol

[100] Supramolecular recognition: (a) Cram, D. J.; Hegelson, R. C.; Peacock, S. C.; Kaplan, L. J.; Domeier, L. A.; Moreau, P.; Koga, K.; Mayer, J. M.; Chao, Y.; Siegel, M. G.; Hoffman, D. H.; Sogah, G. D. *J. Org. Chem.* **1978**, *43*, 1930. (b) Olenyuk, B.; Whiteford, J. A.; Stang, P. J. *J. Am. Chem. Soc.* **1996**, *118*, 8221. (c) Droz, A. S.; Diederich, F. *J. Chem. Soc. Perkin 1* **2000**, 4224. (d) Droz, A. S.; Neidlein, U.; Anderson, S.; Seiler, P.; Diederich, F. *Helv. Chim. Acta* **2001**, *84*, 2243. (e) Kyba, E. P.; Gokel, G. W.; de Jong, F.; Koga, K.; Sousa, L. R.; Siegel, M. G.; Kaplan, L.; Sogah, G. D. Y.; Cram, D. J. *J. Org. Chem.* **1977**, *42*, 4173. (f) Telfer, S. G.; Kuroda, R. *Coord. Chem. Rev.* **2003**, *242*, 33. Crystal engineering: (g) Heo, J.; Jeon, Y.-M.; Mirkin, C. A. *J. Am. Chem. Soc.* **2007**, *129*, 7712. (h) Cui, Y.; Lee, S.-J.; Lin, W. *J. Am. Chem. Soc.* **2003**, *125*, 6014. Electronic materials: (i) Koeckelberghs, G.; Verbiest, T.; Vangheluwe, M.; De Groof, L.; Asselberghs, I.; Picard, I.; Clays, K.; Persoons, A.; Samyn, C. *Chem. Mater.* **2005**, *17*, 118. (j) Zhu, Y.; Gergel, N.; Majumdar, N.; Harriott, L. R.; Bean, J. C.; Pu, L. *Org. Lett.* **2006**, *8*, 355.

[101] Von Richter, V. *Chem. Ber.* **1873**, *6*, 1252.

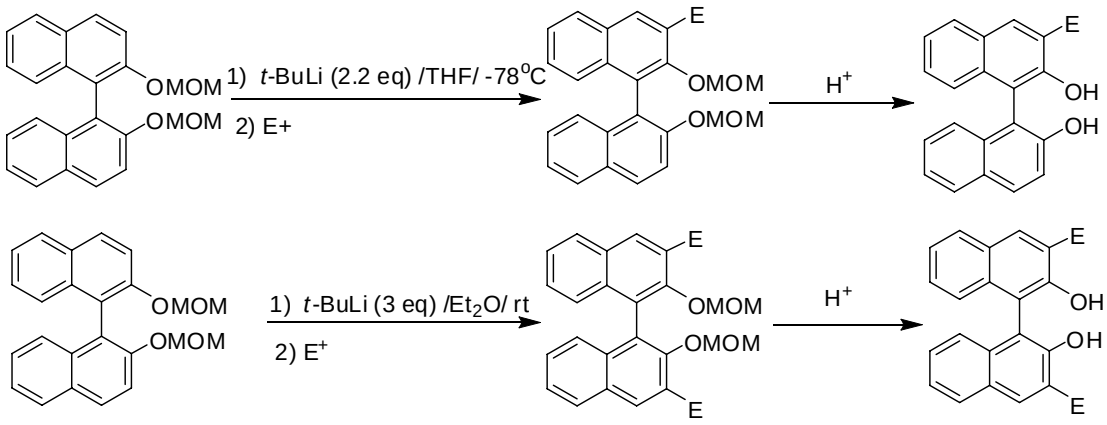
Since then, a wide range of coupling methods in combination with chiral ligands have been developed for the preparation of enantiomerically pure BINOL ligands.[102b]

Since the pioneering work by Noyori in 1979 on the asymmetric reduction of ketones using BINOL-modified aluminum hydrides,[102] there has been an ongoing interest in modified BINOL ligands aimed at tuning its steric and electronic properties as BINOL itself does not always give satisfactory results. Efforts to prepare modified BINOL ligands were mainly focused on introducing different substituents at the C-3, C-4, C-6, C-7 and C-8 positions with varying degrees of success.

5.1.2 3, 3′ SUBSTITUTION PATTERNS

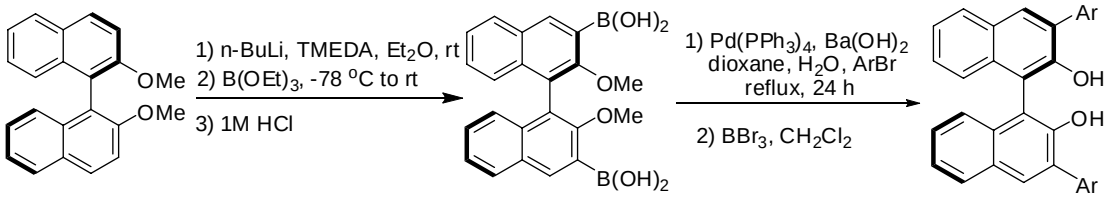
Snieckus and co-workers reported a practical procedure to 3- or 3,3′-substituted BINOLs by directed *ortho*-metalation and Suzuki cross-coupling reaction. 3-Substituted or 3,3'-disubstituted anions can be easily acquired by controlling the amount of the organolithium reagent (*t*-BuLi or *n*-BuLi) at different temperatures. Treatment of these mono- or dianions with various electrophiles *in situ* to afford the desired 3-substituted or 3,3'-disubstituted BINOL derivatives without loss of enantiomeric purity. Reaction of 3-bromo or 3,3′-dibromo-BINOL with aryl boronic acids under Suzuki cross-coupling conditions, followed by MOM deprotection, different 3,3′-diaryl substituted BINOL derivatives could be obtained (Scheme 5.2).[103]

[102] (a) Noyori, R.; Tomino, I.; Tanimoto, Y. *J. Am. Chem. Soc.* **1979**, *101*, 3129. (b) Noyori, R.; Tomino, I.; Nishizawa, M. *J. Am. Chem. Soc*. **1979**, *101*, 5843.
[103] Cox, P. J.; Wang, W.; Snieckus, V. *Tetrahedron Lett.* **1992**, *33*, 2253.



Scheme 5.2 Synthesis of 3- or 3,3′-disubstituted BINOLs

Jørgensen *et al.* reported an alternative Suzuki coupling synthetic route to synthesize 3,3′-diaryl BINOLs by the reaction of the 3,3′-diboronic acid of bis(methoxy)-BINOL with commercially available aromatic bromides (Scheme 5.3).[104]

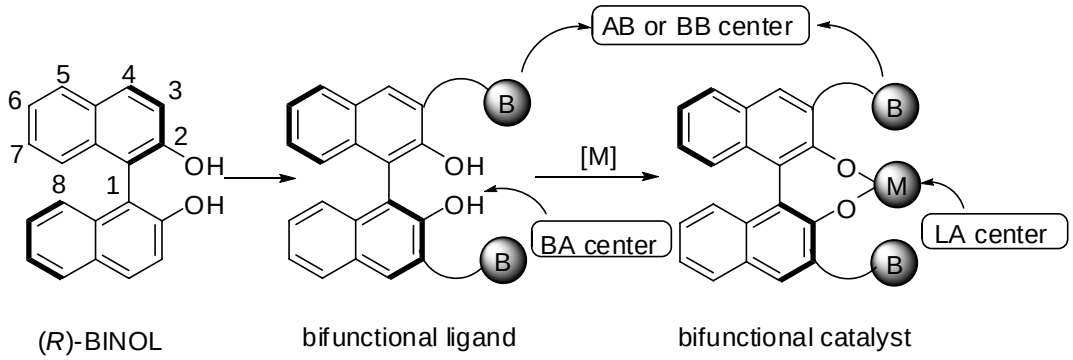


Scheme 5.3 Synthesis of 3,3′-diaryl BINOLs

The combination of a Lewis acid and a Lewis base working in concert has shown great power in stereoselective syntheses.[105] Most interestingly, various bifunctional BINOL ligands and catalysts could be synthesized when additional Lewis basic functional groups are incorporated into BINOL at the 3 and 3′-positions by flexible linkers (Scheme 5.4).[106] When such a ligand is coordinated with metal, the Lewis

[104] Simonsen, K. B.; Gothelf, K. V.; Jørgensen, K. A. *J. Org. Chem.* **1998**, *63*, 7536.
[105] Nájera, C.; Sansano, J.; Saá, J. M. *Eur. J. Org. Chem.* **2009**, 2385.
[106] For reviews on the concept of bifunctional or dual acid/base catalysis, see: (a) Gröger, H. *Chem.–Eur. J.* **2001**, *7*, 5247. (b) Rowlands, G. J. *Tetrahedron* **2001**, *57*, 1865. (c) Shibasaki, M.; Yoshikawa,

acidic metal center could activate electrophiles while the Lewis basic center could activate nucleophiles simultaneously.

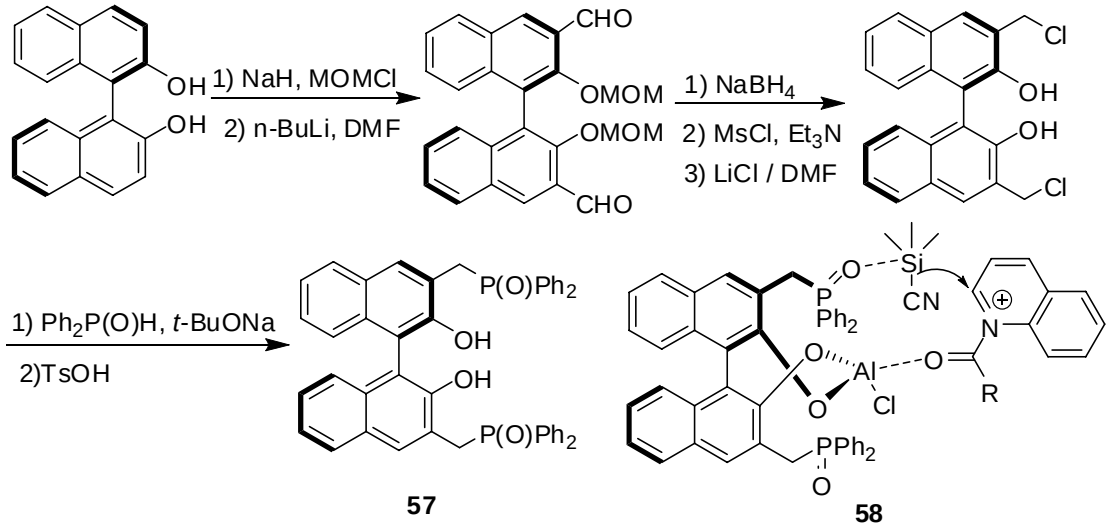


LA = Lewis acid, BA = Br∅nsted acid, LB = Lewis base, BB = Br∅nsted base

Scheme 5.4 Bifunctional BINOL ligands and catalyst: 3, 3′ substitutions patterns

In one such case, phosphine oxide acting as a Lewis base is connected to the 3,3′-postions of BINOL, to give the desired bifunctional ligand **57**, was first synthesized in the Shibasaki laboratory. As an example, in its aluminium complex used for the catalytic enantioselective Reissert reaction of quinolines and isoquinolines, the electron-rich phosphine oxide activates TMSCN while the Lewis acidic aluminium center activates electrophiles in a synergistic manner in transition state **58** (Scheme 5.5).

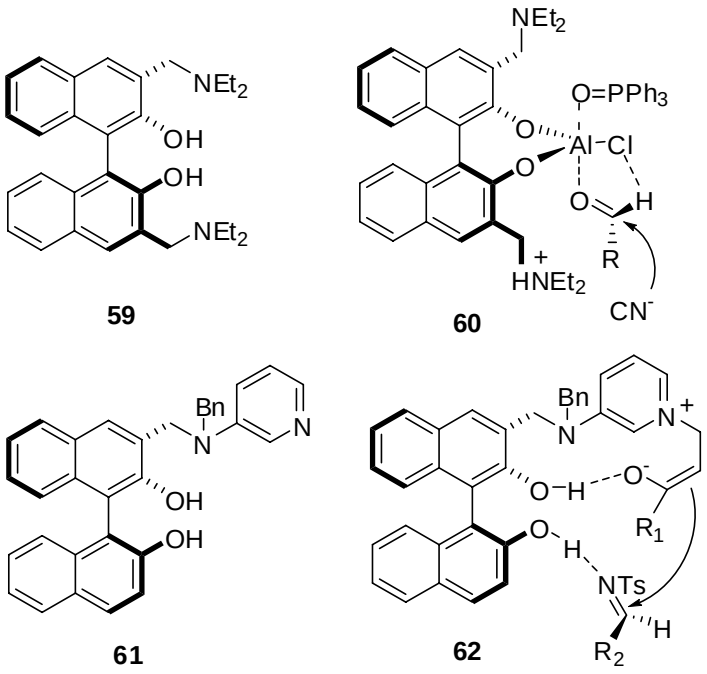
N. *Chem. Rev.* **2002**, *102*, 2187.(d) Shibasaki, M.; Kanai, M.; Funabashi, K. *Chem. Commun.* **2002**, 1989. (e) Ma, J.-A.; Cahard, D. *Angew. Chem., Int. Ed.* **2004**, *43*, 4566. (f) Paull, D. H.; Abraham, C. J.; Scerba, M.T. *et al. Acc. Chem. Res*. **2008**, *41*, 655. (g) Shibasaki, M.; Kanai, M. *Chem. Pharm. Bull.* **2001**, *49*, 511. (h) Hamashima, Y.; Sawada, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 2641. (i) Qin, Y. C.; Pu, L. *Angew. Chem., Int. Ed.* **2006**, *45*, 273. (j) Qin, Y. C.; Liu, L.; Pu, L. *Org. Lett.* **2005**, *7*, 2381. (k) Snider, B. B.; Kiselgof, J. Y.; Foxman, B. M. *J. Org. Chem.* **1998**, *63,* 7945.



Scheme 5.5 Phosphine oxide as Lewis basic unit

In the bifunctional ligand **59**-catalyzed TMSCN addition to aldehydes, the small amount of water incorporated in molecular sieves (4Å) is able to generate HCN *in situ* by hydrolysis of TMSCN. Thereafter, the diethylaminomethyl arm helps deprotonate the HCN while the Al center activate and fix the incoming aldehyde through a strong Al···O=C interaction and additional contact of the Cl···H–C=O as shown in transition state **60**.[107] In the enantioselective aza-Morita–Baylis–Hillman reaction catalyzed by bifunctional catalyst **61**, dually activated transition state **62** has been proposed (Scheme 5.6). [108]

[107] (a) Casas, J.; Nájera, C.; Sansano, J. M.; Saá, J. M. *Org. Lett.* **2002**, *4*, 2589. (b) Casas, J.; Nájera, C.; Sansano, J. M.; Saá, J. M. *Tetrahedron* **2004**, *60*, 10487.
[108] (a) Matsui, K.; Takizawa, S.; Sasai, H. *J. Am. Chem. Soc.* **2005**, *127*, 3680. (b) Matsui, K.; Tanaka, K.; Horii, A.; Takizawa, S.; Sasai, H. *Tetrahedron: Asymmetry* **2006**, *17*, 578. (c) Matsui, K.; Takizawa, S.; Sasai, H. *Synlett* **2006**, 761.



Scheme 5.6 Bifunctional BINOL ligand **59** and catalyst **61**

5.1.3 8, 8′ SUBSTITUTIONS PATTERNS

The rotational barrier of 8,8′-C–H bonds contributes significantly to the configurational stability of BINOL, hence direct modification of this special moiety provides another important strategy to change its scaffold. In addition, the chiral core defined by the two naphthyl rings provides an ideal chiral environment for the transfer of stereoinformation (Figure 5.2). The exclusive direct functionalization of the 8,8′-positions is also believed to have interesting implications in asymmetric induction. Several types of substituents had been placed on this position, both electron-donating and electron-withdrawing, and also with additional binding sites in order to prepare modified BINOL ligands with better properties.

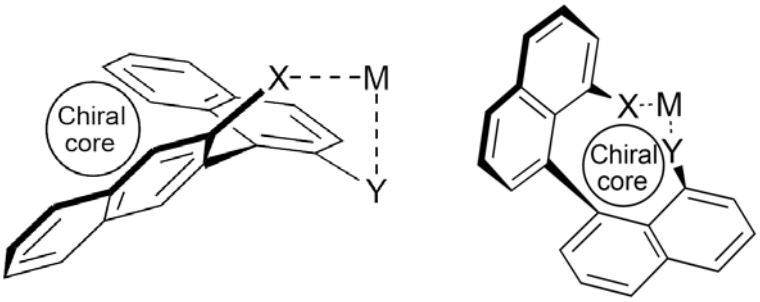
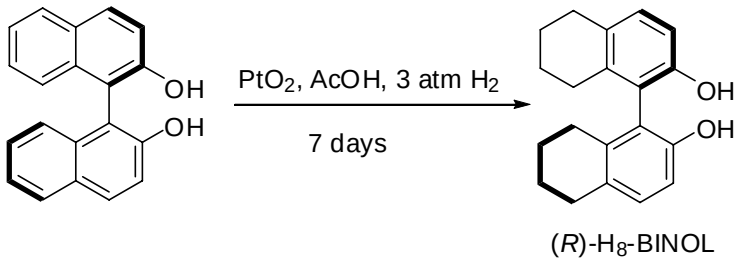


Figure 5.2 The chiral core defined by 8,8′ position

For example, partial hydrogenation of the original skeleton of BINOL provides one case of this important strategy. Cram first successfully synthesized H_8-BINOL in 94% yield by partial PtO_2-catalyzed hydrogenation of BINOL in acetic acid under mild conditions (Scheme 5.7). Thereafter, more convenient preparation methods

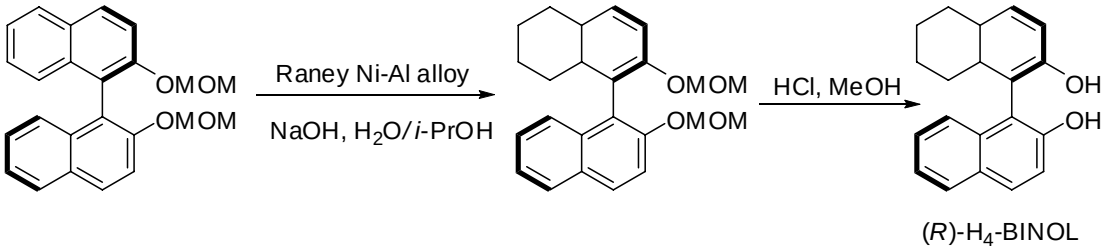


Scheme 5.7 Synthesis of H_8-BINOL

with high optical purity and high yield had also been achieved.[109] Reduction of protected MOM-BINOL with Ni-Al alloy resulted in the formation of H_4-BINOL

[109] (a) Cram, D. J.; Helgeson, R. C.; Peacock, S. C.; Kaplan, L. J.; Domeier, L. A.; Moreau, P.; Koga, K.; Mayer, J. M.; Chao, Y.; Siegel, M. G.; Hoffman, D. H.; Sogah, G. D. Y. *J. Org. Chem.* **1978**, *43*, 1930. (b) Sugimura, T.; Yamada, H.; Inoue, S.; Tai, A. *Tetrahedron: Asymmetry* **1997**, *8*, 649. (c) Guo, H.; Ding, K. *Tetrahedron Lett.* **2000**, *41*, 10061. (d) Korostylev, A.; Tararov, V. I.; Fischer, C.; Monsees, A.; Börner, A. *J. Org. Chem.* **2004**, *69*, 3220. (e) Takasaki, M.; Motoyama, Y.; Yoon, S.-H.; Mochida, I.; Nagashima, H. *J. Org. Chem.* **2007**, *72*, 10291.

(Scheme 5.8).[110] Subsequently, more useful method for the synthesis of optically pure H_4-BINOL derivatives were also reported.[111]



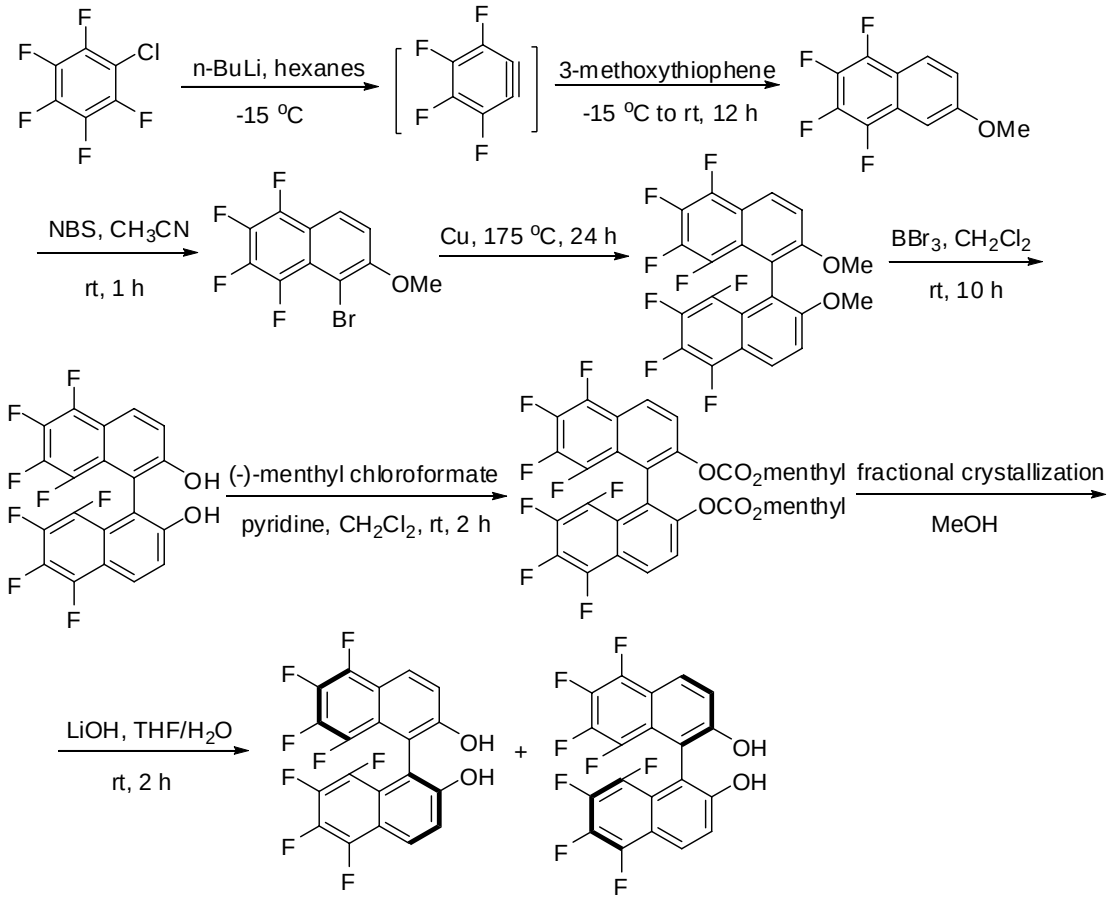
Scheme 5.8 Synthesis of H_4-BINOL

The enantioselective addition of organozinc reagents to aldehydes has been selected as the benchmark reaction to determine the catalytic capability of BINOL, H_8-BINOL and H_4-BINOL. The enantioselectivity achieved with H_4-BINOL–Ti complex is higher than that obtained with BINOL but is slightly lower than the case using H_8-BINOL under the same conditions. The order of asymmetric induction efficiency (BINOL<H_4-BINOL<H_8-BINOL) is largely attributed to the change of dihedral angle in the binaphthyl moiety after partial reduction.[16] H_4-BINOL and H_8-BINOL also exhibit better efficiency and enantioselectivity in many asymmetric reactions compared to BINOL itself.[112]

To elucidate the effect of fluorine substitution on configurational stability and electronic perturbation of the aromatic system, substitution of hydrogens by fluorines at different positions of BINOL giving F_8-BINOL and F_4-BINOL was performed. The first synthesis and chiral resolutions of F_8-BINOL (Scheme 5.9) and F_4-BINOL

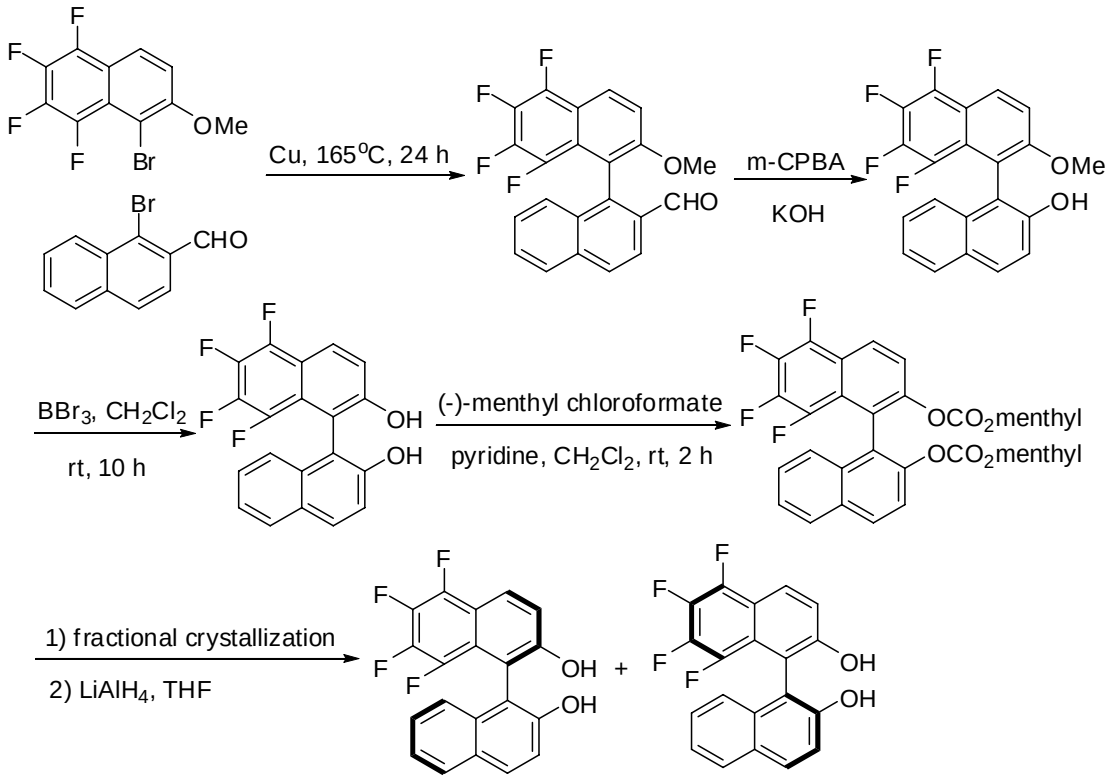
[110] Shen, X.; Guo, H.; Ding, K. *Tetrahedron: Asymmetry* **2000**, *11*, 4321.
[111] (a) Heumann, L. V.; Keck, G. E. *J. Org. Chem.* **2008**, *73*, 4725. (b) Li, X.; Ding, Q.; Ge, J.; Xie, J.; Xu, D. *J. Org. Chem.* **2009**, *74*, 1785.
[112] (a) Terry, T.-L.; Au, Y.; Chan, S.-S.; Chan, Albert S. C. *Adv. Synth. Catal.* **2003**, *345*, 537. (b) Iida, T.; Yamamoto, N.; Matsunaga, S.; Woo, H.-G.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2223. (c) Lin, Y.-M.; Fu, I.-P.; Uang, B.-J. *Tetrahedron: Asymmetry* **2001**, *12*, 3217. (d) Kim, J. G.; Camp, E. H.; Walsh, P. J. *Org. Lett.* **2006**, *8*, 4413. (e) Wang, B.; Feng, X.; Huang, Y.; Liu, H.; Cui, X.; Jiang, Y. *J. Org. Chem.* **2002**, *67*, 2175. (f) Chan, A. S. C.; Zhang, F.-Y.; Yip, C.-W. *J. Am. Chem. Soc.* **1997**, *119*, 4080. (g) Zhang, F.-Y.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1997**, *8*, 3651. (h) Long, J.; Hu, J.; Shen, X.; Ji, B.; Ding, K. *J. Am. Chem. Soc.* **2002**, *124*, 10.

(Scheme 5.10) were accomplished by Yudin.[113] Substitution of hydrogens by fluorines at the 5,6,7,8 or 5,5′, 6,6′, 7,7′, 8,8′ positions of BINOL has a strong effect on distribution of electron density around aromatic skeleton but slightly influences on the torsion angle. The most important outcome was the dramatically increased configurational stability of F_8-BINOL and F_4-BINOL.



Scheme 5.9 Synthesis and optical resolution of F_8-BINOL

[113] (a) Yudin, A. K.; Martyn, L. J. P.; Pandiaraju, S.; Zheng, J.; Lough, A. *Org. Lett.* **2000**, *2*, 41. (b) Yekta, S.; Krasnova, L. B.; Mariampillai, B.; Picard, C. J.; Chen, G.; Pandiaraju, S.; Yudin, A. K. *J. Fluorine Chem.* **2004**, *125*, 517. (c) Chen, Y.; Yekta, S.; Martyn, L. J. P.; Zheng, J.; Yudin, A. K. *Org. Lett.* **2000**, *2*, 3433.

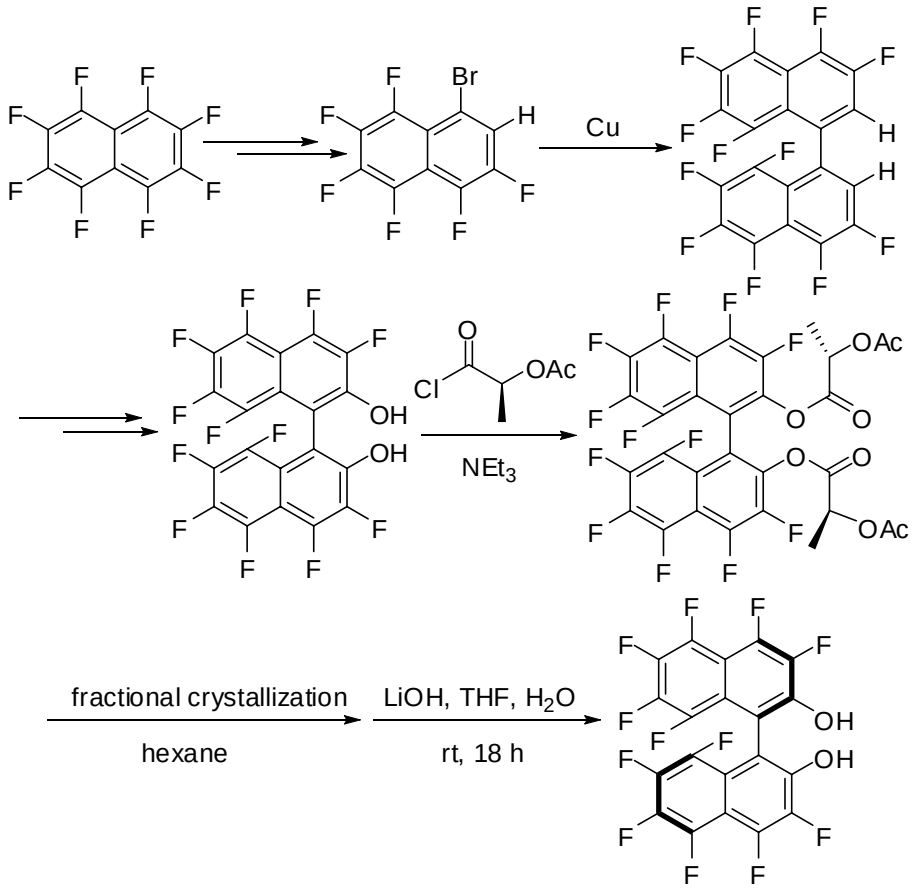


Scheme 5.10 Synthesis and optical resolution of F_4-BINOL

In terms of catalytic applications, sulfoxidation[114] as well as the glyoxylate ene reaction[115] were explored. For instance, it was found that the (*R*)-F_8-BINOL–Ti system catalyzed the sulfoxidation reaction giving higher enantioselectivity (89% *ee* in CH_2Cl_2) than the (*R*)-BINOL–Ti system (7% *ee* in CH_2Cl_2 and 22% *ee* in CCl_4). Highly enantioselective "pseudo-meso" aggregates obtained by combining (*R*)-BINOL with (*R*)-F_8-BINOL, were also applied in the enantioselective glyoxylate-ene reaction to furnish the corresponding ene-product in 53% yield and 92% *ee*.

[114] (a) Martyn, L. J. P.; Pandiaraju, S.; Yudin, A. K. *J. Organomet. Chem.* **2000**, *603*, 98. (b) Yekta, S.; Krasnova, L. B.; Mariampillai, B.; Picard, C. J.; Chen, G.; Pandiaraju, S.; Yudin, A. K. *J. Fluorine Chem.* **2004**, *125*, 517.
[115] Pandiaraju, S.; Chen, G.; Lough, A.; Yudin, A. K. *J. Am. Chem. Soc.* **2001**, *123*, 3850.

McDonald reported a synthetic route of F_{12}-BINOL (Scheme 5.11).[116] The introduction of F_{12}-BINOL for asymmetric catalysis applications is more interesting as high Lewis or Brønsted acidity could be obtained for F_{12}-BINOL.

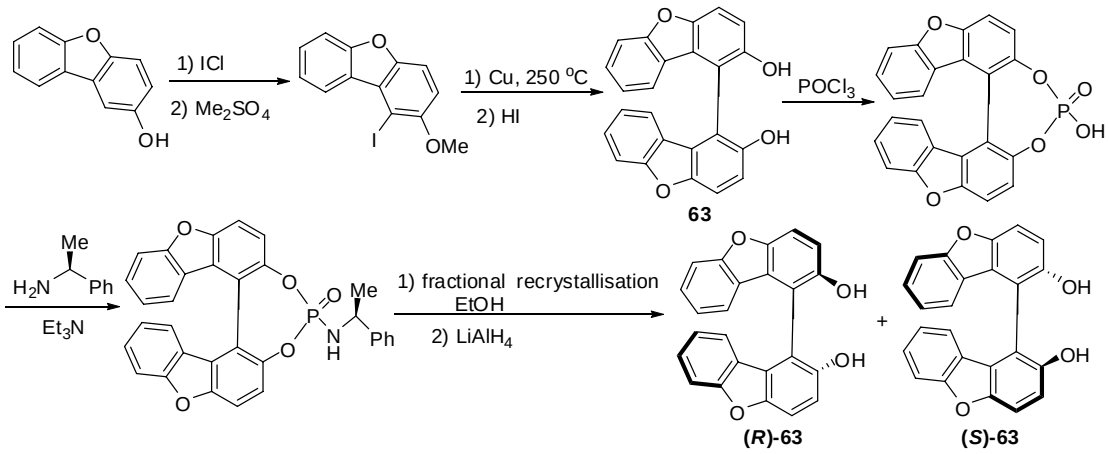


Scheme 5.11 The synthetic route and optical resolution of F_{12}-BINOL

The dibenzofuran unit is present in metabolites of lower plant lichens and is also a useful building block for organic molecules.[117] The synthesis and resolution of C_2-symmetric 1,1′-bi(dibenzofuranyl)-2,2′-diol (BIFOL, **63**) has been reported. Recrystallisation of its 1:1 mixture of diastereomeric cyclic phosphoramidates using (–)-(*S*)-l-phenylethylamine as chiral auxiliary gave both enantiomers in >98%

[116] Morrison, D. J.; Riegel, S. D.; Piers, W. E.; Parvez, M.; Mcdonald, R. *Chem. Commun.* **2006**, 2875.
[117] (a) Tsang, K. Y.; Diaz, H.; Graciani, N.; Kelly, J. W. *J. Am. Chem. Soc.* **1994**, *116,* 3988. (b) Schwartz, E. B.; Knobler, C. B.; Cram, D. J. *J. Am. Chem. Soc.* **1992**, *114,* 10775.

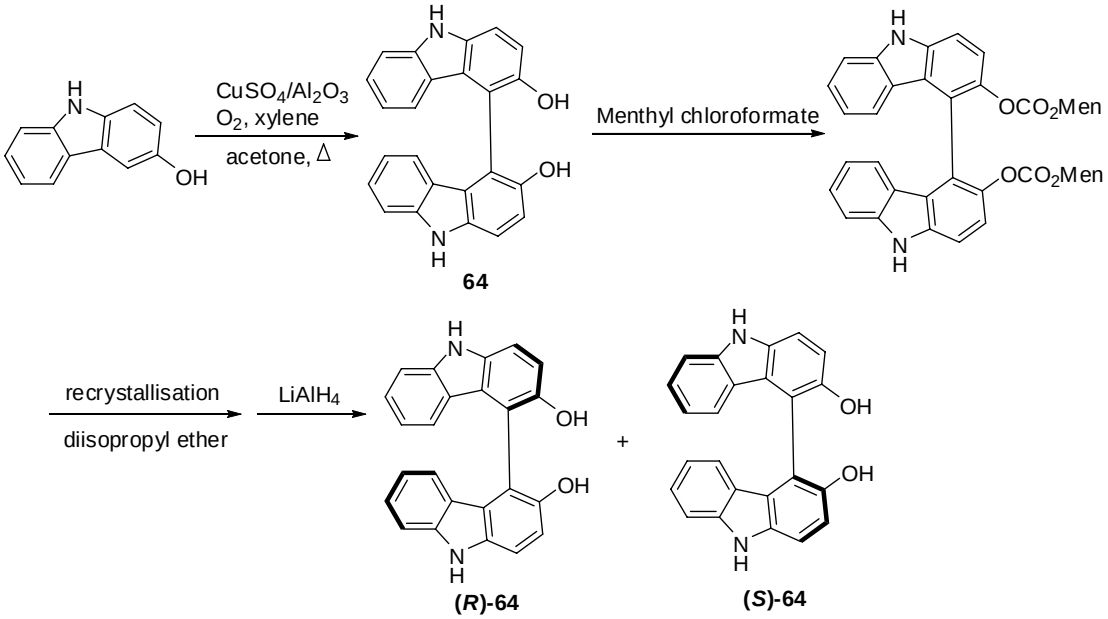
enantiopurity and good yields. The configuration of BIFOL was determined by X-ray analysis of one of the diastereomeric phosphoramidates.[118]



Scheme 5.12 The synthetic route and optical resolution of BIOFL **57**

An oxidative phenol coupling catalyzed by $CuSO_4/Al_2O_3$ allowed the one-step formation of BICOL (**64**), a new chiral bidentate ligand based on the bicarbazole backbone, from 3-hydroxycarbazole.[119] Menthyl chloroformate was successfully used as resolving reagent for the resolution of BICOL (Scheme 5.13). Subsequently, BICOL derivatives BICAP, a new family of carbazole-based diphosphine ligands was also reported.[120]

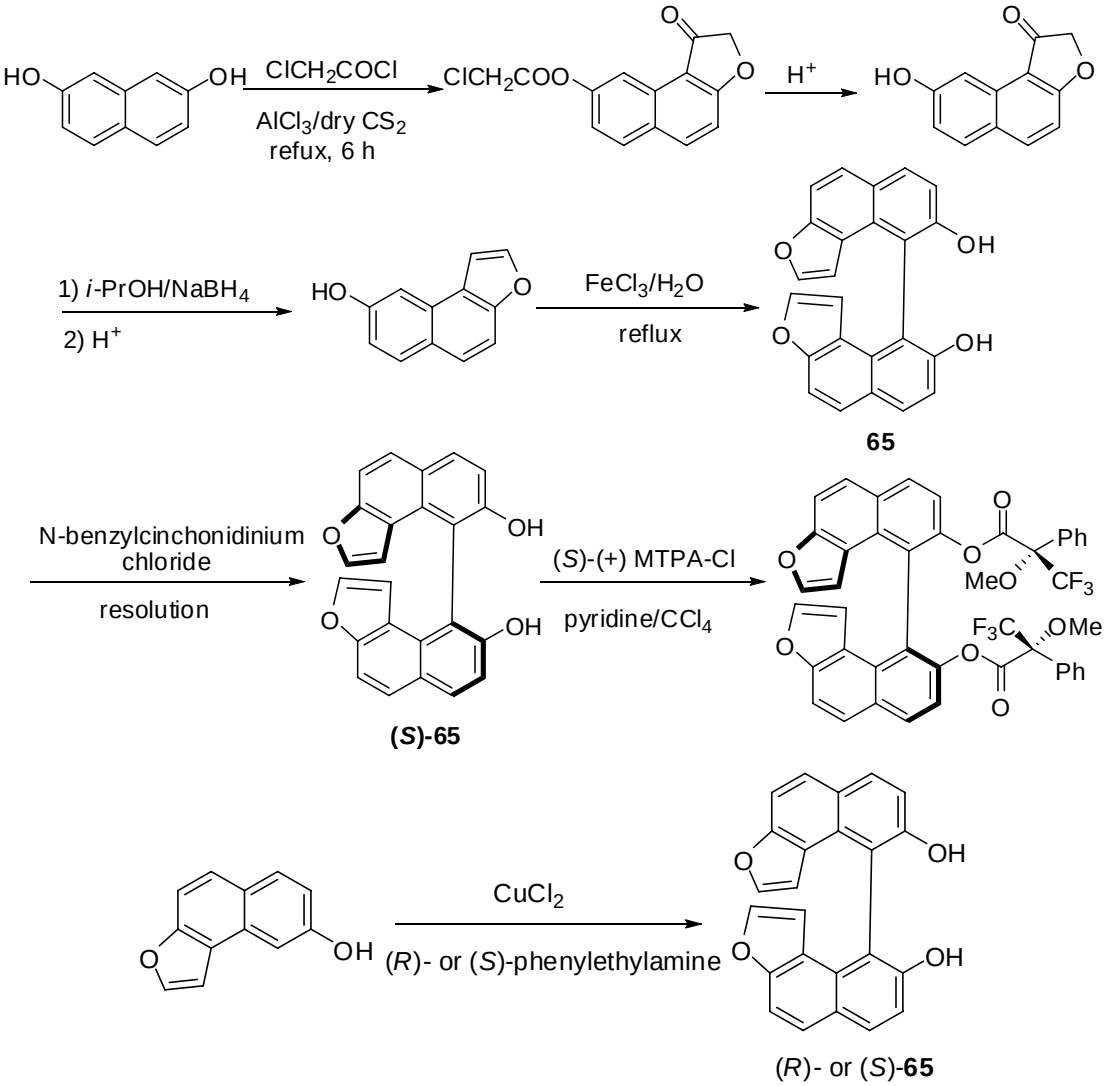
[118] Gelpke, A. E. S.; Fraanje, J.; Goubitz, K.; Schenk, H.; Hiemstra, H. *Tetrahedron* **1997**, *53*, 5899.
[119] Botman, P. N. M.; Postma, M.; Fraanje, J.; Goubitz, K.; Schenk, H.; van Maarseveen, J. H.; Hiemstra, H. *Eur. J. Org. Chem.* **2002**, 1952.
[120] Botman, P. N. M.; Fraanje, J.; Goubitz, K.; Peschar, R.; Verhoeven, J. W.; van Maarseveen, J. H.; Hiemstra, H. *Adv. Synth. Catal.* **2004**, *346*, 743.



Scheme 5.13 The synthetic route and optical resolution of BICOL **64**

A $FeCl_3$-catalyzed oxidative coupling protocol gave [9,9′]bi[naphtha(2,1-b)furanyl]-8,8′-diol (**65**) in high yield, of which a furan ring is embedded at the 8,8′-positions of BINOL.[121] The configuration of one of the resolved enantiomers was established by X-ray analysis of a Mosher's acid diester derivative. This furo-fused BINOL derivative exhibited better fluorescence properties thus offering the exciting possibility as chiral fluorescent sensors for different classes of compounds. The enantioselective synthesis of [9,9′]bi[naphtho(2,1-*b*)furanyl]-8,8′-diol, (*R*)-**65** or (*S*)-**65**, also employed the optical antipodes of phenylethylamine in a $Cu^{II}Cl_2$-catalyzed oxidative coupling reaction (Scheme 5.14).

[121] (a) Upadhyay, S. P.; Karnik, A. V. *Tetrahedron Lett.* **2007**, *48*, 317. (b) Karnik, A. V.; Upadhyay, S. P.; Gangrade, M. G. *Tetrahedron: Asymmetry* **2006**, *17*, 1275. (c) Upadhyay, S. P.; Pissurlenkar, R. R. S.; Coutinho, E. C.; Karnik, A. V. *J. Org. Chem.* **2007**, *72*, 5709.



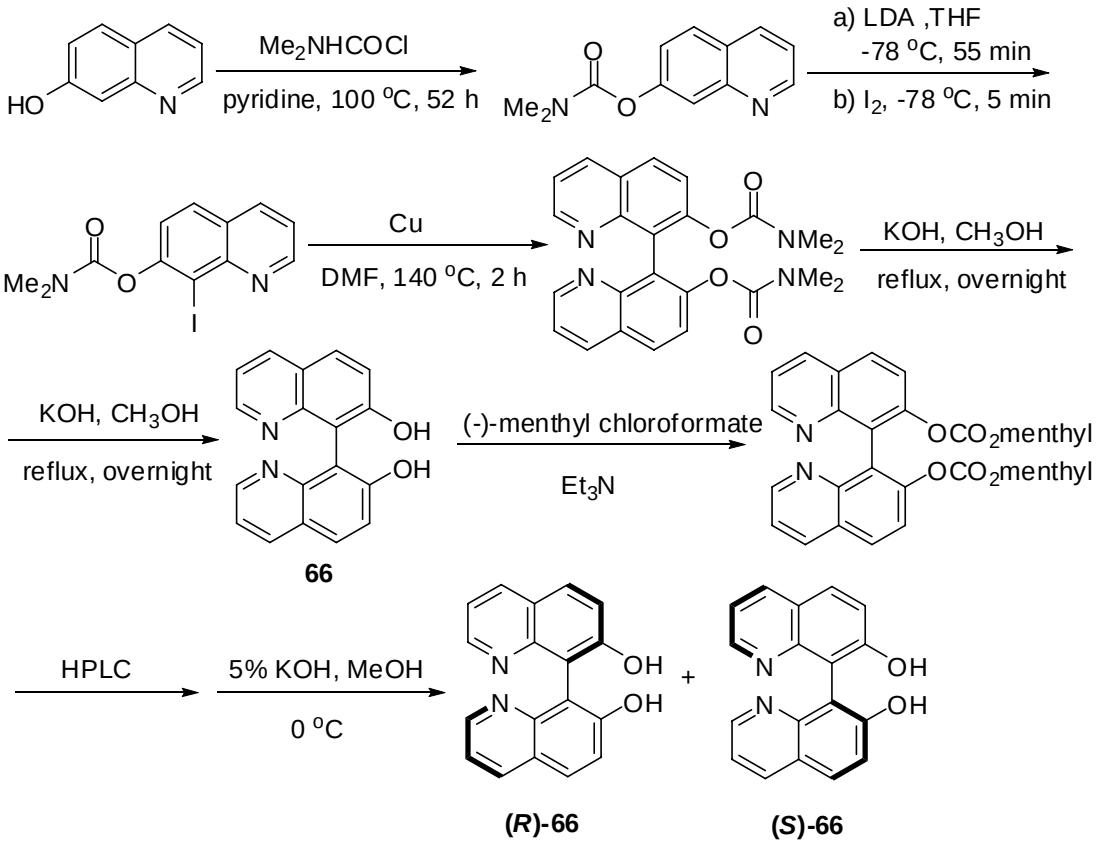
Scheme 5.14 Synthesis and optical resolution of furo-fused BINOL derivative **65**: [9,9′]bi[naphtho(2,1-*b*)furanyl]-8,8′-diol

The axially chiral heterocyclic biaryl ligands have been explored in asymmetric synthesis and present many amazing properties for the discovery of new asymmetric catalytic methods.[122] To probe the effect of the N placement at 8,8′ position of BINOL, the synthesis and resolution of 7,7′-dihydroxy-8,8′-biquinolyl (**66**) has been reported recently.[123] The key step is the oxidative dimerization of *N*,*N*-dialkyl *O*-(8-lithio-7-quinolyl) carbamates with anhydrous ferric chloride or the use of

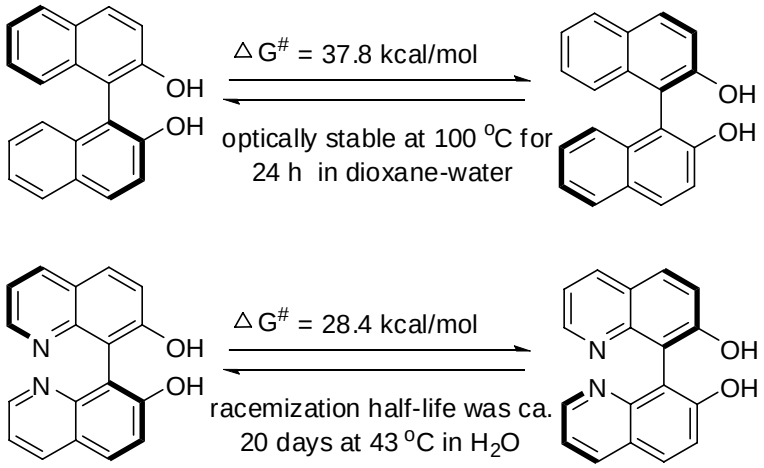
[122] (a) Chelucci, G.; Thummel, R. P. *Chem. Rev.* **2002**, *102*, 3129. (b) Fletcher, N. C. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1831.
[123] (a) Blakemore, P. R.; Kilner, C.; Milicevic, S. D. *J. Org. Chem.* **2005**, *70*, 373. (b) Blakemore, P. R.; Kilner, C.; Milicevic, S. D. *J. Org. Chem.* **2006**, *71*, 8212. (c) Blakemore, P. R.; Milicevic, S. D.; Zakharov, L. N. *J. Org. Chem.* **2007**, *72*, 9368.

Ulmann coupling to construct the biaryl system. 7,7′-Dihydroxy-8,8′-biquinolyl (**66**) was resolved into its enantiomers *via* reverse phase (C18) chromatographic separation of the corresponding epimeric bismenthyl carbonates. The less polar diastereoisomer was revealed to possess a (*S*)-configuration by X-ray crystallographic analysis (Scheme 5.15).

Kinetic studies and subsequent Eyring plot analysis enabled measurement of transition state parameters for the enantiomerization of (*R*)-**66** and (*S*)-**66** and revealed that this ligand is less configurationally stable than BINOL (Scheme 5.16). So it is not stable enough to act as a chiral ligand for asymmetric catalysis.



Scheme 5.15 Synthesis and optical resolution of 7,7´-dihydroxy-8,8´-biquinolyl **66**



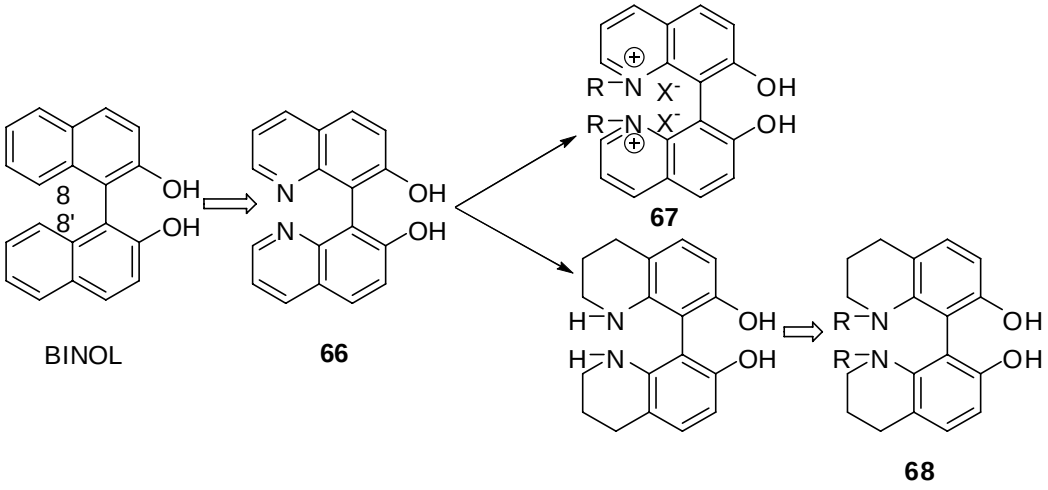
Scheme 5.16 Kinetic studies of BINOL and 7,7′-dihydroxy-8,8′-biquinolyl **66**

5.2 DESIGN, SYNTHESIS AND OPTICAL RESOLUTION OF A NEW BIFUNCTIONAL LIGAND: 1,1'-DIMETHYL-OCTAHYDRO-8,8'-BIQUINOLINE-7,7'-DIOL

In connection with our interest to explore new chiral ligand for asymmetric catalysis, we become interested in introducing heteroatom into the 8,8′-positions of BINOL. However, upon replacement of 8-C by a sp^2-hybridized N-atom, the resulting bifunctional 7,7'-dihydroxy-8,8'-biquinolyl (**66**) was found to be configurationally unstable at room temperature to serve as a useful chiral ligand. Furthermore, its high polarity and insolubility in common organic solvents and tedious resolution limited its application in asymmetric catalysis.

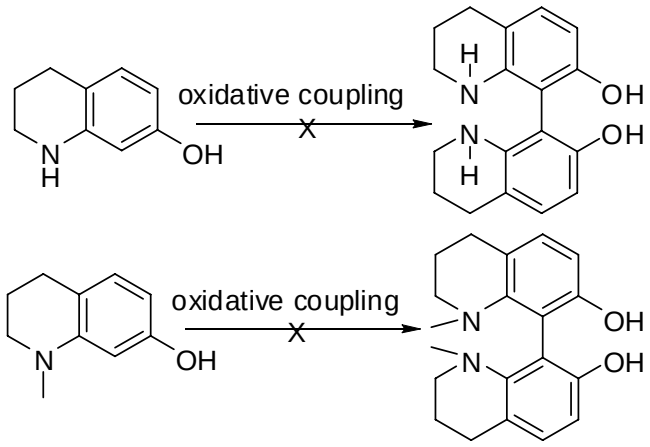
To resolve this problem, we envisaged that ligand **67** and **68** should be configurationally stable and could serve as chiral ligand for asymmetric synthesis at room temperature. Preliminary results showed that alkylation of the sp^2-hybridized groove N-atom was difficult.[124] However, alkylation of a sp^3-hybridized groove N-atom should be easier. To this end, we succeeded in the synthesis and chiral resolution of the new bifunctional ligand **68**, which is configurationally stable at room temperature to serve as a new chiral ligand for asymmetric catalysis. The octahydro biquinolyl fragment of **68** should considerably induce considerable electronic perturbation and steric tuning as an new aza analogue of BINOL (Scheme 5.17).

[124] When MeI was used to conduct methylation of **66**, only trace of mono methylation product was observed. Further work is in progress.



Scheme 5.17 Design of new bifunctional ligands **67** and **68**: aza analogues of BINOL

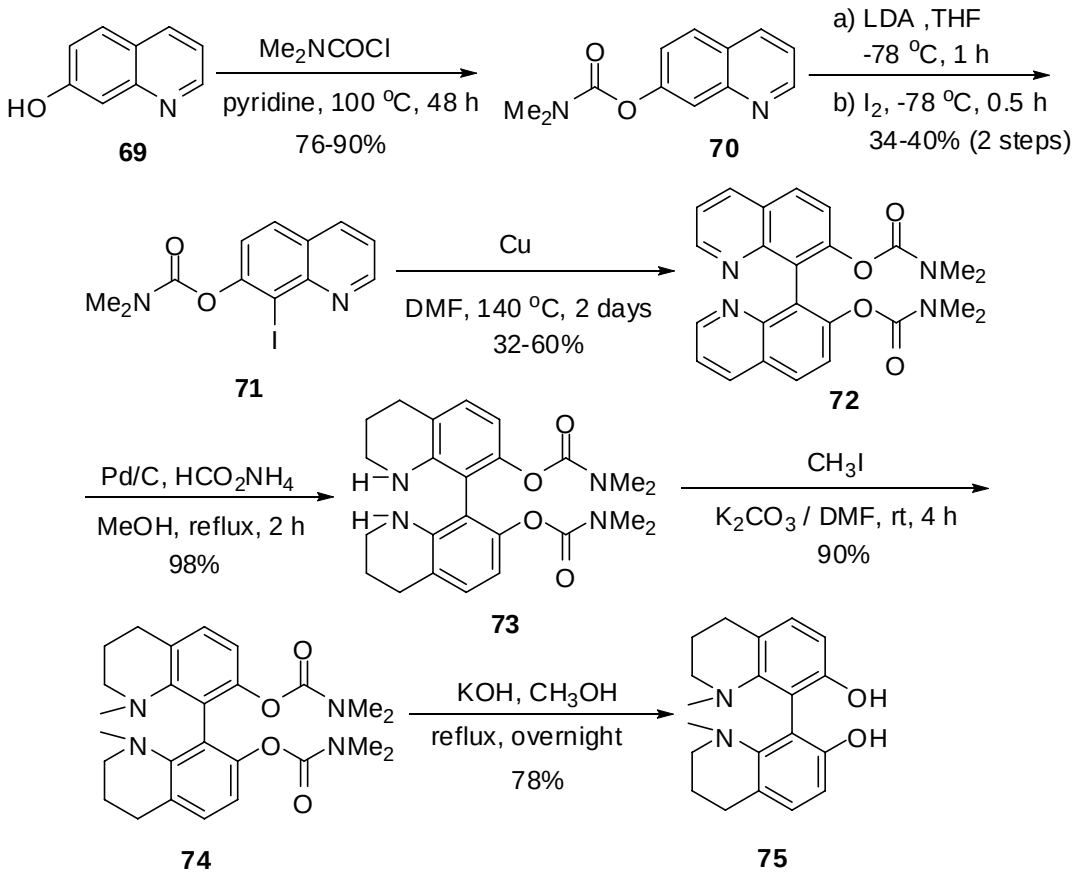
Initial efforts to synthesize the target molecule **67** or **68** by various direct oxidative coupling reactions of 7-tetrahydroquinolinol or 1-methyl-7-tetrahydroquinolinol were unsuccessful (Scheme 5.18).[125] Failure of the coupling reactions probably arises from poisoning of the metal by the basic nitrogen atom.



Scheme 5.18 Failure of oxidative coupling

[125] The common single-electron oxidants methods tested are as follows. (a) Noji, M.; Nakajima, M.; Koga, K. *Tetrahedron Lett.* **1994**, *35*, 7983. (b) Ding, K.; Wang, Y.; Zhang, L.; Wu, Y.; Matsuura, T. *Tetrahedron* **1996**, *52*, 1005. (c) Jiang, P.; Lu, S. *Synth. Commun.* **2001**, *31*, 131. (d) Vyskocil, S.; Smrcina, M.; Lorenc, M.; Tislerova, I.; Brooks, R. D.; Kulagowski, J. J.; Langer, V.; Farrugia, L. J.; Kocovsky, P. *J. Org. Chem.* **2001**, *66*, 1359.

Eventually, the established Ullmann coupling strategy proved to be successful for the construction of the biaryl system.[126a] Starting from 7-hydoxyquinoline (**69**), under the protection of dimethylaminocarbonyl chloride, carbamate **70** was obtained in 76-90% yield. Direct *ortho*-metalation of carbamate **70** was carried out with LDA in THF at –78 °C, after which a solution of iodine in THF was added to the lithium salt solution of **70** at –78 °C to afford **71** in 34-40% yield. Ullmann coupling of iodide **71** with copper catalyst furnished biaryl **72** in 32-60% yield. The quinoline part of **72** was effectively reduced to give biquinolyl **72** quantitatively in the presence of ammonium formate and Pd/C. Methylation of the amine **73** was accomplished using iodomethane with potassium carbonate as base, and finally culminating at basic methanolysis of the carbamate groups of **74** to afford the target molecule **75** in good



69 **70** **71** **72** **73** **74** **75**

Scheme 5.19 Synthesis of bifunctional chiral ligand **75**

yield (Scheme 5.19). Compound 75 was observed to be less polar than 66 and exhibited good solubility in a wide range of common organic solvents such as CH_2Cl_2, $CHCl_3$ and THF which evaded the solubility problem for future application. An X-ray crystallographic analysis of **75** provided definitive proof of structure and revealed a preferred transoid conformation with the angle between the two aromatic ring planes being 124.97° (Figure 5.3). The angle between the two quinolyl ring planes of racemic **75** as its dimethanol solvate is 104.5° and racemic BINOL is only slightly transoid in the solid state (angle between naphthyl ring planes is 91.4°). N···H–O contact distances for intramolecular hydrogen bonds are 1.84 and 0.9 Å.

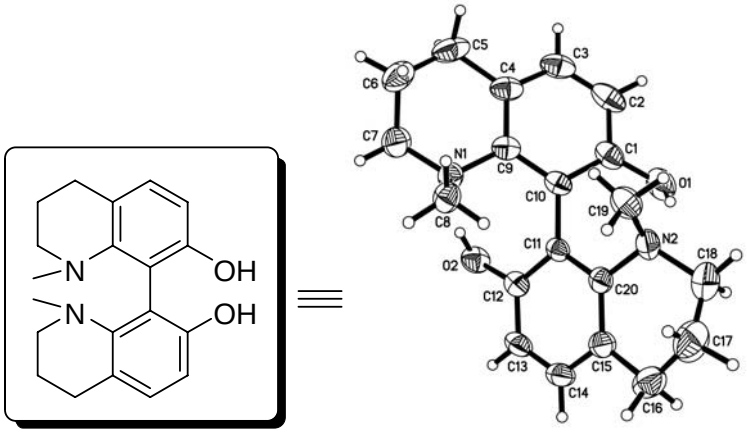
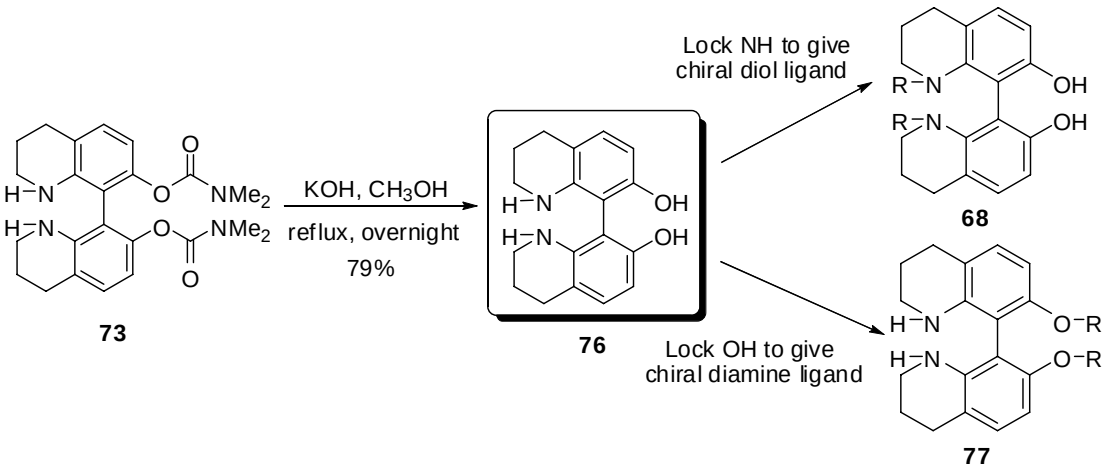


Figure 5.3 Crystal structure of **75**

Key intermediate **76** is obtained (Figure 5.22) upon removal of the carbamate protecting group by treating **72** with KOH in MeOH. If we lock the NH group, we will get diol ligand **68**, and if the OH group was locked, the diamine ligand **77** would be obtained (Scheme 5.20).



Scheme 5.20 Synthesis of ligand **68 and 77**

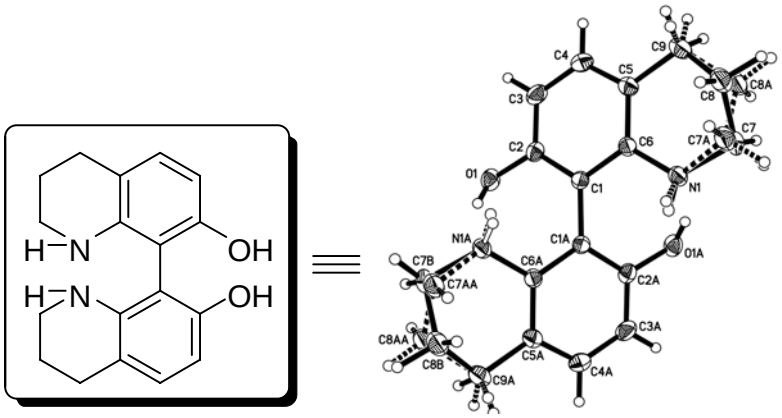
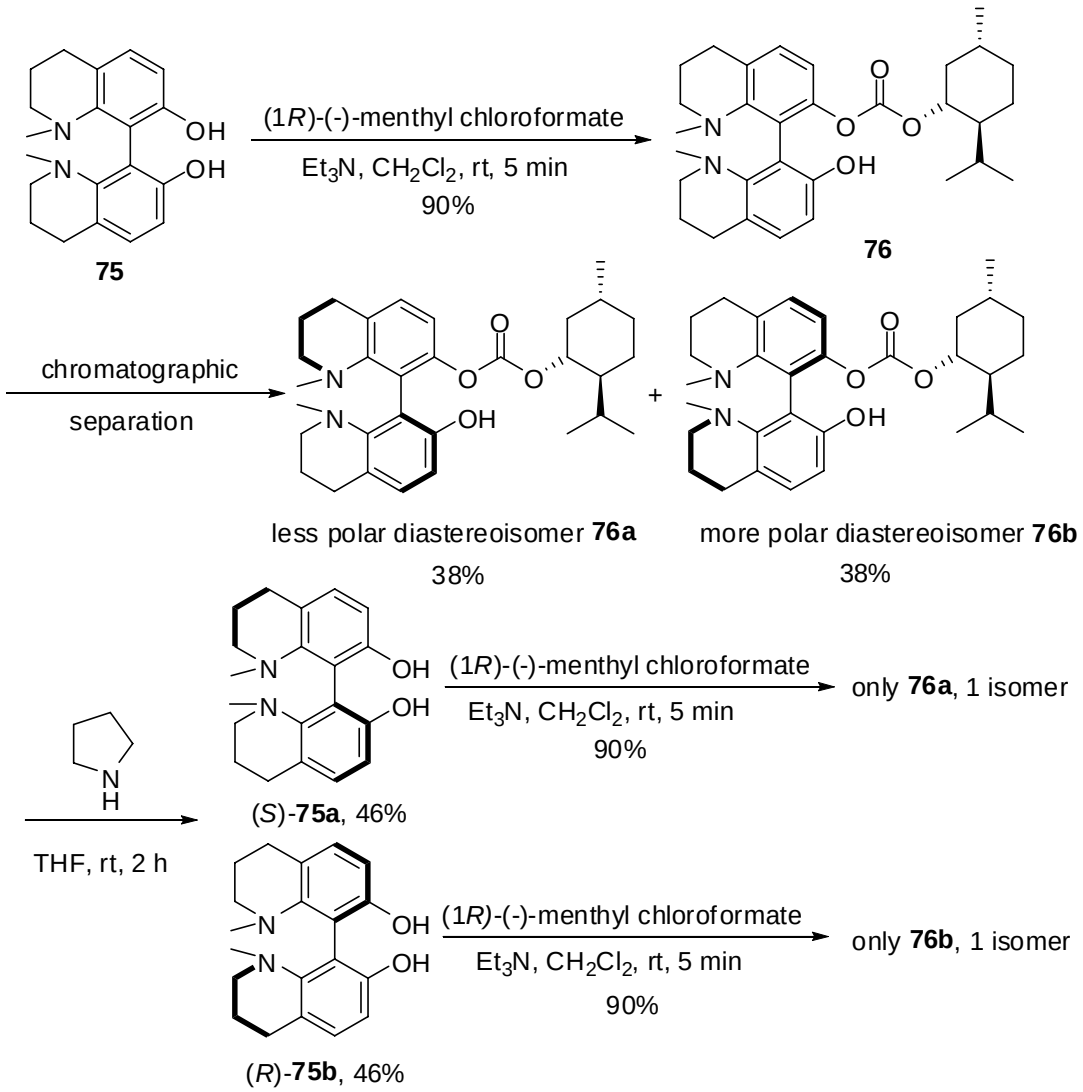


Figure 5.4 Crystal structure of **76**

With an efficient synthesis of **75** established, its resolution was next explored. We found that the general methods using fractional crystallization of diastereomeric complexes prepared with a variety of chiral resolution reagents such as *N*-benzylcinchonidinium chloride or *trans*-1,2-diaminocyclohexane were unsuccessful.[126] This initial failure implied that lower acidity of the phenol groups rendered hydrogen bonding formation with the chiral reagents more difficult as the piperidine unit made the aromatic rings more electron-rich. However, the chromatographic resolutions methods for the resolution of BINOL, especially the

[126] (a) Wang, Y.; Sun, J.; Ding, K. *Tetrahedron* **2000**, *56*, 4447. (b) Schanz, H. J.; Linseis, M. A.; Gilheany, D. G. *Tetrahedron: Asymmetry* **2003**, *14*, 2763.



Scheme 5.21 Resolution of new chiral ligands and configuration determination

chromatographic separation of diastereomeric bismenthyl carbonate derivatives, have been demonstrated extremely useful.[127] When excess of (–)-menthyl chloroformate was employed in the presence of triethylamine at room temperature, bismenthyl carbonates and monocarbonate were obtained simultaneously. However, different from the previous report,[130] the bismenthyl carbonate could not be resolved by fractional recrystallization or column chromatography. To our delight, instead the monomenthyl carbonate **76** could be separated by column chromatography (Scheme

[127] For resolution of BINOL through separation of the bis[(-)-menthoxycarbonyl] derivatives, see: Fabbri, D.; Delogu, G.; Lucchi, D. O. *J. Org. Chem.* **1995**, *60*, 6599.

5.21). Significant chemical shift differences were observed in the ^{1}H NMR (Figure 5.5).For the menthyl moiety in **76a** and **76b**, the C-22 proton appears as a triplet at δ 4.37 ppm and 4.28 ppm respectively. The C-25 methyl group also shows significant difference as a doublet at δ 0.63 and 0.70 ppm respectively.

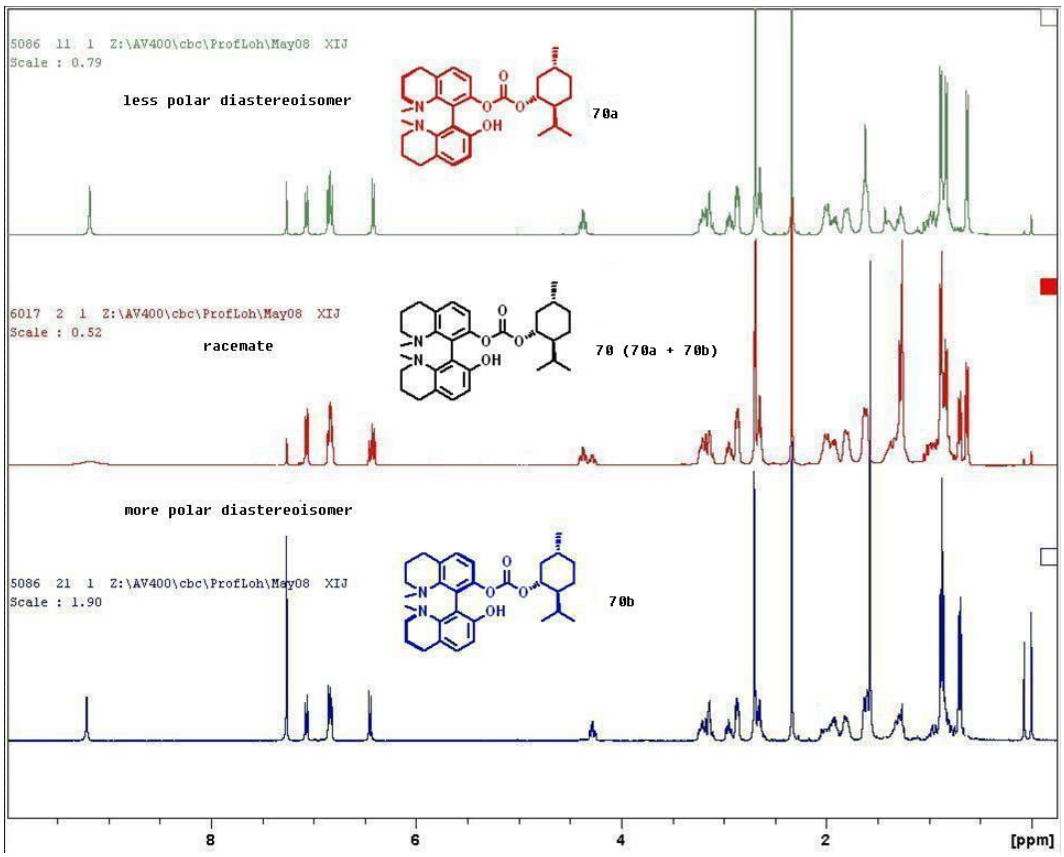


Figure 5.5 ^{1}H NMR of **76**, **76a** and **76b**

The structure of the less polar diastereoisomer **76a** was determined by X-ray crystallographic analysis (Figure 5.6) and is assigned to possess a (*S*)-configuration relating it to the configuration of (1*R*,2*S*,5*R*)-menthyl moiety. Clean removal of chiral auxiliary groups from **76a** and **76b** was achieved with pyrrolidine in THF at room temperature, where (*S*)-**75a** and (*R*)-**75b** were obtained in good yields respectively. To determine the enantiomeric excess, reinstallation of menthyl carbonate units to freshly prepared enantioenriched (*S*)-**76a** or (*R*)-**76b** gave the corresponding **75a** or **75b** as

single diastereoisomer which confirmed the optical purity of each enantiomer (≥99% *ee*). This issue was further confirmed by chiral HPLC (Chiralpak OD-H column, hexane/2-propanol 95:5, 1 mL/min) to afford a single peak in each case for (*S*)-**75a** or (*R*)-**75b** with retention times of 18.4 and 20.8 min respectively. Each enantiomer has

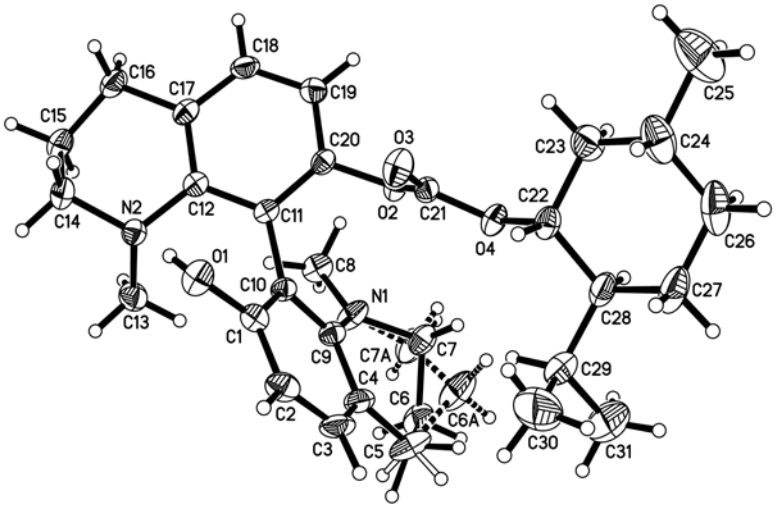
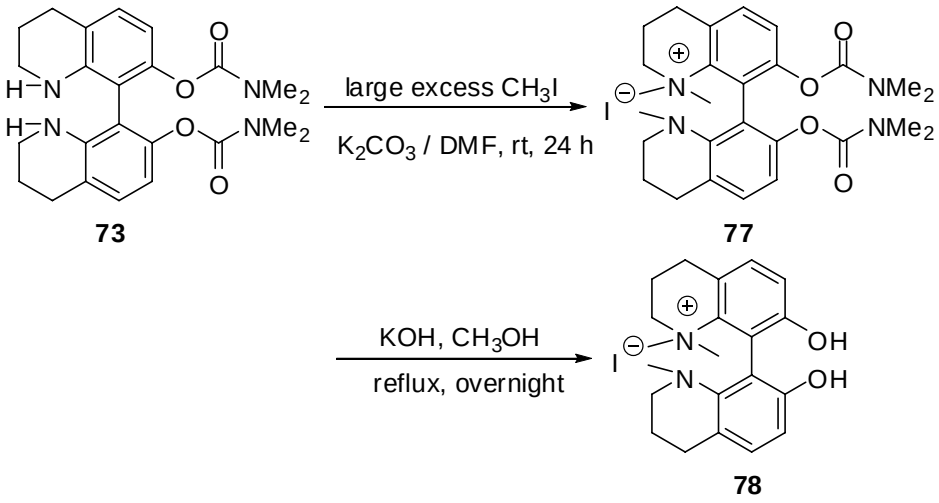


Figure 5.6 Crystal structure of **76a**

been stored at room temperature for several months without any drop in its enantiopurity.

When we conducted the methylation of **73** using large excess of iodomethane, the ionic intermediate **77** was obtained in moderate yield without optimization. As a result, the interesting ionic ligand **78** was in hand after deprotection, which provided a unique chiral ionic liquid candidate for future investigations, considering the on-going exploration of chiral ionic liquids and chiral salts in asymmetric catalysis (Scheme 5.22).[128] (Scheme 5.22).

[128] For reviews on chiral ionic liquids, see: (a) Luo, S.; Zhang, L.; Cheng, J. P. *Chemistry–An Asian Journal* **2009**, *4*, 1184. (b) Baudequin, C.; Baudoux, J.; Levillain, J.; Cahard, D.; Gaumont, A. C.; Plaquevent, J. C. *Tetrahedron: Asymmetry* **2003**, *14*, 3081. (c) Ding, J.; Armstrong, D. W. *Chirality* **2005**, *17*, 281. (d) Baudequin, C.; Brégeon, D.; Levillain, J.; Guillen, F.; Plaquevent, J. C.; Gaumont, A.-C. *Tetrahedron*: *Asymmetry* **2005,** *16*, 3921. (e) Headley, A. D.; Ni, B. *Aldrichimica Acta* **2007**, *40*, 107. (f) Chen, X.; Li, X.; Hu, A.; Wang, F. *Tetrahedron: Asymmetry* **2008**, *19*, 1. (g) Bica, K.; Gaertner, P. *Eur. J. Org. Chem.* **2008**, 3235. (h) Winkel, A.; Vasu, P.; Reddy, G.; Wilhelm, R.



73 **77** **78**

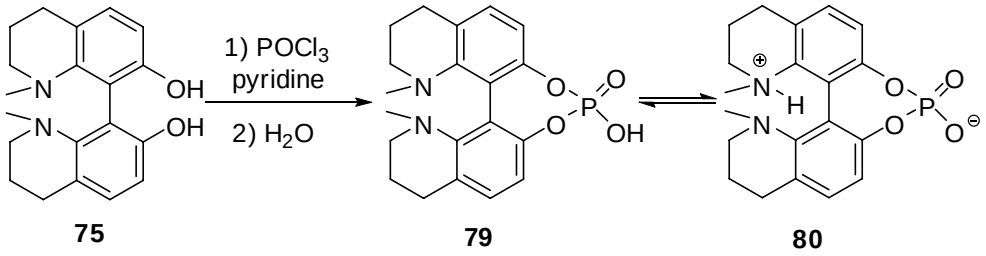
Scheme 5.22 Synthesis of ionic ligand **78**

Recently, significant progress has been made in the development of chiral Brønsted acid catalysis using BINOL-derived phosphoric acids for enantioselective organic transformations. [129] BINOL-derived chiral phosphoric acid catalyzed asymmetric reactions always require modification of the 3,3′-position with bulky groups to provide the necessary steric environment for stereocontrol as the phosphoric acid generally could only interact with one of the substrate. We envisaged that bifunctional catalyst **79** could interact with the two substrates concurrently, providing an intriguing scaffold for a plausible well-defined transition state with its bifunctionality, thus avoiding the chemical complexity of modifying the 3,3′-position. Upon treatment of **75** with phosphoryl chloride in pyridine followed by hydrolysis provided bifunctional catalyst **79** in high yield (Scheme 5.23). Its crystal structure has been determined which revealed that it exists as zwitterion **80** (Figure 5.6). The

Synthesis **2008**, 999. For a review on ionic liquid tagged chiral catalysts or chiral ligands, see: (i) Šebesta, R.; Kmentova, I.; Toma, S. *Green Chem.* **2008**, *10*, 484.

[129] For leading references, see: (a) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356. (b) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566. For recent reviews, see: (c) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (d) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (e) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999. (f) Connon, S. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 3909. (g) Terada, M. *Chem. Commun.* **2008**, 4097.

dihydral angle is 45.96° and the *N*-methyl group is almost orthogonal to the ring plane due to strong steric repulsion. This interesting bifunctional catalyst **80** has great potential application in asymmetric catalysis.



Scheme 5.23 Synthesis of bifunctional catalyst **80**

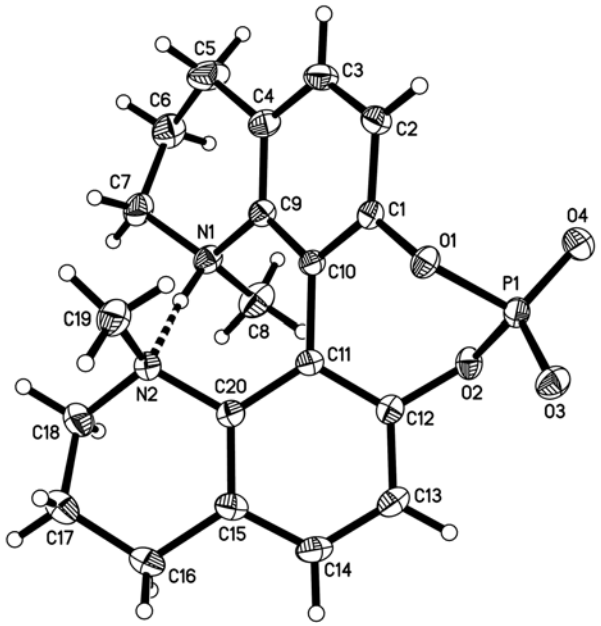
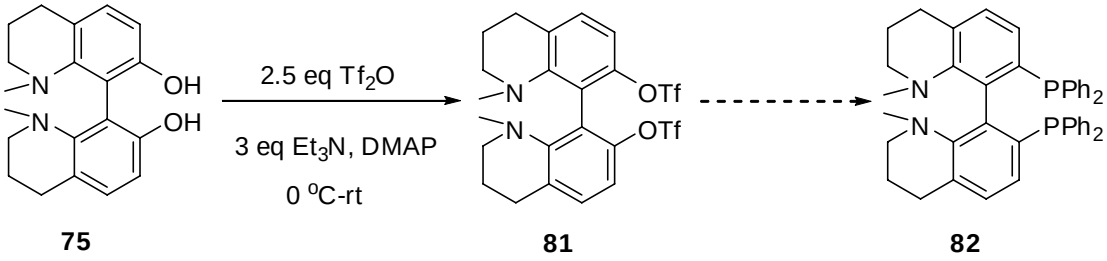


Figure 5.6 Crystal structure of **81**

To further explore the application of this new skeleton, treatment of **75** with Tf_2O under base conditions afforded triflate **81** (Figure 5.7). Further transformation of **81** to diphophine ligand **82** failed in the preliminary study (Scheme 5.24).



75 **81** **82**

Scheme 5.24 Synthesis of **81** and **82**

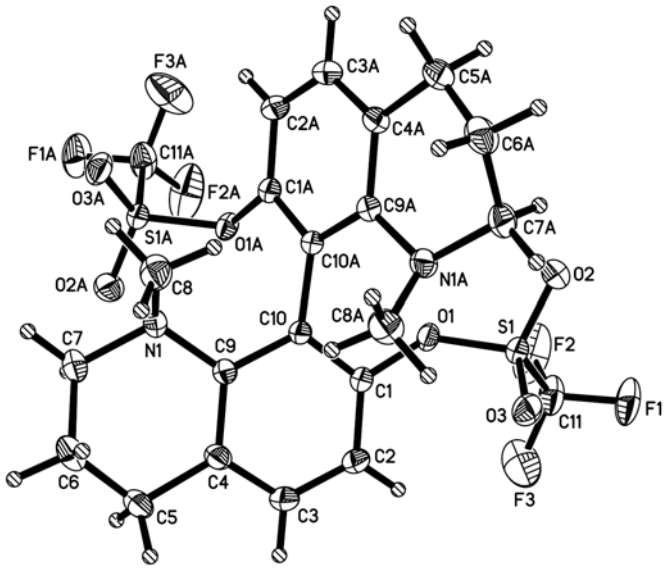


Figure 5.7 Crystal structure of triflate **81**

5.3 CONCLUSION

In summary, we have developed a new bifunctional ligand 1,1′-dimethyl-octahydro-8,8′-biquinoline-7,7′-diol as an aza analogue of BINOL. Both the enantiomers of 1,1′-dimethyl-octahydro-8,8′-biquinoline-7,7′-diol (**75**) could be easily obtained *via* short steps. Its application in asymmetric catalysis is highly anticipated. This new member of the aza BINOL family will open up new areas for catalyst design and provide synthetic material in many fields such as chiral supramolecular recognition and crystal engineering.

CHAPTER 6

Experimental Section

6.1 GENERAL INFORMATION

Experiments involving moisture and/or sensitive compounds were performed under a positive pressure of nitrogen in oven-dried glassware equipped with a rubber septum inlet. Solvents and liquid reagents were transferred by oven-dried syringes cooled in a dessicator or *via* double-tipped cannular needles. Reaction mixtures were stirred with Teflon-coated magnetic stirring bars unless otherwise stated. Moisture in non-volatile reagents/compounds was removed by the addition of the stated amount of anhydrous THF, followed by the removal of the solvent and traces of moisture *in vacuo* by means of an oil pump (~30 mmHg, 23-50 ^{o}C) and subsequent purging with nitrogen.

All experiments were monitored by analytical thin layer chromatography (refer to section under "Chromatography"). Solvents were removed *in vacuo* under ~30 mmHg and heated with a water bath at 23 ^{o}C using Büchi rotary evaporator cooled with circulating ethylene glycol / water mixture (1:1) at -5 ^{o}C.

Materials

Reagents were purified prior to use unless otherwise stated following the guidelines of Perrin and Armareg [130]. Solvents such as hexane, ethyl acetate, dichloromethane and water were freshly distilled prior to use. Anhydrous THF was obtained by distillation under nitrogen atmosphere from a deep purple solution resulting from sodium and benzophenone. Anhydrous dichloromethane was distilled over calcium hydride under nitrogen atmosphere. Azeotropic drying of starting

[130] Perrin, D. D. and Armarego, W. L. *Purification of Laboratory Chemicals*; 3rd ed., Pergamon Press, Oxford. 1988.

materials or reagents was performed by the addition of the stated amount of anhydrous tetrahydrofuran, ensued by azeotropic removal of tetrahydrofuran with traces of moisture *in vacuo* followed by subsequent purging with nitrogen.

Triethylamine, toluene and dimethyl sulfoxide were distilled over calcium hydride and stored over molecular sieves to maintain dryness. DMF was distilled over Linde type 4A molecular sieve prior to usage. 1*N* and 4*N* hydrochloric acid was diluted from concentrated 37% solution using deionised water. 3*M* sodium hydroxide solution was prepared from sodium hydroxide pearls. Saturated solutions of ammonium chloride, sodium chloride, sodium bicarbonate, and sodium carbonate were prepared from their respective solids.

Chromatography

Analytical thin layer chromatography was performed using Merck 60 F_{254} pre-coated silica gel plates (0.25 mm thickness). Visualization was accomplished with UV light (254 nm) and iodine crystals, potassium permanganate solution or ceric molybdate solution followed by heating on a hot plate.

Flash column chromatography was performed using Merck Silica Gel 60 (0.010-0.063 nm) and freshly distilled solvents. Columns were packed as slurry of silica gel in hexane/CH_2Cl_2 and equilibrated with the appropriate solvent/solvent mixture prior to use. The solute was loaded neat or as a concentrated solution using the appropriate solvent system. The elution was assisted by applying pressure with an air pump.

Instruments & Equipments

Infrared Spectroscopy

Infrared spectra were recorded on a Shimadzu IR Prestige-21 FT-IR Spectrometer. Solid samples were analyzed as a KBr pressed-disk while liquid samples were either examined neat between NaCl salt plates or as a solution in dichloromethane using NaCl liquid cells.

Optical Rotation

Optical rotation was measured using a JASCO P-1030 Polarimeter equipped with a sodium vapor lamp at 589 nm. Concentration is denoted as *c* and was calculated as grams per milliliters (g/100 mL) whereas the solvent was indicated in parentheses (*c*, solvent).

Mass Spectroscopy

Mass spectrometry was performed by the staffs in the Division of Chemistry and Biological Chemistry of the Nanyang Technological University. MS (EI) spectra were recorded on a Thermo Finnigan Polaris Q GCMS. MS (ESI and APCI) spectra were recorded on a Thermo Finnigan LCQ Deca XP Max. HRMS (EI, ESI, FAB) spectra were recorded on a Thermo Finnigan MAT 95 XP. MS and HRMS were reported in units of mass of charge ratio (*m/z*).

Nuclear Magnetic Resonance Spectroscopy

Proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectroscopy were performed on a Bruker Avance 300, 400 and

500 NMR spectrometers. Boron (^{11}B) nuclear magnetic resonance and fluorine (^{19}F) nuclear magnetic resonance were performed on a Bruker Avance 300 NMR spectrometer.

Chemical shifts were reported as δ in units of parts per million (ppm) downfield from tetramethylsilane (δ 0.00), using the residual solvent signal as an internal standard: deuterio chloroform-*d*, $CDCl_3$ (^{1}H NMR, δ 7.26, singlet; ^{13}C NMR, δ 77.00, triplet); deuterio methanol, CD_3OD (^{1}H NMR, δ 3.31, singlet; ^{13}C NMR, δ 49.2, septet).

Multiplicities were given as: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplets), br (broad), dd (doublet of doublets), dt (doublet of triplets), ddd (doublet of doublet of doublets) and ddt (doublet of doublet of triplets). Coupling constants (*J*) were recorded in Hertz (Hz). The number of protons (n) for a given resonance was indicated by nH.

Nomenclature

Systematic nomenclature for the compounds would follow the numbering system as defined by IUPAC. Compounds were named with assistance from CS Chemdraw Ultra 10.0 software.

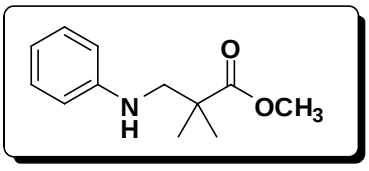
6.2 A NOVEL, WATER TOLERANT CHIRAL INDIUM COMPLEX

General procedure for one-pot three-component Mannich-type reactions in water

Benzaldehyde (distilled, 0.05 mL, 0.5 mmol) and indium complex **4** (20 mg, 0.025 mmol, 0.05 equiv.) were mixed and stirred at room temperature in water (5 mL) for 10 min before the addition of aniline (distilled, 0.06 mL, 0.6 mmol, 1.2 equiv.). The resulting mixture was stirred at room temperature for 30 min. 1-Methoxy-1-trimethylsilyloxypropene (0.2 mL, 1 mmol, 2 equiv.) was then added. The suspension was stirred at room temperature for 1 day and then extracted with ethyl acetate (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The products were obtained in 69% yield after silica gel column chromatography.

Characterization of products

Methyl 2,2-dimethyl-3-(phenylamino)propanoate



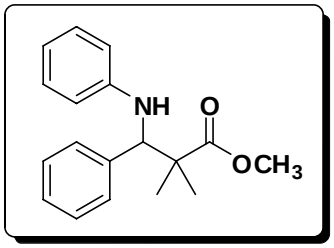
Yellowish solid;

R_f = 0.61 (ethyl acetate/hexane = 1:4);

^{1}H NMR (300M, $CDCl_3$): δ 7.19-7.13 (m, 2H), 6.70-6.60 (m, 3H), 3.67 (s, 3H), 3.23 (s, 2H), 1.27 (s, 6H);

^{13}C NMR (75M, $CDCl_3$): δ 177.5, 148.5, 129.2, 117.4, 112.9, 68.6, 52.7, 52.0, 43.7, 23.6;

Methyl 2,2-dimethyl-3-phenyl-3-(phenylamino)propanoate



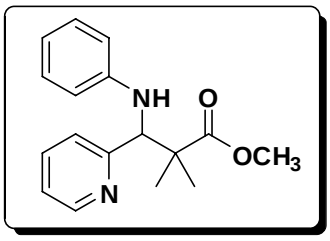
Yellowish solid;

R_f = 0.61 (ethyl acetate/hexane = 1:4);

^{1}H NMR (300M, $CDCl_3$): δ 7.27-7.21 (m, 5H), 7.03 (t, *J* = 7.5 Hz, 2H), 6.58 (t, *J* = 6.9 Hz, 1H), 6.49 (d, *J* = 8.1 Hz, 2H), 4.78 (s, 1H), 4.48 (s, 1H), 3.64 (s, 3H), 1.26 (s, 3H), 1.16 (s, 3H);

^{13}C NMR (75M, $CDCl_3$): δ 177.0., 146.9, 139.2, 129.0., 128.3, 128.0, 127.4, 117.3, 113.4, 64.4, 52.1, 47.0, 24.5, 20.7;

Methyl 2,2-dimethyl-3-(phenylamino)-3-(pyridin-2-yl)propanoate



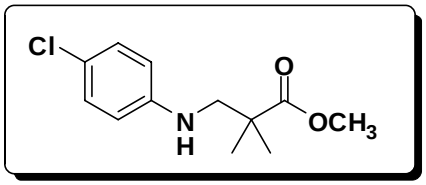
Yellowish oil;

R_f = 0.55 (ethyl acetate/hexane = 1:2);

^{1}H NMR (300M, $CDCl_3$): δ 8.18 (d, *J* = 7.8 Hz, 1H), 7.49 (td, *J* = 7.5, 1.5 Hz, 1H), 7.18 (d, *J* = 7.8 Hz, 1H), 7.09-7.04 (m, 3H), 6.67-6.59 (m, 3H), 5.16 (d, *J* = 6.8 Hz, 1H), 4.76 (d, *J* = 6.0 Hz, 1H), 3.64 (s, 3H), 1.24 (s, 6H);

^{13}C NMR (75M, $CDCl_3$): δ 177.0, 159.2, 148.8, 136.1, 129.1, 123.1, 122.4, 117.7, 113.9, 64.9, 51.9, 47.5, 23.4, 21.6;

Methyl 3-(4-chlorophenylamino)-2,2-dimethylpropanoate



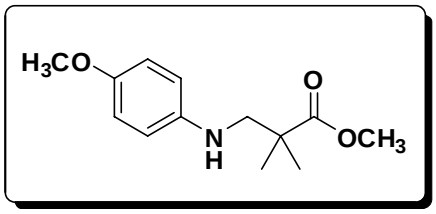
Colorless solid;

R_f = 0.55 (ethyl acetate/hexane = 1:4);

^{1}H NMR (300M, $CDCl_3$): δ 7.09 (d, *J* = 8.8 Hz, 2H), 6.53 (d, *J* = 8.8 Hz, 2H), 3.97 (s, 1H), 3.67 (s, 3H), 3.19 (s, 2H), 1.26 (s, 6H);

^{13}C NMR (75M, $CDCl_3$): δ 177.4, 147.0, 129.0, 121.8, 113.9, 52.7, 52.0, 43.6, 23.5;

Methyl 3-(4-methoxyphenylamino)-2,2-dimethylpropanoate



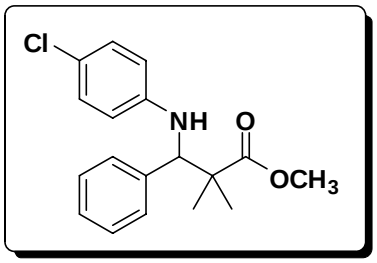
Brown solid;

R_f = 0.47 (ethyl acetate/hexane = 1:4);

^{1}H NMR ($CDCl_3$): δ 6.79-6.73 (m, 2H), 6.64-6.58 (m, 2H), 3.75 (s, 3H), 3.68 (s, 3H), 3.19 (s, 2H), 1.28 (s, 6H);

^{13}C NMR ($CDCl_3$): δ 177.5, 152.0, 142.7, 114.8, 114.3, 55.7, 54.0, 51.9, 43.5, 23.5;

Methyl 3-(4-chlorophenylamino)-2,2-dimethyl-3-phenylpropanoate



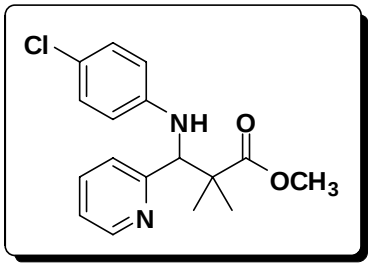
Yellowish solid;

R_f = 0.58 (ethyl acetate/hexane = 1:4);

^{1}H NMR (400M, $CDCl_3$): δ 7.30-7.23 (m, 5H), 6.97 (d, *J* = 8.7 Hz, 2H), 6.41 (d, *J* = 8.7 Hz, 2H), 4.87 (d, *J* = 7.0 Hz, 2H), 4.42 (d, *J* = 7.4 Hz, 1H), 3.65 (s, 3H), 1.27 (s, 3H), 1.15 (s, 3H);

^{13}C NMR (100M, $CDCl_3$): δ 177.0, 145.5, 138.7, 128.8, 128.2, 128.1, 127.6, 121.9, 114.5, 64.6, 52.1, 46.9, 24.7, 20.7;

Methyl 3-[(4-chlorophenyl)amino]-2,2-dimethyl-3-(2-pyridyl) propanoate



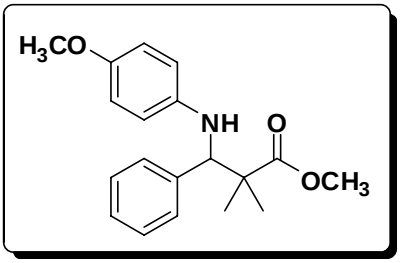
Yellowish wet-solid;

R_f = 0.53 (ethyl acetate/hexane = 1:2);

^{1}H NMR (300M, $CDCl_3$): δ 8.54 (d, *J* = 4.3 Hz, 1H), 7.57 (t, *J* = 7.8 Hz, 1H), 7.22-7.12 (m, 2H), 7.01 (d, *J* = 8.4 Hz, 2H), 6.58 (d, *J* = 8.7 Hz, 2H), 5.21 (br, 1H), 4.68 (s, 1H), 3.67 (s, 3H), 1.24 (s, 3H), 1.22 (s, 3H);

^{13}C NMR (75M, $CDCl_3$): δ 176.9, 158.7, 149.8, 148.9, 136.0, 128.9, 123.0, 122.4, 122.3, 115.1, 65.2, 52.0, 47.4, 23.5, 21.3;

Methyl 3-[(4-methoxyphenyl)amino]-2,2-dimethyl-3-phenylpropanoate



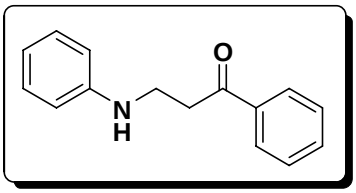
Dark brown wet-solid;

R_f = 0.50 (ethyl acetate/hexane = 1:4);

^{1}H NMR (300M, $CDCl_3$): δ 7.32-7.21 (m, 5H), 6.65 (d, *J* = 9.0 Hz, 2H), 4.47 (d, *J* = 9.0 Hz, 1H), 3.65 (s, 6H), 1.22 (s, 3H), 1.13 (s, 3H);

^{13}C NMR (75M, $CDCl_3$): δ 177.1, 151.9, 141.2, 139.3, 128.3, 127.9, 127.3, 114.7, 114.6, 65.1, 55.6, 52.0, 47.1, 24.4, 20.4;

1-Phenyl-3-(phenylamino)propan-1-one



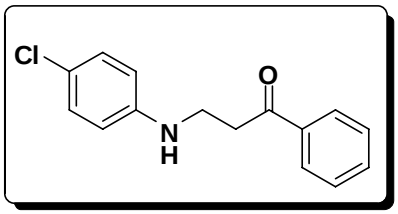
Yellowish oil;

R_f = 0.29 (ethyl acetate/hexane = 1:4);

^{1}H NMR (300M, $CDCl_3$): δ 7.85 (d, *J* =.7.4 Hz, 2H), 7.47 (t, *J* =.7.3 Hz, 1H), 7.36 (t, *J* =.7.8 Hz, 2H), 7.09 (t, *J* =.7.7 Hz, 2H), 6.62 (t, *J* =.7.3 Hz, 1H), 6.56 (d, *J* =.8.0 Hz, 2 H), 3.52 (t, *J* =.6.1 Hz, 2H), 3.18 (t, *J* = 6.1 Hz, 2H);

^{13}C NMR (75M, $CDCl_3$): δ 199.3, 147.7, 136.6, 133.3, 129.3, 129.2, 128.6, 128.0, 117.5, 113.0, 38.7, 37.6;

3-[(4-Chlorophenyl) amino]-1-phenylpropan-1-one



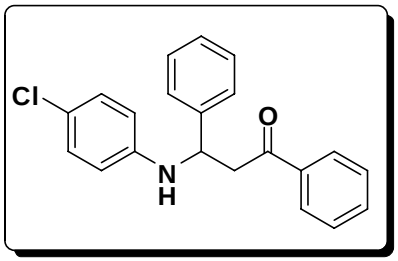
Colorless oil;

R_f = 0.26 (ethyl acetate/hexane = 1:4);

^{1}H NMR (300M, $CDCl_3$): δ 7.94-7.91 (m, 2H), 7.59-7.54 (m, 1H), 7.47-7.41 (m, 2H), 7.13-7.08 (m, 2H), 6.57-6.53 (m, 2H), 4.16 (br, 1H), 3.55 (t, *J* =.6.0 Hz, 2H), 3.24 (t, *J* =.6.0 Hz, 2H);

^{13}C NMR (75M, $CDCl_3$): δ 199.1, 146.3, 136.5, 133.4, 129.0, 128.6, 127.9, 122.0, 114.0, 38.7, 37.3;

3-[(4-Chlorophenyl)amino]-1,3-diphenylpropan-1-one



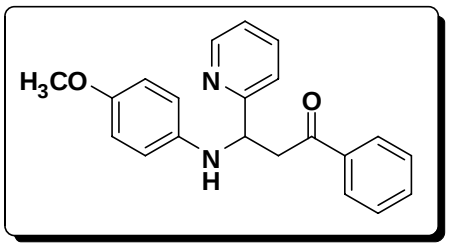
Yellowish solid;

R_f = 0.48 (ethyl acetate/hexane = 1:4);

^{1}H NMR (300M, $CDCl_3$): δ 7.90 (d, *J* =.7.5 Hz, 2H), 7.56 (t, *J* =.7.5 Hz, 1H), 7.49-7.39 (m, 4H), 7.32 (t, *J* =.7.5 Hz, 1H), 7.25-7.21 (m, 1H), 7.01 (d, *J* =.8.7 Hz, 2H), 6.47 (d, *J* =.8.7 Hz, 2H), 4.94 (dd, *J* = 5.4, 7.5 Hz, 1H), 4.61 (s, 1H), 3.52-3.36 (m, 2H);

^{13}C NMR (75M, $CDCl_3$): δ 198.1, 145.6, 142.5, 136.6, 133.5, 128.9, 128.7, 128.6, 128.3, 127.5, 126.3, 122.4, 114.9, 54.9, 46.2;

3-[(4-Methoxyphenyl)amino]-1-phenyl-3-(2-pyridyl)-propan-1-one



Dark brown wet-solid;

R_f = 0.29 (ethyl acetate/hexane = 1:2);

^{1}H NMR (300M, $CDCl_3$): δ 8.56 (d, *J* = 4.8 Hz, 1H), 7.92 (d, *J* = 7.2 Hz, 2H), 7.61-7.38 (m, 5H), 7.12 (t, *J* = 5.0 Hz, 1H), 6.75 (d, *J* = 9.0 Hz, 2H), 6.66 (d, *J* = 9.0 Hz, 2H), 5.16 (t, *J* = 6.3 Hz, 1H), 3.75-3.56 (m, 5H);

^{13}C NMR (75M, $CDCl_3$): δ 198.7, 161.3, 152.3, 149.1, 140.8, 136.6, 136.5, 133.1, 128.4, 128.0, 122.2, 122.1, 115.3, 114.7, 56.3, 55.5, 43.9;

6.3 A NEW MODULARLY DESIGNED BICYCLIC ORGANOCATALYSTS

General procedure for the catalytic asymmetric Michael addition of aldeydes to nitrostyrene

To a mixture of catalyst **4** (1.6 mg, 0.01mmol, 0.1 equiv.), DMAP (1.2 mg, 0.01 mmol, 0.1 equiv.) and nitrostyrene (0.1 mmol) in CH_3OH (0.5 mL), aldehyde (0.2-0.4 mmol, 2-4 equiv.) was added at room temperature. The reaction mixture was stirred for the time indicated in Table 2.2, then the crude mixture was purified by preparative TLC (ethyl acetate/hexane = 1:4) to afford the Michael products. The relative and absolute configurations of the Michael adducts were determined by comparison with ^{1}H NMR spectroscopic analysis and optical rotation. Both enantiomeric excess and diastereomeric excess were determined by HPLC with Daicel Chiralpak AS-H, AD-H or OD-H columns, unless indicated otherwise. Please refer to chapter 6.4 for the characterization of the nitroalkane products.

6.4 A NEW MODULARLY DESIGNED BICYCLIC ORGANOCATALYSTS

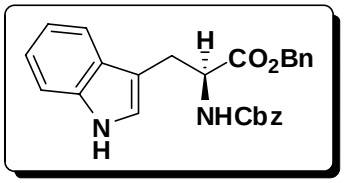
6.4.1 Application to catalytic asymmetric Michael addition of aldeydes to nitrostyrene

General procedure for the catalytic asymmetric Michael addition of aldeydes to nitrostyrene

To a 4 mL sample vial equipped with a magnetic stirring bar, the catalyst (2.76 mg, 0.01 mmol, 0.05 equiv.), DMAP (1.2 mg, 0.01 mmol, 0.05 equiv.), nitroalkene (0.2 mmol), aldehyde (0.4 mmol, 2 equiv.) were added followed by MeOH or water (0.5 mL) at room temperature. For more bulky aldehydes, addition of more aldehydes (0.8 mmol, 4 equiv.) with heating up to about 60 ^{o}C is necessary to accelerate this reaction. The reaction mixture was stirred for the time indicated in Table 3.2, and then it was directly purified by preparative TLC (ethyl acetate/hexane = 1:4) to afford the product as inseparable isomers. Both enantiomeric excess and diastereomeric ratio (*syn*/*anti*) were determined by HPLC using chiral AS-H, AD-H or OD-H columns or ^{1}H NMR (for products where the *anti* diastereomer peak can not be located in HPLC) in comparison with the literature reported values.

Characterization of catalysts

(*S*)-Benzyl 2-(benzyloxycarbonylamino)-3-(1*H*-indol-3-yl)propanoate (14)



To a stirred suspension of (*S*)-(**13**) (2.45 g, 7.2 mmol) in 10 mL anhydrous CH_2Cl_2, was added DMAP (88 mg, 0.72 mmol, 0.1 equiv.) and benzyl alcohol (1.28 g, 11.8 mmol, 1.6 equiv.). DCC (1.48 g, 7.2 mmol, 1 equiv.) in 5 mL CH_2Cl_2 was slowly added to the mixture at 0 ^oC and the resulting mixture was allowed to warm to room temperature and stirred for 2 h. The white precipitate was filtered and the solvent was removed to afford the product as a colourless oil (3 g, 98%).

$[\alpha]_D^{20}$ = +50 (*c* = 1.0, $CHCl_3$, 365 nm);

R_f = 0.29 (ethyl acetate/hexane = 1:2);

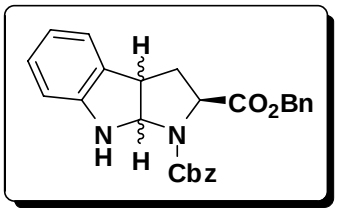
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (br, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.41-7.33 (m, 9H), 7.26-7.20 (m, 3H), 7.12 (t, *J* = 8.0 Hz, 1H), 6.76 (d, *J* = 2.0 Hz, 1H), 5.47 (d, *J* = 8.0 Hz, 1H), 5.18-5.10 (m, 4H), 4.82 (q, *J* = 8.0 Hz, 1H), 3.34 (d, *J* = 5.1 Hz, 2H);

^{13}C NMR (100 MHz, $CDCl_3$): *δ* 171.8, 155.8, 136.1, 136.0, 135.1, 128.5, 128.4, 128.3, 128.0, 127.5, 127.4, 126.9, 122.9, 122.0, 119.5, 118.5, 111.2, 109.4, 67.1, 66.8, 54.6, 27.8;

FTIR (neat): 3395, 3343, 1742, 1458, 1377, 721 cm^{-1};

HRMS (ESI) calcd. for $C_{20}H_{20}O_4N_2$ 429.1814 $[M+H]^+$, found 429.1821.

(2*S*,3*aR*,8*aR*)-Dibenzyl 3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indol-1,2(2*H*)-dicarboxylate (15)



N-benzyloxycarbonyl-*L*-trptophan benzyl ester (**14**) (1.18 g, 2.75 mmol) was dissolved in 5 mL TFA and stirred for two days, then the solution was added dropwise to a vigorously stirred two phase mixture of 100 mL saturated Na_2CO_3 and 100 mL CH_2Cl_2. The organic phase was separated and the aqueous solution was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with brine, dried with anhydrous $MgSO_4$ and purified by column chromatography (ethyl acetate /hexane = 1:7-1:4) to give the poduct as a colorless oil (1.04 g, 88%).

Major isomer:

$[\alpha]_D^{20}$ = +52.9 (*c* = 1.8, $CHCl_3$, 365 nm);

R_f = 0.34 (ethyl acetate/hexane = 1:2);

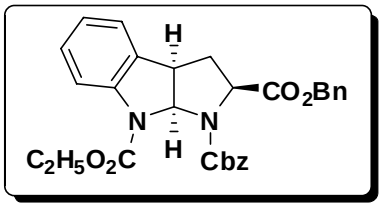
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.19 (m, 8H), 7.13-1.12 (m, 1H), 7.07-7.04 (m, 1H), 7.02-6.97 (m, 2H),6.67 (t, *J* = 8.0 Hz, 1H), 6.49 (d, *J* = 8.0 Hz, 1H), 5.60 (d, *J* = 8.0 Hz, 1H), 5.24 (s, 1H), 5.04 (d, *J* = 43,12 Hz, 1H), 4.73 (d, *J* = 12 Hz, 1H), 4.56 (dd, *J* = 7.6, 2.3 Hz, 1H), 4.32 (d, *J* = 12.3 Hz, 1H), 3.90 (q, *J* = 6.5 Hz, 1H), 2.66-2.53 (m, 2H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3, 154.7, 149.9, 135.5, 128.6, 128.4, 128.3, 128.0,128.0, 128.0, 127.9, 127.9, 127.8, 124.0, 118.7, 109.1, 77.4, 67.1, 66.7, 59.1, 45.0, 34.4;

FTIR (neat): 3032, 2953, 1751, 1701, 1610, 1416, 731 cm^{-1};

HRMS (ESI) calcd. for $C_{20}H_{20}O_4N_2$ 429.1814 $[M+H]^+$, found 429.1818.

(2*S*,3*aR*,8*aS*)-1,2-Dibenzyl 8-ethyl 3,3a-dihydropyrrolo[2,3-*b*]indole-1,2,8(2*H*,8a*H*)-tricarboxylate (16)



To a solution of **15** (4.28 g, 10 mmol) in 20 mL THF, was added Na_2CO_3 (1.60 g, 15 mmol, 1.5 equiv.) and 10 mL H_2O. Ethyl chloroformate (0.88 mL, 12 mmol, 1.2 equiv.) was slowly added to the solution at 0 ^oC, the mixture was allowed to warm to room temperature and stirred overnight. After which 20 mL water was added and the two phase was separated and the aqueous solution was extracted with ethyl acetate (3 × 5 mL). The combined organic extracts were washed with brine, dried with anhydrous $MgSO_4$ and purified by column chromatography (ethyl acetate/hexane = 1:5-1:2) to give the product as a colorless oil (4.3 g, 86 %).

$[\alpha]_D^{20}$ = -10.8 (*c* = 1.04, $CHCl_3$, 365 nm);

R_f = 0.24 (ethyl acetate/hexane = 1:2);

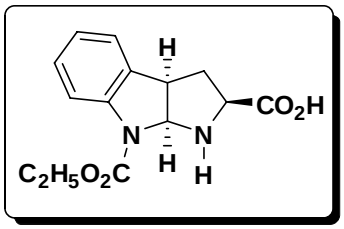
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53 (br, 1H), 7.27-7.23 (m, 8H), 7.14 (t, *J* = 8.3 Hz, 1H), 7.09-7.04 (m, 4H), 6.94 (t, *J* = 7.5 Hz, 1H), 6.47 (d, *J* = 6.2 Hz, 1H), 5.14 (q, *J* = 15 Hz, 2H), 4.72-4.68 (m, 2H), 4.36 (d, *J* = 12.6 Hz, 1H), 4.18(br, 1H), 3.96 (t, *J* = 6.8 Hz,1H), 2.64-2.49 (m, 2H), 1.26-1.20 (m, 3H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 170.9, 154.1, 153.5, 142.7, 136.4, 135.3, 131.2, 128.8, 128.6, 128.5, 128.4, 128.1, 127.9, 127.6, 124.0, 123.5, 116.9, 67.4, 66.8, 61.9, 59.6, 45.0, 33.9, 14.5;

FTIR (neat): 3018, 2957, 1717, 1605, 1483, 748 cm^{-1};

HRMS (ESI) calcd. for $C_{29}H_{29}O_6N_2$ 501.2026 $[M+H]^+$, found 501.2018.

(2*S*,3*aR*,8*aS*-Dibenzyl 8-ethoxycarbonyl 1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylic acid (12)



16 (5.01 g, 10 mmol) was dissolved in 20 mL methanol prior to addition of 10% Pd/C (1.06 g, 1 mmol, 0.1 equiv.). The mixture was stirred overnight at room temperature with a H_2 balloon, filtered with celite and the solvent was removed to give a colorless oil. After which CH_2Cl_2 was added, and a white solid precipitated out. The mixture was cooled and filtered to give the product as a white solid (2.76 g, 100%).

$[\alpha]_D^{20}$ = -15.9 (*c* = 0.4, CH_3OH, 365 nm);

R_f = 0.59 (CH_2Cl_2:CH_3OH = 4:1);

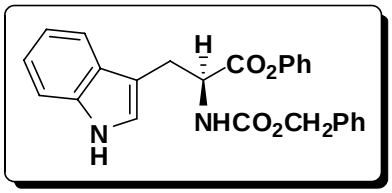
^{1}H NMR (400 MHz, CD_3OD): δ 7.77, 7.52 (br, 1H), 7.26-7.20 (m, 2H), 7.04 (t, *J* = 7.6 Hz, 1H), 5.86 (d, *J* = 8.6 Hz, 1H), 4.38 (br, 2H), 4.14-4.09 (m, 1H), 4.02 (t, *J* = 7.6 Hz, 1H), 2.88-2.80 (m, 1H), 2.31-2.27 (m, 1H), 1.41 (t, *J* = 6.7 Hz, 3H);

^{13}C NMR (100 MHz, CD_3OD): δ 172.5, 152.1, 140.9, 131.5, 128.1, 124.2, 123.0, 113.6, 77.9, 62.0, 60.0, 44.0, 35.1, 13.4;

FTIR (neat): 3177, 2725, 1721, 1629, 1570, 1462, 1377, 760, 721 cm^{-1};

HRMS (ESI) calcd. for $C_{14}H_{17}O_4N_2$ 277.1188 $[M+H]^+$, found $[M]^+$ 277.1188.

(*S*)-Phenyl 2-(benzyloxycarbonylamino)-3-(1*H*-indol-3-yl)propanoate (21)



$[\alpha]_D^{20}$ = +5.4 (*c* = 2.1, $CHCl_3$);

R_f = 0.41 (ethyl acetate/hexane = 1:4);

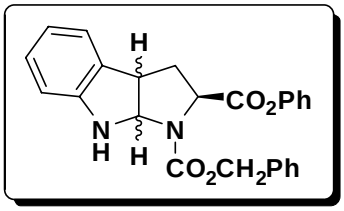
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.24 (d, *J* = 22.1 Hz, 1H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.29-7.25 (m, 6H), 7.17-7.14 (m, 2H), 7.06 (q, *J* = 7.5 Hz, 1H), 6.90-6.85 (m, 3H), 5.49-5.44 (m, 1H), 5.12-5.03 (m, 2H), 4.93 (t, *J* = 6.0 Hz, 1H), 3.40 (d, *J* = 5.0 Hz, 2H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.9, 156.1, 150.4, 136.3, 129.5, 128.6, 128.3, 128.2, 127.6, 126.2, 123.2, 122.4, 121.4, 119.9, 118.8, 111.5, 109.5, 67.2, 55.0, 28.0;

FTIR (neat): 3428, 3019, 1759, 1719, 1605, 1493, 1416, 1217, 1059, 928, 756 cm^{-1};

HRMS (ESI) calcd. for $C_{25}H_{23}N_2O_4$ 415.1658 $[M+H]^+$, found 415.1652.

(2*S*)-1-Benzyl 2-phenyl 3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole-1,2(2*H*)-dicarboxylate (22)



$[\alpha]_D^{20}$ = +119.9 (*c* = 1.4, $CHCl_3$);

R_f = 0.55 (ethyl acetate/hexane = 1:4);

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 (d, *J* = 7.5 Hz, 1H), 7.37-7.28 (m, 4H), 7.19-7.05 (m, 5H), 6.76 (q, *J* = 1.6 Hz, 1H), 6.53 (d, *J* = 8.0 Hz, 1H), 6.46 (d, *J* = 8.0 Hz,

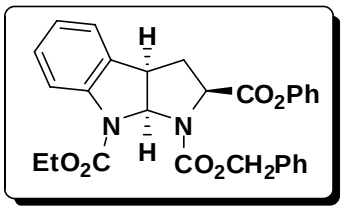
1H), 6.25 (d, *J* = 8.0 Hz, 1H), 5.67 (d, *J* = 6.8 Hz, 1H), 5.25 (d, *J* = 7.0 Hz, 1H), 5.13 (d, *J* = 12.5 Hz, 1H), 4.75 (dd, *J* = 8.5, 1.5 Hz, 1H), 3.97 (br, 1H), 2.78-2.72 (m, 2H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.2, 154.6, 150.4, 150.2, 136.2, 136.1, 128.8, 128.3, 128.6, 128.5, 128.2, 128.1, 127.6, 125.7, 124.2, 121.1, 118.9, 109.4, 77.4, 67.3, 59.1, 45.2, 34,6;

FTIR (neat): 3400, 3055, 2957, 1753, 1713, 1605, 1483, 1416, 1263, 975, 752 cm^{-1};

HRMS (ESI) calcd. for $C_{25}H_{23}N_2O_4$ 415.1658 $[M+H]^+$, found 415.1658.

(2*S*,3a*R*,8a*S*)-1-Benzyl 8-ethyl 2-phenyl 3,3a-dihydropyrrolo[2,3-*b*]indole-1,2,8(2*H*,8a*H*)-tricarboxylate (23)



$[\alpha]_D^{20}$ = -15.3 (*c* = 2.7, $CHCl_3$, 589 nm);

R_f = 0.17 (ethyl acetate/hexane = 1:4);

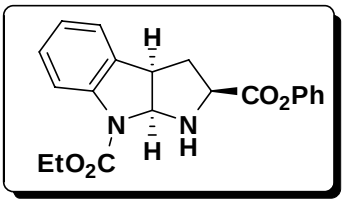
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.66 (br, 1H), 7.33-7.19 (m, 8H), 7.14-7.11 (m, 3H), 7.04-6.99 (m, 2H), 6.48 (br, 1H), 5.22-5.17 (m, 2H), 4.84 (br, 1H), 4.25 (br, 2H), 3.92 (t, *J* = 6.9 Hz, 1H), 2.66 (d, *J* = 13.4 Hz, 1H), 2.55-2.49 (m, 1H), 1.22 (br, 3H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 169.3, 153.0, 149.9, 142.3, 135.9, 131.0, 128.6, 128.3, 128.0, 127.6, 127.5, 125.2, 123.7, 123.2, 120.9, 120.6, 116.5, 77.3, 67.0, 61.5, 59.1, 44.4, 33.2, 14.0;

FTIR (neat): 3368, 3064, 2982, 1713, 1591, 1483, 1379, 1049, 910, 866, 733 cm^{-1};

HRMS (ESI) calcd. for $C_{28}H_{27}N_2O_6$ 487.1869 $[M+H]^+$, found 487.1864.

(2*S*,3a*R*,8a*S*)-8-Ethyl 2-phenyl 1,2,3,3a-tetrahydropyrrolo[2,3-*b*]indole-2,8(8a*H*)-dicarboxylate (24)



$[\alpha]_D^{20}$ = -12.2 (*c* = 1.4, $CHCl_3$, 589 nm);

R_f = 0.32 (ethyl acetate/hexane = 1:4);

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82 (d, *J* = 8.0 Hz, 1H), 7.38-6.96 (m, 8H), 6.47 (d, *J* = 8.0 Hz, 1H), 4.30-4.21 (m, 2H), 4.08 (d, *J* = 7.5 Hz, 1H), 3.96 (t, *J* = 6.5 Hz, 1H), 2.70-2.61(m, 1H), 2.59-2.54 (m, 1H), 1.31 (t, *J* = 6.5 Hz, 3H);

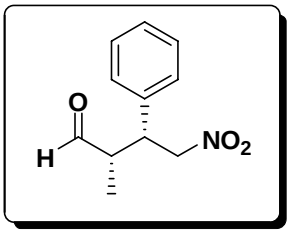
^{13}C NMR (125 MHz, $CDCl_3$): δ 172.4, 153.1, 142.4, 135.9, 131.9, 128.8, 128.1, 127.7, 125.3, 124.2, 120.8, 114.1, 78.3, 61.1, 58.4, 43.2, 35.8, 14.1;

FTIR (neat): 3389, 3053, 2980, 1755, 1593, 1487, 1381, 1053, 912, 831, 746 cm^{-1};

HRMS (ESI) calcd. for $C_{20}H_{21}N_2O_4$ 353.1501 $[M+H]^+$, found 353.1498.

Characterization of nitroalkane product

(2*S*,3*R*)-2-Methyl-4-nitro-3-phenylbutanal



The title compound was prepared from propionaldehyde and (*E*)-(2-nitrovinyl)benzene according to the general procedure. Both enantiomeric excess and diastereomeric ratio were determined by HPLC with an OD-H column at 210 nm (2-propanol:hexane = 10:90), 1.0 mL/min; major enantiomer t_{major} = 22.06 min, minor enantiomer t_{minor} = 30.05 min. $[\alpha]_D^{20}$ = -28.8 (*c* = 2.2, $CHCl_3$, 589 nm).

R_f = 0.18 (ethyl acetate/hexane = 1:4);

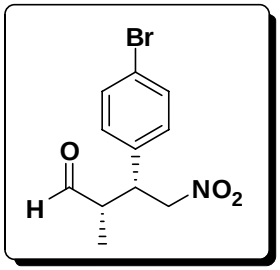
^{1}H NMR (300 MHz, $CDCl_3$): δ 9.72 (d, *J* = 1.5 Hz, 0.85H) (*syn* isomer), 9.72 (d, *J* = 1.5 Hz, 0.15H) (*anti* isomer), 7.37-7.29 (m, 3H), 7.22-7.16 (m, 2H), 4.83-4.65 (m, 2H), 3.87-3.77 (m, 1H), 2.87-2.72 (m, 1H), 1.21 (d, *J* = 7.3 Hz, 0.5H) (*anti* isomer), 1.01 (d, *J* = 7.3 Hz, 2.5H) (*syn* isomer);

^{13}C NMR (75 MHz, $CDCl_3$): δ 202.3, 136.6, 129.1, 128.1, 78.1, 48.4, 44.0, 12.1;

IR (thin film): 3030, 2970, 2931, 1724, 1603, 1552, 1454, 1379, 758, 702 cm^{-1};

HRMS (ESI-TOF): Calcd. for $C_{11}H_{14}NO_3$: 208.0974 $[M+H]^+$, Found: 208.0971.

(2*S*,3*R*)-3-(4-Bromophenyl)-2-methyl-4-nitrobutanal



The title compound was prepared from propionaldehyde and (*E*)-1-bromo-4-(2-nitrovinyl)benzene according to the general procedure. Both enantiomeric excess and diastereomeric ratio were determined by HPLC with an AD-H column at 230 nm (2-propanol:hexane = 5:95), 1.0 mL/min; major enantiomer t_{major} = 18.59 min, t_{minor} = 13.77 min. $[\alpha]_D^{20}$ = -24.6 (*c* = 2.1, $CHCl_3$, 589 nm).

R_f = 0.18 (ethyl acetate/hexane = 1:4);

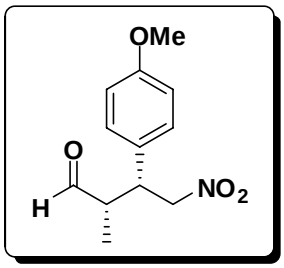
^{1}H NMR (300 MHz, $CDCl_3$): δ 9.69 (d, *J* = 1.5 Hz, 0.8H) (*syn* isomer), 9.52 (d, *J* = 1.5 Hz, 0.2H) (*anti* isomer), 7.50-7.46 (m, 2H), 7.12-7.05 (m, 2H), 4.82-4.56 (m, 2H), 3.84-3.74 (m, 1H), 2.83-2.70 (m, 1H), 1.21 (d, *J* = 7.3 Hz, 0.6H) (*anti* isomer), 1.00 (d, *J* = 7.3 Hz, 2.4H) (*syn* isomer);

^{13}C NMR (75 MHz, $CDCl_3$): δ 201.8, 135.7, 132.3, 129.8, 122.1, 77.8, 48.2, 43.5, 12.2;

IR (thin film): 2976, 2935, 2879, 1726, 1553, 1489, 1377, 1010, 779, 717 cm^{-1};

HRMS (ESI-TOF) Calcd. for $C_{11}H_{13}NO_3Br$: 286.0079 $[M+H]^+$, Found: 286.0081.

(2*S*,3*R*)-3-(4-Methoxyphenyl)-2-methyl-4-nitrobutanal



The title compound was prepared from propionaldehyde and (*E*)-1-methoxy-4-(2-nitrovinyl)benzene according to the general procedure. Both enantiomeric excess and diastereomeric ratio were determined by HPLC with an AS-H column at 230 nm (2-propanol:hexane = 5:95), 1.0 mL/min; major enantiomer t_{major} = 42.10 min, minor enantiomer t_{minor} = 60.77 min. $[\alpha]_D^{20}$ = -4.6 (*c* = 1.3, $CHCl_3$, 589 nm).

R_f = 0.13 (ethyl acetate/hexane = 1:4);

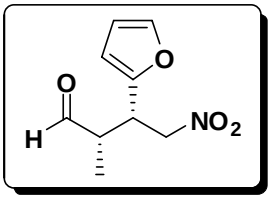
^{1}H NMR (300 MHz, $CDCl_3$): δ 9.70 (d, *J* = 1.4 Hz, 0.6H) (*syn* isomer), 9.53 (d, *J* = 1.4 Hz, 0.4H) (*anti* isomer), (7.27-7.07 (m, 2H), 6.87-6.67 (m, 2H), 4.78-4.60 (m, 2H), 3.78 (s, 3H), 3.78-3.73 (m, 1H), 2.81-2.69 (m, 1H), 1.21 (d, *J* = 7.2 Hz, 1.11H) (*anti* isomer), 0.99 (d, *J* = 7.2 Hz, 1.89H) (*syn* isomer);

^{13}C NMR (75 MHz, $CDCl_3$): δ 202.5, 129.2, 129.1, 128.3, 114.4, 78.3, 55.2, 48.6, 43.3, 12.0;

IR (thin film): 2978, 2937, 2839, 1726, 1612, 1557, 1514, 1379, 1253, 1182, 1033, 833, 725 cm^{-1};

HRMS (ESI-TOF) Calcd. for $C_{12}H_{16}NO_4$: 238.1079 $[M+H]^+$, Found: 238.1081.

(2*S*,3*S*)-3-(Furan-2-yl)-2-methyl-4-nitrobutanal



The title compound was prepared from propionaldehyde and (*E*)-2-(2-nitrovinyl)furan according to the general procedure. Both enantiomeric excess and diastereomeric ratio were determined by HPLC with an AD-H column at 220 nm (2-propanol:hexane = 0.8:99.2), 1.0 mL/min; major enantiomer t_{major} = 30.44 min, minor enantiomer t_{minor} = 26.29 min. $[\alpha]_D^{20}$ = -20 (*c* = 2.0, $CHCl_3$, 589 nm).

R_f = 0.17 (ethyl acetate/hexane = 1:4);

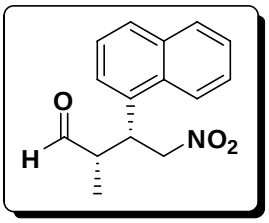
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.70 (s, 0.87H) (*syn* isomer), 9.62 (s, 0.13H) (*anti* isomer), 7.35 (s, 1H), 6.30-6.29 (m, 1H), 6.17 (d, *J* = 3.22 Hz, 1H), 4.77-4.67 (m, 2H), 4.13-4.05 (m, 1H), 2.87-2.76 (m, 1H), 1.22 (d, *J* = 7.31 Hz, 0.48H) (*anti* isomer), 1.06 (d, *J* = 7.31 Hz, 2.52H) (*syn* isomer);

^{13}C NMR (100 MHz, $CDCl_3$): δ 201.6, 149.9, 142.7, 110.4, 108.7, 75.8, 47.1, 37.6, 11.0;

IR (thin film): 3152, 3123, 2974, 2938, 2880, 1724, 1557, 1458, 1377, 1150, 1013, 814, 741,702 cm^{-1};

HRMS (ESI-TOF) Calcd. for $C_9H_{12}NO_4$: 198.0766 $[M+H]^+$, Found: 198.0761.

(2*S*,3*R*)-2-Methyl-3-(naphthalen-1-yl)-4-nitrobutanal



The title compound was prepared from butyraldehyde and (*E*)-1-(2-nitrovinyl)naphthalene according to the general procedure. Both enantiomeric excess and diastereomeric ratio were determined by HPLC with an AD-H column at 220 nm (2-propanol:hexane = 0.8:99.2), 1.0 mL/min; major enantiomer t_{major}= 43.3 min, minor enantiomer t_{minor} = 37.6 min. $[\alpha]_D^{20}$ = -21.1 (*c* = 2.4, $CHCl_3$, 589 nm).

R_f = 0.33 (ethyl acetate/hexane = 1:4);

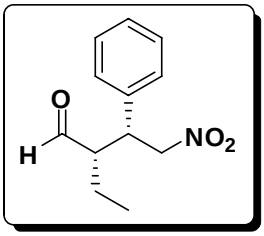
^{1}H NMR (100 MHz, $CDCl_3$): δ 9.75 (d, *J* = 1.6 Hz, 0.85H) (*syn* isomer), 9.62 (d, *J* = 1.6 Hz, 0.15H) (*anti* isomer), 8.14-8.10 (m, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.61-7.41 (m, 3H), 7.35 (d, *J* = 7.1 Hz, 1H), 4.94-4.76 (m, 3H), 3.01-2.96 (m, 1H), 1.21 (d, *J* = 7.3 Hz, 0.45H) (*anti* isomer), 0.97 (d, *J* = 7.3 Hz, 2.55H) (*syn* isomer);

^{13}C NMR (100 MHz, $CDCl_3$): δ 202.5, 134.1, 133.3, 131.9, 129.2, 128.6, 126.9, 126.0, 125.3, 123.9, 122.4, 77.9, 49.2, 37.4, 12.5;

IR (thin film): 3049, 2978, 2936, 1730, 1715, 1552, 1377, 1246, 799, 779 cm^{-1};

HRMS (ESI-TOF) Calcd. for $C_{15}H_{16}NO_3$: 258.1130 $[M+H]^+$, Found: 258.1138.

(2*S*,3*R*)-2-Ethyl-4-nitro-3-phenylbutanal



The title compound was prepared from butyraldehyde and (*E*)-(2-nitrovinyl)benzene according to the general procedure.The enantiomeric ratio was determined by HPLC with an OD-H column at 220 nm (2-propanol:hexane = 5:95), 1.0 mL/min; major enantiomer t_{major} = 40.61 min, minor enantiomer t_{minor} = 51.74 min. The diastereomeric excess was determined by ^{1}H NMR. $[\alpha]_D^{20}$ = -99.5 (*c* = 1.1, $CHCl_3$, 589 nm).

R_f = 0.27 (ethyl acetate/hexane = 1:4);

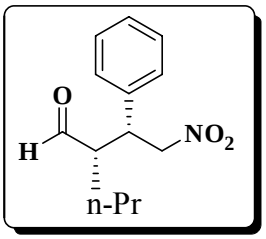
^{1}H NMR (300 MHz, $CDCl_3$): δ 9.71 (d, *J* = 2.5 Hz, 0.91H) (*syn* isomer), 9.47 (d, *J* = 2.5 Hz, 0.09H) (*anti* isomer), 7.36-7.27 (m, 3H), 7.20-7.17 (m, 2H), 4.80-4.59 (m, 2H), 3.84-3.75 (m, 1H), 2.72-2.64 (m, 1H), 1.55-1.43 (m, 2H), 1.21 (t, *J* = 7.5 Hz, 0.33H) (*syn* isomer), 0.82 (t, *J* = 7.5 Hz, 2.67H) (*anti* isomer);

^{13}C NMR (75 MHz, $CDCl_3$): δ 203.2, 136.8, 129.0, 128.2, 128.0, 78.5, 54.9, 42.6, 20.3, 10.6;

IR (thin film): 2967, 2936, 2878, 1720, 1553, 1456, 1379, 1244, 758, 702 cm^{-1};

HRMS (ESI-TOF) Calcd. for $C_{12}H_{16}NO_3$: 222.1130 $[M+H]^+$, Found: 222.1129.

(2*S*,3*R*)-2-Methyl-4-nitro-3-phenylbutanal



The title compound was prepared from *n*-pentanal and (*E*)-(2-nitrovinyl)benzene according to the general procedure. Both enantiomeric excess and diastereomeric excess were determined by HPLC with an OD-H column at 220 nm (2-propanol : hexane = 2 : 98), 1.0 mL/min; major enantiomer t_{major}= 37.02 min, minor enantiomer t_{minor} = 50.49 min. $[\alpha]_D^{20}$ = -25.2 (*c* = 1.3, $CHCl_3$, 589 nm).

R_f = 0.41 (ethyl acetate/hexane = 1:4);

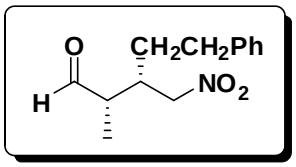
^{1}H NMR (300 MHz, $CDCl_3$): δ 9.71 (d, *J* = 2.80 Hz, 0.73H), (*syn* isomer), 9.48 (d, *J* = 2.8 Hz, 0.27H) (*anti* isomer), 7.38-7.27 (m, 3H), 7.19-7.16 (m, 2H), 4.87-4.61 (m, 2H), 3.84-3.74 (m, 1H), 2.77-2.60 (m, 1H), 1.76-1.09 (m, 4H), 0.93 (d, *J* = 7.0 Hz, 0.81H) (*anti* isomer), 0.81 (t, *J* = 7.0 Hz, 2.19H) (*syn* isomer);

^{13}C NMR (75 MHz, $CDCl_3$): δ 203.3, 136.8, 129.1, 128.2, 128.0, 78.4, 53.8, 43.2, 29.5, 19.8, 13.9;

IR (thin film): 3030, 2959, 2931, 2872, 1722, 1603, 1553, 1454, 1379, 764, 702 cm^{-1};

HRMS (ESI-TOF) Calcd. for $C_{13}H_{18}NO_3$: 236.1287 $[M+H]^+$, Found: 236.1290.

(2*S*,3*S*)-2-Methyl-3-(nitromethyl)-5-phenylpentanal



The title compound was prepared from *(E)*-(4-nitrobut-3-enyl)benzene and propionaldehyde according to general procedure. The enantiomeric excess was determined by HPLC with Chiralpak AD-H column at 210 nm (2-propanol:hexane = 2:98), 1 mL/min, t_{major} = 15.4 min, t_{minor} = 14.4 min, the diastereomeric ratio was determined by ^{1}H NMR. $[\alpha]_D^{20}$ = -2.2 (*c* = 2.7, $CHCl_3$, 589 nm);

R_f = 0.31 (ethyl acetate/hexane = 1:4);

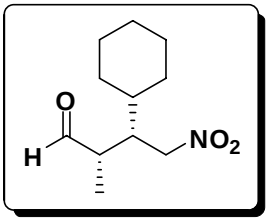
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.64 (d, *J* = 13.9 Hz, 0.43H) (*anti* isomer), 9.61 (d, *J* = 13.9 Hz, 0.57 H) (*syn* isomer), 7.32-7.14 (m, 5H), 4.56-4.51 (m, 1H), 4.79-4.42 (m, 1H), 2.81-2.57 (m, 4H), 1.87 (m, 2H), 1.17 (d, *J* = 17.2 Hz, 1.71H) (*syn* isomer), 0.95 (d, *J* = 17.2 Hz, 1.29H) (*anti* isomer);

^{13}C NMR (100 MHz, $CDCl_3$): δ 202.7, 140.5, 128.7, 128.2, 126.4, 76.6, 47.0, 36.8, 33.2, 30.3, 9.1;

IR (thin film): 3026, 2968, 2880, 1724, 1553, 1454, 700 cm^{-1};

HRMS (ESI-TOF) Calcd. for $C_{13}H_{18}NO_3$: 236.1287 $[M+H]^+$, Found: 236.1287.

(2*S*,3*S*)-3-Cyclohexyl-2-methyl-4-nitrobutanal



The title compound was prepared from *(E)*-(2-nitrovinyl)cyclohexane and propionaldehyde according to general procedure. The enantiomeric excess was determined by HPLC with Chiralpak AD-H column at 210 nm (2-propanol:hexane = 1:99), 1 mL/min, t_{major} = 17.0 min, t_{minor} = 19.1 min, the diastereomeric ratio was determined by ^{1}H NMR. $[\alpha]_D^{20}$ = -17.2 (*c* = 1.1, $CHCl_3$, 589 nm),

R_f = 0.40 (ethyl acetate/hexane = 1:4);

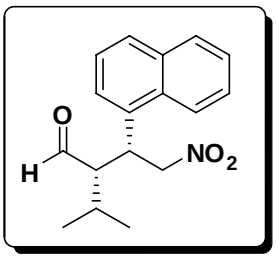
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.68 (s, 1H) (*anti* isomer + *syn* isomer), 4.59 (dd, *J* = 5.3, 13.4 Hz,1H), 4.38 (dd, *J* = 6.8, 13.4 Hz, 1H), 2.61-2.54 (m, 2H), 1.81-1.56 (m, 5H), 1.50-1.41 (m, 1H), 1.27-0.90 (m, 5H), 1.11 (d, *J* = 7.0 Hz, 1.2H) (*anti* isomer), 1.20 (d, *J* = 7.0 Hz, 1.8H) (*syn* isomer);

^{13}C NMR (125 MHz, $CDCl_3$): δ 203.0, 75.2, 46.2, 43.5, 38.0, 31.6, 29.9, 26.3, 26.3, 26.1, 9.9;

IR (neat): 2971, 2930, 2855, 1717, 1557, 1380, 1161, 1128, 950, 816, 735 cm^{-1};

HRMS (ESI-TOF): Calcd. for $C_{11}H_{20}NO_3$: 214.1443 $[M+H]^+$, Found: 214.1446.

(2*S*,3*R*)-2-Isopropyl-3-(naphthalen-1-yl)-4-nitrobutanal



The title compound was prepared from *(E)*-1-(2-nitrovinyl)naphthalene and isovaleraldehyde according to general procedure. The enantiomeric excess was determined by HPLC with Chiralpak AD-H column at 254 nm (2-propanol:hexane = 10:90), 1 mL/min, t_{major} = 13.7 min, t_{minor} = 16.8 min, the diastereomeric ratio was determined by ^{1}H NMR. $[\alpha]_D^{20}$ = -178 (*c* = 0.23, $CHCl_3$, 589 nm);

R_f = 0.27 (ethyl acetate/hexane = 1:4);

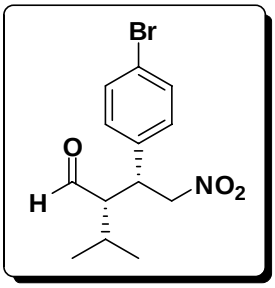
^{1}H NMR (300 MHz, $CDCl_3$): δ 10.0 (d, *J* = 2.4 Hz, 0.96H) (*syn* isomer), 9.76 (d, *J* = 2.4 Hz, 0.04H) (*anti* isomer), 8.18 (brs, 1H), 7.85 (dd, *J* = 24.0 Hz, 7.5 Hz,, 2H), 7.64-7.40 (m, 3H), 7.34 (d, *J* = 7.5 Hz, 1H), 4.89-4.79 (m, 2H), 3.09 (brs, 1H), 1.79 (s, 1H), 1.14 (d, *J* = 6.9 Hz, 3H), 0.84 (d, *J* = 6.9 Hz, 3H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 204.8, 134.3, 133.4, 131.7, 129.4, 128.6, 126.9, 126.1, 125.4, 124.1, 122.3, 78.4, 64.5, 28.2, 25.1, 21.7, 18.1;

IR (neat): 3048, 2963, 2739, 1715, 1557, 1512, 1464, 799, 779, 758 cm^{-1};

HRMS (ESI-TOF) Calcd. for $C_{17}H_{20}NO_3$: 286.1443 $[M+H]^+$, Found: 286.1441.

(2*S*,3*R*)-3-(4-Bromophenyl)-2-isopropyl-4-nitrobutanal



The title compound was prepared from *(E)*-1-bromo-4-(2-nitrovinyl)benzene and isovaleraldehyde according to general procedure. The enantiomeric excess was determined by HPLC with Chiralpak AD-H column at 254 nm (2-propanol:hexane = 10:90), 1 mL/min, t_{major} = 7.6 min, t_{minor} = 7.2 min, the diastereomeric ratio was determined by ^{1}H NMR. $[\alpha]_D^{20}$ = -30.2 (*c* = 0.27, $CHCl_3$, 589 nm);

R_f = 0.50 (ethyl acetate/hexane = 1:4);

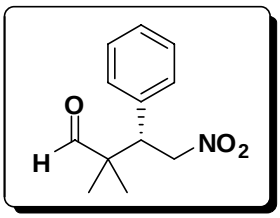
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.91 (d, *J* = 2.0 Hz, 0.98H) (*syn* isomer), 9.50 (d, *J* = 2.0 Hz, 0.02H) (*anti* isomer), 7.48 (d, *J* = 8.4 Hz, 2H), 7.07 (d, *J* = 8.4 Hz, 2H) 4.67 (dd, *J* = 12.7 Hz, 4.3 Hz, 1H), 4.54 (dd, *J* = 12.7 Hz, 4.3 Hz, 1H), 3.88 (dt, *J* = 10.5 Hz, 4.3 Hz, 1H), 2.75 (ddd, *J* = 6.0 Hz, 3.8 Hz, 2.1 Hz, 1H), 1.73-1.68 (m, 1H), 1.12 (d, *J* = 7.2 Hz, 3H), 0.86 (d, *J* = 7.2 Hz, 3H);

^{13}C NMR (100 MHz, $CHCl_3$) δ 203.9, 136.2, 132.4, 129.6, 122.1, 78.7, 58.5, 41.4, 28.0, 21.6, 17.0;

IR (neat): 2725, 1712 1566, 1338,1261, 821, 719 cm^{-1};

HRMS (ESI-TOF) Calcd. for $C_{13}H_{17}NO_3Br$: 314.0392 $[M+H]^+$, Found: 314.0384.

(*S*)-2,2-Dimethyl-4-nitro-3-phenylbutanal



The title compound was prepared from (*E*)-(2-nitrovinyl)benzene and isobutyraldehyde according to the general procedure. The enantiomeric ratio were determined by HPLC with Chiralpak OD-H column at 210 nm (2-propanol:hexane = 15:85),. 1 mL/min, t_{major} = 19.7 min, t_{minor} = 13.9 min, $[\alpha]_D^{20}$ = -4.3 (*c* = 1.6, $CHCl_3$, 589 nm).

R_f = 0.14 (ethyl acetate/hexane = 1:10);

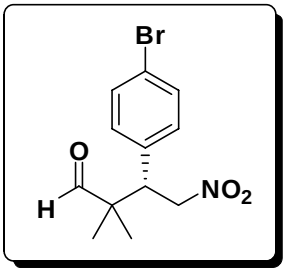
^{1}H NMR (300 MHz, $CDCl_3$): δ 9.53 (s, 1H), 7.36-7.26 (m, 3H), 7.21-7.18 (m, 2H), 4.85 (dd, *J* = 12.9 Hz, 11.2 Hz, 1H), 4.68 (dd, *J* = 12.9 Hz, 4.2 Hz, 1H), 3.78 (dd, *J* = 11.2 Hz, 4.2 Hz, 1H), 1.14 (s, 3H), 1.01 (s, 3H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 204.2, 135.4, 129.1, 128.7, 128.2, 76.6, 48.5, 48.2, 21.7, 18.9;

IR (thin film): 2922, 1728, 1556, 1454, 1379, 704 cm^{-1};

HRMS (ESI-TOF) Calcd. for $C_{12}H_{16}NO_3$: 222.1130 $[M+H]^+$, Found: 222.1123.

(*S*)-3-(4-Bromophenyl)-2,2-dimethyl-4-nitrobutanal



The title compound was prepared from *trans*-1-bromo-4-(2-nitrovinyl) benzene and isobutyraldehyde according to general procedure.The enantiomeric excess was determined by HPLC with Chiralpak AD-H column at 210 nm (2-propanol:hexane = 10:90), 1 mL/min; t_{major} = 11.5 min, t_{minor} = 9.3 min, $[\alpha]_D^{20}$ = -2.4 (*c* = 2.9, $CHCl_3$, 589 nm);

R_f = 0.24 (ethyl acetate/hexane = 1:4);

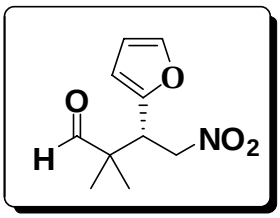
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.49 (s, 1H), 7.46 (d, *J* = 8.2 Hz, 2H), 7.08 (d, *J* = 8.2 Hz, 2H), 4.80 (t, *J* = 12.9, 1H), 4.67 (dd, *J* = 13.2 , 4.2 Hz, 1H), 3.75 (dd, *J* = 11.4 , 4.0 Hz, 1H), 1.12 (s, 3H), 1.00 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 203.8, 134.5, 131.9, 130.7, 122.2, 76.0, 48.1, 47.9, 21.7, 18.9;

IR (thin film): 2922, 2725, 1722, 1560, 1543, 1009, 880, 849, 721 cm^{-1};

HRMS (ESI-TOF) Calcd. for $C_{12}H_{15}NO_3Br$: 300.0235 $[M+H]^+$, Found: 300.0212.

(*S*)-3-(Furan-3-yl)-2,2-dimethyl-4-nitrobutanal



The title compound was prepared from *trans*-2-(2-nitrovinyl) furan, and isobutyraldehyde according to general procedure. The enantiomeric excess was determined by HPLC with Chiralpak OD-H column at 210 nm (2-propanol:hexane = 20:80), 1 mL/min, t_{major} = 12.5 min, t_{minor} = 8.3 min, $[\alpha]_D^{20}$ = +1.5 (*c* = 2.8, $CHCl_3$, 589 nm);

R_f = 0.33 (ethyl acetate/hexane = 1:4);

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.52 (s, 1H,), 7.37 (s, 1H), 6.31 (dd, *J* = 1.9, 1.2 Hz, 1H), 6.21 (d, *J* = 3.2 Hz, 1H), 4.75 (dd, *J* = 12.9, 11.0 Hz, 1H), 4.58 (dd, *J* = 12.9 Hz, 3.9 Hz, 1H), 3.92 (dd, *J* = 11.0 Hz, 3.9 Hz, 1H), 1.17 (s, 3H), 1.04 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 203.5, 149.8, 142.8, 110.4, 109.7, 74.9, 48.2, 42.3, 21.2, 19.1;

IR (thin film): 2972, 1726, 1557, 1470, 1433, 1377, 1148, 885, 818, 741 cm^{-1};

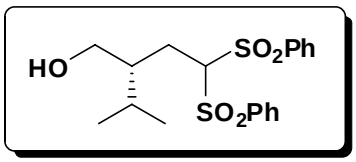
HRMS (ESI-TOF) Calcd. for $C_{10}H_{14}NO_4$: 212.0923 $[M+H]^+$, Found: 212.0926.

6.4.2 Application to Other Organocatalytic Enantioselective Reactions

General procedure for the catalytic asymmetric Michael addition of aldeydes to vinyl bis-sulfones

To a mixture of 1,1-bis(phenylsulfonyl)ethylene (30.8 mg, 0.1 mmol, 1 equiv.) and catalyst **12** (2.76 mg, 0.01 mmol, 0.1 equiv.), DMAP (1.2 mg, 0.01 mmol) in MeOH, was added isoveraldehyde (34.4 mg, 0.4 mmol, 4 equiv.) and stirred for 2 h. Then the solution was cooled to 0 ^{o}C and $NaBH_4$ was added to reduce the product to a primary alcohol. After the reaction was quenched with water, the mixture was extracted with ethyl acetate (3 × 5 mL) and the combined organic extracts were dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash column chromatography (ethyl acetate/hexane = 1:1) to afford the product **25** (31.7 mg, 80%) as a yellow light solid.

(*R*)-2-Isopropyl-4,4-bis(phenylsulfonyl)butan-1-ol (25)



The title compound was prepared from isoveraldehyde and 1,1-bis(phenylsulfonyl)ethylene according to the general procedures. The enantiomeric excess was determined by HPLC with Chiralpak AS-H column at 220 nm (2-propanol:hexane = 20:80), 0.5 mL/min, t_{major} = 40.0 min, t_{minor} = 47.0 min. $[\alpha]_D^{20}$ = +3.1 (*c* = 2.3, $CHCl_3$, 589 nm);

Yellow light solid;

R_f = 0.15 (ethyl acetate/hexane = 1:2);

1H NMR (300 MHz, $CDCl_3$): δ 7.98-7.93 (m, 4H), 7.72-7.67 (m, 2H), 7.59-7.54 (m, 4H), 5.22 (dd, *J* = 3.3, 7.2 Hz, 1H), 3.73 (dd, *J* = 3.3, 11.0 Hz, 1H), 3.51 (dd, *J* = 7.9, 11.0 Hz, 1H), 2.37-2.13 (m, 2H), 1.78-1.57 (m, 3H), 0.85 (d, *J* = 3.4 Hz, 3H), 0.82 (d, *J* = 3.4 Hz, 3H);

13C NMR (75 Hz, $CDCl_3$): δ 138.0, 137.7, 134.5, 129.7, 129.5, 129.1, 129.0, 81.6, 64.7, 44.4, 29.8, 26.1, 19.4, 19.2;

HRMS (ESI-TOF) Calcd. for $C_{19}H_{25}SO_2$: 333.1347 $[M+H]^+$, Found: 333.1342.

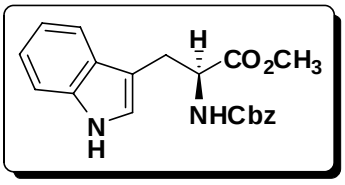
6.5 A NEW CLASS OF STRUCTURALLY RIGID TRICYCLIC CHIRAL LIGANDS FOR ASYMMETRIC SYNTHESIS

General procedure for the enantioselective reduction of ketones

To an oven-dried 10 mL round-bottom flask equipped with a magnetic stirring bar was added new chiral ligand **51a** (0.07 mmol, 0.10 equiv.). The ligand was azeotropically dried with anhydrous THF (2 × 2 mL) prior to the addition of 1.5 mL of THF. Then $BH_3 \cdot Me_2S$ (0.87 mmol, 10 mol/L, 1.2 equiv.) was added under nitrogen at room temperature and the mixture was stirred at 80 ˚C for 3 h. A solution of ketone (0.7 mmol, 1 equiv.) in dry THF (0.5 mL) was added dropwise by syringe pump over a period of 1 h at reflux temperature. Then the reaction mixture was cooled and quenched by dropwise addition of methanol (5 mL). After concentration by rotatory evaporation, the product was purified by column chromatography on silica gel (ethyl acetate/hexane = 1:5) to afford the corresponding secondary alcohol. The enantiomeric excess was determined by chiral HPLC analysis employing a Daicel Chiracel column.

Characterization of ligands

(*S*)-*N*-benzyloxycarbonyl-L-tryptophan methyl ester (**46**)



To a stirred suspension of (*S*)-*N*-Benzyloxycarbonyl-L-tryptophan **13** (2.45 g, 7.2 mmol, 1 equiv.) in 10 mL anhydrous CH_2Cl_2, was added DMAP (0.1 g, 0.82 mmol, 0.1 equiv.) and methanol (0.28 g, 11.8 mmol, 1.6 equiv.). DCC (1.48 g, 7.2 mmol, 1 equiv.) in CH_2Cl_2 solution was slowly added to the mixture at 0 ˚C and then it was allowed to warm to room temperature and stirred for 2 h. After twice filtration and evaporation, the residue was purified by flash column chromatography (ethyl acetate/hexane, 1:4-1:2) to afford the desired product (*S*)-**46** as a colourless oil (2.5 g, 98%). $[\alpha]_D^{20} = 45.9$ (*c* = 1.1, $CHCl_3$, 589 nm).

R_f = 0.19 (ethyl acetate/hexane = 1:2);

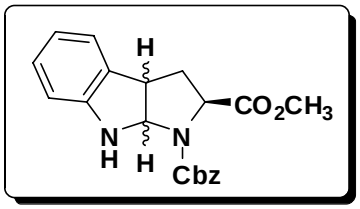
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.94 (br, 1H), 7.49 (d, *J* = 7.7 Hz, 1H), 7.25-6.98 (m, 9H), 6.81 (s, 1H), 5.84 (d, *J* = 8.7 Hz, 1H), 4.98 (d, *J* = 3.2 Hz, 2H), 4.68 (q, *J* = 7.3 Hz,1H), 3.25 (s, 3H), 3.21 (m, 2H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 172.2, 155.9, 141.8, 136.8, 134.9, 128.6, 127.8, 126.9, 123.4, 122.3, 120.0, 118.4, 112.1, 109.4, 67.0, 65.1, 55.1;

FTIR (KBr, neat): 1707, 1508, 1456, 1436, 1215, 742 cm^{-1};

HRMS (EI) calcd. for $C_{20}H_{20}O_4N_2$ 352.1418, found $[M]^+$ 352.1425.

(2*S*)-1-Benzyl-2-methyl-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole-1,2(2*H*)-dicarboxylate (**47**)



N-Benzyloxycarbonyl-L-tryptophan methyl ester (*S*)-**46** (1.34 g, 3.8 mmol) was dissolved in 10 mL TFA and stirred for two days, then the solution was added dropwise to a vigorously stirred two phase system consisting of saturated 100 mL Na_2CO_3 and 100 mL CH_2Cl_2. The two phases were separated and the aqueous solution was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with brine, dried with anhydrous $MgSO_4$ and purified with flash column chromatography (ethyl acetate/hexane, 1:7-1:4) to give the product as a colorless oil **47** (0.8 g, 60%).

Major isomer:

R_f = 0.32 (ethyl acetate/hexane = 1:4);

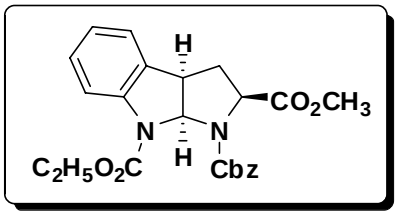
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.24 (m, 5H), 7.05-6.99 (m, 2H), 6.68 (q, *J* = 8.9 Hz, 1H), 6.60 (d, *J* = 7.6 Hz, 1H), 5.59 (t, *J* = 6.6 Hz, 1H), 5.30-5.09 (m, 2H), 3.92 (q, *J* = 6.5 Hz, 1H), 3.19 (s, 1H, CH_3), 3.10 (s, 2H, CH_3), 2.65-2.54 (m, 2H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 154.6, 150.1, 136.2, 129.0, 128.6, 128.4, 127.6, 127.5, 127.4, 127.0, 124.0, 118.7, 109.1, 77.4, 67.0, 59.1, 51.9, 45.0, 34.0;

FTIR (KBr, neat): 1732, 1712, 1602 cm^{-1};

HRMS (EI) calcd. for $C_{20}H_{20}O_4N_2$ 352.1418, found $[M]^+$ 352.1413.

(2*S*,3a*R*,8a*S*)-1-Benzyl-8-ethyl-2-methyl-3,3a-dihydropyrrolo[2,3-*b*]indole-1,2,8(2*H*,8a*H*)-tricarboxylate (48a)



47 (0.8 g, 2.27 mmol) was dissolved in 5 mL THF, then Na_2CO_3 (0.36 g, 3.40 mmol, 1.5 equiv.) in 5 mL H_2O was added. Ethyl chloroformate (0.27 mL, 2.72 mmol, 1.2 equiv.) was slowly added to the solution at 0 ˚C and stirred overnight. Then 10 mL water was added and the aqueous solution was extracted with ethyl acetate (3 × 5 mL). The combined organic extracts were washed with brine, dried with anhydrous $MgSO_4$ and purified by flash column chromatography (ethyl acetate/hexane, 1:4-1:2) to afford the desired product as a colorless oil (0.78 g, 81%).

$[\alpha]_D^{20}$ = +4.5 (*c* = 5.1, $CHCl_3$, 589 nm);

R_f = 0.43 (ethyl acetate/hexane = 1:2);

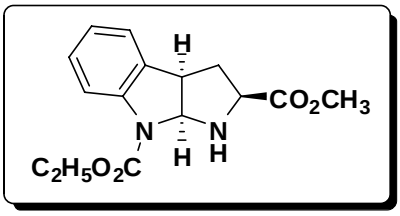
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 (d, *J* = 7.5 Hz, 1H), 7.38-7.10 (m, 7H), 6.99 (t, *J* = 7.4 Hz, 1H), 6.49 (d, *J* = 6.5 Hz, 1H), 5.19 (s, 2H), 4.67 (d, *J* = 8.5 Hz, 1H), 4.33–4.17 (br, 1H), 4.00 (t, *J* = 7.1 Hz,1H), 3.13 (s, 3H), 2.65–2.43 (m, 2H),1.35-1.23 (br, 3H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1, 153.6, 152.9, 142.2, 135.9, 130.8, 128.2, 128.0, 127.9, 127.7, 127.5, 127.5, 123.5, 122.9, 116.2, 77.1, 66.7, 61.3, 58.9, 51.4, 44.5, 33.2, 13.9;

FTIR (KBr, neat): 1728, 1712, 1697, 1604, 1483 cm^{-1};

HRMS (EI) calcd. for $C_{23}H_{24}O_6N_2$ 424.1629, found $[M]^+$ 424.1619.

(2*S*,3a*R*,8a*S*)-8-Ethyl-2-methyl-1,2,3,3a-tetrahydropyrrolo[2,3-*b*]indole-2,8(8a*H*)-dicarboxylate (50a)



48a (0.77 g, 1.82 mmol) was dissolved in 5 mL CH_3OH and 10% Pd/C (0.19 g, 0.18 mmol, 0.1 equiv.) was added to the solution and stirred for 12 h under H_2 balloon at room temprature. When TLC showed full depletion of the starting material, the suspension was filtered on celite and the filtrate was evaporated. The residue was purified by flash column chromatography (ethyl acetate/hexane, 1:4-1:2) to give the product as a colorless oil (0.47 g, 89%).

$[\alpha]_D^{20}$ = 42.6 (*c* = 1.4, $CHCl_3$, 589 nm);

R_f = 0.62 (ethyl acetate/hexane = 1:2);

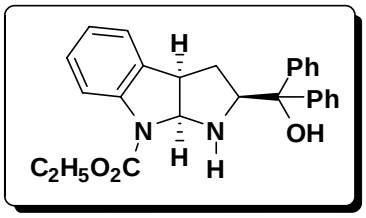
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.86 (d, *J* = 7.5 Hz, 0.5 H), 7.47-7.27 (m, 0.5H), 7.24 (d, *J* = 7.4 Hz, 2H), 7.05 (t, *J* = 7.5 Hz, 1H), 5.80 (d, *J* = 6.8 Hz, 1H), 4.45 (q, *J* = 6.6 Hz, 2H), 3.99 (d, *J* = 7.6 Hz, 2H), 3.41 (s, 3H), 2.73-2.64 (m, 1H), 2.49 (d, *J* = 11.2 Hz, 1H), 1.50 (t, *J* = 6.0 Hz, 3H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 174.1, 152.5, 128.7, 127.8, 126.1, 124.5, 122.8, 114.3, 78.4, 60.9, 57.8, 50.7, 43.7, 34.8, 15.1;

FTIR (KBr, neat): 1732, 1712, 1602, 1487 cm^{-1};

HRMS (EI) calcd. for $C_{15}H_{18}O_4N_2$ 290.1261, found $[M]^+$ 290.1249.

(2*S*,3a*R*,8a*S*)-Ethyl 2-(hydroxydiphenylmethyl)-1,2,3,3a-tetrahydropyrrolo[2,3-*b*]indole-8(8a*H*)-carboxylate (51a)



To a solution of **50a** (0.48 g, 1.65 mmol) in 5 mL THF was added dropwise 2M phenyl magnesium chloride (2.1 mL, 4.2 mmol, 2.5 equiv.) in THF solution at 0 ^{o}C and the mixture was allowed to stir for 0.5 h prior to addition of 5 mL water. The two phases were separated and the aqueous solution was extracted with ethyl acetate (3 × 5 mL). The combined organic extracts were washed with brine, dried with anhydrous $MgSO_4$ and purified by flash column chromatography (ethyl acetate/hexane, 1:10) to give the product as a colorless solid (205 mg, 30%).

$[\alpha]_D^{20}$ = -78.3 (*c* = 0.6, $CHCl_3$, 589 nm);

R_f = 0.85 (ethyl acetate/hexane = 1:6);

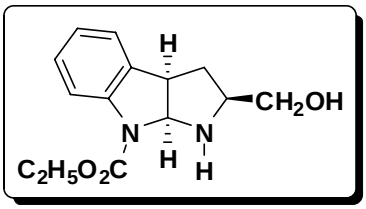
^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.56 (d, *J* = 7.6 Hz, 2H), 7.44 (d, *J* = 7.4 Hz, 2H), 7.32-7.14 (m, 7H), 7.03 (d, *J* = 7.2 Hz, 1H), 6.94 (t, *J* = 9.3 Hz, 1H), 5.65 (br, 1H), 4.47 (t, *J* = 6.6 Hz, 1H), 4.26 (br, 2H), 4.04 (br, 1H), 3.74 (q, *J* = 7.2 Hz, 1H), 2.04 (br, 1H), 1.84-1.76 (m, 1H), 1.43-1.32 (m, 1H), 1.27-1.11 (m, 3H);

^{13}C-NMR (100 MHz, $CDCl_3$): δ 154.0, 147.2, 144.6, 128.4, 128.0, 127.9, 126.9, 126.6, 125.7, 125.3, 124.6, 124.2, 122.9, 114.9, 75.7, 63.8, 44.1, 32.8, 22.7, 14.1;

FTIR (KBr, neat): 1699, 1487, 1381, 1307 cm^{-1};

HRMS (EI) calcd. for $C_{26}H_{26}O_3N_2$ 414.1938, found $[M]^+$ 414.1915.

(2*S*,3a*R*,8a*S*)-Ethyl 2-(hydroxymethyl)-1,2,3,3a-tetrahydropyrrolo[2,3-*b*]indole-8(8a*H*)-carboxylate (51b)



Colorless oil (86%);

$[\alpha]_D^{20}$ = -10.3 (*c* = 1.8, $CHCl_3$, 589 nm);

R_f = 0.15 (ethyl acetate/hexane = 1:1);

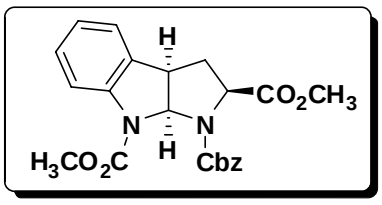
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.80 (br, 0.55H), 7.43 (br, 0.35H), 7.17 (t, *J* = 7.0 Hz, 1H), 7.11 (d, *J* = 7.4 Hz, 1H), 6.96 (t, *J* = 7.4 Hz, 1H), 5.64 (br, 1H), 4.29 (br, 2H), 3.82 (d, *J* = 5.5 Hz, 1H), 3.42 (d, *J* = 5.1 Hz, 1H), 3.31 (br, 1H), 3.11 (dd, *J* = 10.5 Hz, 7.3 Hz, 1H), 2.39-2.34 (m, 1H), 1.68-1.63 (m, 1H), 1.26 (br, 3H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 152.8, 140.8, 133.6, 127.8, 123.9, 122.8, 114.7, 78.2, 64.6, 61.3, 58.8, 44.0, 34.3, 14.5;

FTIR (neat): 3368, 2932, 2870, 1697, 1603, 1487, 1381, 1310, 1055, 752 cm^{-1};

HRMS (ESI) calcd. for $C_{14}H_{19}N_2O_3$ 263.1396 $[M+H]^+$, found 263.1396.

(2*S*,3a*R*,8a*S*)-1-Benzyl 2,8-dimethyl 3,3a-dihydropyrrolo[2,3-*b*]indole-1,2,8(2*H*,8a*H*)-tricarboxylate (48c)



Colorless oil (82%);

$[\alpha]_D^{20}$ = +11.5 (*c* = 2.0, $CHCl_3$, 589 nm);

R_f = 0.31 (ethyl acetate/hexane = 1:4);

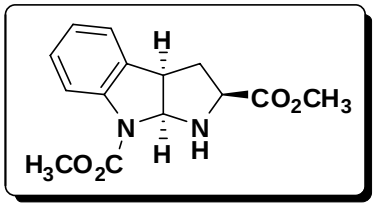
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, *J* = 7.2 Hz, 1H), 7.33-7.29 (m, 5H), 7.19 (t, *J* = 7.8 Hz, 1H), 7.09 (d, *J* = 7.4 Hz, 1H), 6.97 (t, *J* = 7.4 Hz, 1H), 6.42 (d, *J* = 5.9 Hz, 1H), 5.20-5.12 (m, 2H), 4.64 (d, *J* = 8.4 Hz, 1H), 3.96 (t, *J* = 6.8 Hz, 1H), 3.52 (br, 3H), 3.13 (s, 3H), 2.62-2.47 (m, 2H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2, 170.6, 153.5, 142.3, 135.9, 130.8, 128.3, 128.2, 128.1, 127.7, 123.6, 123.2, 116.3, 67.0, 59.9, 59.1, 52.2, 51.6, 44.8, 33.6, 20.3, 13.7;

FTIR (neat): 3401, 1722, 1713, 1605, 1483, 1416, 1263, 1047, 976, 752 cm^{-1};

HRMS (ESI) calcd. for $C_{22}H_{23}N_2O_6$: 411.1556 $[M+H]^+$, found 411.1553.

(2*S*,3a*R*,8a*S*)-Dimethyl 1,2,3,3a-tetrahydropyrrolo[2,3-*b*]indole-2,8(8a*H*)-dicarboxylate (50c)



Colorless oil (91%);

$[\alpha]_D^{20}$ = -24.1 (*c* = 1.5, $CHCl_3$, 589 nm);

R_f = 0.17 (ethyl acetate/hexane = 1:4);

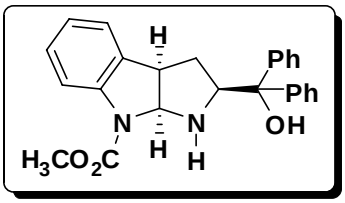
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76 (d, *J* = 7.2 Hz, 0.6H), *δ* 7.32 (d, *J* = 7.4 Hz, 0.4H), *δ* 7.12 (d, *J* = 7.3 Hz, 2H), 6.94 (t, *J* = 7.3 Hz, 1H), 5.65 (d, *J* = 6.8 Hz, 1H), 4.11 (br, 5H), 3.29 (s, 3H), 2.62-2.52 (m, 1H), 2.38-2.34 (m, 1H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 173.8, 152.8, 141.7, 131.8, 127.8, 124.0, 122.5, 113.9, 78.2, 58.3, 57.4, 43.4, 35.8;

FTIR (neat): 3387, 2955, 2924, 1715, 1603, 1487, 1445, 1381, 1072, 752 cm^{-1};

HRMS (ESI) calcd. for $C_{14}H_{17}N_2O_4$ 277.1188 $[M+H]^+$, found 277.1182.

(2*S*,3a*R*,8a*S*)-Methyl 2-(hydroxydiphenylmethyl)-1,2,3,3a-tetrahydropyrrolo[2,3-*b*]indole-8(8a*H*)-carboxylate (51c)



Colorless solid (36%);

$[\alpha]_D^{20}$ = -20.0 (*c* = 0.3, $CHCl_3$, 589 nm);

R_f = 0.52 (ethyl acetate/hexane = 1:5);

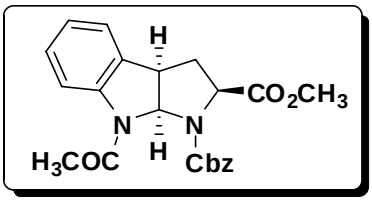
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 (br, 0.5H), 7.49 (d, *J* = 7.5 Hz, 2H), *δ* 7.36 (d, *J* = 7.2 Hz, 2H), 7.25-7.05 (m, 8H), 6.95 (d, *J* = 7.2 Hz, 1H), 6.87 (t, *J* = 7.5 Hz, 1H), 5.56 (br, 1H), 4.41 (dd, *J* = 9.6, 6.3 Hz, 1H), 3.95 (s, 1H), 3.71-3.62 (m, 4H), 2.80 (br, 1H), 1.98-1.89 (m, 1H), 1.76-1.66 (m, 1H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 153.3, 147.0, 144.6, 140.7, 133.6, 128.5, 128.0, 127.9, 126.9, 126.5, 125.7, 125.2, 123.0, 114.8, 77.8, 75.6, 63.8, 52.7, 43.7, 32.6;

FTIR (neat): 3414, 3051, 1719, 1601, 1489, 1271, 1068, 758 cm^{-1};

HRMS (ESI) calcd. for $C_{25}H_{25}N_2O_3$ 401.1865 $[M+H]^+$, found 401.1871.

(2*S*,3a*R*,8a*R*)-1-Benzyl 2-methyl 8-acetyl-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole-1,2(2*H*)-dicarboxylate (48d)



Colorless oil (82%);

$[\alpha]_D^{20}$ = +30.0 (*c* = 0.8, $CHCl_3$, 589 nm);

R_f = 0.08 (ethyl acetate/hexane = 1:4);

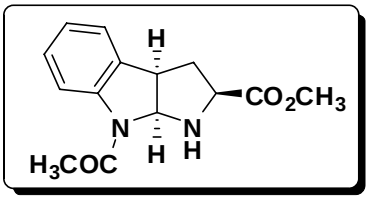
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95 (s, 1H), 7.30-7.18 (m, 6H), 7.11 (d, *J* = 7.2 Hz, 1H), 7.02 (t, *J* = 7.4 Hz, 1H), 6.20 (s, 1H), 5.12 (s, 2H), 4.60 (d, *J* = 8.5 Hz, 1H), 4.01 (t, *J* = 6.1 Hz, 1H), 3.06 (s, 3H), 2.66 (s, 3H), 2.57-2.48 (m, 2H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1, 170.3, 154.1, 143.0, 135.7, 131.0, 128.5, 128.0, 127.6, 124.5, 124.0, 123.6, 118.7, 78.2, 67.3, 59.3, 51.8, 45.0, 33.3, 23.3;

FTIR (neat): 3425, 2952, 2854, 1716, 1666, 1603, 1479, 1410, 754, 734 cm^{-1};

HRMS (ESI) calcd. for $C_{22}H_{23}N_2O_5$ 395.1607 $[M+H]^+$, found 395.1608.

(2*S*,3a*R*,8a*S*)-Methyl 8-acetyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylate (50d)



Colorless oil (88%);

$[\alpha]_D^{20}$ = -39.6 (*c* = 0.9, $CHCl_3$, 589 nm);

R_f = 0.08 (ethyl acetate/hexane = 1:1);

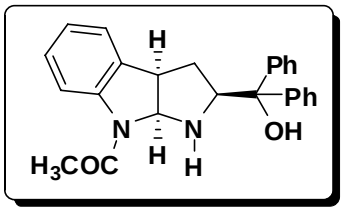
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10 (d, *J* = 8.0 Hz, 1H), 7.23-7.12 (m, 2H), 6.99 (t, *J* = 11.3 Hz, 1H), 5.63 (d, *J* = 7.3 Hz, 1H), 3.97-3.80 (m, 2H), 3.27 (s, 3H), 2.66-2.50 (m, 2H), 2.37 (s, 3H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 173.5, 168.7, 142.3, 131.9, 128.1, 124.1, 123.8, 116.7, 79.3, 59.2, 51.8, 44.8, 35.7 23.7;

HRMS (ESI) calcd. for $C_{14}H_{17}N_2O_3$ 261.1239 $[M+H]^+$, found 261.1228

FTIR (neat): 3345, 2952, 2875, 1733, 1652, 1482, 1394, 1130, 920, 755, 733 cm^{-1};

1-((2*S*,3a*R*,8a*S*)-2-(Hydroxydiphenylmethyl)-1,2,3,3a-tetrahydropyrrolo[2,3-*b*]indol-8(8a*H*)-yl)ethanone (51d)



Yellowish solid (28%);

$[\alpha]_D^{20}$ = -52.6 (*c* = 0.7, $CHCl_3$, 589 nm);

R_f = 0.45 (ethyl acetate/hexane = 1:1);

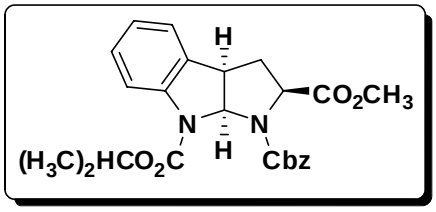
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.16 (d, *J* = 7.5 Hz, 1H), *δ* 7.54 (d, *J* = 6.0 Hz, 2H), *δ* 7.44 (d, *J* = 7.5 Hz, 2H), 7.28-6.99 (m, 8H), 5.80 (d, *J* = 8.4 Hz, 1H), 4.58-4.47 (m, 1H), 3.91-3.68 (m, 1H), 2.41 (s, 3H), 2.18-1.99 (m, 1H), 1.90-1.71 (m, 1H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 169.1, 146.8, 144.6, 141.0, 139.6, 136.2, 133.5, 128.5, 128.0, 126.9, 125.6, 125.2, 123.6, 117.2, 113.8, 78.8, 75.6, 63.6, 42.0, 32.4, 24.9;

FTIR (neat): 3054, 1653, 1482, 1265, 737, 705 cm^{-1};

HRMS (ESI) calcd. for $C_{25}H_{25}N_2O_2$ 385.1916 $[M+H]^+$, found 385.1913.

(2*S*,3a*R*,8a*S*)-1-Benzyl 8-isopropyl 2-methyl 3,3a-dihydropyrrolo[2,3-*b*]indole-1,2,8(2*H*,8a*H*)-tricarboxylate (48e)



Colorless oil (87%);

$[\alpha]_D^{20}$ = +2.7 (*c* = 0.8, $CHCl_3$, 589 nm);

R_f = 0.41 (ethyl acetate/hexane = 1:4);

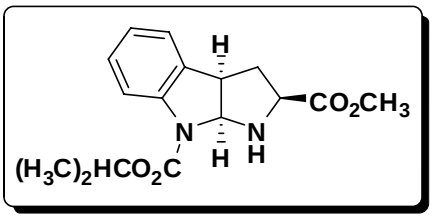
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (d, *J* = 7.4 Hz, 1H), 7.33-7.26 (m, 6H), *δ* 7.21 (t, *J* = 7.7 Hz, 1H), 7.11 (d, *J* = 7.4 Hz, 1H), 6.99 (t, *J* = 6.8 Hz, 1H), 6.49 (d, *J* = 6.5 Hz, 1H), 5.18 (br, 2H), 4.65 (d, *J* = 8.6 Hz, 1H), 4.00 (t, *J* = 6.7 Hz, 1H), 3.12 (s, 3H), 2.66-2.48 (m, 2H), 1.97 (br, 1H), 1.98-1.89 (m, 1H), 0.95 (d, *J* = 5.8 Hz, 6H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 171.6, 153.5, 142.6, 136.3, 131.1, 128.5, 128.3, 127.9, 123.9, 123.4, 116.8, 72.1, 67.2, 59.3, 51.9, 44.7, 34.1, 27.7, 19.1;

FTIR (neat): 2957, 1722, 1713, 1605, 1483, 1416, 1263, 1047, 975, 752 cm^{-1};

HRMS (ESI) calcd. for $C_{24}H_{27}N_2O_6$: 439.1869 $[M+H]^+$, found 439.1857.

(2*S*,3a*R*,8a*S*)-8-Isopropyl 2-methyl 1,2,3,3a-tetrahydropyrrolo[2,3-*b*]indole-2,8(8a*H*)-dicarboxylate (50e)



Colorless oil (89%);

$[\alpha]_D^{20}$ = -20.7 (*c* = 1.9, $CHCl_3$, 589 nm);

R_f = 0.42 (ethyl acetate/hexane = 1:4);

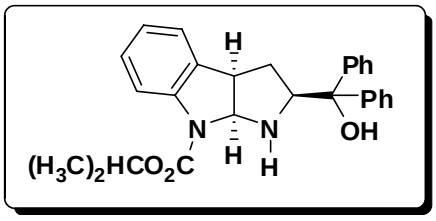
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 6.8 Hz, 0.6H), 7.38 (d, *J* = 6.8 Hz, 0.4H), 7.18-7.13 (m, 2H), 6.98-6.93 (m, 1H), 5.75-5.68 (m, 1H), 5.22-5.13 (m, 1H), 3.91-3.89 (m, 2H), 3.32 (s, 3H), 2.66-2.57 (m, 1H), 2.47-2.39 (m, 1H), 1.38-1.32 (m, 6H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.4, 152.7, 142.0, 132.4, 128.5, 124.3, 121.8, 113.8, 79.2, 68.1, 58.1, 52.1, 43.2, 35.6, 30.6, 21.5;

FTIR (neat): 3387, 2959, 1713, 1694, 1603, 1487, 1385, 1047, 970, 750 cm^{-1};

HRMS (ESI) calcd. for $C_{16}H_{21}N_2O_4$ 305.1501 $[M+H]^+$, found 305.1506.

(2*S*,3a*R*,8a*S*)-Isopropyl 2-(hydroxydiphenylmethyl)-1,2,3,3a-tetrahydropyrrolo[2,3-*b*]indole-8(8a*H*)-carboxylate (51e)



Colorless solid (29%);

$[\alpha]_D^{20}$ = -55.0 (*c* = 0.2, $CHCl_3$, 589 nm);

R_f = 0.38 (ethyl acetate/hexane = 1:5);

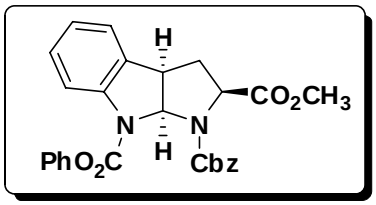
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57 (d, *J* = 7.7 Hz, 2H), *δ* 7.44 (d, *J* = 7.4 Hz, 2H), 7.36-7.14 (m, 8H), 7.05 (d, *J* = 7.3 Hz, 1H), 6.96 (t, *J* = 7.4 Hz, 1H), 5.70 (br, 1H), 4.50 (dd, *J* = 9.7, 6.2 Hz, 1H), 3.83-3.74 (m, 3H), 2.08-1.99 (m, 1H), 1.85-1.75 (m, 1H), 1.56 (s, 6H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 162.6, 149.8, 144.8, 137.7, 128.5, 128.0, 126.9, 126.6, 125.7, 125.2, 123.1, 121.5, 114.9, 75.8, 64.0, 52.8, 32.8, 30.3, 22.8, 14.3;

FTIR (neat): 3019, 1722, 1713, 1605, 1483, 1416, 1218, 928, 772 cm^{-1};

HRMS (ESI) calcd. for $C_{27}H_{29}N_2O_3$ 429.2178 $[M+H]^+$, found 429.2184.

(2*S*,3a*R*,8a*S*)-1-Benzyl 2-methyl 8-phenyl 3,3a-dihydropyrrolo[2,3-*b*]indole-1,2,8(2*H*,8a*H*)-tricarboxylate (48f)



Colorless oil (87%);

$[\alpha]_D^{20}$ = +5.2 (*c* = 4.4, $CHCl_3$, 589 nm);

R_f = 0.26 (ethyl acetate/hexane = 1:2);

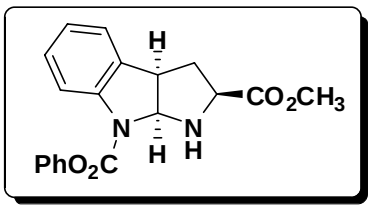
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (s, 1H), 7.37 (t, *J* = 7.2 Hz, 1H), 7.28-7.21 (m, 7H), 7.17 (d, *J* = 7.2 Hz, 2H), 7.05 (t, *J* = 7.6 Hz, 1H), 6.64 (d, *J* = 5.6 Hz, 1H), 5.22 (d, *J* = 11.6 Hz, 1H), 5.10 (s, 1H), 4.73 (s, 1H), 4.10 (t, *J* = 6.8 Hz, 1H), 3.17 (s, 3H), 2.69-2.55 (m, 2H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6, 151.7, 150.8, 142.2, 136.1, 131.1, 129.3, 129.0, 128.8, 128.4, 128.2, 128.0, 126.1, 125.6, 125.3, 124.0, 123.9, 121.7, 116.7, 77.4, 67.5, 59.5, 52.1, 45.1, 34.3;

FTIR (neat): 3429, 2951, 1726, 1714, 1605, 1481, 1411, 911, 755, 732 cm^{-1};

HRMS (ESI) calcd. for $C_{27}H_{25}N_2O_6$ 473.1713 $[M+H]^+$, found 473.1711

(2*S*,3a*R*,8a*S*)-2-Methyl 8-phenyl 1,2,3,3a-tetrahydropyrrolo[2,3-*b*]indole-2,8(8a*H*)-dicarboxylate (50f)



Colorless oil (89%);

$[\alpha]_D^{20}$ = -75.2 (*c* = 1.2, $CHCl_3$, 589 nm);

R_f = 0.29 (ethyl acetate/hexane = 1:4);

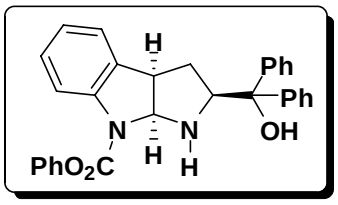
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, *J* = 8.0 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.27-7.22 (m, 3H), 7.17 (t, *J* = 7.6 Hz, 2H), 6.99 (t, *J* = 7.6 Hz, 1H), 5.88 (d, *J* = 7.6 Hz, 1H), 3.91 (d, *J* = 7.6 Hz, 1H), 3.55 (s, 1H), 3.33 (s, 3H), 2.64-2.56 (m, 1H), 2.41-2.35 (m, 1H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.9, 150.5, 141.3, 140.2, 132.9, 132.2, 129.2, 128.1, 125.6, 124.8, 124.2, 123.3, 121.7, 114.4, 78.8, 58.4, 51.9, 43.6, 35.9;

FTIR (neat): 3393, 3020, 1728, 1603, 1484, 1384, 1216, 756 cm^{-1};

HRMS (ESI) calcd. for $C_{19}H_{19}N_2O_2$ 307.1447 $[M+H]^+$, found 307.1437.

(2*S*,3a*R*,8a*S*)-Phenyl 2-(hydroxydiphenylmethyl)-1,2,3,3a-tetrahydropyrrolo[2,3-*b*]indole-8(8a*H*)-carboxylate (51f)



Colorless solid (21%);

$[\alpha]_D^{20}$ = -1.8 (*c* = 0.6, $CHCl_3$, 589 nm);

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57 (d, *J* = 7.5 Hz, 2H), 7.44 (d, *J* = 7.5 Hz, 2H), 7.34-7.13 (m, 8H), 7.05 (d, *J* = 7.5 Hz, 1H), 6.96 (t, *J* = 7.2 Hz, 1H), 5.67 (d, *J* = 8.4 Hz, 1H), 4.50 (dd, *J* = 9.6 Hz, 6.0 Hz, 1H), 3.82-3.74 (m, 3H), 2.08-1.98 (m, 1H), 1.85-1.75 (m, 1H);

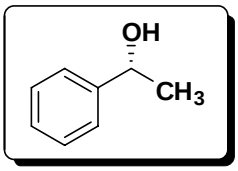
^{13}C NMR (75 MHz, $CDCl_3$): δ 147.1, 144.7, 128.5, 128.0, 126.9, 126.6, 125.8, 125.2, 123.1, 114.9, 77.2, 75.7, 63.8, 52.7, 32.6;

FTIR (neat): 3370, 2926, 1606, 1596, 1450, 1472, 1266, 756 cm^{-1};

HRMS (ESI) calcd. for $C_{30}H_{27}N_2O_3$ 463.2022 $[M+H]^+$, found 463.2030.

Characterization of Chiral Alcohol

(*R*)-1-Phenylethanol



Colorless oil, 98% yield, 81 % *ee*, $[\alpha]_D^{25}$ = -14.9 (*c* = 1.0, CH_2Cl_2, 589 nm);

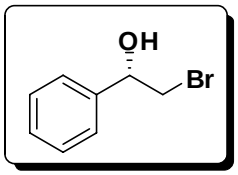
R_f = 0.41 (ethyl acetate/hexane = 1/5);

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28-7.17 (m, 5H), 4.72 (q, *J* = 6.5 Hz, 1H), 3.23 (br, 1H), 1.37 (d, *J* = 6.5 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 145.7, 128.2, 127.1, 125.3, 70.0, 24.9;

The enantiomeric excess was determined by chiral HPLC analysis, employing a Dacicel Chiralcel OD column (hexane : *i*-propanol = 95:5, 1 mL/min): t_1 = 8.66 min (major), t_2 =10.33 min (minor).

(*S*)-2-Bromo-1-phenylethanol



Colorless oil, 95% yield, 92% *ee*, $[\alpha]_D^{25}$ = +55.3 (*c* = 0.5, CH_2Cl_2, 589 nm);

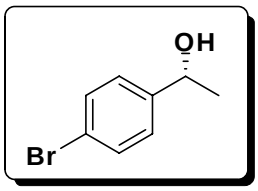
R_f = 0.50 (ethyl acetate/hexane = 1/4);

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.32 (m, 5H), 4.92 (d, *J* = 8.6 Hz, 1H), 3.65-3.51 (m, 2H), 2.70 (br, 1H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 140.3, 128.7, 128.4, 125.9, 73.8, 40.2;

The enantiomeric excess was determined by chiral HPLC analysis, employing a Dacicel Chiralcel OD column (hexane : *i*-propanol = 95 : 5, 0.5 mL/min): t_1 = 23.30 min (major), t_2 = 27.13 min (minor).

(*R*)-1-(4-Bromophenyl)-ethanol



Colorless oil, 94% yield, 76% *ee*, $[\alpha]_D^{25}$ = +18.0 (*c* = 3.0, CH_2Cl_2, 589 nm);

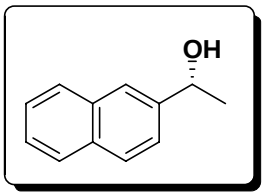
R_f = 0.33 (ethyl acetate/hexane = 1/4);

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 7.6 Hz, 2H), 4.87 (q, *J* = 3.7 Hz, 1H), 1.47 (d, *J* = 6.4 Hz, 3H*);*

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.8, 131.6, 127.1, 121.2, 69.8, 25.2;

The enantiomeric excess determined by chiral HPLC analysis, employing chiral HPLC analysis, employing a Dacicel Chiralcel OB-H column (hexane : *i*-propanol 95 : 5, 0.5 mL/min): t_1 = 7.57 min (minor), t_2 = 8.38 min (major).

(*R*)-1-(2-Naphthyl)-ethanol



Colorless oil, 99% yield, 89% *ee*, $[\alpha]_D^{25}$ = +21.9 (*c* =2.2, CH_2Cl_2, 589 nm);

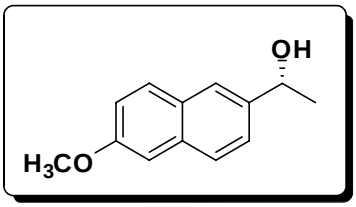
R_f = 0.38 (ethyl acetate/hexane = 1/4);

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77-7.71 (m, 4H), 7.44-7.41 (m, 3H), 4.95 (q, *J* = 6.4 Hz, 1H), 2.42 (brs, 1H), 1.50 (d, *J* = 6.5 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.1, 133.1, 132.7, 128.0, 127.8, 127.5, 125.9, 125.5, 123.7, 123.6, 70.1, 24.9;

The enantiomeric excess was determined by chiral HPLC analysis, employing a Dacicel Chiralcel AS-H column (hexane : *i*-propanol = 97 : 3, 1 mL/min), retention times (min): t_1 = 14.04 min (major) , t_2 = 16.47 min (minor).

(*R*)-1-(2-Naphthyl)-ethanol



Colorless solid, 92% yield, 70 % *ee*, $[\alpha]_D^{25}$ = +26.7 (*c* = 1.6, CH_2Cl_2, 589 nm);

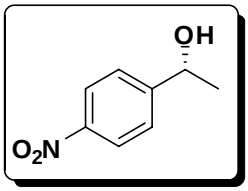
R_f = 0.32 (ethyl acetate/hexane = 1/4);

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68-7.65 (m, 3H), 7.42 (d, *J* = 6.3 Hz, 1H), 7.13-7.08 (m, 2H), 4.93 (q, *J* = 4.4 Hz,1H), 3.87 (s, 3H), 2.34 (br, 1H), 1.51 (d, *J* = 4.8 Hz, 3H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 157.5, 140.9, 133.9, 129.3, 128.6, 127.0, 124.3, 123.7, 118.8, 105.6, 70.3, 55.2, 25.0;

The enantiomeric excess determined by chiral HPLC analysis, employing a Dacicel Chiralcel OD column (hexane : *i*-propanol = 95:5, 1 mL/min): t_1 = 15.76 min (minor), t_2 = 22.53 min (major).

(*R*)-1-(4-Nitrophenyl)-ethanol



Colorless oil, 96 % yield. 92 % ee, $[\alpha]_D^{25}$ = +26.7 (*c* = 1.6, CH_2Cl_2, 589 nm);

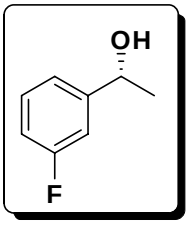
R_f = 0.33 (ethyl acetate/hexane = 1/4);

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.17 (d, *J* = 8.7 Hz, 2H), 7.53 (d, *J* = 8.7 Hz, 2H), 5.01 (q, *J* = 6.5 Hz, 1H), 1.51 (d, *J* = 6.5 Hz, 3H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 153.2, 147.2, 126.1, 123.6, 69.4, 25.4;

The enantiomeric excess determined by HPLC analysis (Daicel Chiralcel OB-H column, hexane: 2-propanol = 95:5, 1 mL/min). Retention time: t_{minor} = 20.71 and t_{major} = 21.48 min.

(*R*)-1-(3-Fluorophenyl)-ethanol



Colorless oil, 97 % yield. 86 % ee, $[\alpha]_D^{25}$ = +17.8 (*c* = 0.9, CH_2Cl_2, 589 nm);

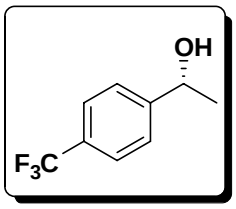
R_f = 0.45 (ethyl acetate/hexane = 1/4);

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27-7.20 (m, 1H), 7.05-7.00 (m, 2H), 6.93-6.87 (m, 1H), 4.76 (q, *J* = 6.5 Hz, 3H), 3.4 (br, 1H), 1.38 (d, *J* = 6.5 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$): δ 164.4, 161.2, 148.5 (d, *J* = 6.6 Hz), 129.8 (d, *J* = 8.3 Hz), 120.9 (d, *J* =2.8 Hz), 113.9 (d, *J* =22.1 Hz), 112.2 (d, *J* =22.1 Hz), 69.4, 25.0.

The enantiomeric excess determined by PLC analysis (Daicel Chiralcel OB-H column, hexane: 2-propanol = 99:1, 1 mL/min). Retention time: t_{minor} = 17.58 and t_{major}= 27.14 min.

(*R*)-1-(4-Trifluoromethylphenyl)-ethanol



Colorless oil, 99% yield. 97% ee, $[\alpha]_D^{25}$ = +38.6 (*c* = 1.0, CH_2Cl_2, 589 nm);

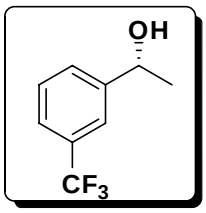
R_f = 0.39 (ethyl acetate/hexane = 1/4);

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53 (d, *J* = 8.1 Hz, 2H), 7.36 (d, *J* = 8.2 Hz, 2H), 4.84-4.76 (m, 1H), 4.00 (d, *J* = 3.6 Hz, 1H), 1.39 (d, *J* = 6.5Hz, 3H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 149.1, 129.4 (q, *J* = 32.0 Hz), 125.6, 125.2 (q, *J* = 3.8 Hz), 122.4, 69.5, 25.0;

The enantiomeric excess determined by HPLC analysis (Daicel Chiralcel OJ column, hexane: 2-propanol = 99.8: 0.2, 1.0 mL/min). Retention time: t_{major} = 36.92 and t_{minor} = 47.81min.

(*R*)-1-(3-Trifluoromethylphenyl)-ethanol



Colorless oil, 93% yield. 86% ee, $[\alpha]_D^{25}$ = +22.7 (*c* =3.1, CH_2Cl_2, 589 nm);

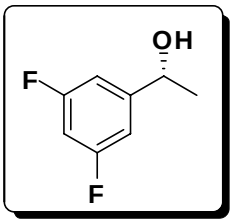
R_f = 0.28 (ethyl acetate/hexane = 1:4);

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (s, 1H), 7.50 (s, 2H), 7.43 (q, *J* = 7.4 Hz, 1H), 4.88 (br, 1H), 2.84 (br, 1H), 1.44 (d, *J* = 6.3 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 146.7, 130.7 (q, *J* = 31.9 Hz), 128.9, 128.7, 125.5, 124.1 (q, *J* = 3.7 Hz), 122.1 (q, *J* = 3.7 Hz), 69.7, 25.2.

The enantiomeric excess determined by HPLC analysis (Daicel Chiralcel OBH column, hexane: 2-propanol = 99:1, 1.0 mL/min). Retention time: t_{minor} = 5.47 and t_{major}= 7.79 min.

(*R*)-1-(3,5-Fifluorophenyl) ethanol



Colorless oil, 99 % yield. 95% ee, $[\alpha]_D^{25}$ = +34.8 (*c* = 1.3, CH_2Cl_2, 589 nm);

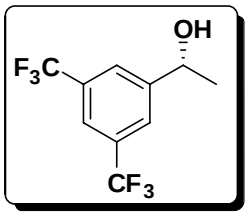
R_f = 0.39 (ethyl acetate/hexane = 1:4);

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.93-6.86 (m, 2H), 6.67-6.66 (m, 1H), 4.92-4.84 (m, 1H), 1.90 (d, *J* = 3.6 Hz, 1H), 1.48 (d, *J* = 6.5 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.8 (d, J = 12.7 Hz), 161.5 (d, J = 12.7 Hz), 150.0 (t, J = 8.3 Hz), 108.1 (d, J =25.5 Hz), 108.2 (d, J = 8.9 Hz), 102.6 (d, J =25.5 Hz), 69.5, 25.2;

The enantiomeric excess determined by HPLC analysis (Daicel Chiralcel OB-H column, hexane: 2-propanol = 97:3, 1.0 mL/min). Retention time: t_{minor} =6.50 and t_{major} = 9.37 min.

(*R*)-3,5-Bistrifluoromethylphenyl ethanol



Colorless solid, 98 % yield. 93 % ee, $[\alpha]_D^{25}$ = + 15.0 (*c* = 1.4, CH_2Cl_2, 589 nm);

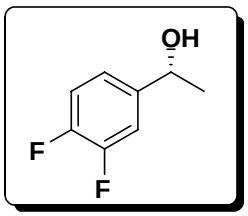
R_f = 0.48 (ethyl acetate/hexane = 1:4);

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84-7.77 (m, 3H), 5.02-5.00 (m, 1H), 4.92-4.84 (m, 1H), 2.70 (d, *J* = 3.6 Hz, 1H), 1.52 (d, *J* = 6.5 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 148.2, 131.7 (q, *J* = 33.0 Hz), 150.0 (t, *J* = 8.3 Hz), 125.6 (d, *J* = 2.5 Hz), 124.7, 122.0, 69.3, 25.4;

The enantiomeric excess determined by HPLC analysis (Daicel Chiralcel OB-H column, hexane: 2-propanol = 99.5: 0.5, 1.0 mL/min). Retention time: t_{minor} = 9.57 and t_{major}= 10.34 min.

(*R*)-1-(3,4-Difluorophenyl) ethanol



Colorless solid, 99 % yield. 95 % ee, $[\alpha]_D^{25}$ = +27.4 (*c* = 2.0, CH_2Cl_2, 589 nm);

R_f = 0.26 (ethyl acetate/hexane = 1:4);

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20-7.01 (m, 3H), 4.83-4.80 (m, *J* = 6.5 Hz, 1H), 2.53 (s, 1H), 1.43 (d, *J* = 6.5 Hz, 3H);

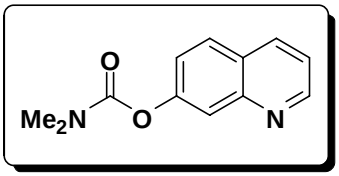
^{13}C NMR (75 MHz, $CDCl_3$): δ 151.5 (dd, *J* = 12.4, 62.6 Hz), 148.2 (dd, *J* = 12.4, 62.6 Hz), 142.8 (dd, *J* = 4.9, 1.0 Hz), 121.2 (q, *J* = 3.9 Hz), 117.0 (d, *J* = 17.0 Hz), 114.3 (d, *J* = 17.0 Hz), 69.2, 25.2;

The enantiomeric excess determined by HPLC analysis (Daicel Chiralcel OB-H column, hexane: 2-propanol = 97: 3, 1.0 mL/min). Retention time: t_{minor} = 7.73 and t_{major}= 8.50 min.

6.6 A NEW BIFUNCTIONAL LIGAND: 1,1'-DIMETHYL-OCTAHYDRO-8,8'-BIQUINOLINE-7,7'-DIOL

Synthesis and characterization of ligands

Quinolin-7-yl dimethylcarbamate (70)



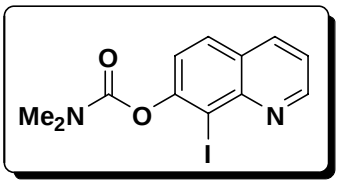
7-Hydroxyquinoline (20 g, 138 mmol) was dissolved in pyridine (120 mL) prior to addition of dimethylaminocarbonyl chloride (40 mL, 290 mmol, 2.1 equiv.) under N_2. The mixture was heated to 100-110 °C and stirred for 36 h. After the mixture was allowed to cool to room temperature, the pyridine was removed *in vacuo*, followed by the addition of H_2O (200 mL). The aqueous solution was extracted with ethyl acetate (3 × 100 mL). The residual aqueous phase was made alkaline (pH > 8) by the addition of 5% w/v aq. NaOH, and extracted again with ethyl acetate (3 × 50 mL) and the combined organic extract was flushed through a column to remove the black precipitate. After which the eluent was concentrated *in vacuo*, and the crude residue was further purified by column chromatography (eluting with ethyl acetate/hexane = 1:3) to yield carbamate **70** (25 g, 84%) as a white solid.

R_f = 0.17 (ethyl acetate/hexane = 1:1);

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.86 (d, *J* = 4.1 Hz, 1H), 8.07 (d, *J* = 8.2 Hz, 1H), 7.82 (d, *J* = 1.6 Hz, 1H), 7.76 (d, *J* = 8.9 Hz, 1H), 7.37 (dd, *J* = 8.9, 2.1 Hz, 1H), 7.30 (dd, *J* = 8.2, 4.2 Hz, 1H), 3.11 (s, 3H), 3.01 (s, 3H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 154.2, 151.9, 150.5, 148.5, 135.5, 128.3, 125.6, 122.4, 120.3, 119.8, 36.4, 36.2 ppm;

8-Iodoquinolin-7-yl dimethylcarbamate (71)



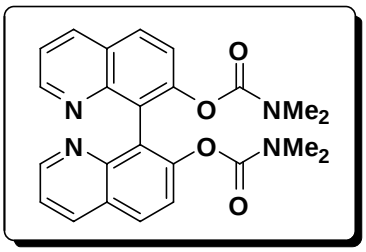
n-BuLi (17.3 mL, 1.6 M in hexanes, 27.7 mmol, 1.2 equiv.) was added dropwise to a solution of *i*-Pr_2NH (4.1 mL, 28.9 mmol, 1.25 equiv.) in anhydrous THF (50 mL) at –10 °C under N_2 and stirred for 10 min. The LDA solution was then cooled to –78 °C and carbamate **70** (5.0 g, 23.1 mmol) in anhydrous THF (20 mL) was added slowly over 10 min and continued to stir for 90 min at –78 °C prior to careful addition of I_2 (5.9 g, 23.1 mmol, 1 equiv.) in anhydrous THF (20 mL) over 10 min. The resulting mixture was stirred for 15 min at –78 °C and subsequently the reaction vessel was released from the cooling bath. Saturated aqueous $Na_2S_2O_3/NH_4Cl$ (100 mL, 1:1) was then added to the mixture with vigorous stirring. The aqueous layer was extracted with ethyl acetate (3 × 50 mL) and the combined organic extract was washed with H_2O and brine and then concentrated *in vacuo*. The crude residue was further purified by column chromatography (eluting with ethyl acetate/hexane = 1:2) to yield **71** (3.16 g, 40%) as a milky white powder.

R_f = 0.24 (ethyl acetate/hexane = 1:2);

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.99 (d, *J* = 4.2 Hz, 1H), 8.11 (d, *J* = 8.2 Hz, 1H), 7.79 (d, *J* = 8.8 Hz, 1H), 7.43 (d, *J* = 8.8, 1H), 7.40 (d, *J* = 4.2 Hz, 1H), 3.28 (s, 3H), 3.08 (s, 3H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 153.7, 153.5, 151.6, 148.0, 136.4, 128.9, 126.5, 123.1, 121.3, 98.3, 36.8 ppm;

8,8'-Biquinoline-7,7'-diyl bis(dimethylcarbamate) (72)



Copper bronze was stirred with a 2% solution of iodine (1 g, 3.9 mmol) in acetone (49 g) for 10 minutes. The mixture was filtered and collected on a Buchner funnel. The resulting solid was washed by stirring into slurry with a 1:1 solution of concentrated HCl (30 mL) in acetone (30 mL) prior to second filtration. The residual copper bronze was then washed with acetone and dried in a vacuum desiccator to be used immediately. To a stirred solution of **71** (3.96 g, 11.6 mmol) in anhydrous DMF (32 mL) was added freshly prepared copper bronze (2.94 g, 46 mmol, 4 equiv.) in one portion and resulting suspension was heated to 140 °C and stirred for 6 h under N_2. After the mixture was cooled to room temperature, the aqueous NH_3 (25%, 150 mL) solution was added slowly and the aqueous solution was extracted with ethyl acetate (3 × 50 mL). The combined organic extract was washed with H_2O and brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude residue was further purified by column chromatography (eluting with MeOH/CH_2Cl_2 = 1:30) to yield 8,8'-biquinolyl **72** (1.3 g, 52%) as a yellow solid. If the commercially available copper bronze is used directly, it is necessary to stir the reaction mixture for 2 days to get reasonable yield.

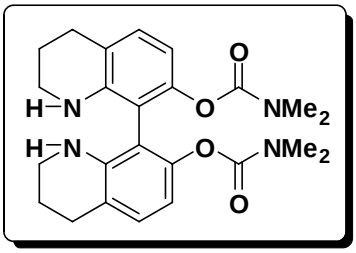
R_f = 0.48 (CH_2Cl_2:MeOH = 25:1);

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.78 (d, *J* = 3.3 Hz, 2H), 8.22 (d, *J* = 8.0 Hz, 2H), 7.93 (d, *J* = 8.9 Hz, 2H), 7.73 (d, *J* = 8.9 Hz, 2H), 7.34 (dd, *J* = 8.2, 4.2 Hz, 2H), 2.72 (s, 6H), 2.11 (s, 6H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 153.8, 150.4, 150.2, 147.8, 136.0, 128.1, 125.9, 125.3, 123.6, 120.2, 36.3, 35.4 ppm;

1,1',2,2',3,3',4,4'-Octahydro-8,8'-biquinoline-7,7'-diyl bis(dimethylcarbamate)

(73)



To an oven dried round-bottom flask was added **72** (2.0 g, 4.6 mmol), HCO_2NH_4 (14.6 g, 232 mmol, 50 equiv.) and MeOH (50 mL). Then 10% Pd/C (0.25 g, 2.33 mmol, 0.05 equiv.) was added into the mixture in a very slow manner. The mixture was heated at 80 °C under N_2 for 2 h with stirring and allowed to cool to room temperature. After filtration with celite, the filtrate was concentrated *in vacuo* and CH_2Cl_2 was added, washed with saturated $NaHCO_3$ solution and brine, and dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residue was further purified by column chromatography (eluting with ethyl acetate/hexane = 1:1) to yield **73** (1.99 g, 98%) as a pale yellow solid.

R_f = 0.27 (ethyl acetate/hexane = 1:4);

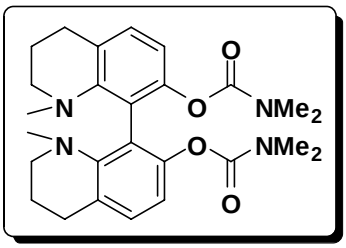
^{1}H NMR (300 MHz, $CDCl_3$); δ 6.90 (d, *J* = 8.1 Hz, 2H), 6.44 (d, *J* = 8.1 Hz, 2H), 3.96 (s, 2H), 3.25-3.08 (m, 4H), 2.77-2.71 (m, 10H), 2.62 (s, 4H), 1.97-1.84 (m, 2H), 1.82-1.70 (m, 2H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 154.9, 148.1, 144.1, 128.5, 118.1, 110.7, 109.1, 41.6, 35.7, 34.0, 27.0, 21.7;

FTIR (KBr, neat): 721, 1377, 1458, 2853, 2924, 2953, 3422 cm^{-1};

HRMS (ESI) calcd. for $C_{24}H_{30}N_4O_4$ $[M+1]^+$: 439.2345, found 439.2328.

1,1'-Dimethyl-1,1',2,2',3,3',4,4'-octahydro-8,8'-biquinoline-7,7'-diyl bis(dimethylcarbamate) (74)



A portion of solid K_2CO_3 (1.8 g, 13.6 mmol, 3 equiv.) was added into a solution of **73** (2.0 g, 4.56 mmol) in anhydrous DMF. Then CH_3I (0.9 mL, 14.4 mmol, 3 equiv.) was added dropwise to the solution over 5 min. The mixture was stirred at room temperature under N_2 for 6 h. Then it was quenched with H_2O and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with H_2O and brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residue was further purified by column chromatography (eluting with ethyl acetate/hexane = 1:2) to yield **74** (1.91 g, 90%) as a pale yellow solid.

R_f = 0.33 (ethyl acetate/hexane = 1:4);

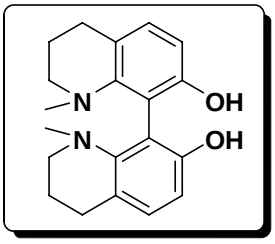
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.83 (d, *J* = 8.6 Hz, 2H), 6.57 (d, *J* = 8.6 Hz, 2H), 2.98-2.92 (m, 2H), 2.87 (s, 8H), 2.79 (s, 5H), 2.76 (s, 5H), 2.63-2.57 (m, 10H), 2.33 (s, 6H), 1.80-1.63 (4H, m) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 154.1, 148.4, 146.8, 127.4, 124.0, 118.9, 112.5, 52.2, 41.2, 36.2, 31.1, 28.3, 20.8 ppm;

FTIR (KBr, neat): 721, 1377, 1458, 2853, 2924, 2953 cm^{-1};

HRMS (ESI) calcd. for $C_{26}H_{34}N_4O_4$ $[M+1]^+$: 467.2658, found 467.2636.

1,1'-Dimethyl-1,1',2,2',3,3',4,4'-octahydro-8,8'-biquinoline-7,7'-diol (75)



A solution of **74** (2.4 g, 5.15 mmol) in 10 wt.% methanolic KOH (50 mL) was stirred at reflux for 20 h. The resulting solution was allowed to cool to room temperature and concentrated *in vacuo*. The residue was dissolved in H_2O and the pH adjusted to 7 by careful addition of 1M aq. HCl. The aqueous phase was saturated with NaCl and extracted with ethyl acetate (6 × 50 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residue was further purified by column chromatography (eluting with ethyl acetate/hexane = 1:4) to yield **75** (1.3 g, 78%) as a white solid.

R_f = 0.36 (ethyl acetate/hexane = 1:4);

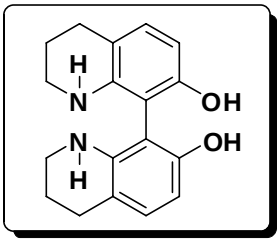
^{1}H NMR (300 MHz, $CDCl_3$): δ 10.3 (s, 2H), 7.02 (d, *J* = 8.2 Hz, 2H), 6.76 (d, *J* = 8.3 Hz, 2H), 3.27 (td, *J* = 13.2, 2.3 Hz, 2H), 3.10 (dt, *J* = 13.2, 3.7 Hz, 2H), 2.86-2.83 (m, 4H), 2.52 (s, 6H), 2.03-1.90 (m, 2H), 1.85-1.75 (m, 2H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 154.5, 144.2, 130.4, 120.9, 120.0, 115.4, 51.8, 42.2, 27.6, 17.2.;

FTIR (KBr, neat): 721, 1377, 1456, 1634, 2853, 2922, 2953, 3420, 3445 cm^{-1};

HRMS (ESI) calcd. for $C_{20}H_{24}N_2O_2$ $[M+1]^+$: 325.1916, found 325.1902.

1,1',2,2',3,3',4,4'-Octahydro-8,8'-biquinoline-7,7'-diol (76)



A solution of **73** (2.2 g, 5 mmol) in 10 wt.% methanolic KOH (50 mL) was stirred at reflux for 20 h. The resulting solution was cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in H_2O and the pH adjusted to 7 by careful addition of 1M aq. HCl. The aqueous phase was saturated with NaCl and extracted with ethyl acetate (6 × 50 mL), the combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residue was further purified by column chromatography (eluting with ethyl acetate/hexane = 4:1) to yield **76** (1.17 g, 79%) as a white solid.

R_f = 0.29 (ethyl acetate/hexane = 1:4);

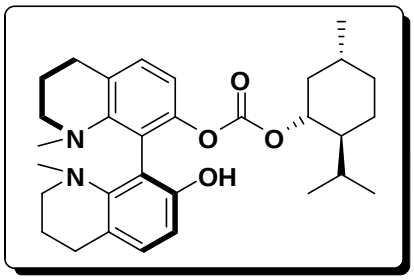
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.92 (d, *J* = 8.1 Hz, 2H), 6.33 (d, *J* = 6.9 Hz, 2H), 5.09 (br, 2H), 3.83 (br, 2H), 3.22 (d, *J* = 5.4 Hz, 4H), 2.74 (t, *J* = 5.9 Hz, 4H), 1.90 (t, *J* = 5.6 Hz, 4H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 153.1, 143.5, 131.1, 113.9, 104.0, 101.2, 41.7, 26.7, 21.9;

FTIR (neat): 3275, 3020, 1598, 1464, 1216, 1176, 759, 668 cm^{-1};

HRMS (ESI) calcd. for $C_{18}H_{21}N_2O_2$ $[M+1]^+$:297.1603, found 297.1603;

(*S*)-7'-Hydroxy-1,1'-dimethyl-1,1',2,2',3,3',4,4'-octahydro-8,8'-biquinolin-7-yl (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl carbonate (76a)



To an oven dried round-bottom 10 mL flask equipped with a magnetic stirring bar was added racemate ligand **75** (300 mg, 0.92 mol), CH_2Cl_2 (5 ml) and Et_3N (0.17 mL, 1.1 mmol). Then (–)-menthyl chloroformate (0.24 mL, 1.1 mmol, 1.2 equiv.) was added to the solution with stirring. The reaction mixture was stirred for 0.5 h and quenched with water. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic extracts were washed with brine (10 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified *via* column chromatography (eluting with ethyl acetate/hexane = 5:1) to afford **76a** (177 mg, 38%) as colorless solid and **76b** (177 mg, 38%) as a colorless oil.

R_f = 0.31 (ethyl acetate/toluene = 1:10);

$[\alpha]_D^{20}$ = -97.4 (*c* = 1.4, CH_2Cl_2, 589 nm);

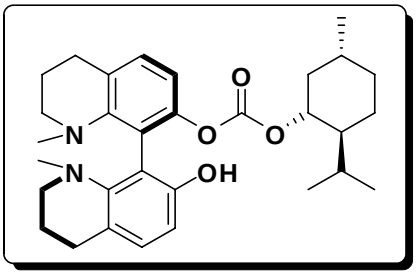
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.18 (s, 1H), 7.07 (d, *J* = 8.4 H, 1H), 6.84 (dd, *J* =11.2, 8.1 Hz, 2H), 6.41 (d, *J* = 8.1 Hz, 1H), 4.37 (td, *J* = 11.0 Hz, 1H), 3.22-3.10 (m, 3H), 2.98-2.91 (m, 1H), 2.89-2.84 (m, 2H), 2.69 (s, 3H), 2.64 (m, 2H), 2.33 (s, 3H), 2.01-1.90 (m, 3H), 1.81-1.79 (m, 2H), 1.63-1.60 (m, 4H), 1.31-1.25 (m, 1H), 1.05-0.95 (m, 3H), 0.88 (d, *J* = 6.6 Hz, 3H), 0.83 (d, *J* = 7.0 Hz, 3H), 0.63 (d, *J* = 6.9 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 154.5, 153.1, 147.8, 147.3, 144.9, 129.7, 129.4, 126.8, 126.0, 120.1, 117.1, 112.0, 108.7, 78.7, 52.6, 51.6, 47.1, 41.6, 41.4, 40.6, 34.0, 31.4, 28.7, 27.5, 25.5, 23.0, 22.0, 21.3, 21.0, 16.9, 16.0;

FTIR (KBr, neat): 721, 1377, 1456, 1634, 2853, 2922, 2953, 3420, 3445 cm^{-1};

HRMS (ESI) calcd. for $C_{31}H_{42}N_2O_4$ $[M+1]^+$: 507.3223, found 507.3222.

(*R*)-7'-Hydroxy-1,1'-dimethyl-1,1',2,2',3,3',4,4'-octahydro-8,8'-biquinolin-7-yl (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl carbonate (76b)



R_f = 0.23 (ethyl acetate/toluene = 1:10);

$[\alpha]_D^{20}$ = +47.8 (*c* = 0.9, CH_2Cl_2, 589 nm);

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.21 (s, 1H), 7.07 (d, *J* = 8.4 Hz, 1H), 6.84 (dd, *J* = 11.2, 8.1 Hz, 2H), 6.45 (d, *J* = 8.1 Hz, 1H), 4.28 (td, *J* = 11.0 Hz, 1H), 3.25-3.09 (m,

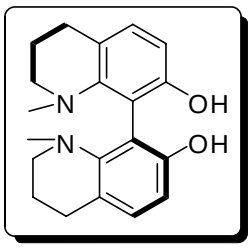
3H), 2.97-2.92 (m, 1H), 2.88-2.85 (m, 2H), 2.70 (s, 3H), 2.69-2.59 (m, 2H), 2.33 (s, 3H), 2.04-1.89 (m, 3H), 1.86-1.78 (m, 2H), 1.63-1.60 (m, 4H), 1.57 (s, 1H), 1.32-1.24 (m, 3H), 0.87 (d, J = 7.2 Hz, 6H), 0.70 (d, J = 7.2 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 154.7, 152.4, 147.8, 147.3, 145.0, 129.9, 129.5, 127.0, 126.3, 119.9, 116.8, 116.3, 112.0, 108.8, 78.4, 52.3, 51.5, 46.9, 41.6, 41.4, 40.2, 34.1, 31.1, 28.6, 27.5, 25.8, 23.0, 21.9, 20.8, 16.9, 16.1 ppm;

FTIR (KBr, neat): 721, 1377, 1456, 1634, 2853, 2922, 2953, 3420, 3445 cm^{-1};

HRMS (ESI) calcd. for $C_{31}H_{42}N_2O_4$ $[M+1]^+$:507.3223, found 507.3222.

(*S*)-1,1'-Dimethyl-1,1',2,2',3,3',4,4'-octahydro-8,8'-biquinoline-7,7'-diol (75a)



76a (32.4 mg, 0.1 mmol) was dissolve in 2 mL THF and 0.1 mL pyrrolidine was added. The mixture was stirred at room temperature for 2 h and the solvent was then evaporated and the residue purified *via* column chromatography (eluting with ethyl acetate/hexane = 1:5) to afford (*S*)-**75a** as a colorless solid (29 mg, 90%).

$[\alpha]_D^{20}$ = -88.9 (*c* = 6.3, CH_2Cl_2, 589 nm);

R_f = 0.36 (ethyl acetate/hexane = 1:4);

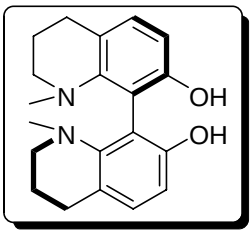
^{1}H NMR (300 MHz, $CDCl_3$): δ 10.3 (s, 2H), 7.02 (d, J = 8.2 Hz, 2H), 6.76 (d, J = 8.3 Hz, 2H), 3.27 (td, J = 13.2, 2.3 Hz, 2H), 3.10 (dt, J = 13.2, 3.7 Hz, 2H), 2.86-2.83 (m, 4H), 2.52 (s, 6H), 2.03-1.90 (m, 2H), 1.85-1.75 (m, 2H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 154.5, 144.2, 130.4, 120.9, 120.0, 115.4, 51.8, 42.2, 27.6, 17.2.;

FTIR (KBr, neat): 721, 1377, 1456, 1634, 2853, 2922, 2953, 3420, 3445 cm^{-1};

HRMS (ESI) calcd. for $C_{20}H_{24}N_2O_2$ $[M+1]^+$: 325.1916, found 325.1902.

(*R*)-1,1'-Dimethyl-1,1',2,2',3,3',4,4'-octahydro-8,8'-biquinoline-7,7'-diol (75b)



76b (32.4 mg, 0.1 mmol) was dissolve in 2 mL THF and then 0.1mL pyrrolidine was added, then the mixture was stirred at room temperature for 2 h, then the solvent was evaporated and the residue was purified *via* column chromatography (eluting with ethyl acetate/hexane = 1:5) to afford (*R*)-**75b** as colorless solid (29 mg, 90%).

$[\alpha]_D^{20}$ = +88.9 (*c* = 6.3, CH_2Cl_2, 589 nm);

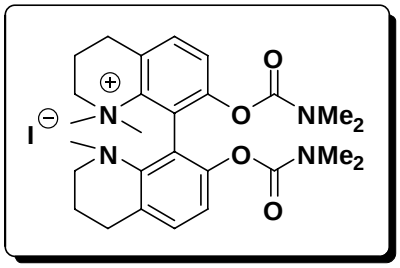
R_f = 0.36 (ethyl acetate/hexane = 1:4);

^{1}H NMR (300 MHz, $CDCl_3$): δ 10.3 (s, 2H), 7.02 (d, *J* = 8.2 Hz, 2H), 6.76 (d, *J* = 8.3 Hz, 2H), 3.27 (td, *J* = 13.2, 2.3 Hz, 2H), 3.10 (dt, *J* = 13.2, 3.7 Hz, 2H), 2.86-2.83 (m, 4H), 2.52 (s, 6H), 2.03-1.90 (m, 2H), 1.85-1.75 (m, 2H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 154.5, 144.2, 130.4, 120.9, 120.0, 115.4, 51.8, 42.2, 27.6, 17.2;

FTIR (KBr, neat): 721, 1377, 1456, 1634, 2853, 2922, 2953, 3420, 3445 cm^{-1};

HRMS (ESI) calcd. for $C_{20}H_{24}N_2O_2$ $[M+1]^+$: 325.1916, found 325.1902.



A portion of solid K_2CO_3 (1.8 g, 13.6 mmol, 3 equiv.) was added into solution of **73** (2.0 g, 4.56 mmol) in 10 mL DMF. Then CH_3I (4 mL, 16 mmol, 14 equiv.) was added dropwise to the solution. The mixture was sealed and stirred vigorously at room temperature under N_2 for 24 h. Then it was quenched with H_2O and the aqueous layer was extracted with ethyl acetate (5 × 100 mL). The combined organic extract was washed with H_2O and brine, filtered and concentrated *in vacuo*. The residue was further washed with CH_2Cl_2 to give the desired product **77** (0.77 g, 36%) as a pale yellow solid.

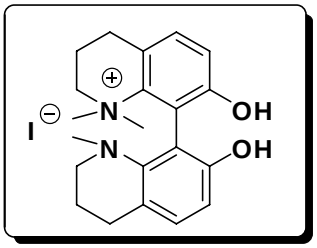
R_f = 0.18 (CH_2Cl_2:CH_3OH = 10:1);

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51 (d, *J* = 8.7 Hz, 1H), 7.34 (d, *J* = 8.7 Hz, 1H), 7.13 (d, *J* = 8.4 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 4.61-4.54 (m, 1H), 4.10-3.96 (m, 1H), 3.78 (s, 3H), 3.41 (s, 3H), 3.18 (q, *J* = 7.2 Hz, 2H), 2.96 (t, *J* = 4.2 Hz, 2H), 2.82-2.80 (m, 8H), 2.47 (s, 3H), 2.43 (s, 3H), 2.32 (s, 3H), 2.05-1.91 (m, 1H), 1.78 (s, 2H), 1.73-1.62 (m, 1H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 152.6, 152.0, 148.8, 147.0, 146.6, 141.0, 131.4, 130.4, 127.2, 126.2, 124.3, 122.8, 118.3, 115.3, 67.9, 55.9, 54.0, 51.8, 41.5, 36.1, 36.0, 35.7, 35.1, 27.0, 25.8, 17.6, 16.6 ppm;

FTIR (KBr): 3420, 2922, 1734, 1638, 1458, 1377, 721 cm^{-1};

HRMS (ESI) calcd. for $C_{21}H_{28}N_2O_2I$ $[M+1]^+$: 467.1196, found 467.1181.



A solution of **74** (0.6 g, 1 mmol) in 10 wt.% methanolic KOH (10 mL) was stirred at reflux for 20 h. The resulting solution was allowed to cool to room temperature and concentrated *in vacuo*. The residue was dissolved in H_2O and the pH adjusted to 7 by careful addition of 1M aq. HCl. Then the residue was filtered and washed with CH_2Cl_2 and dried to yield **78** (0.34 g, 56%) as a white solid.

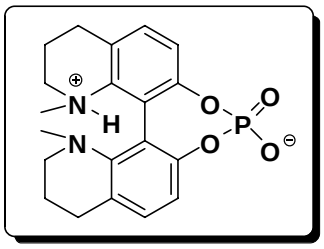
R_f = 0.43 (CH_2Cl_2:CH_3OH = 4:1);

^{1}H NMR (500 MHz, CD_3OD): δ 9.81 (s, 1H), 9.13 (s, 1H), 7.14 (d, *J* = 12.0 Hz, 1H), 6.99 (d, *J* = 8.4 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 6.43 (d, *J* = 8.2 Hz, 1H), 3.79 (t, *J* = 5.7 Hz, 2H), 3.43 (s, 3H), 3.09 (s, 3H), 2.92-2.87 (m, 4H), 2.65-2.62 (m, 2H), 2.33 (s, 3H), 2.26-2.23 (m, 1H), 2.16-2.11 (m, 1H), 1.94-1.82 (m, 1H), 1.57-1.49 (m, 1H);

^{13}C NMR (100 MHz, CD_3OD): δ 158.1, 155.7, 149.1, 143.3, 133.2, 132.3, 130.0, 122.9, 122.5, 121.0, 119.0, 115.6, 109.8, 70.2, 56.4, 55.5, 53.8, 42.1, 29.0, 27.7, 20.5, 18.8;

FTIR (neat): 3421, 2924, 1636, 1466, 1375, 1153, 721 cm^{-1};

HRMS (ESI) calcd. for $C_{27}H_{38}N_4O_4I$ 609.1938 $[M+H]^+$, found 609.1915.



Ligand **75** (67 mg, 0.2 mmol) was dissolved into 1 mL of pyridine under N_2 atmosphere. To the resulting solution was added phosphorus oxychloride (0.03 mL, 1.5 equiv.) at room temperature and the reaction mixture was stirred for 12 h. Then 1 mL of water was added and the resulting suspension was stirred for additional 30 min. The mixture was were concentrated *in vacuo* and further purified by column chromatography. The title compound **80** was isolated as white solid in quantitative yield.

R_f = 0.52 (CH_2Cl_2:MeOH = 4:1);

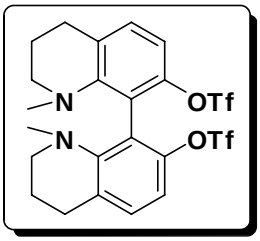
^{1}H NMR (300 MHz, CD_3OD): δ 7.47 (d, *J* = 8.4 Hz, 2H), 7.30 (dd, *J* = 8.4, 1.2 Hz, 2H), 3.62-3.48 (m, 4H), 3.05 (t, *J* = 4.1 Hz, 4H), 2.64 (s, 6H), 2.31-2.22 (m, 2H), 2.07-2.01 (m, 2H);

^{13}C NMR (75 MHz, CD_3OD): δ 149.8, 149.7, 138.6, 138.5, 132.6, 132.5, 127.7, 127.6, 121.7, 121.6, 120.5, 120.4, 50.1, 43.6, 25.3, 15.0;

FTIR (KBr, neat): 756, 1107, 1470, 1599,1673, 2349, 2951, 3019 cm^{-1};

HRMS (ESI) calcd. for $C_{20}H_{24}N_2O_4P[M+1]^+$:387.1474, found 387.1465.

1,1'-Dimethyl-1,1',2,2',3,3',4,4'-octahydro-8,8'-biquinoline-7,7'-diyl bis(trifluoromethanesulfonate) (81)



To a solution of **75** (78 mg, 0.24 mmol) in CH_2Cl_2 (5 mL), was added Et_3N (0.1 mL, 0.72 mmol, 3 equiv.) and DMAP (3 mg, 0.02 mmol, 0.1 equiv.). The mixture was cooled to 0 ^oC prior to slow addition of Tf_2O (0.1 mL, 0.6 mmol, 2.5 equiv.). The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts were washed with water (5 mL) and brine (5 mL), dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography (eluting with ethyl acetate/hexane = 2:1) to afford the desired product **81** as a yellow solid (0.11 g, 78%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02 (d, *J* = 8.4 Hz, 2H), 6.71 (d, *J* = 8.3 Hz, 2H), 3.21-3.15 (m, 2H), 3.09-3.03 (m, 2H), 2.72 (dd, *J* = 10.8, 5.2 Hz, 2H), 2.48 (s, 6H), 1.92-1.84 (m, 4H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 147.7, 129.3, 128.2, 116.0, 109.7, 42.7, 40.9, 28.8, 20.9 ;

HRMS (ESI) calcd. for $C_{22}H_{23}N_2O_6S_2F_6$ 589.0902 $[M+H]^+$, found $[M]^+$ 589.0903.

Appendix

UNEXPECTED DOMINO RING CLOSURE: HIGHLY STEREOSELECTIVE CONSTRUCTION OF A TETRACYCLIC INDOLE ALKALOID RING SYSTEM

7.1 INTRODUCTION

The discovery of new efficient methods for the construction of polycyclic rigid ring systems present in natural products with excellent region- and diastereo-selectivity is an important goal for both academic and industrial researchers.[131] Domino or cascade reactions allow the formation of rigid ring systems in one-pot manner which avoids laborious isolation of intermediates in multistep synthesis of complex molecules. However, the development of a highly stereoselective domino reaction for the construction of indole polycyclic rings still remains a intricate challenge.[132] The 1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole **83** is present in many indole alkaloids such as physostigmine, flustramines, urochordamines and mollenines (Figure 3.3). The tetrahydroimidazo[1,2-a]indole system **84** is also found in many natural products such as tryptoquivalines, asperlicins, fiscalins, fumiquinazolines and kapakahines (Figure 7.1).[133]

[131] Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134.
[132] (a) Song, H.; Yang, J.; Qin, Y. *Org. Lett.* **2006**, *8*, 6011. (b) Yang, J.; Song, H.; Xiao, X.; Wang, J.; Qin, Y. *Org. Lett.* **2006**, *8*, 2187. (c) Yang, J.; Wu, H.-X.; Shen, L.-Q.; Qin, Y. *J. Am. Chem. Soc.* **2007**, *129*, 13794. (d) Shen, L.-Q., Zhang, M.; Wu,Y.; Qin, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134.
[133] (a) Yamazaki, M.; Fujimoto, H.; Okuyama, E. *Tetrahedron Lett.* **1976**, *17*, 2861. (b) Fujimoto, H.; Negishi, E.; Yamaguchi, K.; Nishi, N.; Yamazaki, M. *Chem. Pharm. Bull.* **1996**, *44*, 1843. (c) Chang, R. S.; Lotti, V. J.; Monaghan, R. L.; Birnbaum, J. et al. *J. Antibiot.* **1988**, *41*, 878. (d) Wong, S. M.; Musza, L. L.; Kydd, G. C.; Kullnig, R.; Gillum, A. M.; Cooper, R. *J. Antibiot.* **1993**, *46*, 545.

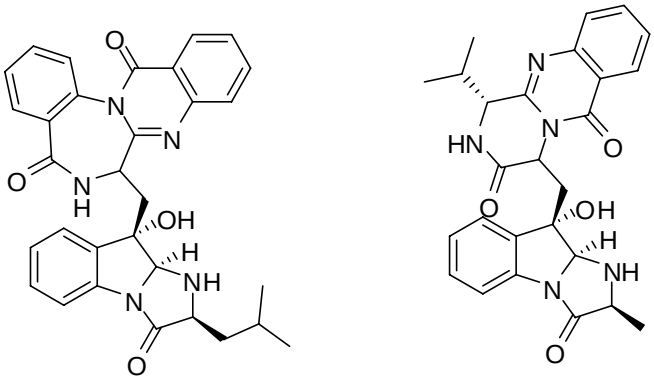
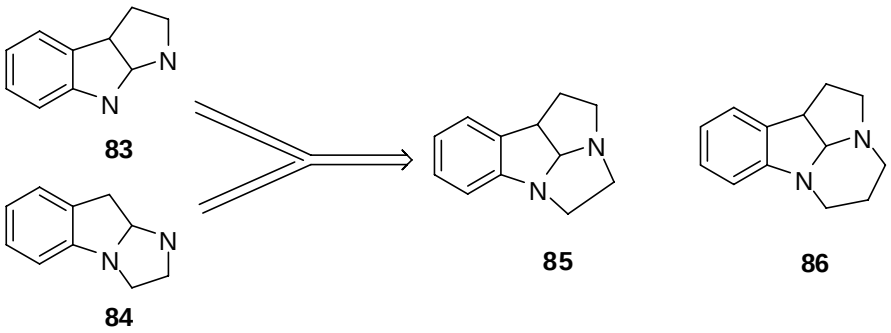


Figure 7.1 Natural products having tetrahydroimidazo[1,2-a]indole **84**

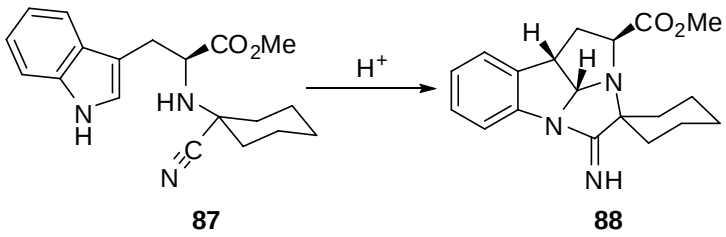
Tetracyclic [6,5,5,5] ring system **85** can be considered as a combination of tetrahydropyrrolo[2,3-*b*]indole **83** and tetrahydroimidazo[1,2-*a*]indole **84** (Scheme 7.1).[124] As such, the synthesis of tetracyclic [6,5,5,5] ring system **85** and [6,5,5,6] ring system **86** is of great interest and should be highly valuable for organic synthesis.



Scheme 7.1 Tetracyclic [6,5,5,5] ring system **83** and [6,5,5,6] ring system **84**

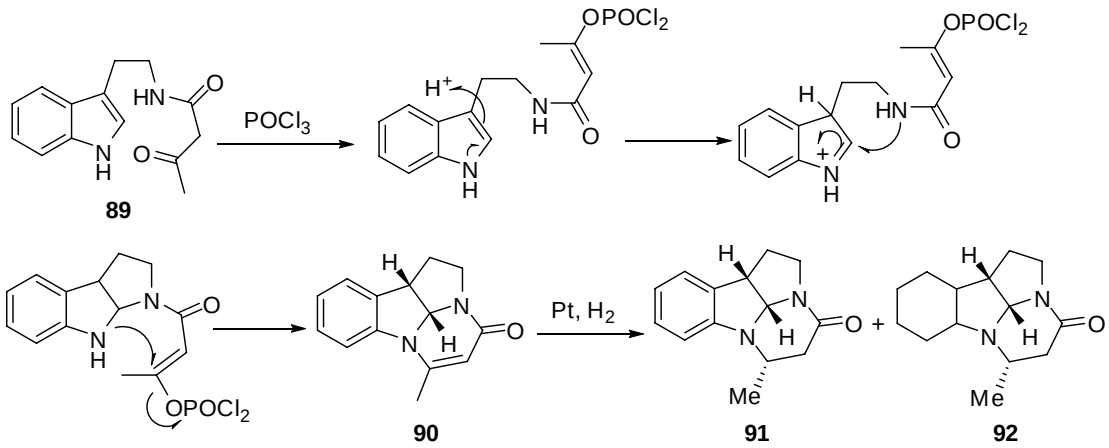
An acid-promoted cyclization of **87** furnished the tryptophan-based α-amino nitriles **88**, possessing the tetracyclic [6,5,5,5] ring (Scheme 7.2), the structure of which was established by 2D NMR.[134]

[134] (a) González-Vera, J. A.; García-López, M. T.; Herranz, R. *Org. Lett.* **2004**, *6*, 2641. (b) González-Vera, J. A.; García-López, M. T.; Herranz, R. *J. Org. Chem.* **2005**, *70*, 8971.



Scheme 7.2 Acid-promoted cyclization of **85**

Treatment of the amide **89** with phosphoryl chloride in dichloromethane (1.1 equiv) gave indoline **90**. Prior to first step cyclization, the acetyl group was activated by attack of phosphoryl chloride to assure the second step cyclization. The indoline **90** is unstable, reverting to starting material when stored for a few days. Hydrogenation of **90** provided the stable amine **91** and the perhydro derivative **92** (Scheme 7.3).[135]



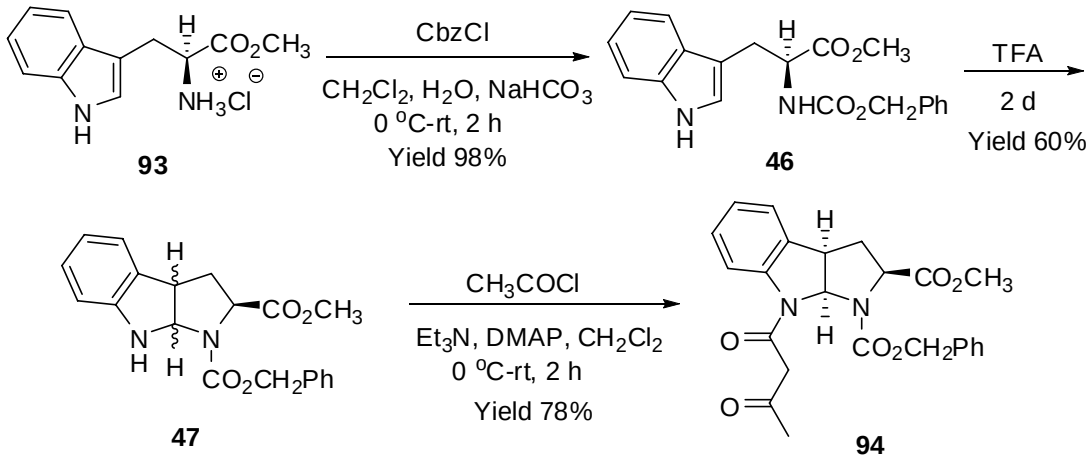
Scheme 7.3 Phosphoryl chloride catalyzed ring closure of **87**

[135] Jackson A. H.; Shannon P. V.; Wilkins, R. D. J. *J. Chem. Soc., Chem. Commun.***1987**, 653.

7.2 RESULTS AND DISCUSSION

During the course of our synthetic efforts aimed at developing a novel rigid chiral ligand for asymmetric catalysis, we identified an unexpected domino ring closure process which provided an easy and stereoselective access to tetracyclic [6,5,5,6] ring system **86**.[136]

Starting from commercially available L-tryptophan methyl ester **93**, initial protection of the ammonium nitrogen atom with benzyl chloroformate in the presence of sodium bicarbonate, followed by acid-catalyzed ring closure afforded the hexahydro[2,3-*b*]pyrroloindole **47** in an overall yield of 60% as an *endo/exo* mixture of isomers. Subsequent acetylation of **47** with 5 equivalents of acetyl chloride in the presence of Et_3N and DMAP afforded the unexpected Claisen condensation product **94**. When l equivalent and 2 equivalents of acetyl chloride were employed, compound **94** was also obtained as the major product in 41% and 71% yields respectively (Scheme 7.4). The ^1H NMR spectrum of **94** is somewhat obscure due to the existence of rotamers. A single crystal was grown from an ether/hexane (1:1) mixture which



Scheme 7.4 Formation of unexpected product **94**

[136] Xiao, J.; Loh, T. P. *Tetrahedron Lett.* **2008**, *49*, 7184.

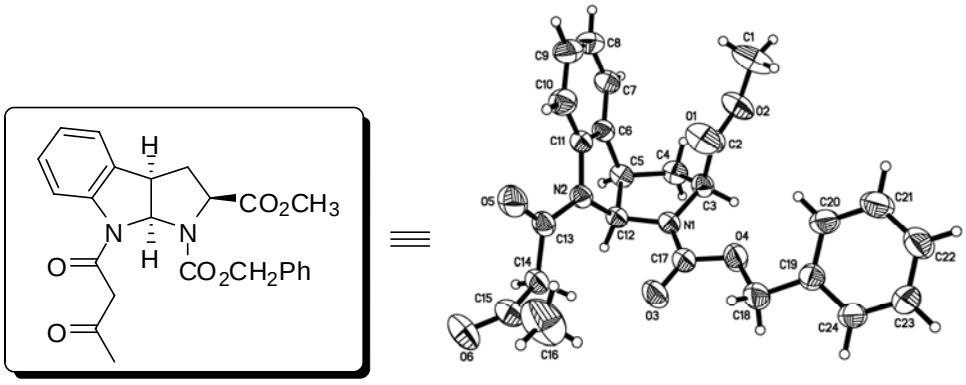
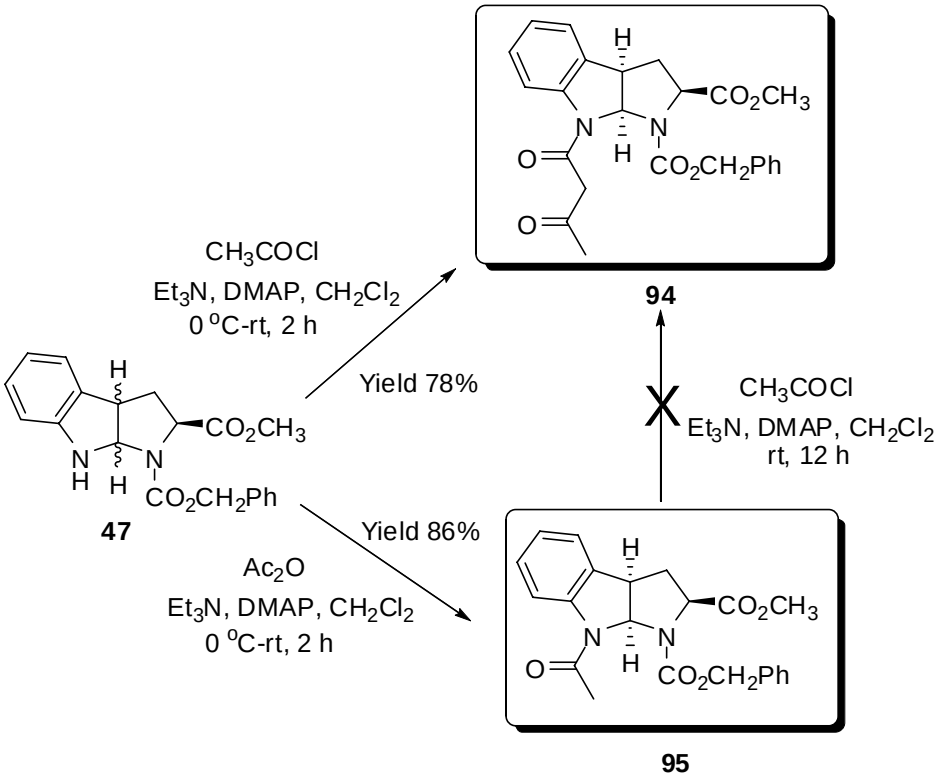


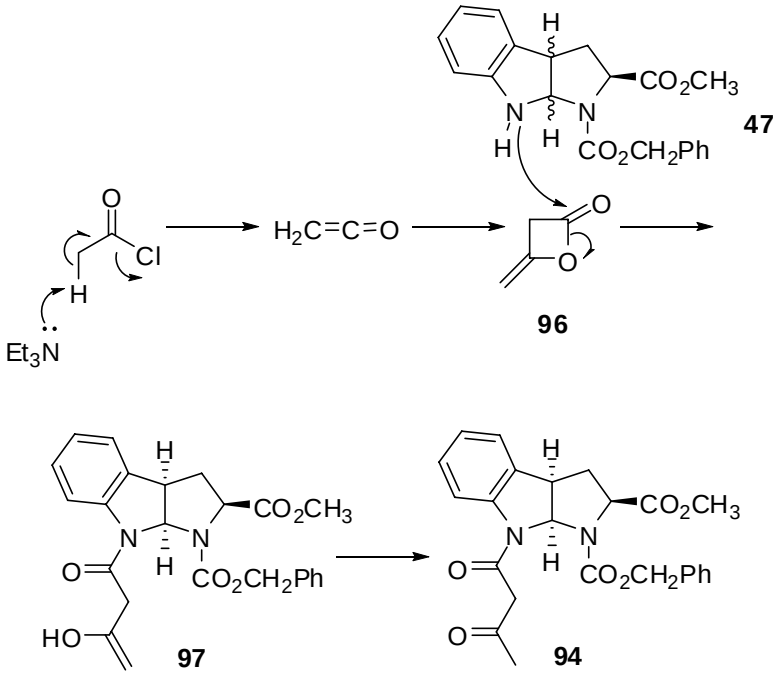
Figure 7.2 X-ray crystal structure of **94**

helped confirm the structure of **94** (Figure 7.2). Even when we decreased the reaction temperature, slowed down the addition rate and reduced the amount of acetyl chloride, compound **94** was still obtained as the major product (Scheme 7.4). However, the desired acetylation product **95** could be acquired by the use of acetic



Scheme 7.5 Synthesis of desired product **95**

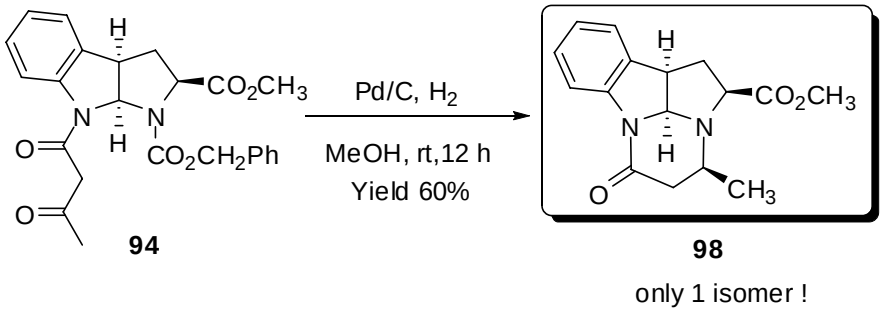
anhydride and Et_3N. Treatment of **95** with acetyl chloride in the presence of base failed to yield **94** (Scheme 7.5). This was probably due to the formation of ketene in the presence of acetyl chloride and Et_3N, followed by rapid dimerization to give *β*-lactone **96**, which was then attacked by the secondary amine moiety in **47** to afford **97**, and finally affording the desired product **94** after tautomerization (Scheme 7.6).



Scheme 7.6 Proposed mechanism for the formation of **94**

As demonstrated by the crystal structure, compound **94** adopts an envelope-like conformation. It is very clear that the methyl ester group is directly under the phenyl ring wherein the alternative orientation is blocked by the bulky benzyloxy group. The rigid and sterically encumbered nature could account for our failure to carry out a Grignard addition to the methyl ester. Thus deprotection of the benzyloxy group is essential for the success of this transformation. In the next step, deprotection followed by filtration to remove Pd/C, gave a colourless crystalline solid **98** in good yield. The ^1H NMR spectrum showed that the signal of the acetyl CH_3 protons was shifted

significantly upfield from δ 2.33 ppm to 1.41 ppm, compared to the corresponding signal in **94** (Scheme 7.7). To elucidate its precise structure, a crystal suitable for X-



94 **98**

only 1 isomer !

Scheme 7.7 Unexpected domino ring closure

ray analysis was grown by slow evaporation from a mixture of CH_2Cl_2 and hexane. As shown in Figure 7.3, a new six-membered ring D was formed which was fused to the two heterocyclic ring A and B. The methyl ester group preferred the *endo*-conformation.

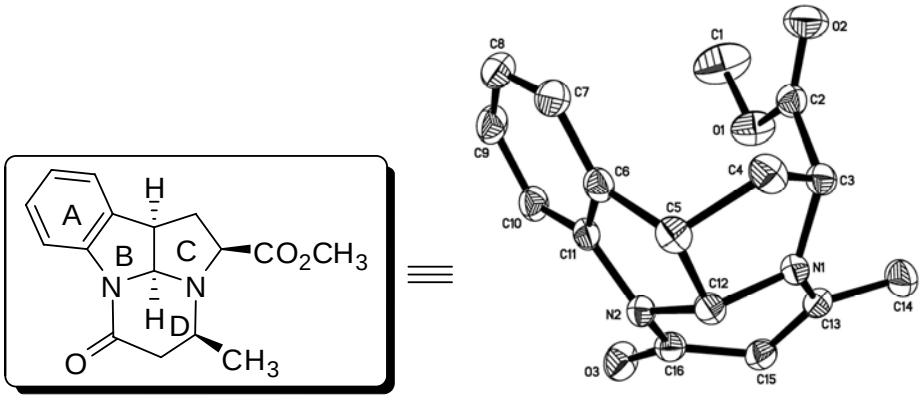
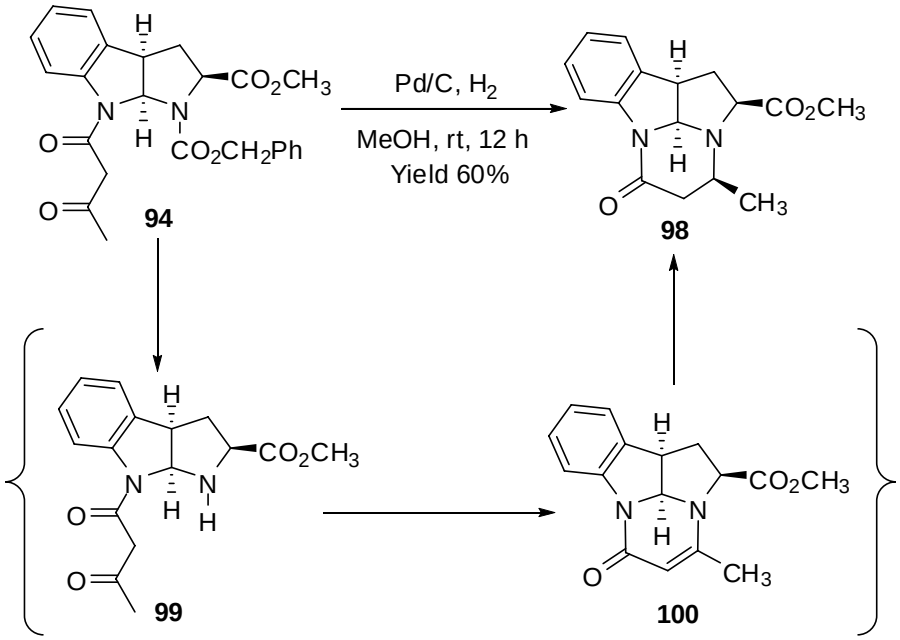


Figure 7.3 X-ray crystal structure of **98**

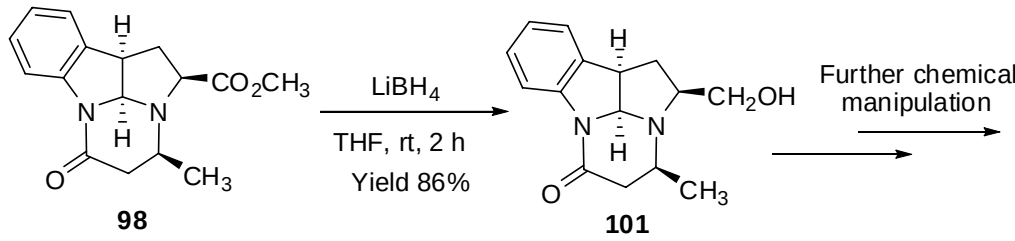
The proposed mechanism for the formation of **98** involved two steps, firstly, deprotection of the benzyl carbamate in the presence of Pd/C and H_2 to afford intermediate **99**, followed by reductive amination where the amine attacks the

carbonyl group to give **100** which undergoes reduction by H_2 to afford the final product **98** (Scheme 7.8).



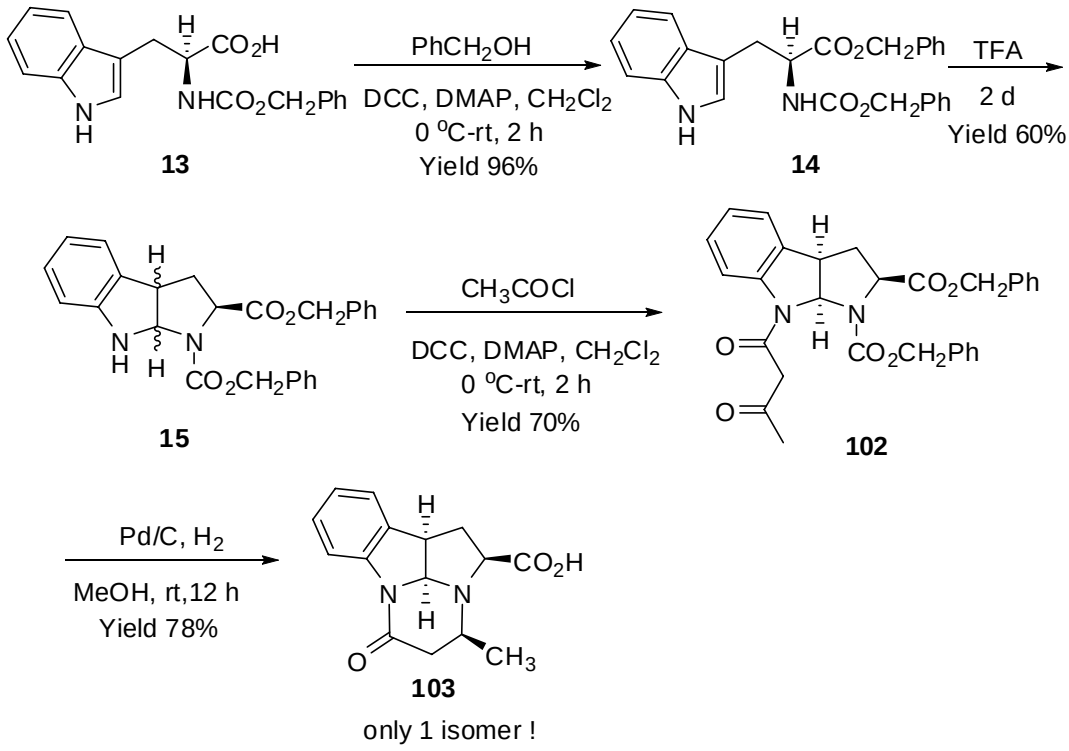
Scheme 7.8 Proposed mechanism for the formation of **98**

Chemical functionlization of compound **98** was next explored in order to further manipulate the tetracyclic ring system. An initial attempt to carry out a Grignard addition to the carboxylate group still failed due to the rigid scaffold of the ring system. However, reduction of **98** with $LiBH_4$ was successfully performed in THF to yield the chiral alcohol **101** as single isomer which can be further manipulated (Scheme 7.9).



Scheme 7.9 Functionalization of tetracylic ring **98**

To test the generality of this new finding, commercially available N_α-carbobenzyloxy-L-tryptophan **13** was first treated with benzyl alcohol using DCC coupling to afford **14** which underwent acid-catalyzed ring closure to provide the hexahydro[2,3-*b*]pyrrolo indole **15**. Reaction of **15** with excess acetyl chloride and Et_3N provided **102** in 70% yield. Finally, hydrogenation gave the chiral tetracyclic acid **103** as a single isomer in 78% yield (Scheme 7.10).



Scheme 7.10 Synthesis of tetracyclic acid **103**

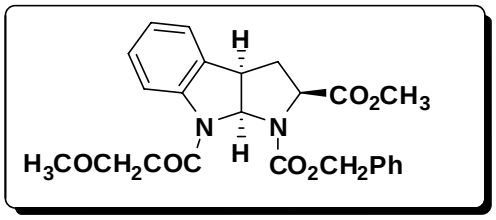
7.3 CONCLUSION

In summary, an unexpected domino ring closure process was found to provide an easy, clean and efficient way for the stereospecific construction of tetracyclic indole alkaloid ring system. Structural manipulation of these new compounds provides other versatile synthetic building blocks.

7.4 EXPERIMENTAL SECTION

Synthesis and characterization of compounds

(2*S*,3a*R*,8a*R*)-1-Benzyl 2-methyl 8-(3-oxobutanoyl)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1,2(2H)-dicarboxylate (94):



To a solution of **47** (0.51 g, 1.45 mmol) and Et_3N (1.4 mL, 10 mmol, 7 equiv.) in dry CH_2Cl_2 (10 mL) was added DMAP (18 mg, 0.15 mmol, 0.1 equiv.). The mixture was cooled to 0 ^oC prior to slow addition of acetyl chloride (0.55 mL, 7.25 mmol, 5 equiv.) and the reaction mixture was allowed to stirr for 2 h before addition of water (1 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic extracts were washed with brine (10 mL) and dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography (ethyl acetate/hexane, 1:4 to 1:2) to afford the product **94** (0.49 g, 78%) as a colourless solid.

$[\alpha]_D^{20}$ = +8.0 (*c* = 0.5, $CHCl_3$, 589 nm);

R_f = 0.13 (ethyl acetate/hexane = 1:2);

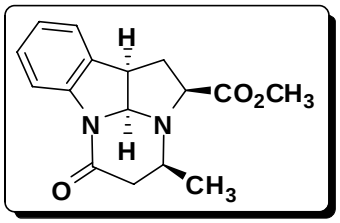
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.97 (d, *J* = 9.8 Hz, 1H), 7.43-7.22 (m, 6H), 7.22-7.16 (m, 1H), 7.13-7.04 (m, 1H), 6.15 (d, *J* = 9.8 Hz, 1H), 5.12 (s, 2H), 4.86(d, *J* =

16.0 Hz, 1H), 4.58 (d, *J* = 12.2 Hz, 1H), 4.19-3.99 (m, 2H), 3.06 (s, 3H), 2.75-2.70 (m, 1H), 2.61-2.50 (m, 1H), 2.33 (s, 2H), 2.12-1.95 (m, 1H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 203.7, 171.3, 167.8, 154.4, 144.2, 142.7, 135.8, 131.3, 128.6, 127.6, 125.1, 123.6, 119.2, 77.9, 67.3, 59.8, 52.4, 45.7, 33.3, 31.0;

HRMS (**EI**) calcd: 436.1629 ; found: 436.1630 (M^+);

IR(KBr): 3032, 2951, 2250, 1712, 1600, 1109, 912, 754, 732, 700 cm^{-1};



(2*S*,3*aR*,8*aR*)-1-Benzyl 2-methyl 8-(3-oxobutanoyl)-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole-1,2(2H)-dicarboxylate **94** (300 mg, 0.69 mmol) was dissolved in 5 mL of methanol and 10% Pd/C (75 mg, 0.069 mmol, 0.1 equiv.) was added. The mixture was stirred overnight at room temperature under a H_2 balloon. After filtration through celite and evaporation, the residue was purified by column chromatography (ethyl acetate/hexane, 1:4 to 1:2) to afford product **96** (118 mg, 60%) as a crystalline solid.

$[\alpha]_D^{20}$ = +30.0 (*c* = 0.5, $CHCl_3$, 589 nm);

R_f = 0.29 (ethyl acetate/hexane = 1:1);

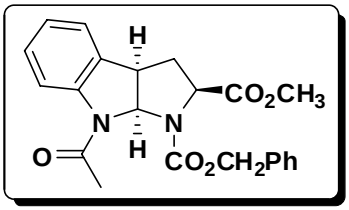
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89 (d, *J* = 7.8 Hz, 1H), 7.17 (d, *J* = 7.8 Hz, 2H), 7.03-6.98 (td, *J* = 0.9, 7.6 Hz, 1H), 5.37 (d, *J* = 7.6 Hz, 1H), 3.99 (dd, *J* = 2.3, 8.4 Hz, 1H), 3.90-3.72 (m, 2H), 3.36 (s, 3H), 2.76-2.51 (m, 2H), 2.31-2.12 (m, 2H), 1.41 (d, *J* = 1.6 Hz, 3H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 174.5, 168.6, 142.8, 132.7, 128.1, 124.1, 124.0, 116.6, 83.0, 60.3, 52.1, 48.9, 43.7, 37.8, 37.7, 19.3;

IR(KBr): 2926, 1717, 1655, 1479, 1396, 1252, 1065, 772, 719 cm^{-1};

HRMS (EI) calcd: for $C_{16}H_{18}N_2O_3$ 286.1312; found: 286.1305 (M^+).

(2*S*,3a*R*,8a*S*)-Methyl 8-acetyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole-2-carboxylate (95)



To a solution of **47** (1.6 g, 4.5 mmol) and Et_3N (5 mL, 35.7 mmol, 8 equiv.) in dry CH_2Cl_2 (20 mL) was added DMAP (55 mg, 0.45 mmol, 0.1 equiv.). The mixture was cooled to 0 ^oC prior to slow addition of acetic anhydride (2.1 mL, 22.5 mmol, 5 equiv.) and the reaction mixture was allowed to stir for 2 h before addition of water (1 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic extracts were washed with brine (10 mL) and dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography (ethyl acetate/hexane, 1:4 to 1:2) to afford the product **95** as a colourless oil (1.0 g, 86% yield).

$[\alpha]_D^{20}$ = -39.6 (*c* = 0.9, $CHCl_3$, 589 nm);

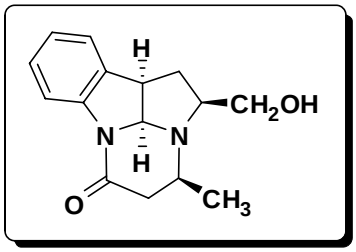
R_f = 0.15 (ethyl acetate/hexane = 1:4);

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10 (d, *J* = 8.0 Hz, 1H), 7.23-7.12 (m, 2H), 6.99 (t, *J* = 11.3 Hz, 1H), 5.63 (d, *J* = 7.3 Hz, 1H), 3.97-3.80 (m, 2H), 3.27 (s, 3H), 2.66–2.50 (m, 2H), 2.37 (s, 3H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 173.5, 168.7, 142.3, 131.9, 128.1, 124.1, 123.8, 116.7, 79.3, 59.2, 51.8, 44.8, 35.7 23.7;

FTIR (neat): 3345, 2952, 2875, 1733, 1652, 1482, 1394, 1130, 920, 755, 733 cm^{-1};

HRMS (ESI) calcd. for $C_{14}H_{17}N_2O_3$ 261.1239 $[M+H]^+$, found 261.1228.



To a solution of **96** (49 mg, 0.17 mmol) in THF/CH_3OH (1:1) (2 mL) at 0 °C was added $LiBH_4$ (10 mg, 0.46 mmol, 2.7 equiv.). The mixture was allowed to warm to room temperature and stirred for 2 h before addition of water (2 mL). The aqueous layer was extracted with ethyl acetate (3 × 5 mL), and the combined organic extracts were washed with brine (5 mL) and dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography (ethyl acetate) to afford the product **98** (38 mg, 86%) as a colourless oil.

$[\alpha]_D^{20}$ = +79.6 (*c* = 0.5, $CHCl_3$, 589 nm);

R_f = 0.33 (EA);

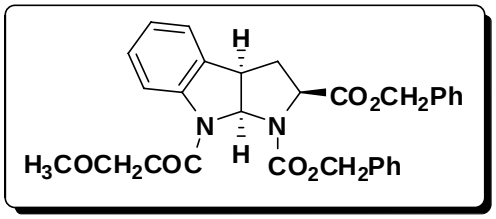
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87 (d, *J* = 7.8 Hz, 1H), 7.23 (t, *J* = 7.4 Hz, 2H), 7.07 (t, *J* = 7.5 Hz, 1H), 5.19 (d, *J* = 7.9 Hz, 1H), 3.79-3.71 (m, 1H), 3.60-3.49 (m, 2H), 3.40-3.27 (m, 2H), 2.81 (dd, *J* = 17.1 , 8.1 Hz, 1H), 2.62-2.52 (m, 1H), 2.20 (dd, *J* = 17.4, 6.6 Hz, 1H), 2.05 (dt, *J* = 12.9, 3.9 Hz, 1H), 1.83 (s, 1H), 1.35 (d, *J* = 6.9 Hz, 3H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 169.3, 141.7, 134.1, 128.0, 124.6, 124.5, 83.7, 63.4, 61.6, 49.6, 42.2, 40.2, 36.5, 21.0;

IR(thin film): 3054, 2930, 1721, 1681, 1485, 1414, 1265, 737, 705 cm^{-1};

HRMS (ESI) Calcd. for $C_{15}H_{19}N_2O_2$: 259.1447 $[M+H]^+$, Found: 259.1429.

(2*S*,3*aR*,8*aR*)-Dibenzyl-(3-oxobutanoyl)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1,2(2H)-dicarboxylate (100)



To a solution of **15** (1.0 g, 2.4 mmol) in dry CH_2Cl_2 (10 mL), was added Et_3N (1.2 g, 12.1 mmol, 5 equiv.) and DMAP (29 mg, 0.24 mmol, 0.1 equiv.). The mixture was cooled to 0 ^oC and acetyl chloride (9.7 mmol, 4 equiv.) was added dropwise and the reaction mixture was allowed to stirr for 2 h before addition of water (1 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic extracts were washed with brine (10 mL) and dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography (ethyl acetate/hexane, 1:1) to afford the product **100** (0.86 g, 70%) as a colourless oil.

$[\alpha]_D^{20}$ = +4.0 (*c* = 0.5, $CHCl_3$, 589 nm);

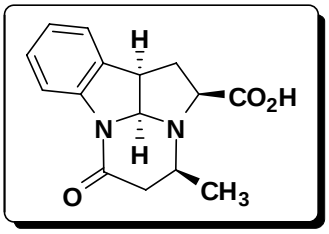
R_f = 0.10 (ethyl acetate/hexane = 1:2);

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82 (d, *J* = 7.5 Hz, 1H), 7.21-6.93 (m, 13H), 6.08(d, *J* = 6.0 Hz, 1H), 5.02 (d, *J* = 12.3 Hz, 1H), 4.92 (d, *J* = 12.3 Hz, 1H), 4.76 (d, *J* = 16.2 Hz, 1H), 4.59-4.53 (m, 2H), 4.21 (d, *J* = 12.3 Hz, 1H), 4.11-3.99 (m, 2H), 2.69-2.65 (m, 1H), 2.52-2.43 (m, 1H), 2.23 (s, 3H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 203.8, 170.4, 166.6, 154.8, 142.8, 135.6, 135.1, 131.4, 128.7, 128.5, 128.4, 128.2, 127.9, 127.8, 124.8, 123.8, 119.4, 78.5, 67.7, 66.9, 59.7, 52.0, 45.4, 33.4, 30.8;

IR(thin film): 2928, 2855, 1728, 1715, 1662, 1456, 1377, 1267, 1167, 752, 737 cm^{-1};

HRMS (ESI) Calcd. for $C_{30}H_{29}N_2O_6$: 513.2026 $[M+H]^+$, Found: 513.2025.



100 (51 mg, 0.1 mmol) was dissolved in 5 mL of methanol and 10% Pd/C (11 mg, 0.1 mmol, 0.1 equiv.) was added. The mixture was stirred overnight at room temperature under a H_2 balloon. After filtration through celite and evaporation, the residue was purified by column chromatography (CH_2Cl_2/MeOH, 10:1) to afford product **101** (21 mg, 78%) as a yellowish crystalline solid.

$[\alpha]_D^{20}$ = +66.7 (*c* = 0.51 $CHCl_3$, 589 nm);

R_f = 0.45 (CH_2Cl_2:CH_3OH = 1:4);

^{1}H NMR (400 MHz, CD_3OD): δ 7.79 (d, *J* = 8.0 Hz, 1H), 7.27 (d, *J* = 7.4 Hz, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.07 (t, *J* = 7.5 Hz, 1H), 5.41 (d, *J* = 7.7 Hz, 1H), 3.99 (dd, *J* = 2.8, 8.4 Hz, 1H), 3.95-3.89 (m, 1H), 3.83-3.76 (m, 1H), 2.87-2.79 (m, 1H), 2.68-2.59 (m, 1H), 2.39-2.32 (m, 1H), 2.19 (d, *J* = 12.4 Hz, 1H), 1.36 (d, *J* = 6.8 Hz, 3H);

^{13}C NMR (100 MHz, CD_3OD): δ 176.5, 170.7, 142.2, 133.5, 127.4, 124.3, 124.2, 116.2, 83.2, 60.5, 48.9, 43.2, 38.1, 37.9, 18.6;

IR(thin film): 2926, 2853, 1647, 1636, 1458, 1377, 1261, 1153, 966, 874, 721 cm^{-1};

HRMS (ESI) Calcd. for $C_{15}H_{17}N_2O_3$: 273.1239 $[M+H]^+$, Found: 273.1230.

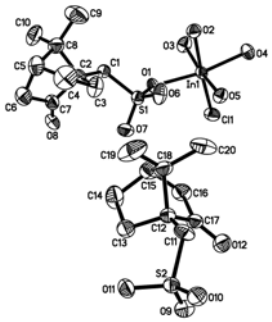


Table 1. Crystal data and structure refinement for **4**

Identification code	**4**	
Empirical formula	C_{21} H_{39} Cl_4 In O_{12} S_2	
Formula weight	804.26	
Temperature	298(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 6.9145(2) Å	α= 90?
	b = 15.3916(6) Å	β= 92.321(2)?
	c = 15.5826(6) Å	γ = 90?
Volume	1657.02(10) $Å^3$	
Z	2	
Density (calculated)	1.612 Mg/m^3	
Absorption coefficient	1.214 mm^{-1}	
F(000)	820	
Crystal size	0.20 x 0.15 x 0.04 mm^3	
Theta range for data collection	1.86 to 27.50°.	
Index ranges	-8<=h<=8, -19<=k<=19, -20<=l<=20	
Reflections collected	34477	
Independent reflections	7580 [R(int) = 0.0432]	
Completeness to theta = 27.50	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9530 and 0.7932	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7580 / 23 / 397	
Goodness-of-fit on F^2	1.062	
Final R indices [I>2sigma(I)]	R1 = 0.0428, wR2 = 0.1203	
R indices (all data)	R1 = 0.0535, wR2 = 0.1327	
Absolute structure parameter	-0.04(3)	
Largest diff. peak and hole	1.769 and -0.819 $e.^{-3}$	

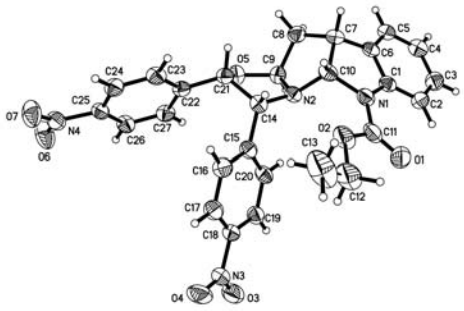


Table 1. Crystal data and structure refinement for **17**

Identification code	**17**	
Empirical formula	$C_{27}H_{24}N_4O_7$	
Formula weight	516.50	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 9.9537(5) Å	α= 90?
	b = 10.8148(4) Å	β= 90?
	c = 23.3315(10) Å	γ = 90?
Volume	2511.57(19) $Å^3$	
Z	4	
Density (calculated)	1.366 Mg/m^3	
Absorption coefficient	0.101 mm^{-1}	
F(000)	1080	
Crystal size	0.30 x 0.30 x 0.20 mm^3	
Theta range for data collection	2.22 to 27.00°.	
Index ranges	-12<=h<=12, -13<=k<=13, -29<=l<=29	
Reflections collected	17460	
Independent reflections	3104 [R(int) = 0.0469]	
Completeness to theta = 27.00	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9802 and 0.9705	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3104 / 0 / 344	
Goodness-of-fit on F^2	1.124	
Final R indices [I>2sigma(I)]	R1 = 0.0518, wR2 = 0.1096	
R indices (all data)	R1 = 0.0670, wR2 = 0.1275	
Absolute structure parameter	-10(10)	
Largest diff. peak and hole	0.265 and -0.349 $e.^{-3}$	

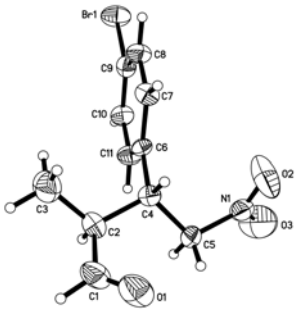


Table 1. Crystal data and structure refinement for **20**

Identification code	**20**	
Empirical formula	C_{11} H_{12} Br N O_3	
Formula weight	286.13	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 10.6835(6) Å	α= 90?
	b = 8.7762(5) Å	β= 97.709(4)?
	c = 12.7768(7) Å	γ = 90?
Volume	1187.13(12) $Å^3$	
Z	4	
Density (calculated)	1.601 Mg/m^3	
Absorption coefficient	3.454 mm^{-1}	
F(000)	576	
Crystal size	0.40 x 0.38 x 0.04 mm^3	
Theta range for data collection	1.61 to 30.70°.	
Index ranges	-14<=h<=15, -11<=k<=12, -18<=l<=18	
Reflections collected	23631	
Independent reflections	6685 [R(int) = 0.0520]	
Completeness to theta = 30.70	99.3 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.8742 and 0.3387	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6685 / 1 / 291	
Goodness-of-fit on F^2	1.080	
Final R indices [I>2sigma(I)]	R1 = 0.0463, wR2 = 0.1263	
R indices (all data)	R1 = 0.0862, wR2 = 0.1494	
Absolute structure parameter	0.049(15)	
Largest diff. peak and hole	0.679 and -0.448 $e.^{-3}$	

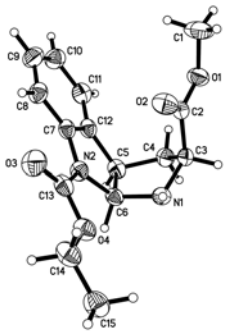
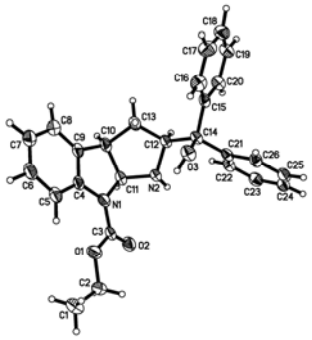


Table 1. Crystal data and structure refinement for **50a**

Identification code	**50a**	
Empirical formula	$C_{15}\ H_{18}\ N_2\ O_4$	
Formula weight	290.31	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 7.9402(2) Å	α= 90?
	b = 11.7992(3) Å	β= 90?
	c = 15.7954(4) Å	γ = 90?
Volume	1479.84(6) $Å^3$	
Z	4	
Density (calculated)	1.303 Mg/m^3	
Absorption coefficient	0.095 mm^{-1}	
F(000)	616	
Crystal size	0.20 x 0.18 x 0.15 mm^3	
Theta range for data collection	2.15 to 30.59°.	
Index ranges	-10<=h<=11, -16<=k<=16, -22<=l<=22	
Reflections collected	35185	
Independent reflections	2575 [R(int) = 0.0594]	
Completeness to theta = 30.59	99.1 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9858 and 0.9812	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2575 / 0 / 196	
Goodness-of-fit on F^2	1.056	
Final R indices [I>2sigma(I)]	R1 = 0.0512, wR2 = 0.1272	
R indices (all data)	R1 = 0.0710, wR2 = 0.1490	
Absolute structure parameter	-10(10)	
Largest diff. peak and hole	0.183 and -0.225 $e.^{-3}$	



Crystal data and structure refinement for **51a.**

Identification code	**51a**	
Empirical formula	$C_{26}H_{26}N_2O_3$	
Formula weight	414.49	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 11.7241(6) Å	α= 90°.
	b = 5.6398(3) Å	β= 100.171(3)°.
	c = 16.4582(9) Å	γ = 90°.
Volume	1071.14(10) $Å^3$	
Z	2	
Density (calculated)	1.285 Mg/m^3	
Absorption coefficient	0.084 mm^{-1}	
F(000)	440	
Crystal size	0.25 x 0.08 x 0.04 mm^3	
Theta range for data collection	1.76 to 27.99°.	
Index ranges	-15<=h<=15, -7<=k<=6, -21<=l<=21	
Reflections collected	9241	
Independent reflections	4937 [R(int) = 0.0399]	
Completeness to theta = 27.99°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9966 and 0.9792	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4937 / 1 / 381	
Goodness-of-fit on F^2	1.022	
Final R indices [I>2sigma(I)]	R1 = 0.0486, wR2 = 0.1034	
R indices (all data)	R1 = 0.0829, wR2 = 0.1271	
Absolute structure parameter	-1.4(14)	
Largest diff. peak and hole	0.199 and -0.302 $e.Å^{-3}$	

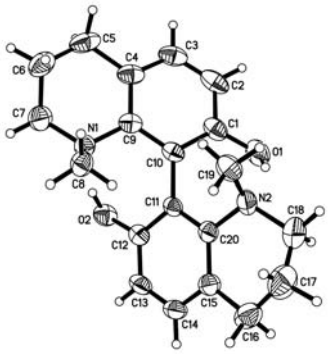
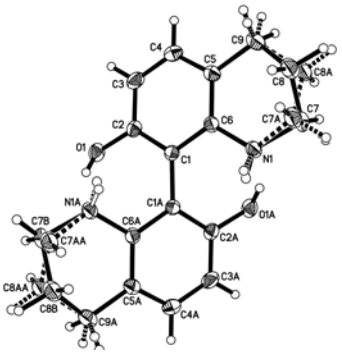


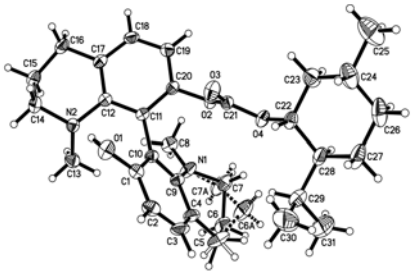
Table 1. Crystal data and structure refinement for **75**.

Identification code	**75**	
Empirical formula	$C_{20}H_{24}N_2O_2$	
Formula weight	324.41	
Temperature	223(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 8.3172(8) Å	α= 90?
	b = 8.6512(8) Å	β= 90?
	c = 23.528(2) Å	γ = 90?
Volume	1692.9(3) $Å^3$	
Z	4	
Density (calculated)	1.273 Mg/m^3	
Absorption coefficient	0.083 mm^{-1}	
F(000)	696	
Crystal size	0.22 x 0.22 x 0.20 mm^3	
Theta range for data collection	1.73 to 26.06°.	
Index ranges	-10<=h<=10, -9<=k<=10, -28<=l<=25	
Reflections collected	10643	
Independent reflections	1928 [R(int) = 0.0611]	
Completeness to theta = 26.06	99.1 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9837 and 0.9821	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1928 / 0 / 221	
Goodness-of-fit on F^2	1.120	
Final R indices [I>2sigma(I)]	R1 = 0.0545, wR2 = 0.1634	
R indices (all data)	R1 = 0.0693, wR2 = 0.1814	
Absolute structure parameter	10(10)	
Largest diff. peak and hole	0.366 and -0.255 $e.^{-3}$	



Crystal data and structure refinement for compound **76**.

Identification code	compound **76**	
Empirical formula	$C_{18}H_{20}N_2O_2$	
Formula weight	296.36	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C2/c	
Unit cell dimensions	a = 20.4836(11) Å	α= 90°.
	b = 4.6090(2) Å	β= 97.350(2)°.
	c = 15.6300(9) Å	γ = 90°.
Volume	1463.49(13) $Å^3$	
Z	4	
Density (calculated)	1.345 Mg/m^3	
Absorption coefficient	0.088 mm^{-1}	
F(000)	632	
Crystal size	0.30 x 0.25 x 0.20 mm^3	
Theta range for data collection	2.00 to 30.55°.	
Index ranges	-28<=h<=28, -6<=k<=6, -22<=l<=22	
Reflections collected	12938	
Independent reflections	2234 [R(int) = 0.0322]	
Completeness to theta = 30.55°	99.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9825 and 0.9739	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2234 / 62 / 129	
Goodness-of-fit on F^2	1.073	
Final R indices [I>2sigma(I)]	R1 = 0.0470, wR2 = 0.1313	
R indices (all data)	R1 = 0.0554, wR2 = 0.1442	
Largest diff. peak and hole	0.425 and -0.177 $e.Å^{-3}$	



Crystal data and structure refinement for compound **76a**

Identification code	compound **76a**	
Empirical formula	$C_{31}\ H_{42}\ N_2\ O_4$	
Formula weight	506.67	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 12.3403(4) Å	α= 90°.
	b = 14.6166(4) Å	β= 90°.
	c = 15.2085(5) Å	γ = 90°.
Volume	2743.21(15) $Å^3$	
Z	4	
Density (calculated)	1.227 Mg/m^3	
Absorption coefficient	0.080 mm^{-1}	
F(000)	1096	
Crystal size	0.30 x 0.30 x 0.24 mm^3	
Theta range for data collection	1.93 to 29.25°.	
Index ranges	-16<=h<=16, -14<=k<=20, -20<=l<=19	
Reflections collected	33944	
Independent reflections	4149 [R(int) = 0.0418]	
Completeness to theta = 29.25°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9809 and 0.9763	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4149 / 7 / 359	
Goodness-of-fit on F^2	1.184	
Final R indices [I>2sigma(I)]	R1 = 0.0421, wR2 = 0.1068	
R indices (all data)	R1 = 0.0596, wR2 = 0.1319	
Absolute structure parameter	-10(10)	
Largest diff. peak and hole	0.303 and -0.325 e.$Å^{-3}$	

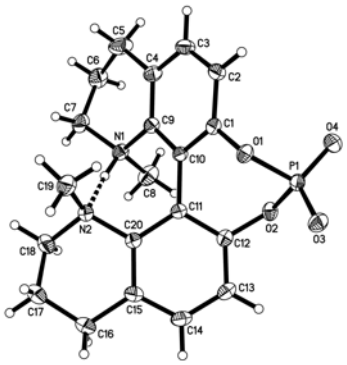


Table 1. Crystal data and structure refinement for **78**

Identification code	**78**	
Empirical formula	$C_{20}\ H_{33}\ N_2\ O_9\ P$	
Formula weight	476.45	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pbca	
Unit cell dimensions	a = 11.7507(3) Å	α= 90?
	b = 17.9535(4) Å	β= 90?
	c = 22.0258(5) Å	γ = 90?
Volume	4646.70(19) $Å^3$	
Z	8	
Density (calculated)	1.362 Mg/m^3	
Absorption coefficient	0.171 mm^{-1}	
F(000)	2032	
Crystal size	0.30 x 0.30 x 0.25 mm^3	
Theta range for data collection	2.27 to 30.50°.	
Index ranges	-16<=h<=16, -25<=k<=25, -31<=l<=31	
Reflections collected	173383	
Independent reflections	7086 [R(int) = 0.0395]	
Completeness to theta = 30.50	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9585 and 0.9505	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7086 / 1 / 334	
Goodness-of-fit on F^2	1.079	
Final R indices [I>2sigma(I)]	R1 = 0.0376, wR2 = 0.1040	
R indices (all data)	R1 = 0.0518, wR2 = 0.1185	
Largest diff. peak and hole	0.593 and -0.497 $e.^{-3}$	

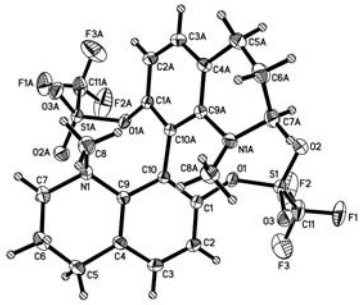


Table 1. Crystal data and structure refinement for **79**.

Identification code	**79**	
Empirical formula	$C_{22}\,H_{22}\,F_6\,N_2\,O_6\,S_2$	
Formula weight	588.54	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C2/c	
Unit cell dimensions	a = 20.7842(6) Å	α= 90?
	b = 9.1415(3) Å	β= 108.385(2)?
	c = 13.4235(4) Å	γ = 90?
Volume	2420.27(13) $Å^3$	
Z	4	
Density (calculated)	1.615 Mg/m^3	
Absorption coefficient	0.310 mm^{-1}	
F(000)	1208	
Crystal size	0.30 x 0.25 x 0.25 mm^3	
Theta range for data collection	2.07 to 36.34°.	
Index ranges	-34<=h<=31, -15<=k<=13, -19<=l<=22	
Reflections collected	25137	
Independent reflections	5843 [R(int) = 0.0283]	
Completeness to theta = 36.34	99.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9266 and 0.9128	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5843 / 0 / 173	
Goodness-of-fit on F^2	1.059	
Final R indices [I>2sigma(I)]	R1 = 0.0389, wR2 = 0.1071	
R indices (all data)	R1 = 0.0534, wR2 = 0.1211	
Largest diff. peak and hole	0.527 and -0.348 $e.^{-3}$	

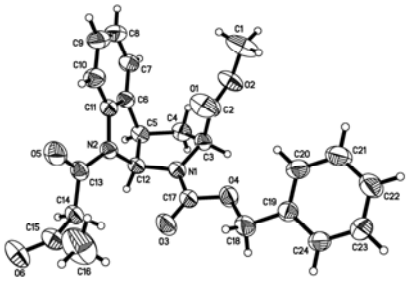


Table 1. Crystal data and structure refinement for **92**.

Identification code	**92**	
Empirical formula	$C_{24}H_{24}N_2O_6$	
Formula weight	436.45	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 10.0800(3) Å	α= 90?
	b = 11.1128(3) Å	β= 90?
	c = 19.7964(6) Å	γ = 90?
Volume	2217.53(11) $Å^3$	
Z	4	
Density (calculated)	1.307 Mg/m^3	
Absorption coefficient	0.095 mm^{-1}	
F(000)	920	
Crystal size	0.30 x 0.30 x 0.20 mm^3	
Theta range for data collection	2.06 to 30.55°.	
Index ranges	-14<=h<=14, -15<=k<=15, -27<=l<=28	
Reflections collected	55454	
Independent reflections	6785 [R(int) = 0.0305]	
Completeness to theta = 30.55	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9813 and 0.9721	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6785 / 0 / 291	
Goodness-of-fit on F^2	1.012	
Final R indices [I>2sigma(I)]	R1 = 0.0420, wR2 = 0.1094	
R indices (all data)	R1 = 0.0555, wR2 = 0.1203	
Absolute structure parameter	-0.4(8)	
Largest diff. peak and hole	0.208 and -0.170 $e.^{-3}$	

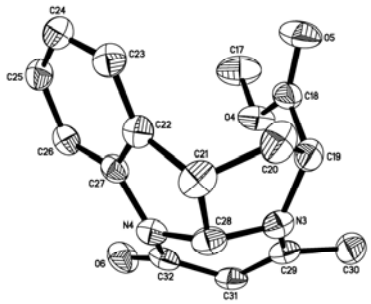
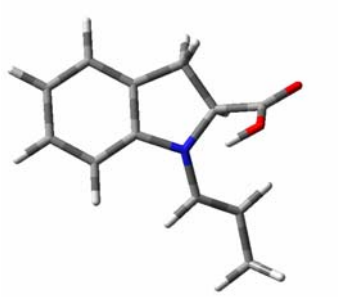


Table 1. Crystal data and structure refinement for **94**.

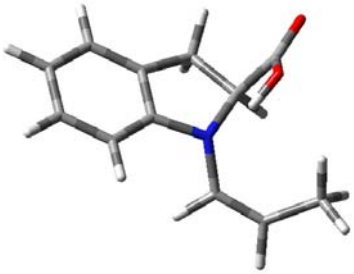
Identification code	**94**	
Empirical formula	$C_{16}H_{16}N_2O_3$	
Formula weight	284.31	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 7.8856(3) Å	α= 90?
	b = 11.8532(4) Å	β= 90?
	c = 30.1827(11) Å	γ = 90?
Volume	2821.16(18) $Å^3$	
Z	8	
Density (calculated)	1.339 Mg/m^3	
Absorption coefficient	0.094 mm^{-1}	
F(000)	1200	
Crystal size	0.30 x 0.20 x 0.20 mm^3	
Theta range for data collection	1.35 to 30.52°.	
Index ranges	-11<=h<=9, -15<=k<=16, -42<=l<=43	
Reflections collected	32601	
Independent reflections	8593 [R(int) = 0.0308]	
Completeness to theta = 30.52	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9815 and 0.9724	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	8593 / 0 / 383	
Goodness-of-fit on F^2	1.023	
Final R indices [I>2sigma(I)]	R1 = 0.0409, wR2 = 0.1005	
R indices (all data)	R1 = 0.0519, wR2 = 0.1071	
Absolute structure parameter	0.6(7)	
Largest diff. peak and hole	0.262 and -0.230 $e.^{-3}$	



syn enamine **a**

C	0.614823	-1.762966	-0.622825
C	1.696524	-0.748989	-0.331425
C	1.114144	0.455467	0.084237
C	-0.698358	-0.922742	-0.541169
H	0.712414	-2.239429	-1.602535
H	0.612741	-2.567000	0.124262
H	-1.110084	-0.736021	-1.540151
N	-0.297880	0.347976	0.090875
C	-1.771091	-1.669168	0.262200
O	-1.780270	-1.400598	1.583464
O	-2.506374	-2.484338	-0.237927
C	3.077459	-0.875761	-0.388745
H	3.529976	-1.810110	-0.711746
C	3.881913	0.214998	-0.033844
H	4.963418	0.129731	-0.080993
C	1.900655	1.548678	0.446186
H	1.462050	2.485935	0.773323
C	3.291800	1.410408	0.379333
H	3.918479	2.254492	0.654153
C	-1.143516	1.467430	0.006264
H	-0.671158	2.391680	0.325491
C	-2.427206	1.467542	-0.381091
H	-1.159836	-0.657725	1.732664
H	-2.911861	0.543982	-0.690947
C	-3.277013	2.706212	-0.403722
H	-3.666981	2.906141	-1.410735
H	-4.148807	2.606379	0.256973
H	-2.712856	3.588945	-0.082571

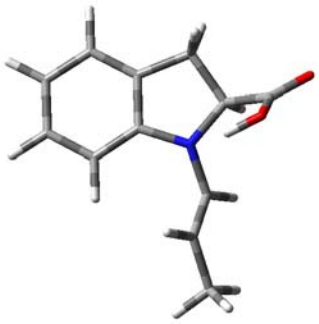
SCF Energy = -670.297643041 hartree
Zero-point correction (ZPE) = 0.229366 hartree



syn enamine **b**

C	-0.390238	1.394591	-1.219587
C	-1.519508	0.643647	-0.551466
C	-1.013729	-0.509669	0.060240
C	0.869996	0.709069	-0.620455
H	-0.425370	1.267138	-2.309320
H	-0.376538	2.468682	-1.016947
H	1.638955	0.529139	-1.374944
N	0.403451	-0.589446	-0.058981
C	1.499733	1.607258	0.465931
O	1.599535	1.049063	1.686126
O	1.876131	2.729262	0.228192
C	-2.883959	0.903884	-0.516587
H	-3.287330	1.795897	-0.989188
C	-3.737005	-0.002999	0.125791
H	-4.804688	0.193121	0.161325
C	-1.847598	-1.423389	0.700553
H	-1.442724	-2.308074	1.183183
C	-3.221148	-1.156315	0.721148
H	-3.890517	-1.852377	1.219116
C	0.966349	-1.823655	-0.483620
C	2.262391	-2.162360	-0.531903
H	1.190320	0.157537	1.609643
H	0.215034	-2.546556	-0.796236
H	2.464520	-3.150495	-0.940442
C	3.464166	-1.369990	-0.099353
H	3.208731	-0.538337	0.561801
H	4.165750	-2.016323	0.442118
H	4.017681	-0.960268	-0.955937

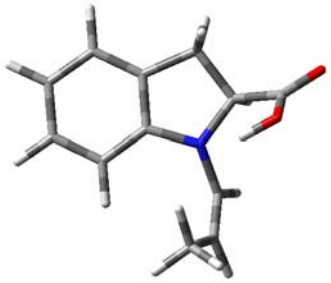
SCF Energy = - 670.293819166 hartree
Zero-point correction (ZPE) = 0.229829 hartree



anti enamine **c**

C	0.444628	-2.025845	-0.303902
C	1.547863	-1.007204	-0.139229
C	0.986973	0.266824	0.018452
C	-0.805956	-1.135416	-0.564868
H	0.605597	-2.733135	-1.121943
H	0.313196	-2.616385	0.612885
H	-1.020478	-1.081546	-1.641093
N	-0.435373	0.196431	-0.036781
C	-2.048874	-1.709613	0.121862
O	-2.286035	-1.215496	1.353534
O	-2.724590	-2.577736	-0.373275
C	2.925585	-1.174113	-0.098232
H	3.363485	-2.161649	-0.221579
C	3.745657	-0.053931	0.090120
H	4.825005	-0.170933	0.117655
C	1.787166	1.390199	0.207591
H	1.350488	2.377209	0.312571
C	3.175215	1.211407	0.238692
H	3.815520	2.078273	0.378545
C	-1.223205	1.293844	-0.483426
H	-1.685215	1.159262	-1.465001
C	-1.417340	2.419854	0.209939
H	-1.638280	-0.492463	1.495436
H	-0.976313	2.510785	1.202270
C	-2.210862	3.589057	-0.294955
H	-3.024725	3.840095	0.397576
H	-1.586619	4.487736	-0.387508
H	-2.650151	3.383215	-1.276685

SCF Energy = - 670.293461826 hartree
Zero-point correction (ZPE) = 0.228903 hartree

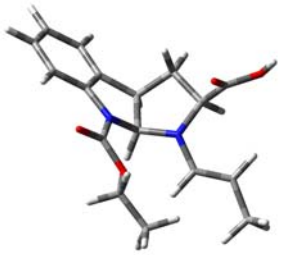


anti enamine **d**

C	-0.018186	-2.026246	0.006589
C	1.269122	-1.236005	0.033789
C	0.979845	0.124721	-0.128170
C	-1.037498	-0.990055	-0.551954
H	0.017746	-2.923668	-0.616821
H	-0.307118	-2.345074	1.017434
H	-1.170053	-1.130442	-1.633777
N	-0.425016	0.328576	-0.264790
C	-2.411761	-1.147442	0.104373
O	-2.608564	-0.359958	1.180682
O	-3.226414	-1.953626	-0.272272
C	2.581326	-1.653209	0.212974
H	2.811102	-2.708508	0.338328
C	3.607991	-0.699554	0.215214
H	4.639067	-1.014570	0.346199
C	1.987278	1.085176	-0.133315
H	1.758147	2.134443	-0.285508
C	3.307369	0.652627	0.041179
H	4.109064	1.386270	0.034107
C	-0.914460	1.422861	-1.041906
C	-1.085615	2.665662	-0.580409
H	-1.828090	0.232505	1.236630
H	-1.157025	1.183233	-2.079903
H	-1.445079	3.403414	-1.295953
C	-0.839390	3.152522	0.817444
H	-0.540240	2.342963	1.489359
H	-0.047265	3.912554	0.839205
H	-1.741452	3.629176	1.222097

SCF Energy = - 670.292710430 hartree

Zero-point correction (ZPE) = 0.229212 hartree

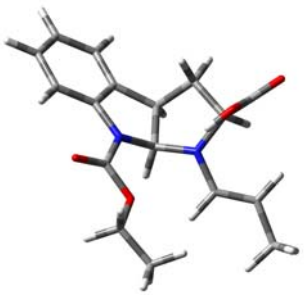


syn enamine **A**

C	2.317253	0.425596	-0.079496
C	2.482760	-0.782657	-0.774622
C	0.177617	-0.103916	-1.002930
C	1.130027	-1.315288	-1.159221
H	-0.005180	0.436744	-1.937684
H	1.077889	-1.720655	-2.174576
N	0.952011	0.802790	-0.089580
C	0.568993	-2.333302	-0.131202
H	0.764459	-3.371314	-0.411303
H	1.028580	-2.149221	0.844347
C	-0.943794	-2.028180	-0.068650
H	-1.510268	-2.681807	-0.747207
N	-1.061177	-0.643278	-0.497498
C	0.492883	2.001811	0.406920
O	1.126763	2.751728	1.127752
O	-0.768850	2.252880	-0.017319
C	-1.371410	3.442707	0.542389
H	-0.759845	4.309026	0.271967
H	-1.363987	3.357552	1.633156
C	-1.473021	-2.241356	1.350543
O	-1.329398	-1.486065	2.280887
O	-2.099755	-3.441925	1.458277
H	-2.364509	-3.525762	2.394146
C	3.744500	-1.337503	-0.938972
H	3.867611	-2.272731	-1.480055
C	3.412057	1.086604	0.479991
H	3.276556	2.010448	1.024591
C	4.677937	0.515894	0.304791
H	5.541540	1.022499	0.727633
C	4.854477	-0.676578	-0.399507
H	5.849422	-1.093776	-0.525535
C	-2.781415	3.546591	-0.007206
H	-3.371593	2.665501	0.262492
H	-3.272529	4.433767	0.407373
H	-2.773236	3.640422	-1.098532
C	-2.293367	-0.175218	-0.956346
H	-2.225026	0.783705	-1.459146
C	-3.485367	-0.778505	-0.816625
H	-3.570382	-1.722802	-0.282755
C	-4.764046	-0.198970	-1.355784
H	-4.586872	0.752558	-1.870444
H	-5.248447	-0.877181	-2.072387
H	-5.496611	-0.012878	-0.557742

SCF Energy = -1070.27086981

Zero-point correction (ZPE) = 0.354393

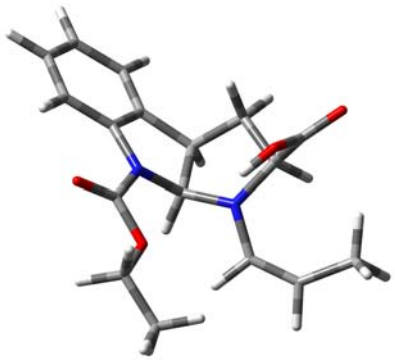


syn enamine **B**

C	2.314188	0.417552	-0.076147
C	2.461103	-0.798361	-0.759337
C	0.153576	-0.119009	-0.938252
C	1.101578	-1.332159	-1.117841
H	-0.068211	0.405778	-1.872800
H	1.030547	-1.729786	-2.135253
N	0.943816	0.796928	-0.059363
C	0.558558	-2.359161	-0.093222
H	0.770182	-3.394906	-0.366770
H	1.012133	-2.171863	0.885775
C	-0.954832	-2.080867	-0.046814
H	-1.488241	-2.688373	-0.789359
N	-1.080124	-0.649709	-0.362338
C	0.509739	2.031141	0.374963
O	1.176165	2.826071	1.011664
O	-0.779136	2.248363	0.012659
C	-1.337184	3.502765	0.476468
H	-0.728275	4.323493	0.086031
H	-1.271455	3.530887	1.568266
C	-1.536977	-2.428331	1.330912
O	-1.598476	-1.391404	2.187609
O	-1.861314	-3.550191	1.636378
C	3.717684	-1.361845	-0.936138
H	3.828119	-2.304081	-1.467230
C	3.418881	1.081371	0.458293
H	3.297971	2.014504	0.990036
C	4.679292	0.502411	0.270335
H	5.551783	1.010060	0.672683
C	4.838195	-0.699692	-0.421452
H	5.828863	-1.123634	-0.557245
C	-2.772487	3.576740	-0.007864
H	-3.362318	2.739511	0.378002
H	-3.228270	4.509480	0.341388
H	-2.821538	3.562785	-1.101860
C	-2.313514	-0.209307	-0.894727
H	-2.254930	0.776286	-1.343283
C	-3.482968	-0.862080	-0.841158
H	-3.556274	-1.834437	-0.358753
C	-4.758869	-0.303071	-1.406641
H	-5.184869	-0.967501	-2.170529
H	-5.526364	-0.186513	-0.629469
H	-4.599300	0.677541	-1.869123
H	-1.349079	-0.591069	1.676648

SCF Energy = - 1070.27180798

Zero-point correction (ZPE) = 0.354653

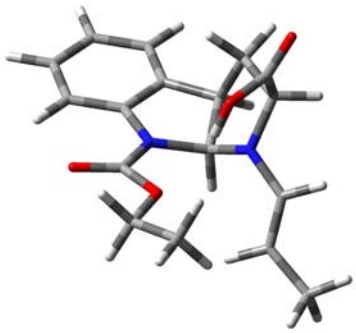


syn enamine **C**

C	2.300297	0.288398	-0.031250
C	2.397101	-0.931742	-0.716751
C	0.162490	-0.086417	-1.020038
C	1.022151	-1.366444	-1.147072
H	0.052144	0.459574	-1.961749
H	0.975885	-1.760770	-2.167013
N	0.959859	0.759896	-0.078041
C	0.353663	-2.343823	-0.148450
H	0.454455	-3.390831	-0.441624
H	0.819397	-2.233664	0.835879
C	-1.131260	-1.914370	-0.097375
H	-1.740537	-2.536746	-0.760876
N	-1.150164	-0.512483	-0.547027
C	0.585706	2.018675	0.344100
O	1.269563	2.767495	1.016607
O	-0.669927	2.312187	-0.075577
C	-1.183163	3.592616	0.367894
H	-0.478483	4.375683	0.074063
H	-1.236492	3.585907	1.461123
C	-1.668578	-2.079856	1.332984
O	-1.731399	-0.940046	2.043809
O	-1.966201	-3.157081	1.791685
C	3.619346	-1.579355	-0.835379
H	3.691854	-2.524443	-1.367927
C	3.419342	0.872284	0.562637
H	3.335497	1.808772	1.095755
C	4.645033	0.208865	0.432632
H	5.529103	0.653123	0.881931
C	4.755394	-0.997957	-0.260330
H	5.720262	-1.488391	-0.350355
C	-2.548020	3.781913	-0.266272
H	-3.224658	2.966060	0.005973
H	-2.984415	4.725542	0.078413
H	-2.472583	3.819138	-1.358140
C	-2.279621	0.012286	-1.217888
H	-2.016719	0.890112	-1.797670
C	-3.572006	-0.356068	-1.222482
H	-1.485272	-0.214161	1.429112
C	-4.353595	-1.431432	-0.515466
H	-3.770589	-2.096036	0.121348
H	-5.127895	-0.976542	0.117361
H	-4.882749	-2.060146	-1.244411
H	-4.188039	0.280060	-1.856861

SCF Energy = - 1070.26482028

Zero-point correction (ZPE) = 0.354984

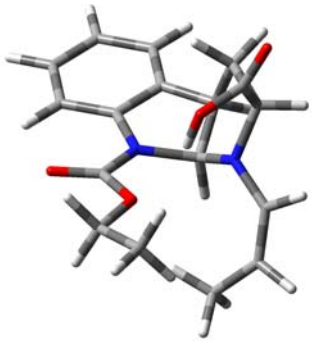


anti enamine **D**

C	-2.192429	0.634856	0.193907
C	-2.555215	-0.650648	0.628111
C	-0.200796	-0.385911	0.998100
C	-1.307128	-1.455009	0.869396
H	-0.047688	-0.032639	2.022214
H	-1.343349	-2.074668	1.770913
N	-0.775431	0.755817	0.192507
C	-0.826000	-2.285030	-0.351221
H	-1.162823	-3.323097	-0.321463
H	-1.212541	-1.840252	-1.273244
C	0.721476	-2.188344	-0.306259
H	1.155860	-3.089029	0.144592
N	1.003117	-1.007748	0.519215
C	-0.107826	1.829889	-0.346729
O	-0.634388	2.826654	-0.804940
O	1.239361	1.626537	-0.346674
C	2.028756	2.721119	-0.884944
H	1.944242	3.573232	-0.202802
H	1.603754	3.017231	-1.846990
C	1.314693	-2.070038	-1.721235
O	1.697837	-0.831436	-2.082401
O	1.396508	-3.020224	-2.461975
C	-3.891801	-1.010680	0.728280
H	-4.169284	-2.006060	1.066268
C	-3.160663	1.575608	-0.156605
H	-2.875230	2.562026	-0.493561
C	-4.504464	1.196741	-0.052622
H	-5.272123	1.919257	-0.316301
C	-4.875628	-0.074769	0.387364
H	-5.926169	-0.339171	0.465586
C	3.458615	2.231752	-1.014868
H	3.524106	1.391117	-1.713312
H	4.087870	3.043234	-1.396258
H	3.854399	1.908902	-0.047250
C	2.199818	-0.966385	1.255071
H	2.839494	-1.825742	1.059436
C	2.602395	-0.022303	2.117328
H	1.991195	0.862317	2.281091
C	3.888307	-0.111123	2.890971
H	4.536735	0.754584	2.698619
H	3.709503	-0.133010	3.974931
H	4.452518	-1.013832	2.630948
H	1.568531	-0.221477	-1.321825

SCF Energy = - 1070.26865670

Zero-point correction (ZPE) = 0.354347

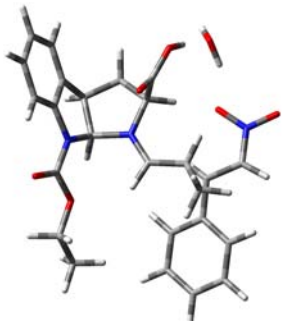


anti enamine **E**

C	2.099727	-0.654681	-0.012732
C	2.536948	0.573297	0.510388
C	0.217604	0.327665	1.059606
C	1.337820	1.379948	0.927510
H	0.163737	-0.124317	2.051434
H	1.467452	1.918284	1.871637
N	0.682665	-0.739427	0.088894
C	0.773414	2.319047	-0.170947
H	1.149920	3.341109	-0.097433
H	1.049140	1.935623	-1.158154
C	-0.763025	2.264341	0.024634
H	-1.110842	3.126713	0.606019
N	-1.008378	1.013932	0.760883
C	-0.060293	-1.692560	-0.566730
O	0.397929	-2.628929	-1.194055
O	-1.398290	-1.447472	-0.462813
C	-2.257529	-2.433267	-1.099351
H	-2.137742	-3.383797	-0.570422
H	-1.920470	-2.575327	-2.129009
C	-1.498268	2.316899	-1.324989
O	-1.940489	1.134032	-1.788148
O	-1.632557	3.348606	-1.938285
C	3.888302	0.888320	0.535840
H	4.223936	1.839423	0.941679
C	3.006241	-1.582133	-0.525553
H	2.663019	-2.523019	-0.931697
C	4.365783	-1.249017	-0.495522
H	5.086665	-1.961677	-0.887021
C	4.811094	-0.035060	0.030004
H	5.872592	0.194359	0.046962
C	-3.680108	-1.911440	-1.027012
H	-3.782342	-0.971336	-1.578379
H	-4.359108	-2.645699	-1.473933
H	-3.986265	-1.740310	0.009558
C	-2.150239	0.949516	1.578062
H	-2.769410	1.834945	1.451437
C	-2.585663	0.013850	2.439405
H	-1.754232	0.432382	-1.123987
C	-2.015105	-1.323252	2.832901
H	-1.335532	-1.738616	2.086280
H	-1.478520	-1.275759	3.791725
H	-2.826292	-2.048788	2.970584
H	-3.508681	0.285531	2.947598

SCF Energy = - 1070.26332004

Zero-point correction (ZPE) = 0.354781

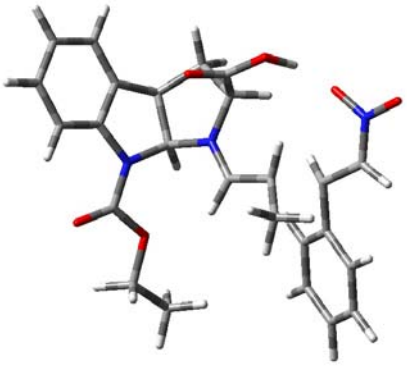


Model TS **A** (with water)

C	-3.530557	-0.930491	-0.024005
C	-3.641584	0.156346	-0.895862
C	-1.389808	-0.662939	-0.992193
C	-2.360622	0.335682	-1.683965
H	-0.801807	-1.280570	-1.669984
H	-2.508445	0.065921	-2.736258
N	-2.238684	-1.513092	-0.156987
C	-1.687472	1.717208	-1.565429
H	-1.041525	1.902895	-2.430032
H	-2.416888	2.528429	-1.509077
C	-0.822607	1.634052	-0.294196
H	0.090224	2.228630	-0.413776
N	-0.463419	0.213481	-0.220329
C	-1.930398	-2.798911	0.231840
O	-2.668076	-3.533808	0.856475
O	-0.680215	-3.148961	-0.181575
C	-0.285801	-4.503943	0.159050
H	-1.085203	-5.184832	-0.143601
H	-0.182872	-4.572170	1.246617
C	-1.549641	2.093889	0.994999
O	-1.780605	3.402070	1.058134
O	-1.886718	1.320536	1.862375
C	-4.821568	0.886771	-0.956035
H	-4.915180	1.733397	-1.631871
C	-4.580800	-1.313851	0.805441
H	-4.480326	-2.157782	1.473349
C	-5.762710	-0.569401	0.735063
H	-6.595342	-0.846162	1.375604
C	-5.889651	0.518552	-0.131410
H	-6.816800	1.083022	-0.163068
C	1.017213	-4.797742	-0.558316
H	1.807903	-4.102733	-0.258502
H	1.345257	-5.814149	-0.315142
H	0.889102	-4.730644	-1.643850
C	0.537454	-0.253984	0.512965
H	0.646166	-1.335506	0.497175
C	1.518182	0.539617	1.166082
H	1.220533	1.574015	1.311516
C	2.163903	-0.055524	2.404304
H	3.051597	0.522448	2.682642
H	1.468067	-0.022111	3.250258
H	2.469149	-1.095772	2.251856
C	2.885227	0.848207	-0.160240
H	2.238174	0.935718	-1.029391

C	3.489245	2.101645	0.164858
H	4.374794	2.235015	0.767251
C	3.753975	-0.368785	-0.219716
C	3.433794	-1.388637	-1.130061
C	4.894515	-0.534987	0.582380
C	4.224143	-2.532429	-1.242426
H	2.563272	-1.272013	-1.772384
C	5.683078	-1.680698	0.477741
H	5.177239	0.236734	1.291285
C	5.352420	-2.684423	-0.434033
H	3.964948	-3.298448	-1.968482
H	6.562548	-1.785124	1.107320
H	5.972056	-3.572760	-0.519625
N	2.873390	3.269415	-0.174775
O	3.354701	4.371800	0.152653
O	1.772499	3.208719	-0.859789
O	-0.268968	4.891668	-0.537413
H	0.633234	4.479429	-0.626073
H	-0.503244	5.189833	-1.427690
H	-1.266161	3.939127	0.380667

SCF Energy = -1660.83606625
Zero-point correction (ZPE) = 0.519253



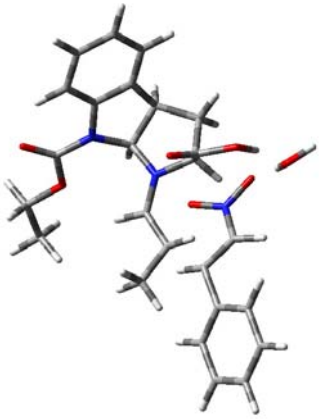
Model TS **B** (without water)

C	3.570125	0.580467	0.115314
C	3.681044	-0.424125	-0.849212
C	1.496426	0.533271	-1.008117
C	2.459555	-0.429894	-1.744904
H	0.970982	1.240604	-1.648872
H	2.713502	-0.031351	-2.734641
N	2.321355	1.252589	-0.042544
C	1.695279	-1.760828	-1.893377
H	1.187042	-1.795276	-2.862123
H	2.367678	-2.620326	-1.842561
C	0.640990	-1.791756	-0.765430
H	-0.322884	-2.148365	-1.130262
N	0.492416	-0.373527	-0.372957
C	2.070611	2.531676	0.409623
O	2.809032	3.173597	1.128150
O	0.871184	2.983699	-0.051143
C	0.529791	4.335791	0.353309
H	1.384054	4.985939	0.148803
H	0.356645	4.340770	1.434108

C	1.085914	-2.673895	0.432958
O	0.356366	-3.767348	0.644511
O	2.058222	-2.392229	1.095526
C	4.821270	-1.213809	-0.905171
H	4.917043	-1.997150	-1.652940
C	4.576225	0.820048	1.046419
H	4.476846	1.605135	1.783274
C	5.717509	0.014184	0.981613
H	6.517158	0.177828	1.698502
C	5.844966	-0.991869	0.021323
H	6.739692	-1.606753	-0.004974
C	-0.704072	4.748302	-0.425404
H	-1.545789	4.076466	-0.229677
H	-0.998575	5.761534	-0.131430
H	-0.504024	4.749673	-1.502035
C	-0.438579	0.068928	0.462330
H	-0.435481	1.145512	0.613078
C	-1.456003	-0.727920	1.057093
H	-1.199419	-1.781877	1.100733
C	-2.028676	-0.212623	2.366564
H	-2.930009	-0.777926	2.626593
H	-1.310616	-0.345501	3.183598
H	-2.293939	0.848442	2.312795
C	-2.866891	-0.911554	-0.201495
H	-2.262131	-1.062334	-1.092560
C	-3.577766	-2.097652	0.170540
H	-4.486472	-2.119511	0.752556
C	-3.629035	0.377046	-0.260872
C	-3.266986	1.337197	-1.219040
C	-4.702101	0.671022	0.595404
C	-3.953019	2.546778	-1.325682
H	-2.447346	1.122727	-1.901840
C	-5.387315	1.882072	0.495047
H	-5.011214	-0.050303	1.345021
C	-5.016516	2.825292	-0.464525
H	-3.664984	3.265392	-2.088440
H	-6.217089	2.085400	1.166502
H	-5.555876	3.764898	-0.546089
N	-3.036080	-3.329301	-0.052002
O	-3.600601	-4.361274	0.353277
O	-1.914866	-3.401182	-0.708667
H	-0.499792	-3.780981	0.116326

SCF Energy = - 1584.39884194

Zero-point correction (ZPE) = 0.494339



Model TS **C** (with water)

C	-3.728275	0.185967	-0.411241
C	-3.604276	-1.030849	0.269226
C	-1.752290	0.350125	0.859136
C	-2.477901	-0.947405	1.279668
H	-1.387288	0.961473	1.683537
H	-2.880350	-0.848539	2.294921
N	-2.716098	1.081181	0.038131
C	-1.398138	-2.036392	1.240288
H	-0.852501	-2.056952	2.187197
H	-1.807269	-3.031428	1.049810
C	-0.417977	-1.593893	0.127997
H	0.598813	-1.823659	0.424702
N	-0.574749	-0.134342	0.083194
C	-2.774575	2.450515	-0.096539
O	-3.640699	3.057493	-0.694833
O	-1.722587	3.046290	0.529212
C	-1.734205	4.495008	0.499644
H	-2.658419	4.845136	0.968901
H	-1.744210	4.825528	-0.543191
C	-0.654695	-2.296632	-1.217698
O	-0.237745	-3.574331	-1.198530
O	-1.153707	-1.781509	-2.187566
C	-4.482490	-2.072360	0.000167
H	-4.394923	-3.019763	0.526417
C	-4.719584	0.394853	-1.365868
H	-4.807692	1.344211	-1.876093
C	-5.594868	-0.664371	-1.628275
H	-6.374922	-0.528602	-2.372272
C	-5.482575	-1.885719	-0.960378
H	-6.172177	-2.693616	-1.186853
C	-0.502600	4.974669	1.243405
H	0.415074	4.632318	0.753541
H	-0.489849	6.069708	1.263738
H	-0.499258	4.609880	2.275212
C	0.350245	0.715349	-0.343141
H	0.089127	1.757492	-0.176622
C	1.589642	0.435761	-0.963567
H	1.711008	-0.575654	-1.346411
C	2.071713	1.520822	-1.916412
H	3.098342	1.338561	-2.239853
H	1.442017	1.558874	-2.814053
H	2.038044	2.510931	-1.444557

C	2.976097	0.323514	0.553391
H	2.722679	1.273683	1.014120
C	2.710309	-0.805756	1.367179
H	3.135568	-1.783407	1.193793
C	4.261610	0.328371	-0.197335
C	5.056924	1.484994	-0.196827
C	4.724492	-0.801437	-0.893618
C	6.286928	1.508865	-0.854320
H	4.711734	2.367731	0.335718
C	5.949410	-0.776010	-1.556408
H	4.119539	-1.703782	-0.924068
C	6.737077	0.378362	-1.537157
H	6.891516	2.411516	-0.833542
H	6.290022	-1.658751	-2.090603
H	7.692519	0.395973	-2.054089
N	1.728532	-0.770772	2.310672
O	1.387846	-1.873496	2.880794
O	1.146103	0.309098	2.600668
O	1.315154	-3.976145	1.085126
H	1.387040	-3.285225	1.796565
H	1.303581	-4.826567	1.547569
H	0.263541	-3.776861	-0.364382

SCF Energy = -1660.83004325
Zero-point correction (ZPE) = 0.518898

Water

O	-0.024248	0.000000	-0.017137
H	0.025062	0.000000	0.950263
H	0.904123	0.000000	-0.293580

SCF Energy = - 76.4089533236
Zero-point correction (ZPE) = 0.021168

Water

List of Publications and Patents

1. Design and Synthesis of a Novel, Water Tolerant Indium Complex: Application to One-pot Three-component Mannich-type Reactions in Water.

   Jian Xiao and Teck-Peng Loh, *Synlett*, **2007**, 5, 815-817.

2. Unexpected Domino Ring Closure: Highly Sstereoselective Construction of a Tetracyclic Indole Alkaloid Ring System.

   Jian Xiao and Teck-Peng Loh, *Tetrahedron Lett.* **2008**, 49, 7184-7186.

3. Design, Synthesis and Optical Resolution of New Bifunctional Ligand: 1,1'-Dimethyl-octahydro-8,8'-Biquinoline-7,7'-diol.

   Jian Xiao and Teck-Peng Loh, *Org. Lett.* **2009**, 11, 2876-2879.

4. Chemzymes: A New Class of Structurally Rigid Tricyclic Amphibian Organocatalyst Inspired by Natural Product.

   Jian Xiao, Feng-Xia Xu, Yun-Peng Lu, Teck-Peng Loh, *Org. Lett.* **2010**, in press. DOI: 10.1021/ol9029758.

5. Hexahydropyrrolo[2,3-b]indole: A New Class of Structurally Rigid Tricyclic Skeleton For Asymmetric Catalysis.

   Jian Xiao, Zhen-Zhou Wong, Yun-Peng Lu, Teck-Peng Loh, submitted for publication.

6. A New Class of Modularly Designed Bicyclic Organocatalysts: Fine Tuning by Self Assembly.
   Jian Xiao, Feng-Xia Xu, Teck-Peng Loh, Manuscript in preparation.

7. Jian Xiao and Teck-Peng Loh, Novel Tricyclic Chiral Ligands: ITTO Ref: PAT/041/08/09/US PRV.

8. Jian Xiao and Teck-Peng Loh, Design, Synthesis and Optical Resolution of New Bifunctional Ligand: 1,1'-Dimethyl-octahydro-8,8'-Biquinoline-7,7'-diol: patent application number of 61/178,722.

Conferences

1. A new class of structurally rigid tricyclic amphibian organocatalyst inspired by natural product.
   Jian Xiao and Teck-Peng Loh, *The Second Waseda-NTU Symposium in Chemistry*, March 13, **2009**, Singapore.

2. Design and syntheses of a new class of structurally rigid tricyclic chiral ligands and their application for enantioselective reduction of ketone. Jian Xiao and Teck-Peng Loh, *ACS ProSpectives Conference "Organic Reactions & Syntheses"* October 26-28, **2008**, Philadelphia, Pennsylvania, USA.

3. Design and syntheses of a new class of structurally rigid tricyclic chiral ligands and their application for enantioselective reduction of ketone.
   Jian Xiao and Teck-Peng Loh, *5th PERCH-CIC Congress (Centre for innovation in chemistry: postgraduate education and research program in chemistry)*, May 6-9, **2007**, Pattaya, Thailand.

4. A new class of structurally rigid tricyclic chiral ligands.
   Jian Xiao and Teck-Peng Loh, *International Symposium on Catalysis and Fine Chemicals*, December 16-21, **2007**, Singapore.

5. Design and syntheses of new chiral catalysts for asymmetric synthesis.
   Jian Xiao and Teck Peng Loh, *1st Penang International Conference for Young Chemists*, May 24-27, **2006,** Penang, Malaysia.